Peer Review File

Article information: https://dx.doi.org/10.21037/med-21-33

Review Comments

Reviewer A

Comment 1: At first, the authors need to have this manuscript re-written by a scientist who speaks English as a primary language. It needs considerable editing for grammar and for improving clarity. Especially for Abstract, it needs to be modified.
Reply 1: **We modified the abstract as requested.**
Changes in the text: section: section: abstract

Comment 2: Please use abbreviation correctly.
Reply 2: **we checked and modified abbreviations, as suggested.**

Comment 3: Introduction is almost the same as Abstract and needs to be modified.
Reply 2: **We modified the abstract as requested, also according to editorial office's suggestions.**
Changes in the text: section: abstract

Comments 4 and reply 4:
Line 57, extra gonadal should be extragonadal: reply **modified as requested**

Line 58, AFP should be alfa-fetoprotein (AFP). After this, please use AFP: reply **modified as requested**

After Line 102 chemotherapy (CHT), chemotherapy should be CHT: reply **modified as requested**

I cannot understand the meaning line 128, "BEP X3 of 4 cycles": reply **modified as " 3 or 4 cycles of BEP"**

Line 139, progression-free survival should be PFS. After this, please use PFS; reply **modified as requested**

After Line 148 high dose CHT (HDCHT), please use HDCHT: reply **considering that the acronym HDCT is more common than HDCHT, we did not modify it (i.e the JCO article of Indiana University: Adra N, Abonour R, Althouse SK, Albany C, Hanna NH, Einhorn LH. High-Dose Chemotherapy and Autologous**

Peripheral-Blood Stem-Cell Transplantation for Relapsed Metastatic Germ Cell Tumors: The Indiana University Experience. *J Clin Oncol*. 2017;35(10):1096-1102. doi:10.1200/JCO.2016.69.5395)

Please correct the grammatical usage of "however": reply **modified as requested**

I cannot understand the sentence of line 177-178: reply **modified as "without marker elevation or other malignant germ cell tumour components".**

Please correct line 218 "Carboplatin/etoposide-based regimen HDCT was: reply **corrected as "Carboplatin/etoposide-based HDCT was the most frequent regimen reported"**

Line 258 and 259, 2 should be □: reply **modified as requested**

Line 297, between should be among: reply **modified as requested**

Line 300-301, the authors describe "Liquid biopsy-based microRNA biomarkers represent one of the most exciting research fields" in line 285 Beyond microRNA, please describe specifically that liquid biopsy is a promising strategy in equivocal clinical scenarios: reply **we modified as "Liquid biopsy represent one of the most exciting research fields in GCTs with potential implications also in primary mediastinal tumours (line 378-379). We discussed the potential role in equivocal clinical scenarios in lines. We also added a discussion on the potential role of liquid biopsy in general due to molecular heterogeneity over time, and on cfDNA (lines 379-387).**

Reviewer B

Congratulations to the authors on your extensive review with tremendous effort. The entire manuscript was well written with good language and layout. The following are my comments.

Comment 1: How did you define the so-called high volume or highly experienced centers for treating mediastinal germ cell tumor?

Reply 1: **We added this paragraph in the discussion: "An analysis from the National Cancer Database, including patients with seminoma and nonseminomatous GCT, showed that increased hospital GCT case volume was**

associated with significant differences in survival outcomes, in particular for more advanced disease (25). Hospitals were classified by case volume as high (99th percentile, ≥26.1 cases annually), high-intermediate (95-99th percentile, 14.6-26.0 cases annually), intermediate (75-95th percentile, 6.1-14.5 cases annually), low-intermediate (25-75th percentile, 1.8-6.0 cases annually), and low (25th percentile,<1.8 cases annually). Defining a threshold for high volume centers for PMGCTs is challenging, considering the rarity of the disease. However, it is likely that those centers with strong experience in GCTs treatment and high surgical expertise may offer the best treatment plan also to this rare disease". We also added this sentence referred to HDCT "However, the threshold for what is high-volume has not been clearly defined (27)".
Changes in the text: lines 315-323; line 330-331

Comment 2: The incidence and surgical outcome of growing teratoma syndrome should be described more clearly.
Reply 2: **we added this paragraph on growing teratoma syndrome, citing largest series in GCTs "Various series on growing teratoma syndrome in GCTs showed that surgical treatment, even if technically challenging, may be curative and local recurrence may be related to incomplete resection".**
Changes in the text: lines 251-253

Comment 3: A graphic abstract or figure to depict the knowns and unknowns regarding the PMGCTs is encouraged.
Reply 3: **Thanks for the suggestion. We added a table highlighting the major challenges in PMGCTs and possible solutions.**
Changes in the text: table 1 (added)

Reviewer C

Marandino and Vogl provide a comprehensive update on primary mediastinal germ cell tumors (PMGCTs), including their pathologic features, management, and future considerations for this rare disease. The review is well done.

Comment 1: The authors cover the majority of updates on this disease, but I would recommend the molecular diagnostic portion be expanded slightly to include a recent

study that examined the driver mutations in GCTs co-occurring with hematologic malignancies (PMID: 32897884).

Reply 1: **We thanks the reviewer for this suggestion**. **We included the study, as suggested by the reviewer, and we added a specific paragraph to discuss hematologic malignancies and GCTs.**

Changes in the text: lines 146-15

Comment 2: Additionally, the authors included an important section on liquid biopsy, but it may be worth discussing the possibility that metastatic GCTs may have different molecular profiles from primary lesions, which will require thoughtful strategies for disease diagnosis and monitoring using this modality (PMID: 33163850).

Reply 2: **We included the study (PMID: 33163850) and we discussed the potential role of liquid biopsy in monitoring molecular alterations over time and in the early identification of patients unlikely to respond to chemotherapy.**

Changes in the text: lines 379-387
