Peer Review File

Article information: https://dx.doi.org/10.21037/jgo-23-711

Reviewer A

Recommend additional information on anesthetic management - I.e were any steroids (dexamethasone, hydrocortisone) administered as part of a PONV prophylaxis protocol to any of these patients? This is standard protocol at many institutions. Were there any other significant differences in administered medications throughout the intraoperative period? Additionally - any significant variations in hemodynamics? There are a lot of confounding factors present in the intraoperative anesthetic management that may be interfering with the results so this should be mentioned.

Reply to reviewer A: Thank you for pointing out that we didn't mention the PONV protocol in our article, we used ramosetron for preventing PONV, and this has been added in the article. For your second comment, there weren't other significant differences in medications except we only used sufentanil (i.v.) in SGA patients and ropivacane (epi.) in EGA patients. For hemodynamic variations, this can be a confounding factor, and we are sorry didn't mention this part, we controlled the blood pressure and heart rate fluctuations in both groups under 20% of the initial level and this was added in the article.

Changes in the text: PONV protocol(page 6, line 8-9), the hemodynamic control protocol was added (page 6, line 5-7).

Reviewer B

Comment 1: First, the title needs to indicate both short-term and long-term outcomes such as inflammatory biomarkers and prognosis outcomes. My major concern for this study is the outcomes did not include the metastasis, since the authors has argued that the opioids would influence the metastasis.

Reply 1: Thank you for your suggestion on the title. We changed and added information as you suggested. As you are concerned, we are sorry that we didn't mention tumour metastasis as we

argued in the main text. We searched and follow-up patients and obtained the metastasis results, and this part was added to the result.

Changes in the text: Title was changed, see page 1, line 2-4. Metastasis result was added in the result and the table. (page 10, line 8-9; table 7)

Comment 2: Second, the abstract needs some revisions. The background did not briefly indicate the potential clinical significance of this research focus and what the current knowledge gap is. The methods need to describe how these outcomes were measured and how these patients were followed up prospectively. The results need to briefly summarize the clinical characteristics of the two intervention arms and quantify the findings on prognosis outcomes. The conclusion needs comments for the clinical implications of the findings, not to repeat the findings again.

Reply 2: Thank you for your suggestion, we are sorry that the abstract part was poor written, and we tried our best to improve, and make changes.

Changes in the text: page 1, line 30-31; page 2, line 1-4,9-11,20-25.

Comment 3: Third, the introduction is poor. Since prognosis outcomes are more clinically relevant than inflammatory biomarkers, the authors should have the literature review focus on prognosis outcomes. The authors also need to analyze the potential reasons for the inconsistent findings on the roles of anaesthesia-related factors on inflammatory biomarkers and prognosis outcomes and clearly explain why RCTs are needed to address this controversy.

Reply3: Thank you for your suggestion on the introduction. It's true that prognosis are more clinically relevant, but as we mentioned in the method part, our primary outcome was IL-4/IFN-γ, and the sample size was also calculated based on the previous study in IL-4/IFN-γ. Also, we added the reasons for the need of RCTs, and rewrote some part in the introduction.

Changes in the text: Page 3, line 28-34. Page 4, line 1-8, 11-20.

Comment 4: Fourth, in the methodology of the main text, please explain why non-inferiority design was adopted. As I commented above, the primary outcome should be prognosis and metastasis, so the authors need to substantially revise this part. Please also describe the details of follow up of patients. In statistics, please ensure $P<0.05$ is two-sided

Reply 4: Thank you for your kind suggestion. As we mentioned in the last paragraph of the introduction, we aimed to determine whether the effect of SGA on immune system, tumour prognosis are comparable to EGA, but not assuming that SGA is superior to EGA in tumour

prognosis. And it is very sorry that our design of the study cannot be changed, but future studies mainly focusing on tumour prognosis and metastasis can be designed. The follow-up of patients is described and added to the paper. Also, P<0.05 (two-sided) was confirmed and added.

Changes in the text: The follow-up protocol was added in the main text. (Page 7, line 23-25)

Comment 5: Finally, please consider to review and cite some related papers: 1. Thomas TE, Bowers K, Gomez D, Morgan O, Borowsky PA, Dutta R, Abu Y, Roy S, Rojas KE. The association between perioperative opioids and breast cancer recurrence: a narrative review of the literature. Transl Breast Cancer Res 2023;4:12. 2. Hao X, Zhou Y, Ling Y, Miyoshi H, Sumitani M, Chan KY, Park HJ, Feng Z, Rao Y. Effects of high-dose opioid analgesia on survival, pain relief, quality of life and adverse drug reactions in cancer and neuropathic pain patients: a retrospective cohort study in real-world clinical practice. Ann Transl Med 2022;10(18):998. doi: 10.21037/atm-22-4242. 3. Memeo R, Pisani AR, Ammendola M, de'Angelis N, Inchingolo R. A new era for hepatocellular carcinoma. Hepatobiliary Surg Nutr 2023;12(1):135-136. doi: 10.21037/hbsn-23-10.

Reply 5: Thank you for your suggested papers, we have read them thoroughly and cited the paper.

Changes in the text: The paper was cited in reference 6.

Reviewer C

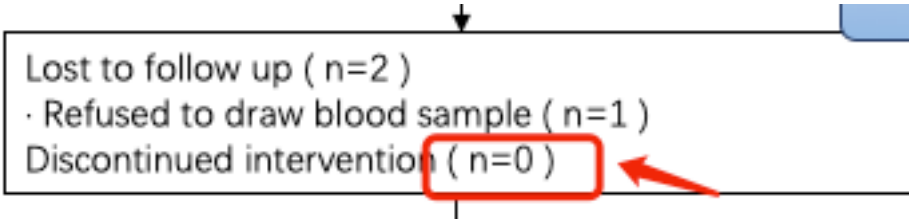
1. Please structure your Main Text as: **Introduction, Methods, Results, Discussion, Conclusion**. Please add "Conclusion" section for your manuscript.

Reply 1: We are so sorry for the carelessness. The conclusion section was added.(Page 13, line 7)

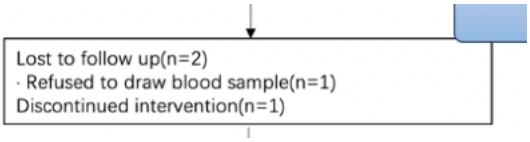
2. Ref.41 was not cited in text, please check.

Reply 2: We are sorry for the missing citation. In the previous revision, we added a Ref.6, and the number was disordered. The right citation of Ref.41 was updated in the text. (Page 12, line 6)

3. Figure 2: Please check if it should be "(n=1)".



Reply 3: Thank you for your notice. It is (n=1) in Fig 2 in the article, please check.



4. **CONSORT Checklist** needs to be re-checked and updated, please make the following revisions both to your manuscript and CONSORT checklist accordingly:

a. Item 9: allocation **concealment** method has not been described in your paper. Please check.

Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	Page 5/line 3-6	method/ paragraph 1

b. Item 23: please fill in "Abstract/Paragraph 5".

Registration	23	Registration number and name of trial registry	page 4/ line 20-24	method/ paragraph 1

c. Item 24: please fill in "Footnote/Paragraph 2".

Protocol	24	Where the full trial protocol can be accessed, if available	page 4/line 24	method/ paragraph 1

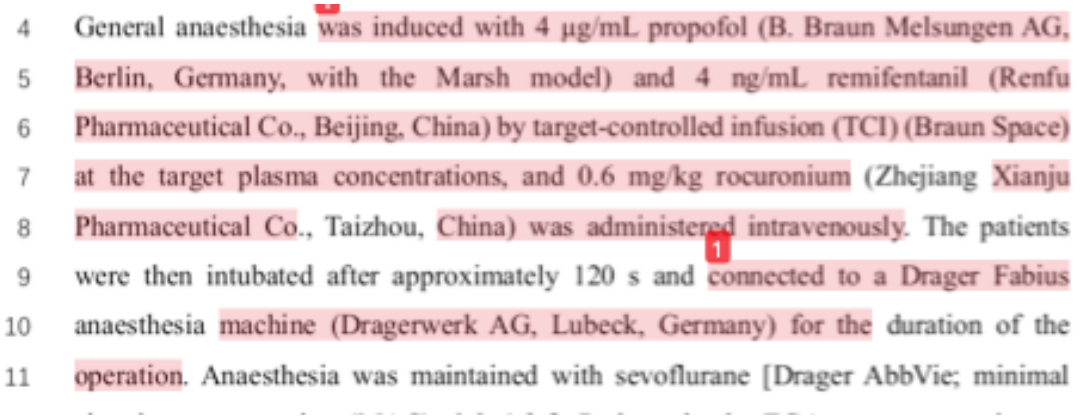
d. And you should complete Table 2 in CONSORT checklist, it's for **Abstract**. Thus, please pay attention to the Page/Line number and Section/Paragraph filled in this table. For example, "Section" here should be all filled out with "Abstract". For items not mentioned in Abstract, you could just fill "N/A" instead.

Table 2 Items to include when reporting a randomized trial in a journal or conference abstract

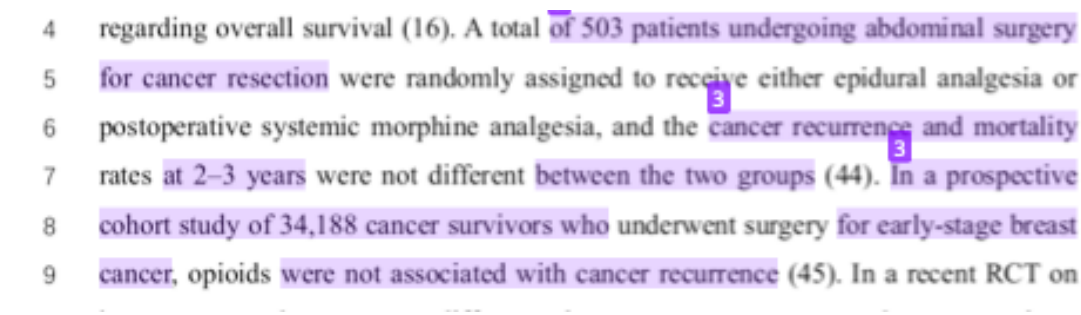
Item	Description	Reported on Page Number/Line Number	Reported on Section/Paragraph
Title	Identification of the study as randomized		
Authors *	Contact details for the corresponding author		
Trial design	Description of the trial design (e.g. parallel, cluster, non-inferiority)		
Methods			
Participants	Eligibility criteria for participants and the settings where the data were collected		
Interventions	Interventions intended for each group		

Reply 4: Thank you for your suggestion, for comment a., we already added the allocation concealment method in the text (page 5, line8-11). For b,c,d., the information was added in the CONSORT Checklist.

5. Originality checking of below parts show high duplication. Please revise your paper to lower the duplication rate.



4 General anaesthesia was induced with 4 μg/mL propofol (B. Braun Melsungen AG,
5 Berlin, Germany, with the Marsh model) and 4 ng/mL remifentanil (Renfu
6 Pharmaceutical Co., Beijing, China) by target-controlled infusion (TCI) (Braun Space)
7 at the target plasma concentrations, and 0.6 mg/kg rocuronium (Zhejiang Xianju
8 Pharmaceutical Co., Taizhou, China) was administered intravenously. The patients
9 were then intubated after approximately 120 s and connected to a Drager Fabius
10 anaesthesia machine (Dragerwerk AG, Lubeck, Germany) for the duration of the
11 operation. Anaesthesia was maintained with sevoflurane [Drager AbbVie; minimal



4 regarding overall survival (16). A total of 503 patients undergoing abdominal surgery
5 for cancer resection were randomly assigned to receive either epidural analgesia or
6 postoperative systemic morphine analgesia, and the cancer recurrence and mortality
7 rates at 2–3 years were not different between the two groups (44). In a prospective
8 cohort study of 34,188 cancer survivors who underwent surgery for early-stage breast
9 cancer, opioids were not associated with cancer recurrence (45). In a recent RCT on

Reply 5: Thank you for your kind suggestion. We have already made changes to the text according to the high-duplicated parts.(Page 5, line 21-28; page 12, line 21-26)