Author’s response to reviews

Title: Cytoreductive Surgery and Hyperthermic Intra-operative Peritoneal Chemotherapy with Cisplatin for Gastric Peritoneal Carcinomatosis Monocentric phase-2 nonrandomized prospective clinical trial

Authors:

Baki Topal (baki.topal@med.kuleuven.be)

Karel Demey (karel.demey@uzleuven.be)

Halit Topal (halit.topal@uzleuven.be)

Joris Jaekers (joris.jaekers@uzleuven.be)

Eric Van Cutsem (eric.vancutsem@uzleuven.be)

Vincent Vandecaveye (vincent.vandecaveye@uzleuven.be)

Xavier Sagaert (xavier.sagaert@uzleuven.be)

Hans Prenen (hans.prenen@uzleuven.be)

Version: 1 Date: 24 Jul 2017

Author’s response to reviews:

Reviewer reports: Q&A

Megan McNally (Reviewer 1): There are a few areas where grammatical changes need to be changed (i.e. run on sentence, commas that aren't necessary). Otherwise, nicely written manuscript.

Mio Kitano (Reviewer 2): The authors in this manuscript present the result of a single-institution phase II, non-randomized clinical study to evaluate long-term survival after CRS+HIPC with cisplatin in patients with gastric PC and to define selection criteria for this treatment modality. There is currently no sufficient data on survival benefit or patient selection criteria to recommend routine use of CRS+HIPC in patients with gastric PC. There were 32 patients who met selection criteria and they demonstrated median OS of 16 months in their entire study cohort and median OS of 24.7 months with 1-year OS rate of 90% in patients who had PCI scores <13 or no PC on small bowel combined with PC on <4 non-small bowel regions. The morbidity and mortality rates related to the procedure were 72% and 0%, respectively. They concluded that there is
survival benefit in patients undergoing CRS+HIPC with cisplatin, provided a CCR-0 and R0 resection, in those patients with PCI scores below 13 and to those without PC on small bowel combined with PC on fewer than 4 non-small bowel regions.

This is a very well written manuscript and I commend the authors for addressing this controversial topic in a prospective manner.

Q1. In the method section, selection criteria is described in Table 1. Impossibility to obtain CCR-0 and R0 resection at the end of CRS are listed on the exclusion criteria. How were those criteria determined prior to intervention? Was this based on pre-operative imaging or diagnostic laparoscopy? What kind of imaging modality did the patients have prior to CRS (CT scan and/or MRI with peritoneal protocol)? Was diagnostic laparoscopy routinely employed in this study?

A1. Pre-operative work-up is now described more in detail in the methods-section on page 7:

"Tumour burden and resectability prior to surgery were assessed using CT-scan of the abdomen and thorax, and whole-body diffusion MRI-scan with peritoneal protocol. Patients with clinically relevant ascites were excluded from the study, which was defined as ascites necessitating percutaneous trans-abdominal drainage or ascites throughout the entire peritoneal cavity measuring more than one cm width on CT-scan prior to CRS+HIPC. Diagnostic laparoscopy was employed routinely to evaluate PCI score and completeness of resectability before CRS+HIPC. At the time of laparotomy, two surgeons independently assessed resectability and scored the PCI to reach a consensus in case of different individual assessments."

Q2. Among the exclusion criteria, clinical relevant ascites is listed. Please clarify the definition as most patients with PC will have some degree of ascites.

A2. See supra A1

Q3. In the method section, you mention that there are 30 patients who received cisplatin-based systemic therapy in neoadjuvant setting and 22 in adjuvant setting. The numbers add up to 52 patients. Is this because 20 patients received both? Perhaps clarify by breaking them down into neoadjuvant, adjuvant, and peri-operative chemotherapy? How was the decision made who gets neoadjuvant vs adjuvant chemotherapy? Was there any survival benefit in patients who received perioperative chemotherapy?
A3. We've now written in the methods section on page 6 the 'systemic chemotherapy part’ more clearly as follows: "Systemic cisplatin-based combination chemotherapy was administered in neo-adjuvant setting in 30 patients, of whom 21 were clinically fit to receive adjuvant chemotherapy within 3 months after surgery. Two patients (PCI score 6) refused neo-adjuvant systemic chemotherapy and were considered for primary surgery. One of these 2 patients was not fit for adjuvant chemotherapy due to postoperative anastomotic fistula and insufficient recovery from surgery.” Our policy is to treat all patients with neo- plus adjuvant chemotherapy whenever it’s feasible and safe.

As shown in Table 2 adjuvant systemic chemotherapy didn’t affect long-term survival in this small patient series (p=0.8)

Q4. XRT is allowed before or after to CRS+HIPC. Did any of the patients receive XRT? This is not mentioned in the result. If some patients received XRT, was there any impact on OS or DFS?

A4. At the time of study design, the possibility of radiotherapy was added to the study-protocol. Though no patient in this study received neither pre- nor post-operative radiotherapy. We now have added one sentence in the methods section on page 6 “No patient received radiotherapy, neither in neo-adjuvant nor in adjuvant setting.”

Q5. Some patients in this study presented with metachronous/recurrent disease. Did the initial stage at diagnosis have any impact on disease burden, OS, or DFS in those patients with recurrent disease? Did the patients with recurrent disease have lower disease burden as they should have been under surveillance and did patients with synchronous disease present with higher disease burden?

A5. The median PCI score in patients with synchronous vs. metachronous PC was 7 (range 1-20) vs. 10 (range 2-15) (p=0.383).

As shown in Table 2 the timing of PC (synchronous or metachronous) didn’t have any impact on long-term survival in this small patient series (p=0.9). We didn’t mention these figures in the text as we believe they don’t add any scientific value. Of course if the reviewers would prefer to add it to the text, we’re willing to do so.

Q6. Figure 1 demonstrates OS after CRS+HIPC with cisplatin for PC. Both the KM curve and the Table demonstrating Number at risk divide the patient cohort into Group A and Group B.
The groups, however, are described as Group 1 and Group 2 underneath the Number at risk table. Please clarify.

A6. We’ve corrected group 1 into group A and group 2 into group B

Q7. Figure 1 demonstrates OS after CRS+HIPC with cisplatin for PC. On the Table demonstrating the number at risk, what time interval does each column represent?

A7. Columns in the table of 'figure legends' correspond with time-intervals in figure 1: 12 months. As these numbers are put underneath Figure 1, we didn’t repeat the time intervals in the legend-table

Q8. The authors concluded that there is survival benefit in patients undergoing CRS+HIPC with cisplatin, provided a CCR-0 and R0 resection, in those patients with PCI scores below 13 and to those without PC on small bowel combined with PC on fewer than 4 non-small bowel regions. On the Figure 1 legend, definition of Group1 (A) and Group 2 (B) is confusing. Groups 1 (A) is the "favorable" group as mentioned in author's conclusion. Why do the numbers overlap? Shouldn't Group 2 (B) have PCI >14 or the presence of PC on the small bowel plus >5 non-small bowel regions?

A8. Group A is indeed the favourable group: PCI score 12 or less, OR the absence of PC on small bowel plus 3 or less non-small bowel regions.

Group B: PCI score 13 or more, OR the presence of PC on small bowel plus 4 or more non-small bowel regions.

We believe our formulation is clear enough already, but we’re willing to accept any other correct formulation as well.

Q9. The authors mention in discussion that CCR-0 and R0 resection are important determinants for this (their favorable) outcome. Patients who were deemed impossible to undergo CCR-0 and R0 resection were excluded from the study. This study included highly selected patients who could undergo CCR-0 and R0 resection, therefore, this is not a fair statement as they did not compare CCR-1 and R0 vs non-CCR-1 and R1-2 patients on patient outcomes.

A9. We agree a definite comparison is not possible in our study. We’ve adapted our statement in the discussion section on page 13, and as the literature supports it, we gave it some nuance as follows: "Completeness of cytoreduction (CCR-0) and R0-resection may contribute to this favourable outcome. Other factors with a positive effect on survival may be the absence of
postoperative mortality, appropriate selection of patients, and high rates of systemic chemotherapy in neo-adjuvant and adjuvant settings."

Q10. The authors mention in discussion, "Other factors with a positive effect on survival are the absence of post-operative mortality, appropriate selection of patients, and high rate of systemic chemotherapy in neo-adjuvant and adjuvant settings". How did the authors arrive to this statement and please clarify, as according to Table 2, there was no statistical significance in use of neoadjuvant or adjuvant chemotherapy on OS. Additionally, is it a fair statement of say absence of post-operative mortality has positive effect on survival? Especially, since there was no mortality in this study?

A10. Please see supra A9 + A3

Q11. In the background, there should be an appropriate reference(s) after the sentence on line 51 of page 4, after "…offering patients improved survival".

A11. Three relevant references have been added, and other references renumbered accordingly.

Q12. If improvements to the English language within your manuscript have been requested, you should have your manuscript reviewed by someone who is fluent in English. If you would like professional help in revising this manuscript, you can use any reputable English language editing service. We can recommend our affiliates Nature Research Editing Service (http://bit.ly/NRES BS) and American Journal Experts (http://bit.ly/AJE BS) for help with English usage. Please note that use of an editing service is neither a requirement nor a guarantee of publication. Free assistance is available from our English language tutorial (https://www.springer.com/gb/authors-editors/authorandreviewertutorials/writinginenglish) and our Writing resources (BMC_WRITING_RESOURCES_URL http://www.biomedcentral.com/getpublished/writing-resources). These cover common mistakes that occur when writing in English.

A12. Improvements to the English language have already been done by ILT (Prof. H.Vekemans): https://ilt.kuleuven.be/english/