Answers to the Reviewers' Comments (line by line)

We would like to thank reviewers for taking out time and effort to review our manuscript, ESPS manuscript NO: 31334, submitted to the 'World Journal of Critical Care Medicine' titled, 'Critical Care Management and ICU Outcomes following Cytoreductive Surgery with Hyperthermic Intraperitoneal Chemotherapy'. We are pleased to have an opportunity to provide a response to our reviewers and submit revised manuscript. Below we have provided a detailed and itemized response to all queries. Changes have also been highlighted in the manuscript text.

A. Reviewer code: 03598924

1. In discussion, ICU Course and Complications: line 5 must be modified to: the purpose of CRS is the performance of complete or near complete cytoreduction. The purpose of HIPEC administration is the eradication of the microscopic residual tumor. HIPEC is effective in eradicating cancer emboli less than 3 mm in their largest diameter.

- we modified line 5 in discussion per reviewer's comments.

2. In page 9, line 9, it has been written twice et al:

-we removed one et al from page 9 line 9 in our manuscript.

B. Reviewer code: 00502932

- No revision suggested by reviewer.

C. Reviewer code: 02496740

1. Page 1 line 13-14: Why this procedure increase mortality? Could you explain it?

- The CRS and HIPEC surgical procedure is technically challenging and has a potential for increased mortality. High peritoneal tumor burden and extent of cytoreduction affects perioperative morbidity and mortality. More the number of organs resected, higher is the morbidity and mortality. High peritoneal tumor load (PCI >16) is an independent predictor of poor long term survival. We are citing an article with reference in the manuscript, no. 15 in the references.

Tabrizian P1, Shrager B, Jibara G, Yang MJ, Romanoff A, Hiotis S, Sarpel U, Labow DM. Cytoreductive surgery and hyperthermic intraperitoneal chemotherapy for peritoneal

carcinomatosis: outcomes from a single tertiary institution. *Gastrointest Surg.* 2014 May;18(5):1024-31. doi: 10.1007/s11605-014-2477-5. Epub 2014 Feb 28
.

2. Page 4: Line 2-8: Could you provide some numeric criteria about ICU admission? And extubation?

- We used standard clinical criteria for ICU admission like need for invasive mechanical ventilation, need for invasive hemodynamic monitoring to direct hemodynamic interventions, Mean arterial pressure (MAP) < 65 mmHg or systolic blood pressure (SBP) < 90 mmHg and need for ongoing fluid resuscitation and vasopressors like norepinephrine, vasopressin, epinephrine drip, requirement of large amount of iv fluids and blood products intraoperatively for bleeding and hemodynamic instability. This was subjective and determined by the anesthesiology team. Patients were left on mechanical ventilation after OR if they were hemodynamically unstable requiring iv fluids and high dose vasopressors, require higher Fi02/PEEP levels, or did not have good mental status for extubation.

- Criteria for extubation was determined by anesthesiologists in the OR. Standard criteria were used like good mental status, recovery from muscular paralysis and anesthesia, hemodynamic stability with SBP> 90 mmHg and MAP> 65 mmHg with no or minimal vasopressor support, adequate oxygenation and ventilation, requirement of large volume of iv fluids and blood products intraoperatively leading to fluid overload state. This was based on clinical discretion of the anesthesiology team.

Changes have been made in the manuscript and highlighted.

3. Page 7 line 7-8: Need details about vasopressor dosages.

Standard recommended dosages of vasopressors were used in all patients, norepinephrine was the vasopressor of choice.

Norepinephrine: 0-35 mcg/min
Vasopressin: .04 units/ min (not titrated)
Epinephrine: 0-35 mcg/min
Phenylephrine: 0-300 mcg/min

Changes have been made in the manuscript and highlighted.

4. Page 7 line 10: How many patients do you intend?

- 18 out of 51 patients (33%) required mechanical ventilation for more than 48 hours for reasons including non cardiogenic pulmonary edema, fluid overload, aspiration or pneumonia. Out of total of 170 adult patients above 18 years of age who underwent CRS and HIPEC therapy

between January 1, 2007 and December 31, 2012, 51 patients were admitted to surgical ICU postoperatively and were included in the study.

5. Page 7 line 12: Which are the findings?

- Our findings of 33% patients (18/51) requiring prolonged mechanical ventilation for more than 48 hours. It has been included in the discussion. Page 7 line 8.

6. Page 7 line 14-15: the concepts should be exploded.

- Our findings of patients requiring postoperative mechanical ventilation (>48 hours) are different from other series (Cooksley et al and Schmidt et al) where most of the patients were either extubated prior or within 3 hours of ICU arrival. We explain our different findings by the level of sickness in our patients requiring prolonged mechanical ventilation. These were the patients who required re intubation, developed septic shock, Acute respiratory distress syndrome (ARDS), surgical complications like anastomotic leaks and intra abdominal abscesses requiring OR or Interventional radiology (IR) guided drainage.

7. Page 8 line 7-9: Are there available data in literature to be compared?

- Lopez-Basave et al (2014) in their study titled, 'Intensive Care Unit Admission after Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy. Is It Necessary?' reported 3 out of 39 patients (7.68%) developing acute renal failure but none requiring renal replacement therapy and recovered with medical management.

- A study by Sugarbaker et al titled, on 356 patients undergoing CRS and HIPEC procedure, titled, 'Prospective morbidity and mortality assessment of cytoreductive surgery plus perioperative intraperitoneal chemotherapy to treat peritoneal dissemination of appendiceal mucinous malignancy' reported incidence of line sepsis to be 17% for grade 3 adverse events and 3% for grade 4 adverse events. They categorized the severity of adverse events by grading them from grade 0 to 4. They also reported reintubation rate of 5% and cardiac arrythmias incidence of 6%

- Kemal J.M et al (2013) in their retrospective study on 13 patients post CRS and HIPEC titled, 'The perioperative course and anesthetic challenge for cytoreductive surgery with hyperthermic intraperitoneal chemotherapy' reported reintubation in 2/13 (15%) , arrhythmia in 1/13 (7%) and renal failure in 0/13 (0%) patients.

- Cooksley et al did retrospective review on 69 patients undergoing CRS and HIPEC therapy titled, 'Post-operative critical care management of patients undergoing cytoreductive surgery and heated intraperitoneal chemotherapy (HIPEC) reported one case of line sepsis 1/69 (1.5%) and no cases developing acute renal failure and arrhythmia.

Our findings are similar to studies in the literature. All these studies have been cited and referenced. (References 27-30 in our manuscript)

8. Page 8 line 10-14: Could you introduce the mortality and morbidity rate?

- Can you please clarify the question? We have included the reported morbidity and mortality in literature at high volume centers.

9. Page 10 line 6-7: In my opinion, these results could be better in the 'ICU course and complications' paragraph.

- we modified and moved the whole paragraph under 'ICU course and complications' per reviewer's comments.

D. Reviewer code: 02974589

1. **Introduction: there are more randomized trials. Within ovarian cancer, there is one trial (CRS +/- HIPEC). Likewise, within gastric cancer, there is one trial (CRS+/- HIPEC). In colorectal cancer, there is one trial from Amsterdam (reference 3 and 4 refer to the same trial, just a later follow up). However, just recently a new randomized trial was published by Cashin et al in European Journal of Cancer. This could be relevant to cite.**

- we included the randomized trial by Cashin et al (2016), titled, 'Cytoreductive surgery and intraperitoneal chemotherapy versus systemic chemotherapy for colorectal peritoneal metastases': A randomised trial, *European Journal of Cancer* 53 (2016) 155e162 with citation.

It is cited in Introduction line 7-9, reference no. 5 in our manuscript.

2. Concerning methodology: Many centers admit to the ICU for all patients at least 1 day. You have done differently. I am assuming that the 51 patients were admitted to the ICU directly after surgery. It would be interesting in table 3 to have the readmission rate to ICU. In other words, in the non-ICU group, how many ended up in the ICU at some later point during the hospital stay? And in the ICU group, how many were re admitted to the ICU during the hospital stay? While difficult to draw conclusions, it seems relevant in determining the safety of letting patients go directly to the surgical ward.

- 6 out of 51 patients (12%) in the ICU group were readmitted to the ICU during hospital stay due to complications. In the non ICU group, 3 out of 119 patients (2.5%) required ICU care at some point in their hospital course. We have included this in Table 3.

3. Results section: second line please define LOS in first instance.

- we defined LOS per reviewer's comments as 'length of stay' in our results section.

4. Discussion: 'Hyperthermia lead to directly cytotoxic effect and increases the depth of penetration'- please provide a reference for this.

- we provided the reference for this with citation, titled, 'Technology of Hyperthermic Intraperitoneal Chemotherapy in the United States, Europe, China, Japan, and Korea', *Cancer J* 2009;15: 249–254) in discussion, ICU course and complications: line 8-9, reference 24 in our manuscript.

5. Discussion: '… due to the peritoneal-plasma barrier' please provide a reference for this.

- we provided the reference for this with citation, titled, 'Technology of Hyperthermic Intraperitoneal Chemotherapy in the United States, Europe, China, Japan, and Korea', *Cancer J* 2009;15: 249–254) in discussion, ICU course and complications: line 10-11, reference 24 in our manuscript.

6. Results: What kind of fluid replacement was used. Was albumin given? How much? How much Ringer?

- We used both crystalloids (Plasmalyte, ringer's lactate, normal saline) and human albumin (5%) for fluid replacement. We do not have the data for exact amount of albumin and other fluids like ringer lactate. At our center, our practice is that we use crystalloids initially for fluid replacement for the first 3-4 litres, then, supplement with colloids like 5% albumin if patients need more fluid replacement and resuscitation.

7. Discussion: 'as well as well suppression' please remove one 'well'.

- we removed one 'well'.

8. References: reference 24 and 4 are the same. Please just cite once.

- we removed reference 24 from the list.