Original Article

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

Chaoxia Liu^, Xiaomin Ran, Ziyi Wang, Keqiang Zhang

Department of Gynecologic Oncology, Hunan Cancer Hospital, Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, Changsha, China

Contributions: (I) Conception and design: C Liu; (II) Administrative support: K Zhang; (III) Provision of study materials or patients: X Ran; (IV) Collection and assembly of data: Z Wang; (V) Data analysis and interpretation: C Liu; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Keqiang Zhang, MD. Department of Gynecologic Oncology, Hunan Cancer Hospital, Affiliated Cancer Hospital of Xiangya School of Medicine, Central South University, No. 283 Tongzipo Road, Yuelu District, Changsha 410013, China. Email: zhangkeqiang@hnca.org.cn.

Background: The prognosis remains poor after standard chemoradiotherapy in locally advanced cervical cancer patients with pelvic and/or para-aortic lymph node metastases. Programmed cell death receptor-1 (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 study included patients with pelvic and/or para-aortic lymph node positive diseases [International Federation of Gynecology and Obstetrics (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 [standard deviation (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, 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 85.3% (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.

^ ORCID: 0000-0003-3450-4787.

Keywords: Locally advanced cervical cancer; pelvic and/or para-aortic lymph node metastases; programmed cell death receptor-1 inhibitors (PD-1 inhibitors); concurrent chemoradiotherapy

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Introduction

Cervical cancer is the fourth most common malignancy among women worldwide and the leading cause of cancer-related death in women (1), with almost 85% of cases occurring in developing countries. Tumor staging is critical for treatment decision making and determining the prognosis of patients. For patients with locally advanced cervical cancer [International Federation of Gynecology and Obstetrics (FIGO) 2009 stage IIB–IVA], who were used standard therapies, the estimated 5-year overall survival (OS) rate is approximately 24–61%, while for those with pelvic and/or para-aortic lymph node metastases, this decreases to 23.8–40.0% (2). Patients with lymph node metastases, particularly those with para-aortic lymph node involvement, are more likely to develop distant metastases after standard concurrent chemoradiotherapy. While theoretically, increasing the dose of radiotherapy may improve local disease control (3), the potential toxicity to adjacent normal tissues means the disease control and survival rates of patients with pelvic lymph nodes >2 cm (4) and abdominal para-aortic lymph nodes >1 cm (5) may be further compromised. Therefore, more efficient treatment strategies are urgently needed to improve the prognosis of the patients.

Programmed cell death receptor-1 (PD-1) inhibitor has shown promising antitumor activity in the treatment of recurrent cervical cancer. A phase II study of pembrolizumab, a humanized anti-PD-1 monoclonal antibody, showed an objective response rate (ORR) of 12.2% in previously treated advance cervical cancer (6). In addition, a double-blind phase 3 trial of pembrolizumab plus paclitaxel and cisplatin with or without bevacizumab showed significantly prolonged progression-free survival (PFS) and OS in patients with persistent, recurrent, or metastatic cervical cancer (7). The timing of the combination of PD-1 inhibitors and chemotherapy is very important. The early combination of PD-1 inhibitors and chemotherapy may provide better survival benefits than the late combination (8). The combination of immunotherapy with radiotherapy also showed a synergistic effect (9). The potential mechanisms may involve an abscopal effect mediated by radiotherapy that induces the migration of dendritic cells and cross-penetration of tumor antigens, which in turn leads to the activation and proliferation of T cells. Additionally, radiotherapy may increase the density of tumor-infiltrating lymphocytes within tumors (10). Immunotherapy with durvalumab [a humanized monoclonal antibody against programmed death ligand 1 (PD-L1)] after concurrent chemoradiotherapy has been reported to significantly improve PFS and OS in unresectable stage III non-small cell lung cancer patients (11). In cervical cancer, several studies have explored the efficacy and safety of PD-1 inhibitor plus chemoradiotherapy in locally advanced disease, and PD-L1 inhibitors are generally used as a primer or during or after chemoradiotherapy, without anti-PD-1 maintenance treatments (12-14). The present study was conducted to explore the efficacy and safety of adding PD-1 inhibitors to concurrent chemoradiotherapy in locally advanced cervical cancer patients with pelvic and/or para-

Highlight box

Key findings

- PD-1 inhibitor combined with concurrent chemoradiotherapy is well tolerated and effective in treating locally advanced cervical cancer patients with pelvic and/or para-aortic lymph node metastases.

What is known and what is new?

- Several studies have identified the efficacy and safety of PD-1 inhibitor plus chemoradiotherapy in locally advanced cervical cancer
- This study used PD-1 inhibitor plus chemoradiotherapy in locally advanced cervical cancer with pelvic and/or para-aortic lymph node metastases showed improving PFS and manageable toxicity.

What is the implication, and what should change now?

- PD-1 inhibitor plus chemoradiotherapy promoted tumor response and long-term efficacy in the treated of locally advanced cervical cancer with pelvic and/or para-aortic lymph node metastases. This treatment should be explored in further studies.

aortic lymph node metastases. We present this article in accordance with the STROBE reporting checklist (available at https://cco.amegroups.com/article/view/10.21037/cco-23-70/rc).

Methods

Study design and patients

This was a retrospective cohort study of PD-1 inhibitors plus chemoradiotherapy or radiotherapy in the curative treatment of locally advanced cervical cancer (FIGO 2009 stage IIB–IVA). All consecutive patients with pelvic and/or para-aortic lymph node positive diseases who had received PD-1 inhibitors plus chemoradiotherapy or radiotherapy were screened between April 1, 2020, and March 31, 2022, at the Hunan Cancer Hospital. Eligible patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2, histologically confirmed adenocarcinoma, squamous cell carcinoma, or adenosquamous carcinoma of the cervix, and pelvic and/or para-aortic lymph node involvement with a short axis diameter of ≥1 cm on baseline computed tomography (CT) or magnetic resonance imaging (MRI) scanning. The baseline clinicopathological characteristics included: age, ECOG performance status, histologic type, FIGO stage, tumor diameter, lymph node metastases, short axis of pelvic lymph node diameter, squamous cell carcinoma antigen and PD-L1 status. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of Hunan Cancer Hospital {No. 2022-[124]} and informed consent was taken from all the patients.

Procedures

Concurrent chemoradiotherapy was routinely offered for locally advanced cervical cancer patients and usually consisted of external radiotherapy and three-dimensional brachytherapy, plus concurrent cis-platinum chemotherapy (30–40 mg/m^2 weekly). External radiotherapy was delivered with seven-filed intensity-modulated radiation therapy (IMRT) or volumetric-modulated arc therapy (VMAT). The total dose of the planning target volume was 45.0–50.4 Gy for the whole pelvic region, a boost dose of 10–15 Gy for the tumor bed, and 58–64 Gy for the pelvic or para-aortic lymph nodes at a fraction of 1.8–2.0 Gy. After external radiotherapy, three-dimensional brachytherapy was delivered at a fraction of 6 Gy, two fractions per week, for 4–5 fractions. Concurrent chemotherapy may have been omitted for fragile patients who were deemed to be either unable or unwilling to undergo chemotherapy (e.g., elderly patients with poor performance status). Adjuvant chemotherapy (paclitaxel 135–175 mg/m^2 plus cis-platin 50 mg/m^2, 2–4 cycles) was generally recommended for patients in good clinical conditions 2–3 weeks after chemoradiotherapy or radiotherapy.

After careful evaluation of the clinical conditions and PD-L1 expression status of patients, PD-L1 inhibitor was recommended for those considered to potentially benefit from immunotherapy plus chemoradiotherapy and were positively stained for PD-L1 [a combined positive score (CPS) ≥1] as determined with the Dako PD-L1 22C3 pharmDx kit according to the manufacturer's instruction. The CPS was developed as the number of PD-L1-staining cells (tumor cells, lymphocytes, and macrophages) divided by the total viable tumor cells then multiplied by 100. The PD-L1 inhibitor was given concurrently with chemoradiotherapy/radiotherapy and adjuvant chemotherapy if available, and continued for at least 1 year unless disease progression, adverse events, or patient refusal occurred, and for up to 2 years.

Clinical outcomes and follow-up

Tumor response was routinely assessed with computed tomographic and/or MRI 3 months after chemoradiotherapy or radiotherapy and every 3 months thereafter, according to the response evaluation criteria in solid tumors version 1.1 (RECIST v1.1). Positron emission tomography-CT was performed when clinically indicated. ORR was defined as the percentage of patients achieving complete response (CR) or partial response (PR). PFS was defined as the time from treatment initiation to the date of disease progression or death from any cause. The data were censored at the time of last available contact or data cutoff date (August 31, 2022). The baseline clinicopathological characteristics collected age, ECOG performance status, histologic type, FIGO stage, tumor diameter, lymph node metastases, short axis of pelvic lymph node diameter, squamous cell carcinoma antigen and PD-L1 status. Patients were regularly followed up at the outpatient clinic every 3 months and interviewed by telephone call or WeChat when the scheduled clinic visit could not take place. Adverse events were graded according to the Common Terminology Criteria Adverse Events (CTCAE) version 5.0.

Table 1 Baseline characteristics of the patients

Variables	Total (n=29)
Age (years), mean ± SD	55.8±8.8
ECOG performance status, n (%)	
0	18 (62.1)
1	7 (24.1)
2	4 (13.8)
Histologic type, n (%)	
Squamous cell carcinoma	27 (93.1)
Adenocarcinoma	2 (6.9)
FIGO stage, n (%)	
IIB	4 (13.8)
IIIA–IIIB	21 (72.4)
IVA	4 (13.8)
Tumor diameter, n (%)	
≥5 cm	23 (79.3)
<5 cm	6 (20.7)
Lymph node metastases, n (%)	
Pelvic	29 (100.0)
Para-aortic	11 (37.9)
Short axis of pelvic lymph node diameter, n (%)	
≥1.5 cm	13 (44.8)
1.0–1.49 cm	16 (55.2)
Retroperitoneal lymph node involvement, n (%)	
Yes	11 (37.9)
No	18 (62.1)
Lymph node involved, n (%)	
Single group	5 (17.2)
Multiple group	24 (82.8)
Squamous cell carcinoma antigen, n (%)	
>30 μg/L	13 (44.8)
≤30 μg/L	15 (51.7)
Unknown	1 (3.5)
PD-L1 status, n (%)	
CPS ≥1	22 (75.9)
CPS <1	2 (6.9)
Unknown	5 (17.2)

SD, standard deviation; ECOG, Eastern Cooperative Oncology Group; FIGO, International Federation of Gynecology and Obstetrics; PD-L1, programmed death ligand 1; CPS, combined positive score.

Statistical analysis

The primary statistical analysis was descriptive. Continuous variables were expressed as mean and standard deviation (SD) and categorical variables as frequency and percentage. The 95% confidential intervals (CIs) were estimated for ORR using the Clopper-Pearson method. Median PFS of all patients and PFS of subgroup (patients who were PD-L1 positive and those who were PD-L1 negative or unknown) were estimated with the Kaplan-Meier method and 95% CIs were estimated with the Log-Log transformation method. All statistical analysis was performed with SPSS version 23.0 (IBM SPSS Inc., USA).

Results

Patient characteristics and treatment

Between April 2020 and March 2022, a total of 29 patients who received PD-1 inhibitor (18 sintilimab and 11 camrelizumab) plus chemoradiotherapy or radiotherapy were included for analysis. As shown in *Table 1*, the mean age of patients was 55.8 (SD: 8.8) years and most had squamous cell carcinoma (93.1%) and stage IIIA–IIIB disease (72.4%). Twenty-four patients underwent a PD-L1 expression test, which showed 22 were positively stained and two were negatively stained. The remaining five patients were not tested for PD-L1 due to the unavailability of tumor tissue.

Of the 29 patients, 25 received PD-1 inhibitor concurrently with chemoradiotherapy or radiotherapy, while the other four initiated anti-PD-L1 therapy later due to a poor tumor response to radiotherapy. The median number of cycles of anti-PD-L1 therapy was 16 (range, 2–34) (*Table 2*). Nineteen (65.5%) patients were treated with PD-1 inhibitor for at least 1 year. Five patients did not receive concurrent chemotherapy, primarily because of their older age and poor performance (n=2), mild to moderate renal dysfunction (n=2), and patient refusal (n=1). Eighteen (62.1%) patients received adjuvant chemotherapy.

Clinical outcomes

Three months after concurrent therapy, 15 (51.7%) patients achieved CR and 13 (44.8%) achieved PR, resulting in an ORR of 96.6% (95% CI: 0.828, 0.993). The remaining patient showed oligometastasis to the liver on CT scan which was treated with liver ablation therapy combined with chemotherapy (paclitaxel and cisplatinum) and

Table 2 Treatment details

Variables	Total (n=29)
PD-1 inhibitor, n (%)	
Camrelizumab	11 (37.9)
Sintilimab	18 (62.1)
PD-1 inhibitor treatment	
Median number of cycles [range]	16 [2–34]
Concurrent cisplatin chemotherapy, n (%)	
Yes	24 (82.8)
No	5 (17.2)
Adjuvant chemotherapy, n (%)	
Yes	18 (62.1)
No	11 (37.9)

PD-1, programmed cell death receptor-1.

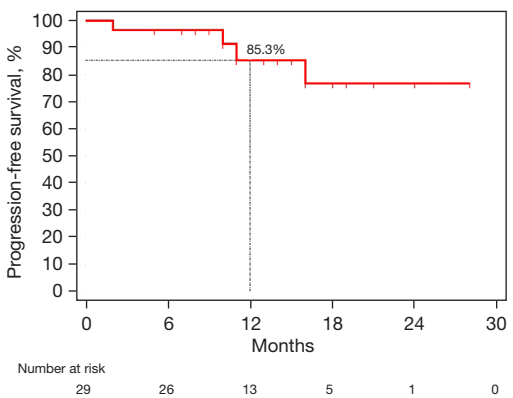

Figure 1 Kaplan-Meier analysis of progression-free survival.

sintilimab for three cycles then maintained with sintilimab without disease progression at the data cutoff date (August 31, 2022).

During a median follow-up of 14 (range, 5–30) months, the median PFS was not mature (*Figure 1*), and the estimated 1- and 2-year PFS rates were 85.3% (95% CI: 60.1%, 95.2%) and 76.8% (95% CI: 47.0%, 91.2%), respectively. Three patients developed progressive disease during the follow-up. One patient had recurrent disease at the vesicoureteral junction 11 months after treatment initiation and another had local recurrence with anterior rectal wall involvement. The remaining patient had distant metastasis to the supraclavicular lymph nodes and was still receiving supraclavicular radiotherapy plus chemotherapy. No patient died during the follow-up.

In the subgroup analyses, the estimated 1-year PFS rate was 91.7% (95% CI: 73.9%, 97.2%) in the 22 patients who were positively stained for PD-L1, and 64.3% (95% CI: 36.7%, 87.6%) in the seven patients who were either negatively stained or were unknown for PD-L1. However, there was no significant difference in PFS with respect to age (<60 *vs.* ≥60 years), FIGO stage (IIB, IIIA–IIIB *vs.* IVA), tumor diameter (<5 *vs.* ≥5 cm), short axis of pelvic lymph node diameter (1.0–1.5 *vs.* >1.5 cm), retroperitoneal lymph node metastases (yes *vs.* no), lymph node involved (single group *vs.* multiple groups), concurrent chemoradiotherapy (yes *vs.* no), and adjuvant chemotherapy (yes *vs.* no).

Safety

Treatment-related adverse events (TRAEs) of any grade occurred in 27 (93.1%) patients and were most commonly a decrease in the white blood cell count (82.8%), anemia (58.6%), and fatigue (48.3%) (*Table 3*). TRAEs of grade 3 or greater occurred in eight (27.6%) patients. There were no treatment-related deaths.

Immune-related adverse events (irAEs) were reported in 12 (41.4%) patients (*Table 3*). Three patients experienced serious irAEs, including one with immune myocarditis and immune hepatitis, one with immune hepatitis and thrombocytopenia, and the other with injection reaction. Among 11 patients who received camrelizumab, eight developed grade 1–2 reactive cutaneous capillary endothelial proliferation (RCCEP) which was most prevalent at the time of camrelizumab initiation (course one to two). In these patients, the symptoms peaked at course four to six, then shrunk and became sporadic thereafter.

Discussion

Concurrent chemoradiotherapy has been the standard care for patients with locally advanced cervical cancer. A previous randomized phase III study of concurrent chemoradiotherapy, in which most patients (60%) had stage IIb diseases and only 13% of patients had pelvic lymph node metastases, showed a 2-year PFS rate of 60% in node-positive cervical cancer patients (15). The phase II JGOG1066 study reported a 2-year PFS rate of 66% in stage III–IVA cervical cancer patients receiving chemoradiotherapy combined with high-dose-rate intracavitary brachytherapy. In patients with pelvic lymph node metastases, the 2-year PFS rate was about 60%, and

Table 3 Adverse events

Treatment-related adverse events	Total (n=29), n (%)	
	Grade 1–2	≥ Grade 3
Hematologic		
White blood cell decreased	24 (82.8)	3 (10.3)
Anemia	17 (58.6)	0 (0.0)
Platelet count decreased	11 (37.9)	2 (6.9)
Non-hematologic		
Fatigue	14 (48.3)	0 (0.0)
Nausea	11 (37.9)	0 (0.0)
Elevated transaminases	9 (31.0)	0 (0.0)
RCCEP	8 (27.6)	0 (0.0)
Diarrhea	4 (13.8)	0 (0.0)
Rash	2 (6.9)	0 (0.0)
Herpes zoster infection	2 (6.9)	0 (0.0)
Hypothyroidism	2 (6.9)	0 (0.0)
Hepatitis	0 (0.0)	2 (6.9)
Myocarditis	0 (0.0)	1 (3.4)
Injection reaction	1 (3.4)	0 (0.0)
Immune-related adverse events		
RCCEP	8 (27.6)	0 (0.0)
Hypothyroidism	2 (6.9)	0 (0.0)
Immune hepatitis	0 (0.0)	2 (6.9)
Rash	2 (6.9)	0 (0.0)
Immune myocarditis	0 (0.0)	1 (3.4)
Platelet count decreased	0 (0.0)	1 (3.4)
Injection reaction	1 (3.4)	0 (0.0)

RCCEP, reactive cutaneous capillary endothelial proliferation.

notably, was found to decrease from 77% to 39% with an increase in tumor size from <5 to ≥7 cm (16). When the diameter of tumor was ≥5 cm, the mortality and disease progression rate increased significantly (17). However, the prognosis of patients with pelvic and/or para-aortic lymph node metastases remains poor, with a high risk of distant metastases like lung, liver, bone, even abdominal nodule (18), and so on. In other studies, the recurrent rate was approximately 22–30% in patients with lymph node metastases (19-21), while more than doubled in those with para-aortic lymph node metastases (22). Regrettably, the randomized phase III OUTBACK Trial failed to demonstrate survival benefits of adjuvant chemotherapy following chemoradiation for locally advanced cervical cancer (23). Nimotuzumab combined with chemoradiotherapy enhanced the PFS of locally advanced cervical cancer patients, but OS did not reach statistical significance (24). Therefore, there is an unmet need to explore more effective treatment strategies and improve the prognosis of patients.

In the present study, we explored the efficacy and safety of adding PD-1 inhibitor to concurrent chemoradiotherapy in patients with high-risk cervical cancer. All included patients had lymph node metastases at baseline, approximately 38% had para-aortic lymph node involvement and 83% had multiple groups lymph node involvement. Almost 80% of patients had a tumor diameter of 5 cm or larger. The findings of our study showed an ORR rate of 96.6% at 3 months after radiotherapy and the estimated 1- and 2-year PFS rates were 85.3% and 76.8%, respectively. Toxicity was generally manageable. Similar results of a 3-month ORR rate of 95.5% and 96.0% were observed in recent studies of toripalimab or camrelizumab in combination with chemoradiotherapy in locally advanced cervical cancer, respectively (14,25). The phase I NRG GY17 study of atezolizumab as a primer or concurrent with chemoradiotherapy showed a 12-month disease-free survival of 72% in node-positive locally advanced cervical cancer (26). Additionally, a previous phase I study of adjuvant immunotherapy with ipilimumab after chemoradiotherapy showed a 12-month PFS rate of 81% in patients with locally advanced (FIGO stage IB2 to IVA) disease with positive pelvic or para-aortic lymph nodes, or both. Notably, that study indicated an upregulated PD-1 expression after chemoradiotherapy that sustained during sequential immunotherapy (27). PD-L1 expression has been explored as a potential biomarker for selecting patients who might benefit from anti-PD-1/PD-L1 therapy in advanced cervical cancer (6,7). Most (75.9%) of our patients were confirmed to be positively stained for PD-L1 before treatment initiation, while two patients were known to be negatively stained and in five patients staining was undetected. Intriguingly, only one of the 22 PD-L1 positive patients developed progressive disease during the follow-up, while 3 of the 7 other patients had progressive disease. These results suggest the potential role of PD-L1 expression as a promising biomarker for prognostic prediction. However, due to a small sample size and limited follow-up time, the definitive role of PD-L1 expression in

predicting response to anti-PD-1/PD-L1 therapy requires further clarification.

Most patients experienced at least one TRAEs when treated with PD-1 inhibitor combined with concurrent chemoradiotherapy, and the safety profile was generally consistent with that reported for sintilimab, camrelizumab, and chemoradiotherapy (25,28,29). The irAEs most involved the organ systems, including the skin, gastrointestinal tract, liver, endocrine organs, and lungs (30). Cardiovascular irAEs are also included in the analysis because of their fatal toxic effects (31). In this study, one patient developed immune myocarditis/hepatitis and another developed immune hepatitis during anti-PD-1 therapy, highlighting the importance of continuous monitoring of patients.

Conclusions

We explored the add-on effect of immune checkpoint inhibitors to standard concurrent chemoradiotherapy in improving clinical outcomes in locally advanced cervical cancer patients with pelvic and/or para-aortic lymph node metastases. The findings of our study showed PD-1 inhibitor combined with concurrent chemoradiotherapy improved tumor response and PFS, with manageable toxicity. However, due to the retrospective study design and small sample size, further studies are required.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://cco.amegroups.com/article/view/10.21037/cco-23-70/rc

Data Sharing Statement: Available at https://cco.amegroups.com/article/view/10.21037/cco-23-70/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://cco.amegroups.com/article/view/10.21037/cco-23-70/coif). All authors report that this study was supported by Hunan Cancer Hospital Climb Plan (No. 2020IITA003). The authors have no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of Hunan Cancer Hospital {No. 2022-[124]} and informed consent was taken from all the patients.

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