Zeng et al. Radiation Oncology (2025) 20:112
https://doi.org/10.1186/s13014-025-02688-7

Radiation Oncology

STUDY PROTOCOL

Open Access

Moderately hypofractionated online adaptive radiotherapy (SWIFT-1) in cervical cancer patients: study protocol for a multi-centered, open-label, two-arm, phase III, randomized controlled study

Zheng Zeng[1†], Yining Chen[2†], Jie Qiu[1], Bo Yang[1], Zhiqun Wang[1], Xiangyin Meng[1], Yuliang Sun[1], Junfang Yan[1*], Ke Hu[1*] and Fuquan Zhang[3*]

Abstract

Background External beam radiotherapy (EBRT) is an essential component of standard treatment for locally advanced cervical cancer. Moderately hypofractionated radiotherapy (MHRT) offers the potential to reduce treatment burden while compromising efficacy. Although various studies have investigated the safety and efficacy of MHRT, high-quality evidence remains inadequate. The lack of integration of modern radiotherapy techniques in many existing studies may lead to an overestimation of MHRT-associated toxicity.

Methods This prospective, multi-center, randomized controlled, non-inferiority phase III trial aims to evaluate the non-inferiority of moderately hypofractionated online adaptive radiotherapy (oART) compared to conventional fractionated radiotherapy (CFRT). A total of 440 participants will be enrolled and randomly assigned in a 1:1 ratio to either the MHRT or CFRT group. Both groups will receive concurrent chemoradiotherapy, and a subset of eligible patients will undergo immunotherapy. The prescribed EBRT dose for the MHRT group will be 43.35 Gy in 17 fractions, with a simultaneous integrated boost of 54.4 Gy in 17 fractions to positive lymph nodes. The CFRT group will receive 45 Gy in 25 fractions, with a simultaneous integrated boost of 60 Gy in 25 fractions to positive lymph nodes. The primary endpoint will be 3-year progression-free survival. Secondary endpoints will include the complete response rate, tumor regression following EBRT, overall survival, locoregional progression-free survival, metastasis-free survival, cervical cancer-specific survival, acute and late toxicity, and quality of life.

†Zheng Zeng and Yining Chen contributed equally to this work.

*Correspondence:
Junfang Yan
yanjfang@pumch.cn
Ke Hu
huke8000@126.com
Fuquan Zhang
zhangfq@pumch.cn

Full list of author information is available at the end of the article

Discussion This randomized controlled trial will prospectively investigate whether MHRT is non-inferior to conventional fractionation in terms of efficacy and safety. Furthermore, the trial will evaluate the potential of moderately hypofractionated oART as a clinically viable alternative to CFRT for the treatment of locally advanced cervical cancer.

Trial registration This trial was registered at ClincalTrials.gov (NCT06641635) on October 12, 2024.

Keywords Moderately hypofractionated, Online adaptive radiotherapy, Cervical cancer, Randomized controlled trial

Background

Cervical cancer is the fourth most commonly diagnosed malignancy among women worldwide with a higher prevalence in developing countries, where it continues to pose a significant public health challenge [1].

Concurrent chemoradiotherapy is the standard treatment for locally advanced cervical cancer (LACC) [2]. Within this regimen, external beam radiotherapy (EBRT) is typically delivered using conventional fractionation radiotherapy (CFRT), with a prescribed dose of 45–50.4 Gy administered in 25–28 fractions over approximately two months [3]. Limited resources and barriers to radiotherapy access place a disproportionate burden on low- and middle-income countries, which account for 80% of global cervical cancer cases [4]. The long treatment course further strains radiotherapy resources. Moderately hypofractionated radiotherapy (MHRT) is an alternative treatment approach that delivers an equivalent dose in fewer fractions compared to conventional fractionation [5]. The course of MHRT, 3–4 weeks in duration, reduces both patient burden and treatment costs in comparison to the standard 5-week fractionation for EBRT [6]. MHRT has become the standard treatment for breast and prostate cancer [7, 8]. However, in cervical cancer, there is limited research on its role as an alternative to the conventional fractionation.

A retrospective study of 62 patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIB cervical cancer, who received 39 Gy in 13 fractions using a two-field technique, reported a 5-year disease-free survival (DFS) rate of 59%. However, 8.1% of patients experienced late grade 3 rectal toxicity [9]. In another single-arm prospective study involving 50 patients with FIGO stage IB-IIIC1 cervical cancer, 40 Gy in 16 fractions were administered using three-dimensional conformal radiation therapy. The study reported a 3-year DFS rate of 92.7%, while 20% of patients experienced acute grade 3 gastrointestinal toxicity [10]. Current evidence indicates that although MHRT may offer comparable efficacy, it may also be associated with higher toxicity rates.

Online adaptive radiation therapy (oART) employs artificial intelligence to iteratively re-optimize radiotherapy plans in real time, accounting for dynamic anatomical changes in tumors and organs at risk (OARs) throughout the course of treatment [11]. By mitigating intra-fraction organ variations, oART enhances target volume coverage, reduces radiation exposure to OARs, and minimizes margins in cervical cancer radiotherapy, thereby reducing the risk of treatment-related toxicities [12, 13]. Our previous research reported the administration of 45–50.4 Gy in 1.8 Gy daily fractions for postoperative cervical and endometrial cancer patients. The results showed that only 24% of patients experienced grade 2 acute gastrointestinal toxicity, and no acute genitourinary toxicity was observed [14]. Moreover, our team conducted a single-center Phase I clinical study (NCT05994300) investigating the use of MHRT in cervical cancer based on oART. This study demonstrated a 100% clinical complete response rate in one month, with only three patients experiencing grade 3 acute diarrhea, all of whom recovered within one week. No grade 3 or higher acute genitourinary toxicities were observed [15].

Drawing on the results from our phase I trial (NCT05994300) and previous studies, we have designed a phase III, multi-center, randomized controlled trial (RCT) to investigate the non-inferiority of efficacy and safety between moderately hypofractionated oART and CFRT.

Methods

Study design

This multi-center, prospective, open-label, phase III randomized controlled trial will be conducted at four medical institutions in China. The study evaluates two EBRT regimens combined with concurrent chemotherapy, followed by brachytherapy. In the standard treatment arm, CFRT delivers 45 Gy in 25 fractions, with or without a simultaneous regional lymph node boost to 60 Gy. The experimental arm utilizes MHRT, delivering 43.35 Gy in 17 fractions, with or without a regional lymph node boost to 54.40 Gy. Both regimens are administered at five fractions per week. To evaluate whether the 3-year progression-free survival (PFS) rate in the experimental group is non-inferior to that in the control group, this study adopts a non-inferiority design. Based on previous studies, a 3-year PFS rate of 70% is expected in both groups, with a non-inferiority margin set at 12% [16, 17]. According to the National Comprehensive Cancer Network (NCCN) guidelines for cervical cancer (Version 1.2025), concurrent immunotherapy is permitted during radiotherapy for patients classified as FIGO 2014 Stage IIIA, IIIB, or IVA, as well as select FIGO 2018 Stage III–IVA cases [3].

This study has been approved by the Ethics Committee of Peking Union Medical College Hospital (Approval No. K6852) and registered on ClinicalTrials.gov (NCT06641635).

Endpoints

Primary endpoints

The primary endpoint of this study is 3-year PFS, which is defined as the proportion of patients who remain free from disease progression or death at three years after randomization.

Secondary endpoints

3-month complete response rate (CRR), 3-year overall survival (OS), 3-year locoregional progression-free survival (LPFS), 3-year metastasis-free survival (MFS), 3-year cervical cancer-specific survival (CSS), tumor regression after EBRT, acute and late treatment-related toxicities, and quality of life (QoL).

Eligible criteria

Inclusion criteria

1. Patients should provide written informed consent voluntarily, at least 30 days prior to enrollment.
2. Age between 18 years and 75 years at the time of diagnosis.
3. Histologically confirmed cervical cancer, with histological subtypes limited to squamous carcinoma, adenocarcinoma or adenosquamous carcinoma.
4. FIGO stage IB1 to IIIB cervical cancer; FIGO stage IIIC1 cervical cancers with a maximum metastatic lymph node diameter of less than 2 cm and no involvement of common iliac chain.
5. Planned definitive chemoradiotherapy with EBRT and concurrent weekly cisplatin (± immunotherapy), followed by brachytherapy.
6. Eastern Cooperative Oncology Group performance status of 0–1 and the ability to tolerate supine positioning for at least 30 min.

Exclusion criteria

1. History of surgery for cervical cancer, excluding pelvic lymphadenectomy, lymph node dissection, or cervical conization.
2. Prior history of abdominal or pelvic radiation.
3. Pregnancy or lactation.
4. Active infections and fever.
5. Severe comorbidities and seropositive status that may significantly impact adherence to the clinical trial, including but not limited to unstable cardiovascular disease, renal dysfunction, chronic hepatitis, poorly controlled diabetes mellitus, psychiatric disorders and acquired immunodeficiency syndrome.

Randomization

After screening for eligibility, patients will be randomized into two groups (1:1) in balanced permuted blocks: the MHRT group (experimental group) or the CFRT group (control group). Stratification factors for randomization will include FIGO stage for cervical cancer (IB to IIB vs. IIIA to IIIC1) and immunotherapy status (yes vs.no) and a block size of 4 will be utilized. The randomization process will be carried out by statisticians from the School of Public Health at Soochow University, using SAS Proc Plan for generating the block randomization scheme. This study is an open-label trial for both investigators and participants.

Radiotherapy

Target volumes definition

The approach has been extensively described in previous studies [12]. Before simulation and treatment session, patients will be instructed to empty their bladder and rectum one hour and forty minutes prior to their appointment, and then to consume 450–500 ml of water within 10 min, adjusted based on their height and weight. All patients underwent a single CT simulation in the supine position with thermoplastic immobilization and received intravenous contrast administration when no contraindications were present.

Clinical target volumes (CTV) will be contoured separately. In the MHRT group, CTV delineation followed the guidelines for oART, comprising the clinical target volume of the uterus (CTV-U), cervix (CTV-C), and lymph nodes (CTV-N). CTV-U encompasses the entire uterine body, while CTV-C includes the vagina, uterine cervix, and parametria. CTV-N encompasses the pelvic lymphatic drainage regions, including the common, internal, and external iliac, obturator, and presacral lymph nodes. Gross tumor volume node (GTVnd) includes any involved pelvic lymph nodes with a diameter of ≥ 1 cm on computed tomography (CT) or magnetic resonance imaging (MRI), or those exhibiting positive uptake on positron emission tomography-computed tomography (PET-CT) [18]. PET-CT imaging is recommended when accessible, particularly for patients with equivocal or suspicious lymph nodes on CT or MRI, to aid in the identification of pelvic and para-aortic nodal metastasis.

A 5 mm margin will be added to the CTV-C, CTV-U, and CTV-N to create the corresponding planning clinical target volumes. A 3 mm margin will be applied to metastatic lymph nodes to define the planning gross tumor volume of node [12, 19]. The margin of EBRT may be adjusted for individual patients based on the first five fractions of treatment, taking CTV-U mobility into account. This margin strategy is tailored to leverage the advantages of oART over conventional non-adaptive radiotherapy.

In the CFRT group, the CTV includes the uterus, cervix, parametrium, upper vagina, and pelvic lymphatic drainage regions, encompassing the internal iliac, external iliac, obturator, presacral, and common iliac lymph nodes. The GTVnd includes pelvic lymph nodes with a short-axis diameter ≥ 1 cm on CT or MRI, or those exhibiting positive uptake on PET-CT [18]. The specific radiation target area may be adjusted based on factors such as positioning errors, image guidance techniques, and prior clinical experience at each center, such as positioning errors, image guidance techniques, and previous experience. The CTV should adequately account for the mobility of the uterus, cervix, and vagina to ensure proper coverage. A 15 mm margin is added around the uterus and cervix, and a 6–8 mm margin is applied in all other directions to delineate the planning target volume (PTV) [20, 21].

Based on the NCCN guideline recommendations, pelvic and extended field radiotherapy (EFRT) is indicated for patients with documented common iliac and/or para-aortic lymph node involvement [3]. In our study, patients with multiple pelvic lymph node metastases received standard pelvic-field radiotherapy for cervical cancer, as EFRT is not routinely required for this patient population.

Dose prescription

For MHRT group, the prescribed dose for planning clinical target volumes is 43.35 Gy in 17 fractions, once daily, 5 days a week. The prescribed dose for planning gross tumor volume of node is 54.4 Gy in 17 fractions with a simultaneous integrated boost. Assuming an α/β ratio of 10 Gy for tumor tissue and 3 Gy for late-responding normal tissue [22], the equivalent dose in 2-Gy fractions (EQD2) was calculated to be 45.34 Gy for MHRT and 59.84 Gy for the lymph node boost, both delivered over 25 fractions.

For CFRT group, the prescribed dose of PTV is 45 Gy in 25 fractions over five weeks and simultaneous or sequential lymph node boost, a total cumulative dose of 60 Gy in 25 fractions. The corresponding EQD2 values are 44.25 Gy for PTV and 62 Gy for the lymph node boost.

Treatment planning and dose constraints

In the MHRT group, patients receive daily oART. In the CFRT group, patients are treated with fixed-field intensity-modulated radiation therapy (IMRT), volumetric modulated arc therapy (VMAT), or tomotherapy. It is required that at least 95% of the PTV receives 100% of the prescribed dose, and less than 1% of the PTV receives more than 110% of the prescribed dose. The detailed dose constraints for treatment planning are provided in Table 1.

oART procedure

The oART procedure has been thoroughly described in previous studies [23]. For each treatment fraction, the first iterative cone beam computed tomography (iCBCT) was acquired after bladder and rectal preparation. Based on this scan, the CTVs and OARs were automatically

Table 1 Dose-volume constraints of OARs

OARs	MHRT group		CFRT group	
	Soft Constraint	Hard Constraint	Soft Constraint	Hard Constraint
Bowel	D50% ≤ 18 Gy V35Gy ≤ 30% V40Gy ≤ 200 cc D2cc ≤ 45.50 Gy Lymph node boost: D2cc ≤ 46.75 Gy	D50% ≤ 20 Gy V35Gy ≤ 70% V40Gy < 250 cc - Lymph node boost: D5cc ≤ 46.75 Gy	V40Gy ≤ 30% V45Gy ≤ 200 cc D2cc ≤ 47.50 Gy Lymph node boost: D2cc ≤ 54 Gy	V40Gy ≤ 70% V45Gy < 250 cc - Lymph node boost: D5cc ≤ 54 Gy
Bladder	V40Gy ≤ 50%	V43.35 Gy ≤ 50% Lymph node boost: V45Gy ≤ 50%	V45 Gy ≤ 50%	V50 Gy ≤ 50%
Rectum	V40 Gy ≤ 50% V30 Gy ≤ 60%	V43.35 Gy ≤ 50% Lymph node boost: V45Gy ≤ 50%	V45 Gy ≤ 50% V30 Gy ≤ 60%	V50 Gy ≤ 50%
Femur head	V30Gy ≤ 15%	Dmax < 47 Gy	V30 Gy ≤ 15%	Dmax < 55 Gy
Marrow	V10Gy ≤ 80% V20Gy ≤ 66%	V10Gy ≤ 90% V20Gy ≤ 75%	V10 Gy ≤ 80% V20Gy ≤ 66%	V10Gy ≤ 90% V20Gy ≤ 75%
Spinal cord	Dmax ≤ 35 Gy	Dmax ≤ 40 Gy	Dmax ≤ 40 Gy	Dmax ≤ 45 Gy

OARs, organs at risk; MHRT, moderately hypofractionated radiotherapy; CFRT, conventional fractionation radiotherapy contoured and subsequently reviewed and manually adjusted by a radiation oncologist. Both the adapted plan and the scheduled plan were then generated and evaluated according to target coverage and dose constraints, with the plan best meeting the clinical goals selected for treatment. After plan approval, a second iCBCT was performed to verify the positions of the CTVs and OARs. Treatment proceeded if intrafractional motion remained within acceptable limits; otherwise, additional iCBCT scans and re-contouring were conducted. The daily oART workflow is illustrated in Fig. 1.

Brachytherapy

Following EBRT, all patients will undergo three-dimensional MRI- or CT-guided high-dose-rate intracavitary brachytherapy, combined with interstitial implantation when clinically indicated. MRI-guided brachytherapy is recommended for patients. The treatment will consist of either five fractions of 6 Gy or four fractions of 7 Gy, prescribed to the high-risk CTV, encompassing the entire cervix and any residual tumor, in accordance with each center's clinical practices. The quality of radiotherapy will be assessed by a qualified central vendor both prior to study initiation and for each patient's treatment plan throughout the study. Treatment planning will follow Groupe Européen de Curiethérapie– European Society for Radiotherapy and Oncology and NCCN guidelines to ensure adequate target coverage and OARs sparing [3, 24]. The planning aims include achieving a cumulative total EQD2 to the high-risk CTV D90 (minimum dose to 90% of the volume) of ≥ 80 Gy, taking into account contributions from both EBRT and brachytherapy. For OARs, the following cumulative dose constraints will be applied. Soft constraints: bladder $D_{2cc} < 80$ Gy, rectum $D_{2cc} < 65$ Gy, sigmoid colon $D_{2cc} < 70$ Gy, and small bowel $D_{2cc} < 70$ Gy. Hard constraints: bladder $D_{2cc} < 90$ Gy, rectum $D_{2cc} < 75$ Gy, sigmoid colon $D_{2cc} < 75$ Gy, and small bowel $D_{2cc} < 75$ Gy. Contouring and dose reporting will adhere to International Commission on Radiation Units and Measurements Report 89 standards [25].

Concurrent chemotherapy ± PD-1 inhibitor

All patients will receive concurrent weekly cisplatin (40 mg/m² per week) as a single agent for a minimum of three weeks. For patients unable to tolerate chemotherapy, alternative regimens may include reduced-dose cisplatin, paclitaxel, or carboplatin. According to the NCCN guidelines, patients classified as FIGO 2014 Stage IIIA, IIIB, IVA or select FIGO 2018 Stage III–IVA is permitted to receive concurrent chemotherapy ± pembrolizumab.[3] For enrolled patients in this study, pembrolizumab may be added to patients with FIGO 2018 stage III cervical cancer based on clinical considerations [26]. Considering drug accessibility, other approved immunotherapy agents may serve as alternative treatment options. Cisplatin, other alternative chemotherapy regimens, or immunotherapy will all be administered intravenously.

Follow up

Assessments for primary and secondary endpoints will be conducted before treatment and repeated weekly throughout the treatment course. Patients demonstrating persistent central residual tumor within 3 months post-radiotherapy may be candidates for a three-dimensional image-guided brachytherapy boost. In such cases, both the boost dose and total cumulative radiation dose must be meticulously recorded and calculated. Follow-up examinations will occur every three months during the first two years and every six months during the third year.

Tumor response will be assessed according to Response Evaluation Criteria in Solid Tumors version 1.1 by investigators [27], with disease progression primarily monitored through regular physical exams, hematological and biochemical laboratory tests, squamous cell carcinoma antigen levels, and pelvic MRI or chest/abdomen/pelvis CT. If disease progression is suspected during follow-up, PET-CT will be performed when available to evaluate the extent of recurrence and guide subsequent treatment. All cases of disease progression will be thoroughly documented.

Acute toxicity will be assessed from the start of treatment until three months post-treatment, while late toxicity will be evaluated from three months onward during routine follow-up visits. Acute toxicity will be assessed using the Common Terminology Criteria for Adverse Events version 5.0 (supplementary file 1), while late toxicity will be evaluated according to the Radiation Therapy Oncology Group criteria. Patient-reported toxicity and QoL will be measured using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 and the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Cervical Cancer Module 24. The flowchart of the study process is shown in Fig. 2.

Sample size calculation

To assess whether the PFS at 3 years in the experimental group is non-inferior to that in the control group, a non-inferiority design will be employed. The enrollment period is set at 24 months, followed by a 36-month follow-up period, with a one-sided $\alpha = 0.025$ and $\beta = 0.20$. Informed by the literature, the 3-year PFS rates for both the experimental and control groups are approximately 70%[16,17]. The non-inferiority margin for 3-year PFS is set at 12%, which corresponds to a hazard ratio (HR) non-inferiority margin of 1.527. According to the survival analysis non-inferiority sample size formula for two groups, the sample size per group is approximately 195.

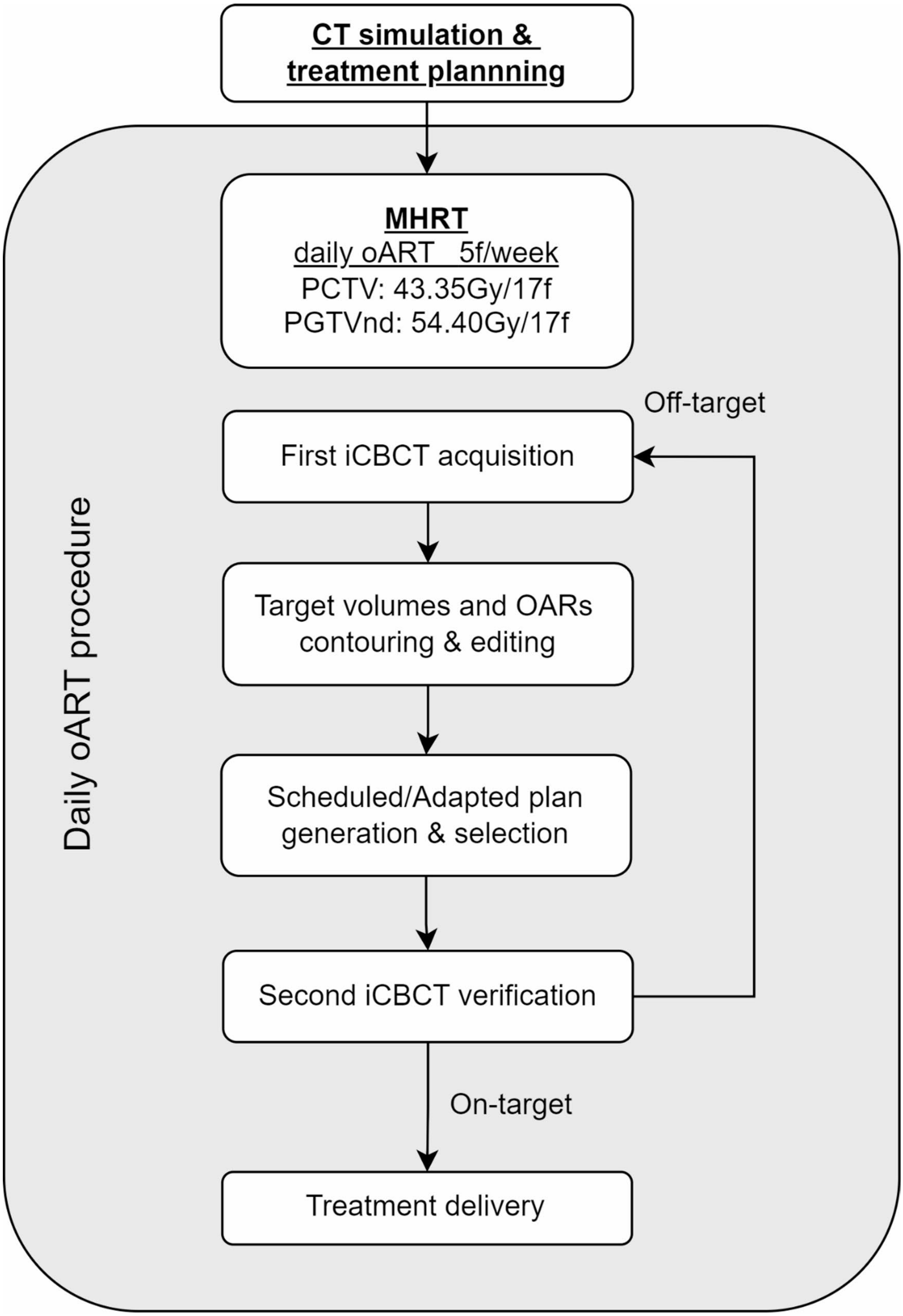

Fig. 1 Workflow for daily online adaptive radiotherapy. CT, computed tomography; oART, online adaptive radiotherapy; MHRT, moderately hypofractionated radiotherapy; PCTV, planning clinical target volume; PGTVnd, planning gross tumor volume of node; iCBCT, iterative cone beam computed tomography; OARs, organs at risk

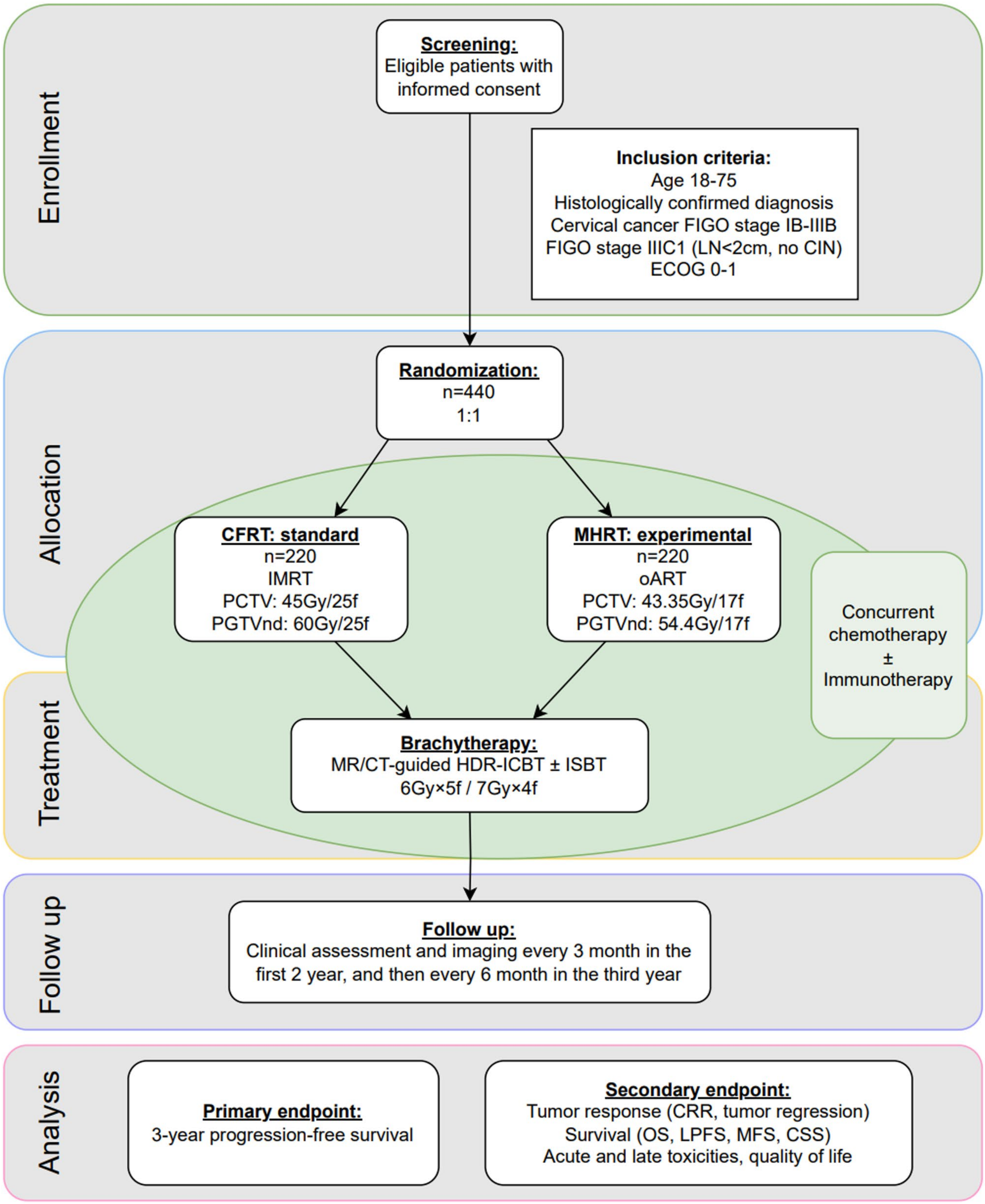

Fig. 2 Flowchart of the process of the study phases. FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; CIN, common iliac nodes; ECOG, Eastern Cooperative Oncology Group; IMRT, Intensity modulated radiotherapy; oART, online adaptive radiotherapy; CT, computed tomography; MRI, Magnetic resonance imaging; HDR, high dose rate; ICBT, intracavity brachytherapy; ISBT, interstitial brachytherapy; CRR, complete response rate; OS, overall survival; LPFS, locoregional progression-free survival; MFS, metastasis-free survival; CSS, cervical cancer-specific survival

Considering a 10% dropout rate, the required sample size per group is adjusted to 220, resulting in a total sample size of approximately 440 participants.

This clinical trial is planned to be conducted across four medical institutions. A total of 440 patients will be enrolled across these institutions, with 220 assigned to the experimental group and 220 to the control group.

Statistical analysis

The full analysis set, comprises all randomized patients, is the primary evaluation population for all efficacy endpoints, including the primary endpoint. The per-protocol set includes all patients in the full analysis set population who have received the planned therapy in its entirety and for whom documentation related to the primary endpoint is complete. Analyses of the per-protocol set population serve as sensitivity analyses to assess the robustness of the results from the intention-to-treat analysis. Patients in the full analysis set in who have initiated the planned therapy are included in the safety set, which serves as the primary evaluation population for toxicity and other safety endpoints.

The primary endpoint, PFS, along with other long-term survival outcomes, OS, LPFS, MFS, CSS, will be analyzed using the Kaplan-Meier method. Differences in survival outcomes between MHRT and CFRT groups will be assessed using the log-rank test. The false positive rate will be set at 0.025 for one-sided tests and 0·05 for two-sided tests. Non-inferiority of PFS will be declared if the upper limit of the one-sided 97.5% confidence interval (CI) for HR is less than 1.527. HR and 97.5% CI will be estimated using a Cox proportional hazard model, with treatment group as a factor. Differences in the CRR will be evaluated using the Chi-square test. Toxicities will be described as categories and grades by investigators, and will also be reported as scores from questionnaires for QoL by patients. And it will be compared using Rank Sum Test if necessary. Comparisons of tumor regression after EBRT and toxicities between the two groups will be performed using the independent sample t test, Mann-Whitney U test, or Rank Sum Test and Chi-square test, depending on the normality, homogeneity of variance, and data types. Subgroup analyses will be conducted based on the same stratification factors applied for randomization. The same statistical methods will be utilized to evaluate differences in primary and secondary endpoints across the subgroups, as previously outlined.

To assess futility, interim analyses will be conducted using Bayesian predictive probability in a non-inferiority design. Statistical analyses and programming will be performed using SAS version 9.4.

Data quality assurance (QA) and monitoring

To ensure data quality, treatment consistency, and patient safety, a standardized QA program has been implemented across all participating sites. A unified radiotherapy protocol outlines the definitions of target volumes, dose prescriptions, and constraints for OARs.

A QA team—comprising radiation oncologists, medical physicists, and radiation therapists—was established at the lead center. Prior to trial initiation, each site was required to submit simulation CT scans and iCBCT images from two eligible but non-enrolled patients: one with lymph node boost and one without. These submissions included delineated target volumes and OARs, as well as both conventional and moderately hypofractionated adaptive radiotherapy plans. Additionally, brachytherapy contours and plans were also submitted. All Digital Imaging and Communications in Medicine files were reviewed and approved by the QA team.

During the trial, the first 20 EBRT and brachytherapy plans will be audited, followed by monthly random checks of two cases per site. In the MHRT arm, daily online adaptive planning follows standardized algorithms with periodic audits. QA site visits and virtual meetings ensure protocol adherence and resolve deviations.

In addition to radiotherapy-specific QA, overall study conduct is regularly reviewed by a monitor from independent data monitoring committee 1–4 times a month for each center as part of quality assurance process. Enrollment, reported adverse events and long-term survival will be continuously monitored to uphold ethical standards and protect the safety and interests of the participants.

Discussion

This report presents a phase III, multi-center RCT that is designed to compare survival, local control, tumor response, toxicities, and QoL between MHRT and CFRT in cervical cancer.

In terms of the endpoint design of this study, both efficacy and safety outcomes were carefully considered. In cervical cancer radiotherapy research—particularly with hypofractionated regimens—QoL and late toxicity have become increasingly recognized as critical endpoints in clinical trials [28]. While traditional outcomes such as PFS and OS remain important, they may not adequately reflect the long-term functional and psychosocial burden experienced by patients [29]. MHRT may offer benefits such as reduced treatment duration and healthcare resource utilization, it may also present distinct late toxicity profiles that warrant vigilant monitoring [30]. Late effects involving the bladder, bowel, and sexual function can significantly impact patients' daily lives and emotional well-being [31]. Therefore, the integration of both physician-reported toxicity and patient-reported QoL measures is essential for a comprehensive assessment of treatment outcomes [30]. Our study highlights the importance of including long-term toxicity and QoL as key secondary endpoints in clinical trial design, offering a more holistic evaluation of MHRT in the management of cervical cancer.

As for the design of radiotherapy target volumes—particularly in patients with multiple small pelvic lymph node metastases but no common iliac or para-aortic involvement—the NCCN guidelines recommend standard pelvic irradiation with nodal boosts as appropriate, reserving EFRT for cases with confirmed upper nodal involvement [3]. The incidence of isolated para-aortic lymph node recurrence following curative pelvic radiotherapy is relatively low, reported between 1.7% and 3.2%. This suggests that routine prophylactic EFRT may not be necessary [32]. Wang et al. [33] reported that comparison to pelvic radiotherapy, prophylactic EFRT was no associated with improved OS, DFS, local control, and distant failure in cervical cancer patients with FIGO stage IIIC1 disease. The EFRT group showed a trend toward increased incidence of grade 3 or higher chronic toxicities. Advancements in radiotherapy techniques, notably IMRT and oART, have significantly improved the precision of radiation delivery to pelvic lymph node regions [14]. These technologies better spare healthy tissue, reducing side effects. Thus, standard pelvic radiotherapy remains appropriate for patients with multiple small pelvic nodes but no common iliac or para-aortic involvement, balancing efficacy and safety per current guidelines.

Previous trials have reported the efficacy and safety of MHRT in cervical cancer, but their study design differ significantly in terms of radiotherapy techniques, dose delivery, and inclusion criteria. As a result, these differences, coupled with the limited number of available studies on MHRT for cervical cancer, makes it difficult to draw definitive treatment recommendations. For instance, one retrospective study enrolling patients with FIGO stage IIIB cervical cancer used a two-field technique to deliver 39 Gy in 13 fractions, reporting a 5-year DFS rate of 59% and 8.1% late grade 3 rectal toxicity [34]. Another single-arm prospective study, focusing on stage IB-IIIC1 cervical cancer patients, administered 40 Gy in 16 fractions using three-dimensional conformal radiation therapy. And in this study, acute grade 3 gastrointestinal and genitourinary toxicity were observed in 20% and 6% of patients, respectively, while late toxicities included grade 2 genitourinary toxicity in 6% patients, and grade 2–3 gastrointestinal toxicity in 12% and 4% of patients [10].

Compared to the studies outlined above, RCT design would provide more robust evidences. An ongoing phase II RCT (NCT04070976) is conducted to compare the safety and tumor response rate between CFRT (45 Gy/25f) and MHRT (37.5 Gy/15f) in patients with FIGO stage III cervical cancer. However, this trial uses a four-field box technique for EBRT [35]. Another ongoing phase II randomized RCT by Prasartseree et al. is comparing MHRT with 44 Gy in 20 fractions to CFRT with 45 Gy in 25 fractions, both delivered using IMRT/VMAT. This trial reported higher acute gastrointestinal and genitourinary toxicity in the MHRT arm, though the differences were not statistically significant. It was also noted that non-inferior margin of this study should be re-evaluated to draw more reliable conclusions, mitigating false-positive results and supporting the clinical applicability of MHRT if proven non-inferior to CFRT [36]. Two other phase II RCTs are comparing MHRT (40 Gy/15f) and CFRT (45 Gy/25f) using VMAT, but their outcomes have not been published yet [37, 38]. Notably, these RCTs did not incorporate oART, and the clinical outcomes suggested a higher incidence of adverse events in MHRT group compared to the CFRT group.

The radiotherapy technique selected for this RCT aims to compare advanced technologies. oART focuses on reducing toxicity by minimizing margin expansion and enhancing treatment precision. The control group in this RCT receives standard treatment utilizing modern radiotherapy techniques, including fixed-field IMRT, VMAT, and tomotherapy, representing a high standard of treatment delivery. In a prospective, single-center phase I trial (NCT05994300), we reported one of the cases, a patient with FIGO stage IIIC1 cervical cancer, who received moderately hypofractionated oART with a prescribed dose of 43.35 Gy/17f to CTV and a simultaneous integrated boost of 54.40 Gy/17f to GTVnd [39]. This regimen led to improved dosimetry and a reduction in toxicity, providing foundational evidence for this ongoing phase III trial. The current phase III RCT also includes patients with FIGO stages IB1 to IIIC1 cervical cancer, aiming to draw more broadly applicable conclusions for the treatment of LACC.

Trial status

The protocol version number and date: version 3.0, 26 August 2024. The study was conceived and designed in 2023. Enrollment began in September 2024 and is expected to end in September 2026. At the time of manuscript preparation, enrollment in this study has started.

Conclusion

The objective of this study is to evaluate the non-inferiority of MHRT compared to CFRT. The trial will assess long-term survival, tumor response, toxicity, and QoL. Should MHRT be proven non-inferior, it may facilitate the adoption of a shorter, more cost-effective radiotherapy regimen for cervical cancer patients. The results of this trial are expected to provide crucial evidence to guide treatment strategies for definitive chemoradiotherapy in LACC.

Abbreviations

CFRT	Conventional fractionated radiotherapy
CI	Confidence interval
CIN	Common iliac nodes
CRR	Complete response rate
CSS	Cancer-specific survival
CT	Computed tomography
CTV	Clinical target volumes
CTV-C	Clinical target volume of the cervix
CTV-N	Clinical target volume of the lymph nodes
CTV-U	Clinical target volume of the uterus
DFS	Disease-free survival
EBRT	External beam radiotherapy
ECOG	Eastern Cooperative Oncology Group
EFRT	Extended field radiotherapy
EQD2	Equivalent dose in 2-Gy fractions
FIGO	International Federation of Gynecology and Obstetrics
GTVnd	Gross tumor volume node
HDR	High dose rate
HR	Hazard ratio
iCBCT	Iterative cone beam computed tomography
ICBT	Intracavity brachytherapy
IMRT	Intensity modulated radiation therapy
ISBT	Interstitial brachytherapy
LACC	Locally advanced cervical cancer
LN	Lymph node
LPFS	Locoregional progression-free survival
MFS	Metastasis-free survival
MHRT	Moderately hypofractionated radiotherapy
MRI	Magnetic resonance imaging
oART	Online adaptive radiotherapy
OARs	Organs at risk
OS	Overall survival
PCTV	Planning clinical target volume
PET-CT	Positron emission tomography with computed tomography
PFS	Progression-free survival
PGTVnd	Planning gross tumor volume of node
PTV	Planning target volume
QA	Quality assurance
QoL	Quality of life
RCT	Randomized controlled trial
VMAT	Volumetric modulated arc therapy

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13014-025-02688-7.

Supplementary Material 1

Acknowledgements

The authors gratefully acknowledge the valuable statistical support and assistance provided by Professor Yueping Shen from Soochow University.

Author contributions

Z.Z. and J.Y. conceived and designed the study protocol. Z.Z. and Y.C. drafted the initial manuscript. F.Z., K.H., and J.Y. critically reviewed and revised the manuscript for important intellectual content. J.Q., B.Y., Z.W., X.M., and Y.S. contributed to clinical trial coordination. Z.Z. and Y.C. provided methodological input and conducted the literature review. All authors reviewed and approved the final version of the manuscript.

Funding

This work was supported by National Key R&D Program of China, Ministry of Science and Technology of the People's Republic of China (Grant No. 2022YFC2407100, 2022YFC2407101), CAMS Innovation Fund for Medical Sciences (CIFMS) (Grant No. 2023-I2M-C&T-B-039). The funding source was not involved in design of the study and collection, analysis, and interpretation of data and writing the manuscript.

Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The study protocol was approved by the ethics committee at Peking Union Medical College Hospital. Protocol version 3.0 was approved on August 26, 2024. All participants should provide written informed consent prior to randomization and are free to withdraw at any time. There are no dissemination plans of this trial.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Department of Radiation Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, NO.1 Shuaifuyuan Wangfujing, Dongcheng District, Beijing 100730, China
[2]Eight-year Medical Doctor Program, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[3]Department of Radiation Oncology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, NO.1 Shuaifuyuan Wangfujing, Dongcheng District, 100730 Beijing, China

Received: 15 April 2025 / Accepted: 4 July 2025
Published online: 16 July 2025

References

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Cancer J Clin. 2024;74(3):229–63.
2. Rose P, Bundy BN, Watkins EB, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. New Engl J Med. 1999;340(15):1144–53.
3. Network NCC. NCCN Clinical Practice Guidelines in Oncology: Cervical Cancer. 2025; Version 1.
4. Rahangdale L, Mungo C, O'Connor S, Chibwesha CJ, Brewer NT. Human papillomavirus vaccination and cervical cancer risk. BMJ. 2022;379:e070115.
5. Abu-Gheida I, Reddy CA, Kotecha R, et al. Ten-Year outcomes of moderately hypofractionated (70 Gy in 28 fractions) intensity modulated radiation therapy for localized prostate Cancer. Int J Radiat Oncol Biol Phys. 2019;104(2):325–33.
6. Yaremko HL, Locke GE, Chow R, Lock M, Dinniwell R, Yaremko BP. Cost minimization analysis of hypofractionated radiotherapy. Curr Oncol. 2021;28(1):716–25.
7. Morgan SC, Hoffman K, Loblaw DA, et al. Hypofractionated radiation therapy for localized prostate cancer: an ASTRO, ASCO, and AUA Evidence-Based guideline. J Clin Oncol. 2018;36(34):JCO1801097.
8. Meattini I, Becherini C, Boersma L, et al. European society for radiotherapy and oncology advisory committee in radiation oncology practice consensus recommendations on patient selection and dose and fractionation for external beam radiotherapy in early breast cancer. Lancet Oncol. 2022;23(1):e21–31.
9. Muckaden MA, Budrukkar AN, Tongaonkar HB, Dinshaw KA. Hypofractionated radiotherapy in carcinoma cervix IIIB: Tata memorial hospital experience. Indian J Cancer. 2002;39(4):127–34.
10. Gandhi A, Rastogi M, Yadav U, et al. A pilot study of moderately hypofractionated whole pelvic radiotherapy with concurrent chemotherapy and

image-guided high dose rate brachytherapy for locally advanced cervical carcinoma. Int J Radiat Oncol Biol Phys. 2022;114(3):S89.
11. Astrom LM, Behrens CP, Storm KS, Sibolt P, Serup-Hansen E. Online adaptive radiotherapy of anal cancer: normal tissue sparing, target propagation methods, and first clinical experience. Radiother Oncol. 2022;176:92–8.
12. Wang G, Wang Z, Guo Y, et al. Evaluation of PTV margins with daily iterative online adaptive radiotherapy for postoperative treatment of endometrial and cervical cancer: a prospective single-arm phase 2 study. Radiat Oncol. 2024;19(1):2.
13. Shelley CE, Bolt MA, Hollingdale R, et al. Implementing cone-beam computed tomography-guided online adaptive radiotherapy in cervical cancer. Clin Transl Radiat Oncol. 2023;40:100596.
14. Wang G, Wang Z, Zhang Y, et al. Daily online adaptive radiation therapy of postoperative endometrial and cervical Cancer with PTV margin reduction to 5 mm: dosimetric outcomes, acute toxicity, and first clinical experience. Adv Radiat Oncol. 2024;9(7):101510.
15. Zeng Z. Yan. Moderated hypofractionated online adaptive radiotherapy in locally advanced cervical cancer: A prospective 1 clinical trial. Int J Radiat Oncol Biol Phys. 2024;120:S17–8.
16. Mileshkin LR, Moore KN, Barnes EH, et al. Adjuvant chemotherapy following chemoradiotherapy as primary treatment for locally advanced cervical cancer versus chemoradiotherapy alone (OUTBACK): an international, open-label, randomised, phase 3 trial. Lancet Oncol. 2023;24(5):468–82.
17. Wang W, Zhang F, Hu K, Hou X. Image-guided, intensity-modulated radiation therapy in definitive radiotherapy for 1433 patients with cervical cancer. Gynecol Oncol. 2018;151(3):444–8.
18. Zeng Z, Wang W, Liu X, et al. Optimal cisplatin cycles in locally advanced cervical carcinoma patients treated with concurrent chemoradiotherapy. Clin Transl Oncol. 2023;25(10):2892–900.
19. Yen A, Choi B, Inam E, et al. Spare the bowel, don't spoil the target: optimal margin assessment for online cone beam adaptive radiation therapy (OnC-ART) of the cervix. Pract Radiat Oncol. 2023;13(2):e176–83.
20. Gandhi AK, Sharma DN, Rath GK, et al. Early clinical outcomes and toxicity of intensity modulated versus conventional pelvic radiation therapy for locally advanced cervix carcinoma: a prospective randomized study. Int J Radiat Oncol Biol Phys. 2013;87(3):542–8.
21. Tyagi N, Lewis JH, Yashar CM, et al. Daily online cone beam computed tomography to assess interfractional motion in patients with intact cervical cancer. Int J Radiat Oncol Biol Phys. 2011;80(1):273–80.
22. Bacorro W, Baldivia K, Dumago M, et al. Phase 1/2 trial evaluating the effectiveness and safety of dose-adapted hypofractionated pelvic radiotherapy for advanced cervical cancers ineligible for chemotherapy (HYACINCT). Acta Oncol. 2022;61(6):688–97.
23. Wang G, Chen Y, Wang Z et al. A prospective Single-Arm study of daily online adaptive radiation therapy for cervical Cancer with reduced planning target volume margin: acute toxicity and dosimetric outcomes. Int J Radiat Oncol Biol Phys 2025.
24. Potter R, Tanderup K, Kirisits C, et al. The EMBRACE II study: the outcome and prospect of two decades of evolution within the GEC-ESTRO GYN working group and the EMBRACE studies. Clin Transl Radiat Oncol. 2018;9:48–60.
25. Hodapp N, [The ICRU. Report 83: prescribing, recording and reporting photon-beam intensity-modulated radiation therapy (IMRT)]. Strahlenther Onkol. 2012;188(1):97–9.
26. Lorusso D, Xiang Y, Hasegawa K, et al. Pembrolizumab or placebo with chemoradiotherapy followed by pembrolizumab or placebo for newly diagnosed, high-risk, locally advanced cervical cancer (ENGOT-cx11/GOG-3047/KEYNOTE-A18): a randomised, double-blind, phase 3 clinical trial. Lancet. 2024;403(10434):1341–50.
27. Schwartz LH, Seymour L, Litiere S, et al. RECIST 1.1 - Standardisation and disease-specific adaptations: perspectives from the RECIST working group. Eur J Cancer. 2016;62:138–45.
28. Viswanathan AN, Beriwal S, De Los Santos JF, et al. American brachytherapy society consensus guidelines for locally advanced carcinoma of the cervix. Part II: high-dose-rate brachytherapy. Brachytherapy. 2012;11(1):47–52.
29. Kirchheiner K, Potter R, Tanderup K, et al. Health-Related quality of life in locally advanced cervical Cancer patients after definitive chemoradiation therapy including image guided adaptive brachytherapy: an analysis from the EMBRACE study. Int J Radiat Oncol Biol Phys. 2016;94(5):1088–98.
30. Cho WK, Park W, Kim SW, Lee KK, Ahn KJ, Choi JH. Postoperative hypofractionated Intensity-Modulated radiotherapy with concurrent chemotherapy in cervical cancer: the POHIM-CCRT nonrandomized controlled trial. JAMA Oncol. 2024;10(6):737–43.
31. Pieterse QDM, ter Kuile CP, Lowik MM, van Eijkeren M, Trimbos MA, Kenter JBMZ. An observational longitudinal study to evaluate miction, defecation, and sexual function after radical hysterectomy with pelvic lymphadenectomy for early-stage cervical cancer. INT J GYNECOL CANCER. 2006;16(3):1119–29.
32. Cho WK, Kim YI, Park W, Yang K, Kim H, Cha H. Para-aortic lymph node recurrence after curative radiotherapy for cervical cancer. Int J Gynecol Cancer. 2019;29(7):1116–20.
33. Wang W, Liu X, Meng Q, Zhang F, Hu K. Prophylactic Extended-Field irradiation for patients with cervical Cancer treated with concurrent chemoradiotherapy: A Propensity-Score matching analysis. Int J Gynecol Cancer. 2018;28(8):1584–91.
34. Muckaden MBA, Tongaonkar H, et al. Hypofractionated radiotherapy in carcinoma cervix IIIB: Tata memorial hospital experience. Indian J Cancer. 2002;9:127–34.
35. Cantu D. Phase II randomized controlled trial of concomitant chemoradiotherapy with standard fractionation compared to hypofractionated concomitant chemoradiotherapy followed by brachytherapy, for clinical stage III cervical Cancer patients (NCT04070976). 2020.
36. Prasartseree T, Dankulchai P, Sittiwong W, Thephamongkhol K. HYPOCx-iRex (TCTR20210812003) A phase II RCT: 44 Gy/20F VS 45 Gy/25F CCRT in cervical cancer: Six-month Post-RT update. Int J Radiat Oncol Biol Phys. 2023;117(2):S41.
37. Mendez L. Hypofractionated External-Beam radiotherapy for intact cervical Cancer (HEROICC-Trial): A feasibility study (NCT04583254) 2023.
38. Tehran University of Medical Sciences Comparison of Clinical. Response and toxicity of Hypo-Fractionated chemoradiation with standard treatment in patients with uterine cervix Cancer (NCT04831437). 2021.
39. Zeng Z, Zhang F, Yan J. Moderated hypofractionated online adaptive radiotherapy in locally advanced cervical cancer: A case report. Cureus. 2024;16(8):e66552.

Publisher's note