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Intensity-modulated radiation therapy (IMRT)-based concurrent chemoradiotherapy (CCRT) with Endostar in patients with pelvic locoregional recurrence of cervical cancer

Results from a hospital in the Qinghai-Tibet Plateau

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Abstract

The treatment of recurrent cervical cancer, especially pelvic locoregional recurrence, is very challenging for gynecologic oncologists. This study investigated the efficacy and safety of intensity-modulated radiation therapy (IMRT)-based concurrent chemoradiotherapy (CCRT) with Endostar, a novel modified recombinant human endostatin, in patients with pelvic locoregional recurrence of cervical cancer following surgical treatment.This phase 2 study was conducted between May 2018 and May 2019 at a single center in the Qinghai-Tibet Plateau and enrolled 31 patients with pelvic locoregional recurrence of cervical cancer following surgical treatment. All patients were treated with IMRT-based CCRT for 6 weeks and intravenous infusions of Endostar (15 mg/m^2), which were administered on days 1 to 7 of CCRT, followed by rest for 4 weeks. After resting, chemotherapy with cisplatin (70 mg/m^2) plus paclitaxel (135–175 mg/m^2) was given every 3 weeks for a total of 4 treatments.Thirty-one patients were evaluable for the primary endpoint. The mean age was 50.03 years (SD 7.72). The objective response rate was 67.74% and the disease control rate was 83.87% (48.39% achieved a complete response, 19.35% a partial response, 16.13% had disease stabilization, and 16.13% had progressive disease). The most common adverse events were nausea, vomiting, alopecia, neutropenia, and leukopenia; most events were grade 1 or 2 in intensity. Grade 3 toxicities included thrombocytopenia and neutropenia in 2 patients each, and leukopenia in 4 patients. No cases of grade 4 acute toxicity were observed.

IMRT-based CCRT with Endostar infusions is effective and safe. Our results support the use of this treatment for patients with pelvic locoregional recurrence of cervical cancer following surgical treatment.

Abbreviations: AEs = adverse events, CCRT = radical surgery and concurrent chemoradiotherapy, CTV = clinical target volume, GI = gastrointestinal, IMRT = intensity-modulated radiation therapy, NSCLC = non-small cell lung cancer. PTV = planned target volume, RT = radiation therapy, VEGF = vascular endothelial growth factor.

Keywords: antiangiogenesis, CCRT, cervical cancer, IMRT, pelvic locoregional recurrence

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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1. Introduction

Cervical cancer is the third most common cancer in women and the third most common cause of cancer-related death among women, with approximately 570,000 new cases in 2018, comprising 6.6% of all female cancers.[1] Low- and middle-income countries reported 90% of all worldwide deaths in 2018 relating to cervical cancer.[2] Cervical cancer is also one of the most common cancers among women in China, with around 98,900 new cases and 30,500 deaths reported there in 2015.[3] Treatments for cervical cancer include surgery, radiation therapy (RT), and chemotherapy (CRT).[4] Radical surgery and concurrent chemoradiotherapy (CCRT) is the standard mode of treatment worldwide and in China.[5] However, disease recurs in approximately one-third of patients and fewer than 5% of them remain alive at 5 years after recurrence.[6,7] Recurrent cervical cancer can present as a local recurrence or as metastatic disease. Local recurrence is categorized as either central recurrence (cervix or vaginal stump) or noncentral recurrence (pelvic lymph nodes or pelvic side wall). Local recurrence rates following definitive chemoradiation range between 5% and 18%.[8] Currently, few treatment options are available for patients with noncentral recurrence, especially those with

recurrence in the pelvic lymph nodes or pelvic side wall.[9] Thus, the treatment of recurrent cervical cancer is very problematic.

The advent of three-dimensional radiation therapy (3D-RT) and then the more precise mode of intensity-modulated radiotherapy (IMRT) has improved the treatment of cervical cancer.[2,10] By delivering a relatively large dose of RT over a target treatment area, IMRT minimizes the effects of RT in adjacent noncancerous tissue, is associated with greater locoregional control and also fewer gastrointestinal (GI) and hematological toxicities than 3D-RT.[2,11] Nevertheless, RT is marked by high levels of acute and chronic toxicities. The acute toxicities lower the patient's quality of life and frequently lead to premature termination of curative chemotherapy.[12] Novel treatment strategies are needed that have a lower burden of toxicity and are more effective.

Angiogenesis is critical in the development and metastatic spread of cancer.[13] Targeting the angiogenic pathway helps to control disease progression in cervical cancer.[14] Angiogenesis plays an important role in locally advanced cervical cancer, with abnormal vascular endothelial growth factor (VEGF) expression specifically associated with cervical cancer.[15] Bevacizumab is an anti-VEGF monoclonal antibody that has proven to be an effective treatment for recurrent cervical cancer.[16] In a case series describing the use of bevacizumab in 6 heavily pretreated patients with recurrent cervical cancer, 4 achieved a complete response, 1 had a partial response, and 2 achieved disease stabilization; treatment was reportedly well tolerated.[17] Thus, antiangiogenic therapy shows promise in cervical cancer. Recombinant human endostatin (Endostar; YP-16) is a potent angiogenesis blocker that was granted approval in 2005 by China's State Food and Drug Administration (SFDA) for the treatment of non-small cell lung cancer (NSCLC).[18] Endostar improves chemotherapy efficacy in cervical cancer,[19,20] but little is known about the potential advantages of combining IMRT with antiangiogenesis strategies in noncentral recurrences of this disease.

We therefore performed a single-arm phase 2 trial of IMRT-based CCRT and Endostar in a cohort of patients in patients with pelvic locoregional recurrence of cervical cancer following surgical treatment. We evaluated the safety and efficacy of this management strategy for pelvic side wall recurrences of cervical cancer.

2. Materials and methods

2.1. Subjects

A total of 31 patients with pelvic side wall recurrences of cervical cancer following surgery were admitted by the Qinghai Red Cross Hospital between May 2018 and May 2019 and were enrolled into this study. The inclusion criteria were: age between 20 and 70 years; a Karnofsky Performance Status score of ≥70 points; a diagnosis of noncentral recurrence cervical cancer confirmed by 2 or more methods; no history of RT; no history of platinum drug allergies; laboratory findings within the following ranges (at ≤14 days prior to enrolment): hemoglobin ≥100 g/L, neutrophil count $\geq 1.5 \times 10^9$/L, white blood cell count $\geq 3.5 \times 10^9$/L, platelet count $\geq 100 \times 10^9$/L; creatinine ≤1.0 × upper limit of normal; alanine aminotransferase/aspartate aminotransferase ≤1.5, alkaline phosphatase ≤1.5 × UNL, total bilirubin ≤1.5 × UNL; and agreement to participate in follow-up visits. Exclusion criteria included: pregnancy or lactation, previous (<5 years) malignancy, any serious complication that would affect full compliance with treatment, mental illness, and age under 20 years. The study was approved by the Qinghai Red Cross Hospital Institutional Review Board and it was conducted in compliance with national legislation and the Declaration of Helsinki guidelines. Neither the patients nor general public were involved in the design and conduct of the study. All study participants gave written informed written consent before enrollment.

2.2. Study design

This study was a nonrandomized, single-arm, single-institution, phase 2 trial for the treatment of pelvic locoregional recurrence of cervical cancer. The flow diagram of the trial is depicted in Figure 1.

2.3. IMRT details

IMRT planning incorporated computer tomography (CT)-based simulation in the supine position with knee rest. Magnetic resonance imaging (MRI) scans were obtained with an interslice distance of 5 mm, after intravenous contrast taken from the upper edge of the lumbar vertebra to a position situated at 2 cm below

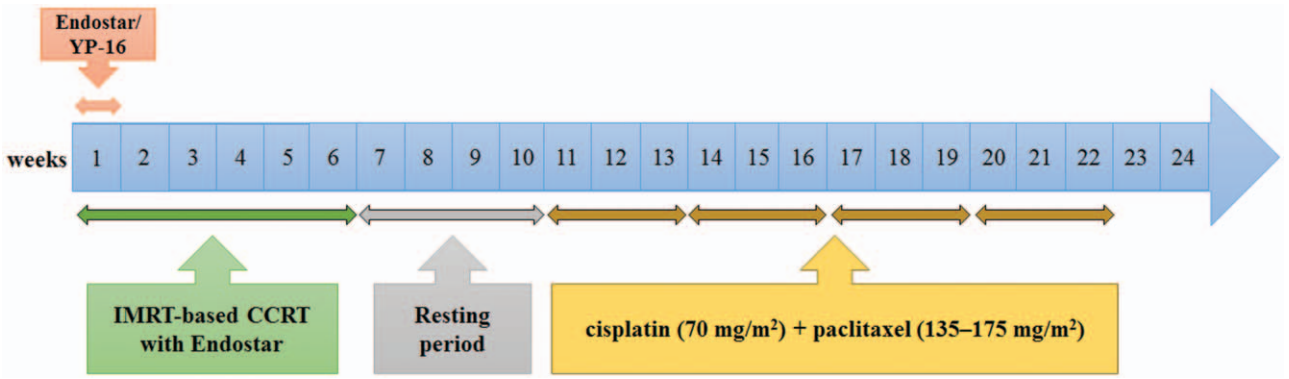

Figure 1. Flow diagram of the trial.

the pubic symphysis. After scanning, the image data were uploaded to the planning system workstation through the network system. Gross tumor volume (GTV) was defined as the macroscopic tumor detected on CT and MRI scans. The clinical target volume (CTV) included CTV plus the cervix, uterus, parametria, and proximal half of the vagina. The planned target volume (PTV) was generally delineated by adding the following margins to the CTV: 1 cm in the superoinferior and anteroposterior direction and 0.5 cm in the mediolateral direction. The pelvic PTV received 50.4 Gy/1.8Gy/28#/6 weeks, while the planned gross tumor volume integrated boost received 64.4Gy/2.3Gy/28#/6 weeks. The decision to implement a concurrent or sequential boost was at the discretion of the physician. All patients received RT to the pelvis via IMRT using the Eclipse version 8.9 treatment planning system (Varian Medical, Palo Alto, CA).[21]

2.4. Chemotherapy and Endostar-targeted treatments

Chemotherapy consisted of weekly cisplatin (40 mg/m^2) for 6 weeks and intravenous infusions of Endostar (15 mg/m^2), which were administered on days 1 to 7 of CCRT. After resting, the patients were administered combination chemotherapy with cisplatin (70 mg/m^2) + paclitaxel (135–175 mg/m^2) every 3 weeks for a total of 4 sessions.

2.5. Safety and efficacy evaluations

Acute toxicity was defined as that occurring within 90 days of treatment. All patients were reviewed weekly during treatment to assess acute toxicity. GI toxicity was graded using the Radiation Therapy Oncology Group scale[22] and hematological toxicity was determined with the Common Terminology Criteria for Adverse Eventsversion 4.0.[23] After the end of treatment, efficacy was evaluated by the Response Evaluation Criteria in Solid Tumors criteria version 1.1.[24]

2.6. Statistical analysis

Statistical analysis was performed using the SPSS Statistics 20.0 software package for Windows (IBM Corporation, NY). Continuous data are expressed as means and categorical variables as percentages.

3. Results

3.1. Demographic and clinical characteristics of the study population

The demographic characteristics of the study participants are shown in Table 1. Ages ranged from 34 to 62 years (mean 50.03 years; SD 7.72). Ethnicity was 58.06% Han Chinese, 16.13% Tibetan, and 25.81% Hui Chinese (Chinese Muslim). The majority of patients (93.55%) had an Eastern Cooperative Oncology Group Performance Status ≤2 and most had stage IB lesions (21/31, 64.52%). All patients had squamous cell carcinoma. Around half of the patients (17, 51.61%) had a cervical tumor with a size of ≥191 cm^3. The median tumor burden was 127.7 cm^3 (SD 89.04).

3.2. Effects of treatment

A total of 31 patients were evaluable for the primary endpoint. Patient response was evaluated for 1 month after the completion of treatment. Fifteen patients achieved a complete response (48.39%), 6 a partial response (19.35%), and 5 each had stable disease or progressive disease (16.13%). The objective response rate was 67.74% and the disease control rate was 83.87% (Table 2).

Table 1

Demographic and clinical characteristics for 31 patients with pelvic locoregional recurrence of cervical cancer following surgical treatment.

Variable	Number of patients	% of total
	Mean ± S.D.	
Age (yrs)	50.03 ± 7.72	
Range	34–62	
<45	7	22.58
≥45	24	77.42
Ethnicity		
Han Chinese	18	58.06
Tibetan	5	16.13
Hui Chinese	8	25.81
Baseline ECOG status		
1	14	41.94
2	17	51.61
3	2	6.45
4	—	—
FIGO stage		
IB	21	64.52
IIA	10	29.03
IIB	2	6.45
Histology		
Squamous cell carcinoma	31	100
Adenocarcinoma	—	—
Tumor burden (cm^3)	127.7 ± 89.04	
<55	6	19.35
<82	10	29.03
≥191	17	51.61

ECOG = eastern cooperative oncology group, FIGO = international federation of gynecology and obstetrics.

3.3. Treatment toxicities

At 1 month, no patients had died. Safety is analyzed in Table 3. The most common adverse events (AEs) (affecting ≥20 patients in either treatment group) were GI disorders (nausea, vomiting), alopecia, neutropenia, and decreases in white blood cell count. Most AEs were grade 1 or 2 in intensity; grade 3 AEs included thrombocytopenia and neutropenia in 2 patients each, and leukopenia in 4 patients. There were no cases of grade 4 acute toxicity (Table 3).

4. Discussion

Approximately 98,900 new cases and 30,500 deaths from cervical cancer were reported in China during 2015.[25] Radical hysterectomy and pelvic lymphadenectomy has been considered to be an effective treatment program for early-stage cervical cancer.[26] However, approximately 14% to 57% of patients experience a central recurrence after radical surgery and, depending on different risk factors, rates of pelvic recurrences fluctuate from between 10% and 74%.[27,28] Recurrent and metastatic cervical cancer are incurable, with 1-year survival rates of between 15% and 20%.[27] Cisplatin-based chemother-

Table 2

Response rates for patients with pelvic locoregional recurrence of cervical cancer following surgical treatment.

Evaluable patients after 1 month of follow-up	n	%
CR	15	48.39
PR	6	19.35
SD	5	16.13
PD	5	16.13
ORR	21	67.74*
DCR	26	83.87†

CR = complete response, DCR = disease control rate, ORR = objective response rate, PD = progressive disease, PR = partial response, SD = stable disease.
* ORR = CR + PR.
† DCR = CR + PR + SD.

apy ameliorates symptoms and prolongs progression-free survival in cervical cancer patients.[29] Improvements in single and combined modality treatment have increased the rates of local tumor control for cervical cancer, but locoregional recurrences after initial (surgical or radiation) treatment still occur.[26] Our study was performed in a single center in the Qinghai-Tibet Plateau. The aim of this study was to evaluate the efficacy and safety of IMRT-based CCRT combined with Endostar in patients with pelvic locoregional recurrence of cervical cancer. Thirty-one of our patients obtained a clinical benefit after treatment, and there were no cases of grade 4 acute toxicity. This treatment schedule therefore appears to be effective and safe for patients.

Pelvic RT plays an important role in the treatment of cervical cancer. IMRT delivers a high dose of radiation to tumor tissue and restricts dose exposure to adjacent noncancerous tissue.[30] However, the side effects of RT greatly compromise quality of life.[2] The most common acute adverse reactions following RT are abdominal pain, diarrhea, hemorrhage, intestinal obstruction, and granulocytopenia.[31] Many patients refuse to undergo RT because of these potential side effects. In our study, the most common AEs were nausea, vomiting, alopecia, neutropenia, and leukopenia, which were grade 1 or 2 in intensity. Thus, IMRT combined with Endostar offers meaningful protection of organs (such as the pelvis) and improves quality of life.

VEGF is critical to the growth of tumor blood vessels[32] and is considered to be an appropriate therapeutic target in cervical cancer.[33] In a phase 2 trial of bevacizumab in recurrent cervical cancer, 11 (23.9%) of the 46 evaluable patients achieved progression-free survival for at least 6 months with a median value of 3.40 months (2.5–4.5 months), and 5 (10.9%) attained a partial response, with a median response duration of 6.2 months (2.8–8.3 months). Median overall survival was 7.29 months (6.1–10.4 months).[34] The use of bevacizumab in cervical cancer has proven to be effective and safe, but is very expensive to administer.[35] Endostar exhibits significant synergistic effects with standard chemotherapy and is very cheap.[36] The efficacy of Endostar has been proven in clinical trials of stage III NSCLC, and has been approved by China's SFDA for use in advanced NSCLC.[37] Hypertension, proteinuria, and hand-foot syndrome are the most common AEs associated with antiangiogenic agents.[14] Not only is Endostar associated with a low rate of AEs,[36,37] but when combined with chemoradiotherapy, Endostar appears to improve early outcomes in patients with advanced cervical cancer, without AEs.[19] Our study, although small, demonstrates good efficacy and safety of Endostar combined with CRT in the treatment of pelvic locoregional recurrence of cervical cancer. Further larger-scale clinical investigations are warranted.

As well as antiangiogenic therapy, agents targeting various biological mechanisms such as epigenetics, the epidermal growth factor receptor, poly(ADP-ribose) polymerase activity, and the mammalian target of rapamycin, represent exciting investigational opportunities. Moreover, explorations of immunotherapy approaches are indicating potential for the development of therapeutic vaccines and immune checkpoint inhibitors. All of these investigations offer new directions for patients such as those who participated in this study.

5. Conclusion

Our results appear to support the use of IMRT-based CCRT with Endostar for patients with pelvic locoregional recurrence of cervical cancer following surgery. Long-term follow-up of our study participants and further studies are needed to confirm the role of Endostar in the management of this disease.

Table 3

Most common treatment-emergent acute adverse events possibly related to study treatment in the 31 evaluable patients.

Adverse events*	Grade 1	Grade 2	Grade 3	Grade 4	Total
Gastrointestinal disorders					
Constipation	17	—	—	—	17
Nausea	21	10	—	—	31
Vomiting	19	10	—	—	29
General disorders					
Pain	6	—	—	—	6
Fatigue	16	3	—	—	19
Skin and subcutaneous tissue disorders					
Alopecia	13	13	—	—	26
Pruritus	3	—	—	—	3
Investigations					
Hemoglobin increased	8	2	—	—	10
Thrombocytopenia	13	3	2	—	18
Neutropenia	9	17	2	—	28
Leukopenia	3	21	4	—	28

* Adverse events were coded using The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

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Writing: Kuan Zhang.

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