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Manuscript Review

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Title: SYSTEMIC CHEMOTHERAPY IN APPENDICEAL ADENOCARCINOMAS WITH PERITONEAL METASTASES. IS IT WORTH IT?

Summary:

The study represents a retrospective analysis of 60 patients referred for cytoreductive surgery (CRS) & heated intra-peritoneal chemotherapy (HIPEC) for peritoneal metastasized epithelial appendiceal neoplasms to determine whether perioperative systemic chemotherapy (SCTx, both neo-adjuvant and adjuvant) confer a survival benefit. The study is timely and discusses an important topic. It is most likely written to help communicate the futility of SCTx in patients suffering from this disease presentation to the more local community of treating physicians. Simply because of its importance and helpful addition to the current literature, the study deserves publication, however I have some major and minor comments and suggestions for the manuscript, prior to it being acceptable for publication. The study has been provided to me by the journal as an anonymized manuscript, which for the purpose of the peer-review is laudable, however a reference list is lacking making it not possible for me to ensure the accuracy of the citations.

Major comments:

The study lacks some important details that would be very relevant interpreting the findings. These include:

- Details regarding the systemic chemotherapy given (what type of oxaliplatinum-base treatments, how many cycles, inclusion of anti-angiogenic agents etc.).
- What was the interval between end of SCTx and surgery?
- The timing of metastatic disease presentation (i.e. pre vs. postoperative)
- How many patients had been deemed palliative by referring physicians and were thus (as is often the case) in poor physical state prior to CRS/HIPEC. What pre-habilitation if any was performed/required?
- Because of the use of preoperative chemotherapy, how many patients presented with complications secondary to this, such as neuropathy or haematologic

impairment? We find that many of our patients who have had preoperative systemic chemo are often anaemic and have low iron levels requiring preoperative optimization etc. The same question applies to the toxicity of postoperative chemotherapy.

- The survival times need to be reported for all the subgroups including median survival, 3- & 5-year survival rates etc. This is particularly important also for the low- vs. high-grade groups and I suggest providing a plot where low- vs. high-grade survival times are compared. Furthermore, whilst only 7 patients received neo-adjuvant SC, it is possible to report their median survival times and compare them to the other patients – whilst bearing the limitations of such comparisons in mind.
- Table 1 is confusing because of its layout. Ideally, the table should consist of five columns as a comparison was performed. Column 1: variables. Column 2: all patients. Column 3: low-grade patients. Column 4: high grade patients. Column 5: p-values
- In the discussion there is a comment regarding the value of neo-adjuvant CTx for liver metastases from colorectal origin. My apologies, but I need to politely object to the statement. The updated Nordlinger et al. trial (EORTC 40983) failed to show any substantial benefit of neo-adjuvant SCTx prior to liver resections. As such the statement made by the authors stands in some contrast to the available evidence. Furthermore, there is no data supporting the use of neo-adjuvant CTx in the context of peritoneal metastasized CRC.

Minor comments:

I suggest re-writing the aims at the end of the introduction to something similar like this:

“The aim of this study was to analyze the patterns of systemic chemotherapy administration in patients with peritoneal metastastatic appendiceal epitelial neoplasms, that were referred for CRS/HIPEC at our institution. Furthermore, we aimed to determine if the use of SC in these patients resulted in a survival advantage or not.”

There are minor linguistic issues which could be corrected as follows:

Mucinous appendiceal neoplasms demonstrate a metastatic site predilection for the peritoneum, *with* systemic distant targets such as liver or lung being extremely rare.

Afterward, the perfusate was drained and anastomoses performed *during the second part* of the procedure.

The histological specimens were classified *according* to the WHO classification for appendiceal tumors.
The chi-square test and Fisher's exact test were used to assess the relationship between categorical variables. *T-test was used to assess differences between means of continuous variables.* P values were considered statistically significant when P <0.05.

All the neoplasms were of mucinous type *with the exception of two, where* one was colonic type adenocarcinoma […]

Neoadjuvant SC (oxaliplatin-based regimens) defined as SC cycles administered previously to the *scheduled* CRS and HIPEC procedure was employed in 7/60 (11,7%) patients, 2 of them corresponding to the group of low-grade histology.

Three patients died *during* the postoperative period (5% postoperative mortality).

Therefore, this terminology *cannot* be applied as histologic diagnosis for clinical or research purposes.

Nevertheless, in a recent analysis of Surveillance, Epidemiology, and Results (SEER) data, patients with stage IV well-*differentiated* mucinous appendiceal adenocarcinomas demonstrated no benefit from systemic chemotherapy[12].

In the present series, 7 patients received *neoadjuvant treatment.*

We found another case published in 2013 [17] with *synchronous* lung metastasis from low-grade appendiceal tumor.

The use of SC in low-grade mucinous adenocarcinoma subtype is not supported by our results, and there is no literature *to date supporting this either*

I would suggest re-writing the last paragraph to something as follows:

The evaluation of the use of SC chemotherapy in the palliative setting in high-grade patients is worthy of a clinical trial before it can be deemed standard of care as it is in colorectal cancer. However, simply deducting knowledge derived from colorectal cancer to appendiceal neoplasms is not justified, as these represent distinct disease entities with their own biologic behavior.