

Peer Review File

Article information: <https://dx.doi.org/10.21037/jgo-23-1011>

Reviewer A

I have read with great interest the paper. In the text, assessment of treatment response should be stressed. Therefore, text would be enhanced by addition of references, such as PMID: 30560501 to better contextualize the issue at hand in oncologic scenario. Strengths of the study supporting evidence and validity of the research should be better reported. Please add details on “patients at risk” in all survival curves.

REPLY: We thank you for your affirmative feedback. We have tried our best to address all of the concerns that you raised. We hope our revision meet your requirements and standards.

1. The assessment of treatment response have been stressed. On page 10 in the “Limitations” section: line 327 to 330.

And needing more reliable diagnostic method to stratify RPLN patients can be helpful to choose more suitable treatment for every patients, such as dynamic contrast-enhanced magnetic resonance imaging parameters (42).

2. “Patients at risk” in all survival curves have been added. On page 18 and 19, Figure 1, 2 and 3.

Reviewer B

1) First, I suggest the authors to indicate the comparisons between PD-1 + IMRT vs. PD-1 alone or IMRT alone, the clinical research design, i.e., a retrospective comparative cohort study, and the effectiveness outcome in the title.

REPLY: Thank you for your helpful comments. We totally agree with your comments and have revised our manuscript accordingly. We hope that we have appropriately addressed this review point.

On page 1, in the “Title” section: line 3 to 5.

PD-1 inhibition combined with intensity-modulated radiotherapy , to better serve patients with retroperitoneal lymph node metastases from gastrointestinal cancer.

2) Second, the abstract needs some revisions. The background did not explain why PD-1 + IMRT is effective and what the current knowledge gap is. The methods need to describe the inclusion of subjects, the assessment of baseline clinical factors, follow up procedures, and measure of effectiveness outcome. The results need to first briefly report the baseline comparability of clinical characteristics

across the three groups. The current conclusion needs to be tone down since this is not a RCT.

REPLY: We thank you for your helpful feedback. We concur with your point. According,we have revised the problems and hope that we have appropriately addressed this revisions.

On page 1 and 2, in the “Abstract” section: line 32 to 62.

Background: *Gastrointestinal (GI) cancer is the most frequent kind of cancer to involve the retroperitoneal lymph nodes (RPLN). Radiotherapy is common treatment of RPLN metastases in patients with gastrointestinal cancer, while radiotherapy is local. Meanwhile, most patients have extra-retroperitoneal metastases. Immunotherapy plus radiotherapy have showed effective in advanced non-small cell lung cancer. However, whether the combination therapy is effective on gastrointestinal cancer with RPLN metastases. In our study, we would estimated the effect of programmed death-1 (PD-1) inhibition in association with intensity-modulated radiotherapy (IMRT)*

Methods: *Metastatic GI cancer patients with RPLN who were treated at a single institution were retrospectively evaluated from October 2016 to April 2023, who all had measurable lesion and received any therapy of PD-1 inhibitors alone, IMRT alone or PD-1 inhibitors plus IMRT. The follow-up were assessed by abdominal computed tomography (CT) every 2 or 3 months to progression , dose-limiting toxicity or death.*

Results: *Among the 98 patients, 46 were treated by PD-1 inhibitors combined with IMRT, 26 were by PD-1 inhibitors only and 26 were by IMRT only. Of those, the median age 62 years (range, 25–84 years). Median progression-free survival (PFS) was 7.5 months and median overall survival (OS) was 10.8 months across the 3 therapy groups. Univariate analysis (UVA) indicated that therapy method ($P=0.032$) and tumor response ($P=0.035$) were significantly related to PFS. In the PD-1 inhibitors plus IMRT group, 1 patient (2.2%) achieved complete response (CR), 30 (65.2%) had partial remission, and 14 (30.4%) had stable disease (SD). There was no case with CR by IMRT or PD-1 inhibitors alone. Objective response rate (ORR; 67.4%) and disease control rate (DCR; 97.8%) were higher in the PD-1 inhibitors combined with IMRT group. In the PD-1 inhibitors plus IMRT and PD-1 inhibitors*

alone groups, hepatitis B virus (HBV)-positive patients had better OS ($P=0.041$) on UVA. Meanwhile, in the PD-1 inhibitors plus IMRT group, we observed superior PFS ($P=0.041$) and OS ($P=0.049$) in HBV-positive patients on UVA.

Conclusions: *PD-1 inhibitors plus IMRT may be a better method for advanced GI cancer patients with RPLN metastases. HBV-positive patients can benefit from either PD-1 inhibitors alone or in combination with IMRT.*

3) Third, in the introduction of the main text, the authors need to review what has been known on the treatments of RPLN and their efficacy and safety data, as well as limitations of prior studies. The authors need to further analyze the clinical needs for combination of PD-1 + IMRT and explain why the combination of the two is more effective and safe than either alone. In addition to the emphasis of knowledge gap, the authors need to analyze the clinical needs for this research focus.

REPLY: Thank you for raising this issue. To appropriately address these concerns, we have properly modified the “introduction” of the main text. By doing so, we hope that our efforts are satisfactory.

On page 3 and 4, in the “Introduction” section: line 87 to 102 and line 116 to 118.

In current literature, abdominal lymph node may be dissected in advanced esophagogastric junction adenocarcinoma; however, it's under argument because of different histologies (10). To RPLN metastases of patients with advanced gastric cancer, D2 lymphadenectomy may be sufficient but accompanied with higher morbidity and mortality(11-13). So the extent of lymphadenectomy is still disputed. The proportional gain of radiotherapy (RT) for patients with isolated RPLN metastasis is similar to that for patients with liver or lung metastases, and RT is reported to increase survival time for patients with RPLN metastasis (14). In colorectal cancer patients group with RPLN metastases only, the ORR and DCR were 62.5% and 85%, respectively. And in the extra-retroperitoneal metastases group, the ORR and DCR were just 17.9% and 75% (15). Moreover, in the study of locally advanced cervical cancer with RPLN metastases, programmed death-1 (PD-1) inhibitors plus chemoradiotherapy/radiotherapy showed effective and safe(16). However, most metastatic gastrointestinal (GI) patients with RPLN metastasis also have extra-retroperitoneal metastases (17), and the data about the combination therapy of PD-1 and IMRT, which treated with GI patients with RPLN metastasis, is

very rare.

The aim of our study is to assess effect of intensity-modulated radiotherapy (IMRT) combined with PD-1 inhibitors for patients with RPLN metastases who maybe improve survival, control disease and alleviate the local symptoms.

- 4) Fourth, in the methodology, please describe the clinical research design, sample size estimation, assessment of baseline clinical characteristics, and details of safety assessment. In statistics, please describe the test of baseline comparability across the three groups and the method for adjusting non-comparable baseline factors. Importantly, the authors need to describe how the three treatments, PD-1 + IMRT vs. PD-1 alone or IMRT alone, were decided, since this information is important for assessing the systemic bias across the three groups.

REPLY: Thank you for your valuable comments. Based on helpful suggestions, we have reworked duly.

On page 4 to 6, in the “Methods” section: line 127 to 134, 143 to 145, 175 to 177, and 180.

The study was retrospective and different treatment methods were based on not only treating physician but also symptoms and disease status of patients. The follow-up time ranged between 4 months and 63 months. Patients were followed up by telephone until August 2023. Before participants in the study, our study was agreed by the Ethics Committee of Ningbo Medical Center Lihuili Hospital and all patients or guardians concluded informed consent. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Clinical characteristics were from patients’ medical documents, containing age, sex, Eastern Cooperative Oncology Group performance status (ECOG PS), hepatitis B virus (HBV), primary tumor site, treatment methods, treatment response and so on.

Based on the National Cancer Institute Common Terminology Criteria for Adverse Events (version 5.0) (24), treatment toxicity was followed up continued for 3 months after termination of therapy by the treating physician.

Survival curves were analyzed using the Kaplan-Meier method to assess the outcomes. By univariate analysis with the log-rank test, the influence of variables potentially impacting progression-free survival (PFS) and overall survival (OS) was evaluated.

- 5) Finally, please cite several related papers: 1. de Jong MHS, Gisbertz SS, van Berge Henegouwen MI, Draaisma WA. Lymph node metastases rate of locoregional and non-locoregional lymph node stations in gastric cancer. *J Gastrointest Oncol* 2022;13(4):1605-1615. doi: 10.21037/jgo-22-147. 2. Hutchings H, Okereke IC. The different routes of lymph node metastases in esophageal cancer and its significance. *J Thorac Dis* 2023;15(11):5873-5876. doi: 10.21037/jtd-23-1373. 3. Liu C, Ran X, Wang Z, Zhang K. Efficacy and safety of PD-1 inhibitor combined with concurrent chemoradiotherapy in locally advanced cervical cancer with pelvic and/or para-aortic lymph node metastases: a retrospective cohort study. *Chin Clin Oncol* 2023;12(4):38. doi: 10.21037/cco-23-70.

REPLY: Thank you for your helpful references to our paper. They have been used by fit situation.

On page 12 and 13, in the “References” section: line 387 and 388, 394 to 396, and 403 to 405.

10. Hutchings H, Okereke IC. The different routes of lymph node metastases in esophageal cancer and its significance. J Thorac Dis 2023;15:5873-76.

13. De Jong MHS, Gisbertz SS, van Berge Henegouwen MI, Draaisma WA. Lymph node metastases rate of locoregional and non-locoregional lymph node stations in gastric cancer. J Gastrointest Oncol 2022;13:1605-15.

16. Liu C, Ran X, Wang Z, Zhang K. Efficacy and safety of PD-1 inhibitor combined with concurrent chemoradiotherapy in locally advanced cervical cancer with pelvic and/or para-aortic lymph node metastases: a retrospective cohort study. Chin Clin Oncol 2023;12:38.