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Prognostic factors and treatment outcomes in chondrosarcoma: a single-institution experience

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ABSTRACT

Aims: Prognostic factors and treatment modalities in chondrosarcoma (CS) remain poorly defined. This study aimed to present our institutional experience with CS patients.

Methods: We retrospectively reviewed the medical records of 69 CS patients treated at our Cancer Institute between 2010 and 2023.

Results: Median age at diagnosis was 47 years, with a slight male predominance (52%) and a median follow-up of 93 months. Grade 1 (34%) and grade 2 (34%) tumors were most common, predominantly affecting the lower extremities (40%) and pelvis (26%). At presentation, 63 patients had localized disease and 6 had metastases; metastases later developed in 13 additional patients, most frequently in the lungs. All 63 patients with localized disease underwent surgery, and 7 received adjuvant chemotherapy (CT). Recurrence developed in 26 patients, of whom 9 were treated with systemic therapy. Among 6 patients with stage IV disease, 5 underwent palliative surgery and received CT. The most commonly used regimens included doxorubicin-based CT, pazopanib, sirolimus, and celecoxib. Among patients who developed metastasis during follow-up, 12/13 died. The median time from diagnosis to metastasis was 17.0 months (95% CI: 10.8–23.1), and median survival thereafter was 21.0 months (95% CI: 12.7–29.2). All six patients metastatic at presentation died, with a median progression-free survival of 7.0 months (95% CI: 2.1–11.8) and OS of 12.0 months (95% CI: 0.0–33.6). OS was 75%, 63%, and 57% at 5, 10, and 15 years, respectively. Female sex, low–intermediate grade, and stage I–II disease correlated with better OS in univariate analysis, but only stage at diagnosis remained significant in multivariate analysis (p=0.002).

Conclusion: Our findings highlight that early tumor stage is the only independent predictor of overall survival, underscoring the critical importance of early diagnosis and timely intervention in CS.

Keywords: Chemotherapy, surgery, radiotherapy, lung metastasis, chondrosarcoma

INTRODUCTION

Chondrosarcoma (CS) is the second most common primary skeletal tumor, with an incidence of ~3 per 100.000 person-years.[1,2] It represents a heterogeneous group with variable histopathology and clinical behavior,[3,4] ranging from locally aggressive, low-grade tumors with limited metastatic potential to high-grade malignancies with poor outcomes.[5] Conventional CS accounts for ~85% of cases, while nonconventional subtypes—clear cell, dedifferentiated (DDCS), myxoid, and mesenchymal (MCS)—comprise 10–15%.[1,6,7] Most conventional CSs (90%) are low–intermediate grade, indolent, and rarely metastasize, whereas high-grade conventional CS and rarer subtypes show high metastatic potential and poor prognosis.[8]

CS is generally refractory to chemotherapy (CT) and radiotherapy (RT), making surgery the primary treatment for low-grade, localized disease.[3] However, surgical resection may be challenging in large or anatomically complex tumors, and tumor biology can evolve, with grade discrepancies observed between biopsy, primary, and metastatic sites due to heterogeneity.[9,10] In such cases, surgery alone may be insufficient given the high risk of recurrence and metastasis,[3,5] whereas high-grade subtypes show greater responsiveness to CT and RT.

Due to the rarity of CS and its relatively long survival, prospective studies comparing prognostic factors or treatment regimens are difficult to conduct. Consequently, most evidence comes from small retrospective and single-institution series, and no consensus exists regarding prognostic factors or treatment algorithms.[11] In this study, we present our Cancer Institute's decade-long experience in managing CS, providing

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an overview of its histopathology, classification, clinical features, treatment approaches, and prognostic factors to contribute to the limited literature.

METHODS

Ethics

The study was conducted with the permission of the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research and Hospital Non-interventional Clinical Researches Ethics Committee (Date: 19.10.2023, Decision No: 2023-10/98). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

Study Design and Patients

The 74 patients diagnosed with CS between 2010 and 2023 in the Department of Medical Oncology of our Cancer Institute were retrospectively evaluated. Five patients were excluded from the study because of missing data. A total of 69 patients were enrolled. The American Joint Committee on Cancer (AJCC) 8 was used for staging. Patients were evaluated for clinicopathologic characteristics, treatment modalities, and prognostic factors. The primary endpoints were disease-free survival (DFS) and overall survival (OS). DFS was defined as the time from curative surgery to recurrence, and OS as the time from diagnosis to death or last follow-up. Patients without recurrence or alive at last follow-up were censored. Several clinicopathologic factors, such as sex, age, histologic subtype, stage, primary site (axial/appendicular), margin (R0/R1), and surgery, CT, and RT, were evaluated for their prognostic impact on DFS and OS.

Statistical Analysis

Continuous variables were reported as medians (range), and categorical variables as percentages. Survival was estimated using Kaplan–Meier curves, with the log-rank test applied for univariate analysis. Variables with $p<0.05$ were entered into a Cox proportional hazards model for multivariate analysis. Statistical significance was set at $p<0.05$. Analyses were performed using SPSS version 26.

RESULTS

Clinicopathologic Profile

Sixty-nine patients were included, with a median age of 47 years (range: 19–86) and a slight male predominance (53%). The most common tumor sites were the lower extremities (40%) and pelvis (26%). Grade 1 (34%) and grade 2 (34%) were the predominant histologies. At diagnosis, 63 patients (91%) had localized disease, while 6 (9%) presented with metastases. In total, 19 patients developed metastases either at presentation or during follow-up, almost all to the lungs (100%), with occasional spread to the liver (10%), thoracic spine (10%), brain (5%), or lymph nodes (5%). Patient characteristics are summarized in Table 1.

Preoperative biopsies were performed in 31 patients, but only 9 matched the final surgical pathology, reflecting a high rate of histologic upgrade or change after resection. Twelve cases initially reported as chondroid lesions, and eight as atypical chondroid tumors, were reclassified as grade 1, grade 2, or myxoid types. One biopsy diagnosed as grade 2 was upgraded to grade 3, and a lesion initially reported as a small round cell tumor was reclassified as mesenchymal CS.

Histopathological evaluation of 21 recurrent or progressive tumors showed that most (n=9) retained their initial grade, while several progressed to higher grades. Specifically, one grade 1 tumor progressed to grade 2, another to grade 3, one grade 3 became undifferentiated, and one undifferentiated tumor was reclassified as grade 3 at recurrence.

Table 1. Patient demographics and clinical characteristics (n=69)

Parameters n (%)			
Median age (range)	47 (19–86)	No	1 (1)
Gender		**Adjuvant RT**	63 (100)
Male	36 (53)	Yes	20 (31)
Female	33 (47)	No	43 (68)
Histological subtype		**Neoadjuvant/adjuvant CT**	63 (100)
Grade 1–2	48 (70)	IMA	3 (4)
Grade 3	6 (9)	NCI	3 (4)
Myxoid	5 (7)	Unknown type	2 (2)
Dedifferentiated	4 (6)	No	55 (87)
Mesenchymal	3 (4)	**Relapse of localized disease**	63 (100)
Clear cell	2 (3)	Yes	26 (41)
Unknown	1 (1)	No	37 (59)
Stage at diagnosis		**Surgery for relapse**	26 (100)
Stage 1–2	47 (68)	Yes	22 (84)
Stage 3	15 (21)	No	4 (15)
Stage 4	6 (8)	**Post-relapse RT**	26 (100)
Unknown	1 (1)	Yes	10 (38)
Tumor site		No	16 (61)
Lower extremity	28 (41)	**Post-relapse CT**	26 (100)
Upper extremity	12 (17)	Yes	9 (34)
Pelvis/ trunk/sternum	26 (38)	No	17 (65)
Mandible/maxilla	3 (4)	**Metastatic status at diagnosis**	
Preoperative biopsy		Localized	63 (91)
Yes	31 (44)	Metastatic	6 (9)
No	38 (55)	**Treatment of metastatic disease**	
Surgery		Palliative surgery	5 (83)
Curative	63 (91)	Palliative RT	4 (66)
Palliative	5 (7)	Palliative CT	5 (83)

CT: Chemotherapy, RT: Radiotherapy, IMA: Ifosfamide plus adriamycin, NCI: Vincristine, doxorubicin, cyclophosphamide, ifosfamide, etoposide

Treatment Modalities for Patients with Initially Localized Disease

The median follow-up was 93 months (range: 77–108). All 63 patients with localized disease underwent curative surgery; margin data were available in 43 patients, with 33 R0 and 10 R1 resections. Adjuvant RT was given to 20 patients. One patient received neoadjuvant CT as combination therapy of

vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide (NCI), and 7 received adjuvant CT, most commonly ifosfamide plus adriamycin (IMA, n=3) and NCI (n=2). CT regimens by histopathology are summarized in **Table 2**.

Recurrence and Metastasis

Recurrence occurred in 26 of 63 patients (41%): 15 had local recurrence, 8 both local and lung metastases, and 3 lung metastases alone; 2 additional patients developed lung metastases after local recurrence. In total, 13 patients developed metastases during follow-up [grade 2 (n=6), grade 3 (n=4), grade 1 (n=1), mesenchymal (n=1), dedifferentiated (n=1)], with a median time to metastasis of 17 months (95% CI: 10.8–23.1). Most recurrences (61%) occurred within 1–3 years, though 6 patients relapsed at 10–15 years. Of recurrent cases, 22 (84%) underwent surgery, 10 (38%) received RT, and 9 (34%) received CT. First-line CT most often included IMA (n=3) or cyclophosphamide adriamycin (CA) (n=6); 4 patients received second-line therapies (pazopanib, gemcitabine/docetaxel, cyclophosphamide/methotrexate/celecoxib, or ifosfamide), and 2 received third-line regimens (sirolimus/cyclophosphamide or gemcitabine/docetaxel). The median number of CT lines administered was 1 (range: 1–3).

Treatment Modalities for Patients with Initially Metastatic Disease

All six patients presenting with metastases [myxoid (n=3), dedifferentiated (n=1), mesenchymal (n=1), grade 2 (n=1)] had lung involvement. Five underwent palliative surgery and four received palliative RT. IMA/CA (n=2), IMA (n=1), CA (n=1), and NCI (n=1) were the most common CT regimens used as first-line therapy, and IMET (ifosfamide, mesna, etoposide) (n=2), gemcitabine/docetaxel (n=1), and methotrexate (n=1) were the most common regimens used as second-line therapy, while gemcitabine/docetaxel (n=1) was the regimen used as third-line therapy. Patients received a median of 2 (range: 0–3) CT lines. Single-agent therapy (n=3) yielded two progressions and one stable disease, whereas combination regimens (n=22) achieved nine stable responses and five progressions. Detailed CT responses for recurrent and metastatic patients are shown in **Table 2**.

Prognostic Factor Analysis for Disease-Free Survival and Progression-Free Survival

In patients with localized disease, DFS was 54%, 54%, and 36% at 5, 10, and 15 years, respectively. Univariate analysis showed no significant impact of sex (p=0.093), age (p=0.604), histologic subtype (p=0.326), margin status (p=0.396), adjuvant RT (p=0.118), or adjuvant CT (p=0.358) on recurrence risk. In contrast, stage at diagnosis (p=0.002) and tumor location (p=0.014) were significant prognostic factors for DFS. Detailed results are provided in **Table 3**.

Time to recurrence was significantly longer in patients with stage I–II tumors and those with appendicular tumors.

Table 2. Chemotherapy regimens by tumor histopathology and best responses to CT (n=69)

Total n (%)	**Grade 1 24 (34)**	**Grade 2 24 (34)**	**Grade 3 6 (8)**	**Myxoid 5 (7)**	**Dedifferentiated 4 (5)**	**Mesenchymal 3 (4)**	**Clear cell 2 (2)**	**Unknown 1 (1)**
Neoadjuvant						NCI 1 (1)		
Adjuvant		IMA 1 (1)	IMA 1 (1)		IMA 1 (1)	NCI 2 (2)		
Localized at diagnosis								
Recurrence 1. line	CA 1 (1) (not assessable)	IMA 2 (2) (1 progressive, 1 stable) CA 3 (3) (1progressive, 2 not assessable)	CA 2 (2) (1 stable, 1 not assessable)					IMA 1 (1) (stable)
2. line		Pazopanib 1 (1) (progressive) Gem/doc 1 (1) (progressive)	Ifosfamide 1 (1) (stable)					Cyc/mtx/ Celecoxib 1 (1) (stable)
3. line		Sirolimus/cyc 1 (1) (not assessable)	Gem/doc 1 (1) (not assessable)					
Metastatic at diagnosis								
First-line				IMA/CA 1 (1) (stable) IMA 1 (1) (stable) CA 1 (1) (progressive)	IMA/CA1 (1) (progressive)	NCI 1 (1) (stable)		
Second-line				IMET 2 (2) (2 not assessable) Gem/doc 1 (1) (stable)	Mtx 1 (1) (progressive)			
Third-line				Gem/doc 1 (1) (stable)				

CT: Chemotherapy, IMA: Ifosfamide plus adriamycin, NCI: Vincristine, doxorubicin, cyclophosphamide, ifosfamide, and etoposide, CA: cyclophosphamide, IMET: Ifosfamide, mesna, and etoposide, Gem/doc: Gemcitabine/docetaxel; MTX: Methotrexate, Cyc: Cyclophosphamide

Table 3. Prognostic factors for disease-free survival (n=63)

Factors	Univariate analysis			Multivariate analysis		
	5-yr PFS (%)	10-yr PFS (%)	p value	HR	95% CI	p value
Entire group	54	54				
Sex			0.093			
Female	66	66				
Male	40	40				
Diagnosis age			0.604			
<47 years	51	51				
>47 years	58	58				
Subtype			0.326			
Clear cell, grade1-2	56	56				
Grade3, dedifferentiated, mesenchymal, myxoid	54	54				
Stage			0.002			
Stage1	54	54		-		
Stage2	78	78		0.621	0.219-1.764	0.371
Stage3	23	23		2.658	1.070-6.605	0.035
Location			0.014			
Appendicular skeleton	66	66		-		
Axial skeleton	37	37		2.081	0.936-4.625	0.072
Surgical margin			0.396			
Negative	64	64				
Positive/closed	60	0				
Adjuvant RT			0.118			
Yes	69	69				
No	47	47				
Adjuvant CT			0.358			
Yes	43	43				
No	56	56				

RT: Radiotherapy, CT: Chemotherapy, HR: Hazard ratio, CI: Confidence interval, p values: <p–0.05.

In multivariate analysis, only stage at diagnosis remained significantly associated with DFS (p=0.013).

All patients with metastases at presentation progressed and died during follow-up, with a median time to progression of 7 months (95% CI: 2.1–11.8).

Prognostic Factor Analysis for Overall Survival

In the entire cohort, OS was 75%, 63%, and 57% at 5, 10, and 15 years, respectively. Univariate analysis identified stage at diagnosis (p<0.001), tumor grade (p=0.001), and sex (p=0.016) as significant prognostic factors for OS. Detailed results are provided in **Table 4**, and survival curves are shown in **Figure**.

Univariate analysis showed significantly longer survival in females, patients with low–moderate grade disease, stage I–II tumors, and those without metastases. In multivariate analysis, only stage at diagnosis remained an independent predictor of survival (p=0.002).

In patients with initially localized disease treated curatively, OS was 80%, 68%, and 68% at 5, 10, and 15 years, respectively. Female patients tended to have better OS than males (86%, 79%, 79% vs. 73%, 53%, 53% at 5, 10, 15 years; p=0.059), and appendicular tumors showed a survival advantage over axial tumors (84%, 80%, 80% vs. 73%, 49%, 49%; p=0.068).

Univariate analysis revealed that stage and grade significantly affected OS: stage I–II tumors had superior outcomes compared to stage III (84%, 84%, 84% vs. 90%, 90%, 90% vs. 58%, 14%, 0% at 5, 10, and 15 years; p<0.001), and low–intermediate grade tumors outperformed high-grade tumors (83%, 72%, 72% vs. 66%, 44%, 44% at 5, 10, 15 years; p=0.026). In multivariate analysis, only stage at diagnosis remained independently significant, with stage I tumors showing a markedly reduced risk of death compared to stage IV (HR=0.099, 95% CI: 0.1–0.5; p=0.011).

In the initially metastatic group, median OS was 12 months (95% CI: 0.1–33.6). The development of metastasis during follow-up was a significant predictor of OS (p=0.001; HR=0.064, 95% CI: 0.1–0.3).

DISCUSSION

The aim of this study was to evaluate the clinicopathological features, treatment modalities, prognoses, and outcomes of patients with CS. We presented a comprehensive overview of all CS cases with varying histological subtypes treated in our

Table 4. Prognostic factors for overall survival (n=69)

Factors	Univariate analysis			Multivariate analysis		
	5-yr OS (%)	10-yr OS (%)	p value	HR	95% CI	p value
Entire group	75	63				
Sex			0.016			
Female	83	77		-		
Male	64	48		1.541	0.554-4.286	0.407
Diagnosis age			0.936			
<47 years	75	58				
>47 years	75	57				
Subtype			0.001			
Clear cell, grade1-2	92	85		-		
Grade3, dedifferentiated, mesenchymal, myxoid	52	37		1.325	0.426-4.126	0.627
Stage			<0.001			
Stage1	90	85		0.099	0.017-0.589	0.011
Stage2	89	89		0.068	0.011-0.420	0.004
Stage3	58	14		0.575	0.166-1.991	0.383
Stage4	17	0		-		
Location			0.125			
Appendicular skeleton	78	74				
Axial skeleton	68	45				
Surgical margin			0.101			
Negative	93	70				
Positive/closed	53	0				

HR: Hazard ratio, CI: Confidence interval, p values: <p–0.05.

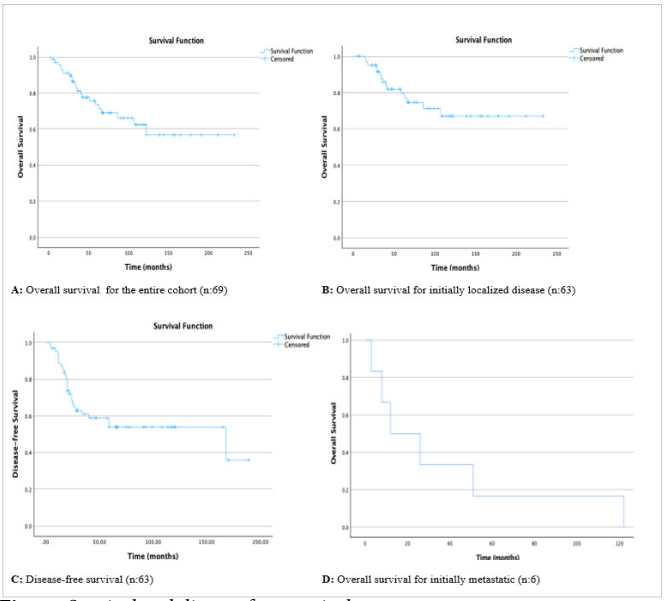

Figure. Survival and disease-free survival curves

clinic. By doing so, we aimed to contribute to the limited body of literature on this rare malignancy and provide additional insights into its management and outcomes.

In the present study, the OS rates at 5, 10, and 15 years were 75%, 63%, and 57%, respectively, consistent with previous reports.[4,12-14] The median age at diagnosis was 47 years, with a slight male predominance (52%), whereas earlier studies reported a median age of ~50 years and nearly equal sex distribution.[4,13,15] Male sex was associated with poorer prognosis in univariate analysis, in line with prior studies,[13,15] although some reports found no significant sex-related survival difference.[11,16]

Histological grade is a major prognostic factor in CS.[8] In our cohort, nearly all metastatic cases were intermediate- or high-grade, and tumor grade significantly influenced OS, consistent with the literature.[11,13] Low-grade CS rarely metastasizes,[4,5,13] but once present, outcomes are poor, often reflecting progression to a more aggressive phenotype.[16-19] In the current study, notably, one patient with an initial low-grade tumor developed metastasis that had transformed to grade 3.

The development of local recurrence or metastasis was associated with significantly worse survival. Most recurrences in our cohort occurred within 1–3 years, but six patients relapsed 10–15 years after diagnosis, consistent with reports of recurrences up to 20 years.[20-22] Although conventional and dedifferentiated histologies were observed in these late cases, the limited sample size precluded firm conclusions about tumor biology and late relapse. These findings emphasize the importance of close surveillance in the first five years and continued long-term follow-up due to the potential for late relapse.

An atypical cartilaginous tumor (ACT), formerly termed grade I CS, refers to tumors of the appendicular skeleton and reflects distinct biological behavior by site.[8] ACTs grow

slowly, behave locally aggressively, and rarely metastasize.[23] In our study, local recurrence occurred in 26% of appendicular and 33% of axial grade I tumors. Overall, axial CSs tend to have poorer outcomes and are treated more aggressively,[3,5,24] although some reports suggest location does not significantly affect survival.[3,4,13] In our cohort (22 axial, 47 appendicular cases), location was a significant prognostic factor for DFS but not OS in univariate analysis. This may relate to the tumor microenvironment, treatment differences by site, or delayed diagnosis due to anatomical constraints.[15]

In our study, stage at diagnosis significantly influenced both DFS and OS in multivariate analysis, with stage II patients showing slightly better outcomes than stage I. Andreou et al.[16] reported no correlation between AJCC stage and outcomes in localized axial or pelvic CS. Notably, histological grading may vary among pathologists,[25] which can alter staging and affect surgical decisions. Larger studies are needed to compare and validate staging systems.

In our cohort, all 19 patients with metastatic disease at diagnosis or follow-up had lung involvement. Similar to other sarcomas, the lung was the predominant metastatic site, with far less frequent spread to the liver, vertebrae, lymph nodes, or brain. Brain metastases are extremely rare, with only 12 cases reported in the literature;[26] in our series, one patient with grade II CS developed lung, brain, and thoracic vertebral metastases. Primary spinal CS is also uncommon[27] and may present with spinal cord compression. In our study, one patient with stage IV mesenchymal-type CS developed spinal paraplegia and received palliative RT for spinal metastasis.

Biopsy is useful for diagnosis and surgical planning but may not accurately determine histological grade due to heterogeneity, sampling error, or interobserver variability.[25,28,29] In our study, preoperative biopsy results matched surgical pathology in only 9 of 31 patients, underscoring the need to integrate clinical, radiological, and histological findings.[30] Recurrent CSs may present with higher grades than the primary tumor;[5,31,32] in our series, 16 of 21 recurrent cases retained the same grade. Some CSs also show unpredictable behavior despite appropriate classification.[13,33,34] Thus, molecular markers and advanced imaging are needed to better predict prognosis, guide therapy, and improve preoperative diagnosis.[30,35,36]

Adequate surgical excision is critical in CS management. In our cohort, patients with negative margins showed a slight, though non-significant, survival advantage, likely limited by sample size. Previous studies, however, have demonstrated significant differences in OS and DFS based on margin status.[4,16]

Low-grade CSs are generally resistant to RT and CT due to their slow growth and low mitotic activity.[5,6,37,38] Nevertheless, RT may be considered for unresectable or borderline cases and for palliation,[37,39,40] while CT shows activity in mesenchymal and dedifferentiated subtypes.[6,7,41] Given the rarity of CS, evidence is limited to retrospective series.[6,37,42] In our study, IMA, NCI, and CA were the most frequently used regimens. CT was mainly administered to mesenchymal, dedifferentiated, or grade III tumors, where higher proliferative potential and aggressive course suggest greater benefit.

In our study, CT was administered across all histologies except clear cell. Only three patients received single-agent therapy, while the rest received combinations. Among recurrent and metastatic cases, combination regimens showed better disease control (5 progressions/9 stable disease) compared to single agents (2 progressions/1 stable disease), though small numbers precluded subtype-specific conclusions. Similarly, Italiano et al.[42] reported higher response rates with combination therapy than with single agents (20% vs. 11%, p=0.09).

Interest in targeted and immunotherapies for advanced or unresectable CS has been increasing, given the limited efficacy of CT and RT. Molecular studies highlight potential targets such as IDH1/2 mutations, hedgehog signaling, and angiogenesis pathways.[2,30] Early-phase trials of IDH inhibitors (e.g., ivosidenib) have shown promise in IDH-mutant CS,[43] while pazopanib has achieved disease stabilization in advanced cases.[1] In contrast, checkpoint inhibitors have yielded limited benefit, likely due to the immunologically "cold" tumor microenvironment,[44] though ongoing studies are testing novel combinations to improve immune responsiveness.[45,46]

Limitations

This study has several limitations. Missing data on factors such as comorbidities, surgical margin width, and RT dose may have influenced outcomes, as these are prognostically relevant in CS.[13,23,33] Competing risks, such as death from other causes, may also affect survival analyses.[13,47,48] Moreover, the long study period may have introduced variability in treatment approaches. The retrospective design, rarity of CS, small sample size, heterogeneity of treatment periods, and reliance on single-center data without external validation limit the generalizability of our findings. Future multicenter studies with larger cohorts are needed to validate and generalize these findings.

CONCLUSION

As a result, this study adds to the limited data on the prognosis of local and metastatic CS. While no novel findings were identified, our results confirm prior knowledge by showing that stage and tumor location predict DFS, whereas stage, sex, and histological subtype influence OS. Multivariate analysis indicated that early tumor stage was the only independent prognostic factor for both DFS and OS. Given the heterogeneity of CS, a multidisciplinary approach with standardized criteria is essential to optimize diagnosis and treatment. The regional longitudinal dataset in our study offers important insights for the clinical management of CS and serves as a valuable reference for future comparative studies.

ETHICAL DECLARATIONS

Ethics Committee Approval

The study was conducted with the permission of the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research and Hospital Non-interventional Clinical Researches Ethics Committee (Date: 19.10.2023, Decision No: 2023-10/98).

Informed Consent

Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure

The authors declared that this study has received no financial support.

Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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