Author's response to reviews

Title: Influence of Oral Glutamine Supplementation on Survival Outcomes in Locally Advanced Non-Small Cell Lung Cancer Patients Treated with Concurrent Chemoradiotherapy

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Author's response to reviews: see over
Dear Editor,

We received the comments of both Reviewers and revised the manuscript, final version of which was also uploaded to the system. The reviewer 2 has presented his/her kind feelings about our effort to improve our manuscript in the first revision, and therefore, we give our thanks to his/her kind comments. The reviewer 3 has criticized our manuscript in few points, most of which have been tried to be addressed with minor modifications and additions by respecting the suggestions, and presented them in a point-by-point manner in the responses to reviewers section below. We hope we could satisfy suggestions by the reviewer 3, which we believe increased relevancy of our current version of manuscript.

Best Regards,

Attachment: Response to reviewers

On behalf of all co-authors,
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Response to Reviewers

Reviewer 2
Reviewer's report:

1. **Comment:** The authors did all their efforts to improve the manuscript - with success! Background, goals, methods and conclusions are now clear and presented in a logical manner.

   **Response:** We are happy to see that we could satisfy the reviewer, and would like to give our special thanks to the reviewer for his/her kind opinion on our effort to improve our manuscript.
Reviewer 3
We appreciate and would like to thank Reviewer 3 for his/her comments of paramount importance which we believe will significantly increase the impact and relevance of results presented in our this current revised version of the manuscript.

Major compulsory revision

1. Comment 1. 1. Abstract: The question posed by the authors is still not clearly defined!

   In backround section of abstract authors posed the main question about survival and then in result section discussed on the first place about side effects treatment.

   Response 1. Since, in our previous study, we have evaluated and showed the efficacy of oral Gln administration on prevention of toxicities related with C-CRT in patients with locally advanced NSCLC (Topkan et al. Lung Cancer 2008), our primary aim in the current study was to investigate the potential positive or negative effects of Gln on survival outcome. Moreover, because radioprotective efficacy observed in our previous study was also confirmed by the present study, these findings were not considered to be presented in the initially submitted form of the manuscript. However, as two of the four reviewers pointed out that a manuscript presenting survival outcome of patients receiving a radioprotector should also include findings related with its radioprotective efficacy, to an effort to satisfy the concerns of the two reviewers, we made somehow obligatory modifications and additions, which were not given in the previously submitted manuscript. Therefore, we would like to state that we are totally in line with the reviewer’s comment about our primary aim was not to give toxicity data in such detailed manner, and would like to ask reviewer's indulge about our modifications in an effort to respond other reviewers’ comments. Nevertheless, to make our aim more clear we added a new sentence “We additionally evaluated role of oral Gln in preventing C-CRT-induced weight change, acute and late toxicities” as the last sentence to “Background” sections of both abstract and main body text as recommended.

2. Comment 2. 2. Background: In this context, exogenous Gln supplementation not only normalizes Gln levels in the body but also selectively increases GSH levels in normal tissue, which may explain its selective radioprotective function [3, 6-8]....

Response 2. We attentively read the article recommended by the reviewer. In this article, it is advocated that supplemental glutamine given at pharmacological doses of 20–40 g might not be adequate to supply the daily amount of Gln needed to be released to plasma, and that Gln supplementation might be effective specifically in inflammatory conditions. Such inquisitive approach to the literature by the authors should be respected scientifically. However, cancer-related data have been inadequately presented in the article, and we believe that 2 issues relevant to the cancer patients receiving C-CRT should be considered. First, cancer itself is a disease associated with chronically active inflammation. As Soeters et al also stated, it is reasonable to estimate that, similar to burns, toxicities secondary to CRT such as esophagitis are inflammatory conditions that might potentially be responsible for increased Gln depletion, if any. Moreover, as we mentioned in the 4th paragraph of the “Discussion” section, the fact that human tumors exhibit a 5- to 10-fold faster rate of Gln consumption than normal healthy tissues might also increase the depletion of Gln. Additionally, Gln depletion may also result in depletion of an antioxidant, GSH, leading to increased toxicities (mucositis, etc.) in healthy tissues. This toxicity, then, may result in a vicious cycle of inflammation and increased Gln depletion.

At this point, 30 g daily doses of oral Gln administration may be inadequate to totally replenish daily amount of Gln released to circulation. However, efficacy of Gln in reducing CRT-induced toxicities and weight loss during treatment shown in our previous study and one presented here suggest the probable potency of Gln even at such relatively small doses. Finally, we would like to give our special thanks to the reviewer for his/her kind recommendation and for projecting a light to the unresolved era that brought our mind an idea to start a new project for a future trial to investigate the validity of our results with Gln supplementation at supra-pharmacological doses (60-100 mg/day).

3. Comment 3. 3.Methods: What was the method to evaluate nutritional status of patients? Just measuring weight?
Which criteria did you use for grading nausea and vomiting?

Response 3. Although we are aware of several comprehensive tools (lean body mass, arm perimeter, etc.) of evaluating nutritional status in cancer patients, and currently use some of them in our routine practice. However, at the time period that the patients included in the study was treated, we unfortunately used only measuring weight, percent weight loss and relative change in BMI.
All toxicity grading measures in the present study were carried out by utilizing RTOG toxicity scoring. We apologize for the missing information, and would like to thank to the reviewer for the recommendation that reminded us our mistake. As recommended, the necessary modifications have been made by addition of the sentence “and graded according to RTOG scoring [19].” with citation of relevant reference. The previous subtitle “Patient evaluation and scoring of ARIE” was also replaced with the new one “Patient evaluation and toxicity scoring”.

4. **Comment 4.** 4. General remark on the paradigm of the study and discussion

In the discussion authors showed data (from references) that exogenous supplementation of glutamine doesn't stimulate tumour growth in various cancers. Furthermore, they also showed data that lack of glutamine in body is associated with promoting tumour growth (your reference 4). So, why the authors main question is the association of glutamine ingestion and its promoting of the tumor growth in NSCLC patients. Are these tumor cells so different than other cancer cells that they expect that association? My be they would consider another approach: regarding to available data they could look for association between the glutamin supplemetation and improved survival?

**Response 4.** In the absence of retrospective studies or prospective randomized controlled trials carried specifically on NSCLC patients, it is neither easy nor reliable to make a firm conclusion about the association, if any, between Gln administration and prolonged survival, or to speculate that different cancer cells respond to Gln in similar or different ways. Likewise, as in any kind of radioprotector, the issue that radioprotective role of Gln on different normal tissues is the same or different also lacks answer. As an example, amiphostine, which is a widely used radioprotector having well-established protection against RT-induced mucositis, has not been shown to have any radioprotector role in preventing RT-induced bone fracture or muscular atrophy. But we may not easily conclude with the available literature on mucositis that amiphostine can also prevent RT-induced osteonecrosis. Therefore, based on favorable results from our previous study, in which we evaluated the impact of oral Gln supplementation in preventing RT-induced esophagitis in patients with locally advanced NSCLC treated with C-CRT, and considering the concerns in the literature that Gln might protect tumor cells, or even promote tumor growth, herein we retrospectively evaluated the potential detrimental or beneficial effect, if any, on survival of this patients. However, as seen on our results, although not statistically significant survival in patients receiving Gln was better than
those who did not receive, which might potentially be related with Gln administration or small study size. Thus, as is the case for any retrospective study, our results suggesting no detrimental effects of Gln supplementation during C-CRT in NSCLC patients on survival outcome may form a base hypothesis for the future prospective trials, rather than being accepted as a guide. As an oncologist, since all our wishes in any primary tumor is to improve survival and quality of life measures, it would be of great importance to validate our results.