Reducing Radiation Target Volume in Radical Radiotherapy for Stage IIb Cervical Cancer: A Single-arm Exploratory Study

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I. Research Background

Cervical cancer is one of the most common malignant tumors in the female reproductive system worldwide. According to the latest data, its incidence and mortality rates still rank among the top for female cancers, especially in developing countries, where 80% of patients are diagnosed at the local advanced stage [1]. As a high-incidence area for cervical cancer in China, the data from the National Cancer Center shows that in 2022, there were approximately 151,000 new cases and 56,000 deaths, and the disease burden and treatment-related toxicities have a significant impact on patients' quality of life.

According to relevant international and domestic guidelines [3,4], early-stage cervical cancer patients are mainly treated with surgical methods. Those who refuse surgery or are unable to undergo surgery due to concurrent internal medical conditions can adopt radical radiotherapy, while patients in the local advanced stage are primarily treated with concurrent chemoradiotherapy (CCRT). Radiotherapy is an important treatment strategy for cervical cancer, which can be involved in the treatment of all stages, especially for patients who have not undergone surgical treatment, radiotherapy is an important curative treatment method. The irradiation range of radical radiotherapy traditionally adopts a large pelvic irradiation, usually including the primary tumor and pelvic lymphatic drainage areas (such as internal iliac, external iliac, obturator and pre-sacral), with the aim of covering potential metastasis-risk areas. However, the resulting toxicities such as radiation-induced colitis, radiation-induced bladder inflammation, bone marrow suppression [5] and sexual function impairment [6] have become increasingly prominent. The rate of pelvic lymph node metastasis in early-stage cervical cancer is relatively low, especially for patients with small tumors, no lymphatic vessel invasion and superficial stromal infiltration [7,8]. The LACC staging range is wide and heterogeneous, and there are many relatively low-risk stage IIIB cervical cancers that are earlier in stage and have smaller tumor volumes with relatively better prognosis. Sakuragi et al. [9] reported that the incidence of pelvic lymph node metastasis in IB, IIA and IIB cervical cancers was 12-22%, 10-27% and 34-43% respectively. However, this study used the 2009 FIGO staging. Our center's statistics for 2018-2022 of 2009 FIGO IIB stage patients showed that there were 116 patients with FIGO IIB stage in 2018, and only 10 cases had lymph node metastasis confirmed by pelvic lymph node resection pathology, with a low incidence of pelvic lymph node metastasis (10/116, 8.6%) in 2018 FIGO IIB stage patients. A multicenter prospective cohort study EMBRACE-I showed that among LACC cervical cancer patients receiving standard treatment modes, low-risk cervical cancer patients had significantly better overall treatment effects than those with a later stage, with significantly higher 5-year local control rate and overall survival rate

[10]. For low-risk patients, routine irradiation of the pelvic lymphatic drainage area may lead to over-treatment, increase acute and long-term toxicity, significantly affecting the quality of life without significantly improving survival. If the prophylactic irradiation of the pelvic lymphatic drainage area is not considered, the target volume of radical radiotherapy will be reduced by at least half, significantly reducing radiation damage to surrounding normal organs, especially the intestine and bone marrow. Especially for young patients or those with more comorbidities, reducing the irradiation range may significantly improve the quality of life and provide better bone marrow reserve protection for concurrent chemotherapy.

Modern imaging techniques (such as high-resolution MRI, enhanced CT, PET-CT) have high sensitivity for lymph node metastasis, and the negative predictive value of lymph node metastasis can reach over 90% [11-13]. Combined with sentinel lymph node biopsy technology, it can more accurately screen patients with extremely low risk of lymph node metastasis. The PHENIX-I [14] study reported at the 2025 SGO conference showed that the rate of non-sentinel lymph node metastasis in patients with early-stage cervical cancer who had negative sentinel lymph nodes was less than 1%. Patients with negative sentinel lymph nodes did not require systematic lymph node dissection, and their survival rate and complications were better than those of traditional surgery. This provided an analogy basis for the reduction of the radiation target area, suggesting the feasibility of similar strategies in the field of radiotherapy. If the lymph nodes are clearly negative on imaging (especially combined with clinical examination), the irradiation range can be selectively reduced. The popularization of intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy (IGRT) has made the dose distribution of the target area more precise, reducing damage to normal tissues. At the same time, image-guided brachytherapy (such as MRI-guided brachytherapy [15]) can increase the dose to the primary lesion, compensating for the local control needs after the reduction of the external irradiation range. The core of radical radiotherapy for cervical cancer lies in the high-dose coverage of the primary lesion (through EBRT combined with brachytherapy). If the primary lesion is well controlled, the absolute risk of lymph node recurrence is generally low. Some retrospective studies have shown that the local control rate of early-stage patients treated with EBRT combined with brachytherapy can exceed 90%, and the lymph node recurrence rate is less than 10% [16]. Patients with locally advanced cervical cancer after radical radiotherapy have a recurrence pattern mainly of distant metastasis, with a significantly higher incidence than local recurrence (77.5% : 36.9%) [17]. Among the 877 patients with locally advanced cervical cancer in our center from 2016 to 2022, 286 cases were in FIGO stage IIb in 2018, and 32 cases had recurrence. The majority were local recurrence or distant metastasis, and only 1 case (1/286, 0.35%) was pelvic lymph node recurrence. The

INTERLACE study published in THE LANCET in October 2024 [18] added induction chemotherapy (carboplatin (AUC2) + paclitaxel (80mg/m2)) for 6 cycles before CCRT for cervical cancer patients (2008 FIGO stage Ib1 positive lymph nodes, Ib2, II, IIIb, IVa). This improved the progression-free survival and overall survival of patients without significantly increasing adverse reactions or delaying the treatment process. Thus, induction chemotherapy was recommended by the latest NCCN cervical cancer guidelines (2025.V4 version) [4]. The addition of various technical means has led to better treatment outcomes for cervical cancer. Therefore, improving the quality of life has become our further pursuit goal. We can attempt "subtraction exploration" under the guarantee of good therapeutic efficacy, trying to reduce the irradiation range when performing radical radiotherapy for cervical cancer with low lymph node metastasis risk to reduce damage to normal tissues.

In recent years, with the advancement of imaging technology and precise radiotherapy techniques, the exploration of reducing the irradiation range has achieved positive progress in multiple tumor types. For example, in early-stage non-small cell lung cancer (NSCLC), the application of stereotactic body radiotherapy (SBRT) precisely focuses on the tumor target area, reducing the irradiation volume to the primary lesion, significantly reducing the radiation dose to normal lung tissue while maintaining a good local control rate [19]. Similarly, in prostate cancer, the application of precise target delineation based on MRI fusion technology and intensity-modulated radiotherapy (IMRT) has reduced the irradiation range from the entire pelvic cavity to the prostate and some surrounding tissues, significantly reducing radiation-induced damage to the gastrointestinal and urogenital systems [20]. These studies provide important analogical basis for reducing the irradiation range in radical radiotherapy for cervical cancer, suggesting that individualized radiotherapy strategies may reduce toxicity while maintaining tumor control effects. At present, immunotherapy is increasingly being used in the treatment of malignant tumors. With the application of immunotherapy, the adjustment of the radiation irradiation range may also affect the efficacy of immunotherapy. Animal models have shown that if radiotherapy does not irradiate the lymphatic drainage area, more immune cells, such as CD8+ T cells and dendritic cells, may be preserved in the lymph nodes, which are crucial for immune responses. Lymph nodes are also the sites where immune cells are activated and proliferated, and preserving them may enhance the efficacy of immunotherapy [21]. Moreover, extensive radiotherapy may lead to lymphopenia, reducing the response rate of immunotherapy [22]. Reducing the irradiation range can minimize this damage to lymphocytes. Additionally, radiotherapy may alter the tumor microenvironment, such as increasing PD-L1 expression, but extensive irradiation may simultaneously damage lymphatic structures, affecting the transportation and activation of immune cells. Precise

radiotherapy that avoids lymph nodes may maintain the functions of these structures and make immunotherapy more effective. When radiotherapy causes tumor cell death, antigens are released, and if the draining lymph nodes are intact, antigen presentation may be more effective, activating systemic immune responses, and combining immunotherapy may produce a stronger distant effect in controlling metastatic lesions [23]. We have previously explored in depth the impact of surgical removal of lymph nodes on immunotherapy after cervical cancer recurrence, and found that the immunotherapy effect was better in patients with recurrent cervical cancer who did not undergo lymph node resection. This was confirmed from a clinical perspective, demonstrating that preserving lymph nodes can enhance the efficacy of immunotherapy. Therefore, low-risk cervical cancer radical radiotherapy can also consider reducing the irradiation range and preserving lymph nodes and lymphatic drainage areas, providing more guarantees for better efficacy of immunotherapy in subsequent disease changes.

Although the NCCN and ESTRO guidelines recommend individualized reduction of the irradiation range for patients with imaging-negative lymph nodes in cervical cancer, specific implementation standards have not yet been unified. Part of the reason is the lack of prospective studies to verify their safety. In clinical practice, traditional large irradiation field radiotherapy is still widely used. Therefore, it is urgent to accumulate evidence through single-arm exploratory studies to clarify the indications and risk stratification criteria for reducing the irradiation range. This single-arm exploratory study aims to verify the safety and effectiveness of reducing the irradiation range in radical radiotherapy for stage IIb cervical cancer. By combining modern imaging, pathological staging, and precise radiotherapy techniques, we explore new strategies to reduce treatment-related toxicity while ensuring tumor control, providing high-level evidence for future guideline updates and clinical practice. The study will focus on local control rate, progression-free survival rate, acute and long-term toxic reactions, and changes in quality of life, laying the foundation for more optimized treatment strategies for cervical cancer patients.

II. Research Objectives

(1) To explore the effectiveness and safety of reducing the irradiation area in the radical radiotherapy for stage IIb cervical cancer, and to provide high-level evidence for future guideline updates and clinical practice.

(2) To observe the radiotherapy toxic and side effects during CCRT, and to verify the benefits brought by reducing the irradiation area to the improvement of patients' quality of life.

Main observation indicators: Bone marrow suppression during CCRT, objective response rate (ORR), disease control rate (DCR), 1-year and 2-year recurrence rates in the pelvic lymphatic drainage area.

Secondary observation indicators: Gastrointestinal and urinary system toxic and side effects during CCRT, incidence of lymphedema, 2-year progression-free survival (PFS).

III. Research Population

Inclusion criteria:

1. Patients voluntarily participate in this study and sign the informed consent form;

2. 50-75 years old;

3. Patients with cervical cancer who have not undergone surgery or chemotherapy and are diagnosed with squamous cell carcinoma by pathological tissue, and HPV high-risk positive;

4. 2018 International Federation of Gynecology and Obstetrics (FIGO) stage IIb (tumor size < 4 cm);

5. ECOG score 0-1, expected survival greater than 6 months;

6. Pregnant women must undergo pregnancy test (serum or urine) 7 days before enrollment, and the result is negative, and are willing to use appropriate contraceptive methods during the trial;

7. The investigator judges that there are no absolute contraindications to radiotherapy and surgery, and can comply with the trial protocol.

Exclusion criteria:

1. Active or uncontrolled severe infection;

2. Liver cirrhosis, decompensated liver disease;

3. History of immunodeficiency, including HIV positive or having other acquired congenital immune deficiency diseases;

4. Chronic renal insufficiency and renal failure;

5. Patients with other malignancies that need treatment and/or newly diagnosed within 5 years;

6. Myocardial infarction, severe arrhythmia, and ⩾ 2 grade congestive heart failure (New York Heart Association (NYHA) classification);

7. Patients who have received pelvic arterial embolization;

8. Patients who have undergone partial or radical hysterectomy;

9. Patients who have received partial or radical hysterectomy;

10. Patients with a history of severe allergic reaction to platinum-based chemotherapy drugs;

11. Patients with comorbidities, need to take drugs with high liver and kidney function impairment during treatment, such as tuberculosis, etc.;

12. Patients who cannot understand the experimental content and cannot cooperate and refuse to sign the informed consent form;

13. Patients with serious conditions that endanger the safety of the patient or affect the completion of the study.

Criteria for discontinuation of treatment by subjects:

1. The study physician considers it necessary to terminate the treatment from the perspective of the best benefit for the patient;

2. Adverse reactions or serious adverse events that cannot be tolerated are confirmed by the investigator;

3. Patients who fail to complete the treatment on schedule and time;

4. Patients withdraw the informed consent;

5. Patients receive other anti-tumor drug treatments (such as immunotherapy, targeted therapy) that affect the judgment of therapeutic efficacy.

IV. Research Design

This study is a single-center, prospective clinical trial in China, and it plans to enroll 60 patients.

1. Patients diagnosed with cervical squamous cell carcinoma through biopsy, before anti-tumor treatment, undergo comprehensive gynecological examinations and imaging evaluations (CT, MRI or PET/CT), and are diagnosed with stage IIb cervical cancer (tumor size < 4 cm) according to the FIGO 2018 staging principle;

2. Induction chemotherapy for 6 times (carboplatin (AUC 2) + paclitaxel (80 mg/m2), q1w);

3. Platinum-containing regimen for concurrent chemoradiotherapy (CCRT)

(1) Concurrent radiotherapy: external irradiation uses rotational intensity-modulated radiotherapy (VAMT), and internal irradiation uses three-dimensional brachytherapy.

(2) Radiotherapy plan:

① The external irradiation range only covers the entire uterus (including the primary lesion of the cervical cancer), bilateral parametrium, and 3 cm below the cervical/vaginal lesions.

② External irradiation dose: 45 Gy/25 fractions; total external irradiation + brachytherapy dose: HR-CTV D90 ≥ 80 Gy (+20%).

③ Normal organ limits (EQD2): bladder D2cc ≤ 80-90 Gy, rectum D2cc ≤ 65-75 Gy, sigmoid colon D2cc ≤ 70-75 Gy.

(4) Concurrent platinum-containing chemotherapy for 5 times (cisplatin 40 mg/m2 q1w, if cisplatin is intolerable, use carboplatin AUC = 2 q1w. Window period 1 week).

⑤ CCRT time is controlled within 56 days. After completing CCRT according to the plan, efficacy is evaluated within 1 week and recorded for analysis.

⑥ If cervical biopsy after CCRT indicates positive pathology, perform adjuvant chemotherapy for 3 courses (TP regimen: paclitaxel 135 mg/m2, cisplatin 50 mg/m2, q3w; if cisplatin is intolerable, TC regimen: paclitaxel 135 mg/m2, carboplatin AUC = 4, q3w; window period 2 weeks) ± three-dimensional brachytherapy (A point or HR-CTV D90 no more than 96 Gy).

4. Short-term efficacy is evaluated according to the WHO's evaluation criteria for solid tumors (RECIST 1.1). All lesions are evaluated within 4 weeks after the end of treatment and every half year thereafter until disease progression, with a window period of 4 weeks.

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