Surgical and multimodality treatment of cardiac sarcomas: A systematic review and meta-analysis

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Abstract

Introduction: Primary cardiac sarcomas (PCSs) are an extremely rare and aggressive type of malignancies that have been described only by a limited number of observational studies. This study aimed to evaluate the currently existing evidence comparing surgical to multimodality treatment of PCS.

Methods: We systematically reviewed Embase, MEDLINE, Cochrane Database, and Google Scholar, from inception to December 2020, for original articles about surgical and multimodality treatment of PCS. The outcomes included were mortality at various time points, resection margin status, and mean estimated survival. The pooled treatment effects were calculated using a random-effects model.

Results: Ten studies including a total of 1570 patients met our inclusion criteria. Surgery was associated with significantly lower mortality when compared to conservative treatment at 1, 2, and 3 years, whereas no significant difference was found at 5 years. Furthermore, multimodality treatment showed significantly lower mortality at 1 year when compared to surgery alone, but not at 2 and 5 years. We found no difference in mortality between angiosarcomas and other PCS subtypes.

Conclusion: Overall, surgery was found to provide a significant mortality advantage to PCS patients up to 3 years following treatment. Multimodality treatment might be of additional benefit, although only within the first year. Prospective randomized studies are needed to further explore these differences in the treatment of PCS.

Keywords

cardiac malignancy, cardiac sarcoma, cardiac tumor
Primary cardiac neoplasms are a rare entity with an incidence of 1.38 per 100,000, thereby being far less common than metastatic cardiac tumors. Malignancies account for a quarter of primary cardiac neoplasms, with sarcomas comprising between 75% and 95% of these. Usually found within the right atrium, primary cardiac sarcomas (PCSs) derive from mesenchymal cells and aggressively impact younger patients with a dismal prognosis. Presenting aggressively but initially asymptomatically, PCS can advance rapidly into a plethora of manifestations such as pulmonary hypertension and edema, congestive heart failure, chest pain, dyspnea, pericardial effusions, arrhythmias, and systemic symptoms of malignancy.

There exists an absence of conclusive clinical evidence for the optimal management of PCS due to the rarity of the disease, and, therefore, multimodal management has been largely guided by retrospective studies limited by small patient numbers and it is often principled by the therapeutic strategies for sarcomas of noncardiac origin. When feasible, complete surgical resection is central to the therapeutic strategies for PCS, as conservative therapy without surgery, radiotherapy, or chemotherapy has shown only a 10% survival rate at 9–12 months. However, even the surgical management of PCS is largely provisional with inconclusive efficacy as it is plagued by dismal multifactorial complications and contraindications, such as severe postsurgical morbidity, potential unresectability of the sarcoma and metastatic spread, and concerns of relatively insignificant increases in patient survival with a disproportionately greater fall in the quality of life. Complete surgical resection can also be accompanied by subsequent radiotherapy and chemotherapy, but despite this, PCS patients continue to have a poor prognosis with a median survival of less than 1 year.

We aim, for the first time, to assess the currently available evidence on the surgical and multimodality treatment of PCS.

METHODS

2.1 Literature search strategy

A systematic review was conducted in accordance with the Cochrane Collaboration published guidelines and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. A literature search was conducted of Embase, MEDLINE, Cochrane, PubMed, and Google Scholar from inception to December 2020 (Figure 1). The search terms used were: ("cardiac sarcoma" OR "heart sarcoma" OR "primary cardiac sarcoma" OR "cardiac malignancy" OR "heart malignancy") AND ("surgery" OR "cardiac surgery" OR "cardiothoracic surgery" OR "surgical treatment" OR "surgical resection" OR "resection" OR "multimodality treatment" OR "Treatment" OR "radiotherapy" OR "chemotherapy"). Further articles were
identified through the use of the "related articles" function on MEDLINE and a manual search of the reference lists of articles found through the original search. The only limits used were the English language and the mentioned time frame. Patient consent and Institutional Review Board (IRB) approval were not necessary for this study as no patients were deployed.

2.2 | Study inclusion and exclusion criteria

Both randomized and observational studies of patients undergoing surgical or multimodality treatment for PCSs were included. Studies were excluded from the review if (1) inconsistencies in the data precluded valid extraction, (2) all patients included in the studies did not receive a diagnosis of PCS, (3) the study was performed in an animal model, (4) studies did not have a comparison group, or (5) the size of the study population was small (<10 patients). Case reports, reviews, abstracts from meetings, and preclinical studies were excluded. By using the following criteria two reviewers (A.A.R. and A.T.L.) independently selected articles for further assessment after the title and abstract review. Disagreements between the two reviewers were resolved by a third independent reviewer (S.T). Potentially eligible studies were then retrieved for full-text assessment.

2.3 | Data extraction and critical appraisal of evidence

All full texts of retrieved articles were read and reviewed by two authors (A.A.R. and A.T.L.) and inclusion or exclusion of studies was decided unanimously. When there was disagreement, a third reviewer (S.T) made the final decision. Using a pre-established protocol, the following data were extracted: first author, study type and characteristics, number of patients, population demographics, tumor characteristics, and survival outcomes. For this review, a data extraction sheet was developed and pilot-tested on three randomly selected included studies, whereupon the sheet was refined accordingly. Data extraction was performed by two review authors (A.A.R. and A.L.). A third author (R.V.) validated the correctness of the tabulated data. Potential inter-reviewer disagreements were resolved by consensus.

2.4 | Data analysis

Odds ratios (ORs) with 95% confidence interval (CI) and p values for mortality at 1, 2, 3, 4, and 5 years were calculated. Forest plots were created to represent the clinical outcomes. χ² tests and I² tests were performed for assessment of statistical heterogeneity. The OR were combined across the studies using a Mantel–Haenszel random-effects model. Funnel plots were constructed to assess publication bias. All analyses were completed using the "metafor" package of R Statistical Software (version 4.0.2 (2020-06-22), Foundation for Statistical Computing, Vienna, Austria). A two-tailed p-value < .05 was considered statistically significant.

3 | RESULTS

3.1 | Study selection and characteristics

The literature search identified 1042 articles. Of these, 319 relevant articles were read in full and assessed according to our inclusion and exclusion criteria. Following the critical appraisal, a total of 10 studies incorporating a total of 1570 patients were included. The studies described outcomes of patients with a diagnosis of PCS who underwent either conservative, surgical, or multimodality treatment. Figure 1 illustrates the study selection process. All the studies included were retrospective non-randomized studies, with seven of them being multicentre (Table 1).9–11.15–18

3.2 | Baseline characteristics

Baseline characteristics of the patients included in the studies are summarized in Table 1. The mean age of the patients in the overall cohort was 47.8 ± 4.1 years, with 48.8 ± 6% of the patients being female. All the patients (100%) received a diagnosis of PCS: 33.3 ± 9.7% angiosarcoma reported in nine studies,9,11–18 13.6 ± 3.3% intimal sarcoma reported in four studies,12,13,15,16 11.6 ± 8.1% synovial sarcoma reported in nine studies,9–16,18 9.8 ± 6.3% spindle-cell sarcoma in four studies,9,14,15,17 7.3 ± 2.9% leiomyosarcoma in six studies,11–13,16–18 6.4 ± 5.4% myxoid liposarcoma in six studies,10–12,14–16 4.0 ± 2.3% osteosarcoma in three studies,13,15,18 and 4.0 ± 2.3% rhabdomyosarcoma in four studies.11–13

3.3 | Tumor and treatment characteristics

Characteristics regarding the PCS and the respective treatment details are provided in Table 2. On average the origin of the PCS was found: 36.2 ± 6.6% in the right atrium (RA), 34.9 ± 8.4% in the left atrium (LA), 9.1 ± 8.1% in the right ventricle (RV), and 7.2 ± 4.1% in the left ventricle (LV). Surgical resection of the cardiac sarcoma (alone or in conjunction with another treatment) was performed on an average in 68.8 ± 7.9% of the patients. Surgical resection alone was performed in 30.1 ± 17.2% of patients, chemotherapy alone was performed in 30.9 ± 16.9% of patients, and radiotherapy alone was performed in 13.8 ± 9.8% of patients. Patients’ surgical margin status was RX in 20.1 ± 13.0%, R0 in 15.5 ± 10.3%, R1 in 39.7 ± 25.4%, and R2 was achieved in 46.8 ± 10.4%. The mean survival time across studies of all patients diagnosed with PCS was of 15.4 ± 8.7 months.
### Table 1  Baseline patient characteristics and types of angiosarcoma

| Study        | Year | Study characteristics | Population number | Mean Age | Female (%) | Angiosarcoma (%) | Synovial sarcoma (%) | Myxoid liposarcoma (%) | Rhabdomyosarcoma (%) | Leiomyosarcoma (%) | Osteosarcoma (%) | Intimal sarcoma (%) |
|--------------|------|-----------------------|-------------------|----------|------------|------------------|------------------------|-----------------------|----------------------|------------------|------------------|---------------------|
| Truong et al. | 2009 | NR, M, NP             | 16                | 51       | 63         | 25               | 13                     | NA                    | NA                   | NA                 | NA                | NA                  |
| Hamidi et al. | 2010 | NR, M, NP             | 210               | NA       | 44         | NA               | 3                      | 3                     | NA                   | NA                 | NA                | NA                  |
| Isambert et al. | 2013 | NR, M, NP             | 124               | 47       | 44         | 32               | 6                      | 2                     | 6                   | 13                | NA                | NA                  |
| Li et al.    | 2014 | NR, NM, NP            | 29                | 41       | NA         | 28               | 17                     | 7                     | 3                   | 7                | NA                | 14                  |
| Randhawa et al. | 2014 | NR, NM, NP           | 42                | 50       | 48         | 21               | 17                     | NA                    | 2                   | 5                | 5                 | 10                  |
| Wu et al.    | 2018 | NR, NM, NP            | 12                | 43       | 50         | 41               | 25                     | 17                    | NA                   | NA                | NA                | NA                  |
| Aboud et al. | 2019 | NR, M, NP             | 17                | 54       | 41         | 24               | 17                     | 6                     | 6                   | NA                | 6                 | 18                  |
| Chen et al.  | 2019 | NR, M, NP             | 61                | 46       | 54         | 39               | 3                      | 3                     | 2                   | 7                | NA                | 13                  |
| Hendriksen et al. | 2020 | NR, M, NP         | 617               | 51       | 48         | 48               | NA                     | NA                    | NA                   | 6                 | NA                | NA                  |
| Yin et al.   | 2020 | NR, M, NP             | 442               | 47       | 48         | 43               | 4                      | NA                    | 5                   | 7                | 1                 | NA                  |

Abbreviations: M, multicentre; NA, not available; NM, non-multicentre; NP, non-prospective; NR, non-randomized; P, prospective, R, randomized.
## Table 2  Tumor and treatment characteristics

| Study               | Year | RA tumor origin (%) | LA tumor origin (%) | RV tumor origin (%) | LV tumor origin (%) | Margin status R0 (%) | Margin status R1 (%) | Margin status R2 (%) | Surgery (%) | Surgery only (%) | Chemotherapy only (%) | Radiotherapy only (%) | Median survival (month) |
|---------------------|------|---------------------|--------------------|--------------------|--------------------|----------------------|----------------------|----------------------|--------------|---------------------|------------------------|------------------------|------------------------|
| Truong et al.⁹      | 2009 | 44                  | 38                 | 6                  | 13                 | NA                   | NA                   | NA                   | 81.3         | 50                  | 18.8                   | NA                     | 8                      |
| Hamidi et al.¹⁰      | 2010 | NA                  | NA                 | NA                 | NA                 | NA                   | NA                   | NA                   | 59.6         | NA                 | NA                     | 23.8                   | 6                      |
| Isambert et al.¹¹    | 2013 | 37                  | 39                 | 6                  | 8                  | 8                    | NA                   | NA                   | 65.3         | 6.5                | 25.6                   | NA                     | 17.2                   |
| Li et al.¹²          | 2014 | 34                  | 41                 | 3                  | 3                  | 31                   | 31                   | 38                   | NA           | NA                 | 24.1                   | 3.5                    | 17                     |
| Randhawa et al.¹³    | 2014 | NA                  | NA                 | NA                 | NA                 | 14                   | NA                   | NA                   | 71.4         | 19                 | 16                     | 2                      | 25                     |
| Wu et al.¹⁴          | 2018 | 40                  | 20                 | NA                 | NA                 | 8                    | 33                   | 58                   | NA           | NA                 | 47.8                   | 7.7                    | 12                     |
| Aboud et al.¹⁵       | 2019 | 26                  | 37                 | 21                 | 5                  | 6                    | 77                   | NA                   | NA           | NA                 | 64.7                   | 23.5                   | 3.7                    |
| Chen et al.¹⁶        | 2019 | NA                  | NA                 | NA                 | NA                 | 8                    | 18                   | 44                   | 75           | NA                 | 18                     | NA                     | 17.5                   |
| Hendriksen et al.¹⁷  | 2020 | NA                  | NA                 | NA                 | NA                 | 25                   | 41                   | NA                   | 60.3         | 25.3               | 15.6                   | 2.8                    | 11                     |
| Yin et al.¹⁸         | 2020 | NA                  | NA                 | NA                 | NA                 | NA                   | NA                   | NA                   | 49.8         | 47.7               | 22.4                   | 7                      |

Abbreviations: LA, left atrium; LV, left ventricle; NA, not available; RA, right atrium; RV, right ventricle.
3.4 | Mortality: Surgical treatment versus no surgery

Surgery (alone or in conjunction with other treatments) was compared to no surgery (conservative, chemotherapy, or radio-chemotherapy), with three studies\(^\text{1,16,17,18}\) reporting mortality at 1, 2, and 3 years, and four studies\(^\text{15,17,18}\) reporting mortality at 5 years (Figure 2). There was evidence of moderate heterogeneity of treatment among studies at 1 year (Figure 2A). However, there was no evidence of heterogeneity of treatment among studies at 2, 3, and 5 years (Figure 2B-D). The pooled effect at 1 year showed significantly lower mortality with surgery compared to the no surgery group (random-effects model: 0.31; 95% CI: 0.13–0.77; p = .031). The pooled effect at 2 and 3 years both showed a significant lower mortality with surgery when compared to no surgery (random effects at 2 years: 0.25; 95% CI: 0.11–0.60; p = .021) (random effects at 3 years: 0.32; 95% CI: 0.11–0.89; p = .041). The pooled effect at 5 years did not show any significant difference between the surgery and no surgery group (random effects: 0.39; 95% CI: 0.14–1.06; p = .058).

3.5 | Mortality: Surgery alone versus multimodality

Surgery alone was compared to multimodality (surgery plus chemotherapy and/or radio-chemotherapy), with six studies reporting mortality at 1, 2, 12, 14, 15, 17, 18 and 2 years,\(^\text{12–15,17,18}\) reporting mortality at 3, 4, and 5 years (Figure 3). There was no evidence of heterogeneity of treatment among studies at 1, 3, 4, and 5 years, while there was low evidence of low heterogeneity of treatment at 2 years. The pooled effect at 1 year (Figure 3A) showed a significant lower mortality with multimodality treatment compared to surgery alone (random-effects model: 3.31; 95% CI: 2.25–4.94; p = .001). The pooled effect at 2, 3, 4, and 5 years (Figure 3B-E) all showed no significant mortality difference between surgery and multimodality (random effects at 2 years: 1.06; 95% CI: 0.49–2.27; p = .859) (random effects at 3 years: 1.11; 95% CI: 0.69–1.79; p = .570) (random effects at 4 years: 0.77; 95% CI: 0.46–1.32; p = .251) (random effects at 5 years: 0.78; 95% CI: 0.20–3.10; p = .517).

3.6 | Mortality: Angiosarcoma versus other types of PCS

Mortality outcomes of angiosarcoma were compared to other sarcoma types group at 1 and 2 years as reported by four studies.\(^\text{1,16–18}\) The evidence of moderate heterogeneity among studies at 1 and 2 years. The pooled effect at 1 year (Figures 4A and 2 years (Figure 4B) showed no significant difference in mortality between angiosarcoma patients and other cardiac sarcoma patients (random-effects model at 1 year: 1.23; 95% CI: 0.60–2.53; p = .421) (random-effects model at 2 years: 2.12; 95% CI: 0.96–4.65; p = .056).

3.7 | Results from multivariate analysis

Due to the data available being too limited, running a sensitivity analysis based on adjusted estimates from the multivariate regression was not feasible. Nevertheless, we report the respective adjusted hazard ratios (aHRs) of studies where available. Two studies reported aHR for surgery alone versus multimodality, Hendriksen et al.\(^\text{17}\) (HR, 0.68; 95% CI: 0.5–0.91; p = .009) and Chen et al.\(^\text{16}\) (HR, 0.72; 95% CI: 0.35–1.48; p = .38). Three studies reported HR for surgery versus no surgery, Chen et al.\(^\text{16}\) (HR, 0.93; 95% CI: 0.35–2.46; p = .89), Isambert et al.\(^\text{17}\) (HR, 1.14; 95% CI: 0.45–2.91; p = N/A) and Yin et al.\(^\text{18}\) (HR, 0.49; 95% CI: 0.37–0.64; p < .001). Two studies reported HR for angiosarcoma versus other types of PCS, Yin et al.\(^\text{18}\) (HR, 1.15; 95% CI: 0.88–1.5; p = .303) and Chen et al.\(^\text{16}\) (HR, 0.93; 95% CI: 0.37–2.36; p = .89).

3.8 | Risk of bias across studies

Funnel plot analysis (Figures S1, S2, and S3) did not disclose asymmetry around the axis for the treatment effect in any of the studied outcomes. Consequently, publication bias related to these outcomes is unlikely. We found no evidence for publication bias, Egger's as well as Begg and Mazumdar tests were not significant for any of the meta-analyses. Funnel plots are available in the Supporting Information section.

![FIGURE 2](forest_plots.png)

**FIGURE 2** Forest plots. Pooled odds ratio and conclusions plot for (A) 1-year mortality, (B) 2-year mortality, (C) 3-year mortality, (D) 5-year mortality. “conservative”: no surgery received; “surgery”: patients who received patients (alone or with other treatments). CI, confidence interval.
DISCUSSION

4.1 Summary of evidence

To our knowledge, this is the first meta-analysis of studies performed to date focussing on the surgical treatment of PCSs. Only a limited number of studies, all observational in nature, and most with a small number of patients exists on the current subject, thus all findings should be interpreted with caution. We found significantly lower mortality at 1, 2, and 3 years when surgery (alone or in conjunction with other treatments) was compared to no surgery (conservative, chemotherapy, or radio-chemotherapy) for the treatment of PCSs. No significant difference between surgery versus no-surgery was found at 5 years postoperatively. We also found significantly lower mortality at 1 year when surgery alone was compared to multimodality treatment (surgery plus chemotherapy and/or radiotherapy). However, no significant difference between surgery and multimodality treatment was found at 2, 3, 4, and 5 years postoperatively. When mortality outcomes of angiosarcomas were compared to the ones of other PCS types, no significant difference at
1 and 2 years were found. Although we intended to analyze with more granularity differences in mortality within the multimodality group, and provide an analysis of postoperative morbidity, the following was not possible due to inconsistencies and the general scarcity in the data reported.

4.2 | PCS: Some comments

PCSs are extremely rare entities, which have been described only by a limited number of observational studies, making both their prognostic outcomes data and their clinical presentation data scarce and prone to bias. In line with previously published clinical studies, our analysis showed that PCSs were found to occur at a relatively young age of 47.8 ± 4.1% years and were almost equally spread across sexes, with 48.8 ± 6% of the patients being female. Likewise, angiosarcomas were found to be the most prevalent type of PCS, standing at 33.3 ± 9.7% prevalence. The following data allows us to compare PCS with noncardiac sarcomas data, indicating the differences both in the age of presentation and the pathological sarcoma subset prevalence. Indeed, patients present at a younger age in PCS when compared to noncardiac sarcoma, with angiosarcoma (vessel neoplasms) being the most prevalent subtype in PCS, while only representing a limited fraction of noncardiac sarcomas. In accordance with the literature, PCS was found to arise mostly in the atria, with a similar distribution between left and right atrium (36.2 ± 6.6% in RA; 34.9 ± 8.4% in LA). The current literature found cardiac sarcomas situated on the right side of the heart to be more bulky, infiltrative, and to lead to earlier metastasis when compared to left-sided PCS, thus also leading to worse outcomes.

4.3 | Surgery or no surgery?

Surgical resection of PCS has been long considered the gold standard treatment for PCS in eligible patients without metastasis at diagnosis. The operation is usually carried out through a median sternotomy, minimal touch technique, and with the use of cardiopulmonary bypass with cardioplegia. Thus, surgical resections remain often the main treatment choice with 68%–77% of the patients reported to be receiving tumor resection, according to our analysis results. However, PCSs are often extremely invasive in nature, making surgical resection and reconstruction particularly complicated and leading to poor outcomes. Indeed, the median survival of PCS patients has been reported in the literature to range between 6 and 18 months, with our analysis showing an average survival of 15.4 ± 8.7 months across studies.

Despite the known complications and risks of surgical resection, this treatment remains essential for the survival of patients beyond the short term (>12 months), with numerous among the published studies illustrating significant survival advantage in patients receiving complete resection of the tumor. Regardless of any post-surgical treatment, patients who are not eligible for full tumor resection have indeed been found to have a mortality of up to 90% within the first year. A single-institution study by Simpson et al. along with similar findings in other studies have reported patients receiving complete surgical resection to have around double the survival of patients without complete resection. Even when interpreting study results, surgical resection margin remains a crucial point of consideration. Bakeen et al. in their study reported a very encouraging 2 years survival rate of 62% in their patients, however, 96% of the patients had R0/R1 resection status, thus possibly explaining the results. Nevertheless, complete surgical resection of PCS is not always feasible, partially due to do the low experience levels when dealing with extensive cardiac resection and partly due to the uncertainty about the diagnosis at the initial surgical exploration stage. Bakeen et al. reported two-thirds of their patients to have received inadequate previous cardiac resection. The trend has also been observed through our analysis with the only R0 being only 15.5 ± 10.3%, R1 being achieved in 39.7 ± 25.4%, and R2 achieved in 46.8 ± 10.4%.

Overall, the findings of this analysis support surgery (when indicated) as an essential part of the treatment plan for patients with PCS. Indeed, as already outlined, significantly lower mortality levels both at 1, 2, and 3 years were found in patients who received surgery either on their own, or in conjunction with other treatments, when compared to patients who only received conservative management or chemotherapy and/or radiotherapy.

4.4 | Surgery versus multimodality treatment

The evidence with regard to the pre- and postoperative treatment of cardiac sarcoma remains scarce and highly controversial. Due to its extremely rare prevalence, no prospective study currently exists reporting on the benefits of radiotherapy, chemotherapy, or chemoradiation. Furthermore, the marked differences between PCS and noncardiac sarcoma make data extrapolation from larger studies on noncardiac sarcoma difficult and not always a feasible option. However, postoperative chemotherapy after surgical resection tends to be recommended even in cases of complete resection with clear surgical margins, mainly due to the possibility of malignant tissue being left. The data on the chemotherapeutic regimens used usually tends to be derived from prospective clinical trials carried out on noncardiac sarcoma patients.

On the one hand, studies have been advocating for a multimodal approach, including surgery and chemotherapy and/or radiotherapy, referring to advantages in terms of survival in the multimodality group. Randhawa et al. found patients undergoing multimodality treatment to have more than twice the survival of patients only treated surgically (36.5 month vs. 14.1 month). On the other hand, other case series and retrospectives studies found no survival advantage in a multimodality approach when compared to surgery on its own.

Our results have for the first time, summarized the evidence available with regard to the multimodality treatment of PCS.
when compared to surgery only. Due to the nature of the data, it was not possible to differentiate between the different subtypes of "multimodality treatment" which were given additionally to surgery. Nevertheless, our results serve as a basis for future prospective and larger scale retrospective studies to take into consideration. Indeed, significantly lower mortality was found only at 1 year postoperatively (Figure 3), while no significant differences were noted from 2-5 years. These results should, however, be interpreted with caution, especially taking into consideration the retrospective nature of the studies and their small scale. Indeed, the therapy selected for each patient might have been related to the predicted prognosis, thus potentially introducing a bias. Furthermore, currently no standardized approach to chemotherapeutic regimens exists. So far, there is no standardized therapy regimen for malignant heart tumors due to the lack of prospective studies with statistically relevant case numbers. The evaluation of the therapy options is therefore difficult and should always be discussed individually for each patient.

4.5 | Mortality in angiosarcoma

Another area of controversy around PCS is the severity of angiosarcoma and its association with a worse prognosis. Angiosarcomas, an endothelial cell tumor, have been found to be the most common type of PCS according to the literature, also supported by the results of our analysis. Their prevalence has been found to range anywhere from 21% to 48% of all PCSs.9-18 They mostly originate in the right atrium and appear as a multicentric mass.21 Similar to other PCSs, they tend to infiltrate into surrounding cardiac tissues, and rapidly metastasize into the lungs, thus making surgical resection a complex option.20 It is indeed due to the complexity of the surgical resection and invasiveness into surrounding structures, including the atrial chamber, the vena cava, and the tricuspid valve, that they are believed to lead to a worse prognosis. Furthermore, the prognosis of angiosarcoma is often poor due to the delayed diagnosis in the presence of metastases. The mean expected survival of angiosarcomas without surgical resection has been found to be of 3.8 ± 2.5 months.31 While surgical resection of angiosarcomas leads to a better prognosis, achieving complete resection remains a known difficulty. The benefits of multimodality treatment in the setting of angiosarcoma are currently unknown, with no standardized chemotherapy regimen established yet. In individual cases, especially in non-metastatic ones, a heart transplant could be considered.22 However, studies have indicated that it did not lead to what was hoped for in terms of survival advantage.33 The survival rate here was comparable to that of patients under palliative care. The results of our analysis indicated no significant difference in mortality at 1 and 2 years when angiosarcomas were compared to other subtypes of PCS. It is important to interpret these results with caution due to the nature of the data, inconsistencies in data reporting, and treatment regimens.

4.6 | Further comments

It is of utmost importance to consider the fact that the outcomes of PCS can be the result of diverse factors, not all of them being necessarily associated with the nature of the treatment itself. Similarly, the degree of impact of covariates and of patient characteristics should not be underestimated. Selection bias remains a point of concern with regards to the data available within this field of research. Indeed, it could be argued that more fragile patients would have been assigned to conservative or nonsurgical treatment, while healthier patients would have undergone surgical treatment of PCS. Therefore, the results of this meta-analysis should be interpreted with caution and consideration should be made on the effects of potential selection bias. In our meta-analysis, we found a mortality advantage from Year 1 to Year 3 with surgery when compared to no surgery; confirming these findings, Yin et al.18 found that the aHR for surgery was significant. However, these findings could not be confirmed in the adjusted Cox regression by Chen et al.16 Similarly, a 1-year mortality advantage was found with multimodality treatment, as confirmed by the aHR by Hendriksen et al.,17 but not confirmed by Chen et al.16

4.7 | Limitations

A major limitation of the evidence included in our review is the non-randomized and retrospective nature of all the studies, with most of them having a small number of patients, thus increases the risk of biases. Moreover, current data were too limited to run a sensitivity analysis based on adjusted estimates from the multivariate regression. Furthermore, no current consensus and standardized chemotherapeutic or radiotherapeutic regimen currently exists for PCS, with differences among them between studies being present. The same was valid with regard to differences in surgical resection and reconstruction techniques used for PCS. Furthermore, due to the nature of the data and inconsistencies in reporting it was not possible to compare the outcomes of the different subtypes in the multimodality treatment group. Considerable statistical heterogeneity is present for some outcomes, which we counterbalanced by using the random-effects model.

5 | CONCLUSION

Surgery has been found, in line with the previously published evidence, to provide a mortality advantage when compared to no surgery at 1–3 years in patients with a diagnosis of PCS. Multimodality treatment was only found to provide lower mortality rates at 1 year,
with no significant difference at 2, 3, 4, and 5 years. Although the data of this metanalysis should be interpreted with caution due to numerous outlined limitations, they serve as a baseline for future prospective studies to be carried out to assess differences in treatment outcomes for PCS patients.

CONFLICT OF INTERESTS
The authors declare that there are no conflict of interests.

SUPPORTING INFORMATION
Additional Supporting Information may be found online in the supporting information tab for this article.

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