PCM PRECISION CANCER MEDICINE
A JOURNAL AIMING TO DELIVER A LASTING BLOW TO CANCER

Peer Review File

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Reviewer A

Dear reviewer A, thank you for your invaluable suggestions and insights.

Authors collected 88 patients of angiosarcoma treated at their institute. It is meaningful to publish this type or study since the incidence of angiosarcoma very rare. In their report, patients who received curative surgery achieved the longest overall survival, but it might due to the bias since patients with smaller tumor with good physical condition tend to receive curative surgery. In fact, they conducted multivariate analysis and showed that the surgery did not affect overall survival. Therefore, I agree with the authors that the curative intent, radical surgery might not an ideal treatment for angiosarcoma of the scalp and face.

I have several comments and questions to the authors as follows:

1. What is the standard therapy of cutaneous angiosarcoma in your institute? Wide-margin resection followed by radiation? I could not see the strategy. I think the current standard treatment of cutaneous angiosarcoma wide margin resection followed by radiation. However, I do not agree with this for patients having >5cm tumors since such patients difficult to achieve complete resection with acceptable margin.

   1. Reply: Thank you for your question. Our current strategy is still wide excision for patients with smaller tumours, however, very few patients fulfil this criterion. Most patients present with larger tumours that will require more extensive surgery.

2. What do you mean by “palliative chemotherapy”? Did you reduce the dose? Or your intent of chemo was palliation?

   2. Reply: We define “palliative chemotherapy” as any treatment that does not

involve radical surgery, as long-lasting cure is unlikely and chemotherapy is given for symptom control, although a subset of patients will experience very good disease control for extended period of months or years, but ultimately the disease is likely to return. We have amended the wording to clear this point up.

Page 4 line 74
"Some patients experienced extended survival with a conservative approach of chemotherapy with or without local consolidation therapy."

Page 15 line 351
"Based on experience, most patients would receive chemotherapy first to prevent severe toxicities from concurrent multimodality treatments."

3. 55 patients had localized disease. Did this exclude lymph node involvement?
   3. For localized disease, we had recorded 1 patient with nodal involvement who went on to have wide resection and neck dissection.

4. Less than half of localized disease patients received surgery. What did the others receive as first-line therapy? Chemoradiation?
   4. 34 localised patients did not undergo surgery. For first line treatment, 13 of them had upfront chemotherapy alone, 6 had chemo-radiotherapy, 10 had radiotherapy to localized disease, 5 opted for no treatment (but 2 received chemotherapy upon progression).

5. In the Cox proportional hazard model for OS, authors should change the reference of "Tumor size". Metastatic is already taken into account as it included in "metastasis at diagnosis". I prefer set "<5cm" as reference.
   5. Thank you for your suggestion.
   We have set <5cm as reference.

	Univariable analysis	
Variable	**HR (95% CI)**	***p*-value**
Tumor size (Ref: < 5cm) (n = 86)		

≥ 5cm	1.74 (0.93 – 3.24)	0.082
Metastatic	2.50 (1.40 – 4.53)	**0.003**

Reviewer B

Well written article that contributes to the literature on a rare, difficulty to study disease
My only contention is dismissing surgery all together without elaborating on surgical techniques utilized
I do not think you can dismiss a treatment option without a standardized approach to surgical or non surgical therapy
It is fair to say our study casts doubt on the utility of radical surgery

Dear reviewer B,

Thank you for your valuable points. You are right that there is no standardized approach for HnN angiosarcoma. While there is a role for surgery in smaller tumours, the literature suggests that some institutions, including this current study, have found that locoregional relapse rates are high.

While going through the case files, all the patients classified as having received surgery with a curative intent, had wide excision, with or without soft tissue cover, and neck dissections were performed for patients with suspected nodal disease.

We will amend the discussion and summary to include your points on surgical heterogeneity, and the controversy of surgery, and the limitations of our current study on drawing conclusions.

Page 16 line 364 conclusion

“For smaller tumours, while wide excision with or without adjuvant radiotherapy is an option, the clinical benefit of a surgical approach, compared to a more conservative approach with upfront chemotherapy, remains unanswered.”

Page 13 line 299 discussion

However, in smaller localized tumours, wide excision may still have a role if it can be achieved without overt complications. (2,20)