Peer Review File
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Reviewer A

I enjoyed reading the study by Dr. Rodriguez-Cid and colleagues examining a single center experience with thoracic sarcomas. I have the following questions and comments:

Comment 1: My greatest concern with this study is that the conclusion that more chemo cycles translates into a longer survival is a tautology. Only patients that are alive and capable of receiving chemo are going to get it thus saying they will survive longer is inherent conclusion of the former statement. I suspect what the authors should conclude is that performance status is the ultimate determinant of longevity.

Reply 1: We understand the reviewer´s point, however, the patients that receive more chemotherapy cycles are those that are responding better to the chemotherapy regimen received and this is the response that translates to a better survival outcome.

Additionally we included the following which focuses on that point at the discussion section lines 288-292: It is important to mention that even though it could be obvious that the number of chemotherapeutic cycles received correlates with a longer survival outcome, the analysis performed and results obtained demonstrate that those patients that receive more chemotherapeutic cycles are those that are responding better to the chemotherapeutical regimen received and this is the response that translates to a better survival outcome.

Comment 2: The population in this paper is quite confusing. I do not think the authors should create such a heterogenous group as the conclusions are determined by the impact of the most common entities. Is one to assume for instance that chemotherapy prolongs the life of patients with unresectable chondrosarcoma? I would rather suggest, they consider breaking this analysis into smaller groups of similar entities.

Reply 2: We understand the reviewer's point of view and recommendation, however, due to the heterogeneity of these tumors and the multiple histological diagnosis doing a smaller group analysis would cause a selection bias error as there is a limited number of patients per histological subtype. Regarding chondrosarcomas, even though they generally do not respond well to chemotherapy we could not make a subdivision specifically for that group due to the limited number of patients with that histological subtype, this applies to all the others histological subtypes.

Comment 3: There is not a single mention of radiation in the entire manuscript. Did the patients receive it. IF not, they need to explain why? I am assuming they at least palliated painful chest wall tumors with radiation. The role of radiation in treatment of these tumors needs to be discussed.

Reply 3: No patient received radiation therapy, even though we know the importance of radiation therapy in specific scenarios for these types of tumors, in our population no patient received radiation therapy.

We added the following in the manuscript in the results section "Treatment Characteristics" line 183-185: It is important to mention that patients in our population did not receive any radiation therapy in the management of their disease, treatment was fully based on chemotherapeutic regimens.

Comment 4: The patient population needs to be better characterized. This would include stage and reason for the designation of unresectable. Is this because they all have metastatic disease or does it include patients with earlier stage disease that are not candidates for surgery due to physiology/comorbidities? This, along with lists of

Reply 4: Patient population include patients either with metastatic disease or unresectable scenarios due to mediastinal, pleural, costal or muscle infiltration which corresponds to a stage T4 based on the TNM staging system.

We included the following in the results section "Treatment characteristics" line 181-182: metastatic tumors or irresectable tumors due to mediastinal pleural, costal of muscle infiltration which corresponds to a stage T4 based on the TNM staging system.

Comment 5: The authors need to be careful with their terminology. I am assuming none of these patients had complete responses thus they need to avoid using terms like "disease free period". I am assuming they mean progression free?

Reply 5: Thank you for your comment, the mistakes were corrected and all mentions of "disease free period" were fixed to "progression-free".

Reviewer B

Comment: This manuscript describes that an adequate initial ECOG, RECIST and receiving a higher number of chemotherapeutic cycles should be used as prognostic factors in the management of primary thoracic sarcomas.

The goal of this study was to verify the prognostic factors of primary thoracic sarcomas. Previous study showed that they were initial ECOG, RECIST. a higher

number of chemotherapeutic cycles is newly information, but we want to know what chemotherapeutical regimens used in this study. Additionally, we also want to know efficacy between regimens in this study.
These are the best important issues.

The authors should mention number of chemotherapeutic cycles of each chemotherapeutical regimen and also efficacy between regimens.

Reply: Even though the main objective of the present study is to identify prognostic factors for the management of primary thoracic sarcomas, as mentioned in the results section "Treatment characteristics" lines 195-196 we understand the reviewer´s point of view regarding the importance of mentioning the efficacy of the chemotherapeutic regimens received. We added the most common regimens used in our population in the section of results "Treatment characteristics" lines 193-197: The chemotherapeutical regimens used in our population were 92 patients treated with epirubicin + cisplatin + ifosfamide (E/C/I), 5 patients with gemcitabine + paclitaxel, 17 patients with doxorubicin + cisplatin, 1 patient with gemcitabine + carboplatin, 31 patients with doxorubicin + ifosfamide, 10 patients with etoposide + carboplatin (10 patients) and 1 patients with gemcitabine + docetaxel. It is important to mention that results analyzing efficacy between regimens is not the main objective of the current study and this analysis will be evaluated in an additional study from our research group.

Additionally, we included the median months for PFS (lines 223-227) and OS (lines 248-251) for each chemotherapeutic regimen used in the respective results sections. We consider important to emphasize that the main objective of the present study is to identify prognostic factors and not evaluate efficacy of the chemotherapeutic regimens used.

Reviewer C

The authors show that performance status of ECOG <2 and the most frequent chemotherapeutic cycles tolerated may be associated with a better prognosis in the highest number of advanced/unresectable cases with primary thoracic sarcomas (PTS).
Although the manuscript is of potential interest, this conclusion would not be fully supported by the described results. The authors should provide more detailed data obtained through the study.

I have the following comments.

Comment 1: The authors should display the Kaplan-Meier curves of PFS and OS in

the group of patients with ECOG <2 or most frequent chemotherapeutic cycles, respectively.
Reply 1: Kaplan-Meier curves of PFS and OS by ECOG (ECOG 0-1 and ECOG 2-3) were included and results were mentioned in their respective results sections of PFS (lines 213-218) and OS (lines 238-241).

Kaplan-Meier by ECOG of PFS is Figure 3, changing the previous figure 3, which is the median OS, now being figure 4. Therefore, Kaplan-Meier of OS by ECOG is figure 5.

We are opened by the journals recommendations of which figures include in the main article and which figures include as supplementary data.

Comment 2: I would recommend that the authors present the data of PFS, and OS of patients underwent surgeries for PTS in the authors' institute besides the literature.
Reply 2: No patient underwent surgery in our population data as they were all metastatic or irresectable disease.

Comment 3: I would suggest that the authors could show causes of death in this study. The authors should explain why a 61.1% ORR was not associated with a better prognosis in the Discussion.
Reply 3: Unfortunately, we do not have the specific causes of death in this study, they were all related to the cancer itself.
ORR not being associated with a better prognosis was explained in the discussion lines 298-302: ORR was not associated with a better prognosis because the response rate is not a surrogate variable. Patients with this type of tumor have a poor prognosis and the fact that they respond to chemotherapy does not indicate that they will live longer because the moment they progress they generally and unfortunately pass away in a few months.

Comment 4: It would be better if a comparison of the efficacy between chemotherapeutical regimens used is mentioned in this paper.
Reply 4: Even though it is not the main objective of the current study, we included the median months of PFS and OS for each chemotherapeutic regimen used in their respective sections of Results.

Comment 5: A large part of the Discussion (P11, Line238, 246, 253, 256; P12, Line 276; etc.) is redundant because it simply restates information included in the Results.
Reply 4: Line 238 was deleted and modified which now appears from line 265-266 as follows: When comparing our epidemiological results with published literature studies focused on PPS and primary CWS report similar incidence between male and female ranging from 44-64% being either male or female with a mean age of 43-62 years old, demonstrating that these tumors do not have a specific age and sex predisposition (18,20,21,23–25).

Comment 6: Line 246 we believe it is needed as it compares the results obtained directly with other studies published in the literature and we believe it should be mentioned. However, it was modified as follows in lines 272-274: In our study, the most common symptom reported was cough in 58.4% of cases followed by thoracic pain (55.4%) and dyspnea (45.2%), similar to what has been reported in the literature.

Reply 6: Line 253 was modified and now appears in lines 278-294 as follows: Histopathological analysis and classification of sarcomas is difficult, even for expert pathologists. The most recent classification used for sarcomas is the WHO Classification of Soft Tissue Tumors. When considering both PPS and primary CWS our study identifies that the most common histology is divided between synovial sarcomas and undifferentiated sarcomas. Previous studies have reported synovial sarcoma as the most common histology specially in PPS similar to what has been reported in our present study (34.4%) with 10.8% being biphasic. In cases where histology is not reported, undifferentiated sarcomas is the most common histology, similar to what was reported in our current study (37.5%) with other common histologies reported in the literature specially in chest wall sarcomas being primitive neuroectodermal, chondrosarcoma and dermatofibrosarcoma (18,20,21,23–27). Of these undifferentiated sarcomas, our population had 21% cases of high grade sarcomas and 6.4% pleomorphic and fusiform, respectively.

Comment 7: Paragraph 12, line 276 was modified to be more concise but also include the results to emphasize the importance of our study. The modification is found in lines 307-317 as follows: Regarding the main objective of the current study, which was identifying prognostic factors in primary thoracic sarcomas, for progression-free survival the number of chemotherapeutic cycles received a poor performance status classified as an ECOG >2 and an increase in RECIST (which evaluates treatment response) were identified. These results indicate that patients who receive a higher number of chemotherapeutic cycles, with an ECOG < 2 and an adequate response are associated with a longer progression-free period. On the other hand, for overall survival, the number of cycles and an ECOG > 2 were identified as prognostic factors. The response to treatment either by evaluating RECIST or ORR was not associated with an increased survival, different from what was observed for PFS.

Reply 7: Additionally, two important points were added based on recommendations from reviewers which can be found in the discussion section:

Lines 319-323: ORR was not associated with a better prognosis because the response rate is not a surrogate variable. Patients with this type of tumor have a poor prognosis and the fact that they respond to chemotherapy does not indicate that they will live longer because the moment they progress they generally and unfortunately pass away in a few months.

Lines 326-330: It is important to mention that even though it could be obvious that the number of chemotherapeutic cycles received correlates with a longer survival outcome, the analysis performed, and results obtained demonstrate that those patients that receive more chemotherapeutic cycles are those that are responding better to the chemotherapeutical regimen received and this is the response that translates to a better survival outcome.

Comment 8: In the sentence “the objective response rate (ORR) (P9, Line202)”, is it correctly “overall”?
Reply 8: Thank you, yes, it should be overall response rate. We fixed it in the manuscript.