Peer Review File

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Reviewer A

This manuscript is well written overall, and the topic is of some interest. However, there are some issues.

Methods
1. The patient population included those with recurrent cancer with previous exposure to chemotherapy. Would this have skewed or affected your results? Would it have been better to simply recruit from patients with de novo diagnoses of primary cancer?
Reply 1: As the reviewer pointed out, six patients who underwent adjuvant chemotherapy were included in this study. However, these patients had more than a year gap between the adjuvant chemotherapy and the start of 1st-line chemotherapy. The effect is considered limited.
Changes in the text: We added a following sentence in the result section (please see Page 7, line 157-158) and added the data to Table 1. “Six patients underwent adjuvant chemotherapy and had more than a year gap between the adjuvant chemotherapy and the start of 1st-line chemotherapy.”

2. Why were patients with ECOG3+ excluded?
Reply 2: Patients with PS3 or higher are generally not candidates for chemotherapy, so we excluded patients with PS3 according to the protocol.
Changes in the text: We have added “according to the protocol” to the result section (see Page 7, line 153).

Results
1. Minor point - "Yellow ethnicity" may not be the correct term. "Japanese ethnicity" only should suffice
Reply 1: We agree.
Changes in the text: We have deleted “and of Yellow” as advised (see Page 7, line 151).

2. Why were only 48 patients analysed out of the 59 who received chemotherapy? Was it not possible to account for other chemotherapy regimens?
Reply 2: Adverse effects differ in chemotherapy regimens. Therefore, to reduce the bias, we selected the combination of the same class of agents, fluoropyrimidine plus oxaliplatin. Other chemotherapy regimens varied and patients’ numbers were small so that we couldn’t analyze them.
Changes in the text: No changes.

3. The incidence of symptoms before chemotherapy between ND and D were not

significantly different. This requires explanation as to why then are the symptoms chosen from CTCAE relevant, if they don't correlate with zinc levels?
Reply 3: As the reviewer pointed out, the incidence of symptoms at baseline was not statistically different between the two groups. However, there were higher tendencies of incidence in many symptoms of the D group (1.4-3.6 times in mouth/throat sores, taste changes, rash, and itching). We considered this was due to a small number of patients detecting the statistical difference.
Changes in the text: We have added this to the discussion section (see Page 10, lines 215-218). “The incidence of symptoms before chemotherapy between ND and D were not significantly different. However, there were higher tendencies of incidence in many symptoms of the D group (1.4-3.6 times in mouth/throat sores, taste changes, rash, and itching). We considered this was due to a small number of patients detecting the statistical difference.”

Discussion
1. It is hard to understand why zinc levels decreased in the ND group with chemotherapy, but increased in the D group. The explanation given is that those in the D group had treatment response and therefore likely had more oral intake. Would that also not occur in the ND group - you have not shown that this group had less treatment response.
Reply 1: The ND group initially had high zinc levels, so even if the nutritional status improved, the effect on the zinc level would been limited.
Changes in the text: We have added a following sentence as advised (see Page 10-11, lines 232-233). “The ND group initially had high zinc levels, so even if the nutritional status improved, the effect on the zinc level might be limited.”

2. It may be difficult to draw statistical conclusions from analysis of the D group given low patient numbers - I suggest this be included in your limitations
Reply 2: We agree.
Changes in the text: We have modified our text as advised (see Page 11, lines 248-249).

3.The multicenter prospective trial by Ito et al (reference 7) suggested that polaprezinc (which also contains zinc + carnitine) seemed to improve symptoms, this raises the question of whether it is the other components other than zinc that are beneficial. This may be worth discussing.
Reply 3: We agree and add “The previous study showed polaprezinc improved dysgeusia and suggested some components other than zinc may contribute to the symptom improvement. This is worth to study further, especially in ND group patients.” to the discussion section.
Changes in the text: We have modified our text as advised (see Page 11, lines 242-244).

Reviewer B

Major points

1) A major limitation of this study is the inconsistency in therapeutic interventions (intervention criteria, drug selection and dosage, etc.) for low zinc levels.

Reply 1: Since this study was observational, the selection of therapeutic regimens was based on the judgment of attending physicians and patients' agreement. We plan a next interventional study with zinc administration in an appropriate cancer and regimen fixed.

Changes in the text: We added the following sentences to the limitation paragraph as advised (please see Page 11, lines 252-254). "Since this study was observational, the selection of therapeutic regimens was based on the judgment of attending physicians and patients' agreement. We should plan a next interventional study with zinc administration in an appropriate cancer and regimen fixed."

2) Fig 4 (c); in Page 6, line 129, authors stated that 'cases treated with zinc acetate hydrate will be excluded from the analyses. In the Zinc ND group, there are supposed to be some cases with a zinc level below 60 at 3 months. In the Zinc ND group, are only drug-free cases included in the 6month analysis? If so, the further decline in Zinc levels at 6 months may be due to the lack of therapeutic intervention.

Reply2: As the reviewer pointed out, the data after zinc administration was not included in the analysis. In routine clinical practice, serum zinc level is generally not tracked, so therapeutic intervention is often not performed and such patients were few.

Changes in the text: No changes.

3) Page, 6, line 127. In this study, the borderline zinc deficiency group was included in the zinc non-deficiency group for analysis. Were the results similar when the borderline zinc deficiency group was included in the deficiency group?

Reply3: Only two out of 48 patients had normal zinc levels more than 80 μg/dL at baseline. Therefore, unfortunately we could not perform the analysis the reviewer kindly recommended.

Changes in the text: No changes.

4) Page 7, line 153. Median follow-up of 17.0 months is too short to discuss OS.

Reply4: We appreciate the advice. We updated the survival data and the cutoff date to August 20, 2023. However, the median follow-up for all patients was still as short as 20.6 months (IQR 10.5–27.5) to assess the OS for CRC patients. Therefore, we added "NA: not assessable" instead of the OS p-value of CRC in Fig. 3.

Changes in the text: We have modified our text as advised (see Page 5, line 103, and Page 7-8, line 160-161) and modified some data (See Fig. 3 and Figure captions)

Minor point

5) Page 5, line 117. Serum zinc levels were measured before and (1, 3, and 6 months) chemotherapy → Serum zinc levels were measured before and 1, 3, and 6 months AFTER chemotherapy?

Reply 5: We agree the recommended modification “Serum zinc levels were measured before and 1, 3, and 6 months after chemotherapy,”
Changes in the text: We have modified our text as advised (see Page 6, lines 122-123).