Peer Review File

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Reviewer A

I have read with interest the study purposed titled: "Validating the PSOGI classification of peritoneal disease from non-carcinoid epithelial appendiceal neoplasms in the curative and palliative setting: An observational retrospective study". The authors have analysed a huge cohort of PMP patients and validated the PSOGI classification in order to predict the survival.

Some major issues must be solved before consider for publication:

Comment 1: The authors should explain how the pathologists have re-classified the entire cohort. Has it been re-studied or the Ronnet classification has been automatically reclassified as PSOGI classification?
Reply 1: The reclassification was automatic, and no pathological review has been conducted. However, the primary pathology report has always included acellular DPAM and signet-ring cell in the PMCA. We have clarified this in the methods section.
Changes in the text: "The peritoneal tumors are routinely classified according to the Ronnett classification system in our department, with the following categories: acellular and cellular disseminated peritoneal adenomucinosis (DPAM), peritoneal mucinous carcinomatosis (PMCA) or PMCA-intermediate (PMCA-I). The presence of signet ring cells was noted separately in the PMCA group. For this study, reclassification of the peritoneal tumors according to the PSOGI classification system was performed. Thus, acellular DPAM was re-classified as Mucin only, cellular DPAM as MCP-1, PMCA and PMCA-I without signet ring cells as MCP-2, and PCMA with signet ring cells (any percentage) as MCP-3."

Comment 2: The PSOGI classification must be study throughout a ROC curve in order to evaluate the accuracy to predict the survival or DFS.
Reply 2: We are a little unsure whether we understand this comment correctly. Since ROC curves are used for continuous variables with a binary outcome, we do not see how this applies to survival data. The PSOGI classification is not continuous either and survival analysis is not easily dichotomized as these data also encompass time to event. If we have misunderstood the comment, please clarify.
Changes in the text: -

Comment 3: The cases classified as adenocarcinomas are not pseudomyxoma peritonei and they only give confusion in the setting of this study. I recommend exclude this group of patients in this study.
Reply 3: As this was suggested also by the other Reviewers, we have excluded the adenocarcinoma group altogether.
Changes in the text: Comprehensive changes throughout the manuscript.

Comment 4: The patients classified as palliative group, is not clear since the CC2-CC3 and palliative (open/close) are differentiated in the flow chart, however CC2 and CC3+palliative are differentiated in the multivariate analysis. I suggest defining this category during all the study in the same way. The palliative group do not increase the interest into this study and it is not relevant in the objective of this study.
Reply 4: We agree with the reviewer that presenting the data like we did can be confusing, and have changed the flowchart and tables/analyses to reflect the numbers of the respective categories (CC 0-3 and open/close). We have opted to keep the palliative group, as previous PSOGI classification validation studies have not evaluated this group. Even though the PSOGI classification is primarily prognostic after complete CRS+HIPEC; as a tool for the disease itself, it is of interest to know the natural course of the disease when inoperable. It could also be important when discussions of re-HIPEC are on the table to know the prognosis if you don't operate.
Changes in the text: Figure 1 and tables 1 and 2 have been changed accordingly.

Comment 5: In the multivariate analysis, the authors have purposed as comparative category CC more than 1, this category as I have explained above must be defined in an only category during all the study.
Reply 5: The multivariable analysis has been done with all CC scores separately (0-3). However, in the text we have written CC>1, which can be confusing and we have therefore adjusted this.
Changes in the text: "CC-score>1" has been changed to "increasing CC-score" throughout.

Comment 6: How have the authors defined the cut-off levels of age and PCI for the multivariate analysis?
Reply 6: The PCI cut-off of 20 was chosen because it is the commonest cut-off for colorectal cancer with peritoneal metastases. The age groups were defined to include approximately one third each of the patients, while also being easy to communicate. Thus, the largest category (50-59 years) included approximately 40% of the patients, and the other two categories 30% each. However, to avoid confusion of how cut-offs were chosen, we have changed both age and PCI to continuous variables in the analyses.
Changes in the text: Table 2 was altered accordingly.

Comment 7: Why the authors have used the MCP-2 as reference group and not the MCP-1 as the studies referred performed?
Reply 7: MCP-2 was chosen as to avoid huge HR estimates with correspondingly huge 95% confidence intervals. However, as suggested, we have changed the analyses to have MCP-1 as the reference group.
Changes in the text: Table 2 and the Results section were changed.

Comment 8: The findings in DFS differences are significant and these results give an important value to the study, I encourage the authors to include this result in the discussion and conclusion.
Reply 8: We agree that this information is interesting, with the caveat that our follow-up for

recurrences is in many cases considerably shorter than that of overall survival, which is complete. We have updated the Discussion with a sentence on this (see below). However, as this is primarily a PSOGI validation study, we have refrained from including this in our Conclusions. We also added a sentence under *Strengths and limitations*, see below.
Changes in the text: We added the following sentence to the first part of the Discussion: "Recurrence-free survival for CRS/HIPEC patients with CC score 0 or 1 was excellent for mucin only patients (93% over both 5 and 10 years), while MCP-1 patients had a 5-year recurrence free survival of 64%, and MCP-2 patients 32%." Under *Strengths and weaknesses*, we added: "Therefore, the follow-up for recurrences is, on average, considerably shorter than that for overall survival, which is complete."

Minor comments:

Comment 9: How the HIPEC regimen has been chosen? There are different protocols in the same centre.
Reply 2: Mitomycin C is our first choice of treatment, however, during this long time period, different pharmacokinetic studies have been performed, leading to differences in treatment choice. Also, some cases of allergy were noted causing a switch in HIPEC regimen.
Changes in the text: Methods section - "Mitomycin C was the primary choice for HIPEC and cisplatin-based or oxaliplatin-based HIPEC was used during some periods when pharmacokinetic studies were being tested in PMP patients."

Comment 10: The description in survival paragraphs must include the significance level achieved for each value analysed.
Reply 10: We have updated the *Survival analysis* section under Results to include 95% confidence intervals for each value reported, which we hope will satisfy the Reviewer's request.
Changes in the text: See survival results.

Reviewer B

The authors report on a large cohort (n=277) patients with PMP and investigated the PSOGI-classification regarding OS and RFS.
The main message of the manuscript is to use the PSOGI classification as it correlated very well with OS.
Nevertheless I have some major and minor remarks:

Comment 1: In the abstract it says : "Sixty patients had palliative debulking or open/close procedure" but in the Results sections it says "..247 (of 277) patients had a CRS and HIPEC, 5 debulking and 17 open/close". Furthermore Table 1 says in total 215 patients had a CC-0/1-score. This would implicate that patients with a CC-2 or even CC-3 score received HIPEC. The authors should comment on this issue.
Reply 1: Early on in the HIPEC program, we administered HIPEC even to patients with bulky

disease remaining (CC-2/3). This is something that we stopped doing after a few years. A comment has been added in the methods section for clarification.
Changes in the text: Methods – "HIPEC was administered primarily to patients reaching a completeness of cytoreduction score 0-1 (CC-score) results. However, early on during the start-up of the Uppsala HIPEC program, some patients with CC 2-3 palliative debulking received HIPEC as well – something that was discontinued after a couple years"

Comment 2: Did the authors perform pre-CRS/HIPEC laparoscopy in order to rule out irresectable disease?
Reply 2: No, we do not do this for the PMP group of patients.
Changes in the text: -

Comment 3: The Methods part is lacking furhter information on the HIPEC itself: (open or closed? perfusion time? Use of sodiumthiodulfat for patients with CDDP HIPEC.
Reply 3: HIPEC is open colosseum method. Perfusion time is 30 minutes for oxaliplatin-based HIPEC, and 90 minutes for mitomycin C-based treatment, and 60 minutes for cisplatin-based HIPEC. Sodiumthiosulphate was not used in the cisplatin-based HIPEC.
Changes in the text: The Methods section (*Patient selection*) has been updated with this information.

Comment 4: The Morbidity-information have to be updated. Oncologists still believe that CRS and HIPEC is a highly morbid procedure which is not true when CRS and HIPEC is compared for example to oncologic pancreatic surgery. Therefore information like Re-OP rate, persistent stoma, anastomotic leakage and so on should be included in the morbidity section.
Reply 4: Thank you for this comment. We have carefully considered this. However, since our primary aim is long-term survival and PSOGI validation. We feel this request falls outside the scope of this study. Furthermore, there are many large PMP studies showing specifics concerning morbidity including the ones asked for by the Reviewer, including a recent national morbidity study from our department reviewing a very detailed in-hospital morbidity and hospital readmission rates (DOI: 10.1186/s12957-020-01837-4).
Changes in the text: No changes made

Comment 5: Furthermore in-hospital and 30d and 90d mortality rates should be mentioned.
Reply 5: We have updated the *Demography* section in the Results with the following line.
Changes in the text: "1 patient (0.4%) died in-hospital. The 30- and 90-day mortality was 0.4% (1 patient) and 1.3% (3 patients), respectively." was added.

Comment 6: Further oncologic informations are lacking? Pre- or post-HIPEC systemic chemo for >MCP-2 patients?
Reply 6: Thank you for this interesting and relevant comment. No patients received preoperative chemotherapy. Almost all of our patients are referral patients from other regions, and in our registry we do not have data on adjuvant chemotherapy use prior to 2018. Unfortunately, we have no access to this information during the study time period. We hope to investigate this in the coming years.

Changes in the text: The *Follow-up* paragraph in the Methods section was updated with the sentence "Reliable information on adjuvant chemotherapy was lacking in the HIPEC registry prior to 2018 (at which point this is collected prospectively in the registry)." Under *Strengths and weaknesses*, we added: "Another weakness is not having complete information on adjuvant chemotherapy, which could be a prognostic factor for survival."

Comment 7: A PCi-cutoff of >19 was defined as being statistically significant. This is for the whole cohort but did the authors define these cut-off for each of the five PSOGI subgroups? This would be highly interesting if a patient with an MCP-2 and MCP-3 have different significant cut-offs.
Reply 7: As mentioned in our reply to Reviewer 1, comment 6, we have changed the PCI variable to continuous instead of categorical. We didn't do any cutoff analyses for the PCI cutoff of 19 previously used. The rationale was that it has been commonly used as a colorectal cancer cutoff for PCI. In order to remove any confusion, we have opted to use PCI as a continuous variable.
Changes in the text: In table 2, the PCI variable is now continuous instead of categorical.

Comment 8: Why is it that MCP-3 patients have the worst survival? in the Discussion the authors do not realy comment on that? How many patients in the adenocarcinoma-group had signet-ring cells? Maybe very few, explaining the better survival compared to the MCP-3 group.
Reply 8: As suggested by several other Reviewers, we chose to exclude the adenocarcinoma group altogether on the basis that adenocarcinoma is not PMP. Signet-ring cell PMP has been recognized as a group with a very poor prognosis, which has been demonstrated by others as well. As signet-cell PMP is exceedingly rare, we have opted not to comment more on it in the discussion
Changes in the text: Comprehensive changes throughout concerning adenocarcinoma being removed from the analysis.

Comment 9: The authors talk about mucin-associcated celluarity. Some authors have shown that mucin-celluarity is significant. This analysis would be very interesting ,especially for the MCP-1 group. Was this analysis performed?
Reply 9: While interesting, this analysis is unfortunately not performed by our pathologists, and is not included in our routine pathology reports.
Changes in the text: No changes made.

Reviewer C

Comment 1: The definition of mucinous adenocarcinoma is not clear. Was it based on the clinical features not being those of pseudomyxoma peritonei? Or was it based on the histological finding of infiltrative invasion in the primary neoplasm? Either approach would be acceptable, but it must be made clear in the text how the classification was made.

Reply 1: The adenocarcinoma group was included as a comparison group to the PMP classes. However, as also suggested by the other Reviewers, we have excluded the adenocarcinoma group altogether.
Changes in the text: Comprehensive changes throughout.

Comment 2: In the statistical analysis section (line 105), this sentence is unclear to me: 'As many of the patients were referred from other regions or nations, follow-up time for death and for recurrent disease differed in some patients.' I suggest rewriting this sentence to make it clearer.
Reply 2: We agree that this sentence was unclear and have rewritten it in a way which will hopefully make it clearer, see below.
Changes in the text: The *Follow-up* paragraph in the Methods section was deleted and re-written, including: "No patients were lost to follow-up for death. Follow-up for death was performed until 2021-01-25. Comprehensive recurrence follow-up was performed at the same time as follow-up of death. The last available follow-up of recurrence was used."

Comment 3: In the Discussion, line 172, 'ref PSOGI' should be corrected to reference 8.
Reply 3: We thank the reviewer for bringing this to our attention and have changed the text accordingly.
Changes in the text: (ref PSOGI) was changed to (8) in the first paragraph under *Comparison with other studies* in the Discussion.

Comment 4: In the Discussion, line 214, I assume the authors mean: 'This was also stressed by Al-Azzawi et al in their article showing that no current guidelines EXIST on how many blocks are needed to classify the mucin as acellular with confidence.'
Reply 4: It seems we forgot a word, as pointed out by the Reviewer.
Changes in the text: The sentence was changed to: "This was also stressed by Al-Azzawi et al in their article showing that there currently are no guidelines on how many blocks are needed to classify the mucin as acellular with confidence (18)."

Reviewer D

This is a paper on PMP PSOGI classification for validation purposes with a Swedish series.
In my view there are some defects in the approach to the work:

Comment 1: "While several previous classification systems thus co-exist, in 2012 the Peritoneal Surface Oncology Group 75 International (PSOGI) sought to reach a consensus and thereby developed the PSOGI classification system for PMP: low grade, high grade, and high grade with signet ring cells, while acellular mucin is classified into its own group."
The validation of PSOGI classification is mainly on the four tiers of PMP peritoneal disease and to include a fifth component, the mucinous adenocarcinoma introduces confusion.
Reply 1: As suggested here and in the comments from the other Reviewers, we have excluded

the adenocarcinoma group altogether.
Changes in the text: Comprehensive changes throughout.

Comment 2: “The PSOGI classification of PMP provides a solid differentiation of prognostic groups after CRS/HIPEC treatment; however, it could not differentiate between MCP-1 (low-grade PMP) and MCP-2 (high-grade PMP) in the palliative setting.”
PSOGI classification and AJCC 8th ed make a prognostic pathological classification groups after treatment. They are not for palliative prognosis.
Reply 2: We still think this is an interesting research question, since a number of patients are ineligible for curative treatment. Understanding the terminal course of the different groups is also relevant. As the reviewer points out, the PSOGI categories are developed in patients undergoing CRS+HIPEC treatment; therefore, we have deleted this part of the aforementioned passage from our Conclusions.
Changes in the text: The conclusion was thus changed to “The PSOGI classification provides a solid differentiation when estimating long-term (5- and 10-year) overall survival prognosis among PMP patients undergoing CRS+HIPEC.”

Comment 3: “Thus, DPAM, PMCA and PMCA-I, and PMCA with signet ring cells (any percentage of signet-cells), were re-classified as mucin only, MCP-1, MCP-2, and 98 MCP-3, respectively. Mucinous adenocarcinomas were included as a separate group for comparison.”
In PSOGI classification Acellular mucin is a new category, PMP low grade is similar to DPAM, PMP high grade would be similar to PMCA and PMP SRC would be similar to PMCA- S.
Then the groups in the study are not correct: DPAM iquals to acellular mucin. Specimens should be re-classified by pathological review.
Reply 3: We are a little unsure of this comment. DPAM is not the same as acellular mucin. Acellular mucin is a subgroup of the previous Ronnett classification of DPAM. However, DPAM classically includes also bands of epithelial cells with up to low-grade dysplasia.
Changes in the text: We re-wrote the histopathology section of the methods part of the manuscript for clarification of Reviewer 1 comment 1. We hope this clarifies how the reclassification was performed.

Reviewer E

Comment 1: This is a useful and confirmatory study of the value of PCI.
Reply 1: We are very pleased that reviewer E found this study useful.
Changes in the text: -