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Protocol

Postoperative hypofractionated radiation in cervical and endometrial tumours: phase II study protocol for a prospective phase II non-randomised trial

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ABSTRACT

Background: For women with endometrial or cervical cancer treated surgically, presence of adverse histopathological features is associated with increased risk of recurrence. While conventional post-op radiotherapy uses standard fractionation to treat these patients, use of hypofractionation is understudied. Study aims to evaluate long-term safety of hypofractionated post-op pelvic radiotherapy in patients with cervical and endometrial cancers. Primary objectives were to assess 3-year cumulative incidence of late grade ≥2 GI or genitourinary toxicity in patients with cervical or endometrial cancer requiring adjuvant (chemo) radiation treated with hypofractionated radiotherapy.
Methods: Single-arm prospective study wherein patients will receive adjuvant RT to a dose of 39 Gy in 13 fractions, with or without concurrent weekly cisplatin. Vaginal brachytherapy (2 fractions of 6 Gy HDR) will follow EBRT based on indication. Patients will be followed at regular intervals for assessment of toxicity (graded using CTCAE v5.0), pelvic control, and QoL (using EORTC QLQ-C30 and CX24/EN24). Age≥18 years; ECOG performance status ≤2; post-op carcinoma of cervix/endometrium requiring adjuvant radiotherapy with/without concurrent chemotherapy were included. Macroscopic residual disease post-operatively; requirement for extended field radiotherapy; prior chemotherapy for any malignancy and previous pelvic radiotherapy were excluded. Primary endpoint was 3-year cumulative incidence of late grade ≥2 gastrointestinal or genitourinary toxicity, as assessed by CTCAE version 5.0. Sample size was 90.
Conclusions: Recruitment is estimated to be completed by 2027 and results may be published by 2028 after adequate follow up.

Keywords: Hypofractionated radiotherapy, Cervical cancer, Endometrial cancer, Postop radiotherapy, Phase II trial, Toxicity, QoL

INTRODUCTION

For women with early-stage cervical cancer treated surgically, the presence of adverse histopathological features is associated with an increased risk of recurrence. These include intermediate-risk factors as defined by Sedlis and high-risk features as outlined by Peters.[1,2] Similarly, patients with endometrial cancer exhibiting high- or high–intermediate-risk features are predisposed to locoregional failures, both in the pelvis and vaginal apex.[3] To reduce this risk, adjuvant radiotherapy, with or without chemotherapy, is recommended to improve locoregional control and overall survival.[4,5]

Conventionally, postoperative radiotherapy is delivered using fractionated schedules of 45-50.4 Gy in 25-28 fractions over 5 to 5.5 weeks, with conformal techniques, with or without a brachytherapy boost. The advent of image-guided intensity-modulated radiotherapy (IG-IMRT) has significantly reduced treatment-related morbidity. PARCER, a phase III randomized trial demonstrated that IG-IMRT reduced 3-year cumulative incidence of grade ≥2 late gastrointestinal adverse events to 21.1%, compared with 42.4% using 3DCRT ($p<0.001$), establishing IG-IMRT as the standard of care for postoperative cervical cancer.[6] The RTOG 1203 (TIME-C) trial also established IG-IMRT as the preferred technique for postoperative radiation in endometrial and cervix cancer, demonstrating significantly reduced 6-week acute patient reported gastrointestinal and urinary toxicities compared with conventional 3DCRT.[7]

In recent years, hypofractionated radiotherapy-delivering higher doses per fraction over a shorter overall treatment time-has emerged as safe and effective strategy in several tumor sites, including breast, prostate, and rectal cancers, where it is now considered standard of care. However, evidence for hypofractionation in gynecological malignancies remains limited. Early phase studies in cervical and endometrial cancers such as the POHIM-RT, POHIM CCRT and SPARTACUS study have primarily focused on feasibility and acute adverse events, with encouraging results but limited long-term follow-up.[8-10]

Given the need to enhance patient convenience, reduce healthcare resource burden, and maintain efficacy while minimizing late adverse events, further evaluation of hypofractionated schedules in gynecological cancers is warranted. The present study aims to investigate the safety and long-term outcomes of postoperative hypofractionated pelvic radiotherapy, with or without chemotherapy and/or brachytherapy, in patients with cervical and endometrial cancer.

METHODS

Trial design

The PARCER II study is a single arm open label phase II trial investigating cumulative incidence of late grade ≥2 gastro-intestinal or genito-urinary adverse events in patients receiving adjuvant hypofractionated external beam radiotherapy to the pelvis for post-operative cervical or endometrial cancer.

Participants

The inclusion criteria for the study include age ≥18 years, ECOG performance status ≤2, and a histologically confirmed diagnosis of carcinoma of the cervix or endometrium requiring adjuvant external beam radiotherapy with or without concurrent chemotherapy.

For patients with post operative cervical cancer, inclusion criteria mandate that patient has undergone hysterectomy with pelvic nodal dissection for squamous, adenocarcinoma, or adenosquamous histology, with either:≥2 intermediate-risk features (tumour size ≥4 cm for squamous; ≥2 cm for adeno/adeno-squamous, deep stromal invasion, or LVSI), or any high-risk feature (involved lymph nodes, parametrial involvement, or positive surgical margins), or patients that are deemed suitable for adjuvant treatment after multidisciplinary discussion, such as when adequate Type III radical surgery is not performed when indicated, but no residual disease is observed on imaging.

For endometrial tumours, any patients with high-intermediate risk features requiring adjuvant whole pelvic radiation, or patients planned for adjuvant radiation with or without concurrent chemotherapy, without systemic therapy were eligible. These include: (1) FIGO 2018 Stage I, grade 1 or 2 with LVSI where pelvic radiotherapy is clinically indicated, stage IB, grade 3 irrespective of LVSI (2) or any of the aforementioned stages with p53 abnormal status, stage II and (3) stage III undergoing pelvic radiotherapy alone (e. g., if systemic chemotherapy is omitted due to patient related factors).

Patients will be excluded if they have macroscopic residual disease (R+ resection) post-operatively, or require extended field radiotherapy (e. g., para-aortic lymph node involvement), or warrant the use of systemic chemotherapy, or have received prior chemotherapy for any malignancy or previous pelvic radiotherapy. Patients with known retroviral disease, or with preexisting medical conditions that may interfere with the assessment of genitourinary (GU) or gastrointestinal (GI) adverse events, including irritable bowel syndrome, subacute intestinal obstruction, anal incontinence, hemorrhoids, urinary incontinence, or persistent urinary tract infections after surgery will also be excluded.

Endpoints

The primary endpoint is three-year cumulative incidence of late grade ≥2 gastrointestinal or genitourinary adverse events, defined as the percentage of patients experiencing CTCAE v5.0 grade ≥2 GI or GU adverse events

occurring more than 90 days after completion of hypofractionated adjuvant radiotherapy.

The secondary endpoints include pelvic control rate (defined as the time since registration to date of local or pelvic relapse or till last follow up; whichever occurs earlier.), disease-free survival (defined as the time since registration to date of relapse, recurrence, or death, or till last follow up; whichever occurs earlier), overall survival (defined as the time from registration to date of death from any cause, or till last follow up, whichever occurs earlier), acute adverse events (defined as any toxicity occurring within 3 months (90 days) of treatment completion. The outcomes will be assessed by physicians during each OPD visit during the course of treatment and reported using the CTCAE v5), quality of life (using EORTC QLQ-C30 and site-specific modules-CX24 for cervical cancer and EN24 for endometrial cancer), and cumulative adverse events score assessed using the C-MOSES system.[11]

Interventions

Patients will undergo CT simulation with both full and empty bladder scans after silver marker placement at the vaginal apex, and radiopaque marker at the introitus. Target delineation will follow the modified RTOG guidelines, using the full bladder scan as the primary dataset.[12,13] Organs at risk are contoured as per standard contouring. Patients will receive hypofractionated EBRT to a dose of 39 Gy in 13 fractions over 2.5-3 weeks, i.e. 3Gy per fraction using IMRT with daily image guidance. Concurrent weekly cisplatin is delivered when indicated in patients with cervical cancer. The dose volume parameters used for PARCER-II are enlisted in Table 2. The proposed dose volume constraints evolved from observations within PARCER study and the long-term gastro-intestinal adverse event data.[6] In the PARCER study, conventional dose fractionation of 50Gy in 25 fractions, at 2Gy per fraction was deployed. For PARCER-II, bowel dose volume parameters for PARCER treatment plans of patients developing grade ≥2 adverse events were evaluated for V15, V30 and V40. The EQD2 dose and volume parameter derived from the PARCER study for late effects for bowel was then converted to iso-effective doses and volumes for PARCER-II dose-fractionation. For PARCER-II, the bowel V12 Gy is considered <800 cc not exceeding 1000 cc, and V30 Gy is <200 cc, not exceeding 250 cc. In conventional dose-fractionation of 2Gy, these correspond to V15 and V40 Gy. The dose constraints for rectum, bladder are D_{max} of <105%. For femoral heads, the dose constraints are D_{max} <100%, and the D_{mean} <12 Gy (Table 2).

After completing EBRT, vaginal brachytherapy (2 fractions of 6 Gy HDR) is planned based on histopathological risk features if present. These include involvement of cervix or vagina or parametrium, or in case of unknown vaginal cut margin. Brachytherapy target includes the upper one-third of the vagina and delivered with single channel BT applicator.

Patients will be followed every 3 months for 2 years, then every 6 months up to 5 years, and annually thereafter. Toxicities are recorded using CTCAE v5.0, with special focus on GI, GU, vaginal, hematologic, and miscellaneous adverse events. Quality of life will be assessed using EORTC QLQ-C30 and CX24/EN24 forms in multiple languages. For patients with recurrence, salvage treatment will be administered as per institutional practice, but further adverse events or QoL data will not be collected.

Sample size

Patients treated with IG-IMRT in PARCER trial were reported to have cumulative incidence of late grade ≥2 gastrointestinal or genitourinary adverse events of 25.5%.[6] Present study is intended to include endometrial and cervical cancer patients. We hypothesized that protocol of abbreviated hypofractionated adjuvant radiation for post-operative cervical and endometrial tumours would be considered unacceptable if the three-year cumulative incidence of late GI or GU adverse events were inferior by 7% or more as compared to PARCER trial results. The primary outcome was assessed at one sided α=0.2 and β=0.20 level. To assess cumulative incidence of late grade ≥2 adverse events, a total of 82 patients will be required. Considering 10% lost to follow-up, a total of 90 patients will be required.

Statistical methods

Kaplan-Meier method will be used to estimate the 3 years grade ≥2 gastrointestinal or genitourinary adverse events and the CI will be calculated by Greenwood's formula. If the upper limit of the 80% CI is lower than the threshold value of 32%, non-inferiority is confirmed and hypofractionated adjuvant radiation will be an option for standard of care in post-operative cervical and endometrial tumours. Quality of life data will be filled by the patient EORTC QLQ-C30 and CX-24 or EN-24. For analysis of QoL, patients who have filled pre radiation questionnaire and at least 1 follow-up questionnaire will be eligible. No QoL scoring will be performed for patients after any relapse. For each QOL domain, score changes will be compared over time. For QOL analysis, liner mixed model will be used which would estimate fixed effects of time and treatment and a treatment-by-time interaction. A significant treatment effect indicates a constant difference in QOL score. A significant treatment-by-time interaction effect suggests that the effect of treatment on the QOL level differs significantly over time. Exploratory analysis will be performed to assess the type of missing data, and it will be treated as missing at random. The results of linear mixed models analysis will be expressed as estimated fixed effects beta (slope), 95% CI, and corresponding p value. Month and severity score (MOSES) will be calculated for each

symptom (13 gastrointestinal and 6 genitourinary) with CTCAE adverse events and time spent in each adverse event. Cumulative-MOSES score will be assessed for organ system (gastrointestinal and genitourinary), by summating MOSES of individual adverse event items respectively.

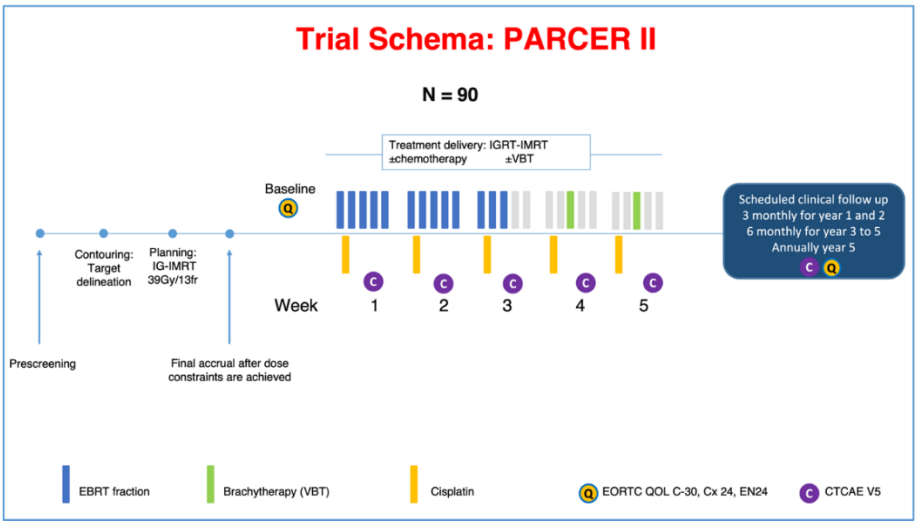

Figure 1: Trial schema-PARCER II.

Table 1: Target and organs at risk delineation.

Target volume	Description
V_FB	Vagina full bladder in full bladder scan
CTV_FB	Clinical target volume (tumour bed) in full bladder scan
V_EB	Vagina empty bladder in empty bladder scan
CTV_EB	Clinical target volume (tumour bed) in empty bladder scan
ITV	Internal target volume-generated by performing union of CTV_FB and CTV_EB
PTV_P	Planned target volume_primary (Tumour bed) after generating a margin of 7 mm around ITV.
CTV_E	Clinical target volume_elective (Elective nodal volume)
PTV_E	Planned target volume_elective (Elective nodal volume) after generating a margin of 5 mm around CTV_E.
PTV_39/13	Combining PTV_P and PTV_E

Table 2: Dose constraints for PARCER II.

	Dose constraints	
Target	PTV_39/13	V95% >95% D_{max}<107% Conformity index <1.10
Organs at risk	Bowel	D_{max} <105% V 12 Gy <800 cc (soft constraint) and not more than 1000 cc (hard constraint) V 30 Gy <200 cc (soft constraint) and in no case more than 250 cc (hard constraint)
	Rectum	D_{max}<105%
	Bladder	D_{max}<105%
	Kidney	D_{mean}<9Gy
	Femoral heads	D_{max}<39Gy D_{mean}<12 Gy

DISCUSSION

PARCER-II explores the feasibility and safety of hypofractionated adjuvant radiotherapy in patients with cervical and endometrial cancers. Hypofractionation offers the potential advantages of the improved patient convenience, optimized use of the radiotherapy resources, and reduced treatment time, but its adoption has been limited due to lack of robust data on late adverse events and oncologic outcomes. Our findings will contribute to a growing body of evidence suggesting that hypofractionated schedules may provide comparable efficacy with acceptable adverse events profiles.

Evidence from prior prospective trials supports this approach. The POHIM-RT study, a phase II multicenter trial, demonstrated that hypofractionated IMRT (40 Gy in 16 fractions) was well tolerated in cervical cancer patients following radical hysterectomy, with a very low incidence of severe acute toxicities (1.6%) and no late grade ≥3 events after a median follow-up of more than three years. Importantly, disease control remained favorable, with a 3-year DFS of 87.1%, highlighting that change in fractionation did not compromise oncologic outcomes.[8] Similarly, the POHIM-CCRT trial extended these findings to high-risk patients receiving concurrent chemoradiotherapy. Acute grade ≥3 gastrointestinal, genitourinary, or hematologic toxicities were observed in only 2.5% of patients, with encouraging survival outcomes (3-year DFS 79.3%, OS 98.0%).[9] These results reinforce the safety and potential efficacy of hypofractionated schedules, even in high-risk postoperative settings. In endometrial cancer, the SPARTACUS trial further demonstrated the feasibility of more hypofractionated regimens, delivering 30 Gy in 5 fractions. It included 61 patients, of which 16 also received sequential chemotherapy. The median follow up in the study was 9 months. Despite the intensified fractionation, adverse events remained limited, with only one patient experiencing grade III gastrointestinal adverse events and the majority reporting only mild to moderate adverse events.[10] Longer follow up results are required to understand the evolution of late adverse events in these patients. Ongoing research continues to test hypofractionated regimens in different clinical scenarios. Long term outcomes published by Gandhi et al used hypofractionated radiation in locally advanced cervical cancer (LACC) to a dose of 40 Gy in 15 fractions along with concurrent chemotherapy and BT. At a median follow up of 45.8 months, the late grade 2 and 3 GI adverse events was observed in 10% and 6% patients respectively.[14] The HYPO-iRex Trial was a phase II randomized control trial in LACC evaluating hypofractionated RT (44Gy/20 fractions) to normofractionated RT (45Gy in 25 fractions) with concurrent chemotherapy and BT that reported on early outcomes. At a median follow up of 19 months, the trial reported grade ≥3 GI adverse events of 21.2% and 14.4% respectively, and no grade >3 GU adverse events.[15] The HEROICC trial (NCT04583254) is directly comparing standard chemoradiation with hypofractionated chemoradiation in LACC. This randomized study is expected to provide robust data on both tolerability and cancer control, as well as feasibility of wider adoption in routine practice.

The major limitation of our study is that while we are evaluating late effects of hypofractionated RT in cervical and endometrial tumours, many patients with endometrial tumours who warrant adjuvant RT also warrant adjuvant systemic chemotherapy. Utilization of systemic chemotherapy is an exclusion criterion for our study as we intended to keep our cohort homogenous and understand radiotherapy effects and then proceed to including all patients. While preliminary data on moderate hypofractionation is now available for feasibility and acute toxicity, we chose to yet continue with a study with moderate rather than extreme hypofractionation as limited long term data is yet available for moderate hypofractionation.

CONCLUSION

The study aims to further enhance understanding of the late effects associated with hypofractionated radiation. If found to be safe, it will pave way for change in adjuvant RT fractionation for postoperative RT.

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Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee Tata Memorial Centre (IEC/3910/2022/00004, dated October 10, 2022).

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