Peer Review File

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Reviewer A

The authors started from the consideration that malnutrition affects up to 51.6% of cancer patients, and cancer associated malnutrition has been associated with a negative impact on survival, quality of life (QoL), and cancer treatment tolerance. They further emphasize that the best intervention for cancer-associated malnutrition has not yet been identified and ONS have been proposed as a modality for preventing or alleviating cancer-associated malnutrition. Consequently, since clinical trials of ONS with or without dietary counselling (DC) have obtained contradictory results, the authors designed this meta-analysis to evaluate the efficacy of ONS compared with DC alone in terms of bodyweight, nutritional status, and QoL in cancer patients receiving chemotherapy. The authors conclude that ONS may be beneficial for cancer patients receiving chemotherapy, particularly those at high risk of malnutrition.

Major comments

The use of ONS in cancer patients undergoing chemotherapy is mainly recommended in two conditions:

a.when patients are malnourished, and this condition might reduce the compliance to toxic oncologic treatments.

b.when severe mucositis due to radiation and chemotherapy can hamper, also in non-malnourished patients too, the standard food intake, and supplementation with ONS might help to overcome this critical period.

- We add the recommendation from ESPEN and ESMO guideline of cancer patients as text in line 70 -74 page 3 ; "According to the ESPEN practical guidelines on clinical nutrition in cancer (9), all cancer patients should receive dietary counseling for adequate energy and substrate requirements, regardless of baseline nutrition status, cancer staging, or a history of previous weight loss. The additional use of ONS was advised to help achieve nutritional goals as an adjunct to dietary counseling (9, 10)."

This meta-analysis is technically perfect, but it does not focus on the true clinical problem.

We do not know anything about the nutritional status of the patients entered the studies (i.e., if their weight was the usual one, we cannot expect any increase in body weight during chemotherapy!), if the treatment was toxic or not. In such conditions why the use of ONS should confer a benefit?

- We emphasized the important of body weight during chemotherapy treatment and the number of cancer patients that have pretreatment weight loss. Pretreatment weight loss and maintaining body weight during chemotherapy correlated with survival outcome in line 61-65 page 3 ;

- change in text "Pretreatment weight loss was common in cancer patients, accounting for 34%, and was associated with poor overall survival (4). Furthermore, in patients with gastrointestinal (GI), lung, and ovarian cancers undergoing chemotherapy, weight stabilization correlated with a significant improvement in survival (5-7). Maintaining body weight during chemotherapy may serve as a surrogate outcome for cancer treatment."

- We acknowledge the limitation in this meta-analysis about baseline nutrition status of cancer patient receiving chemotherapy in line 326-330 page 8 ;

- change in text "There was limited data on baseline pre-cachexia and cachexia from the selected RCTs. Only four RCTs reported baseline nutrition status of patients, making it unable to perform a subgroup analysis based on baseline nutrition scores. Therefore, the benefit of ONS for specific malnourished patients receiving chemotherapy could not be fully assessed in this study."

Finally, finding any variation of the nutritional status and QoL of the patients undergoing an oncologic therapy cannot disregard the response of the tumour to the therapy, which often represents the main factor associated with an improvement of the general status of the patients.

- We acknowledge the limitation in this meta-analysis about baseline nutrition status of cancer patient receiving chemotherapy in line 323-325 page 8;

- change in text "Its limitation was the lack of oncologic outcomes, including progression-free survival, overall survival, or treatment-related side effects."

I am well aware that RCTs in these patients are quite challenging because having a control group without a nutritional support is unethical, but this does not justify drawing conclusions on the efficacy of a treatment when the target population is wrong.

-We explain the important of body during chemotherapy that not only associated with survival outcome but also the QOL. We believe that cancer patients receiving chemotherapy are the target population for evaluated efficacy of ONS adding to dietary counselling regardless of baseline nutrition status and final body weight outcome are important. In line 70-77 page 3;

- change in text "According to the ESPEN practical guidelines on clinical nutrition in cancer (9), all cancer patients should receive dietary counseling for adequate energy and substrate requirements, regardless of baseline nutrition status, cancer staging, or a history of previous weight loss. The additional use of ONS was advised to help achieve nutritional goals as an adjunct to dietary counseling (9, 10). Weight stabilization during chemotherapy was associated

with survival outcomes (5-7). Therefore, cancer patients receiving chemotherapy were the target population for evaluating the efficacy of ONS in terms of body weight changes."

Reviewer B

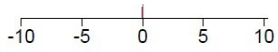
1. **All abbreviations** in figures/tables (including the supplementary appendix) and legends should be explained. Please check all your figures and tables.
   - Add figure titles and detail of abbreviations of figure 1-8 in page 12 of main text
   - Add abbreviation of figures in supplement
   - Add detail of abbreviations in table 1

2. Figures

   (1) Please kindly refill the **attached version** of the PRISMA flowchart in a **Word** file.

   - Please find PRISMA flowchart in the separate Word file

   (2) Please check if any description is needed for **the axis in the forest plot**.



   - Description was showed in each figure above X axis as "favor ONS" and "favor control"

   (3) Please consider using "no less than" or other similar words in the following sentence since **50%** should also be included.

MD of 2.47 kg (95% CI: 0.73 to 4.21, p-value 0.01); female sex more than 50%, with pooled
MD of 2.37 kg (95% CI: 1.33 to 3.42, p-value < 0.01); baseline bodyweight lower than 65 kg,

   - Replace all "more than 50%" to "no less than 50%"

   (4) Please recheck the data in the following sentence.

was heterogeneity between studies (I^2 86.02%, Q test: chi-square 21.46, DF 3, p-value 0.02),
as shown in Figure 8. One of these RCTs had baseline fatigue domain QoL imbalance (25),

   - Revised as suggestion to p-value < 0.01

   (5) The publication year in the Figures is inconsistent with the corresponding references. Please recheck all your figures and tables for this and revise.

Elkort RJ, 1980
Baldwin C, 2011
Sanchez-Lara K, 2014
Cereda E, 2017
Kim SH, 2019
Huang S, 2020
Dou S, 2020
Meng Q, 2020
Huong LT, 2021

28. Elkort RJ, Baker FL, Vitale JJ, Cordano A. Long-term nutritional support as an adjunct to chemotherapy for breast cancer. JPEN J Parenter Enteral Nutr. 1981;5(5):385-90.¶

26. Cereda E, Cappello S, Colombo S, Klersy C, Imarisio I, Turri A, et al. Nutritional counseling with or without systematic use of oral nutritional supplements in head and neck cancer patients undergoing radiotherapy. Radiother Oncol. 2018;126(1):81-8.¶

23. Meng Q, Tan S, Jiang Y, Han J, Xi Q, Zhuang Q, et al. Post-discharge oral nutritional supplements with dietary advice in patients at nutritional risk after surgery for gastric cancer: A randomized clinical trial. Clin Nutr. 2021;40(1):40-6.¶

- Revised year of publication as suggestion in all figures and the table

3. In the text, the references should be cited **numerically (in round brackets) and consecutively in the order of appearance.**

For references cited in **Table 1**, please number them according to the first identification of the table. In your manuscript, Table 1 is behind ***Ref 19***, thus, all references that first appear in Table 1 should be numbered from ***20***. And those references behind Table 2 should be numbered from ***29***. Please kindly rearrange your Table 1 or the reference list.

- Revised (Ref 14 was also used in introduction part. Therefore, the reference number for Table 1 would be 14, 21-28)

4. For **Appendix Table 1**, it is suggested to combine it into one Table or just separate them into Appendix Tables 1 and 2.

- Separate to table 1 and table 2

5. The page information is missing for ***Ref 29***. Please recheck.

- Revised by add page information