Peer Review File

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Reviewer 1

1. PSOGI, AJCC, and WHO: these need to be explained in the abstract.
    a. Response: Thank you for the comment, we explain these abbreviations later in and as a result removed these from the abstract to avoid confusion as it is not imperative for the readers understanding in the abstract.
2. The abstract lack the conclusion and the take-home message.
    a. Response: Thank you for the comment, there is a conclusion sentence at the end of the abstract and it allows the reader to know what they will learn in a very complex subject.
3. Introduction is poorly written.
    a. Response: Thank you for the comment, we have worked on adding content to improve the introduction.
4. WHO classification is widely acceptable, why would you classify ACs based on other classifications? Appendiceal neoplasms should be classified base on the most recent classification not based on PSOGI.
    a. Response: Thank you for the comment, while the WHO classification is widely accepted, PSOGI classification incorporates the histologic assessment of the mucin which is important for prognostication and hence has become a preferred classification system by the PMP specialists.
5. Molecular pathology of each subtype should be explained in more detail not only explain the role of few genes!
    a. Response: Thank you for the comment, we purposely did not go into great detail of every genes associated with each subtype of appendiceal cancer as this beyond the scope of this review.
6. Treatments of ACs should be summarized in a diagram.
    a. Response: Thank you for the comment, we added a table of the treatments of ACs.
7. The role of hereditary is not mentioned.
    a. Response: This is an excellent comment. Unfortunately, due to the rarity of the tumors and currently lacking genetics data, it still remains unclear if there is a true hereditary component to appendiceal neoplasms and subsequent PMP. We imagine that with improvement in further molecular and genetic work in the future, an underlying hereditary component may be uncovered.

8. Several studies have reported the increase in incidence and mortality rates of ACs but this has not been mentioned here?
    a. Response: Thank you for the comment, we have added this data to the introduction as this only strengthens our argument.
9. The voice of the authors is not clear and only some facts have been mentioned in the paper.
    a. Response: Thank you for the comment, we have added more content to improve the voice of the authors.
10. Tumor markers should be explained in more details and for each subtype.
    a. Response: Thank you for the comment, we touched on this from line numbers 252-259. Additional information is not relevant for the purpose of this review.
11. In the abstract, its mentioned that there is inconsistency regarding the classification and terminology and in the conclusion, its mentioned there is currently a greater consistency?
    a. Response: Thank you for the comment, we changed the abstract to state that previously there was inconsistencies and that these inconsistencies have been reduced due to input from multiple societies.

<u>Reviewer 2</u>

1. Would be very interesting to mention potential targets in appendiceal cancer with these mutations. There are papers on this.
    a. Response: Thank you for this comment, we added a few sentences on potential targets in the "Novel Therapies" section starting on line 427.
2. Wake Forest did a trial of MMC v oxaliplatin with no difference which would be worth mentioning in this review
    a. Thank you for the response, the paper that you are mentioning "Personalized identification of optimal HIPEC Perfusion Protocol in Patient-Derived Tumor Organoid Platform" does show that organoids treated with MMC or 200 mg/m^2 heated oxaliplatin for 2 h displayed increased susceptibility in comparison with 30-min 460 mg/m^2. Additionally there is a Canadian Journal of Surgery article that also says there is limited difference. Finally an article in 2014 states that MMC was safer than oxaloplatin. We bring this to discussion on line 426.
3. You never discuss the role of liver/lung mets in decisions to take patients to surgery. This is important as most people reading this likely are not experts
    a. Response: Thank you for the comment. The presence of these metastases is a relative contraindication for surgical intervention, as PSOGI mentioned in their 2021 revision. As relative contraindications are often judged on a case-by-case basis, we only included absolute contraindication guidelines in this paper to maintain clarity.
4. You quote Verwaal, but please remember that paper is in CRC.

a. Thank you for this recommendation, we deleted this portion.

5. Would you mention Prodige 7 (even though it's CRC) as the most important thing about this trial is not the HIPEC since that is widely debated due to timing, chemo type, etc, but rather emphasizes that even in a more aggressive cancer, the CRS can significantly prolong survival compared to therapy alone.

    a. Response: Thank you for this comment, we considered adding the trial of Prodige 7 to this article, but decided not to use it due to the fact this was CRC

6. Discuss the palliative role of CRS/HIPEC in appendiceal cancers where you cannot get a CC0./1 resection. This may be where mucolytics etc will be important.

    a. Thank you for this response, we discuss the role of palliative surgery in line 379

I hope that you pursue these changes, as I feel this will be an excellent inclusion in the literature.

Reviewer 3

I think there are a number of deficiencies.

1. On page 227 the treatment of LAMN is deficient and the description, at line 323, the recommendation against surgery in high volume disease for Adenocarcinoma is hard to understand.
    a. Thank you for the recommendation. We added the treatment guidelines for LAMN to Table 2 to provide more clarity. We reviewed the statement at line 323, and we believe the statement clearly explains that patients with high volume of disease or disease in an inoperable location would not be surgical candidates and can be considered for systemic chemotherapy.

2. We find PCI makes very little difference in Appendix Ca. The strong recommendation of IV chemo prior to surgery is not based on data that I know of (line 325). Nothing about redo-surgery.
    a. Thank you for this response, we state on line 291 that there are better staging and prognostic tools to provide more accurate staging workup and prognostic forecast than PCI.

Reviewer 4

This manuscript is attempts to discuss a fairly complex subject, so I understand the difficulties in attempting to summarize them within a confined review.

Most notable suggestions for improvement:

1. Line 74: For LAMN, muscularis mucosa obliteration is a fairly common finding, and likely one of the most diagnostic features of this entity, though when not present other features as described in the PSOGI 2016 consensus paper become more helpful in

making the diagnosis. I recommend mentioning the other diagnostic criteria. It's the presence of these other features which is diagnostic, rather than simply the low grade mucinous cytology, which can be seen other appendiceal lesions which are often confused, such as serrated polyps, appendiceal diverticulum, and most commonly reactive epithelial changes in the setting of appendicitis. An important distinction from mucinous adenocarcinoma, not mentioned, is the allowance of "pushing" type invasion, in contrast to the infiltrative type of mucinous adenocarcinoma.

   a. Thank you for this comment, we added this information on line 75.

2. Line 81: There are many more pathologic studies looking at the examination of mucin cellularity and presence of extra-appendiceal neoplastic epithelium and prognosis which are not cited, and therefore is not comprehensive.
   a. Thank you for this comment, we understand that there are more pathological descriptions however we focus on the general consensus.

- Line 104: On pathology of HAMN, there is a confusing statement discussing mucinous peritoneal deposits in a section that discusses the primary neoplasm. Your statement suggests the primary lesion should be called a mucinous adenocarcinoma only based on the high-grade mucinous deposits. But primary and deposit nomenclature are separate as per PSOGI guidelines, which you discuss later, and can be discordant, so if primary pathology is HAMN with high-grade mucinous deposits, that does not make it mucinous adenocarcinoma unless additional infiltrative invasion is noted. I would understand that if the primary pathology is not known, then clinical management should favor the worse possibility, but this is not made clear, and this statement is best moved to the discussion on treatment of PMP.

a. Thank you for this comment, we made this statement more clear for the readers.

- Line 108: This is a completely inaccurate and misleading interpretation of the cited paper. Ref 9; H. A. Choudry et al did find a high discordance between referring institution pathologic diagnosis and their own but they had only one HAMN, and their conclusions were that LAMN's were found to be more often confused as adenocarcinoma (24% of cases), hence over-diagnosed as worse entities. No previously diagnosed LAMN or HAMN were re-classified as mucinous adenocarcinomas.

a. Thank you for this comment, we adjusted this to state LAMN and MACA as misdiagnosed causing inappropriate treatment for these two groups.

- Line 148: I disagree with this statement about requiring IHC to differentiate GCC for other appendiceal neoplasms. This diagnosis is purely histomorphologic. Immunohistochemistry, while useful, is not crucial. The requirement for at least a minor component of a well-differentiated goblet cell adenocarcinoma in WHO classification is based on the requirement for presence of classical morphology for diagnosis. Besides demonstrating the presence of a scattered neuroendocrine cell sub-population, all other stains mentioned are non-specific for diagnosis of this entity and not required or even all that helpful.

a. Thank you for this comment, we adjusted the wording to be less strong.

- Line 306: I feel the statement on treatment of HAMN is overly broad and worded too strongly for something mentions as lacking clear recommendations. At best this is a broad over-

generalization. Ref 32 Goverts et al. provides recommendations on management of HAMN which is based on multiple factors, most notably presence or absence of perforation and residual disease. Per recommendations 33 and 34 of this paper, non-perforated HAMN with T<4, cM0, R0, and no postoperative signs of residual disease, adjuvant right hemicolectomy with or without CRS and HIPEC should be considered (not required), per majority consensus, though this is based on low level of evidence and weak support.

a. Thank you for this comment. While we do agree that that there is weak support suggested in PSOGI, current research is pointing towards this current management for HAMN. We adjusted the wording to be less strong.

Further comments

1. Comment 1
    a. In HAMN treatment, you say that expert centers should be treated like adenocarcinoma. I think there is a wide variety of practice without any good guidelines. Additionally, you quote Choudry et al., but their paper says "Appendectomy to include the mesoappendix is sufficient for low-grade (LAMN) and high-grade appendiceal mucinous neoplasms (HAMN), while right hemicolectomy is generally warranted for a mucinous adenocarcinoma (MACA) due to the potential for lymph node metastasis. "
    b. Reply 1
        i. Thank you for this comment, we agree that there is a wide variety of practice, however I believe that the general treatment of care is to treat HAMN like adenocarcinoma. You are correct in that Choudry's paper did state that appendectomy is sufficient for HAMN. However, we now know that there is high risk for metastasis and thus a formal right hemicolectomy is warranted. I have changed the citations.
2. Comment 2
    a. For low grade adenocarcinoma, I would say that we don't do chemo upfront not because we think we can get it, but because chemotherapy by the nature of how it works does not work well on low grade, slowly dividing cancers.
    b. Reply 2
        i. Thank you for this comment, we agree with this comment.
3. Comment 3
    a. Line 413- I think you mixed up morbidity and mortality
    b. Reply 3:
        i. Thank you for this correction, we have made changes to this error.
4. Comment 4
    a. Add lung to lines 446-447
    b. Reply 4:
        i. Thank you for the comment, however this is not a strict contraindication for CRS+HIPEC as there are studies benefiting Hyperthermic intrathoracic chemotherapy (HITHOC)
5. Comment 5
    a. Line 464- CERS --> CRS
    b. Reply 5:

        i. Thank you for this comment, we fixed this typo.
6. Comment 6
    a. " Finally, recurrence in PMP after CERS+HIPEC is incredibly rare 5- and 10-years post operation." This is very variable depending on histology, etc.
    b. Reply 6:
        i. Thank you for the comment, we added this caveat to the statement made to make it more clear.