

Peer Review File

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Reviewer A

I must comment the authors on their well written manuscript titled: “Outcomes of Patients with Esophageal Cancer After Allogeneic Hematopoietic Stem Cell Transplantation”. In order to be suitable for publication, there are a few issues that need to be addressed:

- 1. Please mention the exact type of study design in the methods section. I think this is a case series, rather than a retrospective cohort.**

Reply1: We agree with the reviewers comment and have mentioned the study design (case series in the revised manuscript – Methods Section Line 136

Changes in text: For this retrospective case series, records of adult (≥ 18 years) patients who underwent aSCT at Princess Margaret Cancer Centre, Toronto from Jan 1990- Dec 2020 were screened to identify patients who subsequently developed primary esophageal cancer.

- 2. Why does figure one end at 0.0 probability at 80 months? Did all patients die?**

Reply 2: - We apologize for the confusion provided by the figure – The KM curve ends with a sharp drop as the longest surviving patient died at around 82 months. It does not mean aa surviving patients died as some patients who are alive have their duration of followup less than 82 months (shown as vertical markings in the curve – drops showing patient death. Since the appearance of the figure adds to confusion we have edited the figure to show only followup up to 80 months duration, so that the sharp drop is not visible and thank the reviewer for the suggestion.

Changes – Figure 1 edited.

- 3. In Table 2 mention the time to disease recurrence/ follow-up.**

Reply 3: - We agree with the reviewers comment and have added the extra column in Table 2

Changes – Table 2 edited (highlighted in yellow)

- 4. This is a very heterogenic cohort, please mention this more clearly in the discussion section.**

Reply 4: We agree with the reviewers comment – We have mentioned the same in the discussion section. Discussion Section Line 286

Changes in text - Our study is limited by a small heterogenous cohort of patients with esophageal cancer evaluated over a long period of time, increasing the possibility of patients who were lost to follow up, and subsequently developed esophageal cancer.

- 5. I would like to see some recommendation for future research and implication for daily practice. Should patients be screened routinely for upper GI cancers, to detect early stage cancers? Please comment on this in the discussion section.**

Reply 5: - We agree with the reviewers suggestion that some recommendation for implications in daily practice should be mentioned. We have edited the manuscript to mention some recommendations for the same. Discussion Section line 300-304

Changes in text - . Although there is no evidence for routine / surveillance endoscopy after aHCT, patients presenting with symptoms of non-cardiac central chest pain, dysphagia, odynophagia or unexplained weight loss, should be evaluated thoroughly with barium swallow and upper gastrointestinal endoscopy.

Reviewer B

1. Occupied area

Middle esophageal cancer is the majority of conventional esophageal cancer, but after stem cell transplantation, there is a difference in the occupied site between proximal 4 (40%) middle 2 (20%) and distal 4 (40%).

Reply 1 – We agree with the reviewer that there is a discrepancy in site of esophageal cancer after stem cell transplantation. We believe it is due to the difference in risk factors after stem cell transplantation (like cGVHD) – We have mentioned the same in the revised manuscript. Discussion Section Page 10 Line 234-239

Changes in Text: - Almost all of our patients have squamous cell cancer (SCC) of esophagus (90%) and all of these patients have a history of cGVHD of the oral cavity and oropharynx. Thus cGVHD maybe the reason for increased proportion of SCC (when compared to adenocarcinoma) and increased proportion of proximal esophageal cancer (40%) in this cohort of patients after aHCT.

2. Histology; Histologically, state the reason for SCC regardless of site after stem cell transplantation.

Reply 2 – We agree with the reviewer that there is a discrepancy in histology regardless of site of esophageal cancer after stem cell transplantation. We believe it is due to the difference in risk factors (like cGVHD – which predisposes on SCC and not Adeno Ca) after stem cell transplantation – We have mentioned the same in the revised manuscript. Discussion Section Page 10 Line 234-239

Changes in Text: - Almost all of our patients have squamous cell cancer (SCC) of esophagus (90%) and all of these patients have a history of cGVHD of the oral cavity and oropharynx. Thus cGVHD maybe the reason for increased proportion of SCC (when compared to adenocarcinoma) and increased proportion of proximal esophageal cancer (40%) in this cohort of patients after aHCT.

3. Does the median OS 44 months have a better prognosis than conventional esophageal cancer?

Reply 3 - We thank the reviewer for clarifying the point. We do not think esophageal cancer after BMT has better prognosis that conventional esophageal cancer – we believe the relatively favorable prognosis is due to early detection (only 10% of our patients had distant metastasis at time of diagnosis) – due to increased vigilance and regular follow up. We have clarified the same in the revised manuscript.

Changes in text - Thus, the relatively favorable survival seen in our cohort of patients with esophageal cancer after aHCT may be attributable to the early stage at diagnosis of the malignancy.