

March 17, 2014



Dear Editor,

Please find enclosed the edited manuscript in MS-Word format (file name: 8248-edited.doc).

Title: Advances in the Management of Peritoneal Mesothelioma.

Author: Ali Raza, Wei-Ching Huang, and Kazuaki Takabe

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 8248

Thank you for reviewing our paper (8248-edited.doc) and giving us useful comments and constructive criticism. We believe our paper has been improved considerably by answering all of the concerns that the reviewers have raised. Below are our detailed responses to the reviewers' comments. We hope that our revised manuscript which addressed all of the concerns of the reviewers will now be acceptable for publication. As detailed in the "BPG's Revision Policies for Review," the font has been change to size number 10.

The manuscript has been revised according to the suggestions of reviewers and changes have been highlighted as requested.

Thank you again for reviewing our manuscript for the *World Journal of Gastroenterology*. We hope that we have addressed the concerns and comments adequately.

Sincerely yours,

A handwritten signature in black ink that reads 'Kazuaki Takabe'.

Kazuaki Takabe MD PhD FACS
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Response to Reviewers' Comments

1. All format requests that are present in the text of the paper have been addressed and updated.

2. Reviewer #1 (00009760)

Comment: "Review Paper"

Response: No specific revisions were requested. We greatly appreciate the favorable recommendation for publication by this reviewer.

3. Reviewer #2 (00209921)

Comment: "Raza et al. provide exhaustive and comprehensive review of currently available treatment options of peritoneal mesothelioma, with somewhat heavier emphasis on CS-HIPEC. The review is well written. I would recommend considering mention of histological subtypes, as they significantly impact treatment options (no CS-HIPEC for sarcomatoid subtypes), and prognosis (much improved in cystic and papillary variants). One may consider mentioning bidirectional therapy - a combination of systemic and regional chemotherapy - not mentioned in the review."

Response: We agree with Reviewer #2 that certain histological subtypes do influence prognosis. In accordance with their request, we have updated our comprehensive Table 1 to include these subtypes. Additionally, we have included outcomes of bidirectional (logoregional and systemic) therapy under the *Chemotherapy Agents used for HIPEC* heading. In general, systemic chemotherapy in combination with HIPEC and CRS has infrequently been studied. Deraco et al published a large series in 90 patients and found no statistically difference in overall or progression free survival^[1]. Similarly Yan et al found that post-operative systemic therapy did not significantly impact survival^[2].

- 1.) 50 Deraco M, Baratti D, Hutanu I, Bertuli R, Kusamura S. The role of perioperative systemic chemotherapy in diffuse malignant peritoneal mesothelioma patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 2013; 20(4): 1093-1100.
- 2.) 42 Yan TD, Deraco M, Baratti D, Kusamura S, Elias D, Glehen O, Gilly FN, Levine EA, Shen P, Mohamed F, Moran BJ, Morris DL, Chua TC, Piso P, Sugarbaker PH. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for malignant peritoneal mesothelioma: multi-institutional experience. *J Clin Oncol* 2009; 27(36): 6237-6242.

4. Reviewer #3 (00042473)

Comment: "A review article and a position paper for a targeted therapy for malignant peritoneal mesothelioma (MPM). I have a few suggestions for the authors: 1. The review should be revised as more balanced in terms of molecular targets available on the horizon. 2. The listing of MPM as an occupational disease is somewhat controversial and should be revised, as I am unaware of any MPM having ferruginous bodies recovered in the pathology specimens (which are usually extensive - unlike the thoracic specimens). 3. Several relevant manuscripts quoted in the text fail to appear in the tables, which should be corrected."

Response: We have addressed Reviewer #3's concern about addressing targets on the horizon. We have included a discussion on MUC1, a potential target, for peritoneal mesothelioma and a postulated drug therapy bromelain^[3,4].

- 3.) Pillai K, Pourgholami MH, Chua TC, Morris DL. MUC1 has prognostic significance in malignant peritoneal mesothelioma. *The International journal of biological markers* 2013; 28(3): 303-312.
- 4.) Pillai K, Akhter J, Chua TC, Morris DL. Anticancer property of bromelain with therapeutic potential in malignant peritoneal mesothelioma. *Cancer investigation* 2013; 31(4): 241-250.

We agree with Reviewer #3 that the association of peritoneal mesothelioma and asbestos is weaker compared to its pleural counterpart. We have accordingly revised the epidemiological portion of the Introduction and Abstract.

Lastly, the manuscript references in the tables and text have been updated to be consistent with another.

Specifically in regards to Table 1, the following references were added (for convenience the references below are numbered as they appear in the text of the manuscript):

49.) **Blackham AU**, Shen P, Stewart JH, Russell GB, Levine EA. Cytoreductive surgery with intraperitoneal hyperthermic chemotherapy for malignant peritoneal mesothelioma: mitomycin versus cisplatin. *Ann Surg Oncol* 2010; 17(10): 2720-2727.

50.) **Deraco M**, Baratti D, Hutanu I, Bertuli R, Kusamura S. The role of perioperative systemic chemotherapy in diffuse malignant peritoneal mesothelioma patients treated with cytoreductive surgery and hyperthermic intraperitoneal chemotherapy. *Ann Surg Oncol* 2013; 20(4): 1093-1100.

52.) **Wong J**, Koch AL, Deneve JL, Fulp W, Tanvetyanon T, Dessureault S. Repeat Cytoreductive Surgery and Heated Intraperitoneal Chemotherapy May Offer Survival Benefit for Intraperitoneal Mesothelioma: A Single Institution Experience. *Ann Surg Oncol* 2013. *Surg Oncol* 2012; 19(5): 1416-1424.

55.) **Hesdorffer ME**, Chabot JA, Keohan ML, Fountain K, Talbot S, Gabay M, Valentin C, Lee SM, Taub RN. Combined resection, intraperitoneal chemotherapy, and whole abdominal radiation for the treatment of malignant peritoneal mesothelioma. *American journal of clinical oncology* 2008; 31(1): 49-54.

Our criteria for citing references in Table 1 included at least one year of follow-up and reported median or overall survival for the entire cohort. The following references, although cited in the text, were not added to Table 1 to these exclusions. The reasoning for each reference is also provided.

32.) **Ma GY**, Bartlett DL, Reed E, Figg WD, Lush RM, Lee KB, Libutti SK, Alexander HR. Continuous hyperthermic peritoneal perfusion with cisplatin for the treatment of peritoneal mesothelioma. *The cancer journal from Scientific American* 1997; 3(3): 174-179.

→ This paper had only follow-up of 10 months and largely described the efficacy of treatment only.

51.) **Nonaka D**, Kusamura S, Baratti D, Casali P, Cabras AD, Younan R, Rosai J, Deraco M. Diffuse malignant mesothelioma of the peritoneum: a clinicopathological study of 35 patients treated locoregionally at a single institution. *Cancer* 2005; 104(10): 2181-2188.

→ This paper, unfortunately, did not provide overall or median survival for the entire cohort. Outcomes by prognostic factors including nuclear grade, mitotic count, and completeness of cytoreduction were only given.

53.) **Baratti D**, Kusamura S, Cabras AD, Deraco M. Cytoreductive surgery with selective versus complete parietal peritonectomy followed by hyperthermic intraperitoneal chemotherapy in patients with diffuse malignant peritoneal mesothelioma: a controlled study. *Ann. Surg. Oncol* 2012; 19(5): 1416-1424.

→ This paper, unfortunately, did not provide overall or median survival for the entire cohort. Outcomes were reported by extent of peritonectomy only.

To Table 2, the following reference was added as cited in the text.

58.) **Pillai K**, Pourgholami MH, Chua TC, Morris DL. Oestrogen receptors are prognostic factors in malignant peritoneal mesothelioma. *Journal of cancer research and clinical oncology* 2013; 139(6): 987-994.