Peer Review File

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Reviewer A

1. Important study that compares different perioperative chemotherapy options. With studies like these an optimal HIPEC or HIPEC plus EPIC will emerge.

Answer: We appreciate your comment, and can only agree. We hope a future RCT that more adequately can assess the effect of each treatment.

2. To statistically analyze CC score, the CC-0 was compared to CC-1 through CC-3. How was PCI analyzed? Usually PCI 1-10 vs. PCI >10.

Answer: This was analyzed using Kruskal Wallis as a continuous variable. We, the authors, have discussed this, and believe it is better to preserve the continuous nature of the variable, than to dichotomize it. Either way, a high PCI will show worse prognosis.

3. Can the authors expand first discussion paragraph to explain, if possible, the contrast of improved disease-free survival with no overall survival difference? Are perioperative chemotherapy treatments not durable? Help me understand this paradox.

Answer: Thank you for the opportunity to clarify this issue. Disease-free survival differences are more quickly identified than overall survival differences. With disease-free survival you are just measuring the effect of the locoregional treatment in being able to prevent recurrence. It is common that you will find a disease-free survival benefit, but that doesn't automatically translate to overall survival benefit. Mainly, this is due to the fact that many of the patients have very heterogenous clinical futures. Some recur in the liver or lung, some may receive more curative intent surgery or interventions, some may receive more intense palliative treatments, etc etc. In general, in order to show that you fundamentally alter the clinical future with a treatment, you often need to increase the sample size significantly when going from disease-free survival benefit to overall survival benefit. In order to clarify this in the manuscript, we have added the following information to the first paragraph in the discussion as requested by the author.

"This is probably explained by the fact that the patients will receive a wide array of future treatments. Further curative intent surgeries/interventions, different number of palliative lines of treatment including possibly new trial drugs, etc., make overall survival comparisons difficult to do without significantly increasing the sample size."

4. With the near significant difference in peritoneal recurrences, quality of life data are indicated in future studies. Please comment on conduct of future trials in the discussion.

Asnwer: Thank you for this question. The Swedish Research Council has just recently approved a major grant for the Swedish HIPEC network. We will be conducting two trials back-to-back. One dose-finding study with 5-fluorouracil EPIC (early postoperative intraperitoneal chemotherapy) and then an open label randomized control trial between oxaliplatin HIPEC vs oxaliplatin/irinotecan HIPEC+5-FU EPIC. We have added some information to the discussion.

“In Sweden, one such phase I/III trial program has recently been approved for funding by the Swedish Research Council. This program will dose-titrate a 1-day early postoperative intraperitoneal chemotherapy (EPIC) with 5-fluorouracil and then move into a randomized trial where oxaliplatin HIPEC will be compared to oxaliplatin/irinotecan HIPEC+1-day 5-fluorouracil EPIC for patients with CRC and PM disease.”

5. With the large differences in the use of neoadjuvant chemotherapy (39% vs. 67% vs. 81%), this needs to be standardized in future studies. Please comment on conduct of future trials in the discussion.

Answer: This is a fair point, and definitely something that needs to be better standardized. Sweden has now standardized its peritoneal surface oncology treatment of colorectal PM. The current standard is no neoadjuvant treatment. In case of extensive PM, neoadjuvant chemotherapy is used for the purpose of downstaging. There will be a trial protocol published soon, as such we have opted not to divulge more details in the discussion concerning the future trial plans.

Reviewer B

Good interesting results of HIPEC - oxalipaltin-based, OX-HIPEC or oxaliplatin-irinotecan HIPEC
This study contains important new data.

Thank you for the review comments and for giving us the opportunity to respond to them.