









PARa-aOrtic LymphAdenectomy in locally advanced cervical cancer (PAROLA trial): a GINECO, ENGOT, and GCIG study

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Accepted 16 December 2022
Published Online First
30 January 2023

ABSTRACT

Background Positron emission tomography/computed tomography (PET/CT) fails to detect approximately 25% of aortic lymph node metastasis in patients with PET/CT stage IIIC1 cervical cancer. Surgical staging could lead to treatment modification and to improved para-aortic and distant control.

Primary Objective(s) To demonstrate if chemoradiation with tailored external beam radiation field based on surgical staging and pathologic examination of the para-aortic lymph node is associated with improved 3-year disease-free survival compared with patients staged with PET/CT staging only.

Study Hypothesis Surgical staging followed by tailored chemoradiation will improve disease-free survival while avoiding unnecessary prophylactic extended-field chemoradiation in patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC1 cervical cancer.

Trial Design This is an international multicenter, randomized, phase III study. Eligible patients will be randomized 1:1 between PET/CT staging followed by chemoradiation (control arm), or surgical staging followed by tailored chemo-radiation (experimental arm). Randomization will be stratified by tumor stage according to TNM classification, center, and adjuvant treatment.

Major Inclusion/Exclusion Criteria Main inclusion criteria are histologically proven PET/CT FIGO stage IIIC1 cervical cancer. Main exclusion criteria include unequivocal positive common iliac or para-aortic lymph node at pre-therapeutic imaging PET/CT.

Primary Endpoint(s) The primary endpoint is disease-free survival defined as the time from randomization until first relapse (local, regional, or distant), or death from any cause.

Sample Size 510 eligible patients

Estimated Dates for Completing Accrual and Presenting Results The estimated date for completing accrual will be Q2 2027. The estimated date for presenting results will be Q4 2030.

Trial Registration Number NCT05581121.

INTRODUCTION

Background

Worldwide, cervical cancer is one of the most common malignant diseases. Although cervical cancer is often curable if detected early, more than one third of patients present with locally advanced disease at diagnosis (stages IB3-IVA).¹ Para-aortic lymph node status is the most important prognostic factor in patients with locally advanced cervical cancer, and plays an important role in extra-abdominal lymph node and metastatic spread. The 5-year survival rate of patients with para-aortic lymph node metastasis remains below 40%, with a majority of patients presenting with distant failure.^{2,3} Lymph node extension to the para-aortic area is a key point for the therapeutic strategy since it defines the extension of radiation fields and allows for treatment intensification. In the Retro-EMBRACE cohort of 731 patients, 30% experienced treatment failure. Of these, 9% were located in the para-aortic lymph nodes, and 24% were systemic and para-aortic lymph nodes. The study concluded a need to optimize the treatment strategy to eradicate micro-metastasis in para-aortic lymph nodes and distant organs.⁴ An EMBRACE analysis on nodal failures demonstrated that pathological nodes at diagnosis are mainly located in the pelvis, while nodal failures are more often in the para-aortic lymph node. In the 11% of patients who have a nodal relapse, 68% are para-aortic lymph nodes.⁵ A recent review including 850 patients from three randomized controlled trials concluded that prophylactic extended field chemoradiation significantly reduces para-aortic lymph node recurrence, distant failure, and overall survival.⁶ A bicentric retrospective study including 198 patients with International Federation of Gynecology and Obstetrics (FIGO) stage IIIC1 cervical cancer showed improved 5-year cancer-specific survival and para-aortic lymph node recurrence-free survival in patients with common iliac lymph nodes and three or more pelvic positive lymph nodes treated with prophylactic



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To cite: Martinez A, Lecuru F, Bizzarri N, *et al.* *Int J Gynecol Cancer* 2023;**33**:293–298.

Clinical trial

extended field chemo-radiotherapy.^{7,8} One approach might be to prescribe extended field irradiation to all patients with radiologic findings of pelvic lymph node spread. However, extended-field irradiation is associated with increased incidence and persistence of high grade toxicity in the EORTC, RTOG, and CTAC studies.^{9–11} The high morbidity rates of extended-field chemoradiation associated with conventional radiotherapy reported in these trials have been largely reduced since the use of intensity modulated radiation therapy (IMRT) extended-field chemoradiation, with toxicity rates ranging from 4–10%.^{8,12,13} Reported high grade toxicity is even similar to pelvic chemo-radiation therapy (CRT) in several studies.^{7,12} However, there is still a lack of prospective data with IMRT extended-field chemo-radiation, there are different inclusion criteria in these studies, and there is still no consensus on delineation and dose prescription of IMRT extended-field chemoradiation.⁶

International guidelines differ in staging modalities to assess para-aortic lymph node status in locally advanced disease cervical cancer.¹⁴ 18-Fluorine fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) is the most accurate imaging exam to assess para-aortic lymph node involvement. However, PET/CT underestimates para-aortic lymph node metastasis, and fails to detect small volume disease <5 mm and between 10–15% of cases with aortic lymph node involvement, that will remain undertreated.¹⁵ Pelvic lymph node metastasis is the most important factor associated with extension to the para-aortic lymph nodes. Indeed, PET/CT false-negative results in the para-aortic area have been recorded in <5% of patients without pelvic lymph node involvement, and in 20–30% of patients with pelvic lymph node uptake.^{16–18} For this reason, the European Society of Gynaecologic Oncology (ESGO) and National Cancer Comprehensive Network (NCCN) guidelines consider para-aortic lymph node dissection as an option for staging purposes in patients with positive pelvic nodes and negative para-aortic lymph nodes on pre-treatment FDG-PET/CT.^{19,20} In contrast, prophylactic extended-field chemoradiation may be considered to overcome the PET/CT false negative rate in para-aortic lymph nodes. The latter option could result in overtreatment and unnecessary toxicity in approximately 75% of patients with positive pelvic lymph nodes and negative para-aortic lymph nodes on pre-treatment PET/CT.

Rationale

The survival benefit of surgical staging has been assessed in several retrospective and prospective studies with controversial results.¹⁵ Some studies suggest that survival benefit of surgical staging is associated with removal of small volume disease. Several studies report similar survival data between patients with negative para-aortic lymph nodes and metastatic para-aortic lymph nodes <5 mm in diameter after surgical staging and tailored extended-field chemoradiation.^{16,21} Gold et al performed a post-hoc analysis of three randomized trials from the Gynecologic Oncology Group (GOG) evaluating different chemoradiation strategies.²² Even if patients in the radiological staging group had less advanced disease, smaller tumor size, and better performance status, disease-free and overall survival were significantly improved in the surgical staging group in multivariate analysis. There were also more para-aortic and extra-pelvic recurrences in the radiologically staged group. Methodology of this study was limited by a possible selection bias due to a combination of randomized arms from three different trials.

There are two available randomized phase III trials comparing radiologic to surgical staging in locally advanced disease cervical cancer. The study performed by Lai et al was the first to address this question 20 years ago.²³ A total of 61 patients were randomized to surgical or clinical staging using CT imaging. This study was closed prematurely due to survival differences favoring the clinical staging arm. This study has been largely criticized because of an imbalance between both study arms: patients in the surgical arm had more advanced disease with more stage III-IV and more >6 cm tumors, more unfavorable histology, and less frequent CRT. Finally, two patients with para-aortic lymph node involvement did not receive extended field radiotherapy, and the eight deaths in the surgical group were not related to disease progression but to treatment related complications. High grade toxicity was also reported in >40% of patients. The second randomized phase III study is the recent UTERUS 11 trial performed by the AGO group.³ This study included 240 patients with stage IIB-IVA locally advanced disease cervical cancer and negative para-aortic nodes on pre-treatment CT imaging. Authors found a non-significant 10% increase in disease-free survival, the primary endpoint, in favor of surgical staging. In an ad-hoc analysis, authors reported that surgical staging led to a significant increase in cancer-specific survival, and a significant disease-free survival benefit in patients with stage IIB. Importantly, surgical staging was not associated with a significant increase in delay to chemo-radiation and peri-operative complications were only reported in 7.3% of patients. This trial has been criticized by its methodology, mainly by the sample size population calculation, which can explain the uncertain conclusions.²⁴

The rationale of surgical staging is based on treatment modification of patients with positive pelvic nodes and occult para-aortic lymph node metastasis on pre-treatment PET/CT imaging to improve para-aortic and distant control.

Hypothesis

Current diagnostic tools underestimate a wide range of patients with microscopic and macroscopic para-aortic lymph node involvement.²⁵ We hypothesize that surgical staging followed by tailored chemoradiation will improve disease-free survival while avoiding unnecessary prophylactic extended-field chemoradiation in patients with stage IIIC1 cervical cancer.

METHODS

Trial Design

This is an international multicenter, randomized, phase III study which aims to demonstrate that tailored CRT based on surgical staging and pathologic examination of the para-aortic lymph nodes is associated with increased disease-free survival compared with patients staged with PET/CT only without surgical staging. Secondary objectives include overall survival, metastasis and para-aortic free survival, quality of life, morbidity, evaluation of infra-mesenteric and infrarenal lymph node metastasis rate, survival in patients with small volume para-aortic lymph node disease, and cost-utility analysis. Ancillary studies will include radiomics, biologic, and the SENTI-PAROLA ancillary study, to evaluate the feasibility and accuracy of the para-aortic sentinel lymph node approach.

Table 1 Inclusion and exclusion criteria

Key eligibility criteria	
	Newly diagnosed histologically proven cervical squamous carcinoma, adenocarcinoma, or adenosquamous tumor
	HPV associated tumors (p16+ on IHC or HPV+ test)
	FIGO stage IIIC1 cervical cancer with PET/CT showing FDG-positive pelvic nodes and FDG-negative para-aortic lymph node. The highest positive lymph node must be located inferior to the common iliac bifurcation
	Patients with FIGO stage IIIC1 by positive pelvic sentinel lymph node and FDG-negative common iliac of para-aortic lymph node on PET/CT (performed before or after SLN procedure)
	Patient eligible for pelvic radiotherapy and cisplatin-based chemotherapy with a curative intent as confirmed by a multidisciplinary board
	Age ≥ 18 years at time of study entry
	ECOG performance status < 2 , ie, 0 or 1
	Non-menopausal women should be willing to accept the use an effective contraceptive regimen or have a negative pregnancy test within 72 hours prior to registration
	Patient is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow-up
	PET/CT images should be available for central review
Inclusion criteria	Patients participating in other clinical trials including immunotherapy strategies or additional chemotherapy are also eligible for the study
Exclusion criteria	Unequivocal positive common iliac or para-aortic lymph node at pretherapeutic imaging PET/CT
	Presence of distant metastatic disease
	Other histology than adenocarcinoma, squamous cell carcinoma, and adenosquamous carcinoma
	Women who received any prior treatment for cervical cancer
	Prior surgery for the cervical cancer, except for cone procedure and pelvic lymph node staging
	Previous pelvic radiotherapy
	History of another primary malignancy except for: malignancy treated with curative intent and with no known active disease after 5 years, adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease, adequately treated carcinoma <i>in situ</i> (any location) without evidence of disease.

ECOG, Eastern Cooperative Oncology Group; FDG, fluorodeoxyglucose; FIGO, International Federation of Gynecology and Obstetrics ; HPV, human papillomavirus; IHC, immunohistochemistry; PET/CT, positron emission tomography/computed tomography; SLN, sentinel lymph node.

All eligible patients will be equally randomized between the two following treatment groups.

Control Arm

Standard chemo-radiotherapy and brachytherapy will be conducted according to EMBRACE II and the European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology (ESGO/ESTRO) guidelines. Patients with ≥ 3 positive pelvic lymph nodes will have prophylactic para-aortic chemoradiation.

Experimental Arm

Pre-therapeutic para-aortic lymphadenectomy followed by tailored chemo-radiotherapy and brachytherapy will be undertaken according to EMBRACE II and ESGO/ESTRO guidelines. Pre-therapeutic lymphadenectomy will be performed no later than 3 weeks after PET/CT via the laparoscopic extraperitoneal or transperitoneal approach using either traditional laparoscopy or robotically-assisted laparoscopy. Lymph node dissection will be performed from the common iliac bifurcation to at least the

inferior mesenteric artery, according to international recommendations. Lympho-fatty tissue from and including the common iliac vessels, the aorta, aorto-caval space, and the vena cava will be completely removed to at least the level of the inferior mesenteric artery. Chemo-radiation will start 7 to 10 days after surgery and a maximum 3 weeks after surgical staging.

Exploratory Cohort for Equivocal Lymph Nodes

Patients with equivocal common iliac or para-aortic lymph nodes will be included in an exploratory cohort and treated with surgical staging followed by tailored chemo-radiation.

The PAROLA (PARA-aOrtic LymphAdenectomy in locally advanced cervical cancer) trial has been funded by the French National Cancer Institute, Program Hospitalier de Recherche Clinique Cancer (PHRC-K PHRC-22–161). The trial is also supported by ARCAGY-GINECO, Swiss GO, BGOG (Belgium and Luxembourg Gynaecological Oncology Group), ENGOT (European Network of Gynaecological Oncological Trial groups), GCGI (Gynecological Cancer InterGroup),

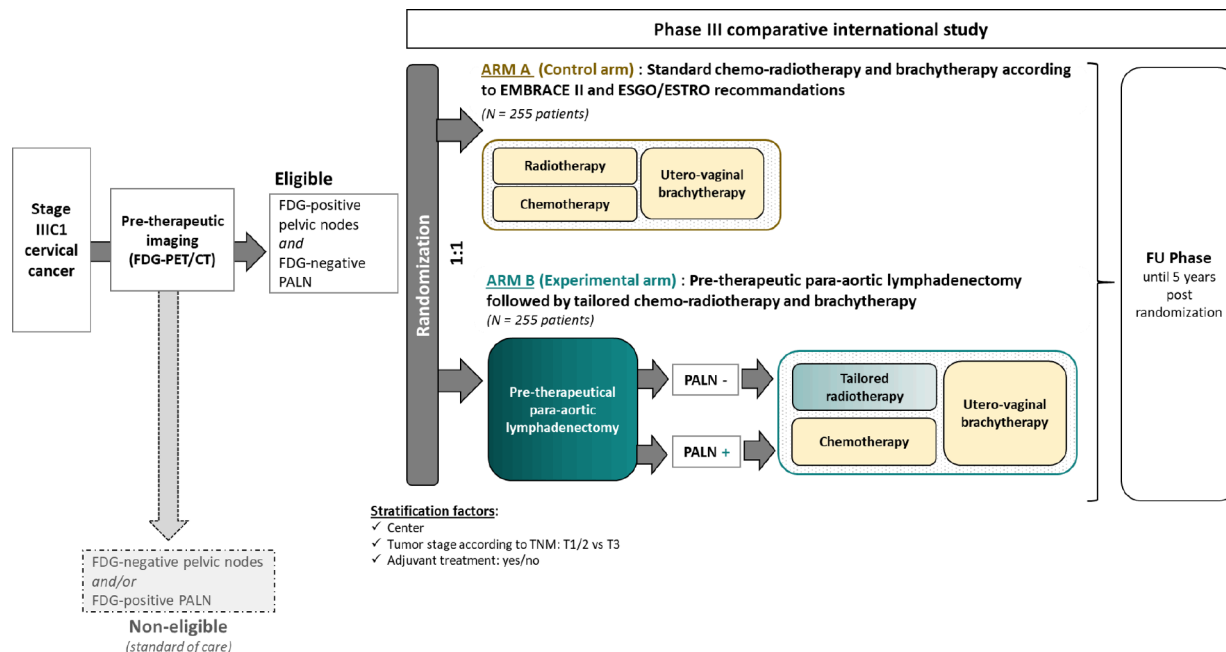


Figure 1 Trial design and randomization scheme. ESGO, European Society of Gynaecologic Oncology; ESTRO, European Society for Radiotherapy and Oncology; FDG, fluorodeoxyglucose; FU, follow-up; PALN, para-aortic lymph node; PET/CT, positron emission tomography/computed tomography.

MITO (Multicenter Italian Trials in Ovarian Cancer and gynecological malignancies) and GEICO (Grupo Español de Investigación en Cáncer de Ovario) cooperative groups.

Participants

Main inclusion criteria are histologically proven PET/CT FIGO stage IIIC1 cervical cancer. Main exclusion criteria include unequivocal positive common iliac or para-aortic lymph node at pretherapeutic imaging PET/CT. Detailed inclusion and exclusion criteria are summarized in Table 1.

Outcomes

The primary endpoint is disease-free survival, defined as the time from randomization until first relapse (local, regional, or distant) or death from any cause. Patients still alive at the time of analysis without documented event (including lost to follow-up) will be censored at the last valid disease assessment. Secondary endpoints include overall survival, cancer specific-survival, metastasis-free survival, surgical and radiation morbidities, quality of life, and cost analyses.

Sample Size

PAROLA is a superiority trial powered to detect an improvement in 3-year disease-free survival from 60% to 70%. This study hypothesis corresponds to detect a hazard ratio of 0.70. A total of 257 events is necessary for 80% power to detect this difference if it is true, using a one-sided log rank test at the 2.5% significance level and a 1:1 randomization. Based on an estimated accrual rate of approximately 10 patients per month for the randomization of 510 patients and a fixed follow-up of 5 years by patient, we can expect to see this number of events 100 months after the start of the study.

Interim Analyses and Stopping Guidelines

An interim analysis for both futility (O'Brien-Fleming boundary) and efficacy (O'Brien-Fleming boundary) will be performed after observation of 129 events. An independent data monitoring committee will review the pre-planned interim analyses (futility and efficacy).

Randomization and Blinding

After verification of eligibility criteria, patients will be randomized by surgical or clinical staging in a 1:1 ratio (Figure 1). Randomization will be centrally processed by the IUCT-Oncopole clinical trials office using the TENALEA Clinical Trial Data Management System (online secure internet). Randomization will be stratified by tumor stage according to TNM classification (T1/2 vs T3), center, and adjuvant treatment (yes/no). Treatment allocation will be performed using the minimization method.

Statistical Methods

The primary endpoint will be analyzed on the intention-to-treat population when the required number of events has been reached. For each arm, disease-free survival rates will be estimated using the Kaplan-Meier method. The primary endpoint analysis will be a Cox regression analysis adjusted on stratification factors with 97.5% confidence intervals (one-sided). Planned subgroup analysis will be performed according to surgical extension (infra-mesenteric or infra-renal), T stage, number of pelvic lymph nodes, size of para-aortic lymph node metastasis, and specific populations (elderly, obese).

DISCUSSION

The role of para-aortic lymph node surgical staging in locally advanced disease cervical cancer remains debatable. Several retrospective, prospective, and two phase III trials show conflicting

results. However, the two phase III trials have several methodological flaws which limit their conclusions. The UTERUS-11 study showed a non-significant 10% increase in disease-free survival in patients with surgical staging; the main limitation of that study was the sample size calculation. The authors estimated a 5-year disease-free survival of 36.5% in the control arm which is lower than that reported on recent studies of chemo-radiation. Five-year disease-free survival is probably around 55–60%, as it finally resulted in this study and in other recent randomized phase III trials.^{3 26 27} The authors also estimated that surgical staging would improve 5-year disease-free survival from 36.5% to 55%, which is excessive, when considering the survival increase of adding chemotherapy to radiotherapy.²⁶ Finally, the UTERUS-11 study was underpowered. UTERUS-11 included patients with both positive and negative pelvic lymph nodes. Pelvic extension is the main factor correlated with para-aortic extension. In the PAROLA trial only patients with FIGO stage IIIC1, at high risk of para-aortic lymph node disease, will be included. UTERUS-11 also performed clinical staging with CT, which is less accurate than PET/CT.²⁸

The key question remains as to whether surgical staging followed by tailored CRT can improve survival in patients with a high risk of para-aortic lymph node extension. We therefore propose a clinical trial with an adequate sample size and realistic hypotheses that will be performed thanks to a large national and international collaborative effort. Our proposal addresses patients with a high risk of para-aortic lymph node spread—patients with stage IIIC1 on pre-treatment PET/CT. The control arm will be treated following EMBRACE II and ESGO/ESTRO recommendations.²⁹ This study aims to answer definitively the controversy between proponents and opponents of surgical staging.

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Contributors All authors made the appropriate contributions, carefully compiling and analyzing data, reading the manuscript and giving their full approval. AM accepts full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

Funding This study was funded by French National Cancer Institute (Grant number: PHRC-22-161).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval Not applicable.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement No data are available.

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