

Peer Review File

Article information: <https://dx.doi.org/10.21037/jtd-23-1054>

Reply to Reviewer A

Thank you for the opportunity to review this paper which looks to describe outcomes for patients with primary malignant cardiac tumours. My comments follow:

Authors: Thank you for your patient and careful comments, which have well demonstrated your unique academic insights and profound academic attainments, brought great enlightenment and help to our scientific research ideas. We have thoroughly revised the manuscript according to your requirements, hoping to meet your requirements. Here's my point-to-point response to your questions:

Comment 1: Abstract-The results section is quite dense and difficult to read and although your present differences between the groups there is no reference to actual survival.

Reply 1: Thank you for your comments. In this report, we noted that the survival rate of pmct was significantly different between different age groups. Survival time was shorter in older patients than in younger patients for all pathologic types. In addition, the survival efficiency was better in patients treated with combination therapy. Considering this paper as a retrospective study, we plotted survival curves according to different subgroups to describe the survival of patients in the cohort. We modified the abstract section to increase the readability of the article.

Changes in the text:

Results: Survival rates for PMCTs differed significantly between age groups, with patients younger than 20 years surviving significantly longer than those older than 80 years. The median survival times of all patients with PMCTs were 22.5, 11, 5, and 1 month for ages less than 20, 20-50, 51-80, and greater than 80 years, respectively (global log-rank $P=0.0026$). In the treatment cohort, for all tumors (HR 1.52, $P<0.001$), sarcomas (HR 1.83, $P=0.002$), and other tumors (HR 2.24, $P=0.017$), survival was lower in patients who did not receive treatment than in those who received only surgery. Survival after diagnosis of sarcoma was lower in patients who received radiotherapy only than in those who received surgery only (HR 1.49, $P=0.046$). However, there was no significant association between treatment and survival for lymphoma and mesothelioma.

Comment 2: Throughout- There are some strange words throughout e.g. line 94, 146, 149, 150, 151 etc...

Reply 2: We are very sorry for some garbled characters in the middle of the article for some unknown reason, we have carefully corrected the whole article.

Changes in the text:

- 2.1 In this report, we described the survival differences between different ages and ...
- 2.2 (b) other unspecified malignant tumors, not classified by ICCC or in situ.
- 2.3 Patients who received radiation therapy (RT) and surgery were identified based on SEER variables.
- 2.4 Receipt of RT was defined as beam radiation or radiation (NOS method or source not specified...
- 2.5 patients who did not receive RT treatment were defined as none or refused.
- 2.6 Survival was defined as the time between diagnosis and death through 31 December 2013.
- 2.7 Chi-square test was used assess significance of the difference between proportions in demographic and tumor characteristics by age and treatment.
- 2.8 However, there was no difference in survival between the 20–50 years and 51–80 years age groups...
- 2.9 However, no significant association was observed between treatments and survival for patients diagnosed with lymphomas and mesothelioma...

Comment 3: Methods - Perhaps a table to describe the registries used and the tumour types would be better than spelling them all out in the sentences of the methods which is not very readable.

Reply 3: Thanks for your comments, we decided to follow your suggestion and add a table to make the article more readable.

Changes in the text:

Other PMCTs were defined as Code I (e), III (c.2), IV (b), VII (b), VIII (d.2), X (b.2), X (b.4), XI (f.10), XII (b), and tumors which were not classified by ICCC or in situ (Table S1).

Table S1 Histopathology of PMCTs differentiate by the ICCC site recode extended ICD-0-3/WHO 2008

Table S1. Histopathology of PMCTs by groups.

Histopathology (ICCC site recode extended ICD-O-3/WHO 2008)
Sarcoma
IX (d.8) Blood vessel tumors
IX(e) Unspecified soft tissue sarcomas
IX (d.6) Leiomyosarcomas
IX (d.7) Synovial sarcomas
IX (b.1) Fibroblastic and myofibroblastic tumors
IX (d.11) Miscellaneous soft tissue sarcomas
IX (a) Rhabdomyosarcomas
IX (d.4) Liposarcomas
IX (d.5) Fibrohistiocytic tumors
Lymphoma
II (a) Hodgkin lymphomas
II (b.1) Precursor cell lymphomas
II (b.2) Mature B-cell lymphomas except Burkitt lymphoma
II (b.3) Mature T-cell and NK-cell lymphomas
II (b.4) Non-Hodgkin lymphomas, NOS
II (c) Burkitt lymphoma
II (d) Miscellaneous lymphoreticular neoplasms
II (e) Unspecified lymphomas
Mesothelioma
Others
III (c.2) PNET
IV (b) Other peripheral nervous cell tumors
I (e) Unspecified and other specified leukemias
VII (b) Hepatic carcinomas
VIII (d.2) Malignant chordomas
X (b.2) Malignant teratomas: extracranial/extragonadal
X (b.4) Yolk sac tumor: extracranial/extragonadal
XI (f.10) Carcinomas of other specified sites
XII (b) Other unspecified malignant tumors
Not classified by ICCC or in situ

PMCTs, primary malignant cardiac tumors; ICCC, International Classification of Childhood Cancer; WHO, World Health Organization.

Comment 4: How were the tumours diagnosed. I would suggest statistical review of the method to only use the chi squared test. Why not use ANOVA or other test rather than using categorical for all these variables?

Reply 4: Thank you for your comments. All data for this study were obtained from public databases. The chi-square test is used to test whether a categorical variable obeys a hypothesized distribution. ANOVA was used to determine if the means of multiple independent groups were significantly different. The chi-square test is used when each variable selected is a categorical variable. ANOVA is used when there is at least one categorical and continuous variable. In this study we categorized age into four age groups and will regard age as a non-continuous variable, so the chi-square test was used.

Results

Comment 5: - Line 213 you mention patients diagnosed with lymphoma were not treated. why is that? not even with steroids? why were they not treated?

- you highlight that treatment choice varied with age - does that not just reflect the tumour type differences between the ages?

Reply 5: All cases in this study were taken from public databases, which provide data that patients diagnosed with lymphoma were not treated. There may have also been many lymphoma patients that received treatment, but we did not obtain information on this subset of patients from public databases. Similarly we do not have data on the treatment of asteroids to analyze. Based on the information available, we looked at differences in the age of patients at initial diagnosis for survival analyses, not to compare differences in survival between patients with different tumor types.

Comment 6: - Line 231 - how did you adjust for subtype, treatment etc? what method was used?

- How were these tumours staged? Were they staged? Does this not have an important impact on treatment decisions and outcome - this point seems to have not been considered at all by the paper but clearly is important for decisions on treatment and then on the survival etc.

- This paper covers 5 decades where diagnosis, treatment and outcomes will have changed impacting on these results.

Reply 6: We used age differences and treatment modalities to adjust for subgroups. First of all, PMCTs is not one type of cancer, there are multiple pathologic types, we first separated the studies by pathologic type and then adjusted the subgroups using age differences and treatment modalities, the studies were all aimed at finding survival differences. Due to the rarity of PMCTs disease, the number of cases we were able to include was insufficient, and subgrouping again would have resulted in too small a number of patients with multiple pathologic types, making it difficult to generalize conclusions. Therefore, no further subgroup analysis was performed to analyze the pathological staging of the patients. Pathologic staging is undeniably important for therapeutic decisions and survival, among other things, and this is one of the limitations of this study.

Comment 7: Discussion: There are a number of very bold and definitive claims made that I dont think are supported by the results. Without consideration of tumour stage, how can any comparison be made of outcomes? You mention for example, that <20 have better survival because they are diagnosed earlier - why should that be? how do you know that? I am not sure I follow this argument?

I think that you have an interesting data set on a large number of primary cardiac tumours, but I wonder if this should be analysed in a different way. Perhaps in a more descriptive manner

looking at the different types of cardiac tumours and looking at the demographics and treatment used etc - ie looking at the data from a different perspective - presenting more of a descriptive analysis of primary cardiac tumours, demographics and outcomes etc, rather than trying to find differences between ages etc, when I dont think you have resolution of the data to do that.

Reply 7: Thank you for your comment, you have brought forward a very important aspect, i.e., the effect of tumor staging on survival, in addition to the fact that different types of cardiac tumors should be studied in a more descriptive way, i.e., looking at the data from different perspectives, with more descriptive analyses of primary cardiac tumors, demographics, and outcomes, etc., which has inspired us for subsequent studies and has guided us very well for future in-depth studies. Considering the low prevalence of cardiac tumors, it is difficult to collect a larger number of cases into the study, and considering multiple factors, too many subgroups may easily lead to too small a sample size for certain subgroups, and the chance factor is large and insufficient to illustrate the problem. In addition, there is a lack of evidence that the pathological staging of cardiac tumors is related to age. However, it is undeniable that the survival of patients is closely related to the pathological staging of the tumor, which will be the focus of our subsequent studies.

Reply to Reviewer B

I found this manuscript to be very intriguing. Although it has several limitations, it is a meaningful paper as it demonstrates that the prognosis of malignant heart tumors in young individuals is better compared to elderly patients. While various factors such as tumor type and treatment methods influence the prognosis, it was somewhat surprising to see that young patients have a more favorable outcome. However, even though the prognosis is considered good, based on the results of this paper, it can be said that even young patients with a positive prognosis may only survive for up to three years, despite combining all current treatment methods.

In the future, understanding the mechanisms of malignant tumor development and discovering preventive measures and fundamentally different treatment approaches from current ones will be the key challenges.

Authors: Thank you for your patient and careful comments, which have well demonstrated your unique academic insights and profound academic attainments, brought great enlightenment and help to our scientific research ideas. We have revised the manuscript according to your requirements, hoping to meet your requirements.

Comment: I am curious about the statement in the abstract's conclusion that 'Minimally invasive diagnostic techniques or circulating tumor assays may be necessary for early diagnosis and treatment decisions.' Has there been sufficient evidence established in this paper to support that early detection improves the prognosis? It seemed a bit abrupt and possibly an overstatement.

Reply: Thank you very much for your comment and we note that such a statement is

inappropriate. Our intent was that techniques for early diagnosis and treatment may be necessary. We believe that early diagnostic and therapeutic techniques such as Minimally invasive diagnostic techniques or circulating tumor assays may help prolong the survival of patients with cardiac tumors. So we have reworked our conclusions.

Changes in the text:

This study confirms that PMCTs have limited treatment options and poor patient survival, especially for elderly patients and patients who receive no treatment. And patients with PMCT of any age, whether treated or not, have poor survival rates. Techniques for early diagnosis and treatment may be necessary. Surgical treatment should have a higher priority for future treatment of patients with sarcomas.

Reply to Reviewer C

This observational cohort study used data from the US Surveillance, Epidemiology, and End Results (SEER) cancer registries in order to describe survival in patients with primary malignant cardiac tumors in relation to age and treatment strategy. Patients were diagnosed from 1973 to 2013.

Data were obtained in 2018 from 18 US cancer registries, and 696 patients with primary malignant cardiac tumors were identified. Survival status was available until 2013.

52 patients were excluded because they were lost to follow up; 101 patients had other/multiple tumors, and 14 patients did not have information on treatment and were also excluded resulting in a final study population of 529 patients.

Survival was analyzed according to age groups and treatment, respectively.

This was an interesting research question and a large study population given that primary malignant cardiac tumors are rare. Important limitations include the very long study period, and the lack of granular patient/tumor/treatment data because this information was not available in the SEER databases.

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Comment 1: The authors may consider adding data from the Human Mortality Database (<https://www.mortality.org/>) to illustrate the difference between survival in the study population and the age-, sex-, and calendar year matched general population. The hazard ratios in Table 3 tells us that older patients (above 80 y) have higher risk of death compared to younger (20-50 y, i.e., the reference category) which is not particularly informative.

Reply 1: Thank you very much for your suggestion, we went to the Human Mortality Database

(<https://www.mortality.org/>) and tried to add some research data. We found that the database This dataset contains national or regional data on all-cause mortality after 2015 collected from a variety of sources, which is a huge amount of data but upon examination it was found that the dataset was not very helpful for this study, mainly because of the large differences in mortality rates across historical periods, it led to the results of our analysis of analyzing the differences in survival rates between the study population and the age-, sex-, and calendar year-matched general population were not convincing.

Comment 2: The authors may want to analyze the effect of age as a continuous variable (in addition to age categories) because categorizing of a continuous variable leads to loss of information.

Reply 2: In this study we divided the age into 4 age groups to investigate the differences in survival of patients in different age groups.

Comment 3: Figure 1 and 2 lacks a “Number at risk” table. Although the study was interesting, the findings were not new (see for example: Sultan I, Bianco V, Habbertheuer A, Kilic A, Gleason TG, Aranda-Michel E, et al. Long-Term Outcomes of Primary Cardiac Malignancies: Multi-Institutional Results From the National Cancer Database. J Am Coll Cardiol 2020;75:2338–47. <https://doi.org/10.1016/j.jacc.2020.03.041>).

Reply 3: Thank you very much for your comment, and we are also concerned about this article you mentioned, and it is undeniable that there are some similarities in our studies, mainly due to the fact that primary cardiac tumors are very rare, and there is less information of all kinds, and insufficient data available for analysis, so it is inevitable that there is a crossover in the conclusions of the studies. The article you refer to focuses on the higher survival of patients who underwent surgery and perioperative chemotherapy for stage III disease compared to patients who did not undergo surgery and does not reflect the difference in age of the patients, which is why we recommend the development of early screening and related diagnostic and treatment techniques, as we found that the mortality rate of older patients is higher and varies by tumor type.

Reply to Reviewer D

Authors: Thank you for your patient and careful comments, which have well demonstrated your unique academic insights and profound academic attainments, brought great enlightenment and help to our scientific research ideas. We have revised the manuscript according to your requirements, hoping to meet your requirements.

Comment 1: This study explored the relationship between patient age, treatment, and survival of PMC using data from the largest cancer registry in the US. The manuscript is well written, the clinical bottom line adds to the current knowledge on the topic and might be of interest for a wide range of readers within different areas of expertise. Limitations are also well stated (retrospective nature, long time frame, poor patients characterization, limited features of

treatment algorithms). All in all the manuscript might deserve publication in the present form after careful revision for several typos.

Reply 1: We are very sorry for some garbled characters in the middle of the article for some unknown reason, we have carefully corrected the whole article.

Changes in the text:

- (1) In this report, we described the survival differences between different ages and ...
- (2) (b) other unspecified malignant tumors, not classified by ICCC or in situ.
- (3) Patients who received radiation therapy (RT) and surgery were identified based on SEER variables.
- (4) Receipt of RT was defined as beam radiation or radiation (NOS method or source not specified...
- (5) patients who did not receive RT treatment were defined as none or refused.
- (6) Survival was defined as the time between diagnosis and death through 31 December 2013.
- (7) Chi-square test was used assess significance of the difference between proportions in demographic and tumor characteristics by age and treatment.
- (8) However, there was no difference in survival between the 20–50 years and 51–80 years age groups...
- (9) However, no significant association was observed between treatments and survival for patients diagnosed with lymphomas and mesothelioma...

Reply to Reviewer E

Interesting job. The authors Wang W et al. present an accurate analysis of data on the medical treatment with and without surgery of patients affected by primary malignant heart tumor, mainly based on age, type of malignant tumor, but also with stratification of the risk of late mortality by other factors. The study is observational with analysis of a very large sample of patients (n=529) (considering the type of pathology). The main value of the study is related to the length of the follow-up and the analysis performed on survival. Although the authors conclude that the best survival is obtained with surgery compared to oncological medical therapy alone in sarcomas and in very young patients (which in any case are a small number, N = 34), the difference in effect, just looking at the graphs of the Figures, turns out to be slightly for the benefit of surgery. The work may therefore be useful to guide a surgical choice in younger patients and in the presence of lesser extent of the neoplastic disease, always considering, however, that survival is in any case very compromised already at 5-10 years of follow-up, both after treatment surgical than without the latter.

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Comment 1: Suggestions: write more clearly in the conclusions that survival is, in any case, very reduced even after surgical treatment.

Reply 1: Thank you very much for your advice, which is very good, and our study does illustrate that survival rates are greatly reduced anyway, even after surgical treatment. We have decided to take your advice.

Changes in the text:

This study confirms that PMCTs have limited treatment options and poor patient survival, especially for elderly patients and patients who receive no treatment. And patients with PMCT of any age, whether treated or not, have poor survival rates. Techniques for early diagnosis and treatment may be necessary. Surgical treatment should have a higher priority for future treatment of patients with sarcomas.

Comment 2: Check for small errors in the text: e.g. Lines 94, 146-152, 161, 221, 225, 253.

Reply 2: We are very sorry for some garbled characters in the middle of the article for some unknown reason, we have carefully corrected the whole article.

Changes in the text:

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- (2) (b) other unspecified malignant tumors, not classified by ICCC or in situ.
- (3) Patients who received radiation therapy (RT) and surgery were identified based on SEER variables.
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- (8) However, there was no difference in survival between the 20–50 years and 51–80 years age groups...
- (9) However, no significant association was observed between treatments and survival for patients diagnosed with lymphomas and mesothelioma...

Reply to Reviewer F

Authors: Thank you for your patient and careful comments, which have well demonstrated your unique academic insights and profound academic attainments, brought great enlightenment and help to our scientific research ideas. We have revised the manuscript according to your requirements, hoping to meet your requirements.

Comment 1: Authors should be complimented for their extensive analysis with practical clinical application. As a minor comment, manuscript is full of mistyping errors. Please address

Reply 1: We are very sorry for some garbled characters in the middle of the article for some unknown reason, we have carefully corrected the whole article.

Changes in the text:

- (1) In this report, we described the survival differences between different ages and ...
- (2) (b) other unspecified malignant tumors, not classified by ICCC or in situ.
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- (9) However, no significant association was observed between treatments and survival for patients diagnosed with lymphomas and mesothelioma...

Reply to editor :

We have made a thorough revision according to the comments of reviewers. We look forward to making reviewers and editors satisfied and receiving your positive feedback as soon as possible.

Reply to Reviewer G

Comment 1: There are multiple mis-writings, which need to be revised. (Line 94, 146, 149, 150, 151, 152, 161, 175, 221, 225, 253, 273)

Reply 1: We are very sorry for some garbled characters in the middle of the article for some unknown reason, we have carefully corrected the whole article.

Changes in the text:

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- 2.2 (b) other unspecified malignant tumors, not classified by ICCC or in situ.
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