Prognostic Factors for Long-Term Survival after Surgical Resection of Primary Cardiac Sarcoma

Anas Aboud[1] Kassar Farha[2] Wan Chin Hsieh[3] Frank Brasch[4] Stephan Ensminger[1] Jan Gummert[2] André Renner[2]

[1] Department of Cardiac and Thoracic Vascular Surgery, University of Schleswig-Holstein, Lübeck Campus, Lübeck, Germany
[2] Department of Thoracic and Cardiovascular Surgery, Heart and Diabetes Center NRW, Ruhr-University Bochum, Bad Oeynhausen, Germany
[3] Department of Cardiovascular Surgery, First Faculty of Medicine, General University Hospital in Prague, Charles University, Prague, Czech Republic
[4] Department of Pathology, Academic Teaching Hospital Bielefeld, Bielefeld, Germany

Address for correspondence Anas Aboud, MD, Department of Cardiac and Thoracic Vascular Surgery, University of Schleswig-Holstein, Lübeck Campus, Ratzeburger Allee 160, 23562 Lübeck, Germany (e-mail: Anas.Aboud@uksh.de).

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Abstract

Background Primary cardiac sarcoma (CS) is an extremely rare disease. This study aims to identify possible prognostic factors for long-term survival.

Methods A total of 17 consecutive patients who were treated for primary CS between 2003 und 2018 at two cardiac centers were investigated. Clinical data and histological characteristics of the tumors were analyzed. Long-term follow-up of all patients were performed.

Results The median age was 54 years (range: 23–74). The tumors originated from the left side of the heart in nine patients. Histologically, there were four angiosarcomas, three intimal sarcomas, and three synovial sarcomas. One- and 7-year survivals were 81.9 and 18.2%, respectively. Low expression levels of K_i-67 tended to be associated with increased survival (log-rank $p = 0.06$). Adjuvant chemotherapy but not radiotherapy regardless of existing metastases was associated with significantly increased survival (log-rank $p = 0.001$).

Conclusion Angiosarcoma was the most common type of CS. The survival of CS patients is poor but prognostic factors, such as K_i-67, may help estimate the course of the disease. Survival could be improved significantly with chemotherapy.

Keywords
- sarcoma
- outcomes
- histopathology

Introduction

Primary cardiac sarcoma (CS) has an extremely rare prevalence (0.001–0.028%).[1–7] Since 1934, when it was first described, CS has remained a diagnostic challenge. Furthermore, there is no clinical consensus on therapy and the prognosis is poor, with median overall survival ranging from 5 to 13 months.[5,6,8–12] Despite its rarity, CS accounts for ~75% of all malignant cardiac tumors in adults,[2,6,7,13] which occur in the right atrium in 90% of cases and tend to be metastatic in approximately 10% of patients,[2,6,11] affecting the lungs and lymph nodes in ~50% of cases.[5,14] Complete surgical excision with or without sequential resection of metastatic tumors has been found to improve long-term survival.[7]

CSs can be classified in a few major histological groups[6,11,15,16]:

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- Angiosarcomas, which account for 30% of malignant cardiac tumors and are histologically characterized by infiltration of the myocardium by spindle cells;
- Rhabdomyosarcomas, making up 20% of all CSs, macroscopically resembling soft nodules with a localized necrotic region in the middle;
- Fibrosarcomas, comprising approximately 10% of all malignant cardiac tumors, are gray and nodular, also presenting bundle spindle cells histologically;
- Leiomyosarcomas, accounting for 9% of all CSs, histologically appear as elongated, tightly packed spindle cells intermingled with areas characterized by only a few cells;
- Liposarcomas, osteosarcomas, cardiac Ewing sarcomas; and
- Undifferentiated sarcomas, typically presenting a malignant spindle cell tumor with regions of necrosis histologically.

To confirm the diagnosis of sarcoma, immunohistochemistry (IHC) is used as an adjunctive diagnostic method, in addition to performing an assessment of the histopathology of the tumors and a differential diagnosis.[6,17–19] IHC does not only provide an improved diagnostic classification of the sarcomas but also a guidance on their prognosis, therapy, and relapse.[20]

Most of the studies published in the literature on the prognostic factors of sarcomas via IHC data focus on the expression of markers for cell kinetics and regulatory proteins of the cell cycle, such as CD31, CD34, FLI-1, von Willebrand factor, keratins (particularly K8, K18, K19, and K20), and ERG for endothelial tumors.[6,18,19,21] The expression of the Ki-67 protein (pKi67) has been found to be highly associated with the proliferation rate of intrinsic cell populations in several malignant tumors, for example, of the breast, soft tissue, lung, prostate, cervix, and central nervous system, thus being deployed as a marker of tumor aggressiveness.[6,18,19,22]

The aim of this study was to investigate possible prognostic factors that are associated with long-term survival of CS patients.

Materials and Methods

Patient Population

All consecutive patients with cardiac tumors who were admitted to two German heart centers (Heart and Diabetes NRW/Bad Oeynhausen, University of Schleswig-Holstein/Campus Lübeck) between 2003 and 2018 were identified ($n = 437$). Of those, 17 patients had primary CS and were included in this study. Patients' demographics, surgical, histological, and oncological data were collected (►**Table 1**). Follow-up was performed in all our patients. The study was approved by the ethical boards of both hospitals.

Histologic Assessment

IHC was performed for all cases according to the criteria set by the World Health Organization in 2002,[23] with a few specimens re-analyzed recently by the pathologist to complete the IHC analysis. The prognostic value of the proliferation factors K_i-67 was investigated in the representative cohort of patients ($n = 17$). The clinical follow-up was also considered with regard to the outcomes derived from the IHC assessment.

Statistical Analysis

Data management and a statistical analysis on the above-mentioned retrospective patient data were performed via IBM SPSS Statistics (IBM Corp., Released 2016; IBM SPSS Statistics for Windows, version 24.0, Armonk, NY). Long-term survival/follow-up was estimated and compared via the Kaplan–Meier's product limit method[24] and a log-rank test, respectively.

Results

As illustrated in ►**Table 1**, the median age of the study population was 54 years (range: 23–74) and 10 patients were male; 23.5% had angiosarcoma, 17.6% intimal sarcoma, 17.6% synovial sarcoma (►**Fig. 1**), 11.8% undifferentiated sarcoma, 5.8% myxoid liposarcoma, 5.8% osteosarcoma, 5.8% rhabdomyosarcoma, 5.8% spindle-cell sarcoma, and the remaining 5.8% phenotype-changing sarcoma (►**Table 2**). In IHC analysis, most patients ($n = 15$) presented with intermediate or high expression levels of Ki-67, while two patients had low Ki-67 activity (►**Table 1**). Further characteristics of these patients are summarized in ►**Table 3**. The first clinical event was respiratory in seven cases, cardiac in six cases, neurological in three cases, and of multiple etiologies in one clinical case. Seven patients reported to have been treated previously for other tumors: of mammary etiology in four cases, prostate in two clinical cases, and gastric in one case. The site of origin was the left side of the heart in nine of the clinical cases analyzed, the right side in seven of them, and the left and right sides in one case. Twelve patients had undergone one surgery and three of them three surgeries. Eleven patients underwent postoperative chemotherapy, four patients underwent radiotherapy, and three patients combined radiochemotherapy. Metastasis was observed in the follow-up in eight clinical cases, most of them pulmonary ($n = 5$), local ($n = 5$), one brain, and one bone metastasis.

Estimated 1- and 7-year survivals were 81.9 and 18.2%, respectively (►**Fig. 2**). The median and mean survival of the entire study population were 20 months (95% confidence interval [CI]: 8.5–31.5) and 33.7 months (95% CI: 17.3–50.2), respectively (►**Fig. 2**).

Additionally, we analyzed the follow-up data depending on the different characteristic, therapeutic, and prognostic factors.

Survival was similar among male and female patients (long-rank $p = 0.17$). Patients with low Ki-67 expression levels presented with a tendency for improved long-term survival (Ki-67 low 100% vs. Ki-67 intermediate/high 0%, log-rank $p = 0.06$, ►**Fig. 3**).

Patients who received postoperative chemo- and/or radiotherapy presented with significantly increased long-term survival (24.8 vs. 0%, $p = 0.01$, ►**Fig. 4**). Radiotherapy alone did not significantly improve survival ($p = 0.42$), while chemotherapy alone was associated with significantly improved survival (27.0 vs. 0%, $p = 0.001$, ►**Fig. 4**).

Table 1 Clinical and histological features of 17 representative patients with primary cardiac sarcoma considered in this study

Patient	Tumor	Operations	Age (y)	Gender	Origin	Tumor Size (cm)	Grade	Ki-67/ MIB1	Margin Status	First event	Follow-up (mo)	Alive	Chemo-therapy	Radio-therapy	Previous tumor history	Metastasis
1	Angiosarcoma	1	54	M	RA	9 × 6 × 1	3	High	R1	Cardiac	12	Yes	Yes	No	Prostate	No
2	Rhabdomyosarcoma	1	69	F	RV	3 × 3 × 2	2	Intermediate	R1	Respiratory	20	Yes	Yes	No	Mammary	No
3	Spindle-cell sarcoma	1	42	F	LA	8.5 × 7.5 × 2	2	Intermediate	Rx	Respiratory	20	No	Yes	No	No	Pulmonary, local, brain
4	Angiosarcoma	1	74	M	RA	5	3	High	Rx	Multiple	0	No	No	No	Prostate	Pulmonary
5	Synovial sarcoma	3	51	F	RV	4.5 × 1.5 × 2	3	High	R1	Respiratory	18	No	No	No	No	Local, pulmonary
6	Synovial sarcoma	1	47	M	MV	3.5 × 3.7	3	High	R1	Respiratory	18	No	Yes	Yes	No	No
7	Intimal sarcoma	1	65	F	LV	4.6 × 3.6	2	Intermediate	R1	Neurological	26	No	Yes	No	Mammary	No
8	Angiosarcoma	1	72	F	LA + RV	4 × 1.5- × 2	3	Intermediate	R1	Neurological	11	No	Yes	No	No	Pulmonary
9	Intimal sarcoma	3	43	F	LA	5.3 × 4.2 × 3.5	3	Intermediate	R1	Respiratory	40	Yes	Yes	No	No	Local, pulmonary
10	Undiff. sarcoma	1	48	M	RA	6.7 × 3.5 × 4	2	Low	R0	Respiratory	84	Yes	Yes	Yes	No	No
11	Changing phenotypes	3	63	M	LA	4.5 × 4- × 3	3	High	R1	Cardiac	55	No	Yes	No	No	Local
12	Undiff. sarcoma	1	51	F	LA	7 × 6.5- × 2	3	Intermediate	Rx	Respiratory	3	No	No	Yes	No	No
13	Osteosarcoma	1	64	F	MV	7.5 × 8.2 × 4.3	3	High	R1	Cardiac	1	No	No	No	Mammary	Bones
14	Myxoid liposarcoma	1	72	F	LA	5.5 × 4.3 × 3	2	Intermediate	R1	Neurological	12	No	No	No	Gastric	No
15	Angiosarcoma	1	24	M	RA + RV	4.7 × 4.2	3	High	R1	Cardiac	7	Yes	Yes	No	No	No
16	Synovial sarcoma	1	23	M	RA	10 × 8 × 4	2	Low	R1	Cardiac	45	Yes	Yes	Yes	No	Local
17	Intimal sarcoma	1	62	F	LA	10.5 × 7.5 × 5.5	3	High	R1	Cardiac	2	Yes	No	No	Mammary	No

Abbreviations: High, high level of expression of K_i-67 or MIB1 (higher than 30%); Intermediate, intermediate concentration of K_i-67 or MIB1 (from 16 to 30%); LA, left atrium; Low, low levels of expression of the proliferation factors K_i-67 or MIB1 (less than 15%); LV, left ventricle; MV, mitral valve; R0 resection, negative margin; R1 resection, positive margin; RA, right atrium; RV, right ventricle; Rx, uncertainty on whether the specimens were free from cancer cells; Undiff. sarcoma, undifferentiated sarcoma.
Note: Changing phenotypes, fibrosarcoma→angiosarcoma→leiomyosarcoma.

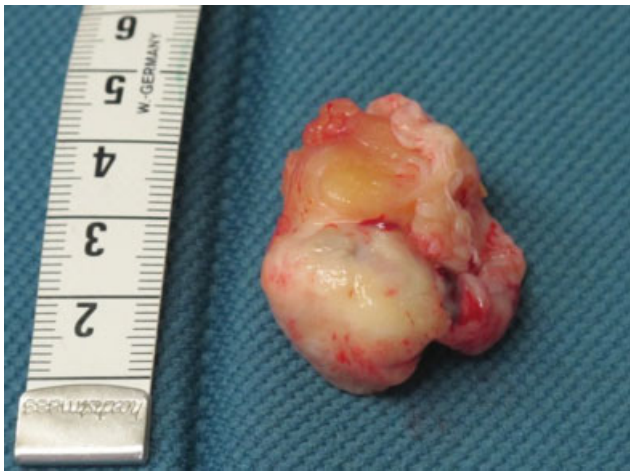

Fig. 1 Synovial sarcoma at the mitral valve in patient number 6.

The presence of metastasis was not found to affect patient survival significantly ($p = 0.38$). Similarly, the tumor location (left or right side of the heart) was not statistically significantly associated with long-term survival.

Discussion

In this retrospective analysis of two German heart centers, we investigated long-term survival (up to 7 years) of patients who underwent surgical resection of primary CS. The main findings of our study can be summarized as follows:

1. The most common CS subtype was angiosarcoma.
2. Overall long-term survival remains low.
3. Expression levels of Ki-67 may be a powerful prognostic factor for long-term survival.
4. Postoperative chemotherapy significantly increased long-term survival.

Table 2 Types of sarcoma in the cohort of representative patients analyzed ($n = 17$)

Sarcoma types, *n* (%)	Left side of the heart	Right side of the heart	Total
Angiosarcoma	0 (0%)	3 (17.6%)	4 (23.5%)[a]
Intimal sarcoma	3 (17.6%)	0 (0.0%)	3 (17.6%)
Synovial sarcoma	1 (5.9%)	2 (11.8%)	3 (17.6%)
Undifferentiated sarcoma	1 (5.9%)	1 (5.9%)	2 (11.8%)
Myxoid liposarcoma	1 (5.9%)	0 (0.0%)	1 (5.9%)
Osteosarcoma	1 (5.9%)	0 (0.0%)	1 (5.9%)
Rhabdomyosarcoma	0 (0.0%)	1 (5.9%)	1 (5.9%)
Spindle-cell sarcoma	1 (5.9%)	0 (0.0%)	1 (5.9%)
Phenotype-changing sarcoma	1 (5.9%)	0 (0.0%)	1 (5.9%)

[a]One patient with angiosarcoma had tumor present both at the left and right sides of the heart.

Table 3 Characteristics of representative patients ($n = 17$)

Patients characteristics	
Total number of patients	17
Age, mean (range)	54 (23–74) y
Sex, *n* (%)	
Males	10 (58.8%)
Females	7 (41.2%)
Location, *n* (%)	
Left side of the heart	9 (52.9%)
Right side of the heart	7 (41.2%)
Left and right sides of the heart	1 (5.9%)
Tumor grading, *n* (%)	
Grade I	0 (0.0%)
Grade II	6 (35.3%)
Grade III	11 (64.7%)
Ki-67/MIB1, *n* (%)	
Low	2 (11.8%)
Medium	7 (41.2%)
High	8 (47.0%)
Margin status, *n* (%)	
Rx	3 (17.6%)
R0	1 (5.9%)
R1	13 (76.5%)
Adjuvant therapy, *n* (%)	
Chemotherapy	11 (64.7%)
Radiotherapy	4 (23.5%)
Any	12 (70.6%)

Angiosarcoma was the most common histologic CS subtype in this study population accounting for 23.5% of the cases which is in agreement with findings derived from published studies.[2,5,8] Intimal sarcoma and synovial sarcoma were the second most common type of CS, accounting for 17.6% of the cases.

The overall survival after surgical resection of CS has been reported to be very poor.[2,4,10] Our results are in line with these reports as overall 7-year survival was only 18.2% with a median survival of 20 months, while in other published studies, the survival of patients with complete or incomplete resection has been found to be 11 and 20 months, respectively.[7,25] It is therefore important to identify prognostic factors that are associated with long-term survival to improve patient outcomes.

In line with other groups, we found no association between patient gender and long-term survival.[2,6,14] Similarly, the location of the CS (e.g., left or right side of the heart) was not associated with long-term survival.

In our study, about half of CS (52.9%) originated from the left side of the heart, which is in line with other studies.[2,7] Furthermore, this study shows, similar to the literature,[2,4,7,10]

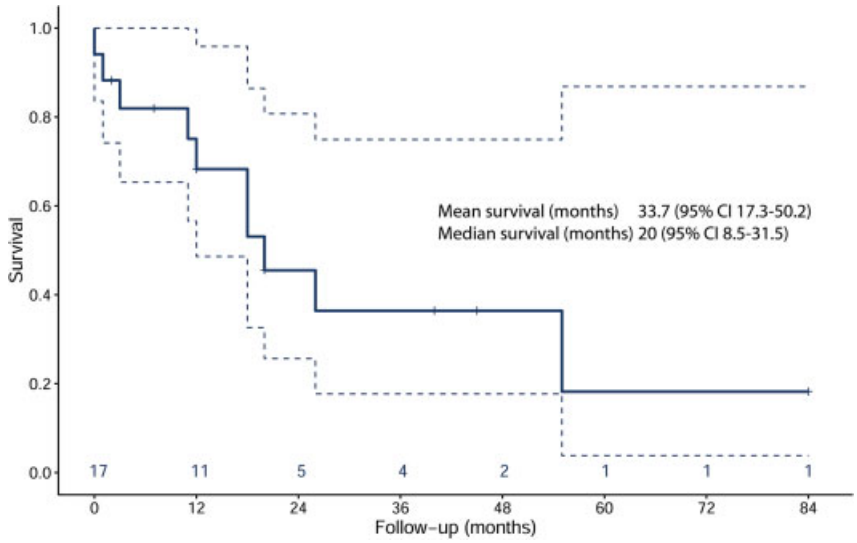

Fig. 2 The Kaplan–Meier's analysis of sarcoma patients with a follow-up of 84 months.

that most of cardiac angiosarcomas tend to arise in the right atrium.

Currently, there are no useful prognostic factors for CS patients available. Gender, age, and histologic types do not appear to be prognostic factors in primary CSs in this and other studies.[2,4,7] In our study, we investigated expression levels of the proliferation factor K_i-67 and its possible role as a prognostic factor for long-term survival. We found that only two patients presented with low Ki-67 expression levels, but both of these patients had a tendency for increased long-term survival compared with patients who had intermediate to high Ki-67 expression levels ($p = 0.06$). This association did not reach statistical significance probably due to the small number of patients and needs to be confirmed in larger patient cohorts. To our knowledge, this relationship has not been described in CS patients before.

Due to the invasive growth behavior of CS, it is difficult to obtain a complete surgical resection of these tumors; nevertheless, a complete resection seems to be a "conditio sine qua non" regarding prognosis and stills an important factor for long-term survival.[2] In our cohort, only one patient underwent R0 resection. This patient was alive after 7 years supporting the suggestion to attempt R0 resection whenever possible. However, the low frequent of R0 resection in our patients may depend on the nature of the CS. It is well known that most types of sarcomas even infiltrate tissues which seem to be healthy macroscopically. This means that, a microscopical tumor infiltration may exist after a tumor-free zone. Additionally, it is mostly not possible to resect an excessive amount of myocardium, which may lead in some cases to irreversible cardiac failure. The use of frozen section in the cardiac surgery is also difficult because of

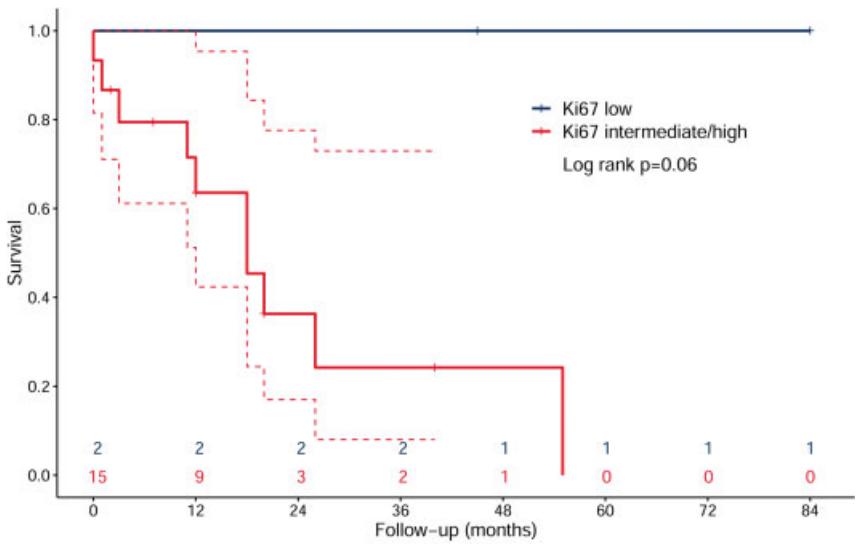

Fig. 3 The long-term follow-up of sarcoma patients depending on Ki-67 expression levels.

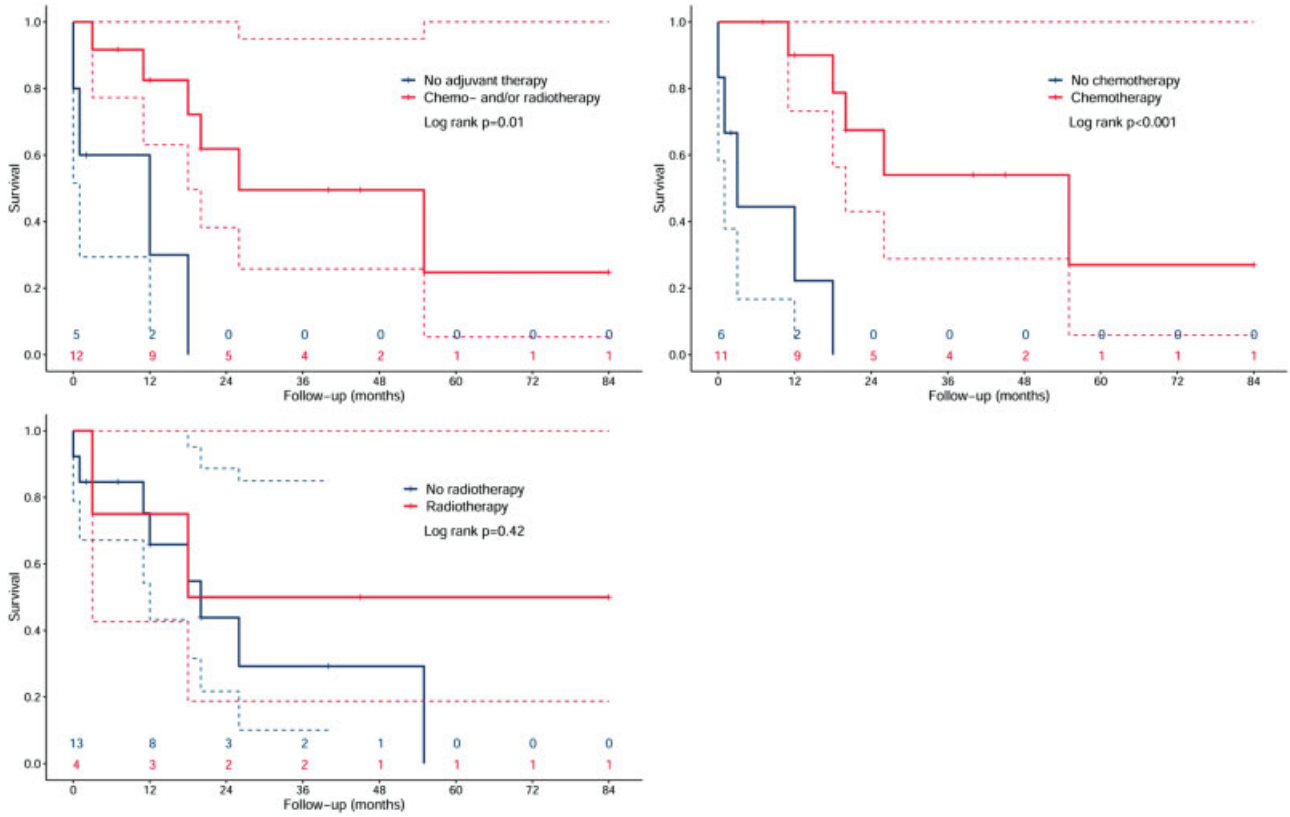

Fig. 4 The effect of postoperative radio- and/or chemotherapy on the long-term results in sarcoma patients after cardiac surgery.

the limited cardiac arrest time. In some patients, a complete CS resection may just achieved with a complete heart explant done with a heart transplantation or implantation of total artificial heart, which already reported in some centers.[26] In two of our patients, the pathologist was not sure with status of the resected margin (Rx resection).

Although clinical outcomes are highly variable in patients who underwent adjuvant postoperative chemotherapy,[2,4,14,27] in this study, adjuvant chemotherapy was found to be associated with significantly longer survival (►**Fig. 4**) as was shown by Putnam et al.[25] Radiotherapy alone seems to have less effect on the prognosis (►**Fig. 4**). These results enforce the theory that chemotherapy plays an essential role in the treatment of CS and should be started as soon as possible. These results support the use of neoadjuvant chemotherapy to further improve long-term outcomes as previously suggested by Ramlawi et al.[7] In our study, none of the patients received neoadjuvant chemotherapy. According to these results, it is essential to discuss every case of cardiac tumor interdisciplinary among oncologist, radiologist, cardiologist, and cardiac surgeon as a part of tumor board meeting even before doing the surgery.

CSs are very pervasive in nature, spreading out from the heart to adjacent structures, such as the lungs.[2] In this study, pulmonary metastases were the most common ones, with five cases, in agreement with previous findings by Kim et al. Interestingly, the presence of metastasis was not found to affect patient survival significantly ($p = 0.38$).

The limitations of this work are the retrospective analysis and the small number of patients.

Conclusion

Long-term prognosis of CS patients remains low. Chemotherapy seems to be the most important factor leading to better survival. Furthermore, low expression levels of the proliferation factor K_i-67 seem to correlate with better long-term survival. Further studies investigating larger patient cohorts are necessary to confirm these findings.

Conflicts of interest

None.

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