CLINICAL STUDY PROTOCOL

Anal Canal-Sparing Technique During Postoperative Pelvic Radiation Therapy for Cervical Cancer Patients to Reduce Hemorrhoids-related Symptoms （ACS-RT）

A Multicenter Randomized Clinical Trial

For any communications regarding this protocol,

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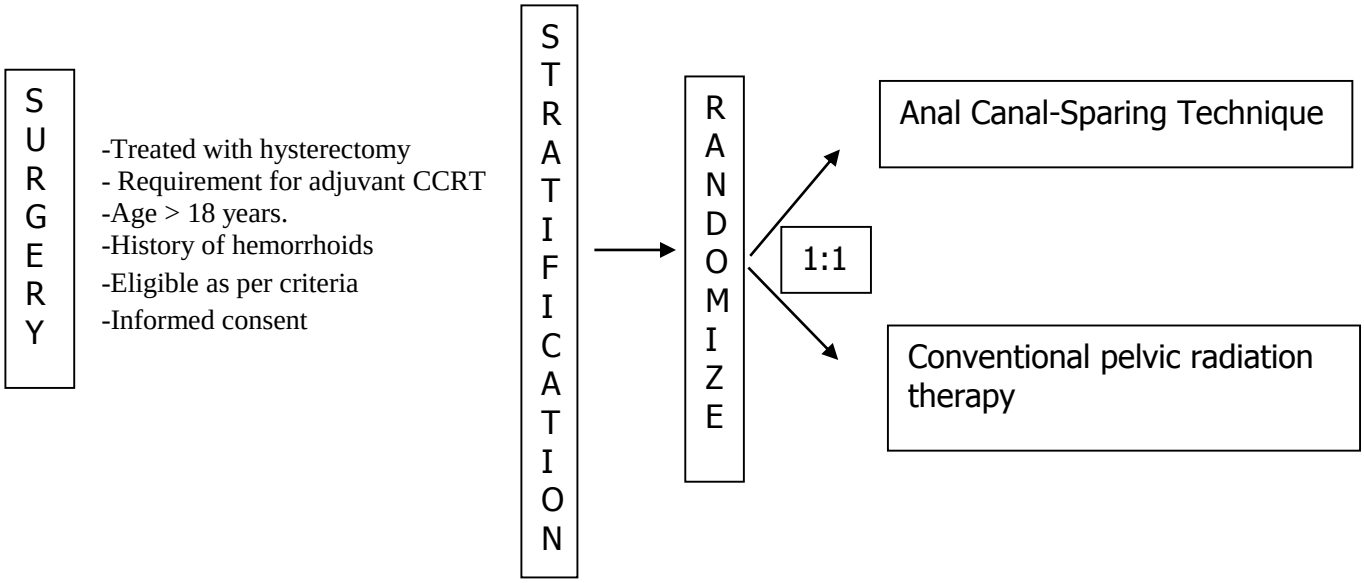
SURGERY
-Treated with hysterectomy
- Requirement for adjuvant CCRT
-Age > 18 years.
-History of hemorrhoids
-Eligible as per criteria
-Informed consent
STRATIFICATION
RANDOMIZE
1:1
Anal Canal-Sparing Technique
Conventional pelvic radiation therapy

1. INTRODUCTION

Radiation therapy (RT) is a main treatment method to improves local control and overall survival for cervical cancer patients with high-risk factors. External beam radiation therapy (EBRT) is particularly important, which plays a crucial role for patients either after surgery or for those ineligible for surgery [1,2]. In recent decades, intensity-modulated radiation therapy (IMRT) has become the mainstream of treatment for cancer patients. Although radiation techniques have improved over the last years, pelvic radiation therapy still causes adverse effects on surrounding normal tissues and organs regularly [3,4], which includes rectum, sigmoid colon, pelvic small bowel loops and ileocecal region. Studies show that 90-95% of patients with pelvic malignancies—including gynecological tumors, urological tumors, colorectal cancer and anal canal cancer—develop varying degrees of radiation-induced intestinal injury. Radiation-induced rectal injury (RRI) is still one of the most common complications of radiation to the pelvis, but which is also the most difficult to treat [5,6].

Radiation-induced rectal injury refers to damage to the rectum caused by radiation exposure, with radiotherapy dosage being the primary contributing factor. RRI can be classified into radiation-induced acute rectal injury (RARI) and radiation-induced late rectal injury (RLRI), clinically demarcated at the 3-month point [7,8]. Typically, the emergence of acute gastrointestinal symptoms is an independent risk factor for the subsequent development of RLRI [9]. RARI patients exhibit diverse and non-specific clinical symptoms that may appear shortly after radiotherapy initiation. These symptoms include increased bowel frequency, urgency, hematochezia, diarrhea, anal pain or tenesmus. Therefore, RARI is required close monitoring, although the symptoms of RARI could always be recovered spontaneously within 3 months after radiation therapy.

However, whether from the symptoms or the pelvic radiation therapy plans, current studies on RARI generally combine the rectum and anal canal. Therefore, the so-called "Radiation-induced rectal injury" is not purely "rectal injury," but includes "radiation-induced rectal and anal canal injury." In addition, the radiation of perianal muscles can also lead to symptoms related to the rectum during pelvic radiation therapy [10,11]. According to current contouring guidelines, whether for gynecologic tumors or

other pelvic malignancies, the anal canal is regarded together with the rectum as the same organ at risk (OAR) when formulating pelvic EBRT plans, and a unified dose constraint standard is applied. The anal canal and its surrounding muscles are not assessed separately. The possible reason is, firstly, that when the prescribed dose of pelvic EBRT is 45-55 Gy (with a fraction size of 1.8-2 Gy), it is considered safe for the anal canal and its surrounding muscles [12]. Secondly, from the perspective of managing radiation-induced toxicities, distinguishing the anal canal, perianal muscles, and rectum may be limited clinical relevance when if symptoms are mild [13]. Thirdly, relying solely on planning CT (Computed Tomography) and pelvic MRI (Magnetic Resonance Imaging) makes it challenging to accurately delineate the anatomical boundaries between the anal canal and rectum, as well as the extent of the perianal musculature [14]. Lastly, there is no promising technique to reduce irradiated dose to the anal canal.

The tolerance dose of the rectum is generally considered to be around 50 Gy[12], however, anal canal–related symptoms may occur at lower doses, particularly in patients with a history of hemorrhoids[15]. During the early phase of radiotherapy, hemorrhoids-associated symptoms such as perianal pain, hemorrhoidal prolapse, rectal bleeding, and perianal skin breakdown may occur. These symptoms are more likely attributable to the aggravation of pre-existing hemorrhoids rather than radiation-induced rectal injury. A study reported that, during external beam radiation therapy for pelvic malignancies, the median induction dose for acute anal canal symptoms was 34.1 Gy (range: 28.8 Gy-50.4 Gy), with a median onset time at 24 days (range: 21-36 days). Patients receiving postoperative adjuvant radiotherapy were more prone to develop acute anal canal reactions compared to those undergoing definitive radiotherapy without surgery ($P = 0.04$). Among the dosimetric parameters, V10 showed a potential association with the occurrence of acute anal canal symptoms ($P = 0.08$)[16], which may suggest that the anal canal deserves more attention during pelvic radiation therapy.

Hemorrhoidal disease (HD) is a common anorectal disorder in adults, arising from increased pressure and abnormal dilation of the hemorrhoidal vascular cushions [17]. The exact incidence of hemorrhoidal disease in the general population remains unclear and may vary across countries and regions [18]. In the United States, it is the third most common gastrointestinal disorder managed in outpatient clinics, affecting up to 75%

of American adults to varying degrees [19]. In China, the saying "nine out of ten people have hemorrhoids" is often used to describe its high prevalence. The main symptoms caused by hemorrhoids include prolapse, local burning, bleeding, perianal pain, and other perianal discomforts [20]. Although it is not a life-threatening condition, it can persistently and severely impact quality of life and increase the healthcare burden on society. In the United States, approximately 4 million medical consultations for hemorrhoidal disease occur each year, with estimated costs exceeding $770 million [21].

Anal canal toxicity should not be a neglected side-effect of pelvic radiation therapy, and greater attention need to be paid to the occurrence of acute hemorrhoids-related symptoms, particularly for cervical cancer patients with hemorrhoids. Female patients, especially those with a history of childbirth, have a markedly higher incidence of hemorrhoids and relatively reduced pelvic tolerance, making the protection of the anal canal especially important. Hemorrhoids-related symptoms can cause varying degrees of local discomfort and psychological stress in patients. Notably, as these symptoms may occur in the early to middle stages of pelvic EBRT, they can compromise patients' adherence to and completion of radiotherapy, while also increase the likelihood of prescriptions for hemorrhoids-related medications. Moreover, for cervical cancer patients, whether undergoing adjuvant radiotherapy or radical radiotherapy, EBRT combined with high-dose rate brachytherapy (BT) is often adopted. If anal canal protection is provided during EBRT, patients will definitely have better tolerance during BT, and the incidence and severity of anal canal-related symptoms will also decrease accordingly.

However, the aggravation of hemorrhoids caused by pelvic radiation therapy has not yet attracted radiation oncologists' attention, and a significant proportion of such hemorrhoidal aggravations are attributed to radiation proctitis. Actually, pelvic normal tissue contouring guidelines for radiation therapy[22] has suggested when treating gynecologic tumors, the acute toxicities and quality of life (QoL) concerns are different for anal canal and rectum. However, because there are no specific dose constraints for anal canal at present, it is contoured as part of the AnoRectum. It also hoped future research may help define anal dose constraints, which may require contouring anal canal and rectum separately. However, there were very limited studies

about the relationship between hemorrhoids aggravation and pelvic radiation therapy, most of which were only retrospective research.

Some studies showed that postoperative pelvic RT may aggravate acute hemorrhoids-related symptoms in patients with hemorrhoids in the era of two/three-dimensional radiation, increasing by 50~70%[13,16]. Although the advent of the IMRT era has improved treatment precision and reduced the radiation dose to the OARs, the incidence of acute anal canal-related symptoms remains relatively high, as these symptoms can occur even at relatively low radiation doses. We have reviewed 15 cervical cancer patients with hemorrhoids who accepted postoperative pelvic RT in 2023 in our center, 9 patients developed acute hemorrhoids-related symptoms, with an incidence rate remaining as high as approximately 60%. For this reason, it remains of significant value to protect anal canal during pelvic radiation therapy in IMRT era, in which separate dose delivery for anal canal and rectum could be achieved.

We tried to develop anal canal-sparing technique to reduce the irradiated dose to anal canal for cervical cancer patients with hemorrhoids who needed postoperative pelvic radiation therapy. Compared with standard pelvic RT plan, the irradiated doses of anal canal and perianal muscles were significantly reduced. The mean doses (Dmean) was reduced from 40 Gy to 30 Gy and the percentage volumes of them that received 20 Gy (V20) was reduced by 15%. A study demonstrated the association between pelvic floor muscle and anorectal injury and radiation dose following prostate cancer radiotherapy, based on dose–response fitting curve, for every 1% reduction in V20, the risk of severe acute anal canal reactions decreased by 2.4% [23]. Correspondingly, our group also evaluated 15 postoperative cervical cancer patients with hemorrhoids and found that, after reducing the deliver dose to the anal canal, only 20.0% (3/15) developed hemorrhoids-related symptoms from the initiation of radiotherapy to four weeks after completion. This incidence was markedly lower compared with patients whose anal canal was not specifically protected.

Minimizing acute toxic effects is of considerable importance to improve quality of life because it has been correlated with late toxic effects in patients with pelvic radiation therapy[9]. Currently, there is no prospective studies about anal canal protection to reduce the incidence of acute anal canal-related symptoms for cervical

cancer patients with hemorrhoids. Herein, we design a multicenter, double-blind RCT in which cervical cancer patients with hemorrhoids were randomly assigned to receive anal canal-sparing or standard postoperative pelvic radiation therapy, in either combined with brachytherapy or not.

2. OBJECTIVES and ENDPOINTS

2.1 Primary Research Objective

To compare the incidence of hemorrhoids-related symptoms between postoperative cervical cancer patients with a history of hemorrhoids receiving anal canal-sparing pelvic radiation therapy and those receiving conventional pelvic radiation therapy. The aim of employing the anal canal-sparing technique is to reduce the incidence of hemorrhoids-related symptoms in this patient population.

2.2 Research Endpoints / Observation Indicators

2.2.1 Primary Endpoint / Primary Observation Indicator

- The primary endpoint is the incidence of radiation-induced hemorrhoids-related symptoms occurring from the initiation of pelvic radiation therapy (including BT) until 4 weeks after its completion.

- The primary observation indicator is assessed by investigators weekly, using the *Radiation Therapy Oncology Group (*RTOG*) / European Organization for Research and Treatment of Cancer (*EORTC*) Acute Radiation Morbidity Scoring Criteria* and the *Pelvic Radiation Therapy Hemorrhoids-Related Symptoms Assessment Scale* (*Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine Version*). The occurrence of any hemorrhoids-related symptom compared to baseline will be considered an event.

2.2.2 Secondary Endpoints / Secondary Observation Indicators

- The secondary endpoints include:

(1) Cumulative incidence of radiation-induced perianal musculature symptoms from the initiation of pelvic radiation therapy (including BT) until 4 weeks after its completion.

(2) Comparison of patient-reported QoL from the initiation of pelvic radiation therapy (including BT) until 4 weeks after its completion.

(3) Comparison of hemorrhoidal medication prescription rates from the initiation of pelvic radiation therapy (including BT) until 4 weeks after its completion.

- The secondary observation indicators:

(1) The radiation-induced perianal musculature symptoms as graded by patients, using *the Low Anterior Resection Syndrome (LARS) questionnaire*, with any symptom emergence from baseline considered an event.

(2) QoL using the *EORTC Core QoL Questionnaire (QLQ-C30) Version 3.0* and *the Cervical Cancer Module (QLQ-CX24)*. Scores will be compared with baseline values.

(3) Hemorrhoidal medication prescription rates: Any prescription of hemorrhoidal medication by the investigators recorded in the medical records from the start of pelvic radiation therapy until 4 weeks after its completion will be documented as a hemorrhoidal medication user.

2.2.3 Exploratory Endpoints / Exploratory Observation Metrics

- Exploratory Endpoints: To explore OARs delineation and dose delivery assessment in anal canal-sparing RT.
- Exploratory Observation Metrics:

(1) Contouring methodology for the anal canal and perianal muscles within pelvic radiation therapy plans utilizing anal canal-sparing

techniques.

(2) Dosimetric evaluation of the anal canal, including V_{10}, V_{15} and D_{mean}.

(3) Dosimetric evaluation of the perianal muscles, including V_{15} and D_{mean}.

3. STUDY POPULATION AND SAMPLE SIZE

3.1 Eligibility Criteria

Participants must meet all of the following criteria on screening examination to be eligible for study inclusion:

3.1.1 Treated with hysterectomy (including total abdominal hysterectomy, vaginal hysterectomy, radical hysterectomy, or laparoscopically assisted vaginal hysterectomy) within 6 weeks prior to study initiation.

3.1.2 Histologically proven diagnosis of cervical carcinoma, including squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma.

3.1.3 Requirement for postoperative adjuvant concurrent chemoradiotherapy (CCRT), defined as follows:

- Patients who underwent radical hysterectomy require postoperative CCRT if they have any of the following: lymph node positivity, positive surgical margins, or parametrial involvement
- Patients with squamous cell carcinoma post-radical hysterectomy require postoperative CCRT if they meet Sedlis criteria (i.e., have two or more of the following risk factors):
    (1) Lymphovascular space invasion (LVSI)
    (2) Deep stromal invasion ≥ 1/3
    (3) Tumor diameter > 4 cm

(4) CCRT should be considered following multidisciplinary team discussion in patients with any high-risk features.

- Patients with postoperative pathological types of adenocarcinoma or adenosquamous carcinoma.

3.1.4 Age > 18 years.

3.1.5 Eastern Cooperative Oncology Group (ECOG) performance status score of 0 or 1.

3.1.6 History of hemorrhoids prior to radiotherapy, with no hemorrhoids-related symptoms for at least 4 weeks before radiation therapy initiation.

3.1.7 Abdominal/pelvic MRI, chest CT, or PET-CT performed before surgery or study enrollment to confirm staging and exclude patients with distant metastasis.

3.1.8 Adequate bone marrow, renal, and hepatic function (all laboratory tests must be completed within 14 days before starting chemoradiotherapy), defined as:

- Hemoglobin ≥ 9.0 g/dL;
- Absolute neutrophil count (ANC) > 1.5×10^9/L;
- Platelet count ≥ 100×10^9/L;
- Serum albumin ≥ 2.5 g/dL;
- Total bilirubin ≤ 1.5 × upper limit of normal (ULN);
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 × ULN;
- Serum creatinine < 1.5 × ULN.

3.1.9 Agreement to undergo anal canal MRI before radiation therapy initiation.

3.1.10 Patient must provide study-specific informed consent form (ICF) prior to study entry.

3.2 Ineligibility Criteria

Participants who exhibit any of the following conditions at screening will not be eligible for admission into the study:

3.2.1 Cervical cancer patients who do not meet the criteria for adjuvant radiation therapy.

3.2.2 Without a confirmed history of hemorrhoids.

3.2.3 Patients contraindicated for MRI (e.g., due to incompatible metallic implants, claustrophobic syndrome, or other contraindications).

3.2.4 Patients who refuse to undergo anal canal MRI.

3.2.5 Patients with radiographically visible residual disease post-surgery requiring boost during the pelvic EBRT.

3.2.6 History of other malignancies.

3.2.7 Prior pelvic radiotherapy resulting in overlapping radiation fields.

3.2.8 History of allergic reaction to platinum-based chemotherapy agents.

3.2.9 Severe and/or active comorbidities precluding tolerance of concurrent chemoradiotherapy.

3.3 Withdrawal/Termination Criteria

3.3.1 Voluntary Withdrawal: Participant decides to discontinue study participation.

3.3.2 Loss to Follow-up: Participant becomes unreachable, leading to withdrawal.

3.3.3 Adverse Event: Occurrence of a Serious Adverse Event (SAE) or significant health problem during treatment necessitating discontinuation of participation.

3.3.4 Failure to Meet Eligibility: Participant no longer satisfies the study's inclusion criteria.

3.3.5 Disease Progression or Death: Participant experiences disease progression or dies during the study period.

3.4 Sample Size

Based on reported studies[14,16,23] and preliminary findings from our group, the anticipated incidence of hemorrhoids-related symptoms was estimated at 60% in the conventional radiotherapy group and 45% in the anal canal-sparing group. A sample size calculation was performed using NCSS PASS software with the following parameters: significance level (α) = 0.05, statistical power (1-β) = 80%, single-sided testing, and a 1:1 allocation ratio. This yielded a requirement of 136 participants per

group. Accounting for an estimated 10% loss of follow-up, a total of 300 participants (150 per group) will effectively test the primary hypothesis.

4. RESEARCH METHODOLOGY

4.1 Study Design

A multicenter RCT double-blinded trail is proposed by the Department of Radiation Oncology at Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine. Collaborating institutions include Suzhou Municipal Hospital, Changzhou Cancer Hospital, and Renji Hospital Affiliated to Shanghai Jiao Tong University School of Medicine.

The study population consists of postoperative cervical cancer patients with a documented history of hemorrhoids requiring adjuvant pelvic radiation therapy. Eligible participants will be randomly allocated to one of two arms:

1. Experimental Arm (i.e. Anal Canal-Sparing Arm): Participants will receive pelvic radiation therapy using anal canal-sparing techniques.

2. Control Arm (i.e. Conventional Radiotherapy Arm): Participants will receive pelvic radiation therapy using standard techniques.

The primary objectives are to compare the incidence of hemorrhoidal symptoms and differences in QoL scores during radiation therapy between the two arms. Concurrently, the study will explore the practical implementation methodology of the anal canal-sparing technique.

4.2 Randomization and Blinding

4.2.1 Randomization

Participants across all centers will be randomized in a 1:1 ratio to either the experimental or control arm using Interactive Web Response System (IWRS) in our

institution. The stratification factor is whether the participants need brachytherapy after EBRT.

4.2.2 Blinding

This study employs a double-blind design. The whole process includes screening, stratification and randomization, target and organ-at-risk delineation, radiotherapy planning evaluation and quality control and participants' symptoms assessment. The treatment allocation will remain blinded from both participants and the outcome assessors (including statisticians). However, the investigators responsible for screening, enrollment and radiotherapy planning/evaluation/quality control will remain unblinded.

Bias Mitigation Strategies:

- Strict Adherence to Blinding: Investigators will rigorously maintain blinding protocols where applicable.
- Centralized Randomization: The IWRS will manage group allocation to ensure randomization integrity and consistency, minimizing selection bias.
- Standardized Training and Procedures: All investigators from every center will receive comprehensive training on study objectives and protocols. Standardized operating procedures (SOPs) will be implemented across all centers to reduce procedural variations and potential biases.
- Blind Data Review: Following study completion, data will be formally locked and subjected to blind review prior to analysis to prevent potential biases.

4.2.3 Unblinding Procedure

Following the completion of the study, all research data will be entered into the database. After verification for accuracy and subsequent database locking, the designated unblinding personnel will perform the unblinding for all blinded investigators and subjects. Unblinding personnel must be fully trained in and strictly adhere to this operational procedure. Relevant records must be maintained to ensure the trace ability of the unblinding process.

Emergency Unblinding Protocol: This clinical trial employs a double-blind design and is a study focused on reducing adverse effects compared to conventional radiotherapy. Consequently, the probability of requiring emergency unblinding is relatively low. If

an emergency occurs during the clinical trial requiring urgent medical intervention for a specific subject, emergency unblinding will be performed immediately. This will involve promptly informing the patient of the specific pelvic radiation therapy regimen they received to ensure they receive timely and targeted medical care.

4.3 Statistical Analysis

An electronic database was established for this study, including the following patient data: name, age, sex, weight, height, ECOG performance status, admission date, surgery date, enrollment date, histologic type, pre- and post-operative staging, follow-up dates, complete blood count, blood biochemistry, tumor markers, anal canal MRI findings, pelvic radiotherapy target doses and organ-at-risk doses, time of onset and severity of hemorrhoids-related symptoms, as well as weekly assessment timelines and findings after symptom appearance.

Descriptive statistics were used to summarize all variables. All statistical analyses were performed using SPSS 20.0 (Version 20.0; Chicago, IL, USA). Continuous variables of enrolled patients, including gender, age, FIGO stage, incidence of related symptoms, and prescription rates of hemorrhoidal medications, were analyzed using the Mann-Whitney U test or Kruskal-Wallis test as appropriate. Categorical data including symptom scores and quality of life scores were analyzed using chi-square tests (χ^2). When less than 20% of cells had expected frequencies <5, Pearson's chi-square values and two-sided asymptotic significance (P-values) were selected. When more than 20% of cells had expected frequencies <5 or any cell had expected frequency <1, Fisher's exact test values and two-sided exact significance (*P* values) were applied. A two-tailed P-value <0.05 was considered statistically significant.

5. RADIATION TREATMENT PLAN

Patients enrolled are randomized to either conventional arm or anal canal-sparing arm for treatment with concurrent chemotherapy.

- Experimental Arm: Anal canal-sparing RT. Patients in this arm will receive pelvic radiation therapy with sparing of the anal canal.

- Control Arm: Conventional RT. Patients in this arm will receive standard pelvic radiation therapy.
- 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 reactions.

5.1 CT Simulation

In order to avoid artifacts and fill organs and obtain accurate image information before CT scan simulation, necessary pre-scanning preparations should be made. It is necessary to empty the rectum before CT simulation, which can not only ensure the stability of the target volume position, but also avoid the increase of the volume of the rectum entering the high-dose area, the increase of irradiation dose, and the aggravation of radiotherapy toxicities. Therefore, it is recommended that patients should not start the simulation scan until they have defecated on the same day. A full bladder can reduce the radiation volume of bladder and small bowel. It is recommended that patients drink 700 to 800ml of water and wait for 45-50 minutes before CT simulation to ensure bladder is comfortably full. The specific steps are as follows: (1) Patient positioning and immobilization: Patients lied on the baseplate in the supine position with thermoplastic trunk mask, vacuum cushion, foaming agent, shaping cushion or a prone positioning board immobilization. For post-operative patients or obese patients where a significant amount of small bowel enters the pelvic cavity, the prone position can be used. (2) CT scan range: The CT scans are obtained from the upper border of L3 vertebral body or T10 vertebral body (if extended coverage is needed) to 5 cm below the ischial tuberosities. If including inguinal lymph nodes, extend inferiorly to 10 cm below the ischial tuberosity. (3) CT scan slice thickness: 3-5 mm.

5.2 Pelvic Radiation Therapy

5.2.1 Technical Factors

Radiation therapy for all enrolled patients may employ IMRT, Volumetric Modulated Arc Therapy (VMAT), or Tomotherapy. Target volume delineation and OAR radiation dose constraints shall comply with RTOG 0418[1] and the NRG Oncology/RTOG

Consensus Guidelines[24]. Pelvic radiation therapy commences 6-8 weeks postoperatively, extendable to 12 weeks under special circumstances.

5.2.2 Clinical Target Volume (CTV)

5.2.2.1 Coverage

CTV should encompass the lymphatic drainage regions of the involved site and adjacent perinodal soft tissues. For patients without lymph node metastasis identified by surgery or imaging, coverage must include the internal iliac, external iliac, obturator, and presacral nodal regions. For patients with heightened risk of nodal metastasis (e.g., large primary tumors, confirmed or suspected pelvic lymph node metastasis), the common iliac nodal region must additionally be covered. For patients with confirmed common iliac and/or para-aortic nodal involvement, extended-field radiotherapy covering both pelvic and para-aortic regions is required, with the superior border reaching the level of the renal vessels (or higher, depending on involved node distribution). For patients with invasion of the lower one-third of the vagina, bilateral inguinal nodal regions must be covered. The vaginal and parametrial CTV should include the proximal vagina and any visible paravaginal or retracted parametrial tissue on CT simulation images. The Internal Target Volume (ITV), accounting for internal organ motion, must also be considered.

5.2.2.2 Delineation Strategy

The iliac vessels are usually used as anatomic markers for initial delineation.

CTV should include the blood vessels themselves, perinodal soft tissues (requiring lateral expansion towards the pelvic sidewall while avoiding the psoas and piriformis muscles), surgical clips (if present).

5.2.2.3 Excluded Structures

In a CTV volume, the bone, intraperitoneal small bowel and iliopsoas muscle adjacent to clinically negative lymph nodes should be avoided. At the same time, the most anterolateral external iliac lymph nodes near the proximal inguinal canal should also be excluded from CTV (i.e. CTV terminates at the level of the femoral heads).

5.2.3 Plan Target Volume (PTV)

PTV entails a margin that accounts for variations in treatment delivery, including variations in organ motion and set-up errors. It is generally suggested that the CTV expands 5-10 mm into the PTV (the margin applied at each treatment center should be based on their measured set-up errors).

5.2.4 Dose Prescription

All patients received conventional fractionation radiotherapy as follows: 1.8-2.0 Gy/ fraction, five times a week, the prescription dose is 45.0-50.4 Gy in 5-5.5 weeks.

5.2.5 OAR Delineation and Dose Constraints

5.2.5.1 Delineation of OAR

Normal tissue structures should also be delineated on CT simulation images. Referring to guidelines [1, 22], the rectum, bladder, small bowel, and femoral heads are defined as OARs on pelvic radiotherapy for cervical cancer. Their specific delineation boundaries are as follows. All centers are advised to adhere to these specifications.

- **AnoRectum:** The rectal contour is delineated on each axial slice of the CT images. The inferior border is the anal verge. The superior border is defined as the level where the rectal shape on axial images transitions from circular and before it curves anteriorly to connect with the sigmoid colon. This definition includes part of the anal canal, but there is no distinguish between the rectum and anal canal for delineation purposes in current guidelines.
- **Bladder:** The bladder contour is delineated on each axial slice of the CT images. The superior border is the dome of bladder, and the inferior border is the fundus of bladder.
- **Bowel Bag:** The bowel bag contour is delineated on each axial slice of the CT images. It encompasses the space surrounding small bowel loops up to the peritoneal edge, as the bowel may move in this space throughout the course of treatment. The inferior border starts from the large bowel loops or the end of small bowel loops, or from the superior border of the AnoRectum structure. The superior

border extends at least 2 cm above the PTV. If the inferior border is defined based on bowel loops, the anorectum is also shown in the CT axial images and should be considered as part of the bowel bag. Otherwise, it should be excluded.

- **Proximal Femurs:** The superior border is the top of the femoral head, including the greater trochanter. The inferior border is the lowest point of the ischial tuberosity (right or left).
- **Delineation Validation:** Following the delineation of the above OARs, slice-by-slice validation must be performed by an experienced radiation oncology medical physicist and a radiation oncologist.

5.2.5.2 OAR Dose Constraints

It is recommended that all centers adhere to the following dose constraints. The specific constraints are:

- **AnoRectum:** V30 < 60%, the minimum acceptable range V50 = 35%.
- **Bladder:** V45 < 35%, the minimum acceptable range V50 = 35%.
- **Bowel Bag:** V40 < 30%, the minimum acceptable range V40 = 35%.
- **Proximal Femurs:** V30 < 15%, the minimum acceptable range V30 = 20%.

5.3 Anal Canal-Sparing Technique

The conventionally contoured "AnoRectum" organ-at-risk (OAR) is separated into two independent structures: the rectum and the anal canal. During pelvic radiotherapy treatment planning, different dose planning objectives are applied to the rectum and the anal canal. The rectum receives doses according to the standard constraint requirements, while the anal canal is assigned the minimum achievable dose, provided that the PTV coverage and other OAR constraints still meet conventional radiotherapy standards. This study also focuses on protecting the perianal musculature, treating it as an independent OAR.

5.3.1 Anatomy of Anal Canal

The anal canal is the digestive system's endpoint, and it plays a crucial role in the maintenance of fecal continence and defecation. It is located in the anal triangle of the perineum, and positioned between the bilateral ischioanal fossae. Anatomically, the anal canal extends from the anal verge to the dentate line, averaging 2.5cm in length in adults. However, the dentate line is not definable on imaging examination [25]. The most clinically relevant concept is the surgical anal canal, which extends between the anal verge and the anorectal ring, averaging 4 cm in length in adults [26]. The surgical anal canal has four boundaries from inferior to superior: (1) Anal Verge (Anocutaneous line): The lowermost boundary of the gastrointestinal tract, commonly referred to as the anal orifice. (2) Intersphincteric Groove (White line): Located approximately 1 cm superior to the anal verge, between the anal verge and the dentate line. It corresponds internally to the junction between the internal and external anal sphincters. Palpable as a groove. (3) Dentate Line (Pectinate line): A serrated line marking the transition from squamous to columnar epithelium and is continuous with the skin, situated approximately 2.5 cm superior to the anal verge. This is the only circular line visible to the naked eye among the four boundaries. (4) Anorectal Ring (Hermann line): Located approximately 1.5 cm superior to the dentate line. The surgical anal canal is divided into three zones from inferior to superior: (1) Cutaneous zone: Between the anal verge and the white line. Lined by squamous epithelium. (2) Intermediate zone (Haemorrhoidal zone): Between the white line and the dentate line. (3) Columnar zone: Between the dentate line and the anorectal ring. Contains the anal columns, forming a 0.5-1.5cm annular region.

The anal canal is surrounded by the internal and external anal sphincters, vital for maintaining continence: (1) Internal anal sphincter: Encircles the upper two-thirds of the anal canal. Composed of thickened, involuntary circular smooth muscle from the rectal wall. (2) External anal sphincter: A voluntary muscle encircling the lower two-thirds of the anal canal (thus overlapping partially with the internal sphincter). It fuses superiorly with the puborectalis muscle of the pelvic floor.

5.3.2 Magnetic Resonance Imaging (MRI) of Anal Canal

All enrolled patients undergo non-contrast MRI of anal canal following screening. Scans are performed using a 3-T MRI scanner equipped with a standard body matrix

coil. The patient is positioned supine, with the positioning laser aligned to the superior border of the pubic symphysis.

The scanning protocol is as follows: (1) High-resolution T2-weighted imaging (T2WI) using a fast spin-echo (FSE) sequence: Acquired in three orthogonal planes (axial, coronal, and sagittal). Images are obtained with a slice thickness of 2-3 mm. Fat suppression is typically not applied. Patients are instructed to maintain shallow, quiet breathing during the scan. (2) Oblique axial planes: Performed perpendicular to the long axis of the anal canal. (3) Oblique coronal planes: Performed parallel to the long axis of the anal canal. (4) T1-weighted imaging (T1WI) axial planes: Acquired with fat suppression [27].

5.3.3 OAR Delineation and Dose Constraints

The MRI and positioning CT images of anal canal were accurately registered, and the rectum, anal canal and surrounding musculature separated and delineated independently according to the fusion images.

5.3.3.1 Delineation of Anal Canal

Delineate according to the definition of the surgical anal canal.

- The superior border: The anorectal ring (Hermann line), typically defined as the level of an imaginary line between the inferior margins of the sacrum and pubis on sagittal MRI, or the line crossing the superior border of the puborectalis sling on coronal images.
- The inferior border**:** The anal verge, defined as the transition between the anal canal epithelium and perianal skin. This is an important landmark on anal canal MRI. The region extending approximately ± 5mm caudally from the anal verge into the perianal skin is typically defined as the anal verge.

5.3.3.2 Delineation of Key Perianal Musculature

Delineate the perianal muscles with reference to anal canal MRI and the 2023 clinical recommendations from the Italian Association of Radiotherapy and Clinical Oncology (AIRO) for female pelvic OAR contouring [28].

- **Anal Sphincter Complex (ASC)**

The Anal sphincter complex comprises the internal anal sphincter (IAS) and the external anal sphincter (EAS).

The IAS is the innermost muscular layer of the anal canal and the distal continuation of the rectal smooth muscle layer. It is intermediate signal intensity and appears hypointense on T2WI sequence. On sagittal MR images, it is clearly visible from the anorectal junction to approximately 1 cm above the anal verge, concentrically surrounded by the EAS. In the proximal anal canal, the IAS appears doughnut-shaped with a visible lumen and a thickness of 2-3 mm. Distally, the lumen is not visible, and the IAS surrounds the upper 2/3 of the anal canal.

The EAS is the outermost muscular layer of the lower anal canal. It extends approximately 1 cm beyond the IAS, with a mean thickness of about 4 mm. It appears low signal intensity on T2WI, originates from the puborectalis muscle, and its deep portion fuses with or is tightly connected to the puborectalis, extending down to the anal orifice. It partially encircles the IAS, separated from it by the intersphincteric space.

- **The Levator Ani Muscle (LAM)**

The LAM is a broad tendinomuscular sheet forming the majority of the pelvic floor, involved in urination, defecation, and maintaining continence. It is isointense to hypointense on T2WI. In the axial plane, it typically has a V-shaped configuration, extending superiorly from the anterior aspect of the pubis, medially towards the puborectalis and anorectum, and laterally towards the dorsal pubis, obturator fascia, and ischiorectal fossa.

5.3.3.3 Delineation of Rectum (excluding anal canal) (Rectum-A)

For the experimental arm utilizing the anal canal-sparing technique, the Rectum-A is defined as the structure resulting from subtracting the delineated anal canal volume from the conventionally defined AnoRectum.

5.3.3.4 Delineation of Other OARs

Other OARs include the bladder, bowel bag, and bilateral proximal femurs. For details, see sections 5.2.5.1.

5.3.3.5 Delineation Validation

Following the delineation of the above OARs, slice-by-slice validation must be performed by an experienced diagnostic radiologist and an experienced radiation oncologist using the registered images of CT and MRI.

5.3.3.6 Dose Constraints

- **Anal Canal:** V10 < 70%, V15 < 60%, Dmean < 30 Gy, the minimum acceptable range V10 < 100%, V20 < 80%.
- **ASC and LAM:** V15 Gy < 70%, Dmean < 30 Gy, the minimum acceptable range V15 Gy < 100%, V20 < 80%.

5.4 Treatment Planning

5.4.1 Treatment Technique

Radiotherapy delivery may utilize IMRT with 5-9 fields, volumetric modulated arc therapy (VMAT) with 1-2 arcs or Tomotherapy. All treatment plans were created for 6-10 MV photons beam.

5.4.2 Dose Calculation

The dose calculation algorithm must incorporate tissue heterogeneity correction, and the calculation grid size is ≤ 3 mm. The treatment plan must meet the following requirements:

5.4.2.1 Target Volume Calculation: All plans achieved full prescription dose coverage to at least 95% of the PTV volume, and > 90% of the prescription dose coverage to at least 99% of the PTV volume.

5.4.2.2 Hot Spots: Volume within the PTV receiving > 110% of the prescription dose should not be delivered to more than 1%. Volume outside the PTV receiving > 105% of the prescription dose should not be delivered to more than 10%.

5.4.2.3 OARs: The maximum dose to any OAR must be < 110% of the prescription dose. Other OARs constraints detailed in Sections 5.2.5.2 and 5.3.3.6. A summary of all target volume and OAR constraints is provided in Table 1.

Table 1. The Target and OARs Dose Constraints

Target volume	
PTV	1. 95% of the PTV volume receives full prescription dose, and ≥ 99% of the PTV volume receives > 90% of the prescription dose.
	2. Volume within the PTV receiving > 110% of the prescription dose must be < 1%, and volume outside the PTV receiving > 105% of the prescription dose must be < 10%.
OARs	
Bladder	V45 < 35%, the minimum acceptable range V50 = 35%
Rectum-A	V30 < 60%, the minimum acceptable range V50 = 35%
Bowel bag	V40 < 30%, the minimum acceptable range V40 = 35%
Proximal femurs	V30 < 15%, the minimum acceptable range V30 = 20%
Anal canal	V10 < 70%, V15 < 60%, Dmean < 30 Gy, the minimum acceptable range V10 < 100%, V20 < 80%.
ASC and LAM	V15 < 70%, Dmean <30 Gy, the minimum acceptable range V15 < 100%, V20 < 80%

5.5 Chemotherapy Regimens Concurrent with Radiotherapy

All patients received concurrent chemotherapy during radiotherapy. The specific regimen options are:

5.5.1 Weekly Cisplatin Regimen: Cisplatin is administered once every 7 days with concurrent radiotherapy for 5 cycles at a dose of 30-40 mg/m². The single dose should not exceed 70 mg/m².

5.5.2 Triweekly Cisplatin Regimen: Cisplatin is administered once every 3 weeks with concurrent radiotherapy for 2 cycles at a dose of 50-70 mg/m².

5.5.3 Carboplatin Alternative: Switching cisplatin to carboplatin in concurrent chemotherapy for patient intolerant to cisplatin.

5.6 Brachytherapy after EBRT

5.6.1 Indications for BT after EBRT

According to the NCCN 2025[29] guidelines and the ABS recommendations[30], postoperative brachytherapy is primarily used as an adjuvant to EBRT, mainly for

patients with positive or close surgical margins. In addition, patients with other high-risk factors or severe and/or complex intermediate-risk factors may also receive brachytherapy. Furthermore, for patients with vaginal involvement or those who underwent less-than-radical surgery, brachytherapy can be considered as a supplemental treatment. Each center should determine, through multidisciplinary discussion, whether brachytherapy is required before randomization.

5.6.2 Dose Calculation

Based on the recommendations of ABS and NCCN, the target volume for conventional postoperative brachytherapy includes the proximal 3-5 cm of the vagina. For patients with positive vaginal margins, the recommended dose fractionation is 6 Gy ×3 fractions (prescription dose reference point at 5 mm beneath the vaginal mucosa), and for those with negative vaginal margins, the recommended dose fractionation is 6 Gy × 2 fractions (prescription dose reference point at 5 mm beneath the vaginal mucosa).

5.6.3 OAR Dose Constraints

The dose constraints for organs at risk in brachytherapy are defined as the combined dose from external beam radiotherapy and brachytherapy, with the dose received by a 2cc volume as the criterion. The limits are as follows:

- **Rectum:** 2cc ≤ 75 Gy (EQD2).
- **Sigmoid colon:** 2cc ≤ 75 Gy (EQD2).
- **Bladder:** 2cc ≤ 90 Gy (EQD2).
- **Small intestine:** 2cc ≤ 75 Gy (EQD2)

5.7 Quality Assurance (QA) in Radiotherapy

As this is a multicenter study, a multicenter QA team will be established to ensure quality control across all aspects of the clinical trial, particularly radiotherapy planning. Throughout the study duration, cross-center QA will be implemented for all stages, including screening, enrollment, radiotherapy planning, hemorrhoids diagnosis, and symptom assessment. In particular, the image-based components such as MRI of anal canal, OAR delineation using the anal canal-sparing technique, treatment planning and

dose calculation will be discussed by online video conference for QA. A standardized assessment review form (see Appendix 1) of anal canal-sparing strategy during postoperative pelvic radiotherapy for cervical cancer patients will be developed and provided to all participating centers for use.

6 OUTCOME AND INDICATOR EVALUATION

6.1 Evaluation of Primary Observation Indicators

The leading endpoint of this study was the incidence of hemorrhoids-related symptoms from the beginning of pelvic radiotherapy to 4 weeks after the end of radiotherapy. Researchers evaluated the main observation indicators referring to the "RTOG/EORTC Acute Radiation Injury Grading Standards" and the "Pelvic Radiotherapy Hemorrhoids-Related Symptom Assessment Form (Shanghai General Hospital Version)" weekly. Any hemorrhoids-related symptoms that occur during the study observation period compared to baseline are considered as an event.

The main observation indicator of this study is the incidence of hemorrhoids-related symptoms and signs in pelvic radiotherapy, using the method of researcher evaluation. Since symptoms and physical symptoms related to hemorrhoids often occur in the middle and late stages of radiotherapy, which is an acute adverse reaction of radiotherapy, we will observe and evaluate them weekly from the beginning of radiotherapy until 4 weeks after the end of radiotherapy. The symptoms and signs related to hemorrhoids mainly include perianal pain, hemorrhoids prolapse, rectal bleeding, perianal skin damage, anal mucosal damage or ulcer, size and shape of hemorrhoids, etc. At present, the evaluation and grading of acute radiation injuries in radiotherapy mainly refer to *the RTOG/EORTC Acute Radiation Injury Grading Standards*, and researchers will also refer to the skin and lower gastrointestinal/pelvic parts of this standard for radiation injury grading. The size and morphology of perianal skin, anal mucosa, and hemorrhoids were comprehensively evaluated and recorded using visual examination, digital rectal examination, and anoscopy.

However, the RTOG standard does not classify symptoms and signs related to hemorrhoids item by item. Meanwhile, limitations still exist in Goliger's hemorrhoids grading. Firstly, only internal hemorrhoids were described, while the clinical

manifestations of external hemorrhoids and mixed hemorrhoids are not included in the evaluation system. Secondly, this grading is mainly based on the degree of hemorrhoids prolapse, and there is insufficient evaluation of other hemorrhoids-related symptoms. To provide a more comprehensive and objective evaluation of hemorrhoids-related symptoms in radiotherapy patients, and to better quantify and compare them, this study will refer to the radiation injury assessment method of RTOG 1203 [31], which refers to the *Expanded Prostate Cancer Index Composite (EPIC) Questionnaire for Intestinal and Adverse Events*. Based on the main observed symptoms and signs in this study, a *Pelvic Radiation Therapy Hemorrhoids-Related Symptoms Assessment Scale* (*Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine Version*) (see Appendix 2) will be developed for researchers to evaluate.

The above assessment includes hemorrhoids-related symptom evaluation before treatment, 3 to 5 radiotherapy sessions (1st week), 8 to 10 radiotherapy sessions (2nd week), 13 to 15 radiotherapy sessions (3rd week), 18 to 20 radiotherapy sessions (4th week), 23 to 25 radiotherapy sessions (5th week), 26 to 28 radiotherapy sessions (5.5 week), the first week of BT, the second week of BT and once a week from the first week to the fourth week after completion of radiotherapy.

6.2 Evaluation of Secondary Observational Indicators

The secondary observation includes the evaluation of symptoms related to perianal muscle radiation injury, score of life quality, and prescription rate of hemorrhoids.

The symptoms related to perianal muscle radiation injury mainly include changes in bowel habits such as impaired bowel control and increased frequency of bowel movements. For symptoms related to perianal muscle radiation injury, participants will refer to *the Low Anterior Resection Syndrome (LARS) Scoring Questionnaire* and conduct self-assessment. Symptom assessment related to perianal muscle radiation injury should be conducted before treatment, 3 to 5 radiotherapy sessions (1st week), 8 to 10 radiotherapy sessions (2nd week), 13 to 15 radiotherapy sessions (3rd week), 18 to 20 radiotherapy sessions (4th week), 23 to 25 radiotherapy sessions (5th week), 26 to 28 radiotherapy sessions (5.5 week), the first week of BT, the second week of BT and once a week from the first week to the fourth week after completion of radiotherapy.

The QoL will be scored based on the *EORTC Core QoL Questionnaire (QLQ-C30) Version 3.0* and *the Cervical Cancer Module (QLQ-CX24)*, which will be self-evaluated by participants. Assess QoL before treatment, 3 to 5 radiotherapy sessions (1st week), 8 to 10 radiotherapy sessions (2nd week), 13 to 15 radiotherapy sessions (3rd week), 18 to 20 radiotherapy sessions (4th week), 23 to 25 radiotherapy sessions (5th week), 26 to 28 radiotherapy sessions (5.5 week), the first week of BT and the second week of BT, as well as in the second and fourth weeks after completion of radiotherapy.

The types of hemorrhoids drugs used are detailed in 8.1.1. From the beginning of radiotherapy to 4 weeks after the end of radiotherapy, any hemorrhoids drug prescribed by the researcher is classified as a hemorrhoid drug user. During the research process, researchers need to keep detailed records of the names, usage methods, and duration of prescription drugs.

6.3 Evaluation of Exploratory Observation Metrics

Exploratory observation metrics include the delineation method and projection dose of organs at risk using anal canal protection techniques, as described in section 5.3 of the anal canal protection plan.

7. INTERRUPTION OF RADIOTHERAPY AND MANAGEMENT OF UNTOWARD REACTION

7.1 Interruption of radiotherapy

Uncontrollable diarrhea or other acute complications may require interruption of radiotherapy, and the reason and duration of such interruption must be recorded. If the total number of days of treatment interruption exceeds 5 days, it is considered a violation of the radiation therapy plan. During the research period, interruptions in radiation therapy should be avoid as far as possible.

Once the radiotherapy is interrupted, synchronous chemotherapy will also be suspended. Chemotherapy suspended due to adverse events does not need to be supplemented after the end of radiation therapy, and chemotherapy will be stopped synchronously after the completion of radiation therapy.

If synchronous chemotherapy needs to be suspended due to chemotherapy related adverse events, radiotherapy will continue.

7.2 Treatment related adverse events (AE)

During the research period, the occurrence and severity of acute radiation toxicity should be evaluated weekly from the beginning of pelvic radiotherapy until 4 weeks after the end of radiotherapy. The acute adverse reactions of concurrent pelvic radiotherapy and chemotherapy for cervical cancer may include fatigue, decreased appetite, nausea, vomiting, diarrhea, constipation, rectal irritation symptoms, frequent urination and difficulty urinating, as well as decreased blood cell count and abnormal liver and kidney function indicators.

All adverse reactions will be evaluated and graded according to the *Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0*. The treatment of common adverse events is shown in Table 2.

Table 2. The treatment of common adverse events

Symptoms related to hemorrhoids (bleeding/pain): CTC grade	**Treatment**
Level 1-2 Level 3 or 4	Strengthen local hygiene and take sitz baths, etc. Provide symptomatic and medical treatment. If unrelieved, withhold radiotherapy and proceed with hemorrhoids therapy.
Diarrhea: CTC grade	**Treatment**
Level 1-2 Level 3 or 4	Dietary modification with emphasis on low-fiber intake. Manage symptomatically; if unrelieved, withhold radiotherapy.
Nausea and vomiting：CTC grade	**Treatment**

Level 1-2 Level 3 or 4	Reduce the infusion rate of chemotherapy drugs Manage symptomatically; if unrelieved, withhold concurrent chemotherapy.
Myelosuppression：CTC grade	**Treatment**
Level 1-2 Level 3 or 4	Monitor closely and adjust chemotherapy dosage as needed. Prompt intervention indicated, with emergent response to infection or bleeding.
Symptoms related to the urinary tract：CTC grade	**Treatment**
Level 1-2 Level 3 or 4	Maintain adequate hydration Manage symptomatically; initiate antimicrobial therapy based on susceptibility testing if necessary.

All Grade 4/5 adverse events occurring from radiotherapy initiation to 4 weeks post-treatment must be reported within 5 days. Serious adverse events (SAE) needs to be reported to the Ethics Committee notification, typically within 24 hours of notification. All events must be recorded in the case report form (CRF).

8. CONCOMITANT MEDICATIONS

Concomitant medications in this study shall be documented continuously from the initiation of the first radiotherapy session until 4 weeks after the final radiotherapy. The names, usage and dosage, start and end times, and reasons for combined medication and treatment should be recorded.

8.1 Permitted Medications and Therapies

8.1.1 Investigators may prescribe medications for hemorrhoids-related symptoms based on clinical evaluation, but patients are strictly prohibited from self-administering any hemorrhoidal treatments or other drugs that may aggravate or alleviate intestinal reactions. Approved symptomatic medications primarily include laxatives, venoactive drugs, topical agents, analgesics, and traditional Chinese medicines.

8.1.2 Therapeutic use of recombinant human granulocyte colony-stimulating factor (G-CSF), thrombopoietin-stimulating agents, platelet transfusion, and other interventions for myelosuppression may be administered by investigators based on clinical assessment.

8.1.3 Appropriate symptomatic medications may be administered for adverse events caused by radiotherapy and/or chemotherapy drugs.

8.1.4 Symptomatic treatment drugs may be provided when patients develop clinical symptoms due to non-neoplastic diseases.

8.1.5 For subjects with comorbid conditions, relevant medications may be continued as needed or adjusted at any time during the study period.

8.2 Prohibited Medications and Therapies

8.2.1 Subjects are not permitted to concurrently participate in other clinical studies.

8.2.2 Subjects must not receive any other anti-tumor medications (including but not limited to chemotherapy, immunotherapy, targeted therapy, or anti-angiogenic drugs) outside those specified in the study protocol.

9. TREATMENT COMPLIANCE

The treatments specified in this study shall be administered under investigator supervision in either inpatient or outpatient settings to monitor compliance. The timing and dosage of radiotherapy, as well as the dates, times, and exact doses of each chemotherapy infusion, must be recorded in the electronic Case Report Form (eCRF).

Poor compliance is defined as the subject's failure to adhere to the protocol-mandated assessments for hemorrhoids-related symptoms (including required examinations and/or questionnaire completion) for non-medical reasons. In such cases,

the investigator shall determine whether to discontinue the subject's treatment based on individual circumstances.

10. TISSUE/SPECIMEN SUBMISSION

NA.

11. APPENDIX

Data collection procedures are cataloged in Appendices 1-5 (complete content mapping available in Table 3).

Table 3. Summary of Supplementary Appendices

Appendix Numbering	Appendix Titles
Appendix 1	**Structured Audit Framework for Anal Canal-Sparing Protocol in Postoperative Pelvic Radiation Therapy of Cervical Cancer**
Appendix 2	**Shanghai General Hospital Hemorrhoids-Specific Symptom Scale for Pelvic Radiation Therapy**

Reference

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Appendix 1

Structured Audit Framework for Anal Canal-Sparing Protocol in Postoperative Pelvic Radiotherapy of Cervical Cancer

<table>
<tr><td>Patient Name</td><td></td><td>ID</td><td></td><td>Auditor</td><td></td></tr>
<tr><td>Prescription</td><td></td><td>Technique</td><td></td><td>Date</td><td></td></tr>
<tr><td colspan="6">Contouring Validation</td></tr>
<tr><td>Structure</td><td>Approved</td><td>Structure</td><td>Approved</td><td>Structure</td><td>Approved</td></tr>
<tr><td>Anal Canal</td><td></td><td>Anal Sphincter</td><td></td><td>Rectum</td><td></td></tr>
<tr><td colspan="6">Dosimetric Compliance Assessment</td></tr>
<tr><td>Structure</td><td>V10</td><td>V15</td><td>V20</td><td>Dmean</td><td>Approved</td></tr>
<tr><td>Anal Canal</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Anal Sphincter</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td>Levator Ani</td><td></td><td></td><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Rectum</td><td>V30</td><td>V50</td><td rowspan="8" colspan="2"></td><td>Approved</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Bladder</td><td>V45</td><td>V50</td><td>Approved</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Bowel Bag</td><td>V40（%）</td><td>V45（cc）</td><td>Approved</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td rowspan="2">Femoral Heads</td><td>V30</td><td></td><td>Approved</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td colspan="5">Protocol Dose Constraints for Trial Eligibility：
Target Coverage：
95% of PTV volume must receive the prescription dose
99% of PTV volume must receive >90% of prescription dose
Organ-at-Risk Constraints：</td><td>Is the patient eligible for the experimental arm?</td></tr>
</table>

Rectum: Ideal: V30 <60%; Minimum acceptable: V50 =35%; Bladder: Ideal: V45 <35%; Minimum acceptable: V50 =35%; Bowel Bag: Ideal: V40 <30%; Minimum acceptable: V40 =35%; Femoral Heads: Ideal: V30 <15%; Minimum acceptable: V30 =20%; Anal Canal: Ideal: V10 <70%, V15 <60%, mean dose <30 Gy; Minimum acceptable: V10 <100%, V20 <80% Perianal Muscles: Ideal: V15 <70%, mean dose <30 Gy; Minimum acceptable: V15 <100%, V20 <80%.	

Appendix 2

Shanghai General Hospital Hemorrhoids-Specific Symptom Scale for Pelvic Radiation Therapy

1. Blood in Stool				
a. Over the past 7 days, how frequently did you notice blood in your stool?				
O Never	O Rarely (1-2 days)	O Occasionally (3-4 days)	O Frequently (5-6 days)	O Almost persistently (daily)
b. Over the past 7 days, what was the most severe form of bleeding you experienced?				
O No bleeding	O Minor blood on toilet paper	O Blood dripping after defecation	O Projective bleeding during/after defecation	

2.Hemorrhoids Prolapse				
a. Over the past 7 days, how frequently did you experience hemorrhoids prolapse during bowel movements?				
O Never	O Rarely (1-2 days)	O Occasionally (3-4 days)	O Frequently (5-6 days)	O Almost persistently (daily)
b. Over the past 7 days, how did the prolapsed hemorrhoids reduce?				
O Spontaneously reduced	O Required manual reduction	O Persistently prolapsed or immediately re-prolapsed after reduction		
Clinical Examination Documentation (Based on visual inspection/external exam and anoscopy)				
a. Hemorrhoids Type: O Internal Hemorrhoids O External Hemorrhoids O Mixed Hemorrhoids				
b. Hemorrhoids Size:				
c. Additional Findings:				

3. Perianal Skin Breakdown				
a. Over the past 7 days, severity of perianal skin breakdown:				
O None	O Follicular dark erythema	O Focal moist desquamation	O Confluent moist desquamation	O Ulceration

4. Anal Mucosal Erosion/Ulceration				
a. Over the past 7 days, severity of anal mucosal changes:				
O None	O Mucosal edema	O Mucosal hyperemia	O Punctate ulceration	O Patchy ulceration

5. Perianal Pain			
a. Over the past 7 days, worst perianal pain intensity:			
Visual Analogue Scale (VAS)			
O 0-2 (Mild)	O 3-5 (Moderate)	O 6-8 (Severe)	O >8 (Excruciating)