All India Institute of Medical Sciences (AIIMS), New Delhi
National Cancer Institute-AIIMS Badsa, Jhajjar
RESEARCH PROPOSAL

1. Title of the project:

A prospective study to evaluate the role of HPV-ctDNA as a predictive and prognostic marker in locally advanced cervical cancer.

2. Introduction

Cervical cancer is the second most common cancer in Indian women. 123907 new cases were diagnosed in 2020, accounting for 18.3% of all new cancer cases in Indian females. It's also responsible for the second highest cancer mortality in India, precisely 77348 as per GLOBOCAN India 2020 data. The 5-year survival rate for carcinoma (Ca) cervix reported from India is approximately 54.5% compared to 60-79% in more developed countries like China and South Korea. Various cancer registries in India have reported that the 5-year overall survival(OS) rates range from 34.5% to 59.6%.
The lack of widespread and readily accessible screening and paucity of HPV vaccination coverage are among the major reasons for the high prevalence of the disease. In India, most cervical cancer patients present at a locally advanced stage leading to poor outcomes.

Given the burden of problem with unsatisfactory outcomes with the current standard of care, there is an unmet need in low-middle-income countries (LMICs), where the majority of cervical cancer cases occur, to devise treatment strategies to improve survival in locally advanced Ca cervix. To improve outcomes, it is crucial to identify patients at high risk of relapse and intensify their treatment, therefore predictive and prognostic biomarkers are needed.

As most cases of cervical cancer are caused by high-risk Human papillomavirus (HPV), it allows us to use HPV cell-free tumour DNA (ctDNA) as a possible marker.

Various retrospective and prospective studies, albeit with a small sample size have demonstrated the relationship of persistent HPV-ctDNA after treatment to an increased risk of relapse.

However, no study to date, to our knowledge has tried correlating the effect of escalation of treatment to HPV-ctDNA levels and progression-free survival (PFS) outcomes.

Moreover, genomics data from cervical cancer is readiy available from the USA, Europe and China. The genomics data in Cervical cancer is scarce with only a few studies reporting on very few samples.

Through this prospective study, we want to explore the effect of consolidation chemotherapy in locally advanced cervical cancer on HPV-ctDNA levels and event-free survival (EFS).

The genomics and transcriptomic analysis will help us identify genomic signatures predicting poor prognosis in Indian patients and find newer targets for testing newer therapies for these

patients. It will also help us identify the unique genomic alterations specific to Indian population compared to what has been reported worldwide.

3. Objectives

Primary Objective

1. To evaluate the correlation of HPVctDNA with event-free survival.

Secondary Objectives

1. To correlate the change of serial ctDNA measurements during treatment with disease recurrence in locally advanced cervical cancer.
2. To correlate the 6-month HPV-ctDNA status with 18f-FDG whole-body PET-CT as a predictor for relapse/recurrence.

Exploratory Objectives

1. To compare the PFS and OS in HPV ctDNA positive patients between patients receiving consolidation chemotherapy v/s observation.
2. To compare the PFS and OS in HPV-ctDNA negative patients between patients receiving chemotherapy v/s observation.

4. Importance of the project:

A prospective study from Canada validated HPVctDNA as a biomarker to predict progression-free survival (PFS) in 70 cervical cancer patients (stage IB to IVa). The study found that patients with persistent detectable HPVctDNA had significantly worse 2-year PFS (82% vs. 24%, P < .001).

However, no clinical study has yet tested the efficacy of using HPVctDNA to measure the utility of consolidation chemotherapy in locally advanced cervical cancer. As part of another phase II randomised controlled trial (RCT), we are testing consolidation chemotherapy in patients with locally advanced cervical cancer (stage III-IVa)- (CERCO – CErvical cancer - Role of COnsolidation chemo).

We will use their blood samples for HPVctDNA estimation at the time of randomisation and 6 months and use this data to find a correlation between HPV-ctDNA as a biomarker to predict PFS and whether consolidation chemotherapy affected outcome compared to observation alone in HPV ctDNA positive patients.

We will also explore the following comparisons-

a). PFS between patients randomised to consolidation chemotherapy with positive and negative HPVctDNA

b). PFS between patients randomised to observation with positive and negative HPVctDNA.

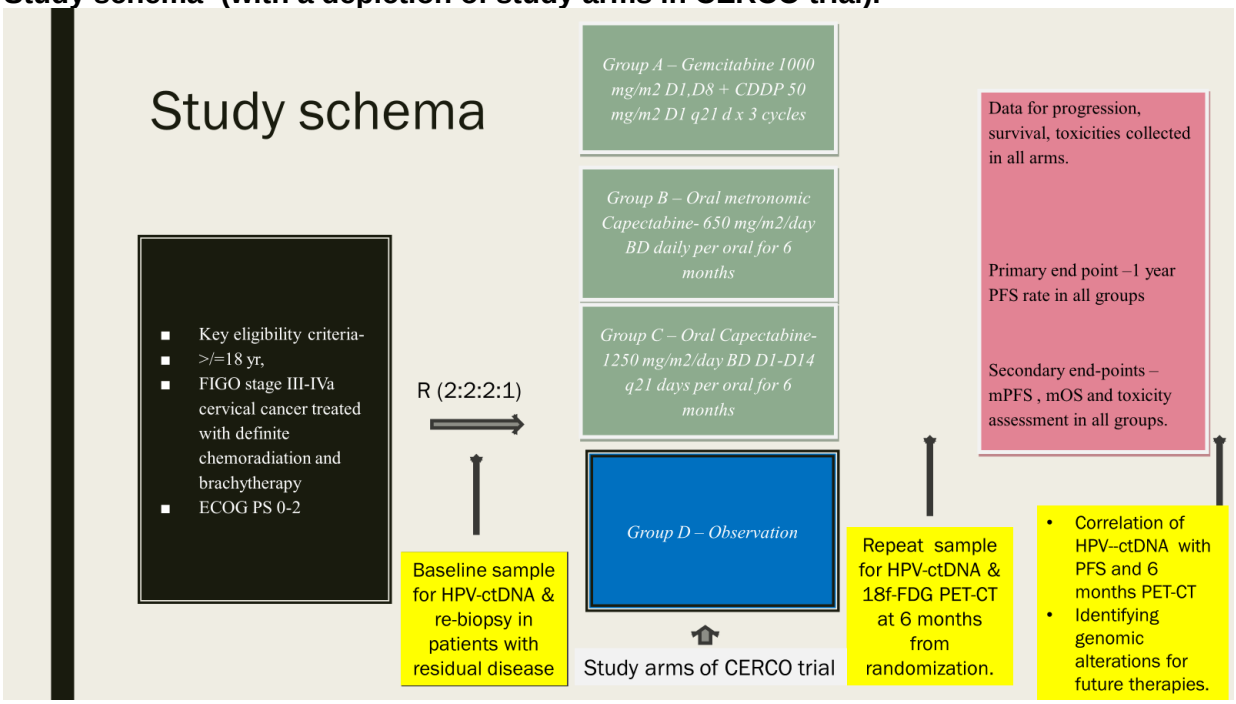
This will be hypothesis-generating to help us identify whether escalation of therapy might improve outcomes in an otherwise poor-prognostic group.

If we observe a significant difference, then this approach will be tested in a phase III trial for both treatment escalation and de-escalation strategies using precision medicine.

This approach will not only improve survival in poor-risk patients but also focus on minimizing toxicities in patients with good oncological outcomes.

5. Work Plan -

Study schema- (with a depiction of study arms in CERCO trial).



- Blood samples from patients enrolled in the CERCO trial will be collected at baseline (at the time of randomisation) and at 6 months from randomisation.
- HPV-ctDNA estimation will be performed at baseline and 6 months using PCR-based assays for E6/E7 oncogenes of HPV.
- A fresh biopsy will be obtained in patients with residual disease at the time of screening for randomisation for transcriptomic/ genomics studies and transferred to CSIR-IGIB along with a paired blood sample (normal control tissue).
- One time 18f-FDG PET-CT will be done at 6 months.
- Patients enrolled in the CERCO study will be followed up as per the trial protocol for PFS and OS.
- Upon maturation of data-

  1). The correlation will be tested between changes in 6-month HPV-ctDNA levels from baseline with PFS and OS.

  2). The correlation will be tested between HPV-ctDNA positive/negative status with PET-CT
  positive/negative status at 6 months.

  3). Correlation of a single-time PET-CT at 6 months with PFS and OS.

4). As exploratory analyses (hypothesis generating)-

PFS and OS will be compared in the following arms -

- Positive HPV-ctDNA at baseline - consolidation chemo v/s Observation
- Negative HPV -ctDNA at baseline - consolidation chemo v/s observation.
- Patients receiving consolidation chemo - Positive v/s negative HPV-ctDNA at baseline
- Patients in observation arms - Positive v/s negative HPV-ctDNA at baseline.

PICOT

Patients - Locally advanced cervical cancer patients (stage III-IVa) enrolled in the CERCO trial

Inclusion criteria (CERCO trial)

- Patients aged 18 years or older
- histologically confirmed carcinoma of the cervix (International Federation of Gynecology and Obstetrics [FIGO] stage IIIA - IVA disease) treated with definite chemoradiation and brachytherapy.
- Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0–2
- Adequate bone marrow and organ function. (Hb >/=8 g.dl, ANC >/=1000/mm3, Platelet count >/= 1lakh/mm3, AST/ALT within three times of ULN, GFR >/= 50 ml/min)
- If history of previous cardiac comorbidity, LVEF of >/=50% by MUGA/ 2D-ECHO.
- Literate enough/ mentally sound to be able to give informed consent.

Exclusion criteria (CERCO trial)

- Progressive disease on chemoradiation
- Could not receive/ complete chemoradiation
- Patients with bilateral hydronephrosis unless at least one side has been stented and renal function fulfils the required inclusion criteria.
- Previous chemotherapy other that concurrent CDDP with pelvic EBRT
- Evidence of distant metastases
- Peripheral neuropathy >/= grade 2 (CTCAE v4.0)
- Patients with other invasive cancers, who had (or have) any evidence of the other cancer present within the last 2 years except skin cancer.
- Serious illness or medical condition that precludes the safe administration of the trial treatment
- HIV positive patients not on HAART.
- CDDP ineligible (eGFR by Cockcroft gault formula </= 50ml/min even after indicated intervention for HDUN/obstructive uropathy, in patients with history of any cardiac comorbidity left ventricular ejection fraction </=50%, any evidence of sensorineural hearing loss >/=grade 2 as per CTCAE v4.0).
- Psychiatric illness/ blindness which precludes informed consent.

Intervention arms - (CERCO trial)

- Arm A: (Intervention arm 1) 3 cycles of adjuvant Gem-CDDP (Gemcitabine 1000 mg/m2, D1 and CDDP 50 mg/m2 D1 q21 days)
- Arm b: (Intervention arm 2) - Oral metronomic Capecitabine- 650 mg/m2/day BD daily per oral for 6 months
- Arm C: (Intervention arm 3) - Oral Capecitabine- 1250 mg/m2/day BD D1-D14 q21 days per oral for 6 months.

Control arm

- Calibration arm (Observation)

Outcome:

Primary Outcome

- To correlate HPV ctDNA at baseline and 6 months with 1 year PFS rate for patients enrolled in CERCO trial

Secondary Outcomes

- To correlate the change of serial ctDNA measurements during treatment with disease recurrence in locally advanced cervical cancer.
- To correlate the 6-month HPV-ctDNA status with 18f-FDG whole-body PET-CT as a predictor for relapse/recurrence.

Exploratory Outcomes

- To compare the PFS and OS in HPV ctDNA positive patients between patients receiving consolidation chemotherapy v/s observation.
- To compare the PFS and OS in HPV-ctDNA negative patients between patients receiving chemotherapy v/s observation.

Time-point

- 1 year from enrollment of last patient in CERCO trial

6. Expected outcome/endpoints:

This study will be hypothesis-generating for future testing in trials for the following end-points-

a). Can HPV-ctDNA be used as a biomarker to predict progression-free survival for designing treatment escalation/de-escalation trials in locally advanced cervical cancer patients?

b). Does HPV-ctDNA status (positive or negative) correlate with 18f FDG- PET positive/negative status and can PET be used as a surrogate for the same?

c). Is there any utility of doing a single time-point PET-CT in locally advanced cervical cancer patients to tailor surveillance and follow-up after treatment completion?

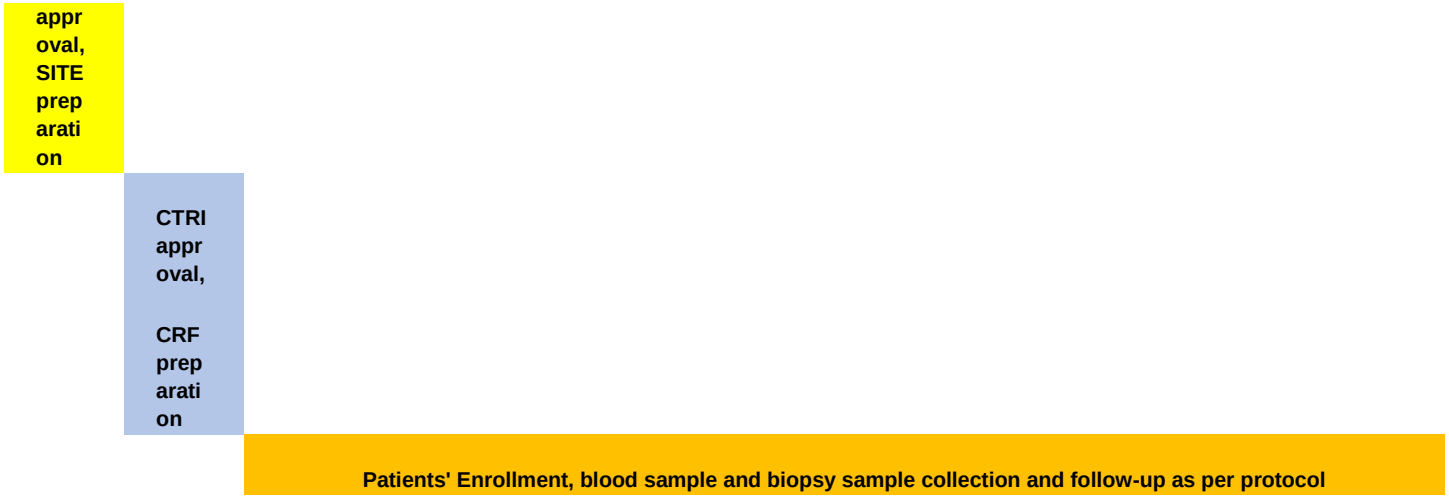
d). What are the genomic signatures predicting response /resistance to treatment? Can different treatment approaches/ newer targeted therapies be tried to improve outcomes in such patients?

7. Timelines: 6 months will be used as part of the fellowship for HPVctDNA processing and data analysis

Year 1												
Months	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12
	Funding secured, IRB											

We are currently at month 3 for CERCO trial.

As part of Sun pharma Research fellowship, Month 12-18 of CERCO trial will be used for samples processing and testing for HPV ctDNA levels in stored samples.



Year 2	0-1	1-2	2-3	3-4	4-5	5-6	6-7	7-8	8-9	9-10	10-11	11-12