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Research Article

Clear cell sarcoma: 20 years of experience at Instituto Nacional de Enfermedades Neoplasicas (INEN)

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Abstract

Background: Clear cell sarcoma (CCS) of soft tissue is a rare disease with a high risk of metastasis to regional lymph nodes and distant organs and a poor survival rate. The aim of this study is to determine the rate of lymph node involvement, the effectiveness of treatment, the risk of recurrence and progression after surgery.

Methods: We collected data from twenty patients diagnosed with CCS and treated in our institute, between 1998 and 2018. Subsequently, survival rates were determined according to local, regional and distant involvement, as well as the prognostic factors.

Results: Twenty patients with CCS were included. The 2-year survival rate was 20%, and the 5-year survival rate was 5%. Patients with CCS with local stage and with tumor size < 5.0 cm were more likely to have a good survival rate.

Conclusion: The initial management is crucial for the prognosis of the disease, with surgery being the mainstay of treatment. This study revealed a high rate of lymph node metastasis, so regional lymph node dissection should be done. Finally, the role of chemotherapy and/or radiotherapy for survival is still unclear.

Keywords: Sarcoma; clear cell sarcoma; soft tissue tumors

INTRODUCTION

Clear cell sarcoma (CCS), formerly known, as malignant melanoma of soft parts, is an unusual disease of tendons and aponeuroses, first described by Enzinger in 1965 [1] as a tumor with melanocytic differentiation, the reason for its confusion with malignant melanoma [2]. Nowadays, its histogenesis is still uncertain; however, molecular analysis revealed that CCSs has a recurrent chromosomal translocation t (12; 22) (q13; q12), which results in the chimeric EWSR1/ATF1 gene, present in 90% of CCS cases, ending the previous association between melanoma and CCS [3, 4]. CCS is a rare but distinct clinicopathologic entity, accounting for approximately 1% of all soft-tissue sarcomas [5].

CCS affects young adults between 20 and 40 years and the usual involvement of regional lymph nodes and lungs [6]. Patients with metastatic disease have a poor prognosis, and those with lymph node involvement have an overall survival rate of 40% at 2 years [7, 8]. However, other literature reports 5-year overall survival rates of 40-68% [8, 9].

The aim of this study was to analyze the clinical characteristics of twenty cases of CCS 1998 and 2018. Subsequently, survival rates according to local, regional, and distant involvement, the effectiveness of surgical treatment, risk of recurrence, and post-treatment disease progression were determined.

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MATERIALS AND METHODS

Patient cohort

We applied to access our institute database and to determine frequency rates. Inclusion criteria included patients with a diagnosis of Clear Cell Sarcomas at the National Institute of Neoplastic Diseases (INEN), between 1998 and 2018. There were 37 patients with CCS identified from the database.

Statistical analysis

Data on affiliation, surgical procedure, pathology report, complications, and follow-up were obtained from the medical records and were recorded in a predetermined collection format.

All 37 cases were re-evaluated by a medical oncologist pathologist with expertise in sarcomas, determining the exclusion of 17 cases, due to incompatibility of the result (n = 15) and loss of material for review (n = 2).

Confirmation of the histologic diagnosis was performed by immunohistochemistry techniques (immunoreactivity for S-100 and HMB-45 protein markers).

Other factors examined, given their prognostic significance were age (≤ 30 years, > 30 years), sex, tumor size (≤ 5cm, > 5cm), location (extremities, trunk, and head), regional lymph node involvement, and treatment.

The treatment received was multimodal, with surgery, chemotherapy, and radiotherapy, with wide local resection at the beginning whenever possible, or amputation and disarticulation of the extremity.

The status of the surgical margin was determined histologically and was classified as negative (without tumor cells in the stained margin) and positive (with tumor cells in the stained margin).

Patients with a risk of recurrence or positive surgical margins were treated with complementary radiotherapy. Additionally, those with the nodal and distant metastatic disease received chemotherapy treatment.

Survival curves were estimated using the Kaplan-Meier method, and the overall survival rate was estimated at the second and fifth years. Numerical variables were analyzed using measures of central tendency and dispersion, while categorical variables were presented as proportions and absolute numbers; the information was analyzed in the IBM SPSS Statistics v. 25 statistical programs.

RESULTS

Twenty patients were included in the study, and their clinical characteristics are summarized in Table 1.

Of the twenty patients with CCS, 11 patients were men and 9 were women. The mean age at the time of diagnosis was 36 years, (range: 19-65 years). The mean tumor size was 6.87 cm (range: 1 cm-19.5 cm). The most common tumor location was the lower extremities (10 cases), followed by the upper extremities (7 cases), trunk (2 cases), and head and neck (1 case). Among patients with a given stage, 4 patients were diagnosed with localized CCS, 11 patients were diagnosed with regional CCS, and 5 patients were diagnosed with distant or metastatic CCS.

In addition, 9 patients underwent surgical resection prior to admission in our institution, of which 3 pre-

Table 1. Clinical features at the first clinical assessment.

	All patients	**Patients with localized tumor**
N	20	4
Gender (M: F)	11: 9	1: 3
Average age (range)	36 years (19-65)	45 years (28-59)
Tumor size (range)	6.87 cm (1-19.5)	3.30 cm (1-5.5)
Time of illness at diagnosis (range)	20 months (1-120)	21 months (3-48)
Location of the lesion		
Upper extremities	7	3
Lower extremities	10	1
Trunk	2	0
Head	1	0
Stage		
Localized	4	4
Regional	11	0
Distant	5	0
Recurrence		
Yes	6	0
No	5	3 *

* One case was not intervened.

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sented positive margins, other 3 negative margins, and another 3 cases had no report of the status of the margins in the anatomic-pathologic report. Finally, from these 9 cases, 4 patients needed a second surgical resection at INEN.

A total of 11 cases were treated surgically in our institution: 4 with wide local resection, 5 with wide local resection and regional lymph node dissection, and 2 with amputation of the limb. The margins in these cases were negative in 8 cases and 3 patients had positives margins.

In the 20 patients with CCS, the 2-year disease-specific survival was 10%, and the 5-year disease-specific survival was 5% (Table 2).

Patients with localized tumor

4 patients were diagnosed with localized CCS, of which 3 cases (75%) were treated surgically at our institute, all of them with tumor size < 5 cm. In addition, 75% were positive for S-100 and HMB-45. On the other hand, the status of the margins in these 3 cases was: 2 presented negative margins and 1 positive margin. Subsequently, 3 patients were treated with adjuvant chemotherapy (QT) and/or radiotherapy (RT): combined therapy (adriamycin + RT or cyclophosphamide + RT) (*n* = 2) and radiotherapy alone (*n* = 1). In addition, 2-year disease-specific surv ival for this group of patients was 25%; the median survival time for these 3 cases was 12 months (range: 7 months-20 months).

On the other hand, one of the 4 cases showed negativity for both immunohistochemical markers, underwent wide local resection with negative margins and adjuvant treatment (adriamycin + RT), and continued with active controls, all without evidence of recurrence, until the end of the study.

Patients with lymph node involvement

Of the 20 cases that made up our population, 11 were diagnosed with regional CCS, lymph node involvement. 63% of the patients had tumor size > 5 cm. All of the cases in this group (100%) were positive for S-100 and 60% for HMB-45. On the other hand, 8 cases underwent surgery, and 7 had recurrence with a mean time of 7 months after surgery. Only 2 cases were re-operated with amputation and emergency surgery, respectively. 6 patients received adjuvant treatment with chemotherapy (QT) and/or radiotherapy (RT); chemotherapeutic treatment was with dacarbazine (*n* = 2), carboplatin (*n* = 1), and interferon (*n* = 1). Two patients received only RT, 2 others only QT, and finally, the other 2 received combined treatment (interferon + RT and Carboplatin + RT). The 2-year disease-specific survival was 9%.

Patients with distant metastases

5 cases were diagnosed with distant or metastatic CCS, all of them with multiple distant organs affected, involving mainly the lung (*n* = 3), and with tumor size > 5 cm in 60% of cases. 80% of cases were positive for S-100, while 60% were positive for HMB-45. None of these cases underwent surgery. However, 4 patients were treated with adjuvant chemotherapy (QT) and/or radiotherapy (RT). Dacarbazine (*n* = 2), carboplatin (*n* = 1) and combined therapy (dacarbazine + RT) (*n* = 1) were administered. The 2-year disease-specific survival was 0%; median survival time was 3 months (range: 0.8 months-7 months). Risk factors for survival are shown in Table 3.

Recurrence

6 cases had a recurrence, all of them with lymph node involvement. Two of them were previously surgical treated and 2 others needed a second surgical resection in our institution with limb amputation. On the other hand, 4 patients received treatment with chemotherapy and/or adjuvant radiotherapy: only one received dacarbazine, another one received combined therapy (interferon + RT), and 2 only radiotherapies. The median time to recurrence was 7.5 months (range: 2-19 months). The 2-year disease-specific survival was 16%, with a median survival of 12 months.

DISCUSSION

Soft tissue sarcomas represent 1.2% of the cases reported annually in our institution [10], and 0.4% correspond to clear cell sarcoma (CCS) [11].

Table 2. Disease-specific survival (DSS) in 2-year and 5-year.

	2-year DSS (%)	5-year DSS (%)
All patients (*N* = 20)	10	5
Patients with localized tumor (*N* = 4)	25	25
Patients with lymph node involvement (*N* = 11)	9	0
Patients with distant metastases (*N* = 5)	0	0

Table 3. Risk factors for survival.

	N [a]	5 years - SCE (%)	*P*-value
Gender			0.824
Male	11	0	
Female	9	11	
Age			0.042
≤ 30	9	0	
> 30	11	9	
Tumor size in cm			0.200
≤ 5	9	11	
> 5	11	0	
Location of the lesion			0.013
Extremities	17	6	
Trunk and head	3	0	
Surgical technique *			0.022
Wide local resection	9	11	
Amputation	2	0	
Surgical margins *			0.212
Positives	3	0	
Negatives	8	13	
Recurrence			
Yes	6	0	
No	5	0	

* Operated in INEN.

Enzinger first described this entity in 1965, where he presented clinical and epidemiological characteristics of 21 cases [1]. In 1994, our institution carried out a review of 11 cases of CCS, which are not part of the group analyzed in the present publication [12].

Despite the lack of clarity of its histogenesis, the theory of the apparent origin in the migration of some cells from the neural crest to the developmental zone is accepted. Advances in the molecular analysis have revealed the presence of the translocation t (12; 22) (q13; q12), which results in the chimeric gene EWSR1/ATF1 in 90% of cases [3, 4, 13-15]. However, this translocation is not specific to this entity since it is also detected in Angiomatoid Fibrohistiocytoma and in hyalinizing clear cell carcinoma of the salivary gland; therefore the results of its detection should be used within the appropriate clinical presentation and morphology [14]. Also, six different types of EWS-ATF1 fusion genes have been found to be involved in this pathology [6] and a less frequent translocation variant, t (12; 22) (q32.3; q12) resulting in the EWSR1-CREB1 fusion [13-15].

CCS tends to occur more frequently in young adult patients between 20 and 40 years and has a greater predilection for the female sex; in addition, it is located mainly in the extremities, deep in the fasciae, generating a slow and painless growth, so they are usually diagnosed as benign nodules, and resected with inadequate margins [5, 7, 8, 16, 17]. Our study, in contrast to what is reported in the literature, found a higher percentage of involvement in male patients (55%), while the predominant location was the extremities (85%).

At INEN, Abugattas *et al*. [12] analyzed 11 cases of CCS, finding the most frequent location at foot or ankle (73% between both). They also described a mortality rate of 91% with a mean follow-up of 18.9 months.

According to its location, it has been described that survival decreases when the lesion is in the trunk [7]; however, since we only obtained 2 cases in this location, it was not significant for the global comparison.

Macroscopically, most of these tumors are small (< 5 cm), but lesions larger than 10 cm have been described. CCS is solid, lobulated, or multinodular, firm, grayish-white, intimately associated with tendons, fascia, or aponeurosis [13-15]. Tumor size has been considered a prognostic factor. A-Bing Li *et al*.[5] determined that a tumor size less than 3 cm corresponded to a favorable prognostic factor, with a specific survival rate for

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this group of 86.2%, while for tumors larger than 3 cm it was 42.8%. Likewise, Kawai *et al*. [16] described tumors larger than 5 cm had a poor prognosis and an increased incidence of local recurrence.

Histologically, the tumor shows a uniform arrangement in nests, bundles, and short fascicles of epithelioid (Figure 1A) to spindle-shaped (Figure 1B) cells, separated by dense fibro-collagenous bands (Figure 1C). The tumor cells show abundant cytoplasm that can be amphophilic to eosinophilic. The nuclei are vesicular with a large reddish central nucleolus. Scattered multinucleated giant cells (Figure 1D) and melanocytic pigment may also be seen. Pleomorphism and elevated mitotic activity are usually absent; features that can be seen in metastases and/or recurrences [13-15].

Immunophenotypically, tumor cells show strong and diffuse expression of melanocytic markers such as S-100 protein, SOX10, HMB-45, Melan A, and Microphthalmia Transcription Factor (MITF). They may also present a variable expression for neuroectodermal markers such as neuronal specific enolase (NSE), synaptophysin, and CD57 [13-15].

The main differential diagnosis is with malignant melanoma since immunophenotypically they are indistinguishable. The clinical presentation (tumor of deep location in distal extremity), the absence of junctional component, and the uniform cytomorphology are key for the diagnosis of CCS, but in some cases, the use of molecular tests such as fluorescence in situ hybridization (FISH) or real-time polymerase chain reaction (RT-PCR) will be necessary for the detection of translocations associated with CCS [13-15].

The gold standard treatment for localized CCS is surgical resection with wide margins, as these determine the patient's prognosis [2, 5, 7, 12]. Huang J. *et al*. [18] determined as poor prognostic factors a tumor size greater than 5 cm, the presence of positive margins, neutrophil-to-lymphocyte ratio (NLR) higher than 2.73, the platelet-to-lymphocyte ratio (PLR) higher than 103.89, and the lymphocyte-to-monocyte ratio (LMR) lower than 4.2.

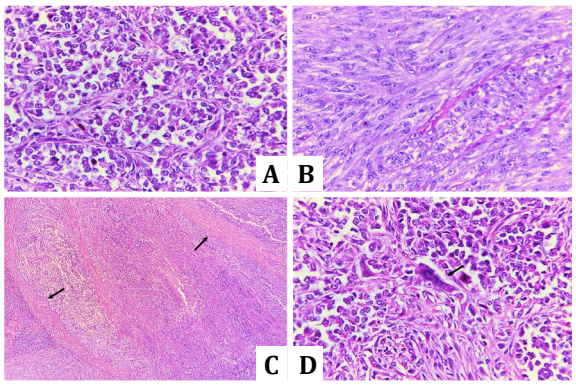

Figure 1. **(A)** The tumor shows short fascicles of epithelioid cells (HE 400X). **(B)** The tumor shows spindle-shaped cells (HE 400X). **(C)** Nests of tumor cells are separated by dense fibro-collagenous bands (HE 100X). **(D)** Scattered multinucleated giant cells may be seen (HE 400X).

Rosenthal *et al.* [19], performed a meta-analysis on the risk of lymph node involvement in different soft tissue sarcomas, finding that regional lymph node involvement in CCS is 18% (range: 4-50%), higher than the risk compared to the other histologic types. For this reason, he recommends for high-risk sarcomas (CCS, angiosarcoma, and epithelioid sarcoma) clinical evaluation of regional lymph nodes by means of PET/CT or PET/MRI for staging, the US of locoregional lymph node basins with biopsy of suspicious lymph nodes, and sentinel lymph node biopsy (SLNB).

Lewis J J *et al*. concluded that mortality in extremity soft tissue sarcoma results from metastasis rather than local recurrence [20], which is consistent with the findings of our study, where survival rates in patients with distant metastases were 0%.

Other authors, such as Bianchi *et al*. [7] report a 5-year survival rate of 56%, similar to that found by Hogar *et al.* [21]. with a 5-year survival rate of 59%.

In our institution, Abugattas [12] found a rate of 55% lymph node metastasis, similar to data in our study, and is the study with the highest rate of lymph node involvement described in the literature (Table 4), which could condition the approach of sentinel lymph node biopsy and/or regional lymph node dissection.

A total of 175 patients with CCS were identified from the SEER database [5]. The 5-year survival rate was 62.9%, and the 10-year survival rate was 51.3%. Patients with CCS with local stage, and with tumor size > 3 cm were more likely to have good survival rates.

Finally, Bianchi *et al*. suggest that follow-up should be by annual radiographic screening with chest CT, PET SCAN, or plain radiography in the first 5 years [7].

CONCLUSIONS

CCS is an entity where initial management is crucial for the prognosis of the disease, with surgery being the mainstay of treatment.

The high rate of lymph node metastasis observed in this study may assist clinicians and surgeons to con-

Table 4. Reported rate of lymph node regional metastases in CCS.

Study (year published)	Study (year published)	Patients (%)
Mazeron 1987 [22]	n/a	11/40 (28%)
Ruka 1988 [23]	1950-1984	1/2 (50%)
Abugattas 1994 [12]	1980-1992	6/11 (55%)
Riad 2004 [24]	1986-2001	2/18 (11%)
Behranwala 2004 [25]	1990-2001	1/25 (4%)
Sherman 2014 [26]	2000-2009	28/101 (28%)
Keung 2018 [27]	1998-2012	86/540 (16%)
Jacobs 2018 [28]	2004-2013	23/105 (22%)
Li 2019 [5]	1973-2009	59/175 (33%)
Falla 2022 (Current Study)	1998-2018	11/20 (55%)
Total	228/1037	22%

sider lymph node dissection in the primary surgery when possible.

A significant role in survival has not yet been demonstrated with respect to the use of chemotherapeutic agents and/or the use of RT.

DECLARATIONS

Author's contributions

A soft copy of all data used for this article are available at the corresponding author, it can be made acquired at a reasonable request.

Availability of data and materials

Not applicable.

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None.

Conflicts of interest

The authors state that there are no conflicts of interest with respect to the research, authorship and publication of this article.

Ethical approval and consent to participate

The clinical data used was from the INEN database, which is a public research resource, and patient consent and ethical approval for the study were not required.

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