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Clinical Trial Protocol

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Postoperative conventional versus hypofractionated intensity-modulated radiation therapy with concurrent chemotherapy in cervical cancer: a prospective multicenter randomized phase III trial (POHIM_P3 trial)

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ABSTRACT

Background: For patients with high-risk factors such as pelvic lymph node metastasis, positive surgical margins, or parametrial involvement, concurrent chemoradiotherapy (CCRT) with whole-pelvic radiotherapy significantly improves survival outcomes. Hypofractionated radiation therapy, which delivers higher radiation doses over fewer sessions, enhances tumor control but raises concerns about increased normal tissue toxicity. A recent Korean phase II study (POHIM-CCRT) evaluated the safety of hypofractionated intensity-modulated radiation therapy (IMRT), delivering 40 Gy in 16 fractions with weekly cisplatin following radical surgery. The results showed minimal acute toxicity. Based on these findings, the present study was designed to assess the oncologic efficacy of hypofractionated CCRT compared to conventional treatment strategies in high-risk cervical cancer patients after radical surgery.
Methods: The POHIM-P3 trial is a phase 3, randomized, multicenter study designed for women with cervical cancer requiring adjuvant CCRT after radical hysterectomy. Participants in the experimental arm receive hypofractionated IMRT to whole pelvis, delivering a total

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Conflict of Interest
No potential conflict of interest relevant to this article was reported.

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Conceptualization: C.W.K., K.H.C., Y.M., E.K.Y., K.Y.S., P.S., K.Y.S., K.Y.J., C.E., K.D.Y., P.W.; Data curation: P.W.; Investigation: L.J.H.; Methodology: C.W.K., P.W.; Project administration: P.W.; Resources: L.J.H., K.H.C., Y.M., E.K.Y., K.Y.S., P.S., K.Y.S., K.Y.J., C.E., K.D.Y., P.W.; Supervision: P.W.; Writing - original draft: C.W.K.; Writing - review & editing: C.W.K., L.J.H., K.H.C., Y.M., E.K.Y., K.Y.S., P.S., K.Y.S., K.Y.J., C.E., K.D.Y., P.W.

dose of 40 Gy in 16 fractions, and the control arm receive conventional radiotherapy with a total dose of 45–50.4 Gy in 25–28 fractions in combination with weekly cisplatin. The primary endpoint of the study is the 3-year disease-free survival and the secondary endpoints included acute and late side-effects, local control rates, and overall survival rates.

Trial Registration: ClinicalTrials.gov Identifier: NCT06509724

Keywords: Cervical Cancer; Radiotherapy; Intensity-Modulated Radiotherapy, Radiation Dose Hypofractionation

INTRODUCTION

Radical hysterectomy is a standard treatment for cervical cancer, along with radical radiotherapy [1]. In a randomized phase III clinical trial by Peter et al. [2], it was demonstrated that for patients who underwent radical surgery for cervical cancer and had pelvic lymph node metastasis, positive surgical margins, or parametrial involvement in postoperative pathological examinations, the addition of concurrent chemotherapy to whole-pelvic radiotherapy significantly improved both disease-free survival (DFS) and overall survival (OS) compared to those who did not receive concurrent chemotherapy. As a result, postoperative concurrent chemoradiotherapy (CCRT) with whole-pelvic radiotherapy has become the standard treatment for patients with these high-risk factors.

Hypofractionated radiation therapy (HFRT) increases the daily dose while reducing the number of treatments, thereby enhancing the radiobiological effect on the tumor and shortening the overall treatment time [3-5]. However, HFRT also increases the radiobiological effects on normal tissues, which may raise the risk of treatment-related side effects [6]. Although HFRT is not yet recommended in guidelines for cervical cancer [1], a few previous studies have reported its use in pelvic region [7,8].

Intensity-modulated radiation therapy (IMRT) is a major radiation therapy (RT) technique to reduce the radiobiological effects on normal tissues by minimizing radiation exposure to normal tissues during HFRT. Recent studies have shown that applying IMRT can reduce acute grade 3 or higher toxicities by up to 15% compared to conventional whole-pelvic CCRT [9-11].

Our research team conducted a multicenter phase II exploratory study in Korea (KROG 17-11) on CCRT with hypofractionated IMRT after surgery for cervical cancer. Weekly cisplatin was combined with hypofractionated IMRT on whole-pelvis. Among 79 patients, only 2 (2.5%) experienced grade 3 or higher acute toxicity [12].

Based on these results, we initiated a phase III randomized trial to compare the effectiveness and safety of conventional radiotherapy (CRT) and HFRT in patients with high-risk factors after radical surgery for cervical cancer.

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MATERIALS AND METHODS

1. Objectives

This study aimed to compare the 3-year DFS between conventional fractionated IMRT and hypofractionated IMRT with concurrent chemotherapy in pathologically high-risk patients after radical surgery for cervical cancer.

2. Trial design

This study is a phase III, multicenter, investigator-initiated, randomized controlled trial. A total of 10 institutions in South Korea is participating until now. Patients will be randomized 1:1 into either the hypofractionation (HFRT) or conventional fractionation (CRT) group. The trial scheme is illustrated in **Fig. 1**.

3. Endpoints

The primary endpoint is the 3-year DFS, defined as the time from surgery to the date of disease recurrence or death from any cause. Secondary endpoints include acute adverse effects, time to progression, local control rate, 5-year OS (time from surgery to death from any cause), and late adverse effects.

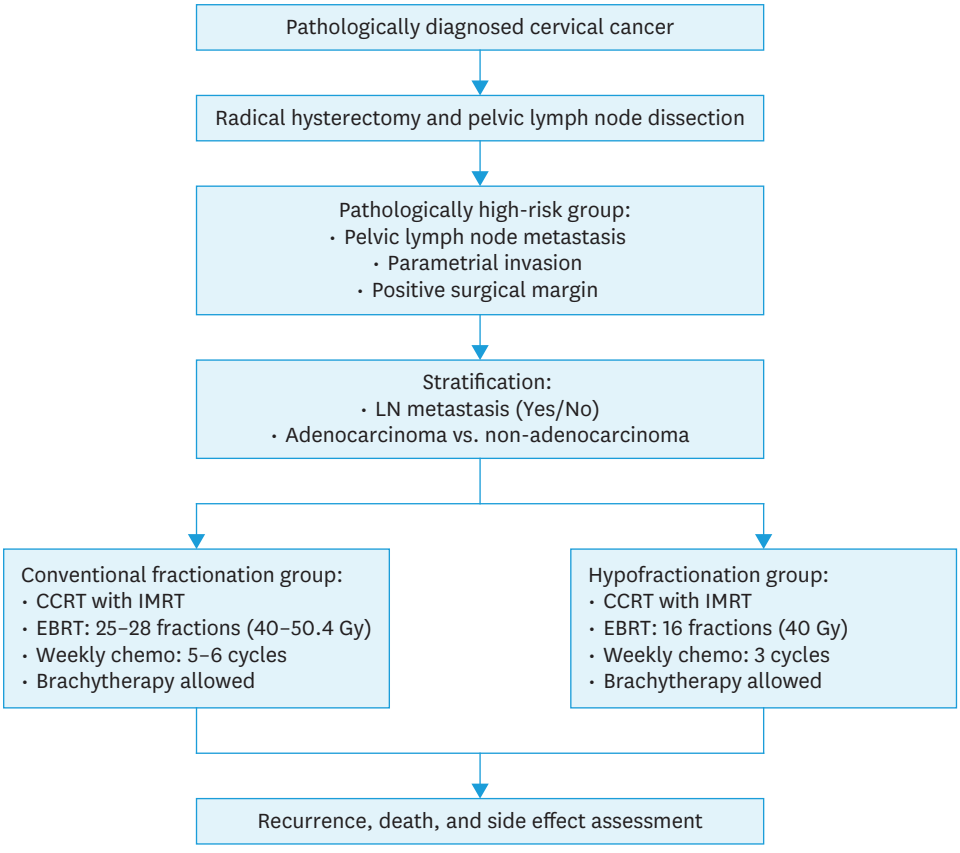

Fig. 1. Study scheme.
CCRT, concurrent chemoradiotherapy; EBRT, external beam radiation therapy; IMRT, intensity-modulated radiation therapy; LN, lymph node.

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4. Participants: eligibility criteria

Patients who met the following selection criteria were included in the study: histologically confirmed cervical cancer with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma; underwent radical hysterectomy and pelvic lymphadenectomy; met indications for postoperative radiotherapy owing to at least one of the following risk factors—pelvic lymph node metastasis, parametrial involvement, or positive surgical margins; were women aged 20 to 75 years; had an Eastern Cooperative Oncology Group performance status of 0–1 within 1 week before study participation; maintained adequate bone marrow function with granulocytes ≥1.0×10^3/μL, platelets ≥30×10^3/μL, hemoglobin ≥9.5 g/dL; had renal function with creatinine <2.0 mg/dL and bilirubin <1.5 mg/dL; and voluntarily provided informed consent. Patients were excluded if they had distant metastases, including ovarian or para-aortic lymph node metastases; had previously received pelvic radiotherapy; underwent radical hysterectomy >3 months prior; had untreated serious acute illnesses, such as stroke, cerebral infarction, or myocardial infarction; received neoadjuvant chemotherapy before surgery; were unable to receive concurrent chemotherapy during radiotherapy; or had a history of another cancer diagnosis within the past 5 years, except for thyroid cancer, skin cancer, or carcinoma in situ.

5. Sample size calculation

Assuming the expected 3-year DFS rates of 71.0% in CRT group [13] and 79.8% in the HFRT group [12], with a 95% confidence interval, 80% power, and a non-inferiority margin of –7%, a total of 134 patients per group are required. Accounting for a 5% dropout rate, 142 patients per group (284 patients in total) are necessary. There calculations were performed using Power Analysis and Sample Size Software 2023, version 23.0.1 (PASS, NCSS Statistical Software, Kaysville, UT, USA).

6. Randomization and stratification

Patients will be randomly assigned to the CRT group or HFRT group using blocked randomization. The stratification factors are presence of lymph node metastasis (yes/no) and histopathology (adenocarcinoma vs. non-adenocarcinoma).

7. Statistical analysis

Survival curves will be generated using the Kaplan-Meier method. Non-inferiority will be assessed within the 7% margin. Categorical variables will be compared using the chi-square test or Fisher's exact test, and continuous variables will be compared using t-tests or Wilcoxon rank sum tests as appropriate.

8. Treatment

Radical hysterectomy and pelvic lymph node dissection will be performed for all patients. During simulation, patients will be positioned in a stable supine position. Immobilization devices can be used to enhance reproducibility and maintain patient positioning throughout treatment sessions. Consistency in bladder volume will be maintained according to the guidelines of each participating institution. Computed tomography simulation will be conducted, with a slice thickness of 2.5 to 5 mm, with contrast enhancement applied based on institutional protocols.

The organs at risk to be delineated include the bladder, rectum, femoral heads, and bowel. The clinical target volume (CTV) will include the vaginal stump and regional lymphatic areas, including the internal, external, and common iliac lymph nodes, as well as the presacral

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Table 1. Dose constraints for organs at risk in conventional and hypofractionated radiotherapy

Group	Per protocol	Acceptable	Unacceptable
Conventional fractionation group			
Bowel	D_{max} ≤50–50.4 Gy		
	$V_{43.5\ Gy}$ ≤30%	>30%, <70%	≥70%
Rectum	$V_{43.5\ Gy}$ ≤80%	>80%, <100%	100%
Bladder	$V_{48.5\ Gy}$ ≤35%	<35%, >70%	≥70%
Femoral head	D_{max} <50–50.4 Gy		
	$V_{43.5\ Gy}$ <40%	>40%, <80%	≥80%
Hypofractionation group			
Bowel	D_{max} ≤40 Gy		
	$V_{35\ Gy}$ ≤30%	>30%, <70%	≥70%
Rectum	$V_{35\ Gy}$ ≤80%	>80%, <100%	100%
Bladder	$V_{39\ Gy}$ ≤35%	<35%, >70%	≥70%
Femoral head	D_{max} <40 Gy		
	$V_{35\ Gy}$ <40%	>40%, <80%	≥80%

lymph nodes, following Radiation Therapy Oncology Group consensus guidelines [14]. To account for internal organ movement and setup errors, a planning target volume (PTV) will be created by applying a margin of at least 7 mm around the CTV. Superior border is set considering the PTV margin from the L4/L5 interspace or the bifurcation of the common iliac artery, and inferior margin is set at the inferior edge of the obturator foramen or the margin from the vaginal cuff.

The prescribed dose for the CRT group will range from 1.8 to 2.0 Gy per fraction, administered over 25 to 28 fractions, for a total dose of 45 to 50.4 Gy. In the HFRT group, a dose of 2.5 Gy per fraction will be delivered over 16 fractions, for a total dose of 40 Gy. Treatment plans should ensure that at least 97% of the prescribed dose encompasses the entire PTV. The minimum dose within the PTV should not fall below 95% of the prescribed dose, and the maximum dose should not exceed 107% of the prescribed dose. Dose constraints for each organ at risk are specified in **Table 1**. All types of IMRT, including rotational techniques, were permitted. Brachytherapy, with a per-fraction dose of 3–7 Gy and a total dose of 10–21 Gy, or an external beam boost, could be administered in according to institutional guidelines.

9. Ethics

This trial complies with the Declaration of Helsinki (2008) and International Council for Harmonization Good Clinical Practice guidelines. Institutional Review Board approval has been obtained from all participating institutions including Samsung Medical Center (IRB No. 2024-04-058).

10. Trial registration

This trial is registered at ClinicalTrials.gov (number: NCT06509724).

DISCUSSION

Hypofractionation offers advantages in terms of patient convenience and healthcare resource utilization. This treatment approach reduces the number of visits required, which is particularly advantageous for patients who travel long distances or have pressing work and family commitments. Additionally, shorter treatment durations can lead to improved healthcare system efficiency. The potential of hypofractionation in cervical cancer lies in its

ability to maintain treatment efficacy while significantly improving the quality of life and treatment compliance for patients. This study is particularly important as it has potential to establish hypofractionated regimens as a standard treatment strategy for cervical cancer.

Emerging evidence, including findings from our own previous research, has demonstrated the safety profile of hypofracionated whole-pelvic RT [7,13,15]. Several prospective studies are currently underway to evaluate the safety and efficacy of various hypofractionated RT regimens for cervical or endometrial cancer [16,17]. A recent study on ultra-hypofractionation, which administered 30 Gy in 5 fractions to patients with endometrial cancer using stereotactic body RT techniques as adjuvant treatment, further supported the safety of hypofractionation for whole-pelvic RT [18].

We believe that IMRT is a critical component in ensuring the safety of hypofractionated regimens. Prior studies evaluating the hypofractionated RT in gynecological malignancies reported unacceptably high toxicity rates when IMRT was not used [16,19]. Consequently, IMRT is essential for the safe implementation of hypofractionated RT in whole-pelvic settings, particularly for CCRT. Notably, a prospective study investigating the outcomes of definitive hypofractionated CCRT for cervical cancer found higher toxicity rates in the hypofractionation cohort compared to the conventional cohort when using 3-dimensional conformal RT and the authors decided to use IMRT exclusively in subsequent cases [19].

Although the safety of hypofractionated RT using IMRT has been demonstrated, concerns remain regarding its oncological efficacy. One major criticism of the POHIM-CCRT trial was that patients received only 3 cycles of cisplatin, which is fewer than the recommended number [20]. The results of POHIM-CCRT trial reported a 3-year DFS rate of 79.3%, comparable to established benchmarks. However, as this was a single-arm study, its findings require validation through comparative studies. The ongoing randomized POHIM-P3 trial, which directly compares hypofractionated and CRT regimens, is expected to provide definitive insights into the efficacy of hypofractionated regimen. If results demonstrate non-inferiority or superiority, hypofractionation could become a new standard in cervical cancer treatment.

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