Incidence, prognostic significance, and survival outcomes of primary cardiac sarcoma: An updated population-based retrospective study

Mohammad Bakri Hammami1, 2, Moh’d Zaki Al-Wawi3,#, Huwaida Fazel1,#, Mohamad Anas Oudih1,4,#

1Department of Clinical Sciences, College of Medicine, University of Sharjah; Sharjah-United Arab Emirates
2Department of Laboratory Medicine and Pathology, Mayo Clinic College of Medicine; Minnesota-USA
3RAK College of Medical Sciences, Ras Al Khaimah Medical and Health Sciences University; Ras Al Khaimah-United Arab Emirates
4Sheikh Khalifa Medical City; Abu Dhabi-United Arab Emirates

ABSTRACT

Objective: Primary cardiac sarcoma, a rare tumor with an aggressive course and imprecise prognosis, constitutes over 95% of all malignant cardiac tumors. Given the sparsely available evidence, there is a paucity of information regarding current knowledge on cardiac sarcoma. This study aimed to determine the incidence and incidence-based rates, patient characteristics, treatment modalities, and survival factors of cardiac sarcoma.

Methods: A retrospective analysis of the incidence, incidence-based mortality rates and characteristics of cardiac sarcoma between 1975 and 2016 was carried out using the Surveillance, Epidemiology, and End Results (SEER) database. The National Cancer Institute’s Joinpoint Regression program was used to calculate the Annual Percentage Changes (APC). Univariate and multivariate regression analysis were used to determine the survival characteristics.

Results: A total 408 patients were identified for the incidence analysis, while 385 eligible patients were identified for the survival analysis. The mean age at diagnosis was 46.3±17.9 years. The incidence rate (per 100,000 per year) of cardiac sarcoma within the indicated years was 0.22, with an increased APC of 1.7 (p=0.013, 95% CI=0.5–2.9). A total of 251 (61.5%) patients underwent surgery, 93 (22.8%) patients received adjuvant radiotherapy, and 197 (50.2%) patients received chemotherapy. Surgical resection, chemotherapy, stage of tumor, and younger age significantly improved the survival outcomes (p<0.001).

Conclusion: Cardiac sarcoma is a rare type of soft tissue sarcomas with poor prognosis. Over the past 30 years, the incidence of cardiac sarcoma has been on the increase. Surgery remains the mainstay of management. Further studies are needed to compare different diagnostic and treatment modalities so as to ascertain the best treatment option that would enhance survival and prognosis of cardiac sarcoma.

Keywords: surveillance, epidemiology, and end results; cardiac sarcoma; incidence; survival; population study

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Introduction

Primary cardiac tumors are rare benign or malignant neoplasms with an autopsy incidence of 0.002%–0.3% (1-3). Nearly one-fourth of primary cardiac tumors in adults are malignant. Primary cardiac sarcoma constitutes approximately 95% of all malignant cardiac tumors that occur primarily as single lesions found in the left atrium (4, 5).

Based on histologic morphologies, cardiac sarcoma is a mesenchymal malignancy is classified into several subtypes (6).

Of these subtypes, angiosarcoma is the most prevalent primary malignancy in adults, whereas rhabdomyosarcoma is more common in children (7). Although classified as aggressive malignant tumors, most cardiac sarcomas are confined to the heart at the time of diagnosis (8). The clinical presentation of cardiac sarcoma depends on the tumor location and pathological type, thus making early diagnosis vital for survival (9).

Transthoracic Echocardiogram has been used frequently to diagnose cardiac sarcoma. Metastasis is typically detected by Whole-Body Computed Tomography (CT) scan and/or Mag-
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Magnetic Resonance Imaging (MRI) (8). Surgery is the mainstay of treatment for cardiac sarcoma followed by radiotherapy and chemotherapy (10). The role and efficacy of radiotherapy and chemotherapy are yet to be fully investigated. Cardiac sarcoma carries an unclear prognosis, with median survival between 1–2 years, which is often shorter in those who do not undergo surgical resection (8).

Information regarding primary cardiac sarcoma in literature is sparse. In that regard, we conducted this retrospective study to investigate the incidence, survival, and characteristics of cardiac sarcomas using the Surveillance, Epidemiology, and End Results (SEER) database, which is the largest cancer database in the United States. We compared our findings to similar reports and discussed factors that improve the survival of these patients.

Methods

Data source

The study data was obtained from SEER-18 registries (November 2018 Subset), which is sponsored by the National Cancer Institute (NCI). The SEER database collects and publishes data from 18 population-based registries, covering approximately 28% of the United States population (11). The data was accessed through SEER*stat software (8.3.6) obtained from SEER and maintained by NCI.

Study population

Data were examined from 1975 to 2016 to identify patients with primary cardiac sarcoma. We included patients with the International Classification of Disease for Oncology codes as follows: soft tissue tumors and sarcomas not otherwise specified (NOS) (8800–8809); fibromatous neoplasms (8810–8839); myxomatous neoplasms (8840–8849); lipomatous neoplasms (8850–8889); myomatous neoplasms (8890–8929); complex mixed and stromal neoplasms (8930–8999); synovial-like neoplasms (9040–9049); and blood vessel tumors (9120–9169). Site code C38.0 was used to specify tumor site as Heart. Year of diagnosis was specified from 1975 to 2016. Only the first primary tumors were included. No duplicate cases were found in the study population.

For the survival analysis, out of 422 patients identified, we excluded cases not diagnosed microscopically (14 cases); cases without active follow-up or autopsy/death certificate only (10 cases); alive patients with zero survival months (3 cases); cases with incomplete dates of survival (5 cases); and cases with unknown cause of death (5 cases). The final number of eligible patients that constitute the study population for the survival analysis was 385 (Fig. 1).

For the incidence analysis, we excluded only cases that were not diagnosed microscopically (14 patients), leaving 408 eligible patients for the analysis.

Tumor types were categorized as myxomatous neoplasms (8840–8849), complex mixed and stromal neoplasms (9040–9049), Lipomatous neoplasms (8850–8889) were grouped as “others” since each had less than 5 cases. Death classification was as follows: “Alive,” “Death attributable to this cancer dx,” and “Death from other cause,” or “unknown.” Surgical treatment variable was categorized as “recommended and performed,” “recommended but not performed,” and “not performed” or “unknown.” Surgical treatment variable was also dichotomized in another variable as either “performed” or “not performed.” Race was categorized as white, black, or others. Year of diagnosis of the tumor was split into 2 groups: those diagnosed before year 2000 and those diagnosed in year 2000 or later.

Statistical analysis

Frequency, survival data, and patient characteristics were obtained using SEER*Stat software (8.3.6) case listing session. Data was imputed into IBM SPSS statistical package v.22 (SPSS Inc, Chicago, IL, USA). Descriptive statistics including mean, standard deviation and percentages were used to express the

HIGHLIGHTS

• Cardiac Sarcoma is a rare tumor with a dim prognosis and increasing annual incidence.
• Surgical resection, chemotherapy, stage and age significantly improved survival.
• Gender, race and radiotherapy were not significant predictors of survival.

Figure 1. Flow chart of cases included for the incidence analysis (408) and survival analysis (385)
patient’s data characteristics. Effects of the categorical variables on survival were assessed using Kaplan–Meier Product limit curves and Log-rank test. Effects of the continuous variables on survival were assessed using Cox proportional hazards regression. After univariate analysis was performed, factors with p-value <0.05 were incorporated into a model. Proportional hazards assumption was evaluated by Log-rank Kaplan–Meier plots. Hazard ratio was reported for all significant factors in the model.

SEER*stat software (version 8.3.6) was used to calculate the incidence rates. NCI’s Joinpoint Regression program (version 4.5.0.1) was used to calculate APC and t-test was used to determine if the APCs were statistically different. Our study was done over a 41-year period (between 1975 and 2016) and rates were adjusted to the year 2000 US standard population and expressed by 100,000 people per year.

For further statistical analysis, Chi-square test was used to compare categorical variables, whereas Fischer’s exact test was used when the frequency was less than 5. T-test and analysis of variance (ANOVA) were used as appropriate to compare continuous data. Kruskal–Wallis H test was used instead of ANOVA when data were not normally distributed. Normality of the data was assessed using Shapiro–Wilk’s test (p>0.05) and visual inspection of the data was via histogram and Q-Q plots. Post hoc pairwise comparisons were performed using Bonferroni adjustment. All statistical tests were two-tailed. P-values of less than 0.05 were considered statistically significant.

**Results**

The study population consisted of 408 eligible patients, out of which, 216 (52.9%) were males and 192 (47.1%) were females. Regarding ethnicity, most of the patients were white (n=314, 77%); 50 (12.3%) were black and others (n=44, 10.8%) included American Indians, Pacific Islanders, and Asians. The demography of patients is summarized in Table 1. Cardiac sarcoma was predominant in patients aged 31–60 years (57.6%). The mean age at time of diagnosis is 46.3±17.9 years. A normal distribution pattern is illustrated in Figure 2.

The incidence rates (per 100,000 per year) of cardiac sarcoma within the indicated years were 0.22 for both males and females. The annual incidence of cardiac sarcoma increased significantly from 1975 to 2015 (APC=1.7%, p=0.013, 95% CI=0.5–2.9). Annual incidence increased significantly in males (APC=3.3%, p=0.032, 95% CI=0.2–6.5), but not in females (APC=3.1%, p=0.081, 95% CI=−1.2–7.5) (Fig. 3).

Histological pattern of primary cardiac sarcoma showed a low level of differentiation in most patients. Poorly differentiated and undifferentiated tumors were the most common, with a combined percentage of 50.2%. Only 5.6% of cases showed mild to moderate differentiation. On the other hand, primary cardiac sarcoma patients appear to have variable stages at the time of diagnosis. Approximately equal cases showed local (30.7%), regional (27%) and distant (38.2%) metastasis. Blood vessel tumors (angiosarcoma) were the most common histologic type in our patients (46.6%).

![Image](https://via.placeholder.com/150)

As for treatment methods, 93 out of 408 (22.8%) patients underwent radiotherapy. On further analysis of treatment before and after the year 2000, radiotherapy was less likely used for patients diagnosed after 2000 (20.5%) than before 2000 (33%).

### Table 1. Demographics and characteristics of cardiac sarcoma patients

| Variables          | Frequency | Percent |
|--------------------|-----------|---------|
| **Age**            |           |         |
| 0–30               | 82        | 20.1    |
| 31–60              | 234       | 57.4    |
| >60                | 92        | 22.5    |
| **Gender**         |           |         |
| Male               | 216       | 52.9    |
| Female             | 192       | 47.1    |
| **Race**           |           |         |
| White              | 314       | 77      |
| Black              | 50        | 12.3    |
| Others             | 44        | 10.8    |
| **Radiotherapy**   |           |         |
| Received radiotherapy | 93     | 22.8    |
| No/Unknown radiotherapy | 309  | 75.7    |
| **Chemotherapy**   |           |         |
| Received chemotherapy | 197    | 48.3    |
| No/Unknown chemotherapy | 205 | 50.2    |
| **Surgery**        |           |         |
| Surgery performed  | 251       | 61.5    |
| Surgery not performed | 151   | 37      |
| **Grade**          |           |         |
| Well differentiated (1) | 2      | .5      |
| Moderately differentiated (2) | 21    | 5.1     |
| Poorly differentiated (3) | 72     | 17.6    |
| Undifferentiated; anaplastic (4) | 133   | 32.6    |
| Unknown            | 180       | 44.1    |
| **Stage**          |           |         |
| Local              | 125       | 30.6    |
| Regional           | 110       | 27      |
| Distant            | 156       | 38.2    |
| Unknown            | 17        | 4.2     |
| **Histology**      |           |         |
| Soft tissue tumors and sarcomas, not otherwise specified | 101 | 24.8 |
| Fibromatous neoplasms | 39    | 9.6     |
| Myomatous neoplasms | 50     | 12.3    |
| Blood vessel tumors | 190    | 46.6    |
| Synovial-like neoplasm | 16     | 3.9     |
| Others             | 12        | 2.9     |
SN (p=0.016, \( \chi^2=5.842 \)). There was no association between radiotherapy and age, gender, stage or grade.

A total of 197 (48.3%) patients received chemotherapy. The mean age of patients who received chemotherapy was 42.5 years, while the mean age of patients who did not receive chemotherapy was 49.4 years. The mean difference (6.9 years) was statistically significant. (p=0.002, F=9.764). Chemotherapy was more likely used in patients with distant spread (p<0.001, \( \chi^2=36.5 \)), Chemotherapy (p=0.010, \( \chi^2=6.719 \)), year of diagnosis (p=0.023, \( \chi^2=5.168 \)), and stage of tumor at diagnosis (p<0.001, \( \chi^2=35.180 \)). Median survival time for patients who underwent surgical treatment was 15.00±1.715 months, while that of those who did not undergo surgery was 5.00±1.176 months. Median survival time for local, regional, and distant stages was 19, 15, and 7 months, respectively. The univariate analysis and survival times are shown in Table 2, while survival plots are shown in Figure 4. All significant variables in the unilateral analysis were also analyzed by Cox proportional hazards regression. Using the model, it was shown that surgical treatment, chemotherapy, and stage of the tumor at time of diagnosis were significant predictors of improved survival. Higher age at diagnosis showed a small increase in hazard ratio. Year of diagnosis affected survival as those diagnosed in the year 2000 and after had better outcomes than those diagnosed before 2000 (10 months vs. 6 months, respectively). On the other hand, gender, race, grade, and radiotherapy were not predictors of survival outcome. Data from the Cox Regression model are summarized in Table 3.

**Table 2. Univariate analysis of factors associated with for survival of cardiac sarcoma patients**

| Variables                      | Log-rank P-value | Median survival time (95% CI) |
|-------------------------------|------------------|-------------------------------|
| **Stage**                     |                  |                               |
| Local                         | <0.001           | 19 months (14.9, 23.1)        |
| Regional                      |                  | 15 months (8.2, 21.8)         |
| Distant                       |                  | 7 months (4.5, 9.5)           |
| **Surgical treatment**        |                  |                               |
| Surgery performed             | <0.001           | 15 months (11.6, 18.4)        |
| Surgery not performed         |                  | 5 months (2.7, 7.3)           |
| **Chemotherapy**              |                  |                               |
| Received chemotherapy         | 0.010            | 15 months (13.1, 16.9)        |
| No/unknown chemotherapy       |                  | 6 months (3.9, 8.1)           |
| **Year of diagnosis**         |                  |                               |
| Before 2000                   | 0.023            | 6 months (1.99, 10.0)         |
| In or after 2000              |                  | 13 months (10.4, 15.6)        |
| **Radiotherapy**              |                  |                               |
| Gender                        | 0.588            |                               |
| Race                          | 0.296            |                               |
Discussion

Our results show a slight predominance of cardiac sarcomas in male group which is similar to what was reported in previous studies done on a smaller number of cases (3, 12-14). The prevalence of cardiac sarcoma was highest among white ethnicity as reported previously (3, 12-14). Figure 1 demonstrated a bell curve which represents a wide age distribution among our study population, with a mean age of 46.3±17.9 years. Similar ranges were reported in previous epidemiological descriptions; however, they were younger than patients with extracardiac sarcomas (46.1 vs. 52.8 years, respectively) (12, 13, 15).

Clinical presentation at the time of diagnosis highly depends on location and grade of the tumor. Our results showed that more than two-thirds of all cases showed signs of metastasis at the time of diagnosis. By time patients present themselves at the clinic, the tumor usually would have aggressively advanced, since these tumors cause symptoms only begin to show symptoms once they start to obstruct blood flow inside the cardiac chambers, which is common in the third or fourth decades of life (16, 17). In a case series of 112 patients, all patients presented at least one of the classic triad of symptoms including obstructive cardiac signs, embolic signs, and constitutional or systemic symptoms. The most common cardiac symptoms were dyspnea and orthopnea, which is caused by progressive congestive cardiac failure (18). Other symptoms reported include fever, chest pain, pericardial tamponade and arrhythmia which can be explained by disturbance of the cardiac electrical activity or destruction of the pericardium once these tumors start to invade surrounding conducting system.

Accurate assessment of the nature of cardiac mass using non-invasive modalities is vital for diagnosis, planning management, and estimating prognosis. Cardiac tumors are diagnosed primarily with transthoracic and transesophageal echocardiograms, which can elaborate the tumor size, shape, mobility, and attachment. MRI and CT scans can further aid diagnosis and staging. Echocardiography can also be useful (19). Despite not having an established role in routine evaluation of cardiac masses, fluorodeoxyglucose positron emission tomography/computed tomography (18F-FDG PET/CT) can detect anatomic and metabolic information, both of which can further aid diagnosis, staging, and prognosis (20). Definitive diagnosis is only done by biopsy.

The overall survival for cardiac sarcoma patients remains poor despite the advancement in diagnosis and management. The reason for this is the lack of clinical trials and meta-analysis studies due to rarity of eligible patients. Angiosarcomas show a less favorable outcome due to their tendency to invade proximal vital structures early (15). A study done by Zhang et al. (21) investigating survival of patients with cardiac angiosarcoma reported a 2-year overall survival of 14.3% which is lower than that of our study (48.1%). However, the 5-year survival rate (10.2%) was comparable to our 5-year survival rate (10.1%), thus indicating poor short-term outcome of angiosarcoma compared to other cardiac malignancies. Another study by Saad et al. (22) investigating survival differences between cardiac non-hodgkin’s lymphoma (NHL) and cardiac angiosarcoma found a significantly higher mean survival in NHL (34 months) compared to angiosarcoma (9 months) (22).

Table 3. Multiple regression analysis of factors associated with survival of cardiac sarcoma patients

| Variables                      | P-value | Hazard ratio (95% CI) |
|--------------------------------|---------|-----------------------|
| **Stage**                      |         |                       |
| Local                          | <0.001  | 1.0 (Ref)             |
| Regional                       | 1.403 (1.022, 1.926) |
| Distant                        | 2.303 (1.647, 3.220) |
| Year of diagnosis              | <0.001  | 0.975                 |
| **Surgical treatment**         |         |                       |
| Surgery performed              | <0.001  | 1.0 (Ref)             |
| Surgery not performed          | 1.870 (1.412, 2.475) |
| **Chemotherapy**               |         |                       |
| Received chemotherapy          | 0.003   | 1.0 (Ref)             |
| No/unknown                     | 1.480 (1.141, 1.919) |
| Age at diagnosis               | <0.001  | 1.017 (1.010, 1.025) |

Figure 4. Comparison of cumulative survival of patients according to (a) surgical treatment (b) stage and (c) year of diagnosis.
While our study focused only on cardiac sarcoma, a study by Antwi-Amoabeng et al. (3) investigated sexual differences between cardiac sarcoma, mesothelioma, and lymphoma. The study revealed that cardiac lymphoma exhibited higher survival while mesothelioma patients had the lowest survival rate. No significant difference in survival rate was found between men and women, which is in line with our findings.

Multiple case series investigated treatment options for cardiac sarcoma and effects of adjuvant and neoadjuvant chemotherapy. Surgery remains the mainstay of treatment for primary cardiac sarcoma. Complete surgical resection was shown to improve survival in our study, which was supported by several previous studies (14, 16, 21-24). The surgery is conducted through median sternotomy with cardiopulmonary bypass under cardiac arrest (8). However, complete resection is not always possible due to diffuse nature of the tumor and wide involvement of the cardiac wall. Resection of wide regions of the heart may lead to irreversible cardiac failure which ultimately decreases the survival time (25).

The rule of chemotherapy is less defined in previous literature. In our study, we found that chemotherapy provides a survival advantage. The use of chemotherapy was higher in patients with distant disease in contrast to those with local tumors. Due to the tendency of the tumor to metastasize microscopically, multiple studies recommend adjuvant chemotherapy even after complete surgical resection with clear margins is performed (8, 25-27). Our data showed that chemotherapy was most likely used in younger patients. The reason can be explained by the fact that older patients have higher burden of co-morbidities which are less likely fitted for aggressive chemotherapy regimens and achievement of smaller impact on survival. Due to the absence of large-center clinical trials, chemotherapy regimens for cardiac sarcomas are often derived from noncardiac sarcoma counterpart data. The most commonly used regimen is doxorubicin+ifosfamide (8, 14). Weekly paclitaxel has also been shown to improve survival and provide up to 70% of tumor control in unresectable angiosarcoma (28).

Our data failed to show any survival advantage with radiotherapy. Moreover, radiotherapy treatment alone was not shown to improve survival in previous studies (25). However, Zhang et al. (21) reported improved prognosis for primary cardiac angiosarcoma treated with radiotherapy. Although postoperative adjuvant radiotherapy was effective in noncardiac soft tissue sarcoma, its role in cardiac sarcoma remains unclear and highly controversial in previous studies. This is mainly due to the high sensitivity of cardiac tissue to radiation injury. Exposure of ventricular wall to radiotherapy increases the risk for cardiac failure and cardiomyopathy (8). Our data showed a significant decrease in the use of radiotherapy for cardiac sarcoma patients after the year 2000, thus reflecting their receding use in management. The risk of side effects due to radiotherapy needs to be balanced against the poor outcome of these patients.

In line with other studies, we found no significant prognostic advantage for gender (14, 25). Similarly, race did not appear to improve prognosis in cardiac sarcoma patients. Younger age, on the other hand, showed a small survival advantage (HR=1.017 for every extra 1 year of age). Similar findings were reported in Randhawa et al. (14). They reported no statistical significance. Zhang et al. (21) reported worse outcome for patients aged >45 years diagnosed with primary cardiac angiosarcoma. Saad et al. (22) reported no significant survival advantage based on gender, age, and race among patients with cardiac NHL and angiosarcoma. The effect in our study is too small to be clinically relevant. Diagnosis of tumor in the year 2000 and after improved survival. This was in line with other studies that showed a similar trend (14, 29). This is explained by the earlier detection of the tumor through advanced imaging modalities and improvement in therapeutic strategies (14).

Despite its rarity, Figure 2 demonstrated (over the study period of 1975 to 2015) that the annual incidence has increased significantly. We suggest that this increase may be as a result of development and accessibility of cardiac imaging techniques including Echocardiography, Cardiac CT, and MRI in the last two decades, coupled with the presence of highly skilled physicians who are able to obtain cardiac biopsies. Similar findings were described by Zhang et al. (21). Saad et al. (22) found a significant increase in the annual incidence of cardiac non-Hodgkin lymphoma, but not cardiac angiosarcoma.

**Study limitations**

To the best of our knowledge, this is the largest and most updated cardiac sarcoma study available. However, the number of patients is still small. Although our results were based on data collected prospectively, this study remains retrospective. Finally, SEER database has limited information on radiotherapy and chemotherapy treatment status, which may limit the conclusions drawn from these two variables. With that in mind, our study does not advocate a certain treatment modality based on these data alone, but on randomized trials and prospective future studies in the same direction.

**Conclusion**

Primary malignant cardiac tumors are very rare and cardiac sarcoma represents the most common type, with angiosarcoma being the most reported histopathology. Over the past 40 years, the incidence of cardiac sarcoma has been on the increase. Cardiac sarcoma has a poor prognosis, since they start causing symptoms when they become aggressively advanced. Non-invasive imaging with Endomyocardial biopsy represents the most common diagnostic method. Complete surgical resection was shown to improve survival, thus remaining the mainstay of treatment for primary cardiac sarcoma. Adjuvant chemotherapy is recommended due to tendency of the tumor to metastasize...
microscopically and because it was shown to improve survival. Further studies are needed to compare different diagnostic and treatment modalities so as to ascertain the best treatment option that would enhance survival and prognosis of cardiac sarcoma.

**Availability of data and material:** The data that support the findings of this study are openly available in the Surveillance, Epidemiology, and End Results Program at https://seer.cancer.gov.

**Ethics approval:** Not required as this is a retrospective study using data from a public-access database.

**Conflict of interest:** None declared.

**Peer-review:** Externally peer-reviewed.

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