Peer Review File

Article information: https://dx.doi.org/10.21037/dmr-22-19

Responses to the Reviewers

March 31, 2022

Dear Reviewers and Editorial Board,

Thank you for consideration of our manuscript, and we are pleased to submit the following revised manuscript for consideration of publication in Digestive Medicine Research entitled: "Malignant Peritoneal Mesothelioma Literature Review: Past, Present, and Future."

Attached you will find our responses to the thoughtful comments, as well as our appropriate modifications via "track changes" in an updated manuscript. We hope that we have adequately addressed the reviewers' insights and concerns.

We appreciate your consideration of this manuscript and look forward to your response.

Sincerely,

Stephanie N. Gregory, MD

Reviewer Comments

Review A

Comment 1: Pathology section. Ref 28 seems of chemotherapy, not of pathological diagnosis.

Reply 1: Originally Ref 28 was: Fujimoto, E., et al. (2017). "First-line chemotherapy with pemetrexed plus cisplatin for malignant peritoneal mesothelioma." Expert Rev Anticancer Ther 17(9): 865-872. This paper does mention the variants benign multicystic mesothelioma and well-differentiated papillary mesothelioma; however, I have changed the reference to the original reference that was used. Ref 28 is now: Daya D, McCaughey WT. Pathology of the peritoneum: a review of selected topics. Semin Diagn Pathol. 1991;8(4):277-89.

Comment 2: Chemotherapy.

The authors introduced a phase III clinical trial comparing pemetrexed with cisplatin compared to cisplatin alone. The reviewer has never seen the phase III study in the area of malignant peritoneal mesothelioma. The reviewer cannot find detailed information in ref [8, 20]. The authors should find out the original reference of the study. Ref 14 seems of HIPEC treatment, not of pemetrexed.

Reply 2: The Phase III clinical trial comparing pemetrexed with cisplatin compared to cisplatin alone is for pleural mesothelioma, for which I have added in pleural mesothelioma into the text and removed ref 8 and 20 from this line. I have added in the original phase III trial ref 52.

Vogelzang NJ, Rusthoven JJ, Symanowski J, Denham C, Kaukel E, Ruffie P, et al. Phase III study of pemetrexed in combination with cisplatin versus cisplatin alone in patients with malignant pleural mesothelioma. J Clin Oncol. 2003;21(14):2636-44.

Although the trial was for pleural mesothelioma, this practice was adapted clinically for MPM. I have added additional information about the International Expanded Access Program that was created for compassionate use for patients with MPM after increased disease response and overall survival from the Phase III clinical trial: ref 53.

Carteni G, Manegold C, Garcia GM, Siena S, Zielinski CC, Amadori D, et al. Malignant peritoneal mesothelioma-Results from the International Expanded Access Program using pemetrexed alone or in combination with a platinum agent. Lung Cancer. 2009;64(2):211-8.

Reference 14 was removed and replaced with ref 53.

Review B

Comment 1:

The authors described borderline malignant variants of peritoneal mesothelioma such as benign multicystic mesothelioma and well-differentiated papillary mesothelioma. The authors further indicated that these variants are considered different biological entities and can be differentiated from their malignant counterparts through lack of invasion as well as no increased cellularity within the stroma.(28,29). The references here do not seem to belong to this description. Also, invasion has been described in several cases of WDPM.

Reply 1:

Originally Ref 28 was: Fujimoto, E., et al. (2017). "First-line chemotherapy with pemetrexed plus cisplatin for malignant peritoneal mesothelioma." Expert Rev Anticancer Ther 17(9): 865-872. This paper does mention the variants benign multicystic mesothelioma and well-differentiated papillary mesothelioma; however, I have changed the reference to the original reference that was used with this paper. Ref 28 is now: Daya D, McCaughey WT. Pathology of the peritoneum: a review of selected topics. Semin Diagn Pathol. 1991;8(4):277-89.

In regards to ref 29, I used this paragraph from the papers discussion of benign mesothelioma to create my sentence: “Another worrisome feature that may deceptively lead one to wrongly assume a malignant nature is increased fibrosis encasing and surrounding benign mesothelial

cells, mimicking invasion. Indeed, one of the most helpful distinguishing histologic features of malignancy is the presence of true invasion. Invasion is a key feature that may be focal and difficult to appreciate. Keratin stains are helpful in these cases to highlight invasive cells diving deep within the stroma. Some features that are more common in mesothelial hyperplasia or benign mesothelioma are lack of invasion and no increased cellularity within the stroma; if papillary formations are present, they should be simple, small to medium, and lined by a single layer of cells with only mild to moderate atypia, growth should be uniform."

I added in a line to discuss the case reports and controversy of well-differentiated papillary mesothelioma.

Comment 2: Authors noted that IHC has been show to detect BAP1 mutation in 27-67% of pleural mesotheliomas. This statement is not accurate, IHC doesn't detect BAP1 mutations and it detects loss of BAP1 staining which occurs due to BAP1 mutation.

Reply 2: I have changed this sentence to state "*BAP1* mutation has been detected in 27-67% of pleural mesotheliomas."