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Efficacy and Safety of Intra-Arterial Infusion Chemotherapy Combined with Early Radiotherapy for Bulky Cervical Cancer

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Abstract

Background: This study aimed to observe the efficacy and safety of early radiotherapy combined with intra-arterial infusion chemotherapy (IACT) for bulky cervical cancer. **Methods**: A total of 20 patients with locally advanced bulky cervical cancer admitted to Yueyang Central Hospital from January 2018 to January 2022 were enrolled. All patients received IACT combined with early radiotherapy (including intracavitary afterloading brachytherapy and external beam radiotherapy). Intracavitary afterloading brachytherapy was performed early after infusion chemotherapy, and external beam radiotherapy was initiated within 2 weeks. Clinical efficacy was evaluated using MRI or CT, and the therapeutic efficacy and adverse reactions were analyzed. **Results**: Among the 20 patients, the overall response rate (ORR) was 100%. Significant necrosis and shedding were observed in 95% of patients after the second brachytherapy session. By the third afterloading treatment, 95% of patients achieved partial response (PR), and 90% achieved complete response (CR) after the entire treatment course. No severe adverse reactions affecting treatment were reported in any patient. **Conclusion**: The combination of radiotherapy within a short period after interventional infusion chemotherapy can significantly improve the short-term efficacy of bulky cervical cancer with good safety.

Keywords

Intra-Arterial Infusion Chemotherapy, Intracavitary Afterloading Brachytherapy, Bulky Cervical Cancer

1. Introduction

Cervical cancer is one of the most common female malignant tumors, seriously threatening women's health worldwide [1]. Statistics show that there were approximately 570,000 new cases of cervical cancer globally in 2022, with 311,000 deaths [2]. In China, cervical cancer is the second most common female-specific malignant tumor after breast cancer, with incidence and mortality rates showing an age distribution trend, mostly affecting women of childbearing age between 20 and 50 years old [3] [4]. The main treatment methods for cervical cancer include surgery, chemotherapy, radiotherapy, and comprehensive therapy [5]. With the advent of the "precision medicine" era, increasing research has been conducted in the field of clinical treatment of cervical cancer. How to effectively reduce the mortality rate of cervical cancer in China, standardize precise treatment methods, and improve patients' quality of life and survival rate are urgent issues to be addressed [6]. This study aimed to observe the efficacy and safety of early high-dose-rate intracavitary afterloading brachytherapy and external beam radiotherapy within a short period after intra-arterial infusion chemotherapy (IACT) for bulky cervical cancer, providing more treatment options for patients with unresectable bulky cervical cancer.

2. Materials and Methods

2.1. General Information

Approved by our Ethics Committee (Ethics Number, 2018-002). This study is a prospective clinical study. A total of 20 patients with pathologically confirmed bulky cervical cancer admitted to Yueyang Central Hospital from January 2018 to January 2022 were selected. The average age of the patients was 52 years (range: 39-75 years), and the average tumor diameter was 8 cm (range: 5 - 15 cm). According to the International Federation of Gynecology and Obstetrics (FIGO) 2018 clinical staging criteria for cervical cancer, 4 cases were in stage IB, 6 cases in stage II, and 10 cases in stage III. All enrolled patients underwent corresponding baseline examinations, had no surgical indications after surgical consultation or refused surgical treatment, and were excluded from distant organ metastasis (brain, liver, lung, bone, etc.). No obvious abnormalities were found in blood routine, liver and kidney function, electrocardiogram, etc. All patients received IACT with cisplatin combined with epirubicin as the main chemotherapy drugs, followed by early high-dose-rate afterloading treatment. Informed consent was signed before treatment initiation (**Table 1**).

Table 1. Patient characteristics.

Characteristic	n (%)
Age(y)	
≤55	11 (55)
>55	9 (45)

Continued

FIGO stage(n)	
I	4 (20)
II	6 (30)
III	10 (50)
Pathology (n)	
Squamous cell carcinoma	20 (100)
Adenocarcinoma	0 (0)
Tumor grading (n)	
Poorly	6 (30)
Moderately	8 (40)
Highly	6 (30)

2.2. Methods

Under the guidance of digital subtraction angiography (DSA), the Seldinger technique was used for unilateral femoral artery puncture, and a 5F Cobra catheter was inserted. First, angiography of the left and right common iliac arteries was performed. On DSA imaging, the uterine artery was thickened and tortuous, with neovascularization in the tumor twisted at different angles, rich capillary networks, and areas of contrast medium staining, defect, delay, and retention, which could clearly show the size and scope of the tumor. The tumor blood supply was mainly from the uterine artery. In advanced patients with tumor invasion of surrounding tissues, other branches of the anterior trunk of the internal iliac artery, such as the obturator artery and internal pudendal artery, could be seen. Tumor vessels were embolized, and 2/3 of the chemotherapy drugs were slowly injected into the side with more significant tumor staining, while 1/3 was injected into the other side. The chemotherapy drugs included cisplatin (80 - 100 mg) and epirubicin (80 - 120 mg) (**Figure 1**). IACT should be performed 1 to 2 times, and subsequent treatment should be decided after discussion by the MDT of the entire hospital. High-dose-rate afterloading treatment (high-dose-rate remote-controlled iridium-192 after loader, radiation intensity 4.5 - 10 Gy, >20 cGy/min) was administered 1 - 3 days after infusion chemotherapy, with a reference dose of 600 - 800 cGy per session at point A, for 2-3 sessions, with a total dose of 18 - 24 Gy. Pelvic external beam radiotherapy was initiated within 2 weeks using an Elekta linear accelerator with volumetric modulated arc therapy (VMAT), with a total dose of 46 - 50 Gy/1.8 - 2 Gy/23 - 25 fractions, 5 times a week. Bladder V45 < 50%, Rectum V45 < 50%, V30 < 60%, Small Bowel D30% < 40 Gy, Spinal Cord D 0.1 cm^3 < 45Gy, Femoral Head V30Gy < 15%. Vaginal irrigation was performed three times a week during radiotherapy to observe tumor regression. Subsequent after-

loading treatment with 500 - 700 cGy at point A was started when the total dose reached 18 - 30 Gy after 10 - 15 external beam radiotherapy sessions, using conventional fractionation. The total dose of combined internal and external radiotherapy should reach more than 85 Gy, and the total radiotherapy time should be completed within 8 weeks.

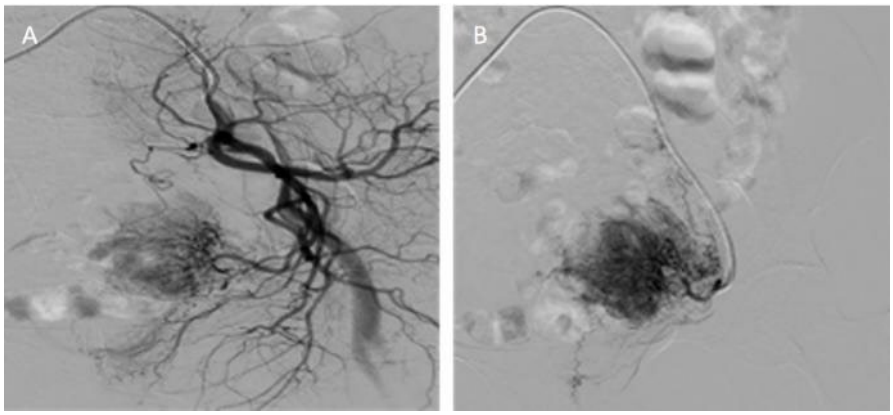

Figure 1. Contrast enhanced image of tumor perfusion chemotherapy. A, pre chemotherapy contrast imaging; B, left tumor arterial infusion chemotherapy.

2.3. Short-Term Efficacy Evaluation Criteria

Short-term efficacy was evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST 1.1), The efficacy evaluation of the tumor lasts for 4 weeks. Complete response (CR): complete disappearance of known tumor lesions maintained for 4 weeks; Partial response (PR): ≥30% reduction in the sum of the longest diameters of tumor lesions maintained for 4 weeks; Stable disease (SD): changes in lesions between PR and PD; Progressive disease (PD): ≥20% increase in the sum of the longest diameters of target lesions. Objective response rate (ORR) = CR + PR. The efficacy was evaluated using MRI every 2 treatment courses. IACT and afterloading therapy should be determined based on the patient's constitution and MDT.

2.4. Adverse Reaction Evaluation Criteria

Adverse reactions during treatment were evaluated using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Grade 0: no adverse reactions; Grade 1: mild adverse reactions; Grade 2: moderate but tolerable adverse reactions; Grade 3: moderate and intolerable adverse reactions; Grade 4: severe adverse reactions.

3. Results

3.1. Short-Term Efficacy

The short-term effective rate was 100% in all patients. Significant necrosis and shedding were observed in 95% of patients after the second brachytherapy session. By the third afterloading treatment, 95% of patients achieved PR, and 90% achieved CR after the entire treatment course (**Table 2**) (**Figure 2**).

Table 2. Short-term effects.

Short-term effects	CR	PR	SD	PD	ORR
n (%)	18 (90)	2 (10)	0 (0)	0 (0)	20 (100)

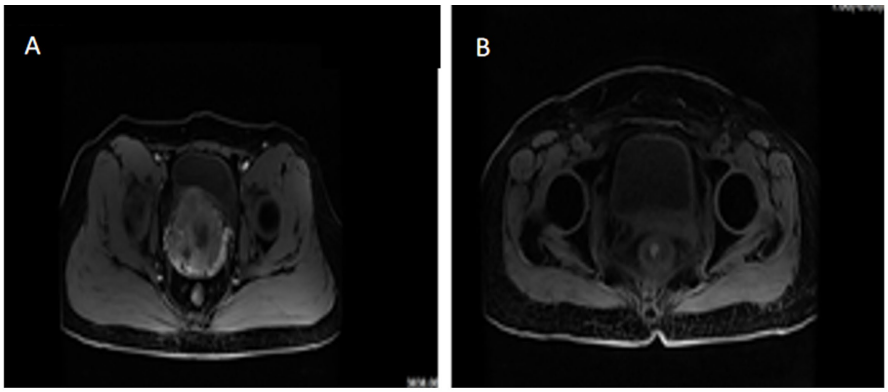

Figure 2. Comparison of MRI images before and after combined treatment. A, pre-treatment MRI; B, MRI after treatment.

3.2. Adverse Reactions

During the entire treatment process, 18 patients experienced gastrointestinal reactions such as lower abdominal distension, loss of appetite, and nausea, all of which were grade 1 - 2; 15 patients developed grade 1 - 2 leukopenia; 5 patients developed symptoms of radiation proctitis. All patients improved after symptomatic treatment, and no grade 3 or above adverse reactions occurred during treatment (Table 3).

Table 3. Recent adverse reactions.

	Any grade	Grade1 (%)	Grade2 (%)	Grade3 - 4 (%)
Lower abdominal pain	18 (90)	15 (75)	3 (15)	0 (0)
Leukopenia	15 (75)	12 (60)	3 (15)	0 (0)
Radiation proctitis	5 (25)	4 (20)	1 (5)	0 (0)

4. Discussion

Cervical cancer is the second most common malignant tumor in women worldwide after breast cancer [3]. Despite the rapid development of tumor treatment methods, surgery, radiotherapy, and chemotherapy remain the mainstays of cervical cancer treatment [5]. Most cervical cancer patients are diagnosed at an advanced stage, and the treatment of advanced patients, especially those with bulky cervical cancer, remains a clinical challenge. Simple surgery has poor efficacy or even loses surgical indications, requiring radiotherapy and chemotherapy. Currently, most guidelines recommend radiotherapy combined with cisplatin-based single-agent or multi-agent chemotherapy for cervical cancer, but few studies

have combined IACT, afterloading treatment, and external beam radiotherapy for cervical cancer [5] [7] [8].

The efficacy of chemotherapy depends on the type and dose of drugs, the affinity of drugs for tumors, the residence time of drugs in tumors, and the degree of drug damage to blood vessel walls. Cisplatin is one of the most common and potent anticancer chemotherapy drugs in clinical practice, with advantages such as a broad anticancer spectrum, effectiveness against hypoxic cells, and strong efficacy. It has good therapeutic effects on lymphoma, germ cell tumors, malignant epithelial tumors, etc., and also has a radiosensitizing effect, occupying an important position in the treatment of cervical cancer [9] [10]. Epirubicin is an antitumor antibiotic that acts as a cell cycle non-specific drug. Its mechanism of action is to directly intercalate between DNA base pairs, inhibit tumor cell transcription, and block the formation of mRNA, thereby preventing DNA and RNA synthesis. Epirubicin can effectively improve the clinical symptoms of cervical cancer patients, prolong their survival, and improve their quality of life [11]. The combination of cisplatin and epirubicin has a strong killing effect on tumor cells, but it also causes degeneration and necrosis of many small blood vessels in the tumor, leading to vascular stenosis and occlusion, and liquefaction necrosis of blood-rich tumor tissue [11].

IACT directly delivers chemotherapy drugs to the uterine artery through interventional methods, increasing the local drug concentration while reducing or blocking the blood supply to the tumor, thereby causing ischemic necrosis of the local lesion and ultimately killing tumor cells [12] [13]. Compared with intravenous chemotherapy, IACT chemotherapy directly acts on the local lesion, preventing the first-pass effect during liver and kidney metabolism, greatly reducing the probability of drug binding to plasma proteins. The local drug concentration in the tumor lesion is several times higher than that in intravenous chemotherapy, thereby improving drug efficacy [14]. Cervical cancer is a locally progressive tumor, and most of its blood supply comes from the internal iliac artery, providing an ideal vascular anatomical basis for IACT for cervical cancer. In this study, 18 patients with bleeding stopped bleeding within 2 - 3 days after interventional treatment, effectively achieving hemostasis. However, interventional treatment cannot be used as a standalone treatment because pelvic organs have extensive collateral circulation. When the main tumor-feeding vessel is blocked, tumor tissue only undergoes temporary ischemic necrosis, and extensive collateral circulation will quickly establish new tumor-feeding vessels and continue to grow. Therefore, early combination with radiotherapy is particularly important.

Radiotherapy for cervical cancer includes brachytherapy (intracavitary afterloading treatment) and external beam radiotherapy, which target different areas. Intracavitary afterloading treatment mainly irradiates the primary lesion area of cervical cancer, while external beam radiotherapy mainly targets the primary lesion, pelvic spread, and lymph node metastasis areas [15]. Due to the special anatomical location of the cervix, small organ mobility, and high radiation tolerance

of the vagina and uterus, brachytherapy is widely used in gynecological tumors such as cervical cancer, endometrial cancer, and vaginal cancer. For gynecological tumors that cannot be surgically treated or have high-risk factors after surgery, brachytherapy is an indispensable part of treatment. Without afterloading radiotherapy, the local radiation dose to the cervix cannot reach the curative dose, and patients with bulky cervical cancer cannot be cured [15]. High-dose-rate afterloading radiotherapy is one of the most important treatment methods for cervical cancer. The combination of afterloading treatment and external beam radiotherapy is a classic treatment model for cervical cancer. Improving the efficacy of afterloading treatment and reducing radiotherapy adverse reactions are hot topics in cervical cancer radiotherapy. Early afterloading treatment has a significant hemostatic effect on bulky cervical cancer, especially three-dimensional afterloading treatment, but its tumor shrinkage effect on bulky cervical cancer is still unsatisfactory. Traditional afterloading treatment usually starts after 15 - 20 sessions of external beam radiotherapy, with a dose of 5 - 8 Gy per session, 1 - 2 times a week. In the late stage of external beam radiotherapy, vaginal edema and fibrosis of varying degrees make it difficult to place the applicator during afterloading treatment, reducing afterloading compliance. Some patients are unwilling to complete the full course of radiotherapy, and residual tumors are still observed in some patients with bulky cervical cancer after external beam radiotherapy. However, administering a high dose of afterloading treatment early in radiotherapy can further accelerate tumor necrosis, reduce local tumor blood flow, and make it difficult for collateral circulation to establish, effectively reducing the tumor size in a short time. Subsequent combination with external beam radiotherapy further enhances the efficacy, thereby prolonging patients' survival and improving their quality of life.

A retrospective analysis of previous cervical cancer cases in our hospital showed that standard concurrent chemoradiotherapy had poor tumor regression effects in advanced patients, especially those with bulky cervical cancer. Some patients even failed to achieve PR due to combined chemoradiotherapy adverse reactions or poor compliance. If residual tumors remain after chemoradiotherapy, the efficacy of subsequent treatment decreases, and survival time is significantly shortened. The method adopted in this study mainly combines interventional IACT with early high-dose-rate brachytherapy, complementing the effects of chemotherapy and brachytherapy. All observed cases showed significant necrosis and regression. External beam radiotherapy was administered after 2 - 3 brachytherapy sessions, and as the tumor shrank and symptoms improved, the efficacy of external beam radiotherapy also improved. After completing the entire treatment, 90% of patients achieved CR. Eighteen patients developed grade 1 - 2 gastrointestinal reactions such as lower abdominal pain and loss of appetite after embolization, 15 patients developed grade 1 - 2 leukopenia, and 5 patients developed grade 1 - 2 radiation inflammation. All improved after symptomatic treatment, and no grade 3 or above toxic reactions occurred during treatment. All patients successfully completed the treatment course.

This study is a single-center clinical study of IACT combined with early afterloading treatment and external beam radiotherapy for bulky cervical cancer. Although the long-term efficacy of this treatment regimen needs further research, its good short-term efficacy and safety are worthy of further exploration, providing more guiding evidence for the treatment of bulky cervical cancer.

5. Conclusion

This study demonstrates that IACT combined with early radiotherapy is a safe and highly effective treatment for bulky cervical cancer. This regimen offers a promising alternative for unresectable cases, warranting further exploration to validate long-term outcomes and optimize clinical guidelines.

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Abbreviations

IACT, intra-arterial infusion chemotherapy; DSA, digital subtraction angiography; RECIST, response evaluation criteria in solid tumors; ORR, objective response rate; CTCAE, common terminology criteria for adverse events.

Author's Contribution

Dahe Zhan and Wangti Xie are responsible for designing research plans, implementing research, collecting clinical data, proposing research ideas, providing technical guidance, imaging guidance, data analysis, revising papers and writing papers.

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Availability of Data and Materials

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

Ethics Approval and Consent to Participate

The study was approved by the Medical Ethics Committee of Yueyang Central Hospital (2018-002) on 2018/01/02.

Conflicts of Interest

This study was independently conducted by the undersigned author in accordance

with the following statement of contribution, and no undue position or financial interest was accepted as a result of conducting the study, thereby re evaluating the independence of the study Sex and scientificity are guaranteed.

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