Instituto de Investigación Sanitaria La Fe	**Application report:** **Own research project**	FPR-IIS -029-02 Version: 05

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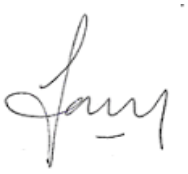
APPLICATION REPORT: OWN RESEARCH PROJECT[1]

Project title: "*Retrospective Study on the Assessment of the Use of **U**terine **M**obilisers in **E**arly-Stage* **E***ndometrial **C**ancer: **MUCEI study***".

Principal Investigator's details:
Name and surname(s): Pablo Padilla Iserte
Research group: Gynaecology Oncology Unit. HUP La Fe

Valencia, 28 January 2019



Pablo Padilla Iserte

Signature of Principal Investigator

[1] Template for submitting basic-clinical research projects (not equivalent to clinical trials), on the initiative of the research groups at IIS La Fe.

RESEARCH TEAM THAT WILL CONDUCT THE PROJECT

	Name and surname	ID Number	Have you submitted your updated SCV (current year) to IIS La Fe? *
Principal Investigator	Raquel Quintana Bertó		X YES ☐ NO
Members of the research team	Santiago Domingo del Pozo		x YES ☐ NO
	Víctor Lago Leal		X YES ☐ NO
	Luís Matute Tobías		X YES ☐ NO
	Pablo Padilla Iserte		X YES ☐ NO
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* IIS La Fe will file the SCVs (standardised curriculum vitae) of the researchers to facilitate the registration of new projects; however, in order to guarantee the validity of the information, the researcher must submit an updated SCV every calendar year.

If you have **NOT attached your SCV before**, you must send it together with this document.

Please fill in the following information if this is the FIRST research project submitted to IIS La Fe for **any of the members of the team**:

PROJECT EXECUTIVE SUMMARY
(maximum 1 page, background/justification, hypothesis/objectives and methodology):

Background/Justification

Endometrial cancer is the most common gynaecological neoplasm in developed countries, accounting for 6% of all cancers in women. It is usually diagnosed in early stages, with disease confined to the uterine cavity (67% of cases).

The typical approach is laparoscopic surgery, with bilateral tubal occlusion as the first surgical procedure, followed by hysterectomy with double adnexectomy as the primary treatment, supported by the use of a uterine manipulator to facilitate the intervention. The need for surgical staging is set out in the ESMO-ESGO-ESTRO consensus, based on data from the preoperative assessment, histological type and baseline status of the patient.

The uterine manipulator or mobiliser is a device inserted via the vagina into the uterus, which allows better mobilisation of the uterus during surgery. At present, there is still some controversy about the use of the manipulator in gynaecological oncology surgeries as it has not been shown to have a worse oncological outcome and it is believed that, hypothetically, there could be a seeding of tumour cells in the lymphovascular space and in the abdomino-pelvic cavity if used.

Hypotheses/Objectives

It has been demonstrated that the insertion of the uterine manipulator puts positive pressure on the endometrial cavity, facilitating a hypothetical passage of tumour cells to the peritoneal cavity through the tubes, without worsening the oncological prognosis. In turn, it is not unusual for the uterus to rupture during surgical manoeuvres using the manipulator, creating a solution of continuity between the tumour and the pelvis, usually confined to the uterine cavity, with exposure of the tumour during surgery.

The main objective of this study is to retrospectively assess two groups of patients: patients who underwent surgery for apparent early-stage endometrial neoplasia by preoperative imaging study in which a uterine manipulator was used and a second group in which uterine manipulation was not used (surgery with a swab or a cup for colpotomy), also assessing the approach route. Thus, the rate of local, locoregional and distant relapses in these patients will be recorded retrospectively and linked to the use or non-use of a uterine manipulator during surgery.

Secondarily, risk factors contraindicating the use of the uterine mobiliser, such as histology, tumour size, lymphovascular infiltration, myometrial infiltration as well as adjuvant therapy (chemotherapy, external radiotherapy, brachytherapy) will also be assessed.

The final objective of this study is to assess, retrospectively, a wide range of patients who underwent surgery for endometrial neoplasia, in order to correlate the safety of the use of the uterine manipulator and the route

of approach. The aim is to cover all histologies (both endometrial and myometrial oncological pathology) to find if there are any pre-surgical factors that may contraindicate the use of the uterine manipulator. To do this, data will be gathered retrospectively:

- preoperative data: age, ECOG, comorbidities, type of diagnosis, histological type.
- intraoperative data: type of surgery, approach route, uterine manipulator (type), surgical time
- anatomical pathology data: histological type and grade, tumour size, lymphovascular space infiltration, myometrial infiltration, number of lymph nodes extracted
- final staging according to FIGO 2009, categorised as IA, IB, II, IIIA, IIIB, IIIC1 and IIIC2.
- adjuvant treatment: Radiotherapy (external RT, brachytherapy), CTX
- relapse data: time elapsed, type of relapse, treatment given
- obtaining PFS and OS

Methodology

A retrospective multicentre study will be conducted to review all patients who underwent surgery for apparent early-stage endometrial neoplasia, classified on the basis of whether or not a uterine mobiliser was used. Analysing the pre-surgical characteristics of the patient, the surgical procedure, histological data, lymph node involvement if surgical staging had been done, adjuvant treatment, relapses (PFS) and treatment, relapse rate and overall survival (OS).

BACKGROUND AND STATE OF THE ART
(Including bibliography, maximum 2 pages)**:**

Endometrial cancer is the most common gynaecological neoplasm in developed countries, accounting for 6% of all cancers in women. It is a typical menopausal pathology (average age 62 years), with an increasing incidence due to longer life expectancy and the increase in obesity among the western population. The most common diagnosis is in the early stages (67% of cases).

Treatment in the early stages is surgical - unless the patient presents a contraindication due to pathology associated with high surgical risk - and the need for adjuvant treatments will be determined by the risk factors determined in the definitive study of the surgical specimen.

Surgical staging proposed by the 2009 FIGO classification includes total hysterectomy with double adnexectomy, pelvic and aorto-caval lymphadenectomy, when required.

As there is no standard definition of the initial stages of endometrial cancer, tumours limited to the uterus or with locoregional extension in the preoperative study will be considered in this study, being susceptible to

primary surgical treatment without the need for surgical techniques that exceed those recommended in the staging: stages I and II. In relation to stage III, both stages classified as III due to microscopic involvement after histological study will be included: IIIA (involvement of serosa and/or adnexa), IIIB (vaginal and/or parametrial involvement) and IIIC1 (pelvic lymph node involvement) and IIIC2 (para-aortic lymph node involvement). An attempt will be made to find a correlation between advanced stages, uterine manipulator and relapse rates, as there is no published data on this type of tumour, in order to assess whether the relapse rate in this group using a uterine manipulator is different, for example, due to the fact of having lymph node involvement.

The use of the uterine manipulator in endometrial cancer surgery is currently in question despite the fact that several studies and meta-analyses conducted by various study groups have shown no evidence of worse oncological outcome.

With the recent publication of the first data from the *LACC* (Locally advanced cancer of the cervix) phase III study, which questions not only the use of the manipulator in hysterectomies for cervical cancer, but also the type of approach (laparotomy *vs* laparoscopy), the use of these devices has also been called into question in other types of gynaecological cancers such as, in this case, endometrial cancer. The main hypothesis is that the positive pressure in the uterine cavity created by the manipulator would lead to a seeding of tumour cells towards the peritoneum and the lymphovascular space, which would lead to a worse oncological outcome and a higher hypothetical rate of locoregional relapse. Currently, however, it has not been established whether such seeding worsens the oncological prognosis in patients. We will use this retrospective study to assess the safety of the approach.

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WORKING HYPOTHESIS

The insertion of the uterine manipulator causes a positive pressure on the endometrial cavity which, hypothetically, would facilitate the passage of tumour cells into the peritoneal cavity through the tubes. In other words, it would contribute to the spread of the disease to other regions thanks to the access of these cells to other intra-abdominal organs. It is also associated with a higher rate of uterine rupture during its use, breaking uterine integrity, exposing tumour cells to the pelvic cavity and/or vagina.

Despite all this, a review of the current literature has failed to demonstrate a worse oncological outcome resulting from the use or non-use of the uterine manipulator.

Therefore, the hypothesis of the project would be to assess by means of a retrospective and multicentre study whether there is indeed a worse oncological outcome in centres that use the uterine manipulator in endometrial cancer surgery compared to others that do not use it. In turn, the recurrence pattern would be assessed to determine whether there are any differences between the approach and the uterine manipulator.

SPECIFIC OBJECTIVES OF THE PROPOSED RESEARCH

PRIMARY Objective

1.- To retrospectively assess the rate of: local, locoregional and distant relapses in patients who have received primary surgical treatment for endometrial cancer, relating it to whether or not a uterine manipulator was used, the approach route, histology, type of surgery and the adjuvant treatment performed.

SECONDARY Objectives

1.- To assess the influence of possible risk factors contraindicating the use of the uterine mobiliser.

2.- To conduct an epidemiological study of the pre-surgical characteristics of women with endometrial cancer.

3.- To collect and analyse the characteristics of the surgical procedure, the histological data and the adjuvant treatment received.

4.- To calculate the relapse rate, disease-free survival and overall survival of these patients, as well as relapse treatment.

RATIONALE FOR INTEREST OF THE PROPOSED RESEARCH (maximum 1 page):

Endometrial cancer has a significant prevalence in our society. It is the most common gynaecological tumour in developed countries (6% of all cancers in women); in Spain more than 5,000 cases were diagnosed in 2018 (SEOM data). Moreover, in recent years, the incidence has increased considerably, partly due to the increase in life expectancy of the population (it is a neoplasm that typically occurs in women during the menopause) and associated risk factors (obesity).

The surgical staging proposed by FIGO includes total hysterectomy with double adnexectomy, pelvic lymphadenectomy and aorto-caval lymphadenectomy, if required. For this, the standard approach is laparoscopic as it shows advantages over the laparotomic approach: shorter hospital stay, better cosmetic results, less need for strong opioid analgesics after the operation, etc. One of the disadvantages of laparoscopy is the increased surgical time required to complete the procedure, which is why uterine mobilisers are sometimes used to make this task easier and to reduce surgical time.

The use of a mobiliser for uterine manipulation continues to be a topic of discussion among gynaecological oncology surgeons. Many advocate the use of the mobiliser on the grounds that it improves exposure of the anatomical planes and therefore allows for a more effective, safer and quicker surgery. However, for others, the use of this technique is not justified due to the risk of seeding of malignant cells and the possibility of invasion of other extrauterine structures, which would increase the stage of the disease and, therefore, lead to a worse oncological outcome.

The spread of tumour cells with positive peritoneal fluid cytology has now been demonstrated; however, a worse oncological outcome has not been demonstrated. In fact, the clinical significance of finding a positive peritoneal fluid cytology in endometrial cancer confined to the uterus is controversial to date.

The main interest of this project is to assess whether the use of the uterine manipulator has worse oncological outcomes than not using it in the surgical treatment of endometrial cancer and, therefore, whether or not it may be feasible to use it with a level of evidence on this multicentre retrospective basis (without being surgeon-dependent).

METHODOLOGY:

Please indicate all relevant items one by one according to the type of project.

a) Study design:

An observational, retrospective, non-randomised, descriptive and analytical multicentre study in which we will study the characteristics of the patients, the details associated with surgery and their survival according to whether or not a uterine manipulator was used.

b) Context:

This project will be conducted in the gynaecological oncology unit at Hospital Universitari i Politècnic La Fe; this unit has extensive experience in the management of endometrial cancer as well as the laparoscopic surgical approach without the use of a uterine manipulator.

Other centres with the same experience in the follow-up of these patients, both those which use a uterine manipulator for surgery and those which do not, will also participate in the study.

Data collection by the Principal Investigator using an electronic system (Excel, Access), following the guidelines and compliance with the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on Data Protection (GDPR) and Organic Law 3/2018 of 5 December on the Protection of Personal Data and Guarantee of Digital Rights.

c) Participants:

Method of patient selection and follow-up.

All patients over 18 years of age who underwent the surgery for apparent early-stage endometrial cancer proposed by FIGO: total hysterectomy with double adnexectomy, pelvic lymphadenectomy and aorto-caval lymphadenectomy, when required. Retrospective follow-up by collecting the necessary information as described above.

Inclusion criteria

1.- Women with endometrial cancer diagnosed at an apparent early stage in the preoperative study, including stages I, II and III after histological study.

2.- Previous pre-surgical biopsy with a diagnosis of endometrial cancer or high suspicion of oncological pathology at myometrial and/or endometrial level.

3.- Surgery has been performed and complete data on surgery, pathological anatomy and follow-up are on record.

4.- Follow-up for at least 2 years after surgery.

Exclusion criteria

1.- Women with advanced stage endometrial cancer (evidence of extrauterine pathology and extensive cervical involvement).

2.- Vaginal use.

3.-No follow-up data or loss of the patient

4-. Follow-up period under 2 years

d) Variables *(define all variables, response, exposures, predictors, confounders and effect modifiers and if applicable provide diagnostic criteria)*

An Excel template of variables to be collected in this study is attached (password HUG2015): **APPENDIX I**

Patient demographic data (age, BMI, comorbidities). Oncological data (tumour size, histological type and grade). Surgical data (surgery time, approach, use of uterine manipulator, procedures). Intraoperative complications. Adjuvant treatment (RT and modality, CTX). Follow-up. Relapse (type of relapse, treatment), with calculation of PFS and OS.

e) Biases derived from variables

The biases inherent in a retrospective study and the handler used

f) Data sources/measurements *(for each variable, indicate data source and details of measurement methods. In case of more than one group, specify comparability of measurement processes).*

Collection of clinical history using the ORION CLINIC or MIZAR (Luna) programme from the list of patients provided by the Documentation Service of all patients diagnosed from 2009-2016 with: Endometrial cancer, endometrial neoplasia, staging surgery.

The researchers undertake to treat all data with confidentiality in accordance with the provisions of Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on Data Protection (GDPR) and Organic Law 3/2018 of 5 December on the Protection of Personal Data and Guarantee of Digital Rights. The investigator or designee will be responsible for accurately recording and verifying patient data. Patients included in the study will be identified only by a numerical code. The dissociation procedure will be carried out by the investigators participating in the study, who will compile a list linking the patients' personal data to the allocated code identifying the patient during the study.

Data generated during the study will be protected from unauthorised use by individuals not involved in the research and will therefore be considered strictly confidential. A file will be prepared containing the study documentation, which will be safeguarded by the researcher.

g) Sample size (also explain how it was calculated)

The estimated sample size, to achieve a 15% difference in disease-free survival between the two groups, with 95% power, 5% alpha error and 95% CI, and 10% loss, requires 526 per group, with a total of at least 1052 cases.

h) Statistical methods *(in the research protocol the investigators should at least identify in advance the analyses for the primary objectives of the study.).*

Statistical analysis will be conducted using the SPSS programme (version 20.0). A descriptive analysis of the data collected will be carried out. A non-parametric Friedmann's test will be performed to determine the homogeneity or linear trend of the categorical variable; a multivariate analysis will also be performed to minimise confounding bias. The significance level will be 5% and a 95% confidence interval will be considered. Proposed tables for statistical calculation are attached.

i) Schedule and work plan

The study will be conducted in accordance with the ethical principles that derive from the Declaration of Helsinki and the standards of Good Clinical Practice.

The study will begin upon approval by the current Committee.

- Data collection from this centre and others:

  April 2019 to August 2019 **.....5 months**

- Data analysis and manuscript preparation:

  September 2019 to December 2019 **.....3 months**

Expected publication of results January 2020

TITLE OF THE RESEARCH PROJECT:

*"Retrospective Study on the Assessment of the **U**se of **U**terine **M**obilisers in **E**arly-Stage **E**ndometrial **C**ancer: **MUCEI study***".

FINANCIAL REPORT

1. Cost that the undertaking of the project may entail *(provide details)*:

Data collection, statistical analysis, preparation of manuscript

2. Type of funding:

x Own funds: (*pre-existing amounts in other projects - active funds in the Foundation, donations and agreements).*

- Amount to be allocated to this project: 0 euros

☐ Other sources of funding (*to be formalised)*

Pablo Padilla Iserte

Signature of the Principal Investigator.