# Pelvic Ultra-Hypofractionated Adjuvant Radiotherapy for High-Intermediate and High-Risk Endometrial Cancer: A Prospective Multicenter Phase II Safety Cohort Study

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# Indice

1. Background and Rationale ..... 4
1.1 Endometrial Cancer and the Role of Adjuvant Radiotherapy ..... 4
1.2 Technological Advances and Toxicity Reduction ..... 4
1.3 Hypofractionation in Pelvic Malignancies ..... 4
1.4 Ultra-Hypofractionated Adjuvant Radiotherapy in Endometrial Cancer ..... 4
1.5 Rationale for the PURE Trial ..... 5
2. Hypothesis ..... 5
3. Objectives ..... 6
3.1 Primary Objective: ..... 6
3.2. Secondary Objectives ..... 6
4. Endpoints and Outcomes measures ..... 6
4.1 Primary Endpoint ..... 6
4.2 Secondary Endpoints ..... 7
4.3 Safety Monitoring Endpoint ..... 7
5. Study Design ..... 8
6. Eligibility criteria ..... 8
6.1 Inclusion Criteria ..... 8
6.2 Exclusion Criteria ..... 8
7. Radiotherapy Planning and Treatment ..... 8
7.1 Patient Preparation and Simulation ..... 8
7.2 Target Delineation and Treatment Planning ..... 9
7.3 Quality Assurance ..... 10
7.4 Treatment Delivery and Image Guidance ..... 10
7.5 Protocol Deviations ..... 10
7.6 Adjuvant Systemic Therapy ..... 11
7.7 Vaginal Vault Brachytherapy Boost ..... 11
8. Pretreatment Evaluation and during treatment ..... 11
9. Registration Procedure ..... 12
10. Sample size, stopping rules and statistical analysis ..... 12
10.1 Sample Size Calculation ..... 12
10.3 Statistical Analyses ..... 12
10.4 Missing Data ..... 13
11. Follow-up ..... 13
12. References ..... 14

# 1. Background and Rationale

### *1.1 Endometrial Cancer and the Role of Adjuvant Radiotherapy*

Endometrial cancer is one of the most common gynecological malignancies in developed countries. In Spain, more than 7,300 new cases are diagnosed annually, making it the fifth most common cancer among women (1).

Adjuvant pelvic radiotherapy is a standard treatment for patients with high-intermediate-risk and high-risk endometrial cancer following surgery. Conventional treatment typically consists of 45–50.4 Gy delivered in 25–28 fractions over five weeks (2,3) Although highly effective in reducing locoregional recurrence, this schedule requires substantial healthcare resources and may represent a logistical burden for patients.

### *1.2 Technological Advances and Toxicity Reduction*

The widespread adoption of intensity-modulated radiotherapy (IMRT), volumetric modulated arc therapy (VMAT), and daily image-guided radiotherapy (IGRT) has substantially improved the therapeutic ratio of pelvic irradiation. By reducing radiation exposure to the bowel, bladder, rectum, and other organs at risk, these technologies have consistently demonstrated lower rates of acute and late GI toxicity compared with historical three-dimensional conformal radiotherapy techniques (4–10)

Evidence from prospective trials, including PORTEC-3 and NRG Oncology/RTOG 1203, has shown that IMRT significantly improves patient-reported bowel and urinary outcomes without compromising disease control or survival. Consequently, modern guidelines recommend IMRT/VMAT as the standard technique for adjuvant pelvic radiotherapy in endometrial cancer (5–7)

### *1.3 Hypofractionation in Pelvic Malignancies*

Advances in treatment planning and image guidance have enabled the safe delivery of larger doses per fraction, facilitating the development of hypofractionated and ultra-hypofractionated treatment schedules.

Hypofractionation is now established in several pelvic malignancies, particularly prostate cancer, where randomized trials have demonstrated equivalent oncological outcomes with shorter treatment duration (11–13). Similarly, short-course radiotherapy has become a standard treatment option in selected patients with rectal cancer (14). Experience with ultra-hypofractionated pelvic nodal irradiation has also demonstrated acceptable toxicity profiles and supports the biological feasibility of delivering pelvic radiotherapy in five fractions (15).

Beyond maintaining efficacy, shorter treatment schedules may improve patient convenience, reduce healthcare resource utilization, and facilitate treatment access, particularly among elderly patients.

### *1.4 Ultra-Hypofractionated Adjuvant Radiotherapy in Endometrial Cancer*

Ultra-hypofractionated radiotherapy has demonstrated feasibility, safety, and efficacy across multiple pelvic malignancies, including prostate cancer, rectal cancer, and gynecologic cancers. Emerging evidence from prospective studies such as SPARTACUS and DeCRESCEndo suggests that pelvic irradiation delivered in five fractions may be a feasible alternative in selected patients with endometrial cancer (16,17)

The SPARTACUS phase I/II trial demonstrated the feasibility and favorable acute toxicity profile of pelvic radiotherapy delivered in five fractions (30Gy/5fx) following surgery for uterine cancer (16). Similarly, the multicenter DeCRESCEndo study reported low gastrointestinal and genitourinary toxicity rates together with excellent locoregional control after adjuvant ultra-hypofractionated pelvic radiotherapy (25Gy/5fx) in high-risk endometrial cancer patients (17).

Additional support comes from the extensive experience with high-dose-per-fraction treatments in gynecological oncology, including postoperative vaginal cuff brachytherapy, image-guided brachytherapy for medically inoperable endometrial cancer, and combined external beam radiotherapy and brachytherapy for locally advanced cervical cancer (18–22). These clinical settings have generated robust evidence regarding pelvic tissue tolerance and long-term oncological safety.

### *1.5 Rationale for the PURE Trial*

Although preliminary studies have demonstrated encouraging safety and efficacy results, prospective evidence supporting ultra-hypofractionated pelvic radiotherapy in endometrial cancer remains limited.

Conventional adjuvant pelvic radiotherapy is typically delivered as 45–50.4 Gy in 25–28 fractions. Planning analyses from the SPARTACUS study suggested that a prescription of 27.5 Gy in five fractions may provide a more favorable balance between target coverage and organ-at-risk sparing than higher ultra-hypofractionated dose levels (23).

Using an α/β ratio of 4.5 Gy, 27.5 Gy in five fractions corresponds to an EQD2 of approximately 42.3 Gy, comparable to the biological dose delivered with conventional adjuvant schedules. Therefore, this regimen is expected to preserve therapeutic effectiveness while substantially reducing treatment duration. Dose conversions are described on **Table 1.**

| TRIAL | SCHEDULE | Dose/fx | EQD2 TUMOR (α/β=10) (*α/β=4.5*) | BED (α/β=10) | EQD2 OAR (α/β= 2) | BED (α/β=2) | EQD2 OAR (α/β =3) | BED (α/β=3) |
|---|---|---|---|---|---|---|---|---|
| **PORTEC-3** | 45Gy/25fx | **1.8 Gy** | **44.3Gy (*43.6Gy*)** | 53.1 | 42.8 | 85 | **43.2** | 72 |
| **SPARTACUS** | 30Gy/5Fx | **6 Gy** | **40Gy (*48Gy*)** | 48 | 60 | 120 | **54** | 90 |
| **PURE** | 27.5Gy/5fx | **5.5 Gy** | **35.5 (*42.31*Gy)** | 42.6 | 51.6 | 103.1 | **46** | 77.9 |

***Table 1*** *Dose conversion based on pivotal trials*

The PURE trial has been designed to prospectively evaluate the safety and feasibility of adjuvant pelvic radiotherapy delivered as 27.5 Gy in five fractions using modern IMRT/VMAT and daily IGRT. By focusing on acute gastrointestinal and genitourinary toxicity and incorporating predefined stopping rules through a Simon two-stage design, the study aims to establish a robust safety framework for future comparative studies and broader clinical implementation.

## 2. Hypothesis

We hypothesize that adjuvant pelvic radiotherapy delivered as 27.5 Gy in five fractions using image-guided IMRT/VMAT is feasible and associated with an acceptable incidence of acute grade ≥2 gastrointestinal and genitourinary toxicity in patients with high-intermediate-risk and high-risk endometrial cancer following surgery.

Furthermore, we hypothesize that treatment compliance, quality of life outcomes, and oncological outcomes will be comparable to those reported with conventional fractionation schedules.

# 3. Objectives

### *3.1 Primary Objective:*

To determine the incidence of acute grade ≥2 gastrointestinal and/or genitourinary toxicity according to CTCAE version 5.0 occurring from treatment initiation until 3 months after completion of radiotherapy.

### *3.2. Secondary Objectives*

***Safety***

To evaluate the incidence of acute grade ≥3 toxicity according to CTCAE v5.0, evaluate the incidence of late grade ≥2 gastrointestinal and genitourinary toxicity and characterize the overall toxicity profile associated with ultra-hypofractionated pelvic radiotherapy.

***Feasibility***

To assess treatment completion rates, evaluate adherence to treatment planning and delivery protocols and assess treatment interruptions and their causes.

***Patient-Reported Outcomes***

To evaluate quality of life using EORTC QLQ-C30, and endometrial cancer-specific quality of life using EORTC QLQ-EN24.

***Oncological Outcomes:***

To estimate locoregional control, disease-free survival, distant metastasis-free survival, cancer-specific survival and overall survival.

# 4. Endpoints and Outcomes measures

### *4.1 Primary Endpoint*

| Endpoint | Definition | Assessment Method | Timeframe |
|---|---|---|---|
| **Acute gastrointestinal and/or genitourinary toxicity** | Incidence of CTCAE v5.0 grade ≥2 GI and/or GU adverse events | Investigator assessment using CTCAE v5.0 | At the end of radiotherapy, at 1 months and 3 months after treatment completion |

### *4.2 Secondary Endpoints*

| Endpoint | Definition | Assessment Method | Timeframe |
|---|---|---|---|
| **Severe acute toxicity** | Incidence of CTCAE v5.0 grade ≥3 GI and/or GU adverse events | CTCAE v5.0 | At the end of radiotherapy, at 1 months and 3 months after treatment completion |
| **Late gastrointestinal toxicity** | Incidence of CTCAE v5.0 grade ≥2 GI adverse events | CTCAE v5.0 | At 3, 6 and 12 months after treatment, up to 5 years |
| **Late genitourinary toxicity** | Incidence of CTCAE v5.0 grade ≥2 GU adverse events | CTCAE v5.0 | At 3, 6 and 12 months after treatment, up to 5 years |
| **Quality of life** | Change from baseline in patient-reported quality-of-life scores | EORTC QLQ-C30 and EORTC QLQ-EN24 questionnaires | Baseline, 5 fraction, 1 month, 3, and 12 months. |
| **Treatment feasibility** | Proportion of patients completing all planned radiotherapy fractions and incidence of major protocol deviations | Treatment records and protocol compliance review | End of radiotherapy |
| **Local control** | Absence of vaginal cuff | Clinical and radiological assessment | Up to 5 years |
| **Regional control** | Absence of pelvic recurrence | Clinical and radiological assessment | Up to 5 years |
| **Distant control** | Absence of tumor at distance | Clinical and radiological assessment | Up to 5 years |
| **Disease-free survival (DFS)** | Time from study enrollment to tumor recurrence or death from any cause. | Clinical follow-up and imaging | Up to 5 years |
| **Overall survival (OS)** | Time from study enrollment to death from any cause | Clinical follow-up | Up to 5 years |

### *4.3 Safety Monitoring Endpoint*

For the Simon two-stage design, treatment-related acute toxicity will be continuously monitored.

A toxicity event will be defined as the occurrence of any CTCAE v5.0 grade ≥2 gastrointestinal or genitourinary adverse event considered at least possibly related to study treatment within the first 3 months after radiotherapy completion.

Safety oversight is the responsibility of the Principal Investigator. No independent Data Safety Monitoring Board (DSMB) has been established for this study, given its single-arm phase II design and the well-characterized safety profile of the intervention.

Study continuation, temporary suspension, or early termination will follow the predefined stopping rules described in the Statistical Considerations section.

# 5. Study Design

Prospective, multicenter, single-arm phase II safety cohort study conducted within the Multihospital Clinical Unit of Radiation Oncology of Aragón (UCMORA) using a Simon optimal two-stage design.

# 6. Eligibility criteria

### *6.1 Inclusion Criteria*

a) Female patients aged ≥18 years.
b) Histologically confirmed endometrial carcinoma (endometrial adenocarcinoma, serous or clear cell carcinoma, carcinosarcoma or dedifferentiated carcinoma).
c) FIGO 2023 stage I–III disease.
d) High-intermediate-risk or high-risk disease according to ESGO/ESTRO/ESP guidelines.
e) Complete surgical staging including hysterectomy and bilateral salpingo-oophorectomy with or without nodal assessment.
f) Indication for adjuvant pelvic external beam radiotherapy as determined by the multidisciplinary tumor board.
g) ECOG Performance Status 0–2.
h) Ability to understand and sign informed consent.
i) Ability to comply with study procedures and follow-up requirements.

### *6.2 Exclusion Criteria*

a) Evidence of distant metastatic disease.
b) Prior pelvic radiotherapy.
c) Previous malignancy likely to interfere with study assessment, except adequately treated non-melanoma skin cancer or in situ carcinoma.
d) Serious uncontrolled medical condition preventing radiotherapy.
e) Pregnancy or breastfeeding.
f) Inability to undergo treatment planning or image-guided radiotherapy.
g) Participation in another interventional trial that may interfere with study outcomes.

# 7. Radiotherapy Planning and Treatment

### *7.1 Patient Preparation and Simulation*

Prior to simulation, optional fiducial markers (carbon or gold) will be placed at the lateral aspects of the vaginal cuff or colpotomy scar to facilitate image guidance.

Patients will undergo CT simulation in the supine position using appropriate immobilization devices. Simulation and treatment will be performed with a comfortably filled bladder and an

empty rectum. Patients will be instructed to void their bladder, drink approximately 200 mL of water, and wait 45 minutes before simulation and treatment. Oral laxatives or rectal enemas may be used when necessary to optimize rectal preparation.

A non-contrast planning CT scan with 3-mm slice thickness will be acquired from approximately the L2 vertebral level to at least 5 cm below the distal vagina.

### *7.2 Target Delineation and Treatment Planning*

Target volumes and organs at risk (OARs) will be delineated according to current RTOG consensus guidelines. Definitions of target volumes and contouring recommendations are summarized in **Table 2.**

| NAME | DEFINITION |
|---|---|
| **PTV-T** | CTV-T + 0.3 cm uniform margin |
| **CTV-T** | 1/3 superior vaginal (with fiducial marker)<br>Parametrial tissue<br>*The CTV should be individualized when there is a positive resection margin, pelvic peritoneal disease, or vaginal involvement. |
| **PTV-N** | CTV-N + 0.3 cm uniform margin |
| **CTV-N** | External Iliac<br>Internal Iliac<br>Distal common Iliac<br>Obturator nodes<br>Presacral and upper common iliac: if cervical involvement or pelvic lymph node involvement (patients with FIGO stage II-IIIC1).<br>* The lymph node target volume may be extended to include the aortic bifurcation or para-aorticnodes, up to or just above the level of the renal vessels, depending on the location and number of positive lymph nodes, site of sentinel lymph nodes, and whether there is extrauterine primary tumor involvement. |
| **OAR:** | -Bladder<br>-Bladder neck<br>-Urethra<br>-Rectum<br>-Sigma<br>-Small bowel<br>-Bowel bag<br>-Sacrum<br>-Pelvic bone<br>-Right hip<br>-Left hip<br>-Fiducial markers<br>-Sacral nerves |

***Table 2*** *Target and OAR delineation*

Radiotherapy will be delivered using inverse-planned IMRT or VMAT techniques. Treatment plans will be optimized to ensure adequate target coverage while respecting predefined dose constraints for OARs. Dose constraints were adapted from the SPARTACUS, STARR, and PACE-B

trials, as well as published studies evaluating ultra-hypofractionated pelvic nodal irradiation (16,35–37).

### *7.3 Quality Assurance*

Patient-specific quality assurance will be performed before treatment initiation according to institutional procedures. Agreement between calculated and measured dose distributions will be evaluated using validated quality assurance methodologies.

### *7.4 Treatment Delivery and Image Guidance*

Patients will receive pelvic radiotherapy to a total dose of 27.5 Gy in 5 fractions delivered on alternate days over approximately 11–15 days. A minimum interval of 36 hours and a maximum interval of 96 hours between fractions is recommended.

Daily cone-beam CT (CBCT) image guidance will be mandatory. Patient positioning will be verified using bony anatomy and fiducial marker matching. Bladder filling and rectal preparation will be assessed before each fraction to ensure treatment reproducibility and compliance with planning objectives.

Adaptive CBCT-guided or MR-guided radiotherapy is permitted according to institutional practice and will be prospectively recorded.

Patients requiring adjuvant vaginal cuff brachytherapy may receive brachytherapy following completion of external beam radiotherapy according to institutional protocols.

### *7.5 Protocol Deviations*

All protocol deviations related to radiotherapy planning and delivery will be prospectively recorded.

Major deviations include:

- Failure to meet mandatory target coverage objectives.
- Exceeding mandatory organ-at-risk dose constraints.
- Omission of one or more planned radiotherapy fractions.
- Treatment interruption resulting in an interval greater than 96 hours between fractions.
- Absence of mandatory daily image guidance.

Minor deviations include:

- Variations in bladder or rectal preparation not requiring treatment replanning.
- Deviations from recommended, but non-mandatory, planning objectives.

The frequency and nature of protocol deviations will be analyzed descriptively and reported as part of the study feasibility assessment.

### *7.6 Adjuvant Systemic Therapy*

Patients who are recommended to receive adjuvant systemic therapy in addition to pelvic radiotherapy can be enrolled in the study with the following guideline: There is at minimum a 3-week interval between any radiation treatment and chemotherapy treatments.

### *7.7 Vaginal Vault Brachytherapy Boost*

Vaginal cuff brachytherapy (VBT) boost is indicated in patients with close or positive vaginal surgical margins or cervical stromal (24,25). Routine use after EBRT in the absence of these risk factors is not supported by current evidence, and its use should be reserved for cases with the aforementioned high-risk features, based on physician criteria.

The prescribed dose is 7 Gy in 1 fraction (HDR or electronic brachytherapy, vaginal cylinder), delivering a cumulative EBRT + VBT EQD2 of 54.7 Gy ($\alpha/\beta = 4.5$). VBT should be delivered within a maximum of 2 weeks after completion of EBRT.

**VBT Boost: Technical Details**

**Target delineation**: Upper one-third of the vaginal mucosa (2–3 cm active length). Extended vaginal segment may be considered in cases with extensive LVSI, high-grade histology, or high-risk features (26,27).

**Dose:** 7 Gy / 1 fraction. Prescribed to the vaginal surface or at 0.5 cm depth depending on clinical situation (28,29). Radiobiological equivalences (EQD2) are described on table 3.

**Dose constraint — Vaginal D2cc:** EQD2 ($\alpha/\beta = 3$ Gy) < 68 Gy. If not met, dose reduction to 6 Gy/fraction may be considered (29).

**Technique:** HDR brachytherapy or electronic brachytherapy with vaginal cylinder. Interstitial brachytherapy if parametrial or other margin involvement requires broader coverage.

**Delivery:** Maximum 2-week interval between last EBRT fraction and brachytherapy.

| Trial | Schedule | Dose/fx | EQD2 Tumor ($\alpha/\beta$=4.5) | EQD2 OAR ($\alpha/\beta$=3) |
|---|---|---|---|---|
| **EBRT** | 27.5 Gy / 5 fx | 5.5 Gy | 42.3 Gy | 46.0 Gy |
| **VBT boost** | 7 Gy / 1 fx | 7.0 Gy | 12.4 Gy | 14.0 Gy |
| **Total** | | | **54.7 Gy** | **60 Gy** |

**Table 3** Radiobiological equivalences of VBT and EBRT

# 8. Pretreatment Evaluation and during treatment

**Table 4** Pretreatment evaluation

| First Consultation | On fraction 5 (end of treatment) |
|---|---|

| | |
|---|---|
| Medical History<br>Fiducial marker placement<br>QLQ-C30 or other QoL questionnaire<br>Baseline toxicities using CTCAE v5.0 4. | Nurse consultation for during treatment toxicities using CTCAE v5.0 4.<br>QLQ-C30 or other QoL questionnaire |

# 9. Registration Procedure

Participants will be assigned a unique study identification number, to assure anonymization, once initial consent is signed. Participants accept to share their medical data for publication or congress presentation.

# 10. Sample size, stopping rules and statistical analysis

### *10.1 Sample Size Calculation*

A Simon two-stage design (optimal design) will be used to evaluate treatment safety. The optimal design was selected because patient safety is prioritized by minimizing the number of patients required in the first stage for the early stopping decision, rather than minimizing the total sample size as in the minimax design.

**Hypotheses (**Power: 80%. Type I error (α): 5% (one-sided))

**H0 (Unacceptable):** An acute gastrointestinal or genitourinary toxicity rate of grade ≥2, occurring during treatment and within the first 3 months after treatment completion, of 40% or higher is considered unacceptable for adjuvant chemoradiotherapy in endometrial cancer.

**H1 (Acceptable):** An acute gastrointestinal or genitourinary toxicity rate of grade ≥2, occurring during treatment and within the first 3 months after treatment completion, of 20% or lower is considered acceptable for adjuvant chemoradiotherapy in endometrial cancer.

### *10.2 Stopping rules*

**First Stage:** A total of 11 patients will be enrolled.

- If 4 or more toxic events are observed, the study will be terminated early for safety concerns.
- If 3 or fewer toxic events are observed, the study will proceed to the second stage.

**Second Stage:** An additional 32 patients will be enrolled, for a total sample size of 43 patients.

**Final Analysis:** If, at the end of the study (N = 43), a total of 13 or fewer toxic events are observed, the safety profile will be considered promising and acceptable for further investigation.

### *10.3 Statistical Analyses*

Categorical variables will be summarized using frequencies and percentages. Continuous variables will be summarized using means, standard deviations, medians, and ranges. Toxicity rates will be reported with exact 95% confidence intervals.

***Survival Analyses***

The Kaplan–Meier method will be used to estimate oncological outcomes as: locoregional control, disease-free survival , distant metastasis-free survival, cancer-specific survival and overall survival. Corresponding 95% confidence intervals will be reported.

### *10.4 Missing Data*

Missing data will be described and reported. Sensitivity analyses may be performed if missing data exceed 10% for the primary endpoint.

## 11. Follow-up

Follow-up should be done at 1 months, 3 months, 6 months and 1 years after treatment, than annually until 5 years after treatment. Blood test, medical visits and CT is recommended, firstly at 3 months after treatment, and each 6 months during after first five years of follow up. Other institutional protocol can be considered.

QoL questionnaire are recommended to be filled during follow-up, as described on table 5.

**Table 5** Follow-up

| **1 months** | **3 months** | **6 months** | **12 months, then at least annually until 60 months** |
|---|---|---|---|
| Acute toxicities using CTCAE v5.0 4.<br><br>QLQ-C30 or other QoL questionnaire | Acute toxicities using CTCAE v5.0 4.<br><br>QLQ-C30 or other QoL questionnaire | Late toxicities using CTCAE v5.0 4.<br><br>QLQ-C30 or other QoL questionnaire | Late toxicities using CTCAE v5.0 4.<br><br>QLQ-C30 or other QoL questionnaire |
| Local control<br>Regional control<br>Distant control<br>Overall survival | Local control<br>Regional control<br>Distant control<br>Overall survival | Local control<br>Regional control<br>Distant control<br>Overall survival | Local control<br>Regional control<br>Distant control<br>Overall survival |

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