Peer Review File

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Reviewer A

Wang et al. investigated the impact of perioperative chemotherapy on the overall survival and cancer-specific survival of individuals diagnosed with sarcomatous carcinoma submitted to surgery and registered in the SEER. They also evaluated how the different histological subtypes influenced these outcomes.

The information is interesting and valuable due to the rarity and heterogeneity of the pathology.

Major comments

Comment 1: The manuscript needs a thorough language and style review. Sometimes, the quality of the writing compromises the understanding of the text.

Reply 1: Thank you for your patience and kindness when reviewing our manuscript. We have given a thorough revision of language and style to our manuscript sentence by sentence. A total of 63 revisions to language have been made.

Changes in the text: We have modified our text as advised (please see the submitted manuscript with revisions highlighted).

Comment 2: It is not clear why the authors excluded patients submitted to pneumonectomy. This should be clarified.

Reply 2: Given that pneumonectomy is highly indicative of metastatic disease and severely impaired lung function, which might result in a confounding effect, we excluded patients submitted to pneumonectomy.

Changes in the text: We have added the explanation into the Method part as advised (see Page 8, line 101 - 102).

Comment 3: Please add the definition of the summary stage.

Reply 3: Our study was based on the SEER database and enrolled pulmonary sarcomatoid carcinoma (PSC) patients from 2000 to 2020. Due to multiple updates in the staging guidelines over the years, the staging criteria might vary by year of diagnosis. As a result, the collected

stage information (stage I/II/III/IV) could not be utilized in our study. As a solution, the SEER database proposed the SEER summary stage, which was directly based on the codes of tumor extension (T stage), lymph node status (N stage), and metastasis status (M stage) in the database. The SEER database would adjust the staging algorithm based on different editions of TNM staging guideline to ensure uniformity in the SEER summary stage criteria over time. Further detailed information is available at https://seer.cancer.gov/seerstat/variables/seer/lrd-stage/.

Changes in the text: We have modified our text as advised (see Page 8, line 109 - 110).

Comment 4: N stage is a powerful prognostic factor. Why this information was not collected?

Reply 4: Given that the SEER summary stage has taken into account the N stage, so we did not collect N stage information due to concern of redundancy. Based on this comment, we have tried to include N stage information into our analyses. Interestingly, we found N stage and SEER summary stage were both independent prognostic risk factors. So in our revised manuscript, we have included N stage into our analyses.

Changes in the text: We have added some data of N stage as advised (see Page 8, line 109; page 10, line 149 – 150; page 11, line 179; and Table 1, Table 2, Table 3, and supplementary files of the submitted revised manuscript).

Comment 5: Perioperative chemotherapy is usually not recommended for tumors smaller than 4,0cm. I suggest the authors exclude patients with tumors less than 3,0 or 4,0 cm and repeat the analyses to see if the results remain the same.

Reply 5: We have compared the survival between the surgery-only and the surgery-plus-chemotherapy groups before and after matching in patients with tumors > 4cm. The results demonstrated consistency with those observed in the overall patient population. Figure 1 of this letter shows the result of survival analyses after matching. We have added this finding into the part of subgroup analyses.

Changes in the text: We have added some new result of subgroups analyses into the revised manuscript (see Page 12 - 13, line 207 - 214).

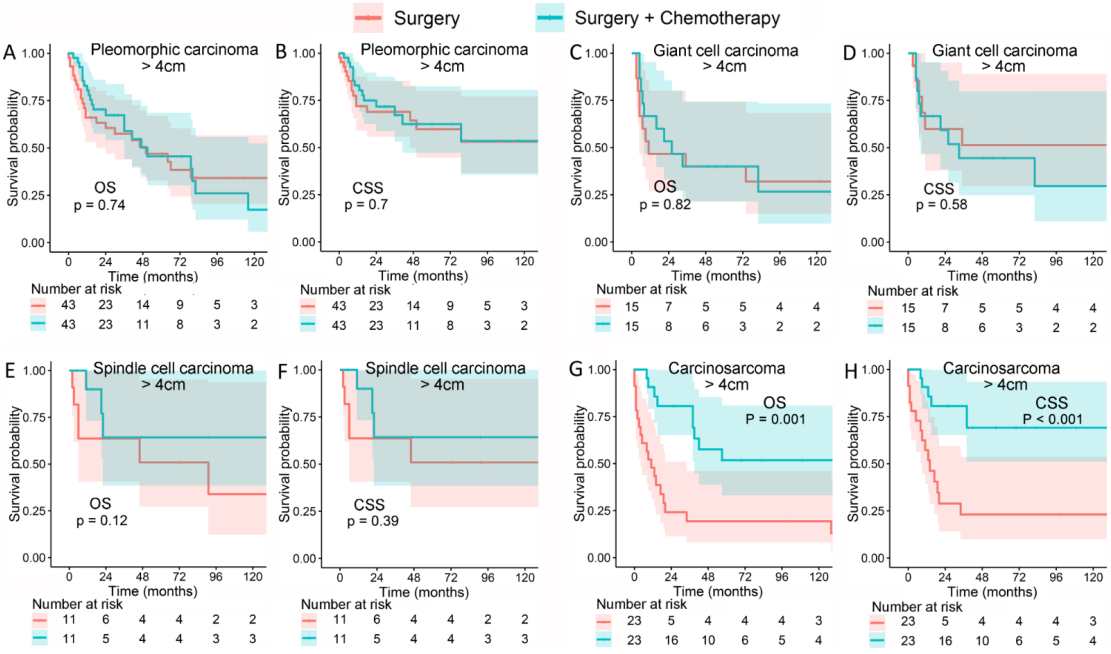

Figure 1 Survival analyses between the surgery-only and the surgery-plus-chemotherapy groups after matching in patients with tumors > 4cm. (A,B) pleomorphic carcinoma; (C,D) giant cell carcinoma; (E,F) spindle cell carcinoma; (G,H) carcinosarcoma. OS: overall survival; CSS: cancer-specific survival.

Comment 6: Platinum-based chemotherapy is the standard perioperative treatment. There is plenty of data showing that alkylating-based chemotherapy is detrimental in the perioperative scenario. I suggest the authors include information regarding the type of chemotherapy employed (platinum-based vs. non-platinum-based).

Reply 6: We understand your concern and fully agree with your advice. But it's a pity that the SEER database does not collect information about the specific chemotherapy regimen used. As a result, we do not have access to this information and are unable to assess the impact of the chemotherapy regimen on our findings. We have added this limitation into our revised manuscript. Additionally, we endeavored to review the pertinent literatures and found only two non-SEER database-based studies had reported the use of non-platinum-based chemotherapy regimen (1, 2). Due to the limited sample size, they did not compare the efficacy of platinum-based and non-platinum-based chemotherapy regimens. Thus, the potential impact of different chemotherapy regimens on our findings remains an interesting question that warrants further assessment based on additional clinical evidence in the future.

Changes in the text: We have added this limitation into our revised manuscript (see Page 17, line 299 - 301).

Reference:

1. Sun L, Dai J, Chen Y, et al. Pulmonary Sarcomatoid Carcinoma: Experience From SEER Database and Shanghai Pulmonary Hospital. Ann Thorac Surg 2020;110(2):406-13.

2. Maneenil K, Xue Z, Liu M, et al. Sarcomatoid Carcinoma of the Lung: The Mayo Clinic Experience in 127 Patients. Clin Lung Cancer 2018;19(3):e323-e33

Comment 7: Some histological subgroups ended up with very few patients. This might have jeopardized the analysis of the impact of chemotherapy. This should be better discussed.

Reply 7: We understand your concern and have revised and interpreted the result of subgroup analyses more cautiously based on your advice. Meanwhile, we have discussed this limitation in the Discussion part and pointed out that the result of subgroup analyses might only be suitable for assessing the trend of effect rather than evaluating absolute effect of the perioperative chemotherapy (PC).

Changes in the text: We have modified our text as advised (see Page 12, line 196 – 206; and Page 17, line 310 – 312).

Comment 8: The authors should reduce the tone they gave to subgroup analyses. Subgroup analyses are meant to check if there is any subgroup in which you can observe any signal that the effect investigated is detrimental. One cannot state that the intervention studied only impacted the subgroup where a reduced event risk was observed.

Reply 8: We have revised and interpreted the result of subgroup analyses more cautiously based on your advice. As commented earlier, the precision of the assessment of the effect of PC, particularly the P value, may be compromised by the limited sample size. In the revised manuscript, we have reduced our tone and just focused on elucidating the trend of the effect in the subgroup analyses, refraining from making definitive statements regarding which subgroup would benefit from PC.

Changes in the text: We have modified our text as advised (see Page 12, line 196 – 206).

Minor comments

Comment 9: When citing others' publications, the authors should use "First Author Last name el al"(ex. Karim et al., instead of Karim, N. A. et al.).

Reply 9: Thank you again for your patience and kindness when reviewing our manuscript. We have revised these expressions of cites as you advised.

Changes in the text: We have modified our text as advised (see Page 13, line 229, 231; Page 14, line 243; Page 15, line 263; and Page 16, line 277).

Reviewer B

While previous studies have reported the effectiveness of perioperative chemotherapy for pulmonary sarcomatoid carcinoma, it remains unclear. Authors showed that perioperative chemotherapy was significantly associated with improved overall survival in pulmonary sarcomatoid carcinoma using propensity score matching. Because pulmonary sarcomatoid carcinoma is a rare disease, it is important to accumulate evidence from observational studies. Furthermore, the present study conducted subset analysis according to histology, using propensity score matching, which suggested the effectiveness of perioperative chemotherapy varies by histologic type.

I would like authors to discuss about following limitation.

Comment 1: The present study showed that perioperative chemotherapy was associated with survival benefit in patients with carcinosarcoma, but not in those with other histologic type of pulmonary sarcomatoid carcinoma. However, due to the decreased sample size in subset analysis, there might be a lack of statistical power. Can we conclude that perioperative chemotherapy does not improve the prognosis of patients with sarcomatoid carcinoma other than carcinosarcoma?

Reply 1: Thank you for your advice. Although our study was based on a database of large sample size, the sample size of some histological subtypes of pulmonary sarcomatoid carcinoma (PSC) was still limited due to the rarity of the disease. We agree that there might be a lack of statistical power in our study and to increase the statistical power. In an effort to increase the statistical power, we have consolidated patients with pleomorphic carcinoma, giant

cell carcinoma, or spindle cell carcinoma into a single group to augment the sample size and repeated survival analysis. After propensity-score matching, the survival benefit of perioperative chemotherapy (PC) was still not observed in those patients (refer to Figure 1 of this letter).

But in order to be rigorous, we have revised the language expression to simply state the observed findings like "Survival benefit of PC was not observed in pleomorphic carcinoma, giant cell carcinoma, or spindle cell carcinoma patients" rather than providing a definitive conclusion that "PC was not beneficial for survival in pleomorphic carcinoma, giant cell carcinoma, or spindle cell carcinoma patients". Additionally, we have added a separate paragraph to discuss about the statistical limitations of our study, with this limitation highlighted as the first point in the paragraph.

Changes in the text: We have modified our text as advised (see Page 3, line 45 - 47; Page 12, line 202 - 203; Page 13, line 211 - 223; and Page 18, line 323 - 324)

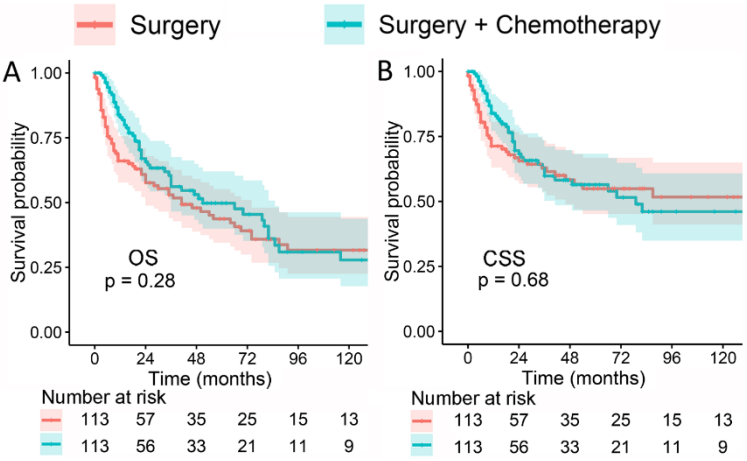

Figure 1 Survival analyses of grouped pleomorphic carcinoma, giant cell carcinoma, and spindle cell carcinoma patients after matching. OS: overall survival; CSS: cancer-specific survival.

Comment 2: In the subset analysis according to histologic type, survival benefit of perioperative chemotherapy was shown in only carcinosarcoma patients. However, multiplicity issue might have been raised due to the repeated log-rank test, which resulted in the small P value by chance.

Reply 2: We recognize the potential for a multiplicity issue when conducting repeated log-rank tests. In our study, we hypothesized that histological subtype might be an important reason influencing the efficacy of PC, which resulted in the controversy surrounding its effectiveness in PSC patients. To test this hypothesis, we conducted repeated survival analyses in different

subtypes of PSC patients. It is important to acknowledge that we cannot rule out the possibility of our findings being a chance occurrence due to the multiplicity issue. But as we mentioned in the Discussion part, pleomorphic carcinoma, spindle cell carcinoma, and giant cell carcinoma did not contain true sarcomatous element while carcinosarcoma did. Additionally, carcinosarcoma shares different molecular profiles from other subtypes. Our findings indicate a survival benefit of PC in carcinosarcoma patients, while such benefit was not observed in pleomorphic carcinoma, giant cell carcinoma, or spindle cell carcinoma patients. Considering these histological characteristics, the likelihood of our findings being a random event due to a multiplicity issue is minimal. Nonetheless, for the sake of rigor, we have pointed out the multiplicity issue and discussed it in the statistical limitation paragraph.

Changes in the text: We have modified our text as advised (see Page 17, line 313 - 319).

Comment 3: The characteristics of patients with giant cell carcinoma after match is shown in supplementary table s5. The proportion of patients with undifferentiated tumor was relatively higher in patients receiving surgery plus perioperative chemotherapy. This might have affected the survival analysis.

Reply 3: Because there were only 18 giant cell carcinoma patients who received PC, the proportion could be significantly influenced by the absolute number of patients. To ensure the robustness of our findings, we have tried to further match the differentiation grade between surgery-only and surgery-plus-chemotherapy groups in giant cell carcinoma patients. Following this additional matching, the clinicopathological characteristics was balanced between groups (refer to Table 1 of this letter). The result showed that survival benefit of PC was still not observed in the giant cell carcinoma patients (refer to Figure 2 of this letter).

In the revised manuscript, we included a new variable, “N stage”, into the propensity-score matching and rematched patients between the groups. The updated result showed that clinicopathological characteristics was balanced between groups (refer to Table 2 of this letter). And the result of survival analysis was still the same as the original findings (refer to Figure 3 of this letter).

Changes in the text: We have modified the corresponding part of our manuscript to this comment after including the N stage into our analysis (see Supplementary Table S5 and

Supplementary Figure S4 of the submitted revised manuscript).

Table 1 The characteristics of giant cell carcinoma patients after further matching differentiation grade [a].

Characteristics	Surgery (N = 18)	Surgery + Chemotherapy (N = 18)	P
Age (year)			1
< 65	9 (50.0)	9 (50.0)	
65 - 75	5 (27.8)	5 (27.8)	
≥ 75	4 (22.2)	4 (22.2)	
Sex			0.289
Female	4 (22.2)	8 (44.4)	
Male	14 (77.8)	10 (55.6)	
Race			0.713
White	15 (83.3)	13 (72.2)	
Black	2 (11.1)	3 (16.7)	
Others [b]	1 (5.6)	2 (11.1)	
Year of diagnosis			0.928
2000 - 2006	4 (22.2)	4 (22.2)	
2007 - 2013	8 (44.4)	9 (50.0)	
2014 - 2020	6 (33.3)	5 (27.8)	
Primary site			0.076
Right upper lobe	8 (44.4)	7 (38.9)	
Right middle lobe	3 (16.7)	0 (0.0)	
Right lower lobe	1 (5.6)	3 (16.7)	
Left upper lobe	6 (33.3)	4 (22.2)	
Left lower lobe	0 (0.0)	4 (22.2)	
Size (cm)			0.571
2 - 4	5 (27.8)	3 (16.7)	
4 - 6	7 (38.9)	10 (55.6)	
> 6	6 (33.3)	5 (27.8)	
Surgery			0.228
Sublobectomy	3 (16.7)	0 (0.0)	
Lobectomy/Bilobectomy	15 (83.3)	18 (100.0)	
Differentiation			0.602
Poorly differentiated	3 (16.7)	2 (11.1)	
Undifferentiated	7 (38.9)	10 (55.6)	
Unknown	8 (44.4)	6 (33.3)	
Summary stage [c]			0.504
Localized	10 (55.6)	7 (38.9)	
Regional	8 (44.4)	11 (61.1)	
Other malignancy [d]			0.732
No	10 (55.6)	12 (66.7)	

Yes	8 (44.4)	6 (33.3)

[a] Values are numbers (percentages), and percentages may not total 100 because of rounding.

[b] Others included Asian/Pacific Islander and American Indian/Alaska Native.

[c] Stage confirmed by the algorithm created by the SEER database. For more information: https://seer.cancer.gov/seerstat/variables/seer/lrd-stage/

[d] Whether developed other in situ/malignant tumor before and after the diagnosis of PSC.

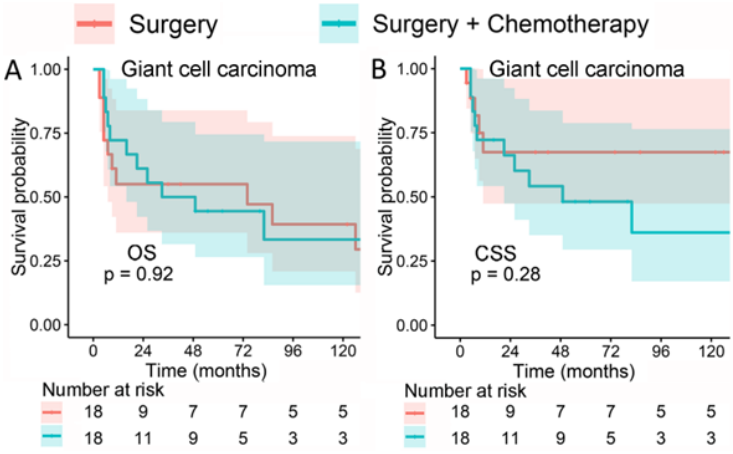

Figure 2 Survival analyses of giant cell carcinoma patients after further matching differentiation grade (before including "N stage" into our study). OS: overall survival; CSS: cancer-specific survival.

Table 2 The characteristics of giant cell carcinoma patients after matching (after including "N stage" into the matching) [a].

Characteristics	**Surgery (N = 18)**	**Surgery + Chemotherapy (N = 18)**	**P**
Age (year)			1
< 65	9 (50.0)	9 (50.0)	
65 - 75	5 (27.8)	5 (27.8)	
≥ 75	4 (22.2)	4 (22.2)	
Sex			1
Female	7 (38.9)	8 (44.4)	
Male	11 (61.1)	10 (55.6)	
Race			0.44
White	16 (88.9)	13 (72.2)	
Black	1 (5.6)	3 (16.7)	
Others [b]	1 (5.6)	2 (11.1)	

Year of diagnosis			0.921
2000 - 2006	4 (22.2)	4 (22.2)	
2007 - 2013	10 (55.6)	9 (50.0)	
2014 - 2020	4 (22.2)	5 (27.8)	
Primary site			0.081
Right upper lobe	7 (38.9)	7 (38.9)	
Right middle lobe	4 (22.2)	0 (0.0)	
Right lower lobe	2 (11.1)	3 (16.7)	
Left upper lobe	5 (27.8)	4 (22.2)	
Left lower lobe	0 (0.0)	4 (22.2)	
Size (cm)			0.718
2 - 4	5 (27.8)	3 (16.7)	
4 - 6	9 (50.0)	10 (55.6)	
> 6	4 (22.2)	5 (27.8)	
Surgery			0.467
Sublobectomy	2 (11.1)	0 (0.0)	
Lobectomy/Bilobectomy	16 (88.9)	18 (100.0)	
Differentiation			0.151
Well/moderately differentiated	1 (5.6)	0 (0.0)	
Poorly differentiated	7 (38.9)	2 (11.1)	
Undifferentiated	7 (38.9)	10 (55.6)	
Unknown	3 (16.7)	6 (33.3)	
N classification			0.566
N0	13 (72.2)	11 (61.1)	
N1	2 (11.1)	4 (22.2)	
N2	3 (16.7)	2 (11.1)	
NX [c]	0 (0.0)	1 (5.6)	
Summary stage [d]			0.737
Localized	9 (50.0)	7 (38.9)	
Regional	9 (50.0)	11 (61.1)	
Other malignancy [e]			0.182
No	7 (38.9)	12 (66.7)	
Yes	11 (61.1)	6 (33.3)	

[a] Values are numbers (percentages), and percentages may not total 100 because of rounding.

[b] Others included Asian/Pacific Islander and American Indian/Alaska Native.

[c] NX indicated that the N stage could not be assessed or the N stage was unknown.

[d] Stage confirmed by the algorithm created by the SEER database. For more information: https://seer.cancer.gov/seerstat/variables/seer/lrd-stage/

[e] Whether developed other in situ/malignant tumor before and after the diagnosis of PSC.

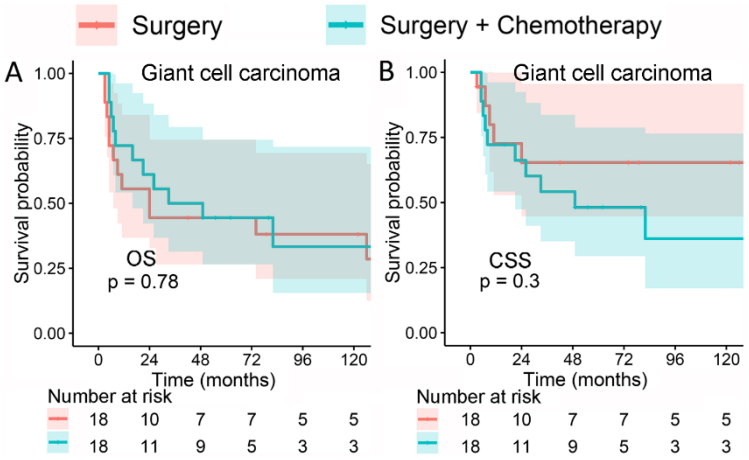

Figure 3 Survival analyses of giant cell carcinoma patients after matching (after including "N stage" into the matching). OS: overall survival; CSS: cancer-specific survival.