

Peer Review File

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Review Comments

1) First, the title needs to indicate efficacy and safety.

Answer: Thanks for your suggestion. We have added “efficacy and safety” in the title. (See page1, line 2).

2) Second, the abstract is not adequate and needs some revisions. The authors did not indicate the knowledge gaps on the efficacy and safety of PD-1 inhibitors combined with concurrent chemoradiotherapy for locally advanced cervical cancer with pelvic and/or para-aortic lymph node metastases. **The methods need to describe the inclusion of subjects, clinical factors collected at baseline, and follow up duration.**

The conclusion needs comments for the clinical implications of the findings.

Answer : Thanks for your comments. We have re-written this part:

Background: The prognosis remains poor after standard chemoradiotherapy in locally advanced cervical cancer patients with pelvic and/or para-aortic lymph node metastases. PD-1 inhibitors have been recommended as the first-line treatment for recurrent cervical cancer. The efficacy of PD-1 inhibitor combined with concurrent chemoradiotherapy in locally advanced cervical cancer was still uncertain. This study aimed to explore the efficacy and safety of PD-1 inhibitors combined with concurrent chemoradiotherapy in locally advanced cervical cancer patients with pelvic and/or para-aortic lymph node metastases.

Methods: This retrospective cohort study included patients with pelvic and/or para-aortic lymph node positive diseases [FIGO stage IIB–IVA] who had received PD-1 inhibitors plus chemoradiotherapy/radiotherapy between April 1, 2020, and March 31, 2022 at the Hunan Cancer Hospital. The baseline clinicopathological characteristics, treatment, and clinical outcomes were collected. The major clinical outcomes were objective response rate (ORR), progression-free-survival (PFS), and treatment-related adverse events (TRAEs).

Results: A total of 29 patients were included. The mean age was 55.8 (SD: 8.8) years. Most patients had stage IIIA–IIIB disease (72.4%) and squamous cell carcinoma (93.1%). All patients had lymph node metastases, including 24 (82.8%) with multiple metastases and 11 (37.9%) with para-aortic lymph node metastases. Among the 29

patients included, 18 received sintilimab and 11 received camrelizumab concurrently with chemoradiotherapy or radiotherapy. The ORR was 96.6% [95% confidence interval (CI): 0.828, 0.993] at 3 months after radiotherapy (including 15 complete responses and 13 partial responses). At the data cutoff (August 31, 2022), the median follow-up was 14 (range, 5–30) months. The median PFS was not mature. The estimated 1- and 2-year PFS rates were 85.4% (95% CI: 60.1%, 95.2%) and 76.8% (95% CI: 47.0%, 91.2%), respectively. TRAEs of any grade occurred in 27 (93.1%) patients, most commonly as a decrease in white blood counts (82.8%), anemia (58.6%), and fatigue (48.3%). TRAEs of grade 3 or greater occurred in eight (27.6%) patients. There were no treatment-related deaths.

Conclusions: PD-1 inhibitor combined with concurrent chemoradiotherapy showed potential benefit in term of tumor response and PFS in locally advanced cervical cancer patients with pelvic and/or para-aortic lymph node metastases. (see page 1, line 28 to page 3, line 65)

3) Third, in the introduction of the main text, the authors need to review available treatment strategies for locally advanced cervical cancer with pelvic and/or para-aortic lymph node metastases, analyze their difficulties, unsatisfactory efficacy and safety outcomes, have comments on the knowledge gaps and limitations of prior studies, and explain why PD-1 inhibitors combined with concurrent chemoradiotherapy is potentially effective and safe.

Answer: Thanks for your comments. Firstly, we added the description as follow, “Patients with lymph node metastases, particularly those with para-aortic lymph node involvement, are more likely to develop distant metastases after standard concurrent chemoradiotherapy”. (see page 3, line 85)

Secondly, the effective and safe of PD-1 inhibitors combined with concurrent chemoradiotherapy were based on several studies, the early combination of PD-1 inhibitors and chemotherapy may provide better survival benefits and immunotherapy combined with radiotherapy also showed synergistic effective. In unresectable stage III non-small cell lung cancer patients, concurrent chemoradiotherapy followed by immunotherapy has been reported to significantly improve PFS and OS. In cervical cancer, the efficacy and safety of PD-1 inhibitor plus chemoradiotherapy has been explored by several studies. So, the combination strategy might be effective and safe (see page 4, line 98 to page 4, line 112)

4) Fourth, in the methodology of the main text, the authors need to describe the sample size estimation of this study and data collection of baseline clinical factors. In statistics, please describe the subgroups to be compared and the corresponding outcomes and statistical methods for the comparisons.

Answer: Because this was a real-world retrospective study and the primary statistical analysis was descriptive, no statistical hypothesis was used and no sample size estimation was performed. Baseline clinical factors had been revised clinicopathologic characteristics. But there are too many specific items to list. Typical characteristics were listed. (see page 6, line 175 to line 178)

Subgroup analysis also was compared for PFS between patients who were PD-L1 positive and those who were PD-L1 negative or unknown, so it was also estimated with Kaplan-Meier method and 95% CIs were estimated with the Log-Log transformation method. (see page 6, line 189)

5) Finally, please consider to cite several related papers: 1. Luo W, Li Y, Ke G, Wu X, Huang X. Extended field or pelvic intensity-modulated radiotherapy with concurrent cisplatin chemotherapy for the treatment of post-surgery multiple pelvic lymph node metastases in cervical cancer patients: a randomized, multi-center phase II clinical trial. *Transl Cancer Res* 2021;10(1):361-371. doi: 10.21037/tcr-20-2573. 2. Guaraldi L, Pastina P, Tini P, Crociani M, Marsili S, Nardone V. Locally advanced cervical cancer treated with chemo-radiotherapy: a case report of a particular recurrence. *Gynecol Pelvic Med* 2021;4:30. 3. Zhang X, Chen Z, Chen J, Wang J, Wang Y, Zhu J. Transl Cancer Re Surgery followed by concurrent radiochemotherapy as treatment for patients with locally recurrent cervical cancer. *s* 2021;10(10):4365-4374. doi: 10.21037/tcr-21-1163.

Answer : Thanks for your suggestion. I have already cited the paper 1(see page 9, line 263, Ref 17), 2(see page 9, line 265, Ref 18) and 3(see page 3, line 86, Ref 3).