VIA MEDICA

REVIEW ARTICLE

Anna M. Czarnecka[1, 2], Paweł Sobczuk[1, 3], Marcin Zdzienicki[1], Mateusz Spałek[4], Monika Dudzisz-Śledź[1], Piotr Rutkowski[1]

[1]Department of Soft Tissue/Bone Sarcoma and Melanoma, Maria Sklodowska-Curie Institute — Oncology Centre, Warsaw, Poland
[2]Department of Experimental Pharmacology, Mossakowski Medical Research Centre, Polish Academy of Sciences, Warsaw, Poland
[3]Department of Experimental and Clinical Physiology, Laboratory of Centre of Preclinical Research, Medical University of Warsaw, Poland
[4]Radiotherapy Department, Maria Sklodowska-Curie Institute — Oncology Centre, Warsaw, Poland

Clear cell sarcoma

Address for correspondence:
Anna M. Czarnecka, MD, PhD
Klinika Nowotworów Tkanek Miękkich, Kości i Czerniaków
Centrum Onkologii — Instytut im. Marii Skłodowskiej-Curie
ul. Roentgena 5, 02–781 Warszawa
Phone: +48 22 546 20 27
Fax: +48 22 643 93 75
e-mail: am.czarnecka@coi.pl

Oncology in Clinical Practice
2018, Vol. 14, No. 6, 354–363
DOI: 10.5603/OCP.2018.0049
Translation:
dr n. med. Hanna Koseła-Paterczyk

ISSN 2450–1654

ABSTRACT

Clear cell sarcoma (CCS), also referred as to melanoma of soft tissues, is a rare malignant tumour of soft tissues. This tumour harbors the characteristic features of soft tissue sarcoma (STS) and is a slowly growing, painless tumour, which then acquires an aggressive course. CCS is characterized by a translocation t(12; 22)(q13; q12), which in addition to the diagnostic implications may be important for targeted treatment in the future. CCS occurs mainly on the limbs, most often shin (in feet and ankle area) in the tendons and aponeurosis, often at a young age. CCS is characterized by high potential to develop metastases in regional lymph nodes (about 30% of cases). In the diagnostic process one should consider performing a sentinel node biopsy with possible subsequent radical lymphadenectomy in the case of metastases detection. Treatment of localized disease is limited to radical local excision with complementary radiotherapy. Due to the resistance to classical chemotherapy and the presence of characteristic molecular abnormalities, trials of molecular targeted therapies in this group of cancers are ongoing. In clinical trials, MET inhibitors, tyrosine kinase inhibitors (TKI) — sunitinib and pazopanib were evaluated. CCS was also one of the subtypes of tumours evaluated in the CREATE clinical trial with crizotinib.

Key words: clear cell sarcoma, crizotinib, sentinel node biopsy, sarcoma, translocation

Oncol Clin Pract 2018; 14, 6: 354–363

Epidemiology

Clear cell sarcoma (CCS) is a rare type comprising approximately 1% of all soft tissue sarcomas [1]. It was first described by Enzinger in 1965 [2], and for many years in the literature it was referred as to clear cell sarcoma of tendons and aponeuroses or malignant melanoma of soft tissue. Clear cell sarcoma is localized mainly in the lower limbs, with majority of cases localized in the area of the foot and ankle, where up to 40% of tumours are located. The upper limb is affected in 25% of cases. Primary CCS tumours usually develope deeply in soft tissues, adjacent to tendons, fasciae, or dissections [3–8]. Rare CCS locations include retroperitoneal space, digestive system, and bones. Cases of CCS developing in the kidney, torso, penis, and in the region of the head and neck or mediastinum were also described. The primary location in the skin is extremely rare with several isolated cases described so far and only one published series of cases of 12 and pooled analysis of 23 patients [9–11].

Tumours occur most often in young adults, in the 2nd–4th decade of life. CCS can develope at any age (including children and adolescents), but a small number of cases of CCS over the age of 40 years have been described [12]. It was proven that radiotherapy is a risk factor for CCS development. It is diagnosed slightly more often in women than in men [12].

Clear cell sarcomas manifest themselves as clinically silent, slow growing lesions [3, 5, 13, 14]. Tumours are often (up to 40%) manifesting as painless, although they may also cause pain, pruritus, paraesthesia, or impaired mobility of the joints [6]. The nodules can be surrounded by edema and be tender to palpation, and may also cause gait disturbances [12].

Despite slow growth and latent progression, CCS is characterized by high aggressiveness — in about 30% of patients lymph nodes or distant metastases are present at the time of diagnosis [7, 13]. Unlike most sarcomas, that metastasize via the circulatory system, approximately 50% of patients with CCS

present with metastases in the lymph nodes [5, 7, 13]. Although most frequent localization of distant dissemination of CCS is the lung, nevertheless numerous metastases to the skin, bones, liver, heart, and brain have also been described [14–16]. Generally, CCS is an aggressive tumour with a tendency of relapse, early metastasis development, and therefore short overall survival (OS) [9].

Biology, genetics, and histopathology

Macroscopically, CCS localize themselves usually around the tendons. They are microscopically characterized by bright, oval, or spindle-shaped cells arranged in collars separated by collagen fibres. A typical feature is the presence of giant polymorphonuclear cells with churned nuclei. CCS cells are present with abundant transparent or pale eosinophil cytoplasm and a centrally located, round nucleus with distinct nucleoli [12, 17, 18].

Because the histological and immunohistochemical features of CCS overlap with the characteristics of spindle cell melanoma and metastatic melanoma with unknown primary site (FPI, focus primarius ignotus), differential diagnosis between these units is still problematic and fraught with significant clinical consequences (Table 1) [9]. CCS exhibits characteristics of melanocyte differentiation, i.e. expression of protein A melanoma, microphthalmia transcription factor (MITF), and HMB-45 antigen, as well as the presence of melanosomes, which makes differential diagnosis of both primary and metastatic lesions difficult (Table 2) [9]. Melanin is present in CCS cells in over 70% of cases [3].

The bright cells are round or spindle-shaped, with a round central nucleus, dispersed chromatin, and a large nucleolus. The cytoplasm is light or pale-colored due to large amounts of glycogen, acid-absorbing. Intracellular melanin is not often visible [3, 6]. The mitotic activity of cells is small — up to 3 mitoses/10 HPF [18].

Hantschke et al. [10] indicate that it is possible to differentiate between CCS and MM (malignant melanoma) based on selected morphological characteristics (Table 1). CCS is characterized mainly by hyalinized sclerotic and reticular framework with tufts of a homogeneous population of tumour cells surrounded by delicate fibrous septa. This cell system is practically not seen in MM. What is more, CCS does not have scattered clusters of atypical melanocytes, but in most cases giant cells can be found with a characteristic rim from many peripherally located nuclei. In addition, the translocation t(12; 22) (q13; q12), observed in CCS most cases, has not been observed in MM [10, 12]. Clear cell sarcoma is a cancer that usually locates deep under the skin, with rare cases of dermal infiltration, which helps differentiate from primary melanoma, which usually also includes the epidermal layer. Differentiation from melanoma metastases is more difficult. It should be remembered that melanoma is characterized by CCS

Table 2. Immunohistochemical staining in the differentiation of clear cell sarcoma (CCS)

Immuno-histochemical staining	CCS	Melanoma	PEC-oma
Cytokeratin	+/–	+/–	–
S-100	+++	+++	+/–
HMB-45	++	++	+
Melan A	++	++	++
Tyrosinase	++	+++	++
Chromogranin	+/–	–	+
CD68	–	+/–	+
Desmin	–	–	++
Vimentin	+++	+++	–
EMA	–	+/–	–
SMA	–	–	++

PEC-oma — perivascular epithelioid cell tumours

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

	Clear cell sarcoma	Malignant melanoma
Location	Deeply seated	Primary focus on the skin
	Often associated with tendons and fascias, it does not infiltrate the dermis	Infiltration of the epidermis
Histopathology	Fusiform and clear cells with small nucleoli, group of cells surrounded by partition walls fibrous	Proliferation of melanocytes in the basal layer
Cell polymorphism	Small	Big
Number of mitosis	Usually small	Often large
Translocation t(11; 22)	Frequent	Absent
BRAF and *NRAS* mutations	Sporadic	Relatively frequent

mitotic activity, atypia, and cellular pleomorphism much higher than for sarcoma. Fibrous bands that separate sarcoma cell sockets are rare in melanoma [18]. Negative staining on epithelial markers helps distinguish sarcoma from metastases of CCS [18].

In diagnosis, the differentiation of CCS and melanoma is important (Table 1). It is helpful to detect the rearrangement of the *EWSR1* gene by means of fluorescent in situ hybridization (FISH) or to determine the presence of mRNA for the EWSR1/ATF1 fusion protein by polymerase chain reaction (PCR) because they are characteristic of sarcoma and are not present in melanoma [19, 20].

After performing basic immunohistochemical staining, CCS can be indistinguishable from melanoma, and additionally we lack validated staining typical only for CCS (Tables 1, 2). Both tumours (MM and CCS) present a similar staining pattern for S100, HMB45, and melan A. This sarcoma is also often positive for tyrosinase, MITF (microphthalmia-associated transcription factor), CD117 (KIT), enolase, CD57, and vimentin. Staining against keratins membrane epithelial antigen, muscle actin, and desmin are negative [7, 17, 18, 21].

The grading of CCS, like other soft tissue sarcoma (STS), is based on the Fédération Française des Centres de Lutte Contre le Cancer (FNCLCC) system, which takes into account the degree of cell differentiation, necrosis, and mitotic activity. The CCS is characterized by a low mitotic index and a rare occurrence of necrosis, which is why most cases are classified as 1 or 2 malignancy [1, 15].

A genetic marker for CCS, which allows us to distinguish it from other cancers, is the translocation t(12; 22) (q13; q12), which is observed in more than 90% of cases [22, 23]. This translocation leads to the fusion of activating transcription factor 1 (*ATF1*) genes from chromosome 12q13 and Ewing sarcoma breakpoint region 1 (EWSR1) from chromosome 22q12, resulting in the EWSR1-ATF1 fusion protein that induces expression from MITF transcription factor specific for melanocytes, its interaction with another sox10 factor, and leads to cell proliferation and melanocytic dedifferentiation, which explains the similarity to melanoma [24]. Several types of fusion proteins have been documented, the most common types being 1 (fusion exon 8 EWS and 4 AFT1) and 2 (fusion exon 7 EWS and 5 ATF1) [25]. The correlation between the type of fusion protein and clinical course of the disease was not demonstrated [26]. The translocation encountered in CCS is t(2; 22) (q34; q12) leading to the formation of the EWSR1/cyclic adenosine 3.5-monophosphate response element binding protein (CREB1 protein) [22]. Both rearrangements may also occur in angiomatoid fibrous histiocytoma [27]. In addition to translocations in CCS, polysomy of chromosome 8 is often encountered [28].

Microphthalmia-associated transcription factor activation leads to the activation of c-Met, which is one of the effectors of its operation. Both cell lines were CCS and the primary tumours exhibit excessive activation of c-Met, which occurs by involving autocrine hepatocyte growth factor (HGF). C-Met expression affects increased invasiveness, chemotaxis, and survival of sarcoma cells. HGF and c-Met are potential therapeutic targets because in vitro studies have shown that blocking them with a neutralising antibody (AMG 102) or an inhibitor (SU-11274), respectively, leads to inhibition of xenografts [29]. Other receptor tyrosine kinases that can be activated in CCS are platelet-derived growth factor β (PDGFR-β) and HER3, which may also be therapeutic targets [30].

Pre-clinical studies suggest that histone deacetylase (HDAC) inhibitors may play a role in the treatment of CCS; including these inhibitors induces apoptosis, inhibiting cell growth, and decreases EWS-ATF1 expression levels in CCS cell lines. Subsequent gene expression studies also suggest other potential therapeutic targets in CCS, including fibroblast growth factor receptor 1 (FGFR1) [31].

Yang et al. [19] showed that *BRAF* and *NRAS* mutations, occurring in 51.6% and 12.9%, respectively, in melanoma, do not occur in CCS. However, Hocar et al. [15] found *BRAF* and *NRAS* mutations in two out of 22 studied cases, which implies that it does not allow to use of *BRAF*/*NRAS* mutations in the diagnosis and differentiation between melanoma and CCS.

Differential diagnosis includes malignant fibrous histiocytoma, rhabdomyosarcoma, fibrosarcoma, liposarcoma, epithelioid sarcoma, and malignant schwannoma (Table 3) [32]. CCS lesions on the limbs in histopathological diagnostics require differentiation with melanocytic tumours, clear cell myelomonocytic tumour of falciform ligament (CCMTs), paraganglioma-like dermal melanocytic tumour (PDMT), and malignant peripheral nerve sheath tumour (MPNST), a monophasic synovial sarcoma subtype (Table 3) [33–35].

Imaging diagnostics

In computed tomography (CT) and magnetic resonance imaging (MRI), CCS appears as benign, well-delimited, and homogenous lesions. MRI should be performed with a gadolinium contrast. In T1-dependent images they show strong amplification, with higher signal intensity than muscles, when T2-dependent are more heterogeneous with variable signal intensity. Outbreaks of decreased signal intensity may correlate with foci of high accumulation of melanin and iron ions [28, 36, 37]. None of the radiological features allow a diagnosis based on MRI, and the final diagnosis depends on the result of histopathological examination. Positron emission tomography (PET)/CT allows detection of areas of increased metabolism and

Table 3. Differential diagnosis of clear cell sarcoma

Malignant blue nevus	**Clear cell sarcoma**
Usually located on the scalp	Usually located on the limbs
Superficial	Deep
Is often formed on the basis of benign nevus blue	Not associated with benign nevus blue
Malignant peripheral nerve sheath tumour	**Clear cell sarcoma**
Negative staining for melanin and HMB-45	Positive staining for melanin and HMB-45
Often pleomorphic	Rarely pleomorphic
High mitotic activity	Low mitotic activity
Often associated with neurofibromatosis	
Epithelioid leiomyosarcoma	**Clear cell sarcoma**
Regular arrangement of cells and partitions	Usually an irregular system of cells and partitions
Negative staining on HMB-45	Positive staining on HMB-45
Positive staining for actin and desmin	Negative staining for actin and desmin
Synovial sarcoma	**Clear cell sarcoma**
Positive staining for cytokeratin (50–80%)	Negative staining for cytokeratin
Negative staining for melanin and HMB-45	Positive staining for melanin and HMB-45
Frequent calcification	Rare calcification
Translocation t(X; 18)	Translocation t(11; 22)
Positive staining on TLE1	Negative staining on TLE1
PDMT	**Clear cell sarcoma**
Located in the skin	Deep location
Not very clear nuclei	Explicit nucleus
No necrosis	Necrosis often found

PDMT — paraganglioma-like dermal melanocytic tumour

diagnostics of CCS metastases, as well as assessment of the effectiveness of surgical (and adjuvant) procedures after treatment procedures initially planned as radical [37, 38].

Treatment of localised disease

A common treatment in patients with CCS is surgical treatment followed by radiotherapy or adjuvant chemotherapy [12]. Neoadjuvant treatment is administered only in exceptional clinical situations, because CCS is a disease highly resistant to chemotherapy and currently there is no chemotherapy regimen (or targeted therapy or immunotherapy) providing optimal treatment in the form of tumour mass reduction [39, 40]. Single reports on the use of neoadjuvant chemotherapy indicate clinical benefit from the use of the EI scheme (epirubicin + ifosfamide) [41] and the MAID scheme (mesna 1500 mg/m^2/day 1–4 + doxorubicin 15 mg/m^2/days 1–3 + ifosfamide 1500 mg/m^2/days 1–3 + dacarbazine 250 mg/m^2/days 1–3 [31, 42, 43]. In single cases, sunitinib was used for pre-operative therapy [44]. Post-treatment follow-up for two years every three months is recommended including, among others, chest CT, due to frequent relapses in the form of metastases to the lungs [12].

Surgery

As with most sarcomas, a broad tumour resection is the only option for radical treatment of localized disease. The goal of surgical treatment should always be to achieve macro- and microscopically negative surgical margins, even if it requires more aggressive treatment in the form of resection of the scar after the previous surgery. This is important because resection of R1 and R2 is associated with a significantly worse prognosis [13]. It is indicated that the margin should be at least 1 cm [45]. In place of radical surgical treatment, radical radiotherapy with 70 Gy (in 2-Gy fractions) was proposed [46].

The most aggressive strategies in the form of amputations do not reduce the risk of relapse or metastasis; therefore, they should only be considered in cases where limb-sparing operations are impossible, e.g. due to infiltration of large nerve trunks [4]. Local treatment may optionally be supported by isolated limb perfusion (tumour necrosis factor-alpha + melphalan) or intra-tumoral injection (interferon-alpha), although such treatments remain the domain of clinical trials [28].

Due to the high incidence of lymph node metastases in CCS, a recently raised subject is the performance of sentinel node biopsy, which may allow earlier detection of metastases in the lymph nodes and improve the

prognosis of patients [47]. Due to the low incidence of CCS, the sentinel node biopsy data are very limited — the studies usually include only a few patients (the largest one comprised 12 patients with CCS) [48]. The percentage of positive sentinel node biopsies ranges from 30% to 50% [47–49]. The role of lymphadenectomy for locoregional control in CCS is still being evaluated [5]. Most authors suggest that it should be performed in cases where metastases in the lymph nodes were confirmed in fine needle aspiration [50, 51]. At the same time, the CCS procedure may include a sentinel node biopsy followed by radical lymphadenectomy in the case of metastases in the sentinel node [47, 52–54].

Adjuvant treatment

European Society for Medical Oncology (ESMO) guidelines recommend the use of adjuvant radiation therapy in the case of grade 2 and 3, locally advanced (> 5 cm, T2–T4), and deeply located (under the fascia) sarcomas. The majority of CCSs are formally classified as G1, hence the numerous controversies regarding adjuvant therapy. In patients with CCS, postoperative radiotherapy should be considered if it is impossible to reach R0 operating margins or if surgery is not possible due to contraindications or refusal of the patient [1]. In various retrospective studies the proportion of patients undergoing adjuvant radiotherapy was around 40% [5], but some studies did not show its effect on the improvement of OS [5]. However, in other studies such a relationship was described. On the other hand, postoperative radiotherapy improves local control of the disease, especially in the group of patients with lymph node metastases and after resection of R1 [28, 53, 55]. Irradiation can be carried out using external beams as well as brachytherapy [28]. In the case of radiotherapy, the recommended dose is 50 Gy per elective area with a dose increase to 60–66 Gy for the area of the resection bed. Neighbouring lymph node regions, in which no sarcoma metastases were found, should not be integrated into the target volume. Due to the lack of consensus, the decision on complementary radiotherapy of nodal groups with CCS metastases should be made individually for each patient. In patients from the National Cancer Centre, Tokyo the M0 patients who received adjuvant chemotherapy had better prognosis (five-year survival, 65%) than those without chemotherapy (five-year survival, 23%) ($p = 0.03$) [8]. Due to the high resistance of CCS to chemotherapy, its use in the adjuvant setting is not routinely recommended [1].

Treatment of metastatic disease

Palliative chemotherapy

Systemic chemotherapy is the treatment of choice for non-operative and disseminated CCSs, although CCS is a disease with a low proportion of patients responding to chemotherapy (4% partial response [PR], 37% disease stabilization [SD], progression free survival [PFS] = 11 weeks) [56]. Data on the selection of chemotherapy regimens in CCS are usually limited to retrospective analyses. The basic treatment regimens are [32]:

— doxorubicin monotherapy 60–90 mg/m^2;
— doxorubicin 60 mg/m^2 + ifosfamide 5–9 g/m^2;
— doxorubicin 60 mg/m^2 + cisplatin 120 mg/m^2.

Patients (35 cases) treated at the Istituto Nazionale dei Tumori in Milan received first-line chemotherapy with doxorubicin + dacarbazine and ifosfamide, two of whom obtained PR, three obtained SD, and six had PD according to RECIST after three months. In all cases, the clinical benefit from treatment (PR/SD) lasted less than six months [57]. The most promising data on chemotherapy was posted by a team from the Japanese Musculoskeletal Oncology Group, in which, from a group of 30 patients with CCS, a partial response was seen in 23% treated with chemotherapy, all of whom received chemotherapy with cisplatin [13]. Unfortunately, subsequent studies have not confirmed the efficacy of platinum derivatives [42], although the overall response rate (ORR) obtained after chemotherapy of M1 patients reached as much as 27% [8]. Of the 24 patients with disseminated CCS treated at the Royal Marsden Hospital and Memorial Sloan-Kettering Cancer Centre in 1990–2009, only one achieved a partial response to the chemotherapy regimen with anthracyclines. Median PFS in the analysed population was 11 weeks in the first line of treatment. Patients received anthracyclines as monotherapy or in combination with ifosfamide, platinum derivatives, or other cytotoxic agents [31, 42]. In an Italian study by Istituto Ortopedico Rizzoli, vincristine chemotherapy with cyclophosphamide and doxorubicin was used in two patients with lung metastases [7]. None of the chemotherapy regimens (doxorubicin, doxorubicin + ifosfamide, doxorubicin + dacarbazine/cyclophosphamide/vincristine) used in patients in the Dutch study from the Antoni van Leeuwenhoek Netherlands Cancer Institute in Amsterdam did bring clinical benefit [55]. Similarly, in the patients from the Hocar et al. study [15] at the Gustave Roussy Institute, doxorubicin, cyclophosphamide, platinum derivatives, dacarbazine, etoposide, ifosfamide, vincristine, interleukin 2, or interferon also showed no superiority in any of the schemes. Administration of chemotherapy with DAV (DTIC + ACNU + VCR) may provide a good response — 200 mg of DTIC, 100 mg of ACNU and 1 mg of VCR was administered intravenously on day 1. DTIC was then administered daily until the 5th day [58]. The efficacy of cisplatin [59] and temozolomide treatment (temozolomide 300 mg days 1–5/30 days) is described in patients with CCS metastases to bone [60].

Treatment in the second and subsequent lines of CCS also has a low efficiency. In a report published by the Turin team, when second-line chemotherapy was given, most patients (88%) and all patients progressed within six weeks without any clinical response; the third line of treatment was used in 30% of patients also with progression. The median survival of patients with metastatic CCS was 37 weeks [41]. In the group treated at the Royal Marsden London Hospital, 12 patients were given second-line chemotherapy, 11 (92%) had progression, and one (8%) had SD. Of the five patients treated with the third-line chemotherapy, four (80%) progressed and only one (20%) achieved SD. Finally, one patient received a fourth line of chemotherapy and maintained SD for four months. The median OS of the diagnosis was 32 months (95% confidence interval [CI] 24–39). The median OS from the onset of palliative chemotherapy was 39 weeks (95% CI 34–45 weeks) [42]. In the following lines, the treatment of patients at the Istituto Nazionale dei Tumori in Milan included the administration of high-dose ifosfamide (five patients), with one having three-month PR, another two being treated with the gemcitabine-docetaxel regimen — the first one had PR (lasting four months), and the second SD. The last of the patients was treated with trabectedin with progression [57].

Available clinical data indicate high resistance of CCS to classical cytostatic, which is also confirmed by *in vitro* studies. In most cases, the choice of the scheme depends on the decision of the multidisciplinary team and the centre's own experience. The rarity of this type of STS does not allow large, multicenter, randomized trials to assess the efficacy of individual drug combinations. Single reports suggest that radiotherapy for CCS metastases may be effective at 60 Gy (fractionation at 2 Gy) [46].

Targeted treatment, immunotherapy

Due to the resistance to classical chemotherapy and the presence of characteristic molecular disorders, research on the use of molecularly targeted therapy in this group of tumours (e.g. MET inhibitors, tyrosine kinase inhibitors — sunitinib, pazopanib) is underway. Because molecular studies (described above) have shown that the development of CCS depends largely on overexpression of HGF and activation of c-Met signalling, this pathway has become an object of translational research. Early studies have shown that inhibition of Met proto-oncogene signalling (hepatocyte growth factor receptor [HGFR]) reduces the growth of CCS cells *in vitro* and *in vivo* [61]. For the phase I study with Met — tivatinib inhibitor (ARQ 197) — seven patients with CCS were included, one had a PR and two had DS [12]. In a phase 2 study (NCT00557609), both objective responses (OR) and DS were seen among 11 patients with CCS. Disease control (PR + SD) was obtained in 36% of patients, and the median duration of the response was three months [61–63]. CCS is also one of the subtypes of tumours assessed in the context of the clinical trial CREATE (EORTC 90101) with crizotinib (2×250 mg *p.o.* dosing). In this study, 26 of 28 patients with CCS had MET (+) disease, one had a confirmed PR for treatment, and 17 patients had SD. The subsequent endpoint of crizotinib efficacy in MET (+) CCS was the disease control rate (DCR), which was 69.2%. In this study the median PFS was 131 days, the median OS was 277 days, and three-, six-, 12-, and 24-months PFS were, respectively, 53.8%, 26.9%, 7.7%, and 7.7%. The authors of the study suggested that the percentage of MET (+) CCS progression-free patients treated with crizotinib is similar to the results obtained in the first line of treatment with doxorubicin in patients with metastatic STS. In further treatment lines, for patients previously treated with chemotherapy, PFS appears to be similar to that obtained with pazopanib in patients with metastatic STS [61, 64].

Only single cases of effective CCS treatment have been described so far with targeted therapy including kinase inhibitors. Mir et al. [65] published a patient with metastatic CCS metastasizing to the myocardium, in which, after application of sorafenib, a reduction in lesion size, clinical benefit was achieved in the form of pain relief and withdrawal of opioids. The time free from progression was 8.2 months [65]. In another case, the OR to treatment with sunitinib is described [66]. 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 tumour cells) in the primary tumour and metastatic tumours. Sunitinib was also used in reinduction at the onset of the disease [44]. Another inhibitor of tyrosine kinases including vascular endothelial growth factor receptor type 2 and 3 (VEGFR-2/-3) studied in CCS is anlotinib, which showed PFS and OS 11 and 16 months in CCS [67].

Other potential therapeutic strategies for CCS include immunotherapy (e.g. anti-PD-1 antibodies) due to the immunophenotypical similarity of CCS to melanomas and existing examples of complete CCS response to interferon (interferon-alpha 2a) [68]. Single cases of the effectiveness of chemo-immunotherapy in CCS have also been described, including the CyVEDIC regimen in combination with RoferonA (cyclophosphamide 500 mg/m^2, vincristine 1.5 mg/m^2, epirubicin 75 mg/m^2, and dacarbazine 750 mg/m^2 *i.v.* q3w with interferon-alpha 2b 9,000,000 IU three times a week *s.c.*) [69].

The first reports on the efficacy of immunotherapy with control point inhibitors in patients with CCS have also been published. The complete response (CR) of recurrence of CCS within the chest wall was described

after pembrolizumab was used in combination with conventionally fractionated radiotherapy — a total of 50 Gy per breast and chest wall volume was added with an additional dose increase of 66 Gy per tumour volume seen in imaging studies before treatment. Treatment was well tolerated despite previous mediastinal irradiation in a nearby volume (first-grade oesophageal toxicity, second-degree skin toxicity). A significant reduction in tumour mass occurred as early as on the 10th day of irradiation, and the overall clinical response was achieved on the 18th day of radiotherapy [70]. Pembrolizumab was also reported to be effective in young patients (2 mg/kg *i.v.* q3w) [71]. Attempts have also been made to develop CCS vaccines. The only published study shows that this method does not seem to be effective. Metastatic tumours from CCS patients were dissected, processed, and prepared for a suspension of single CCS cells that was transduced with an adenovirus vector coding for granulocyte-macrophage colony-stimulating factor (GM-CSF), and samples were irradiated. Vaccines were administered subcutaneously and intradermally once a week for three weeks and then every other week. Although there was an increase in PD-1 expression in the tumour, there were no OR [72]. Due to extremely small cohorts of patients with CCS, they are rarely included in clinical trials, and other data on the efficacy of immunotherapy in CCS are currently not available [73].

Palliative radiotherapy

The literature describes cases of patients with unresectable CCSs, where satisfactory percentages of local disease control were obtained after palliative radiotherapy (39 Gy in fractions of 3 Gy per pelvis CCS area) [74]. Palliative radiotherapy is also applicable in relieving symptoms associated with metastatic CCS to the bones, lymph nodes, brain, or parenchymal organs.

Survival and prognostic factors

Five- and 10-year OS in CCS are 50–70% and 25–50%, respectively [5, 7, 13–15]. Although the local recurrence rate for this tumour was 84% in the Enzinger series, further studies observed 14–26%, and it is currently believed that about 20–55% have local recurrence [5, 15, 58]. Local recurrence may develop several years after initial diagnosis and resection [15]. Up to 40% of patients have metastases in the lymph nodes and 60% have distant metastases, mainly in the lungs [5, 15], and they usually occur within 2–4 years of diagnosis [58]. There have been reports of lung metastases 8–21 years after primary tumour resection [7]. Two-year survival in patients with lymph node or lung metastases in a series of patients at the Instituto Ortopedico Rizzoli was 40% and 0%, respectively. Five- and 10-year survival in localized disease were 72% and 53% [7], respectively, and in the Japanese population the five-year ORR was 47% (M0, 55%; M1, 20%) [8].

In multivariate analysis, significant negative prognostic factors are tumour size > 5 cm, necrosis in the tumour [9, 15], axial location [1, 7], and the presence of metastases at any time during the disease [1]. From histopathological markers only, the presence of necrosis in the tumour is negatively correlated with survival [4]. In the univariate analysis, sex ($p = 0.02$), tumour size ($p = 0.001$), localization (dermis, subcutaneous tissue, below fascia, body cavity) ($p = 0.002$), TNM stage ($p = 0.001$), and surgical margin ($p = 0.04$) were prognostic factors. In multi-factorial analysis, only tumour size ($p = 0.02$) remained an important prognostic factor [8]. In the superficial location of the tumour five-year survival rate is 80% compared to 29% for the deep location of tumour tissues. Worse results are also observed when increasing the size of the tumour. Patients with a tumour larger than 5 cm have only 28% five-year OS, while for tumour size less than 5 cm five-year survival can be expected in 71% of patients. The best prognosis was for patients with primary tumour < 2 cm [55]. In addition, as the TNM increases, the survival rate is lower. In cumulative analyses, gender also affects the survival of the patient. Women have a higher survival rate compared to men (73% compared to 36% five-year survival), although the reason for this correlation is not clear [59]. The local recurrence of the disease is not associated with worse prognosis [7], which corresponds to the theory posited by Lewis et al. [75], saying that mortality in sarcomas located on the limbs is caused by distant metastases and not local recurrence of the disease. Pre-operative duration of symptoms, mitotic index, or vascular invasion do not correlate with the survival time in these patients [16].

In the univariate analysis, among the significant negative prognostic factors, age under 30 years and male gender are also mentioned, but they are not confirmed in multivariate analyses [7]. However, it should be emphasized that in some analyses no significant prognostic factors were confirmed [17]. Discrepancies in data are primarily due to the rarity of this cancer. In the largest CCS study, covering 91 patients, the five-year OS rate was 53.8% (95% CI 41.70–64.22). For patients with initial dissemination, the median OS was 12.7 months (95% CI 10.4–21.5). Negative prognostic factors present in the univariate analysis were: male gender, period between diagnosis and metastatic stage < 24 months, metastases other than pulmonary, and no possibility of complete resection in the case of metastases. In multivariate analysis for all patients, the stage, tumour necrosis, tumour size, and localization are bad prognostic factors [76].

Clinical trials

Currently, numerous clinical trials are underway devoted to the treatment of STS patients, including CCS, comprising trials with checkpoint inhibitors and trials using checkpoint inhibitors in combination with chemotherapy or targeted therapy, using classic cytostatics or classic cytostatics in metronomic therapy, with the use of molecular-targeted drugs or vaccines, with radiotherapy, and studies using systemic therapy, including immunotherapy along with radiotherapy.

An example of a study with the use of immunotherapy in combination with molecular-targeted therapy is the ImmunoSarc study. This is a first- and second-phase study with sunitinib and nivolumab in adult patients with bone and STS (including CCS), locally advanced (unresectable) or metastatic, previously treated with at least anthracycline-based chemotherapy (NCT03277924). The completion of this study is planned for 2020.

An example of a trial using a molecularly targeted treatment is the phase 2 QUILT-3.031 trial using AMG 337, conducted in patients with CCS with a confirmed *EWSR1-ATF1* fusion, advanced or metastatic (NCT03132155). The primary endpoint is response rate confirmed, whereas secondary endpoints are safety and tolerability of OS, PFS, duration of response rate and disease control. The end of this study was initially scheduled for 2020. AMG 337 is an oral MET kinase inhibitor whose safety was first evaluated in the first phase of the study in 11 patients with solid tumours [77].

In addition, based on data published in the clinical trials registry (www.clinicaltrials.gov), numerous other clinical trials are underway in STS, including CCS with different levels of advancement. Also, for some studies conducted in various solid tumours, inclusion of CCS patients was planned. Detailed information on the clinical trials conducted in STS are included in the article entitled "Advances in systemic treatment of advanced soft tissue sarcomas".

Summary and conclusions

Due to the risk of metastases to the lungs even several decades after of diagnosis, it is suggested to carry out radiological assessments (CT, PET, or classic radiograph) for changes in the lungs every year, even after five years of observation [7]. The overall prognosis for CCS patients has not changed for 20 years due to difficulties in the treatment protocol in rare cancers. Surgical treatment may be effective in the case of disease without spreading; however, new drugs and chemotherapeutic regimens should be sought, as well as targeted therapies to improve the results of treatment at a late stage of the disease. Given the young age of many patients and the risk of late relapse, long follow-up periods are necessary, primarily to detect local recurrence at an early stage where local treatment can still be provided with a good therapeutic effect. However, patients who experience recurrence of the metastatic form of the disease die from the disease, and close observation, unfortunately, does not alter the natural course of the disease in these patients [1].

References

1. Cornillie J, van Cann T, Wozniak A, et al. Biology and management of clear cell sarcoma: state of the art and future perspectives. Expert Rev Anticancer Ther. 2016; 16(8): 839–845, doi: 10.1080/14737140.2016.1197122, indexed in Pubmed: 27253849.
2. Enzinger FM. Clear-cell sarcoma of tendons and aponeuroses. An analysis of 21 cases. Cancer. 1965; 18: 1163–1174, doi: 10.1002/1097-0142(196509)18:9<1163::aidcncr2820180916>3.0.co;2-0, indexed in Pubmed: 14332545.
3. Chung EB, Enzinger FM. Malignant melanoma of soft parts. A reassessment of clear cell sarcoma. Am J Surg Pathol. 1983; 7(5): 405–413, doi: 10.1097/00000478-198307000-00003, indexed in Pubmed: 6614306.
4. Lucas DR, Nascimento AG, Sim FH. Clear cell sarcoma of soft tissues. Mayo Clinic experience with 35 cases. Am J Surg Pathol. 1992; 16(12): 1197–1204, doi: 10.1097/00000478-199212000-00006, indexed in Pubmed: 1463095.
5. Clark MA, Johnson MB, Thway K, et al. Clear cell sarcoma (melanoma of soft parts): The Royal Marsden Hospital experience. Eur J Surg Oncol. 2008; 34(7): 800–804, doi: 10.1016/j.ejso.2007.10.006, indexed in Pubmed: 18042498.
6. Malchau SS, Hayden J, Hornicek F, et al. Clear cell sarcoma of soft tissues. J Surg Oncol. 2007; 95(6): 519–522, doi: 10.1002/jso.20730, indexed in Pubmed: 17192915.
7. Bianchi G, Charoenlap C, Cocchi S, et al. Clear cell sarcoma of soft tissue: a retrospective review and analysis of 31 cases treated at Istituto Ortopedico Rizzoli. Eur J Surg Oncol. 2014; 40(5): 505–510, doi: .1016/j.ejso.2014.01.016, indexed in Pubmed: 24560887.
8. Kawai A, Nakayama R, Matsumine A, et al. Clear cell sarcoma of tendons and aponeuroses: an analysis of 75 cases. J Clin Oncol. 2006; 24(Suppl 18): 9572–9572, indexed in Pubmed: 27952899.
9. Bali A, Roy M, Chikkannaiah P, et al. Cutaneous clear cell sarcoma: a rare aggressive tumor with potential diagnostic challenge. J Lab Physicians. 2012; 4(1): 53–55, doi: 10.4103/0974-2727.98677, indexed in Pubmed: 22923926.
10. Hantschke M, Mentzel T, Rütten A, et al. Cutaneous clear cell sarcoma: a clinicopathologic, immunohistochemical, and molecular analysis of 12 cases emphasizing its distinction from dermal melanoma. Am J Surg Pathol. 2010; 34(2): 216–222, doi: 10.1097/pas.0b013e3181c7d8b2.
11. Jin L, Sui Y, Zhu H, et al. Primary mediastinal clear cell sarcoma: a case report and review of the literature. Diagn Pathol. 2017; 12(1): 5, doi: 10.1186/s13000-016-0594-z, indexed in Pubmed: 28086809.
12. Abdollahi A, Khatami F, Tavangar SM. Clear cell sarcoma: a case report and review of literature. Int J Hematol Oncol Stem Cell Res. 2018; 12(1): 65–68, indexed in Pubmed: 29951180.
13. Kawai A, Hosono A, Nakayama R, et al. Japanese Musculoskeletal Oncology Group. Clear cell sarcoma of tendons and aponeuroses: a study of 75 patients. Cancer. 2007; 109(1): 109–116, doi: 10.1002/cncr.22380, indexed in Pubmed: 17133413.
14. Gonzaga MI, Grant L, Curtin C, et al. The epidemiology and survivorship of clear cell sarcoma: a National Cancer Database (NCDB) review. J Cancer Res Clin Oncol. 2018; 144(9): 1711–1716, doi: 10.1007/s00432-018-2693-6, indexed in Pubmed: 29961184.
15. Hocar O, Le Cesne A, Berissi S, et al. Clear cell sarcoma (malignant melanoma) of soft parts: a clinicopathologic study of 52 cases. Dermatol Res Pract. 2012; 2012: 984096, doi: 10.1155/2012/984096, indexed in Pubmed: 22693489.
16. Yang XL, Lu SJ, Xue J, et al. Clear cell sarcoma of the right lumbar region: a case report and review of the literature. Oncol Lett. 2014; 8(4): 1625–1627, doi: 10.3892/ol.2014.2372, indexed in Pubmed: 25202380.
17. Hisaoka M, Ishida T, Kuo TT, et al. Clear cell sarcoma of soft tissue: a clinicopathologic, immunohistochemical, and molecular analysis

of 33 cases. Am J Surg Pathol. 2008; 32(3): 452–460, doi: 10.1097/PAS.0b013e31814b18fb, indexed in Pubmed: 18300804.
18. Auerbach A, Cassarino DS. Clear cell tumors of soft tissue. Surg Pathol Clin. 2011; 4(3): 783–798, doi: 10.1016/j.path.2011.08.005, indexed in Pubmed: 26837648.
19. Yang L, Chen Y, Cui T, et al. Identification of biomarkers to distinguish clear cell sarcoma from malignant melanoma. Hum Pathol. 2012; 43(9): 1463–1470, doi: 10.1016/j.humpath.2011.10.022, indexed in Pubmed: 22406360.
20. Patel RM, Downs-Kelly E, Weiss SW, et al. Dual-color, break-apart fluorescence in situ hybridization for EWS gene rearrangement distinguishes clear cell sarcoma of soft tissue from malignant melanoma. Mod Pathol. 2005; 18(12): 1585–1590, doi: 10.1038/modpathol.3800503, indexed in Pubmed: 16258500.
21. Meis-Kindblom JM. Clear cell sarcoma of tendons and aponeuroses: a historical perspective and tribute to the man behind the entity. Adv Anat Pathol. 2006; 13(6): 286–292, doi: 10.1097/01.pap.0000213052.92435.1f, indexed in Pubmed: 17075294.
22. Mrózek K, Karakousis CP, Perez-Mesa C, et al. Translocation t(12;22)(q13;q12.2–12.3) in a clear cell sarcoma of tendons and aponeuroses. Gene Chromosome Canc. 1993; 6(4): 249–252, doi: 10.1002/gcc.2870060412, indexed in Pubmed: 7685631.
23. Reeves BR, Fletcher CD, Gusterson BA. Translocation t(12;22)(q13;q13) is a nonrandom rearrangement in clear cell sarcoma. Cancer Genet Cytogenet. 1992; 64(2): 101–103, indexed in Pubmed: 1486556.
24. Davis IJ, Kim JJ, Ozsolak F, et al. Oncogenic MITF dysregulation in clear cell sarcoma: defining the MiT family of human cancers. Cancer Cell. 2006; 9(6): 473–484, doi: 10.1016/j.ccr.2006.04.021, indexed in Pubmed: 16766266.
25. Panagopoulos I, Mertens F, Dębiec-Rychter M, et al. Molecular genetic characterization of the EWS/ATF1 fusion gene in clear cell sarcoma of tendons and aponeuroses. Int J Cancer. 2002; 99(4): 560–567, doi: .1002/ijc.10404, indexed in Pubmed: 11992546.
26. Fisher C. The diversity of soft tissue tumours with EWSR1 gene rearrangements: a review. Histopathology. 2014; 64(1): 134–150, doi: 10.1111/his.12269, indexed in Pubmed: 24320889.
27. Rossi S, Szuhai K, Ijszenga M, et al. EWSR1-CREB1 and EWSR1--ATF1 fusion genes in angiomatoid fibrous histiocytoma. Clin Cancer Res. 2007; 13(24): 7322–7328, doi: 10.1158/1078-0432.CCR-07-1744, indexed in Pubmed: 18094413.
28. Mavrogenis A, Bianchi G, Stavropoulos N, et al. Clinicopathological features, diagnosis and treatment of clear cell sarcoma/melanoma of soft parts. Hippokratia. 2013; 17(4): 298–302, indexed in Pubmed: 25031505.
29. Davis IJ, McFadden AW, Zhang Y, et al. Identification of the receptor tyrosine kinase c-Met and its ligand, hepatocyte growth factor, as therapeutic targets in clear cell sarcoma. Cancer Res. 2010; 70(2): 639–645, doi: 10.1158/0008-5472.CAN-09-1121, indexed in Pubmed: 20068147.
30. Negri T, Brich S, Conca E, et al. Receptor tyrosine kinase pathway analysis sheds light on similarities between clear-cell sarcoma and metastatic melanoma. Gene Chromosome Canc. 2012; 51(2): 111–126, doi: 10.1002/gcc.20933, indexed in Pubmed: 22045652.
31. Pearl ML, Inagami M, McCauley DL, et al. Mesna, doxorubicin, ifosfamide, and dacarbazine (MAID) chemotherapy for gynecological sarcomas. Int J Gynecol Cancer. 2002; 12(6): 745–748, indexed in Pubmed: 12445253.
32. Mariappan D, Shashikala Dr. Molecular genetics, diagnosis and management of clear cell sarcoma of hand. IOSR–JDMS. 2016; 15(07): 15–22, doi: 10.9790/0853-1507121522.
33. Deyrup AT. Paraganglioma-like dermal melanocytic tumor: a unique entity distinct from cellular blue nevus, clear cell sarcoma, and cutaneous melanoma. Am J Surg Pathol. 2004; 28(12): 1579–1586, indexed in Pubmed: 15577676.
34. Thyvalappil A, Sudhamani B, Kizhakkethara G, et al. Paraganglioma--like dermal melanocytic tumor. Indian J Dermatol. 2015; 60(1): 80–81, doi: 10.4103/0019-5154.147804, indexed in Pubmed: 25657403.
35. Folpe AL, Goodman ZD, Ishak KG, et al. Clear cell myomelanocytic tumor of the falciform ligament/ligamentum teres: a novel member of the perivascular epithelioid clear cell family of tumors with a predilection for children and young adults. Am J Surg Pathol. 2000; 24(9): 1239–1246, indexed in Pubmed: 10976698.
36. De Beuckeleer LH, De Schepper AM, Vandevenne JE, et al. MR imaging of clear cell sarcoma (malignant melanoma of the soft parts): a multicenter correlative MRI-pathology study of 21 cases and literature review. Skeletal Radiology. 2000; 29(4): 187–195, doi: 10.1007/s002560050592.
37. Tordjman M, Dubois M, de Malherbe M, et al. Clear cell sarcoma of the tongue on MRI and PET/CT. Clin Nucl Med. 2018; 43(4): e118–e121, doi: 10.1097/RLU.0000000000001980, indexed in Pubmed: 29401145.
38. Nguyen BaD, Roarke MC, Ram PC. PET monitoring of clear cell sarcoma of tendons and aponeuroses. Clin Nucl Med. 2007; 32(5): 415–417, doi: 10.1097/01.rlu.0000259615.62178.4d, indexed in Pubmed: 17452880.
39. Hocar O, Cesne ALe, Terrier P, et al. Clear cell sarcoma (CCS) or malignant melanoma of soft parts: a retrospective clinicopathologic study of 52 cases. J Oncol. 2008; 26(Suppl 15): 10576–10576, doi: 10.1200/jco.2008.26.15_suppl.10576, indexed in Pubmed: 27948307.
40. Pasquali S, Gronchi A. Neoadjuvant chemotherapy in soft tissue sarcomas: latest evidence and clinical implications. Ther Adv Med Oncol. 2017; 9(6): 415–429, doi: 10.1177/1758834017705588, indexed in Pubmed: 28607580.
41. Boglione A, Bergnolo P, Canton OD, et al. P04Systemic therapy in clear cell sarcoma (CCS). Annals of Oncology. 2016; 27(Suppl 4): 99, doi: 10.1093/annonc/mdw343.04.
42. Jones RL, Constantinidou A, Thway K, et al. Chemotherapy in clear cell sarcoma. Med Oncol. 2011; 28(3): 859–863, doi: 10.1007/s12032010-9502-7, indexed in Pubmed: 20390470.
43. Yalcin S, Barista I, Tekuzman G, et al. Dramatic response to ifosfamide, mesna and doxorubicin chemotherapy regimen in an adult with clear cell sarcoma of the kidney. J Urol. 1996; 155(6): 2024, doi: 10.1016/s0022-5347(01)66081-6.
44. Tazzari M, Palassini E, Vergani B, et al. Melan-A/MART-1 immunity in a EWS-ATF1 translocated clear cell sarcoma patient treated with sunitinib: a case report. BMC Cancer. 2015; 15: 58, doi: 10.1186/s12885-015-1044-0, indexed in Pubmed: 25880253.
45. Juel J, Ibrahim RM. A case of clear cell sarcoma-A rare malignancy. Int J Surg Case Rep. 2017; 36: 151–154, doi: 10.1016/j.ijscr.2017.05.034, indexed in Pubmed: 28587971.
46. Abdellah A, Soufiane B, Amine B, et al. Clear cell sarcoma of tendons and aponeuroses of the parapharyngeal space: an unusual localization of a rare tumor (a case report and review of the literature). Pan Afr Med J. 2014; 19: 147, doi: 10.11604/pamj.2014.19.147.5364, indexed in Pubmed: 25767667.
47. van Akkooi ACJ, Verhoef C, van Geel AN, et al. Sentinel node biopsy for clear cell sarcoma. Eur J Surg Oncol. 2006; 32(9): 996–999, doi: 10.1016/j.ejso.2006.03.044, indexed in Pubmed: 16672185.
48. Andreou D, Boldt H, Werner M, et al. Sentinel node biopsy in soft tissue sarcoma subtypes with a high propensity for regional lymphatic spread — results of a large prospective trial. Ann Oncol. 2013; 24(5): 1400– –1405, doi: 10.1093/annonc/mds650, indexed in Pubmed: 23372051.
49. Al-Refaie WB, Ali MW, Chu DZ, et al. Clear cell sarcoma in the era of sentinel lymph node mapping. J Surg Oncol. 2004; 87(3): 126–129, doi: 10.1002/jso.20096, indexed in Pubmed: 15334639.
50. Tong TR, Chow Tc, Chan OWh, et al. Clear-cell sarcoma diagnosis by fine-needle aspiration: cytologic, histologic, and ultrastructural features; potential pitfalls; and literature review. Diagn Cytopathol. 2002; 26(3): 174–180, indexed in Pubmed: 11892024.
51. Ferrari A, Casanova M, Bisogno G, et al. Clear cell sarcoma of tendons and aponeuroses in pediatric patients: a report from the Italian and German Soft Tissue Sarcoma Cooperative Group. Cancer. 2002; 94(12): 3269–3276, doi: 10.1002/cncr.10597, indexed in Pubmed: 12115360.
52. Picciotto F, Zaccagna A, Derosa G, et al. Clear cell sarcoma (malignant melanoma of soft parts) and sentinel lymph node biopsy. Eur J Dermatol. 2005; 15(1): 46–48, indexed in Pubmed: 15701594.
53. Nishida Y, Yamada Y, Tsukushi S, et al. Sentinel lymph node biopsy reveals a positive popliteal node in clear cell sarcoma. Anticancer Res. 2005; 25(6C): 4413–4416, indexed in Pubmed: 16334118.
54. Fantini F, Monari P, Bassissi S, et al. Sentinel lymph node biopsy in clear cell sarcoma. J Eur Acad Dermatol Venereol. 2007; 21(9): 1271–1272, doi: 10.1111/j.1468-3083.2007.02164.x, indexed in Pubmed: 17894729.
55. Deenik W, Mooi WJ, Rutgers EJ, et al. Clear cell sarcoma (malignant melanoma) of soft parts: A clinicopathologic study of 30 cases. Cancer. 1999; 86(6): 969–975, doi: 10.1002/(sici)1097--0142(19990915)86:6<969::aid-cncr11>3.3.co;2-q, indexed in Pubmed: 10491522.
56. Constantinidou A, Jones RL, Al-Muderis O, et al. Systemic therapy in clear cell sarcoma. J Clin Oncol. 2010; 28(Suppl 15): 10098–10098, doi: 10.1200/jco.2010.28.15_suppl.10098.
57. Stacchiotti S, Palassini E, Negri T, et al. Clear cell sarcoma (CCR): Clinical behavior and response to chemotherapy. J Clin Oncol. 2010; 28(Suppl 15): 10096–10096, doi: 10.1200/jco.2010.28.15_suppl.10096.
58. Fujimoto M, Hiraga M, Kiyosawa T, et al. Complete remission of metastatic clear cell sarcoma with DAV chemotherapy. Clin Exp Dermatol. 2003; 28(1): 22–24, doi: 10.1046/j.1365-2230.2003.01109.x, indexed in Pubmed: 12558622.

59. Tran H, Asfour V, Chang C, et al. Clear cell sarcoma arising from the iliac wing: case report. I J Oncol. 2009; 6(2): 1–5, doi: 10.5580/24a4.
60. Kumar Kushwaha A, Soni S. Metastatic Clear Cell Sarcoma Role of Temazolamide. Journal of Dental and Medical Sciences 2016. OSR--JDMS. 2016; 15(12, ver. II): 8–9, doi: 10.9790/0853 - 151 2020 8 0 9.
61. Katz D, Palmerini E, Pollack SM. More than 50 subtypes of soft tissue sarcoma: paving the path for histology-driven treatments. Am Soc Clin Oncol Educ Book. 2018(38): 925–938, doi: 10.1200/EDBK_205423, indexed in Pubmed: 30231352.
62. Goldberg J, Demetri GD, Choy E, et al. Preliminary results from a phase II study of ARQ 197 in patients with microphthalmia transcription factor family (MiT)-associated tumors. Journal of Clinical Oncology, 2009. J Clin Oncol. 2009; 27(15S): 10502–10502, doi: 10.1200/jco .2009.27.15s.10502.
63. Wagner AJ, Goldberg JM, Dubois SG, et al. Tivantinib (ARQ 197), a selective inhibitor of MET, in patients with microphthalmia transcription factor-associated tumors: results of a multicenter phase 2 trial. Cancer. 2012; 118(23): 5894–5902, doi: 10.1002/cncr.27582, indexed in Pubmed: 22605650.
64. Schöffski P, Wozniak A, Stacchiotti S, et al. Activity and safety of crizotinib in patients with advanced clear-cell sarcoma with MET alterations: European Organization for Research and Treatment of Cancer phase II trial 90101 'CREATE'. Ann Oncol. 2017 [Epub ahead of print]; 28(12): 3000–3008, doi: 10.1093/annonc/mdx823, indexed in Pubmed: 29741569.
65. Mir O, Boudou-Rouquette P, Larousserie F, et al. Objective response to sorafenib in advanced clear-cell sarcoma. Ann Oncol. 2012; 23(3): 807– –809, doi: 10.1093/annonc/mds005, indexed in Pubmed: 22274882.
66. Stacchiotti S, Grosso F, Negri T, et al. Tumor response to sunitinib malate observed in clear-cell sarcoma. Ann Oncol. 2010; 21(5): 1130–1131, doi: 10.1093/annonc/mdp611, indexed in Pubmed: 20093352.
67. Chi Y, Fang Z, Hong X, et al. Safety and efficacy of anlotinib, a multikinase angiogenesis inhibitor, in patients with refractory metastatic soft-tissue sarcoma. Clin Cancer Res. 2018 [Epub ahead of print], doi: 10.1158/1078-0432.CCR-17-3766, indexed in Pubmed: 29895706.
68. Steger GG, Wrba F, Mader R, et al. Complete remission of metastasised clear cell sarcoma of tendons and aponeuroses. Eur J Cancer. 1991; 27(3): 254–256, indexed in Pubmed: 1827307.
69. Lauro S, Bordin F, Trasatti L, et al. Concurrent chemoimmunotherapy in metastatic clear cell sarcoma: a case report. Tumori. 1999; 85(6): 512–514, indexed in Pubmed: 10774576.
70. Marcrom S, De Los Santos JF, Conry RM. Complete response of mediastinal clear cell sarcoma to pembrolizumab with radiotherapy. Clin Sarcoma Res. 2017; 7: 14, doi: 10.1186/s13569-017-0079-1, indexed in Pubmed: 28725344.
71. Scheinberg T, Lomax A, Tattersall M, et al. PD-1 blockade using pembrolizumab in adolescent and young adult patients with advanced bone and soft tissue sarcoma. J Clin Oncol. 2017; 35(Suppl 15): 3060, doi: .1200/jco.2017.35.15_suppl.3060.
72. Goldberg JM, Fisher DE, Demetri GD, et al. Biologic activity of autologous, granulocyte-macrophage colony-stimulating factor secreting alveolar soft-part sarcoma and clear cell sarcoma vaccines. Clin Cancer Res. 2015; 21(14): 3178–3186, doi: 10.1158/1078-0432. CCR14-2932, indexed in Pubmed: 25805798.
73. Tsukahara T, Emori M, Murata K, et al. The future of immunotherapy for sarcoma. Expert Opin Biol Ther. 2016; 16(8): 1049–1057, doi: 10.1080/14712598.2016.1188075, indexed in Pubmed: 27158940.
74. Kuiper DR, Hoekstra HJ, Veth RPH, et al. The management of clear cell sarcoma. Eur J Surg Oncol. 2003; 29(7): 568–570, doi: 10.1016/s0748-7983(03)00115-x, indexed in Pubmed: 12943620.
75. Lewis JJ, Leung D, Heslin M, et al. Association of local recurrence with subsequent survival in extremity soft tissue sarcoma. J Clin Oncol. 1997; 15(2): 646–652, doi: 10.1200/JCO.1997.15.2.646, indexed in Pubmed: 9053489.
76. Firmin N, Boudou-Rouquette P, Duliege D, et al. Outcome of 91 clear cell sarcoma tumor patients: A retrospective study from the French Sarcoma Group (GSF-GETO). J Clin Oncol. 2018; 36(Suppl 15): 11552–11552, doi: 10.1200/jco.2018.36.15_suppl.11552.
77. Hong DS, et al. First-in-human study of AMG 337, a highly selective oral inhibitor of MET, in adult patients (pts) with advanced solid tumors. J Clin Oncol. 2014; 32(15_suppl): 2508–2508.