Informed Consent Form

Dear Participants:：

Greetings!

You are invited to participate in this multicenter clinical study which aims to utilizing anal canal-sparing technique during postoperative pelvic radiotherapy for cervical cancer patients to reduce hemorrhoids-related symptoms because you meet the eligibility criteria. Please read this informed consent carefully and make an informed decision whether or not to participate in this study. Your participation is entirely voluntary. By signing this consent form, you are enrolled in the study as it is described. If you have any questions about this informed consent, you can ask your study physicians or researcher to explain to you. We encourage you to thoroughly discuss your results with your family and friends before making a decision to participate in this study. You have the right to refuse to participate in or to withdraw from the study at any time without penalty or loss of rights and interests. If you are currently participating in another study, please inform your study physician or researcher. The background, purpose, process and other important information of this study are as follows:

1. Why the study was conducted?

Radiotherapy is an important treatment for cervical cancer and plays a vital role in patients with post-operative or inoperable cervical cancer. According to clinical statistics, 90-95% of patients with gynecological tumors, urinary system tumors, rectal cancer, anal canal cancer and other pelvic tumors will have different degrees of radiation intestinal injury, among which radiation rectal injury is the most common and stubborn, and most of them are mainly symptomatic treatment with limited curative effect.

According to the current treatment guidelines, whether it is gynecological tumors or other pelvic malignancies, the anal canal and the rectum are considered as the same organ-at-risk (OAR) when external pelvic irradiation, and unified radiotherapy dose

limit is given, without separate protection. However, anal canal related symptoms may emerge at relatively low radiation doses, especially in patients with a history of hemorrhoids. Hemorrhoids-related symptoms such as perianal pain, hemorrhoidal prolapsis, rectal bleeding, and perianal skin damage may occur early in radiotherapy, which may be caused by the worsening of hemorrhoids rather than radiation rectal injury.

Hemorrhoids is a common disease of anal canal and tectum in adults. In China, the saying *"nine out of ten people suffer from hemorrhoids"*reflects their staggering prevalence rate. The main symptoms caused by hemorrhoids are prolapsed, local burning, itching, perianal pain and bleeding. Although not life-threatening, hemorrhoids severely and persistently impact quality of life and contribute significantly to societal healthcare burdens.

The research team believes that during pelvic radiotherapy, especially for patients with cervical cancer, more attention should be paid to the occurrence of symptoms related to acute hemorrhoids. The main reasons include: First, the incidence of hemorrhoids is very high in female patients, especially those with a reproductive history, and their pelvic tolerance is relatively poor, so they should pay more attention to the protection of the anal canal; Second, for patients with cervical cancer, whether it is adjuvant radiotherapy or radical radiotherapy, the mode of external irradiation combined with high-dose-rate intracavitary brachytherapy is widely applied. If anal canal-sparing techniques is implemented during external pelvic irradiation, the incidence and severity of anal canal related symptoms will be correspondingly reduced during subsequent brachytherapy. Third, hemorrhoids-related symptoms can cause patients with varying degrees of local discomfort and psychological pressure.

Based on this, we plan to actively prevent and reduce the incidence of acute hemorrhoids-related symptoms caused by external pelvic irradiation through anal canal-sparing techniques for postoperative cervical cancer patients with a history of hemorrhoids requiring pelvic radiotherapy, so as to improve the quality of life of cervical cancer patients. The purpose of this study was to reduce the incidence of

hemorrhoids-related side effects and/or reduce the severity of symptoms associated with pelvic radiotherapy by reducing the dose of exposure to the anal canal and perianal musculatures of pelvic radiotherapy, so that the study did not increase the incidence of adverse events (AEs) and serious adverse events (SAEs).

2. Purpose of the study

This study aims to reduce the incidence of hemorrhoids-related symptoms in patients with postoperative pelvic radiotherapy for cervical cancer by anal canal-sparing techniques.

3. Process of the study

1）How many participants will be involved?

Approximately 300 participants will be enrolled across five medical institutions.

2）Who is eligible to participate in the study?

Inclusion Criteria: ①Age ≥18 years; ②Have a confirmed cervical cancer diagnosis with completed hysterectomy; ③ Require postoperative concurrent chemoradiotherapy based on pathology; ④Have documented hemorrhoids history with complete resolution of symptoms for ≥4 weeks prior to radiotherapy initiation; ⑤Agree to undergo pre-treatment anal canal MRI without contrast; ⑥Voluntarily participate and sign this informed consent form before study commencement.

Your study physician will review your medical history, arrange screening assessments, and determine your final eligibility.

3）Who is ineligible to participate in the study?

Exclusion Criteria: ① Cervical cancer patients without clinical indication for radiotherapy after radical hysterectomy; ②Diagnosed absence of hemorrhoids; ③ Absolute contraindications to MRI (e.g., metallic implants, severe claustrophobia); ④ Declination of anal canal MRI; ⑤ Radiologically evident residual lesions requiring pelvic external beam boost radiotherapy; ⑥ History of other malignancies (except appropriately treated non-melanoma skin cancer or in-situ

carcinomas); ⑦Prior pelvic radiotherapy resulting in overlapping radiation fields; ⑧Documented hypersensitivity to platinum-based chemotherapy; ⑨Severe and/or active comorbidities contraindicating chemoradiotherapy tolerance.

4）Randomization of the study groups

This study has a prospective, multicenter, randomized controlled clinical trial design. The specific process is as follows: First, the researcher will stratify whether you require supplemental brachytherapy after pelvic radiotherapy based on your medical condition. Then, you will be enrolled through a central randomization system via random selection. Participants will be randomly assigned with equal probability (in a 1:1 ratio) to either Control Group (conventional radiotherapy) or Experimental Group (anal canal-sparing radiotherapy).

Following randomization, you will not be informed of your group assignment until the end of the follow-up period. This blinding procedure ensures objective assessment of symptom outcomes throughout the study. Important Notes: ①Your treatment efficacy will not be compromised by group assignment; ②No additional treatment-related adverse effects will occur during treatment; ③The experimental group may potentially mitigate radiotherapy-induced adverse effects.

5）Groups and Treatments

Control Group: You will have an anal magnetic resonance examination before treatment and receive standard pelvic radiotherapy in 5-5.5 weeks.

Experimental Group: You will have an anal magnetic resonance examination before treatment and receive pelvic radiotherapy with sparing of the anal canal in 5-5.5 weeks.

Platinum-containing concurrent chemoradiotherapy utilizes cisplatin as a single agent (or carboplatin if cisplatin intolerant). Simultaneously, symptomatic treatment will be given to reduce the chemotherapy-associated adverse effects. If you require continued brachytherapy and/or chemotherapy after completion of pelvic radiotherapy, it will not affect your subsequent treatment process.

6）Phases of the study

The trial process includes three phases: a screening/baseline period, a treatment period, and a follow-up period. Your participation begins upon signing this informed consent

form.

Screening period:

After signing the informed consent form, you will undergo a screening period examination including: Clinical consultation (demographic data collection, height and weight measurement, medical history review, physical examination; vital signs monitoring; 12-lead electrocardiogram (12-ECG); infectious disease screening; laboratory testing. To ensure timely initiation of your radiotherapy, all screening programs must be completed within 1 week prior to chemoradiotherapy commencement.

- Provide your medical history and basic information to the physician, and actively inform them of your past medical history, treatment history (**including hemorrhoids-related conditions and treatments**), as well as concomitant medications used within the last 30 days.
- Evaluate of ECOG performance status, vital signs, and comprehensive physical examinations (**including anal inspection, digital rectal examination, and anoscopy**).
- Perform blood routine, urine routine, stool routine, occult blood test, blood biochemical examination.
- Perform tumor markers and virology tests.
- Undergo a 12-lead electrocardiogram (ECG) and cardiac ultrasound (echocardiogram) (mandatory during the screening period; during the treatment period, perform if ECG abnormalities are detected, based on clinical judgment).
- Non-contrast MRI of the anal canal (**to evaluate the specific anatomy and length of your anal canal; costs covered by the researcher**).
- Other imaging examinations: If preoperative imaging assessment outside the pelvis (primarily chest and upper abdomen) was not performed, it must be completed during the screening period to determine tumor staging.
- Questionnaire completion: Accurately fill out the following based on your current condition: Low Anterior Resection Syndrome (LARS) Score Questionnaire, EORTC QLQ-C30* (European Organization for Research and

Treatment of Cancer Quality of Life Questionnaire Core 30) and EORTC QLQ-CX24* (Quality of Life Questionnaire for Cervical Cancer Patients).

Treatment period, you will require:

- Once per week: Vital signs monitoring and physical examination (including anal inspection, digital rectal examination and anoscopy), blood routine, blood biochemical examination, urine routine, stool routine and occult blood test.
- Anoscopy is performed every two weeks. Urine and stool tests will be conducted during the 18th to 20th radiotherapy sessions (week 4) and in the first week of brachytherapy.
- Questionnaire completion once per week: Based on your current clinical status, please accurately complete Low Anterior Resection Syndrome Score Questionnaire, EORTC QLQ-C30 and EORTC QLQ-CX24 Questionnaires.
- Receive either standard pelvic chemoradiotherapy or pelvic chemoradiotherapy with sparing of the anal canal depending on your assigned study group.
- Additionally, we will systematically document all adverse events and concomitant medications usage during treatment, and provide protocol-specified management for any unanticipated events arising in the study.

Follow-up period, you will require:

- Once per week: Vital signs monitoring and physical examination (including anal inspection, digital rectal examination).
- Once every two weeks: Blood routine, blood biochemistry and anoscopy
- Questionnaire completion once every two weeks: Based on your current clinical status, please accurately complete Low Anterior Resection Syndrome Score Questionnaire, EORTC QLQ-C30 and EORTC QLQ-CX24 Questionnaires.
- Urine routine, stool routine and occult blood examination were performed in the second week of follow-up.
- Additionally, we will systematically document all adverse events and concomitant medications usage during follow-up period, and provide protocol-specified management for any unanticipated events arising in the study.

7）Prohibited medications and therapies during the study

You are not allowed to participate in other clinical studies at the same time, and you are prohibited from receiving other drugs with anti-tumor indications (such as immunotherapy, anti-angiogenic drugs, etc.) during your treatment.

When you have hemorrhoids-related symptoms that require medical intervention, your physician can prescribe relevant drugs based on clinical conditions, and you should not use hemorrhoids-related drugs and other drugs that aggravate or reduce intestinal reactions. Such drugs mainly include: laxatives, venoactive drugs, topical agents, analgesics and traditional Chinese medicine, etc.

8）How long will the study last?

The study is scheduled to last at least 24 months. Every participant will be involved in about 4 months. You can opt out of the study at any time without forfeiting any benefits you would otherwise have received. However, if you decide to withdraw from the study during the course of the study, it is possible that a relevant examination will be conducted after withdrawal due to your security concerns.

4. Participant Responsibilities

In order to carry out this study smoothly and successfully, please cooperate with the following matters:

- Undergo scheduled examinations and treatments as instructed by the researcher.
- Do not modify current therapies or initiate new treatments without prior approval from the study physician.
- Disclose all health concerns to the study physician, including those you deem minor.
- Report all concomitant medications (including Chinese herbs) used before and during the study.
- Complete a final evaluation by the study physician if discontinuing treatment prematurely for any reason.
- Attend all scheduled safety monitoring visits per protocol requirements.

5. What are the possible risks and discomforts?

Regardless of your randomization to the control or experimental group, you will receive concurrent chemoradiotherapy with potential adverse effects:

1）Radiotherapy-related: Fatigue, radiation dermatitis, mucosal radiation injury, diarrhea, constipation, rectal irritation, urinary frequency, urgency and dysuria, and hematologic abnormalities, etc.

2） Chemotherapy-related: Fatigue, anorexia, nausea, vomiting, constipation, hematologic abnormalities, and hepatic and renal function impairment.

These represent standard treatment risks for your condition and are not increased by study participation.

3）Potential benefits in experimental group: The anal canal-sparing technique may prevent or alleviate hemorrhoidal symptoms including perianal pain, hemorrhoidal prolapsis, rectal bleeding, prolapse, rectal bleeding, itching, and perianal skin breakdown, etc.

4）Risk of blood drawing

During the study, a certain amount of blood is drawn from a vein in the arm, and the risk includes temporary discomfort and/or bruising. Although unlikely, infection, bleeding, blood clotting, or syncope may occur.

5）Risk of imaging examination

For contrast-enhanced MRI or CT examinations requiring contrast agent injection: Although contrast agents demonstrate favorable safety profiles with low frequencies of systemic toxicity or local adverse reactions, unpredictable adverse events may rarely occur in susceptible individuals, including allergic reactions or exacerbation of pre-existing renal impairment. Additionally, contrast extravasation may occur when high-pressure injection meets fragile or narrow vasculature, potentially causing localized pain or tissue injury.

6. What are the possible benefits?

If you agree to participate in this study, you may receive direct medical benefits.

Control Group: You will receive the conventional radiotherapy regimen.

Experimental Group: You will receive free anal canal-sparing technique in addition to conventional radiotherapy. Previous clinical studies have confirmed that for cervical cancer patients with hemorrhoids, the probability of hemorrhoids-related symptoms worsening during conventional radiotherapy is higher. If you are treated with anal canal-sparing techniques, it is not possible to be absolutely certain that your hemorrhoids-related symptoms may be alleviated or not occur, but it may not be effective. In addition, you will receive an assessment of your condition by the study physician and regular follow-up visits.

The data obtained from this study may be of guiding significance to patients with the same condition as you. We extend our sincere appreciation for your valuable contribution to medical advancement.

7. What other treatment options are available?

If you do not participate in this study, you can still continue to receive treatment at your local healthcare institution, and the study physician will choose the best treatment based on your medical condition and overall health status.

8. Study-Related expenses and compensation.

This study respects your voluntary participation and provides no financial compensation.

The primary objective is to reduce radiation exposure to organs-at-risk during pelvic radiotherapy, thereby decreasing the incidence and/or mitigating the severity of hemorrhoids-related adverse reactions. You have a 50% probability of receiving anal canal-sparing technique during radiotherapy. **If randomized to the experimental group, you will undergo pelvic radiotherapy with anorectal protection technique.** If randomized to the control group, you will receive standard treatment without the investigational technique. **Regardless of randomization assignment, you will undergo the anorectal MRI examination and the costs will be covered by the**

researcher. You will be responsible for the cost of radiotherapy, routine medications, diagnostic examinations, laboratory tests and nursing care.

9. Voluntary Participation and Withdraw

You have the right to refuse to participate or to withdraw from the study at any time without penalty or loss of rights and interests. But data processed by researchers before your withdrawal is legally compliant. If data collected prior to withdrawal has already been integrated into the research program, it may continue to be used in this study while protecting your privacy, as removal or similar processing may be infeasible due to cost constraints. Once you decide to participate in this study, please sign this informed consent form to indicate your agreement. Before entering the study, the study physician will conduct screening to confirm whether you are an eligible candidate.

10. Data Confidentiality and Privacy Protection

During the study period, personally identifiable information such as your name and gender will be replaced with codes or numbers and kept strictly confidential. Only relevant physicians will have access to your personal details, ensuring robust protection of your privacy rights. Research findings may be published in journals, but no personally identifiable information about you will be disclosed.

If you agree to participate in this study, all your medical records will be accessible to authorized personnel from the study sponsor, relevant regulatory authorities, and independent ethics committees for the purpose of verifying appropriate study conduct. By signing this informed consent form, you authorize the aforementioned parties to access your information.

11. Contact and Feedback

You can keep abreast of the information and research progress related to this study. If you have study-related questions, please contact the researcher_____, contact

number_____.

If you need to know about the rights and interests of participants during the study, you can contact the Ethics Committee of Shanghai First People's Hospital, contact number 021-36123569 .

Signature Page

Informed Consent Statement:

I have been informed about the purpose, background, process, risks, and potential benefits of this study. I have been given sufficient time and opportunity to ask questions. I am satisfied with the answers and agree to participate in this study.

I have also been informed about whom to contact if I have questions, difficulties, concerns, suggestions for study, or wanted further information or help with study.

I understand that I may choose not to participate in this study or withdraw from the study at any time during the study without any reason.

I acknowledge that should my condition worsen, should I experience serious adverse events, or if my research physician determines that continued participation is not in my best interest, he/she may decide to withdraw me from the study. The sponsor or regulatory authorities may also terminate the study at any time without requiring my consent. If such circumstances arise, the research physician will promptly notify me and discuss alternative options.

I already know that if I get worse, or if I have a serious adverse event, or if my study physician feels that determines that continued participation is not in my best interest, he/she will decide to withdraw me from the study. The sponsor or regulatory authority may also terminate the study during the study period without my consent. If such circumstances arise, the study physician will promptly notify me and discuss alternative options.

I will receive a copy of this signed informed consent form.

I acknowledge that participation in this study requires the use of my personal information and/or imaging data, and I consent to the use and processing of my personal information and/or imaging data for the purposes described in this informed consent form.

☐ Agree ☐ Disagree, Unable to participate in this study。

Subject's signature: _____ Date:_____

Guardian's signature:_____Relationship to Subject ( ) Date:_____

(Required when subject lacks legal capacity or has limited decision-making capacity)

Witness' signature:_____ Date:_____

(Required when subject is illiterate: Witness attests that consent information was fully explained, subject comprehended the content, and voluntarily consented)

Researcher's signature：_____ Date:_____