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Clear cell sarcoma from diagnosis and multidisciplinary treatment to clinical trials

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Abstract

Clear cell sarcoma (CCS), formerly called soft tissue melanoma, is a rare malignant soft tissue sarcoma (STS) characterized by a propensity for lymphatic spread and poor prognosis. Clear cell sarcoma can be distinguished by a t(12; 22) (q13; q12) translocation, which in addition to diagnostic implications may be important for targeted treatment in the future. Clear cell sarcoma occurs mainly on the extremities, most often the shin (in the feet and ankle area), in the tendons, and aponeurosis, often at a young age. Considering the significant ability to develop metastases to regional lymph nodes (about 30% of cases), a sentinel node biopsy (SLNB) should be considered in diagnosis, with possible subsequent radical lymphadenectomy (LND) in the case of metastases. Treatment of localized disease is limited to radical local excision with optional complementary radiotherapy. Due to the resistance to classical chemotherapy and the presence of characteristic molecular abnormalities, research focusing on the use of molecular targeted therapies in this group of cancers is ongoing. In clinical trials, MET inhibitors, and tyrosine kinase inhibitors (TKI) were evaluated. Clear cell sarcoma was also one of the subtypes of tumors assessed in the CREATE clinical trial with crizotinib and IMMUNOSARC with checkpoint inhibitors. However, a poor understanding of the biology and natural course of this sarcoma requires further research to develop an effective treatment and unify clinical guidelines.

Keywords: sarcoma, clear cell, SLNB, MET, immunotherapy

Epidemiology

Clear cell sarcoma (CCS) is an extremely rare type of tumor encompassing approximately 1% of all soft tissue sarcomas (STS) [1]. It was first described by Enzinger in 1965 [2] and was designated in the literature for many years as clear cell sarcoma of tendons and aponeuroses or as malignant melanoma of soft tissue, due to its pathological, genetic, and clinical resemblance to melanoma. Clear cell sarcoma is mostly localized on the lower extremities, with a particular predilection for the vicinity of the foot and ankle joint, where up to 40% of the tumors are found. The upper limb is the site in 25% of the cases. Primary tumors

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occur deep in soft tissues in the vicinity of tendons, fascia, or aponeuroses [3–8]. Less frequent localizations of CCS encompass the retroperitoneal space, the digestive tract, or bones. Clear cell sarcoma developing in the kidney, on the trunk, penis, in the head and neck, or mediastinum have been described. Also, one case of primary CCS located in the central nervous system was described [9]. The primary location in the skin is extremely rare, and so far a few cases have been described and only one published series of 12 cases and a collective analysis of 23 patients [10–12].

The tumors occur most frequently in young adults, from the 2nd to the 4th decade of life. Clear cell sarcoma can occur at any age (also in children and adolescents), but few cases have been described in patients over 40 years old [13]. Slightly more women than men are affected [13].

There are only a few risk factors for CSS, with the best-known influence of radiation, chemicals such as (vinyl chloride, and arsenic) and chronic tissue irritation (lymphedema, foreign body implants) [14].

Predominantly CSS presents as slowly growing lesions with not very pronounced symptoms [3, 5, 15, 16]. Up to 40% of CSS are painless, nonetheless, they also can cause pain, pruritis, paresthesia, or perturbations of joint mobility [6]. Furthermore, CSS may be accompanied by swollen tissue that can be painful at palpation and also cause gait perturbations [13].

In spite of its slow growth and cryptic course, CCS is characterized by high aggressiveness — in about 30% of patients lymph nodes are occupied or distant metastases are present at the moment of diagnosis [7, 15]. In contrast to most sarcomas, which metastasize through the bloodstream, about 50% of patients with CCS present metastases to the lymph nodes [5, 7, 15]. The most common localizations of distant CSS metastases are the lungs, though numerous metastases to the skin, bones, liver, heart, and brain have also been described [16–18]. Generally, CCS is an aggressive neoplasm with a tendency for recurrence, early metastasis, and a short survival period [10]. The most recent large retrospective study showed that median overall survival (OS) for CCS was 57.2 months. Overall estimated 5- and 10-year survival was approximately 50% and 38%, respectively [16], indicating a poor prognosis as most patients are diagnosed at an advanced stage of the disease.

Biology, genetics, histopathology

Pathomorphological characteristics

Under microscopic examination, CCS is characterized by the presence of light oval, epithelioid, or spindle-shaped cells arranged in nests separated by collagen fibers [19]. These clear cells display either a round or spindle-shaped morphology, featuring a centrally located spherical nucleus, diffuse chromatin, and a prominent nucleolus (Fig. 1). Notably, distinctive multinucleate gigantic cells with nuclei arranged in a ring-shaped pattern are observed. The cytoplasm of CCS cells may appear abundant, transparent, or pale and eosinophilic, with a centrally

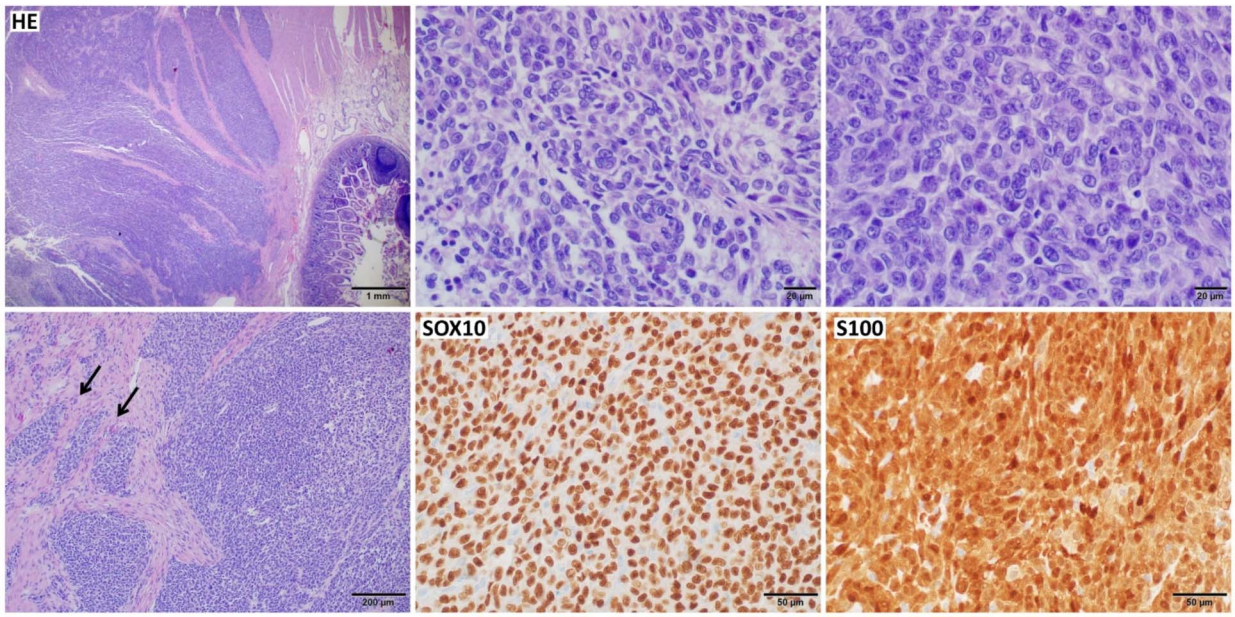

Figure 1. Histopathological image of clear cell sarcoma; tumor located in the large intestine, typically organoid morphology with a framework of fibro-collagenous tissue, nests of epithelioid cells with clear eosinophilic cytoplasm and prominent nucleoli (HE); strong immunohistochemical positive reaction with SOX10 and S100 are helpful in differential diagnostics

Table 1. Differential diagnosis of clear cell sarcoma and malignant melanoma

	Clear cell sarcoma	Malignant melanoma
Localization	Deep location	Primarily skin
	Often associated with tendons and fascia, do not infiltrate the dermis	Infiltration of epidermis
Histopathological appearance	Oval, epithelial, or spindle-shaped and clear cells with small nucleoli, groups of cells surrounded by fibrous septae	Melanocyte proliferation in the basal layer
Cellular polymorphism	Low	High
Number of mitoses	Usually low	Often high
Translocation t(11;22)	Frequent	Absent
***BRAF* and *NRAS* mutations**	Sporadic	Relatively frequent

Table 2. Immunohistochemical staining in differential diagnosis of clear cell sarcoma

	Clear cell sarcoma	Malignant melanoma	PEC-oma
Cytokeratins	+/–	+/–	–
S-100	+++	+++	+/–
SOX10	+++	+++	–
HMB-45	++	++	+
Melan A	++	++	++
Tyrosinase	++	+++	++
Chromogranin	+/–	–	+
CD68	–	+/–	+
CD163	–	–/+	+
Desmin	–	–	++
Vimentin	+++	+++	–
EMA	–	+/–	–
SMA	–	–	++

located spherical nucleus and clear nucleoli. The cytoplasmic lightness is attributed to substantial glycogen content and acidophilia. Intracellular melanin is often not visibly present, and the mitotic activity of these cells is generally low, typically up to 3 mitoses per 10 high-power fields (HPF) [19, 20]. Specific morphological traits, such as a mainly hyalinized sclerotic and reticulate stroma with bundles of a homogeneous population of neoplastic cells surrounded by delicate fibrous septae, could be helpful in differentiation from melanoma (Tab. 1).

Moreover, CCS does not show a distribution of clusters of atypical melanocytes. Still, in most cases, multinuclear, large cells can be found with a characteristic wreath of many peripherally located nuclei [11, 13]. Grading of CCS follows the Fédération Nationale des Centres de Lutte Contre le Cancer (FNCLCC) system, considering cell differentiation, necrosis, and mitotic activity. Clear cell sarcoma is characterized by a low mitotic index and rare occurrence of necrosis, resulting in most cases being classified as malignancy grade 1 or 2 [1, 17].

Immunohistochemical features

Clear cell sarcoma's histological and immunohistochemical properties pose challenges in differential diagnosis, especially concerning spindle cell melanoma and metastatic focus primarius ignotus (FPI) melanoma [10]. Clear cell sarcoma exhibits characteristics indicative of differentiation toward melanocytes, including expression of S100 protein, SOX10, melan A protein, microphthalmia transcription factor (MITF), and antigen HMB-45. Additionally, melanosomes complicate differential diagnosis of both primary lesions and metastases [10]. Melanin is present in over 70% of CCS cases [3]. Immunohistochemical staging of CCS reveals negative markings for AE1/AE3, desmin, CD34, and LCA [19] (Tab. 2).

Genetics

Characteristic genetic abnormalities are beneficial in differential diagnosis, with the t(12;22)(q13;q12) translocation being a distinctive marker found in over 90% of CCS cases (Tab. 1) [21, 22]. This translocation leads to the fusion of the *ATF1* gene (*activating transcription factor 1*) from chromosome 12q13 and *EWSR1* (*Ewing sarcoma breakpoint region 1*) from chromosome 22q12, which leads to the formation of the EWSR1-ATF1 fusion protein, inducing the expression of the melanocyte-specific transcription factor (MITF). Interaction between MITF and SOX10 contributes to the proliferation and melanocytic dedifferentiation of cells, explaining the similarity to melanoma [23]. Several types of these fusion proteins have been documented, the most common ones are type 1 (fusion of exons 8 of EWS and 4 of AFT1) and 2 (fusion of exons 7 of EWS and 5 of ATF1) [24]. No correlation has been found between the type of occurring fusion protein and the clinical course of the disease [25]. Other translocations, such as t(2;22)(q34;q12) leading to the formation of EWSR1/CREB1 protein (Cyclic Adenosine 3,5-Monophosphate Response Element Binding Protein), and chromosome 8 polysomy are also frequent in CCS [21, 26, 27]. Detection methods such as fluorescent *in situ* hybridization (FISH) for the *EWSR1* gene rearrangement and RT-PCR for the EWSR1/ATF1 fusion protein mRNA are useful [28, 29].

Biology and therapeutic targets

One of the pathways activated by MITF involves c-Met, which is an effector protein. Both CCS cell lines and primary tumors show excessive activation of c-Met, which occurs in an autocrine fashion involving hepatocyte growth factor (HGF). c-Met expression affects increased invasiveness, chemotaxis, and survival of the sarcoma cells. HGF and c-Met are potential therapeutic targets as *in vitro* research has shown that blocking them with an appropriate neutralizing antibody (AMG 102) or inhibitor (SU-11274) leads to inhibition of xenograft growth [30]. Other tyrosine kinase receptors that can be activated in CCS are PDGFRB and HER3, which can also be therapeutic targets [31].

Preclinical trials suggest that histone deacetylase (HDAC) inhibitors may play a role in treating CCS. These inhibitors induced apoptosis, inhibited cell growth, and lowered the level of EWS-ATF1 expression in CCS cell lines. A recent drug screening study demonstrated a new potential mechanism of epigenetic changes in CCS. The HDAC inhibitor vorinostat reduced the expression of EWSR1-ATF1 not by modifying chromatin structure but by reducing the level of BRD4, a member of the bromodomain and extraterminal motif protein family [32]. Furthermore, the antiproliferative effect was also achieved with the BRD4 inhibitor JQ1. Also, transcriptional factors such as SOX10 can be effectively targeted with vorinostat, which shows a predominant effect of epigenetics in this sarcoma. Preclinical investigations of gene expression suggest other potential therapeutic targets in CCS, including fibroblast growth factor receptor 1 (FGFR1) [33].

Differential diagnosis

After standard immunohistochemical staining, distinguishing CCS from melanoma becomes challenging, as there are no validated staining methods specific to CCS alone [7]. Both neoplasms (MM and CCS) present a similar staining pattern for S100, SOX10, HMB45, and melan A. Sarcoma is also frequently positive for tyrosinase, MITF, CD117 (KIT), enolase, CD57, and vimentin. Conversely, staining for keratins, epithelial membrane antigen, muscle actin, and desmin is negative [20, 34, 35]. Moreover, Yang et al. [29] have demonstrated that *BRAF* and *NRAS* mutations, present in 51.6% and 12.9% of melanomas, respectively, do not occur in CCS. However, some studies report rare occurrences of *BRAF* and *NRAS* mutations in CCS cases [17]. Differential diagnosis encompasses various neoplasms, including malignant fibrous histiocytoma, rhabdomyosarcoma, fibrosarcoma, liposarcoma, epithelioid sarcoma, and malignant schwannoma (Tab. 3) [36]. Moreover,

Table 3. Differential diagnosis of clear cell sarcoma (CCS)

Malignant blue nevus	**CCS**
– generally localized on the skin of the head – Surface localization – often formed based on a benign blue nevus	– generally localized on extremities – deep localization – not associated with a benign blue nevus
Malignant peripheral nerve sheath tumor	**CCS**
– negative staining for a melanin and HMB-45 – frequently pleomorphic – high mitotic activity – often associated with neurofibromatosis	– positive staining for melanin A and HMB-45 – rarely pleomorphic – low mitotic activity
Epithelioid leiomyosarcoma	**CCS**
– regular pattern of cells and septae – negative staining for S100, SOX10, HMB-45, and other melanocytic markers – positive staining for SMA and desmin	– generally an irregular pattern of cells and septae – positive staining for S100, SOX10, HMB-45, and other melanocytic markers – negative staining for SMA and desmin
Malignant synovial tumor	**CCS**
– positive staining for cytokeratins (50–80%) – negative staining for S100, SOX10, HMB-45, and other melanocytic markers – frequent calcification – t(X;18) translocation – positive staining for TLE1	– negative staining for cytokeratins – positive staining for S100, SOX10, HMB-45, and other melanocytic markers – calcification rare – t(11;22) translocation – negative staining for TLE1
PDMT	**CCS**
– localized in the skin – poorly distinguishable nucleoli – no necrosis	– deep localization – distinct nucleoli – necrosis frequent

PDMT — paraganglioma-like dermal melanocytic tumor

CCS lesions on extremities require differentiation from melanocytic neoplasms, including clear cell myelomonocytic tumor of the falciform ligament (CCMTs), paraganglioma-like dermal melanocytic tumor (PDMT), malignant peripheral nerve sheath tumor (MPNST), and monophasic synovial sarcoma (SS) [37–39]. The genetic marker, the t(12;22)(q13;q12) translocation, is prevalent in over 90% of cases and plays a crucial role in distinguishing CCS from other lesions, especially from melanoma as this aberration has hitherto not been observed [11, 13, 21, 22]. Furthermore, CCS mostly has a deep subcutaneous location, with rare cases of infiltration of the dermis and the epidermal layer, which helps in differentiation from primary melanoma. The

differential diagnosis of CSS metastases can be more complex due to the above-mentioned similarities. It should be remembered that melanoma in general is characterized by a much higher mitotic activity, atypia, and cellular pleomorphism than CCS. Fibrous bands separating nests of sarcoma cells are rare in melanoma [20]. Negative staining for epithelial markers facilitates differentiation of melanoma from CCS metastases [20].

Imaging diagnosis

On computed tomography (CT) and magnetic resonance imagining (MRI), CCS resembles benign lesions in appearance; they are well-separated and homogeneous. Preferentially, MRI should be performed with gadolinium contrast. In T1-dependent images, they show strong enhancement, with a higher signal intensity than muscle, whereas in T2-dependent images, they are more heterogeneous with varied intensity. Foci of lowered signal intensity may correlate with foci with a high accumulation of melanin and iron ions [26, 40, 41]. There are no radiological properties allowing a diagnosis based on MRI, and the final diagnosis depends on the result of histopathological analysis. Positron emission tomography/computed tomography (PET/CT) allows for complete staging by the discovery of areas of increased metabolism and the diagnosis of CCS metastases as well as the evaluation of the effectiveness of surgical (and adjuvant) procedures after treatment procedures initially planned as radical [41, 42]. A clinical trial with a novel PET probe, [^{18}F]-N-(2-(diethylamino)ethyl)-5-(2-(2--(2-fluoroethoxy)ethoxy)ethoxy)picolinamide-([18F]--PFPN), characterized by high melanin affinity showed a beneficial effect in complementary diagnostics of CCS. Together with the standard [^{18}F]-FDG PET, it allows the detection of particularly small lesions in the skin and subcutaneous tissue [43]. Furthermore, some studies suggested the role of ultrasonography in screening for STS, comprising tumor size, echogenicity, texture (homogenous vs. heterogenous), and Doppler pattern [44, 45].

Treatment of localized disease

The standard treatment for CCS patients is surgery followed by radiotherapy or adjuvant chemotherapy, especially following R1 or R2 excision [13]. Neoadjuvant treatment is administered exclusively in exceptional clinical situations, as CCS is highly resistant to chemotherapy. And, currently, there is no regimen ensuring optimal treatment as evidenced by a reduction in tumor size [46, 47]. Single reports on the use of neoadjuvant chemotherapy indicate a clinical benefit in using the EI regimen (epirubicin plus ifosfamide) [48] and the MAID regimen (mesna 1500 mg/m^2/d 1–4 plus doxorubicin 15 mg/m^2/d 1–3 plus ifosfamide 1500 mg/m^2/d 1–3 plus dacarbazine 250 mg/m^2/d 1–3) [33, 49, 50]. Sunitinib has been used in single cases in presurgery therapy [51]. However, recent clinical observations showed a minor benefit from its use in that situation [52]. Considering the findings from one of the most extensive studies on CCS, it is evident that neither neoadjuvant nor adjuvant radiotherapy and chemotherapy significantly impact patients' OS and disease-free survival (DFS) [53]. Moreover, the absence of surgical intervention, even in cases of metastatic disease, is associated with the worst prognosis, underscoring its status as the most advantageous choice for these individuals. Therefore, determining the appropriate stage of the tumor, resection with a wide margin, and optimal post-treatment surveillance seem to be the most beneficial. Observation after treatment is recommended every three months for 2–3 years, subsequently every 6 months, up to 5 years from radical treatment, then once a year, and should, among others, include physical examination (because of frequent local recurrences) and a chest CT to search for lung metastases [13, 54].

Surgery

As in most sarcomas, broad excision of the tumor is the only possible radical treatment of localized disease. The aim of surgical treatment should always be to obtain macro- and microscopically negative surgical margins, even if this requires a more aggressive procedure or additional surgery on the scar [15]. The margin should be at least 1 cm [55]. For this reason, *en bloc* excision with R0 margins is recommended, which means resection of the tumor in a single piece with a space of normal tissue around it. Instead of radical surgery if it is not possible radical radiotherapy of 70 Gy (in 2 Gy fractions) has been proposed [56]. The most aggressive strategies in the form of amputation are currently much less frequently implemented and do not decrease the risk of recurrence or metastases. Therefore, they should be only considered in cases in which limb-sparing surgery is impossible, for example, because of the infiltration of large nerves [4, 57]. Local treatment may be supported by isolated limb perfusion (TNF-alpha plus melphalan) or intratumoral injection (IFN-alpha), though these procedures remain in the domain of clinical trials [26].

Lymph node dissection

Because of the high frequency of metastases to lymph nodes in CCS, a discussion about performing a sentinel lymph node biopsy (SLNB) has emerged. This procedure could permit earlier detection of metastases to lymph nodes and improve the patient's prognosis [58]. Because of the low frequency of CCS occurrence, data concerning surgical node biopsy are very

limited, which makes it difficult to establish strong evidence-based recommendations and management guidelines. The percentage of positive biopsy results of the sentinel node varies from 30 to 50% [58–60]. However, SLNB's impact on patient outcomes is debatable, as only some authors showed a strong trend for improved survival in patients with a negative biopsy [61], while others established no correlation with OS or recurrence-free survival (RFS) [62]. Retrospective analysis of pediatric patients showed that lymph node metastases can be detected in 14.6% of cases, with the involvement of nodes being significantly associated with poorer OS [hazard ratio (HR) = 2.02; confidence interval (CI) 1.38–2.95; $p < 0.001$]. Interestingly, in the case of CCS, SLNB was linked to improved OS (HR = 0.35; CI 0.15–0.78; $p = 0.01$). Additionally, a higher frequency of lymph node sampling was observed in CCS patients (56.3%), highlighting an increased awareness of the metastatic pattern in this particular subtype [63].

The role of lymphadenectomy for locoregional control in CCS is also being evaluated [5]. Most authors suggest that it should be performed in cases when metastases to lymph nodes were confirmed by a fine needle biopsy [64, 65]. At the same time, CCS treatment may encompass SLNB with subsequent radical lymphadenectomy if metastases to the sentinel node are detected [58, 66–68]. Nevertheless, when dealing with lymph node metastases in clinical practice, aggressive treatment is recommended, even if the metastases are isolated. It is important to note that the approach can vary among different clinical centers, as it is primarily based on expert opinions. In such situations, there is a choice of treatment, which may include lymph node dissection (LND), radiotherapy (RT), and chemotherapy (ChT) [69]. According to guidelines, neoadjuvant radiotherapy may be considered. Preoperative chemotherapy is also an option. For patients with a significant number of positive lymph nodes, postoperative radiotherapy at the site of lymph node removal may be included in the treatment plan [70]. Additionally, less commonly used methods, such as regional hyperthermia in combination with systemic chemotherapy and isolated limb perfusion, have demonstrated benefits in these cases [71].

Adjuvant treatment

European Society for Medical Oncology (ESMO) guidelines recommend adjuvant radiotherapy for sarcomas that are deeply localized (subfascial), with grade 2 and 3 malignancy and with large local progression (> 5 cm, T2–T4). Most CCS are formally classified as G1 leading to multiple controversies regarding adjuvant therapy. In CCS patients, postsurgical radiotherapy should be considered if it is impossible to obtain R0 surgical margins or if surgery is not possible due to contraindications or the patient's refusal [1]. In various retrospective analyses, the percentage of patients subjected to adjuvant radiotherapy was about 40% [5]. While some investigations showed no effect on the improvement of OS [5], in others such a correlation has been described. Consequently, postoperative radiotherapy improves local control of the disease, especially in the group of patients with metastases to lymph nodes and after R1 resection [26, 67, 72]. Irradiation can be performed using external beams as well as brachytherapy [28]. In the case of teleradiotherapy, the recommended dose can be 50 Gy in the elective area with an increase of the dose to 60-66 Gy in the area of the post-resection bed (Fig. 2). The target volume should not encompass local lymph nodes if no metastases of the sarcoma have been found. Since there is no consensus, the decision about adjuvant radiotherapy of lymph nodes with detected CCS metastases should be taken individually for each patient. As for adjuvant chemotherapy, in the group of patients from the National Cancer Center, Tokyo, M0 patients who received adjuvant chemotherapy had better prognoses (5-year survival 65%) than patients without chemotherapy (5-year survival 23%) ($p = 0.03$) [8]. Taking into consideration the high resistance of CCS to chemotherapy, its application in adjuvant therapy is not routinely recommended [1].

Treatment of advanced/metastatic disease

Chemotherapy

Systemic chemotherapy is the treatment of choice in nonresectable and disseminated CCS. However, CCS has a low percentage of responses to systemic treatment with 4% partial response (PR), 37% stable disease (SD), and progression-free survival (PFS) of 11 weeks [73].

Furthermore, recent analysis substantiated this pattern, showing median progression-free survival (mPFS) of around 2 months (95% CI 1.2–2.7 months) across various chemotherapy protocols and median overall survival (mOS) of 15 months [74].

Data concerning the choice of chemotherapy regimens in CCS are generally limited to retrospective analyses (Tab. 4). Basic treatment regimens are 1) doxorubicin monotherapy 60–90 mg/m^2, 2) doxorubicin 60 mg/m^2 plus ifosfamide 5–9 g/m^2, 3) doxorubicin 60 mg/m^2 plus cisplatin 120 mg/m^2 [36]. Data from Istituto Nazionale dei Tumori in Milan showed 35 patients who received first-line chemotherapy with doxorubicin plus dacarbazine ± ifosfamide, 2 of these patients achieved a PR, 3 — SD, and 6 PD after 3 months according to RECIST. Nevertheless, in all cases, clinical benefit from the treatment (PR/SD)

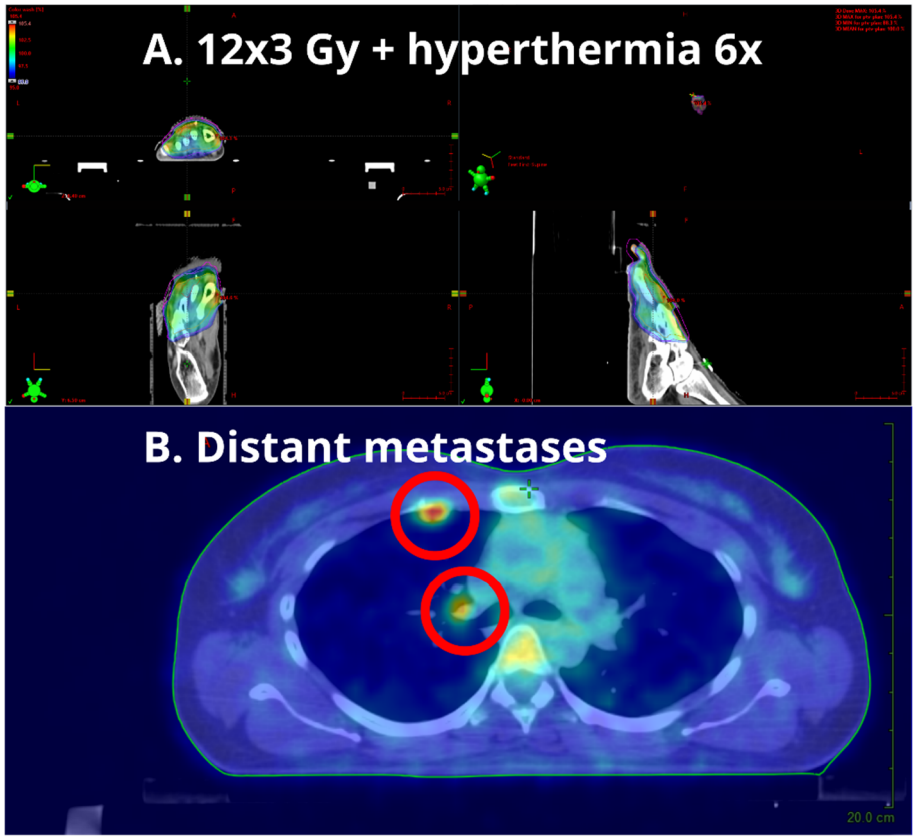

Figure 2. Clear cell sarcoma: radiotherapy planning and distant metastases. The figure shows planning of preoperative intensity-modulated radiotherapy in a patient with recurrent clear cell sarcoma of the left foot (**A**). The patient underwent surgery followed by postoperative radiotherapy (2 Gy to 52 Gy) outside our center in the past. In the presented situation, she received 12 × 3 Gy reirradiation combined with 6 sessions of hyperthermia, then she underwent the second surgery. Furthermore, she developed lymph node metastasis, which was treated with lymphadenectomy. During the evaluation for postoperative lymph node radiotherapy, she underwent positron emission tomography, which revealed pulmonary and mediastinal metastases (**B**)

lasted less than 6 months [75]. More favorable outcomes concerning chemotherapy have been obtained by a team from the Japanese Musculoskeletal Oncology Group, in a group of 30 CCS patients treated with chemotherapy, 23% had a PR, and all of them received a chemotherapy regimen with cisplatin [15]. Subsequent trials failed to validate the efficacy of platinum-derived treatments [49], even though the percentage of objective responses obtained after chemotherapy of M1 patients reached as much as 27% [8].

Among 24 patients with disseminated CCS treated in the Royal Marsden Hospital and the Memorial Sloan-Kettering Cancer Centre in the years 1990–2009, only 1 patient attained a PR to the chemotherapy regimen with anthracyclins. The mPFS rate in the analyzed population was 11 weeks for the first line of treatment. The patients received anthracyclins as monotherapy or in combination with ifosfamide, platinum derivatives, or other cytotoxic drugs [33, 49]. Also, gemcitabine-based therapy in CCS showed limited impact. In a cohort of five patients, the median time to disease progression was 10 weeks (95% CI 7.8–12.1), with only one patient experiencing an extended period of SD when treated with gemcitabine-dacarbazine. OS reached 66 months (95% CI 0.0–162.6). However, in metastatic disease, OS decreased to 28 months (95% CI 10.8–45.1) [76].

In an Italian trial of the Istituto Ortopedico Rizzoli in 2 patients with metastases to the lungs chemotherapy with vincristine with cyclofosfamide and doxorubicin was used, with a poor outcome [7]. None of the chemotherapy regimens (doxorubicin, doxorubicin plus ifosfamide, doxorubicin plus dacarbazine/cyclofosfamide/vincristine) used in patients in the Dutch trial from the Antonie van Leeuwenhoek Netherlands Cancer Institute in Amsterdam achieved a clinical benefit [72]. Similarly, in patients from a trial by Hocar et al. [17] from the Gustave Roussy Institute, who received doxorubicin, cyclofosfamide, platinum derivatives, dacarbazine, etoposide, ifosfamide, vincristine, interleukin 2, or interferon, none of the regimens was superior to the others. Chemotherapy in the DAV regimen (DTIC plus ACNU plus VCR) may bring a good response — 200 mg DTIC, 100 mg

Table 4. Systematic treatment proposed for clear cell sarcoma (CSS)

Substances	Dose	Frequency	Response in CCS	Additional information	Reference
Doxorubicin	60–90 mg/m^2	Day 1 every 3–4 weeks	N/A		[36]
Doxorubicin **Ifosfamide**	60 mg/m^2 5–9 g/m^2	Day 1–3 every 3–4 weeks	N/A		[36]
Doxorubicin **Cisplatin**	60 mg/m^2 120 mg/m^2	Day 1–3 every 3–4 weeks	N/A		[36]
Doxorubicin **Dacarbazine** **Ifosfamide**	60 mg/m^2 750 mg/m^2 +/–	Day 1 every 21 days	18.2% (2/11)		[75]
Cisplatin **Doxorubicin** **Caffeine**	120 mg/m^2 60 mg/m^2 4.5 mg/m^2	Day 1 every 3 weeks Day 1–2 every 3 weeks Day 1–3 every 3 weeks	23% (7/30)	Evaluated multiple schemes for CCS. Response rate for schemes with cisplatin	[15]
Gemcitabine based	N/A	N/A	0%		[76]
Vincristine **Cyclofosfamide** **Doxorubicin**	N/A	N/A	0%		[72]
DAV regimen **Dacarbazine** **Nimusine** **Vincristine**	 200 mg 100 mg 1 mg	Day 1–5 every 3 weeks	100%	Case report	[77]
Temozolomide	300 mg/d,	Day 1–5 every 30 days	N/A		[79]
Tivantinib	120 –> 360 mg	B.i.d.	9% (1/11)		[82]
Crizotinib	250 mg	B.i.d.	3.57% (1/28)		[83]
Sorafenib	400 mg	B.i.d.	100%	Case report	[87]
Sunitinib	N/A	N/A	30% (3/10)		[74]
Pazopanib	800 mg	Daily	0%		[89]
Anlotinib	12 mg	Daily, 2 weeks cycle with 1 week off	N/A	No specific results in CCS, ORR for the whole group 18.75% (6/32)	[91]
Cabozantinib	40 mg/m^2	Daily, 28 days for cycle	N/A	Pediatric population	[94]
CyVEDIC **Roferon A** **Cyclofosfamide** **Vincristine** **Epirubicin** **Dacarbazine** **IFN-α 2b**	 500 mg/m^2 1.5 mg/m^2, 75 mg/m^2 750 mg/m^2 9000000 I.U.	 Every 3 weeks 3 times a week	100%	Case report	[96]
Apatinib **Camrelizumab**	N/A N/A	N/A	25% (3/12)		[98]
Pembrolizumab	2 mg/kg	Every 3 weeks	0%	Only one CCS patient included	[100]
Sunitinib **Nivolumab**	37.5 mg —> 25 mg/d 3 mg/kg	days 1–14 –> daily every 2 weeks from week 3	28.5% (2/7)		[103]

b.i.d. — twice a day please; I.U. — International unit; N/A — not applicable; ORR — overall response rate

ACNU, and 1 mg VCR were given intravenously on day 1. Subsequently, it was given every day up to day 5 [77]. Nevertheless, it is important to note that this evidence stems from individual clinical cases. In patients with CCS metastases to bones, the effectiveness of cisplatin [78] and temozolomide treatment has been described (temozolomide 300 mg d 1–5/30 days) [79].

Therapeutic approaches for second-line and subsequent treatments in the management of CSS exhibit limited efficacy. In a report published by the team from Torino, second-line chemotherapy was used in most patients (88%), and in all patients, progression took place within 6 weeks, with no clinical response noted; the third line of therapy was used in 30% of patients also with progression in a short period. Median survival of patients with metastatic CSS was 37 weeks [48]. In the group of patients treated in the London Royal Marsden Hospital second-line chemotherapy was given to 12 patients — 11 (92%) had progression and one (8%) attained SD. In 5 patients treated with third-line chemotherapy, 4 (80%) progressed and only one (20%) attained SD. Finally, one patient received a fourth line of chemotherapy and maintained SD for 4 months. Median OS from diagnosis was 32 months (95% CI 24–39). Median OS from the start of palliative chemotherapy was 39 weeks (95% CI 34–45 weeks) [49]. In successive lines of treatment patients from the Istituto Nazionale dei Tumori in Milano received high doses of ifosfamide (5 patients), 1 of them had a 3-month PR, and the remaining two were treated in a gemcitabine ± docetaxel regimen; the first patient achieved a PR (lasting 4 months), and the second SD; the last patient was treated with trabedectin and progressed [75].

Existing clinical evidence points to a substantial resistance of CCS to conventional cytostatic agents, a fact also confirmed by *in vitro* studies. Treatment strategies are often determined through the consensus of a multidisciplinary team and the institution's accumulated expertise. The rarity of this specific subtype of STS precludes the feasibility of conducting extensive multicenter randomized trials to assess the efficacy of specific drug combinations.

Targeted therapy

Given CCS resistance to conventional chemotherapy and the presence of distinct molecular aberrations, ongoing investigations are exploring the utility of molecular targeted therapies for CCS, including MET inhibitors as well as tyrosine kinase inhibitors (TKIs), such as sunitinib and pazopanib. As mentioned previously, CCS development depends significantly on the overexpression of HGF and activation of c-Met signaling, thus this pathway has become the focus of translational research. Early studies have shown that inhibition of signaling from the *MET* protooncogene [tyrosine-protein kinase Met hepatocyte growth factor receptor (HGFR)] decreased CCS cell growth *in vitro* and *in vivo* [80]. Subsequently, 7 CCS patients were included in a phase I trial with the selective MET inhibitor — tivantinib (ARQ 197). One patient had a PR and two had SD [12, 80–82]. Clear cell sarcoma was also one of the neoplasm subtypes evaluated in the CREATE clinical trial (EORTC 90101) with crizotinib [dose 2 × 250 mg *per os* (po)]. In this trial 26 of 28 patients with CCS had MET(+) disease, one patient had a confirmed PR to treatment, and 17 patients had SD. The next endpoint of the efficacy of crizotinib in MET(+) CCS was the percentage of patients with disease control [disease control rate (DCR)], and it was 69.2%. In this trial, median PFS was 131 days, median OS — 277 days; 3, 6, 12, and 24-month PFR were 53.8%, 26.9%, 7.7%, and 7.7%, respectively. The authors of the report suggested that the percentage of MET(+) CCS patients without progression during crizotinib treatment is similar to results obtained in the first line of doxorubicin treatment of patients with metastatic soft tissue sarcoma (mSTS). In subsequent lines of treatment, for patients previously treated using chemotherapy, PFS appears to be similar to that obtained using pazopanib in mSTS patients [80, 83]. Also, a multicenter, single-arm phase II study (NCT00557609) with tivantinib recruited 11 CCS patients [84]. In that trial, a PR was observed in one of 11 patients (9%), with median PFS of 1.9 months. Furthermore, in 47 patients with distinct sarcoma subtypes, only CCS showed PR. Recently, a phase II QUILT-3.031 investigation aimed to assess the efficacy of AMG 337, an oral MET inhibitor, in advanced or metastatic CCS harboring *EWSR1-ATF1* gene fusion (NCT03132155) [85]. Due to lack of therapeutic efficacy, the trial was terminated prematurely.

Recently, numerous retrospective studies have indicated limited efficacy of TKIs, such as pazopanib, sorafenib, and sunitinib, in patients diagnosed with CCS [74, 86]. Mir et al. [87] published the case of a patient with disseminated CCS with cardiac muscle metastases, in whom sorafenib caused a decrease in lesion size, a clinical benefit in the form of pain alleviation and opioid drug discontinuation. The progression-free time was 8.2 months. In another case, an observed objective response was described to sunitinib treatment [88]. Sunitinib was also used at a dose of 37.5 mg/day, with a radiological, metabolic, and immunological response (loss of Melan-A/MART-1 expression on tumor cells) in primary and metastatic tumors. Sunitinib was also evaluated in reinduction after disease recurrence [51]. This became a cornerstone for evaluation in larger groups and clinical trials with TKIs for this indication. Large, retrospective analysis enrolled 55 CCS patients, establishing a 30% response rate in the group treated with sunitinib, and PFS of 4 months (95% CI

1–7 months) [74]. Also, a phase II trial was conducted to establish the efficacy of pazopanib in highly chemoresistant sarcomas, including CCS. Given the inclusion of only one patient with CCS, drawing definitive conclusions is challenging. However, the response rates at 12 weeks, as per the RECIST criteria, were observed to be 0.0%, and median PFS, as per the RECIST criteria, was 10.3 months, suggesting a suboptimal response to pazopanib treatment [89]. The subsequent study of TKIs targeting vascular endothelial growth factor receptor (VEGFR) type 2/3 in CCS includes anlotinib, demonstrating PFS and OS of 11 and 16 months, respectively. [90]. Furthermore, the phase II study ALTER0203 (NCT02449343) evaluated the efficacy of anlotinib in various STS, including CCS. Results indicated partial response to treatment, with PFS of 6.27 months (95% CI 1.89–10.65) and overall response rate (ORR) observed in 6 patients [91]. A retrospective analysis of the efficacy of anlotinib, utilizing the aforementioned ALTER0203 trial, involved five CCS patients. The primary findings demonstrated notably favorable results when anlotinib was administered in conjunction with other systemic treatments such as chemotherapy or immunotherapy. Within the group receiving combination therapy with anlotinib, 15 patients attained PR, resulting in an ORR of 24.2% [92]. Cabozantinib, a small molecule inhibitor targeting multiple tyrosine kinases, including MET, underwent evaluation for its efficacy in refractory/recurrent solid tumors in pediatric patients. Within this trial (ADVL1211, NCT01709435), one patient diagnosed with CCS was enrolled, achieving a PR. However, after 7 cycles of a 55 mg/m^2/d dose, disease progression (PD) occurred [93]. The promising outcomes from this trial led to the initiation of a phase II study (NCT02867592). Unfortunately, specific results for CCS were not reported, but among the non-rhabdomyosarcoma and other rare histological subtypes of sarcomas, no instances of PR or complete response (CR) were observed [94]. While preliminary, these findings suggest a role for targeted therapy in CCS treatment. Monotherapy with inhibitors demonstrates a moderate treatment response, but when combined with established therapeutic modalities, the treatment effects appear more favorable compared to the use of inhibitors or chemotherapy as standalone agents.

Immunotherapy

Considering the immunophenotypic similarity of CCS to melanomas and known examples of a complete response to CCS treatment by interferon (Roferon A), potential therapeutic CCS strategies include immunotherapy (e.g. with anti-PD-1 antibodies) [95]. Single cases have also described the effectiveness of chemo-immunotherapy in CCS, including the CyVEDIC regimen combined with Roferon A [cyclofosfamide 500 mg/m^2, vincristine 1.5 mg/m^2, epirubicin 75 mg/m^2, and dacarbazine 750 mg/m^2 *intravenous* (i.v.) q3w with IFN-a 2b 9 000 000 I.U. 3 times per week *subcutaneaous* (sc.)] [96]. Furthermore, immunotherapy in combination with targeted therapy showed efficacy in CCS. A case report of a 9-year-old patient with metastatic CCS showed a 2-year progression-free period under treatment with cabozantinib and nivolumab (PD-1 inhibitor) with hapten di-nitrophenyl modified autologous tumor cells for active immunization [97]. Also, retrospective analysis of a multimodal therapy with apatinib and/or camrelizumab (a PD-1 inhibitor) turned out to be effective in CCS. In a group of 12 patients, 3 had a PR, and 4 had SD; however, grade 3 or 4 adverse events were significantly more common in the apatinib plus camrelizumab combination therapy [98].

Reports have also been published on the effectiveness of immunotherapy by checkpoint inhibitors in combination with radiotherapy in CCS patients. A CR of CSS recurrence within the wall of the chest has been described after pembrolizumab combined with conventionally fractionated radiotherapy — altogether 50 Gy was applied to the volume of the mammary gland and chest wall with an additional increase of the dose to 66 Gy on the volume of the tumor visible on imaging tests before therapy. Treatment was well tolerated despite previous mediastinum irradiation in a similar volume (grade 1 reaction from the esophagus, grade 2 skin toxicity). A significant decrease in tumor mass occurred after 10 days of irradiation, and a complete clinical response was obtained after 18 days of irradiation treatment [99]. Pembrolizumab was also described to be effective in young patients (2 mg/kg IV q3w) [100]. Attempts were also made to develop vaccines against CCS. The only published trial indicates that this method does not appear to be successful. Metastatic tumors from CCS patients were excised, and processed and a suspension of single CCS cells was prepared. The cells were transduced with an adenoviral vector encoding granulocyte macrophage colony-stimulating factor (GM-CSF) and the samples were then irradiated. Vaccines were administered subcutaneously and intradermally once a week for 3 weeks, and then every other week. Even though an increase in PD-1 expression in the tumor was observed, there were no objective responses [101].

Because of the exceptionally small cohorts of CCS patients, they are rarely included in clinical trials and other data on the effectiveness of immunotherapy as the only regimen in treatment [102]. However, in recent years, there has been notable progress in research on exploration of drug combinations involving immunotherapy and targeted therapy. The

IMMUNOSARC trial (NCT03277924) aimed to define CCS answer to the combination of the antiangiogenic regimen, sunitinib and anti-PD-L1 agent nivolumab. In phase I, the recommended dosage of sunitinib and nivolumab was established (sunitinib — 37.5 mg/d as induction on days 1–14, then reduction to 25 mg/d continuously; nivolumab — 3 mg/Kg every 2 weeks from week 3), and the 6-month PFS rate of 48% (95% CI 41–55%) was achieved, and two CCS patients had a PR [103, 104]. In phase II, the evaluation of treatment efficacy revealed mPFS of 3.7 months (95% CI 3.4–4) and mOS of 14.2 months. Additionally, one patient achieved a CR, and another achieved a PR. However, no specific results for CCS in the second phase occurred due to a limited patient cohort and insufficient treatment response in the initial stage [105]. In summary, the assessment of immunotherapy utilizing checkpoint inhibitors in CCS showed infrequent responses and no substantial difference in OS when compared to conventional therapies in patients with metastatic CCS [106].

Palliative radiotherapy

Cases of patients with non-resectable CCS, in whom satisfactory control of local disease was obtained after using palliative radiotherapy (39 Gy in fractions of 3 Gy on the CCS area in the pelvis) have been described in the literature [107]. Single reports suggest that radiotherapy of CCS metastases can be effective at a dose of 60 Gy (fractions of 2 Gy) [108]. Palliative radiotherapy is mostly used in alleviating ailments associated with metastases of CCS to bones, lymph nodes, the brain, and soft tissues. However, this is not standard treatment and should be administered after stratification of benefits and disadvantages.

Survival and prognostic factors

The 5- and 10-year overall survival in CCS are 50–70% and 25–50%, respectively [5, 7, 15–17]. While the initial study by Enzinger reported that the percentage of recurrence of this neoplasm was 84%, subsequent analyses have described it as about 14–26%. Currently, it is generally acknowledged that local recurrence is likely to occur in about 20% to 55% of cases [5, 17, 77]. Local recurrence can develop even after several decades after the first diagnosis and radical resection [17]. In as many as 40% of patients, metastases to lymph nodes are present, and in 60% distant metastases, mainly to the lungs [5, 17] occur generally within 2–4 years from the diagnosis [77]. However, cases of lung metastases 8–21 years after resection of the primary tumor have been described [7]. The 2-year survival rate in patients with metastases to the lymph nodes or lungs, as observed in a patient series from Instituto Ortopedico Rizzoli, was 40% and 0%, respectively. The 5- and 10-year OS rates in patients with localized disease were 72% and 53%, respectively [7]. In the Japanese population, the 5-year overall survival index was 47% (M0; 55%, M1, 20%) [8]. Recent comprehensive observations based on the National Cancer Database (NCDB) confirmed the above-mentioned statistics, with mOS of 57.2 months and estimated 5- and 10-year OS of approximately 50 and 38%, respectively. Thus, when adjusted to staging, 5-year OS for stages I–IV was 75%, 65%, 35%, and 15%, respectively [16]. Multivariate analysis identified several significant negative prognostic factors in clear cell sarcoma (CCS), including tumor size > 5 cm, necrosis in the tumor, axial localization, and the presence of metastases at any time in the disease [1, 4, 7, 10, 17]. Of these, only necrosis in the tumor remained negatively correlated with survival among histopathological markers [4].

In univariate analysis, prognostic factors included sex, tumor size, localization, TNM stage, and surgical margin [15]. However, in multivariate analysis, only tumor size ($p = 0.02$) remained a significant prognostic factor [15]. Specifically, surface localization of the tumor showed 5-year survival of 80%, compared to 29% for deep tissue localization. Patients with larger tumors (> 5 cm) had 5-year survival of 28%, whereas those with smaller tumors (< 5 cm) exhibited 5-year survival of 71% [72]. The TNM stage also correlated with decreased survival. In collective analyses, sex affected patient survival, with women demonstrating higher 5-year overall survival (73% *vs*. 36%) [78]. Local recurrence was not associated with a poorer prognosis, in agreement with the theory that mortality in extremity-localized sarcomas is due to distant metastases rather than local recurrence [7, 109]. Variables such as presurgical symptoms, mitotic index, and invasion of blood vessels did not show a correlation with overall survival [18]. Univariate analysis identified age over 30 years and male sex as significant negative prognostic factors, but these were not confirmed in multivariate analyses [7]. Notably, some analyses found no significant prognostic factors, which can be primarily attributed to the rarity of this neoplasm [34]. In a large, retrospective CCS trial involving 91 patients, 5-year overall survival (OS) was 53.8% (95% CI 41.70–64.22). For patients with initial disseminated disease, median OS was 12.7 months (95% CI 10.4–21.5). Univariate analysis showed negative prognostic factors, including male sex, the period between diagnosis and metastatic disease < 24 months, non-lung metastases, and the inability to achieve total resection in the case of metastases. In multivariate analysis for all stages of the disease, tumor size and location remained poor prognostic factors [53].

Another retrospective study involved 117 patients with CCS from the Bone and Soft Tissue Tumour Registry in Japan. The authors established the role of treatment in patient prognosis; however, neither neoadjuvant/adjuvant chemotherapy (p = 0.895) nor radiotherapy (p = 0.216) was associated with survival, and general type of systemic treatment did not correlate with survival (p = 0.523) [110]. The most recent study on prognostic factors in CCS enrolled 42 patients. Findings supporting the positive impact of radical surgical margins and tumor size < 5 cm on overall survival (OS) were validated. Additionally, novel survival indicators were explored, revealing that in univariate analysis, a neutrophil-to-lymphocyte ratio (NLR) higher than 2.73 (p = 0.0126), a platelet-to-lymphocyte ratio (PLR) higher than 103.89 (p = 0.0147), and a lymphocyte-to-monocyte ratio (LMR) lower than 4.2 (p = 0.0445) were associated with shorter OS. However, in multivariate analysis, only the NLR emerged as an independent prognostic factor for OS [111].

Clinical trials

Numerous attempts to better understand and intensify the treatment of CCS have failed. Given the grim prognosis and the absence of effective treatments, future research efforts should prioritize molecularly targeted therapies and immunotherapy. These approaches hold promise for advancing outcomes, particularly in cases of metastatic or recurrent disease. Notably, the combination of these two modalities appears to be advantageous for such patients. Ongoing research endeavors aim to explore these potential advancements (Tab. 5). Devimistat, an agent focusing on cellular metabolism by increasing cellular stress by targeting the mitochondrial tricarboxylic acid cycle in the mitochondria of cancer cells, has been evaluated in a phase I/II study in patients with relapsed or refractory CCS (NCT04593758). A combination of devimistat and hydroxychloroquine (HCQ), which inhibits autophagy, will be administered to 36 patients with a starting dose of HCQ 600 mg on days 1 through 5 of every 28 days, followed by 2 000 mg/m2 of devimistat administered over 2 hours. After setting up the optimal dosage, phase II will be conducted to assess the duration of response, clinical benefit rate, progression-free survival, overall survival, safety, and patient-reported outcomes [112].

Also, phase II trials with immune checkpoint inhibitors are ongoing. Dostarlimab, an anti-PD-1 monoclonal antibody, will be evaluated in patients with advanced/metastatic CCS (NCT04274023). The main objective will involve evaluating the overall response, as defined by the response rate per RECIST 1.1 after 12 weeks. Additionally, assessments will be conducted for PFS, OS, and clinical benefits [113]. Also, a phase II trial with atezolizumab (anti-PD-L1 antibody) (NCT04458922) is currently underway, assessing clinical benefits in patients with newly diagnosed, unresectable, or metastatic CCS [114]. In addition, seclidemstat, an lysine-specific demethylase 1 (LSD1) inhibitor is currently being assessed in the phase I study (NCT03600649) with and without topotecan and cyclophosphamide in patients with relapsed or refractory Ewing sarcoma and other select sarcomas. The single agent expansion cohort of select sarcoma patients will enroll myxoid liposarcoma patients and patients with other sarcomas that share chromosomal translocations similar to Ewing sarcoma (FET-family translocations). The study will assess the safety and tolerability of seclidemstat, determine the maximum tolerated dose of this molecule,

Table 5. Ongoing clinical trials in clear cell sarcoma

Trial number	Regimens	Phase	Status	Design	Additional information
NCT04593758	HCQ+ devimistat	I/II	Completed, no results posted	HCQ 600 mg days 1–5, 28 days cycle, 600 mg 12 h after initial dose Devimistat 2000 mg/m^2 i.v. 2 h after HCQ	Pediatric population was included at a reduced dose
NCT04274023	Dostarlimab	II	Recruiting	Dostarlimab 500 mg i.v./ d 21-day cycle, 1000 mg i.v./day 1 of every 42-day cycle	Included CCS only
NCT04458922	Atezolizumab	II	Active, not recruiting	Atezolizumab 1200 mg i.v. For every 21-day cycle	
NCT03600649	Seclidemstat	I	Recruiting	Seclidemstat twice daily	Includes select sarcomas including myxoid liposarcoma and other sarcomas that share similar chromosomal translocations to Ewing sarcoma

i.v. — *intravenous*

pharmacokinetics and food effects on pharmacokinetics, and anti-tumor activity [115].

Summary and conclusions

In summary, CCS represents an exceedingly rare subtype of sarcoma characterized by a bleak prognosis, featuring distinct genetic markers such as EWS rearrangement and a propensity for lymph node metastases. Despite extensive research spanning two decades, the overall prognosis remains unchanged. Currently, the standard approach involves surgical excision with clear margins as the optimal treatment strategy. While recent clinical trials explored novel agents, both TKI and MET inhibitors demonstrated only moderate efficacy in CCS. Surgical intervention proves effective in localized disease; however, the young age of many patients and the risk of late recurrence necessitate prolonged observation periods. The primary goal is early detection of local recurrences, enabling timely intervention with favorable therapeutic effects. Unfortunately, patients experiencing recurrence in the form of metastatic disease face a grim prognosis, and vigilant observation does not alter the natural course of the disease in these cases [1]. Encouragingly, ongoing trials investigating combined treatment with kinase inhibitors and checkpoint inhibitors hold promise for improved outcomes. The challenges stem from the rarity of this neoplasm, leading to difficulties in establishing a unified treatment protocol due to limited research samples.

Article Information and Declarations

Author contributions

A.M.C.: writing, first draft, proofreading and editing, conception and design, supervision; P.C.: writing, first draft, proofreading and editing; P.S.: writing, proofreading and editing; M.S.: writing, proofreading and editing, photographs; A.S.-C.: writing, proofreading and editing, photographs; E.B.: writing, proofreading and editing; M.Z.: writing, proofreading and editing; T.Ś.: writing, proofreading and editing; M.D.-Ś.: writing, proofreading and editing; P.R.: writing, proofreading and editing, conception and design, supervision.

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Conflict of interest

The authors declare that there are no conflicts of interest.

Supplementary material

None.

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