SENTINEL LYMPH NODE BIOPSY VS LYMPHADENECTOMY IN STAGE I ENDOMETRIOID ENDOMETRIAL CANCER WITH INTERMEDIATE / HIGH-INTERMEDIATE RISK

A MULTICENTRE RANDOMIZED CLINICAL TRIAL

DEGREE FINAL PROJECT

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Als meus tutors, per l'entrega i dedicació.

A la família, pel recolzament incondicional.

A l'amistat, per contribuir a fer-ho més fàcil.

Als pacients, raó i motor de la nostra professió.

A en Marc Saez, exemple de vocació i professionalitat.

A tot l'equip de Ginecologia i Obstetrícia, per l'acollida.

Stay afraid, but do it anyway.

What's important is the action.

You don't have to wait to be confident.

Just do it and eventually the confidence will follow.

- Carrie Fisher.

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1. ABBREVIATIONS

BMI	Body mass index
BSO	Bilateral salpingo-oophorectomy
BT	Brachytherapy
CT	Computed tomography
EC	Endometrial cancer
EEC	Endometrioid endometrial cancer
ESGO	European Society of Gynecologic Oncology
ESMO	European Society of Medical Oncology
ESTRO	European Society for Radiotherapy and Oncology
FACT-En, version 4	Functional Assessment of Cancer Therapy in Endometrial Cancer Version
FIGO	Federación Internacional de Ginecología y Obstetricia
Hb	Haemoglobin
H&E	Hematoxylin and eosin
IC	Informed consent
ICG	Indocyanine green
IHC	Immunohistochemistry
IQR	Interquartile range
ITC	Isolated tumor cell
LAD	Lymphadenectomy
LN	Lymph node
LVSI	Lymphovascular space invasion
MI	Myometrial invasion
MRI	Magnetic resonance imaging
RF	Risk factors
SD	Standard deviation
SEGO	Sociedad Española de Ginecología y Obstetricia
SLN	Sentinel lymph node
SLNB	Sentinel lymph node biopsy
TV	Transvaginal
US	Ultrasound
WHO	World Health Organization

2. ABSTRACT

BACKGROUND: Nowadays, in stage I endometrioid endometrial cancer (EEC) with intermediate / high-intermediate risk factors (RF), a pelvic and para-aortic lymphadenectomy (LAD) is still performed despite the low evidence for recommending, since not survival advantages have been certainly proofed, and morbidity is almost guaranteed. In this context, sentinel lymph node biopsy (SLNB) has emerged as a viable, more precise, potentially less morbid and with no difference in survival outcomes compared to LAD. However, no prospective randomized trials confirm that assumption.

OBJECTIVE: To compare 5-year disease-free survival (DFS) between SLNB and pelvic and para-aortic LAD in women undergoing stage I EEC with intermediate / high-intermediate RF.
Secondary endpoints are to compare 5-year cancer-specific survival, morbidity and the detection rate of metastatic lymph nodes (LNs) in both procedures (SLNB and complete LAD).

STUDY DESIGN: An independent, multicentre, randomized, controlled, single blinded, parallel grouped and non-inferiority clinical trial.

POPULATION: Women undergoing stage I EEC of intermediate / high-intermediate RF to whom a total hysterectomy with a bilateral salpingo-oophorectomy in a robotic laparoscopic approach will be performed.

MATERIAL AND METHODS: From January 2020 to January 2027, 768 women with stage I intermediate / high-intermediate risk EEC will undergo a SLNB with cervical injection of indocyanine green or a complete LAD at 6 academic centres of Catalonia and are going to be prospectively observed for 5 years to collect survival and morbidity rates, among others. DFS and cancer-specific survival rates will be analysed by Kaplan-Meier, log-rang test and Cox regression.

KEYWORDS: Endometrioid Endometrial Cancer; Intermediate / High-intermediate Risk Factors; Lymph Node; Sentinel Lymph Node; Pelvic and Para-aortic Lymphadenectomy; Robotic Laparoscopic Approach; Disease-Free Survival; Cancer-Specific Survival; Morbidity.

3. INTRODUCTION AND BACKGROUND

a) Presentation

Endometrial cancer (EC) is a malign cellular proliferation, which is formed in the layer of inner lining of the uterus (an organ of the female reproductive system, small and hollow, situated in the pelvis) *(Figure 1)* (1).

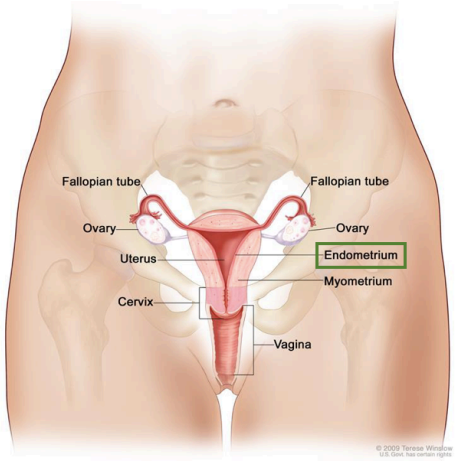

Figure 1: Anatomy of the female reproductive system (1).

Worldwide, there are approximately 320,999 cases of EC diagnosed annually (2,3). According to some data of the Oncology Director Plan of Catalonia, each year, 750 women are diagnosed of EC. In Europe, one or two of every 100 will develop EC at some point of their life (1).

In recent years, the incidence rate of EC has grown in a proportion of 1% yearly (4). Currently, EC is the most common malignant neoplasm of the gynecologic reproductive tract (4–7) and in Spain it is the second on mortality. However, at the moment of the diagnosis, approximately 75% of women have localized illness in the uterus (stage I or early stage) (1) and the high recovery rate with treatment in this stage and its survival rate in 5 years' time from 80 to 85% have created the false belief of dealing with a low-risk disease (1,4,5).

The EC is generally produced in women over 50 years old and, therefore, after the menopause (1,4). The anomalous genital bleeding is the main sign of suspicion that will lead us to dismiss EC by conducting a transvaginal (TV) ultrasound (US) *(Figure 2)* (4). Thus, we are able to measure the thickness of the endometrium. If it is major of 3 or 4 mm, we will obtain a sample doing a biopsy, as the diagnose confirmation of this tumour is determined by an histopathological exam (1,4).

Subsequently, a second histopathological exam will be executed, through the tumour exam removed by surgery (1).

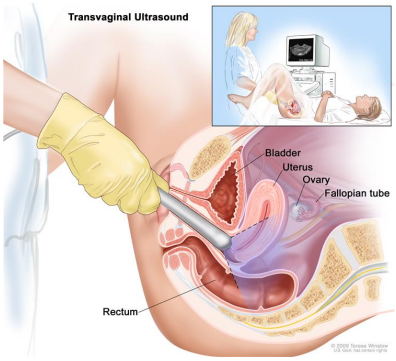

Figure 2: Transvaginal Ultrasound (8).

Nowadays, there is no reliable evidence of why EC is produced, but some risk factors (RF) that increases the probability of producing cancer in a future have been investigated (1). Projections show an increasing incidence of EC related to the ageing population, as well as the increasing prevalence of obesity and metabolic syndromes (3). Consequently, we can deduce that apart from age, obesity (defined as a body mass index > 30) is one of the most significant RF associated with the appearance of this disease (4). Other RF related to the incidence of EC are the exposure to oestrogens, familiar or genetic risk (Lynch II), the precedent of mama cancer, tamoxifen administration, mellitus diabetes, arterial hypertension, tardy menopause (52 or more years), sterility records or nulliparity (4).

When referring to EC, is important to feature that there are at least two types of tumours that differ from each other not only histologically, but also in its biology, prognostic and treatment (4):

- Type I is endometrioid adenocarcinoma (endometrioid endometrial cancer; EEC). It is hormonal dependant (related to oestrogens exposure) and developed by hyperplasia-carcinoma sequence. Generally, it possesses good prognosis and slow evolution.

- Type II has no relationship with oestrogens exposure; accordingly, there is no response to hormonal treatment. By definition, it consists on high grade tumours that correspond histologically with serous clear cell carcinoma and carcinosarcomas. They are more aggressive, mostly diagnosed in more advanced stages and have worse prognosis than type I.

From now on we will focus on the more prevalent type of EC, Type I (EEC), which typically is suffered by women over 50 years (in who the fertility preservation won't be taken in consideration as it would with younger women with strong genic desire).

The dissemination of EC, further to the uterus, arises in a direct form by the infiltration of the myometrium, for contiguity to the cervix and by using the lymphatic drainage, in the lymph nodes (LNs) (9).

LNs are little rounded organs that are involved in the lymphatic system *(Figure 3).* There are LN groups in the neck, axilla, chest, abdomen and groins. Inside the LNs and the lymphatic vases that connect them, flows a clear liquid called lymph (10). Lymphatic circulation can drain proteins and excess interstitial fluid back to the systemic circulation, regulate the immune responses by both cellular and humoral mechanisms, and absorb lipids from the intestine. In the physical circumstances, low amounts of fluid, filter into the interstitial tissues continuously, and are collected by blind-ended lymphatic capillaries back into the blood stream (11). Fatty acids less than 10 carbon atoms will be transported into the portal venous system directly, while fatty acids greater than 10 carbon atoms will be absorbed by lacteals and lymphatic capillaries of small intestine, forming chylomicrons. The mixture of lymph and chylomicrons is called chyle, which is milky white tint, odorless and strongly bacteriostatic due to the large number of lymphocytes (11).

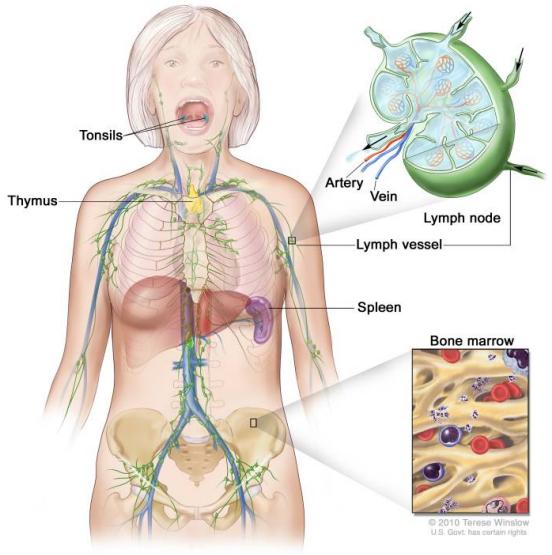

Figure 3: Anatomy of the lymph system showing the lymph vessels and lymph organs, including the lymph nodes, tonsils, thymus, spleen, and bone marrow. Lymph (clear fluid) and lymphocytes travel through the lymph vessels and into the lymph nodes where the lymphocytes destroy harmful substances. The lymph enters the blood through a large vein near the heart (12).

LNs are important parts of the body's immune system and are also important to help determine if cancer cells have acquired the ability to spread to other parts of the body, considering that many types of cancers spread through the lymphatic system, and one of the first sites of dissemination for these are nearby LNs (10).

Surgery is the mainstay of treatment for EC in initial stages (6,7,13) and total hysterectomy (where all the uterus is surgically removed, including the uterus cervix) with the removal of ovaries and Fallopian tubes (bilateral salpingo-oophorectomy; BSO) is considered the base of treatment *(Figure 4)* (4,6,13).

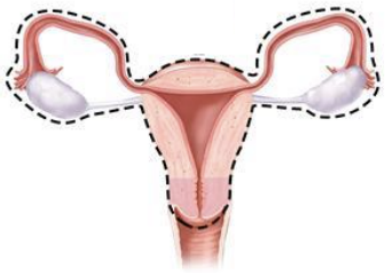

Figure 4: Total hysterectomy with bilateral salpingo-oophorectomy (1).

However, standard surgical staging has to consider the extent of the disease (5) and therefore, it has to include a LN assessment. Already in 1988, the International Federation of Gynaecology and Obstetrics (FIGO) established the need for the evaluation of LNs in every patient who undergoes surgery for a correct staging of EC, since in patients with stage I, LNs are the place where the tumour most frequently metastasizes (9). Nodal involvement is one of the most relevant prognostic factor (2,3,6,14,15) because the presence of compromised LNs is related to worse prognoses and decreased 5-year survival rates to 44 - 52% (5). Therefore, LN status is important to determine tumor stage and to consider which patients can benefit more from a post-surgery treatment (adjuvant radiotherapy, chemotherapy or both) (3,5,9,16).

b) Development

For many physicians, the detection of locoregional nodal metastasis is preferably performed by retroperitoneal LNs dissection (lymphadenectomy; LAD) of the pelvic and para-aortic region (5). However, the execution of LAD is under discussion (3,15–17) because recent studies demonstrated no therapeutic benefit of full LAD in patients with stage I EC (6,13,18).

This controversy is mainly due to the results of 2 independent, large, prospective, randomized and controlled trials that compare the addition of pelvic LAD versus hysterectomy and BSO alone and which failed to demonstrate survival benefits (13,19). They reported that the execution of LAD increase morbidity and worse peri-operative outcomes for patients, without impacting on long-term outcomes because did not improve disease-free survival (DFS) and overall survival, although the methodology of both studies has been criticized (3,7,16).

According to treatment guidelines and international consensus statements, a risk adopted management strategy (Table 1 and 2) is applied in the current clinical concept of EC (3):

- In patients classified as low risk for LNs involvement and recurrence, with a tumor confined to the uterus, no conspicuous intra-abdominal findings and absence of RF, the staging surgery includes a hysterectomy and BSO without LNs assessment.
- In cases of intermediate / high intermediate RF, the best practice remains controversial, resulting in the recommendation that LNs dissection may be performed or not.
- In patients with high RF, a systematic LNs dissection is recommended due to a higher prevalence of nodal involvement

Table 1: Risk groups according to ESMO-ESGO-ESTRO Consensus Conference (3).

	Grading	Histological type	Stage	LVSI
Low risk	G1, G2	Endometrioid	IA	Negative
Intermediate risk	G1, G2		IA	Positive
	G1, G2		IB	Negative
	G3		IA	Negative
High-intermediate risk	G3		IA	Positive
	G1, G2		IB	Positive
High risk	G3		IB	Negative/positive
	G3	Non-endometrioid	IA / B	Negative/positive
			II	Negative/positive

Stage I (early stage): IA = myometrial invasion < 50%; IB = myometrial invasion ≥ 50%

Stage II (advanced stage): = cervical involvement, LVSI = lymphovascular space invasion

Meaning of grading: G1 (well differentiated), G2 (moderately differentiated) and G3 (poorly differentiated).

ESMO: European Society of Medical Oncology, ESGO: European Society of Gynaecologic Oncology, ESTRO: European Society for Radiotherapy and Oncology.

From previous published studies, the American College of Obstetrics and Gynaecology advises that LAD may be dispensed in early-stages low risk patients (5). Moreover, almost all societies (including the Sociedad Española de Ginecología y Obstetricia, SEGO) agree that the recommendation to perform a LAD in early stages EEC at intermediate risk is of low evidence (4) and many studies aimed to suppress this systematic LAD (5,20–22).

Table 2: Risk groups for LNs metastasis and their recommended staging surgery according to (5).

	Cases	Definition	LNs metastasis	Surgery staging
Low risk	27%	Disease in an initial stage and up to 50% MI and G1	< 5%	It may be restricted to total hysterectomy and bilateral salpingo-oophorectomy.
Inter-mediate risk	50%	EEC with up to 50% MI and G2 or G3 (FIGO Stage IAG2 or IAG3), and tumors with deep MI (>50%) and G1 or G2 (FIGO Stage IBG1 or IBG2)	5% - 25%	Uncertain persists for this group in respect of the advantages and disadvantages of systematic LAD in the accuracy of definitive staging, as regards possible therapeutic outcome.
High risk	24%	> 50% MI and G3	25% - 40%	Systematic LAD of the pelvic and para-aortic region.

MI: myometrial infiltration. G: grade. EEC: endometrioid endometrial cancer. LAD: lymphadenectomy.
FIGO: Federación Internacional de Ginecología y Obstetricia

Years ago, LAD became the standard routine in patients with intermediate or high-risk EEC because it has been demonstrated that nearly a quarter of patients with disease clinically confined to the uterus had extra-uterine spread detected after surgical staging, with 11% having nodal disease (6). There are several studies that estimate LNs involvement in patients with stage I EEC and all of them comprise values from 5 to 18% (9,23,24). If myometrial infiltration is < 50% (stage IA), the risk of LNs metastasis decreases to 3 - 5% and if we count the LNs metastases that affect the para-aortic region exclusively, less than 3% of cases are found (19). Consequently, many women are subjected to an unnecessary full staging procedure (25) because most of patients who are subjected to the morbidity of pelvic and para-aortic LAD will not have LNs disease (24).

A pelvic LAD consists of the removal of adipose and lymphatic tissue around the iliac vessels (common, internal and external) bilaterally and in obturator fossa until visualization of the obturator nerve, while the para-aortic LAD comprised the removal of nodes from the aorta and the inferior vena cava to the level of the left renal vein (15).

Longer operative times are necessary if LAD is done and this can be associated with considerable short- and long-time morbidity (3). Moreover, LAD in particular increases postoperative complications, which are not uncommon (25). Furthermore, dissection becomes difficult with increasing obesity (15).

Lymphatic complications are well-known phenomena and have been described by many researchers. A literature search in PubMed was performed for studies of postoperative lymphatic complications and these were divided into lymphatic stasis (lymphedema) and lymphatic leakage (due to the injury of lymphatic channels in surgical procedures, such as lymphorrhea, lymph ascites, lymphocele, chylorrhea, chylous ascites...) *(Figure 5)* (11).

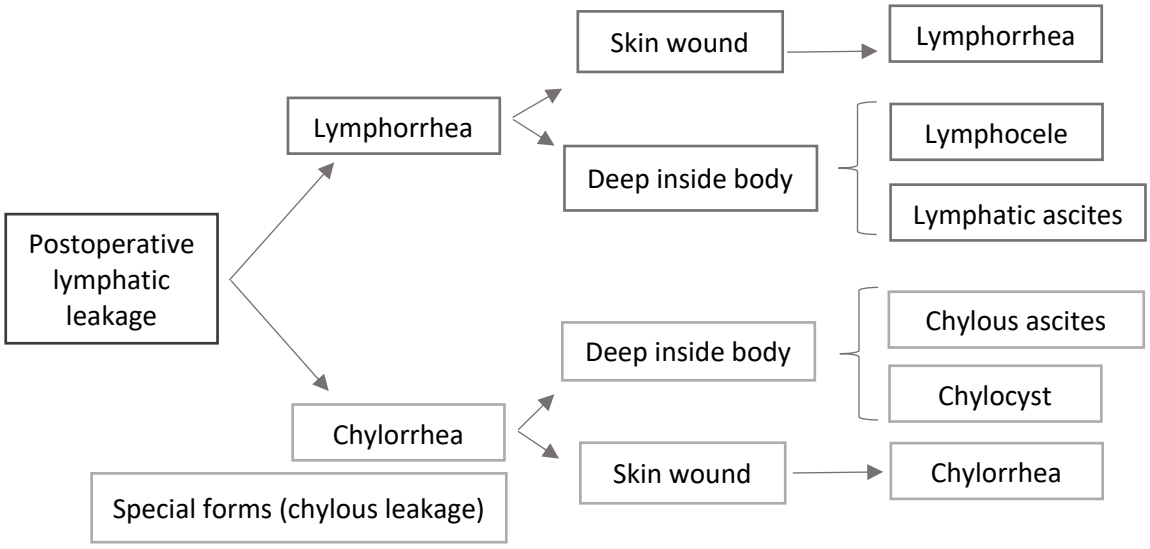

Figure 5: Classification of postoperative lymphatic leakage adapt from (11).

We are going to define some of them to depict a comprehensive view of postoperative complications of LNs dissections:

On the one hand, lymphorrhea is a lymphatic exudation after trauma of lymphatic vessels. Surgical transection of the lymphatics vessels during LAD results in inadequate closure of the lymph channels and continuous drainage of lymphatic fluid lead to lymphorrhea. Deep inside body, lymphorrhea will heal itself in most of the situations, but it also can turn into lymph ascites or lymphocele (11).

Lymphatic ascites is the accumulation of lymph fluid in the peritoneal cavity. Most of LAD lead to the leakage of lymphatic vessels, but they usually stop spontaneously without the consequence of symptomatic ascites. However, some % are symptomatic and require interventions eventually (11).

Lymphocele is a collection of lymph fluid with no inflammatory or granulomatous reaction at the leakage site. Often occurs within 3 – 8 weeks or occasionally 1 year after surgeries. Because of self-limiting, most of lymphoceles are usually asymptomatic, undiagnosed and self-healing without any treatments. However, a 4 – 7% of them are symptomatic due to self-absorption disorder (11).

Besides types of postoperative lymphatic leakage mentioned above, there are some special forms such as chylorrhea or chylous ascites. This classification depends on the following reasons (11):

1- Lymph fluid and chyle are distributed in different lymphatic vessels, that means they could remind of the different preliminary locations of the lymphatic channel leakages.

2- Lymph fluid is clear or straw-colored, similar to the serum of patients. Chyle (the mixture of lymph fluid and chylomicrons) is milky white tint, odorless and rich in triglycerides.

3- Since rich content of triglycerides, the loss of chyle is more likely to induce the nutritional deficiency, immunologic dysfunction or some other complications.

4- The treatments using medium-chain triglyceride diet, somatostatin analogue and so on are thought to be more effective for chylous leakage than for lymph leakage.

5- Compared with postoperative lymph fluid exudation, the drainage of milky white chyle will increase the fear, anxiety and other unhealthy emotion of patients and reduce the trust in their doctors according to clinical observation.

On the other hand, lymphedema is a condition in which protein-rich fluid accumulates in tissues and interstitial spaces due to a failure of lymphatic system, resulting with a volume change and a swelling of the limb (26). In addition, patients may feel pain or discomfort in the affected area and the skin that covers that area may become thick or hard. In addition, there is an increased risk of infection (12). Acquired lower-extremity lymphedema can occurs after external interruption of the lymphatic system when cutting the lymphatic vessels that arrive or leave a LN in the context of EC surgery (12). It can be developed from 6 to 8 weeks after a LAD or do it more slowly. The symptoms may not be noticeable for 18 or 24 months after treatment and sometimes it may take years to appear. Nevertheless, the course of this secondary disorder is often chronic (27).

The risk of leg lymphedema following a LNs dissection has been correlated with the number of LNs removed and it is under-reported with rates varying between 5% and 38%. The debilitating effects of lower limb lymphedema cannot, however, be underestimated since it has a marked effect on the quality of life of long-term survivors because can negatively impact a patient's quality of life physically, mentally, and sexually. From a recent comprehensive review of the literature, lymphedema associated with EC treatment can cause patients to have self-esteem issues, increased anxiety or fear about their disease (26).

Moreover, LAD can also cause vascular, nerve, ureteral and/or intestinal injury, increased blood loss and thromboembolic complications. (3,28). Vascular injuries can be severe complications which can even require conversion to laparotomy when major vessels are involved and they can be life-threatening (28).

Although the introduction of minimally invasive surgery minimizes the occurrence of lymphatic complications dramatically, they still represent a major health problem for patients having LAD (7).

Therefore, in the extent of EEC surgery we have to consider the potential risks and benefits of LAD (3,29):

- Potential risks include increased operative time, postoperative complications, hospital stay and costs.

- Potential benefits include the benefits of the knowledge about LNs involvement: assessment of prognostic factors, tailoring postoperative therapy, facilitating comparison of therapeutic modalities among different institutes and maybe prolonging survival.

c) Outcome

Setman *et al.* concluded that the noninvasive or the minimal invasive assessment of the LNs status to target specific LNs for sampling is more beneficial than complete LAD in EEC (14) and nowadays, there is a wide range of surgical staging practices in this cancer. The spectrum of LNs assessment may consist of sentinel lymph node (SLN) mapping, systematic pelvic or pelvic and para-aortic (full or complete) LAD (3).

SLN mapping or SLN biopsy (SLNB) represents a mid-way between the omission of LNs dissection and the full LAD (7,16), since it was introduced with the aim of decreasing the morbidity associated with LAD without negatively affecting surgical staging and outcomes (24).

SLN is the first node receiving lymphatic drainage from the primary tumor. It is where cancer cells are most likely to spread, and the pathological status of SLN would reflect the overall status of entire lymphatic basin (10,14–16).

SLNB is a procedure in which SLN is identified, removed (by a surgeon) and examined (by a pathologist) to determine if cancer cells are present (10).

- A negative result suggests that cancer has not acquired the ability to spread to nearby LNs or other organs.

- On the other hand, a positive result indicates that cancer is present in SLN, so it also could be found in other regional LNs.

To make a SLNB a surgeon injects a lymphotropic substance near the tumor to locate the position of the SLN (10). Multiple techniques have been reported and various compounds have been used, including blue dyes (i.e., isosulfan blue, patent blue, or methylene blue), indocyanine green (ICG), and technetium-99 (Tc99) either alone or in combination. The route of injection has also been described using various methods: cervical injection, hysteroscopic injection, and subserosal fundal injection either alone or jointly. However, it seems that to use ICG (characterized by a better safety profile in comparison with the others) and cervical injection at the 3- and 9-o'clock positions into the stroma and also submucosally is the most convenient, cost-effective and reproducible approach (6)(7).

Replacement of LAD by SLNB has reduced morbidity with the same diagnostic ability in other cancers. It can be surmised that in EC it would be the same and SLB is increasingly being utilized for EEC staging, although only limited evidence supporting the adoption of SLNB instead of LAD is still available (13).

However, SLNB is an accepted staging method for EEC. It is supported by prospective and retrospective studies that observed low false-negative rates (<5%) and high negative predictive values (> 95%) and approved by the National Comprehensive Cancer Network Guidelines (6,13,24,30).

The use of SLNB for the surgical staging of EEC has gained acceptance among gynecologists and has revolutionized the staging process in presumed early-stage disease, largely replacing systematic pelvic and paraaortic LAD in low risk and also high-risk EEC patients in some institutions (13).

A systematic search utilizing Medline, Web of Science and Embase databases was conducted by How *et al.* and concluded that the SLNB is a feasible and accurate alternative to stage patients with EEC (14).

In a recent metanalysis underlines that SLN is non-inferior to standard LAD in term of detection of paraaortic nodal involvement and recurrence rates; while, focusing on the ability to detect positive pelvic nodes, SLNB could be consider superior to LAD, increasing the detection of metastatic disease (17) via two mechanisms (30):

a) by direct visualization of SLN pathways that may not otherwise have been resected (i.e., pre-sacral and internal iliac sentinel nodes).

b) by enhanced pathology methods increasing detection of micro-metastasis and isolated tumor cells (ITCs), since a key component of SLNB is a technique called ultrastaging that consists of evaluation for the presence of micro-metastasis (tumor clusters > 0.2 - 2.0 mm) and ITCs (single tumor cells or tumor clusters ≤ 0.2 mm) by immunohistochemistry (IHC) in LNs that are negative at initial examination performed using classical hematoxylin-eosin (H&E) staining.

   So SLN algorithm may be more sensitive than pelvic LAD because it can detect additional microscopic metastases that would otherwise be missed by routine evaluations (13,17).

Therefore, contributions of SLNB in EEC could reside in the reduction of surgical morbidity compared with LAD, the detection of anomalous drainage and metastasis that would be unnoticed with conventional methods and in gaining important information on nodal involvement and consequently on prognosis to indicate or not adjuvant treatments (4,7,31).

Similar oncologic outcomes have been reported in retrospective comparative analyses between cohorts of patients undergoing full LAD versus SLNB in cases with low-risk pathologic features and also with high-risk histologic findings (24).

However, prospective randomized studies are needed in order to weigh pros and cons of SLNB widespread adoption (6,7,31).

4. JUSTIFICATION

Once introduced the subject, we can notice that although EC is a grave and prevalent disease, many questions are yet unsolved and need to be answered with a consensus.

One of those questions that has our special interest due to its huge morbid impact that brings on patients, is the current realisation of the pelvic and para-aortic LAD in stage I EEC with intermediate / high-intermediate RF notwithstanding disposing low evidence for recommending it and despite not having solid proofs of survival advantages (2,3,21,22,31,32,4,5,9,14–16,18,19).

It is widely known that LN metastasis are one of the most important prognostic factors in EC (2,3,6,14,15). However, it is worrisome that the role and extent of surgical LN assessment has been debated for over 30 years and is still controversial (6,7,13,16–19,21).

Surely, the key to the controversy is to agree upon a clinically practical, reproducible and reliable method of evaluating LN status to guide prognosis and adjuvant treatment while minimizing morbidity from a procedure that is probably unnecessary and not therapeutic itself (7,16,18,25).

We admit that all LNs surgery might cause adverse events. Nonetheless, we believe that some of those could be reduced or even avoided if we don't remove as many LNs as they are removed in LADs (10,26).

In this contexts, accumulated evidence underlined the safety and effectiveness of SLNB in EEC (7,13,25). This surgical technique has been recognized during the last decade as a less invasive procedure to accurately assess the state of LNs and is emerging as a viable, more precise and potentially less morbid alternative to LAD in the surgical staging of patients with EEC (2,6,7,14,16,25,31).

Although it seems logical, whether SLNB truly reduces the morbidity of surgical staging in EEC as it relates to avoidance of complete LAD is a very important clinical question that still has to be solved. More research into the overall complication rates of women undergoing SLN is needed (15,16).

Moreover, there are no conclusive prospective randomized trials confirming that there is no difference in EEC survival outcomes between SLNB alone vs complete LAD and this long term effectiveness of SLNB has to be assessed before replacing LAD (7,13,15,31).

Recently, 2 comparative studies between SLNB and LAD in EEC have been performed between 2 referral centers, the Mayo Clinic and the Memorial Sloan Kettering Cancer Centre, and these reported no difference in recurrence and death rates among groups. However, the retrospective nature of these studies and the limited follow-up periods limit the value of these findings, making necessary further prospective evaluations (7).

Despite this, oncology guides like SEGO, propose that the applicability of SLNB in EEC would achieve an improved staging (thanks to ultrastaging pathologic techniques previously mentioned) which could modify the adjuvant planification, having an impact in both, morbidity and survival (4).

Nonetheless, although many authors consider that SLNB may upturn survival rates, as we believe that it would imply an important diminution of morbidity, we contemplate the fact that, notwithstanding the same survival rate, it would be a more effective technique than the full LAD.

Having said that, we comprehend that it is desirable to perform a clinical trial which compares the impact of pelvic and para-aortic LAD with the SLNB's one considering the survival and morbidity in short and long periods of the patients undergoing EEC, clinically variables far more valuable in daily practice.

However, as addressing an oncologic process with high recovery and survival rates in treated initial stages matching the one we want to study, we consider that more than cancer-specific survival, clinical efficacy would reside in a low rate of EEC reappearance and, therefore, it is clinically more useful and convenient to focus this trial on 5-year disease-free survival rates.

And is for all the previously mentioned and a lot more that we have regarded the necessity of contemplating this protocol.

5. HYPOTHESIS

In women with stage I EEC with intermediate / high-intermediate risk factors, SLNB as compared to pelvic and para-aortic LAD will show a non-inferior clinical efficacy, but a lower rate of adverse events.

6. OBJECTIVES

a) Primary study objective

To compare 5-year disease-free survival rates between SLNB and pelvic and para-aortic LAD in women undergoing stage I EEC with intermediate / high-intermediate risk factors.

b) Secondary study objectives

- To compare 5-year cancer-specific survival rates between both LNs removal techniques (SLNB and complete LAD).

- To compare morbidity due to SLNB and due to full LAD.

- To compare metastatic LNs detection rate in both LNs assessment procedures.

7. MATERIAL AND METHODS

7.1. STUDY DESIGN

An independent, multicentre, randomized, controlled, single blinded, parallel grouped and non-inferiority **clinical trial.**

7.2. STUDY POPULATION

Women undergoing stage I EEC of intermediate / high-intermediate RF to whom a total hysterectomy with a BSO in a robotic laparoscopic approach will be performed.

a) Inclusion criteria (all fulfilled)

- Age 18 years and older at the time of informed consent.
- Ability to understand and sign an informed consent in Spanish or Catalan.
- Stage I EEC with intermediate / high-intermediate RF since preoperative histopathological exam of the endometrial biopsy suggests EEC with intermediate / high-intermediate RF and image tests (TV US, computerized tomography (CT) and magnetic resonance imaging (MRI)) conclude stage I, as no locally advanced disease or intra-abdominal/distant metastases are seen.
- Patient candidate for surgical treatment according to operability criteria (no general surgical contraindication as a coagulation problem or a serious liver disease).
- Total hysterectomy and BSO planned with a robotic laparoscopic approach.

b) Exclusion criteria (none fulfilled)

- Non-consenting patients.
- Inability to understand written and/or oral study information.
- History of pelvic and / or abdominal irradiation.
- Pregnancy.
- Patients who could not attend follow-up appointments.
- Age > 85 years and World Health Organization (WHO) performance status II or more *(Table 3).*
- WHO performance status III or more.
- Body mass index (BMI) > 40 kg/m2.
- Surgical contraindication to a laparoscopic approach or LAD at surgeon's discretion.
- Anesthesiologic contraindication to a laparoscopic approach at the anesthetist's discretion.
- Pre-existing lower limb lymphoedema grade II or more *(Table 4).*

Table 3: WHO performance status score (33).

Grade	Explanation of activity
0	Asymptomatic (fully active, able to carry on all pre-disease activities without restriction).
1	Symptomatic but completely ambulatory (restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature; for example, light housework, office work).
2	Symptomatic, < 50% in bed during the day (ambulatory and capable of all self-care but unable to carry out any work activities; up and about more than 50% of waking hours).
3	Symptomatic, > 50% in bed, but not bedbound (capable of only limited self-care, confined to bed or chair 50% or more of waking hours).
4	Bedbound (completely disabled, cannot carry on any self-care, totally confined to bed or chair).
5	Death

Table 4: International Society of Lymphology (ISL) Lymphedema Scale adapted from (34) *and* (35)*.*

Stage of lymphedema	Definition
Stage 0 (sub-clinical or latent)	Impaired lymph transport. Asymptomatic; there are no visible changes, but patients may notice a difference in feeling, such as a mild tingling, unusual tiredness, or slight heaviness. Edema is usually not detectable until interstitial volume is approximately 30% above normal.
Stage 1 (early/mild)	The limb appears mildly swollen as the protein-rich fluid starts to accumulate. Edema may be present intermittently, resolve without treatment. It is considered reversible because the skin and tissues haven't been permanently damaged. When you elevate the arm, for example, the swelling resolves. Little or no pitting: when you press the skin, a temporary small dent (or pit) could forms. Little or no limb distortion: 2-3 cm difference in limb circumference. Complaints of feeling of tightness, heaviness, fullness or stiffness. Able to tolerate compression garments.
Stage 2 (moderate; requiring compression)	The affected area is even more swollen. Elevating the arm or other area doesn't help and pressing on the skin does not leave a pit (non-pitting edema). Some changes to the tissue under the skin are happening, such as inflammation, hardening, or thickening. This stage can be managed with treatment, but any tissue damage can't be reversed. ▪ **Early:** 3-5 cm difference in limb circumference. Skin may be shiny, stretched, fragile. Significant limb distortion. May have difficulty buttoning sleeves, fitting into shoes. Unable to tolerate compression garment. Pitting of tissue for up to 20 minutes following gentle pressure. Positive Stemmer's sign. ▪ **Late:** Swelling not relieved by elevation. Non-pitting, brawny edema may also be present due to chronic inflammation, tissue fibrosis. Hyperkeratosis, papillomatosis.
Stage 3 (severe; limiting function):	Greater than 5 cm difference in limb circumference. No pitting, poor skin turgor feels firm (fibrosis). It may be discolored-purple or brownish. Distortion of limb-may swell to 1,5-2,0 times normal size. Lymphorrhea may be present.
Stage 4 (severe; limiting function with ulceration)	Massive distortion. Very high risk for cellulitis.

7.3. SAMPLING

a) Sample size

In a bilateral contrast, with a 5% of risk alpha, a statistical power of 80% (i.e. a 20% of risk beta), and a drop-out rate of 10%, we need a sample size of **384 women per arm** to corroborate that no differences exist in 5-year DFS rates between both LNs removal techniques (SLNB and full LAD); accepting that we consider equality survival a not exceeding 5% difference between arms.

Computations carried out with prof. Marc Saez' software based on the library "pwr" of the free statistical environment R (version 3.6.2).

b) Sample selection

A **consecutive** (non-probabilistic) sampling will be followed in women with EEC stage I risk intermediate or intermediate-high who fulfil all inclusion criteria and none exclusion criteria and come to the functional consultation of oncological gynaecology of one of the hospitals involved in the study; as to recruit the whole sample we proposed a multicentre trial enrolled by:

1- *Hospital Universitari de Girona Dr. Josep Trueta (Girona)*
2- *Hospital Universitari Vall d'Hebron (Barcelona)*
3- *Hospital Universitari de Bellvitge (Barcelona)*
4- *Hospital Clínic de Barcelona (Barcelona)*
5- *Hospital Universitari de Tarragona Joan XXIII (Tarragona)*
6- *Hospital Universitari Arnau de Vilanova (Lleida)*

c) Estimated time of recruitment

Thanks to the actual record of the operated patients with EC at the *Hospital de Girona Dr. Josep Trueta,* we estimate that we would dispose of 25 candidate patients for entering in our study per year. Since this is the only hospital in the province of Girona that realises the treatment of this patients and considering that the province disposes of 186,178 habitants, we have made an approximation of the patients that other hospitals would dispose per year: 57 in Lleida, 106 in Tarragona and 200 between the three hospitals in Barcelona. Thus, ideally, each year we could recruit 388 patients and, therefore, we will need **2 years** for recruiting all the necessary patients to complete our study sample.

7.4. RANDOMIZING AND MASKING

Each time that a patient undergoing stage I EEC with intermediate / high-intermediate RF accepts participating in the trial, she is entered in a data program which assigns every patient in an arm of the study: A or B *(see section 7.5.a. Study Intervention, page 22, and 7.6. Procedures in chronological order, page 30, for more detail of both arms).* Thus, this trial is going to dispose an optimised informatics randomness.

Nevertheless, this cannot be masked at triple or double blind, since LNs surgical techniques utterly disparate are applied and, moreover, physicians who perform them and evaluate its results and complications must be concerned of the surgery already practised. Likewise, the anatomopathologist that studies the surgical samples will notice whether we are addressing a SLNB (where there are only two LNs) or a LAD (where there are multiple LNs).

What we will do is masking the patients who are undergoing it, as they will have to firm the study informed consent (IC) after reading the informative document *(see 16.1. Protocol information sheet for participants, page 53, and 16.2.1 Study informed consent, page 56)* which explains that by random they will undergo a LNs surgery or an alternative one and they will have to firm the IC for both (the LAD and the SLNB), leaving their acceptance of undergoing through any of those two techniques *(see 16.2.2 Surgery informed consent, page 57).*

Furthermore, neither the statistic who analyses the outcome data will not know which surgical treatment has been assigned for each patient.

Therefore, although we blind two people, we say that we are doing a **single blind** as we cannot mask the physician, but the patient. We will describe in detail the bias that this can suppose afterwards *(see part 9. Limitations of the study, strengths and project impact, page 38).*

7.5. STUDY VARIABLES, MEASURE INSTRUMENTS AND DATA COLLECTION

In order to make the gathering and analysis of data easy and reliable, we will dispose a computerised table that during the durance of the study will only be able to see and modify the data manager and the statistics previously contracted *(see 11. Work plan and chronogram, page 43).*
In this table, each patient included in the trial will be numbered with the bar code of her sanity card without the letters (first column of the table) and adjoining (second column of the table), there will be an A or a B, depending on the surgical technique used in the LNs removal.

a) Study intervention

Perform a pelvic and para-aortic LAD (technique which we will name A and we will carry out in study's arm A) or a SLNB (technique which we will name B and we will conduct in arm B).
(See 7.6. Procedures in chronological order, page 30, for technic detail)

In the following table columns, the data manager will note (by order of the external organizing that gathers the data facilitated by the responsible researcher of each centre who is entrusted with collecting the data of all study's patients from his/her centre, *see work plan for more explanation)*, the outcome of the following variables:

b) Primary study outcome

➔ 5-YEAR DISEASE-FREE SURVIVAL

By DFS we comprehend the time period with absence of reappearance of the cancer, which is defined as histological presence of tumour cells or enlarged LNs or detection of pelvic tumour or distant metastasis.

For analysing this variable, if by the anamnesis and/or the physical and gynaecological exploration (abdominal palpation, TV observation with a speculum and vaginal touch), which will be done in all post-surgical successive visits *(see Table 6: Data collection chart, page 35, for visit's temporal detail)* we have a clinical suspicion of reappearance for the presence of any symptom (vaginal bleed, pelvic pain…) or sign (such as palpation of a mass), we will do image techniques (TV US, abdominal-pelvic MRI and thoraco-abdominal CT) and a biopsy (with its histological exam) to confirm it.

If concurred 5 years since the intervention and the patient has not presented any suspicious symptom nor sign, we propose that she undergo a TV US in order to assert with more reliably that she is relieved from the disease 5 years after the surgery.

Though we could define the variable status in every visit in a dichotomous manner (according to the presence of reappearance or not), what we will do is to treat this variable with a survival analysis in order to measure the time until the reappearance. Thus, as it will be explained in part *8. Statistical analysis, page 36*, the variable will be represented through survival curves that will be contrasted in order to see the differences between arms.

c) Secondary study outcome

➔ 5-YEAR CANCER-SPECIFIC SURVIVAL

Despite the fact that we could also define the variable status in a dichotomous manner (according to if the patient dies or not due to the oncological process), we will treat this variable likewise the previous one, by doing a survival analysis, but this one will measure the time until the death of the patient due to EEC. By the same token, we will compose survival curves that we will contrast between arms *(see 8. Statistical analysis, page 36).*

It is necessary to remark that our one and only interest is to include the deaths due to the oncologic process. Provided that the patients pass away for an unconnected cause to neoplasia, they will be excluded from the study.

We propose undergoing these survival analysis 5 years after the surgical intervention. Nevertheless, as we comprehend the large durance and relevance of the study, we propose undertaking an intermediate analysis within 3 years *(see 11. Work plan and chronogram, page 43)* with the 384 patients recruited in the first year so as to analyse the 2-year survival rates to validate that, as we believe thanks to the previous literature, for the moment there are no differences when considering both techniques of LNs assessment survival rates and is convenient to continue with the investigation. Otherwise, the study would be suspended, but we would spread the case to the scientific community by the same token in order to consider the validation of the superior procedure.

➔ MORBIDITY

To analyse it we will focus on some variables *(Table 5)* which can imply a certain degree of morbidity owing to the removal of LNs and we compare them between arms to see if there are any discrepancies. Throughout all the study we will be recording them in different ways and at different times, as we will explain and as it is captured in *table 6, page 36.*

Table 5: Morbidity variables that we will recollect throughout the study

Perioperative data	**Acute* postoperative complications**	**Late* postoperative complications**
Operative time	Nerve and/or vascular injury	Lymphedema
Day of discharge	Intestinal lesion	
Estimated blood loss	Thromboembolic complications	
Difference between Hb pre and post-surgery	Postoperative febrile morbidity	
	Lymphoceles	
Blood transfusion	Lymphatic ascites or chylous ascites	

Hb: Haemoglobin

*Because of the non-existent global consensus about the temporal classification of the complications, we will consider that a complication is acute when it is produced during the first 29 days after the intervention. Therefore, it will be late if it is produced henceforth.

Forthwith, we will detail the definition of every variable and how it will be its gathering:

- **Operative time**

  When concluding the intervention, the surgeon in charge will inform the responsible of collecting the data about the minutes from the initial incision to the last suture.
  Once all the patients of the study have been operated and recorded, an analysis of the median operation time for each arm will be undertaken.

- **Day of discharge**

We will record the day of the operation as day 0 and we will note the day when the discharge is given to each patient as, eventually, the median of the admission days of each arm will be realised.

- **Estimated blood loss**

We will calculate the mL of blood that the patient has lost during the intervention thanks to the receptacle that fills during the surgical aspiration; and, as a result, the mean of lost blood between arms will be compared posteriorly.

- **Difference between haemoglobins (Hb) pre and post-surgery**

The value of Hb of the pre-surgery and post-surgery (undertaken 20 hours after the operation) analytic of each patient will be noted (in g/dL). Thus, we will be able to estimate the difference and once we have all the patients, conduct a mean to detect any differences between arms.

- **Blood transfusion**

We will note down if every patient has needed or not any transfusions during the hospital admission owing to the blood loss in the operation.
Thus, this variable will be categorized with YES or NO so that be able to estimate the total percentage of patients that have needed any transfusion in one arm and the other.

- **Nerve and/or vascular injury caused by ganglion extraction**

The presence or the non-presence of this injury caused by the LNs removal in every patient will be communicated by the surgeon in charge of the intervention (as this is valuated during the operation, searching and looking the more susceptible blood vessels and nerves to be damaged) and, subsequently, the lesion percentage between groups will be obtained.
Normally, this lesions are seen at the moment, but if for example a partial motor nerve lesion was addressed, what we would see is a motor deficiency affecting the leg during the hospital admission and it would be then, with the symptoms appearance, when we would inform it as a YES. If during the admission no symptom is found, we will confirm that is a NO.

- **Intestinal lesion**

Likewise aforementioned, we will report it as a YES or NO in every patient in order to estimate the percentage between arms afterwards.
This damage can pass unnoticed during the operation, producing posterior symptomatology. Provided that everything goes acceptable, we do not contemplate it. But if 5 days later the patient is sceptic, we must discard that it is not due to an intestinal lesion and if it is the case, inform it. Once again, if during the admission there are no signs nor symptoms, we will corroborate this as a NO.

- **Thromboembolic complications** *(according to* (36)*)*

    - **Deep venous thrombosis:** when a blood clot forms in one or more of the deep veins of the body, usually in the legs. When is there suspicion owing to the presence of symptoms we will carry out an US to see the clot and confirm the diagnosis.

    - **Pulmonary embolism:** when a lung blood vessel becomes blocked by a blood clot that travels to the lung from another part of your body. When there is some suspicion because of the presence of signs and symptoms a CT pulmonary angiogram will be demanded in order to confirm it.

Repeatedly, we will undertake a revaluation if suspected and once confirmed we will inform it as a YES. If during the first postoperative month there has been no presence of thromboembolic complications, we will contemplate it as a NO. Once obtained each patient's data, we will be able to have the percentages of this complications in each arm.

- **Postoperative febrile morbidity**

Defined as a temperature > 38ºC according to 2 different measurements ≥ 6 hours apart beyond the first 24 hours after the operation. Thenceforth the reanimation unity or intensive post-surgery cures nurse measures the temperature as it has been described, he or she will note it down in the constant program of the hospital and will communicate the result him/herself to the doctor in charge of communicating patient's data if it is a YES (the patient has postoperative febrile morbidity) or a NO, so that, finally, the statistic could include it in the percentage between arms.

- **Lymphatic leakage**

If by symptoms and/or signs (clear or milky fluid exudate on the wound, swelling under the wound or ascites) we suspect it, the patient will undergo adjuvant examinations.
Throughout the month of the operation, we will inform if there has been any of these complications so as to be able to estimate the percentages between arms.

  - **Lymphocele:** defined as a collection of lymph fluid with no inflammatory or granulomatous reaction at the leakage site. It will be evaluated with anamnesis and physical exploration in the admission and in the posterior visits. If we suspect it by symptoms or signs, an abdominal-pelvic US will be undertaken to confirm it.

  - **Lymphatic ascites or chylous ascites**: defined as a post-surgery abdominal distension that through the US we are able to see that it stems from the free intraabdominal liquid and we cannot attribute any other aetiology.
    In order to confirm the diagnose and, at the same time, treat it, we will do an evacuated paracentesis by which we will be able to analyse the liquid composition and discern if we are addressing a lymphatic or chylous ascites.

- **Lymphedema**

We are going to use a standardized leg measurement protocol pre and post operation (at week 5 and at month 9, 13 and 25) to define it.
The subject had a baseline bilateral leg measurement, which consist of measuring the width of the leg three inches (7,62 cm) above the lateral malleolus, five inches (12,7cm) bellow the patella and five inches (12,7cm) above the patella *(Figure 6)*.

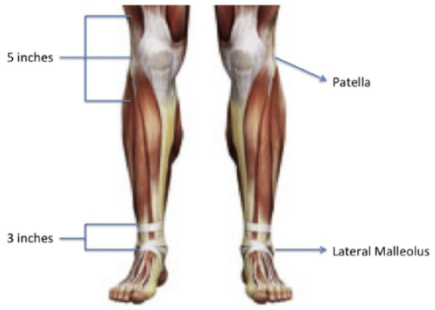

Figure 6: Depiction of standardized leg measurement system (26).

Subjects who had any type of leg measurements increased by greater than 20% using this standardized system by 1 or 2 years post-operatively will be defined as having lymphedema.

The physician in charge of this evaluation will report the result (YES or NO) in order to have it noted down and the percentage of this complication between arms can be calculated.

In every complication, we will have assured that pre-operatively the patient did not present any signs or symptoms of it and, therefore, it has been produced due to the LNs removal. For this reason, a pre-operative exploration and good anamnesis will be completed accordingly *(see section 7.6. Procedures in chronological order, page 30, for more lecture)*

Moreover, so as to improve the visibility of the morbidity that entails this project, the subject filled out a **quality-of-life survey called the Functional Assessment of Cancer Therapy in Endometrial Cancer Version 4 (FACT-En, version 4)** pre and post operation (within a month, within year and within 5 years). The survey asks about pain in the pelvic area, weight concerns, leg appearance, leg function, and generalized pain on the leg *(Figure 7)*.

1) I have discomfort or pain in my pelvic area
2) One or both of my legs are swollen and tender
3) I am bothered by a change in weigh
4) I have certain parts of my body where I experience significant pain
5) Movement of my leg is painful (Right, Left, Both)
6) I have poor range of movement on this side (Right, Left, Both)
7) My leg on this side feels numb (Right, Left, Both)
8) I have stiffness of my leg in this side

Figure 7: Questions from the FACT-En, version 4 quality-of-life-survey (26).

The answer options for all of these questions are rating of 0 to 4:

➔ DETECTION OF LYMPH NODES AFFECTED with SLNB and with LAD.

Just as will be explained in the following procedures part, all the removed LNs from the patients will be sent to the pathological anatomy service in order that expert pathologists analyse them and communicate the clinic in charge whether they are affected or not. The physician will share with the responsible of the data collecting if the patient has or not affected LNs so as to posteriorly evaluate the percentage of patients with affected LNs that have emerged from each arm and therefore compare metastatic LNs detection rate in both LNs assessment procedures.

We consider that a LN is affected if it is metastasised as it presents micro- or macro-metastasis (tumor clústers between 0,2 and 2 mm or > 2 mm, respectively).
(See 7.6. Procedures in chronological order, page 30, for more lecture)

d) Co-variables

Once recruited all the patients, we assure that the randomisation has distributed them accordingly, and that both groups are equivalent with regard to:

➔ AGE (categorized in 4 groups): < 50 years, 50 – 59 years, 60 – 69 years, > 70 years.

➔ BMI (categorized in 2 groups): < 35 kg / m2 or ≥ 35 kg / m2.

➔ Presence of relevant COMORBILITIES: diabetes mellitus and/or systemic arterial hypertension and/or cardiovascular disease. Variable measured as YES or NO.

➔ Socioeconomic level approximated by the educative and occupational level *(according to the Domingo et al. classification, 1989 and 2013)* (37).

So as to see how we are going to verify that there are no significant differences that influence our study see section *8 (Statistical analysis, page 38).*

7.6. PROCEDURES IN CHRONOLOGICAL ORDER

The schedule that this study investigators propose following with the possible participating candidates in this clinical trial consists of 2 main common points for all the patients undergoing EEC. Thanks to them are we able to discern if the patient meets the eligibility criteria for our study and once we inform of it and she accepts participating by signing all the pertinent documents *(see them in 16. Annexes, page 53)* the randomisation will proceed, in order to conduct a LNs removal technique or other depending on the arm in which the patient has been assigned. Once this part has been accomplished, the procedure schedule will be reconnected. In the meantime, all the interesting variables for the study will be gathered *(Table 6, page 35).*

1) ANAMNESIS, PRE-OPERATIVE EXPLORATION AND ICs

In the first visit in oncology gynaecology service, one of the investigating doctors will collect information on each subject, including **age at enrolment, medical comorbidities and BMI.** Preoperative histological diagnosis is decided on specimen obtained from **endometrial biopsy.** Routine preoperative work-up also include a **TV US**, a **pelvic MRI** and a **thoraco-abdominal CT**. Furthermore, we will process an **analysis** and the **valuation of the operability via laparoscopy** will be conducted by the anaesthetist. The **WHO performance status** will also be determined.

If after this we confirm that the patient is tributary to participate on our study, the information sheet will be given to her. Before proceeding with any other step, she will have to sign all the ICs.

Provided that the patient accepts cooperating, she also has to fill out the **FACT-En, version 4** *(Figure 7)* and she had a **baseline bilateral leg measurement** *(Figure 6).*

2) ROBOTIC LAPAROSCOPIC APPROACH USING DA VINCI ®

Once the patient is anesthetized, with ventilator support, tracts and Foley catheter placed, she will be put in Trendelenburg position and with her legs opened.

Firstly, an umbilical incision will be performed so as to insert the first trocar, since through it the insufflation of CO2 will be produced, until 12mmHg, in order to cause a pneumoperitoneum and

be able to insert an optic trocar so as to execute the other incisions and place the other trocars under direct vision in order to minimise the risk of damaging important structures.

The access will be taken place with 5 trocars disposed in a standard way (a horizontal line with the central trocar umbilical-levelled and all of them facing down at the pelvis) *(Image 1).*
Formally placed the 5 trocars, 4 of those will be connected to the 4 arms that the da Vinci ® has, which will be manipulated by a surgeon from the control centre *(Images 1, 2 and 3).*

Image 1: Trocars in position

Image 2: Da Vinci arms

Image 3: Da Vinci control centre

One robot arm will be for the monopolar plier, another for the bipolar, one more for the camera and the light and one last for the grip plier. The remaining trocars will be used for the surgeon that will persist in the left side of the patient, who will be able to use them in convenience for extracting the samples, cleaning the surgical field, placing a plier, an aspirator...

3) REALIZATION OF THE SURGICAL LNs EXERESIS TECHNIQUE ASSIGNED BY RANDOMITZATION

Surgical procedures are going to be performed or supervised by surgeons specialized in gynaecological cancer treatment who will be previously trained in order to perform the surgery uniformly with the same technique, since, as it will be explained in work plan section, page 45, before the outset of the study the protocols to be followed will be standardized as for example, to coagulate we will only use bipolar and monopolar energy.

In each operation there will be 3 surgeons minimum: one will handle the da Vinci ® robot, the other will remain next to the patient's abdomen and will dominate one trocar, whereas the last one will place him/herself in between the patient's feet with a uterus manipulator (instrument, which is used to move the uterus in order to enhance the visualisation).

3.1. EXPERIMENTAL GROUP

a. Cervical injection of indocyanine green

We will reconstruct the ICG with a concentration of 2,5 mg/mL (1 vial of 25mg in 10 cc of physiologic serum) and use 4 cc for the intracervical injection with a 25-gauge spinal needle (1 superficial cc in 9h, some 2 mm, 1 profound cc in 9h, some 0,5 – 1 cm, 1 superficial cc in 3h and finally 1 profound cc in 3h).

All adverse events occurring after injection of ICG will be registered.

b. Retroperitoneal evaluation including excision of all mapped SLNs

Firstly, we will do a retroperitoneal evaluation since identification of SLNs is unnecessary when a gross metastatic intraperitoneal disease is detected because then, the patient will not be a candidate for our study, as her disease will not be confined in the uterus and, therefore, we will not be talking about an stage I EEC with intermediate or high-intermediate RF. Although we have a pre-surgical negative image, this it must be checked before any other step.

Provided that the evaluation is anodyne, we will do an evaluation and dissection of pelvic retroperitoneal spaces, identifying the sentinel drainage pathways that emanate from the parametria thanks to an image system (since we will dispose of a dedicated optical system to visualize drainage of ICG into the lymphatic vessels). We will observe and proceed with the removal of the first LN that communicates with the vessels, since SLN will be the earliest to show a high level of green fluorescence signal *(Image 4).*

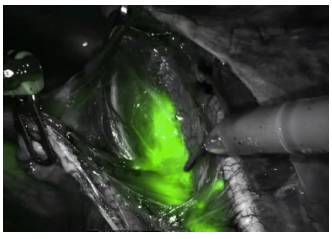

Image 4: SLN visualization

The SLN extraction will be executed by the trocar that is dominated by the surgeon who is situated on the left side of the patient and we are going to perform this process bilaterally.

The main pitfall related to the use of ICG is the removal of only lymphatic vessels (due to colorant dispersion) instead of LN as itself, thing that will have to be reported as no SLN detection. In consequence, this case will be removed from the study. Similarly, if there is no mapping on a hemi-

pelvis, a pelvic LAD is performed and then the patient will be excluded of our study, otherwise the randomization would not be obeyed *(see the limitations section, page 38, for more discussion).*

3.2. CONTROL GROUP

a. **Retroperitoneal evaluation including the conventional pelvic and para-aortic LAD**

We will attempt to make both LADs (the pelvic and the para-aortic) being taken place in block in order to put the correspondent tissue in an endoscopic bag, which will be removed via vaginal after the total hysterectomy and BSO.

4) TOTAL HYSTERECTOMY AND BSO with extraction of the piece via vaginal.

5) SOME RECOLLECTION OF PERIOPERATIVE DATA (operative time and blood loss estimated) AND ACUTE COMPLICATIONS (vascular, nervous, ureteral, intestinal damage…).

Adverse events that cause death or are considered life threatening, unexpected and/or related to study intervention have to be reported within 24h to the study coordinator and to the Safety Monitoring Committee for clinical studies at the respective centers for an independent evaluation.

6) POSTOPERATIVE PATHOLOGIC EXAM

A specialized gynecologic anatomopathologist examined all the extracted specimens, which are saved in identification jars and sent to the service, with H&E staining and with IHC.

If SLNB has been done, pathologic processing of each SLN will include serial sectioning along the longitudinal plane of the node at 2-mm intervals and microscopic examination of all slices with at least 1 representative H&E level, followed by ultrastaging (two adjacent 5µm sections cut from each paraffin block at each of 2 levels 50µm apart and at each level, one slide is stained with H&E and the other with IHC using anti-cytokeratin AE1:AE3) if the initial H&E is negative.
SLNs are considered positive if they demonstrate macro-metastasis or micro-metastasis.
LNs containing ITCs will not be considered metastatic.

7) HOSPITAL ADMISSION

If the operation takes place without significant events, the patient will be admitted one day at the post-surgery intensive cures unit so as to then transfer the patient to conventional hospitalization. During the admission, heparin will be administrated in prophylactic doses to minimize thromboembolic complications.

Twenty hours after the surgery, a blood analysis will be undertaken so as to determine the Hb and during the first 24 post-surgical hours, patients' temperature will be determined in 2 separated measures by 6 or more hours. The results will be gathered, as the necessity of transfusions. If any of the other acute complications mentioned at the variable section is produced, they will by noted down likewise.

8) ADJUVANT THERAPHY *(according to* (38)*)*

Patients with intermediate-risk EEC will undergo through adjuvant brachytherapy (BT).

In the other hand, in patients with high-intermediate-risk EEC adjuvant treatment will depend on the LNs affectation, which would be discovered thanks to the nodal stratification surgery:

- In case of not having affected LN, we will perform an adjuvant BT.
- In case of lymphatic affectation (positive SLN or positive LAD), patients will received adjuvant external radiotherapy.

9) FOLLOW-UP VISITS

All patients received a complete physical and gynecological examination every 4 months for the first year and every 6 months for the next 4 years. In every visit, apart from the exploration, a good anamnesis will be also undertaken just in case the patient presents suggestive symptoms of any complication or reappearance. Like we have explained, if for any sign or symptom we suspect that the patient might have a reappearance, we will make some tests.

Besides, we will take bilateral leg measurements, as performed preoperatively, at week 5 and at month 9, 13 and 25. On the other hand, in the final visit of the 1st month, the 1st year and the 5th year, the FACT-En, version 4 life-quality inquiry will be passed.

Table 6: Data collection chart (temporal scheme which defines when we will collect the variables).

	Basal period		Randomization and surgery	Post-operatory follow up																
				Hospitalization admission	Day of discharge	3	4	5	6	7	8	9	10	11	12	13	14
Visit (anamnesis + general and gynaecology * physical exploration)	1	2															
Week	-2	-1	0	1	2	4	20	36	52	76	100	124	148	172	196	220	244
Month	-1		0	1			5	9	13	19	25	31	37	43	49	55	61
Year	1									2		3		4		5	
Eligibility criteria	✓	✓															
Informed consents	✓																
Preoperative explorations **		✓															
Note if lymph nodes have been affected or not				✓													
Note operative time and estimated blood loss			✓														
Note the need or not of blood transfusions				✓													
Haemoglobin determination		✓		✓													
Fulfil FACT-En, version 4		✓				✓			✓								✓
Evaluate temperature				✓													
Valuate acute postoperative morbidity***				✓		✓											
Perform some tests if there are symptoms or signs of lymphocyst or other complications or reappearance				✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Bilateral leg measurements		✓					✓	✓	✓		✓						
Cancer-specific survival				✓		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
TV US if in 5 years there has been no reappearance																	✓

* Gynaecological examination include abdominal palpation, TV observation with speculum and vaginal touch.

** At least endometrial biopsy, transvaginal ultrasonogram (TV US), pelvic magnetic resonance image (MRI), thoraco-abdominal CT (computed tomography), blood analysis and WHO status score must be performed. FACT-En, version 4: Functional Assessment of Cancer Therapy in Endometrial Cancer Version 4.

***Acute postoperative morbidity: nerve and/or vascular and/or intestinal injury, thromboembolic complications, postoperative febrile morbidity, lymphoceles and lymphatic or chylous ascites.

8. STATISTICAL ANALYSIS

Firstly, the statistic will be explained that for the whole study variable an stratified analysis will be undertaken for the different subgroups, which, according ESMO-ESGO-ESTRO classification, comprise the studied group (intermediate / high-intermediate risk EEC) *(Table 1)*, as multiple studies have replied that the tumour grade is a RF for LN involvement and/or worse prognosis is associated to a minor rate of DFS and overall survival. So that the analysis to be blinded, the statistic will not be concerned about this data, as the subgroups will be numerated in 1,2,3,4 and 5 by row order. Straightaway, he/she will be demanded, once gathered all the variables, to describe the sample that we have according to each of the clinical and sociodemographic variables that has been collected from each arm. Once described both arms, compare the dependent variables with the independent ones to evaluate differences between arms. Lastly, we would be interested in matching comparisons with a multivariate model.

All statistical analysis will be performed with SPSS and in continuation we will vaguely explain how we are going to execute each section.

8.1. DESCRIPTIVE ANALYSIS

We are going to summarize survival dependent variables (5-year DFS and 5-year cancer-specific survival) undergoing medians and interquartile rang (IQR). Furthermore, we will estimate the survival curves of the 5-year DFS and the 5-year cancer-specific survival, using the Kaplan-Meier estimator.

Perioperative data are quantitative variables (except the need of blood transfusion that we understand it like a qualitative variable) and therefore, are going to be summarized with means and standard deviations (SD) or with medians and IQRs, depending on whether variables are symmetrical or asymmetrical, respectively.

The remaining morbidity variables (blood transfusion and postoperative complications) and the presence of LNs affected with both LNs removal techniques, for being qualitative variables, we are going to summarize them with proportions.

All those analyses will be stratified in defined groups for the intervention, as well as we will stratify the different risk subgroups aforementioned.

8.2. BIVARIATE INFERENCE

The difference between the survival curves already mentioned and stratified, will be compared using the log-rank test.

To compare the means and the medians (of the continuous and discrete dependent variables, respectively), we will use the Student's t and the Mann-Whitney's U, respectively.

In order to compare the proportions of the qualitatively dependent variables in both groups of the study the *Chi-square* test will be used and when the expected frequencies are smaller than 5, we will resort to the exact Fisher test.

These analyses will be stratified by the co-variables, which in the case of being quantitative will be categorised as it has been explained previously.
Similarly, once again the different risk subgroups will be stratified.

8.3. MULTIVARIATE ANALYSIS

Given the fact that we have randomized, the confounding and the possible selection bias have been controlled. However:

The relations between the survival variables within 5 years (dependent variables) and the LNs intervention technique (independent variable), will be adjusted in a Cox regression that will be stratified by the defined risk subgroups, controlling for all the co-variables.

The relations between the qualitative dependent morbidity variables (postoperative complications and the necessity of blood transfusion), the presence of LNs affected and the LNs removal technique will be adjusted in logistic regressions, which will also be stratified by the risk subgroups and moreover, controlling for all the co-variables.
The relations between continuous morbidity dependent variables and the intervention technique will be adjusted in linear regressions, controlling for co-variables and stratifying by risk subgroups.

Lastly, relations between the discrete dependent variables and the intervention technique will be adjusted in Poisson regressions, also controlling for covariables and stratifying.

9. LIMITATIONS OF THE STUDY, STRENGHTS AND PROJECT IMPACT

Like all studies, ours might present some biases that would affect the internal validity. In continuation we will mention and explain which strategies we will implement to minimize them, so as to control the systematically error in order to make our study valid.

Firstly, it is worth mentioning our little worrying about **confusion bias**, as it has been already commented that we expect randomizing the clinical trial properly in order to avoid its existence.
Moreover, we will perform a stratified analysis of each subgroup and we will propose a multivariate model adjustment in order to nullify the minimum existence of confusion.
Furthermore, part of the confusion has been eliminated by restringing the sample with the exclusion criteria, as for example patients with morbid obesity have been excluded from the study.

On the other hand, we could find a **selection bias** as in this clinical trial is not feasible doing a random sampling and it is done consecutively. Therefore, we will be extremely attentive so as to control it by recruiting all the patients that come to the consult and meet the eligibility criteria during a long period of time (2 years); essaying not to lose any case.

Nevertheless, since we talk about a long monitoring study, another possible limitation would be that, during the tracking, many losses of patient could be produced. Then, we could be facing a selection bias, as surely the patients that have left the study will not be the same as the ones that continue it. In order to avoid it, since the commence of the study the contact vies of each patient will be broadened, demanding, apart from her personal data, some close contact data so as to be able to localise the patient through another. In addition, we will facilitate the participation by adapting ourselves to the patients' demands, as far as possible.
So as to calculate the sample, a 10% of the losses have been supposed, although we believe in their improbability: no more than a 5% of losses in each arm are expected as patients do not usually dismiss our medical consults, due to the importance and the gravity of their worrying pathology. Therefore, as we suppose that we will not lose the 25% of the sample, these losses do not compromise our study. Furthermore, these losses are expected to be independent to the considerable dependant variables. In other words, we suppose that the censure, in case of being produced, will not be informative.
Alternatively, to facilitate finding statistical significance and giving more validity to an absence of survival differences between arms, in this clinical trial of non-inferiority, an analysis per protocol could be used (only of the patients who completed the study correctly), but this would imply a large study period that would go far beyond the objectives of the present work.

What are we also concerned about is the possible bias that we would have if a patient that by random has been assigned to the SLNB group experiments a non ICG migration or a wrongly migration. Consequently, we cannot undertake the SLNB. Then, these patients would have to undergo a LAD and they would be excluded from the study, being aware of the disequilibrium of the patient's number resultant and that the study conclusions would be provided that we adopt this exclusion attitude. Notwithstanding, this is rare to happen, and hypothetical cases can be neglected. Moreover, to minimize the likelihood of an unsuccessful procedure, we have excluded patients with morbid obesity or history of pelvic and / or abdominal irradiation. In addition, the experience of our surgeons regarding technical and surgical issues and the adherence to a standardized injection protocol will ensure an improved rate of successful procedure.

Another limitation at which we are exposed is the **information bias**, since unfortunately is not possible to achieve a triple blind, as the physicians that perform and evaluate the surgical techniques cannot be masked. We could contemplate the monitoring to be conducted by another non-subjective doctor, but considering economical and personal resources that this would involve it is not seen feasible. Apart from that, is more logical that the physicians who carry out the tracking are those who have undertaken the operation, knowing the complications that there have been or to be and attempting to be as rigorous as possible with the data recollection. Therefore, we assume this lack of blind not accomplished by the clinics, whereas we will try to raise awareness of the objectivity importance in the evaluation during the formative course that will receive all researchers *(see 11. Workplan and chronogram, page 44).* In it, we will train the interviewers and we will inform about the standardize protocols between the different participant centres. This measure also will be valuable for not making a realisation bias, as in this training we will highlight the importance of doing the same monitoring for each group, without encouraging additional interventions for the fact of belonging to a certain group. We believe that with the mentioned consciousness, this lack of blind not accomplished by the physicians should not invalidate the results. Moreover, what we do propose is doing a simple blind by making the patient unaware of which LNs intervention has undergone so that it has no influence in the morbidity that can be explained. As we have mentioned, when entering in the study the patient will accept both LN removal techniques signing ICs. Likewise, the statistic who collects and analyses the outcome data will not know which surgical treatment has been assigned for each patient.

Nevertheless, so as to make the most subjective variable of the study (morbidity) less subjective, it has been contemplated in such a way that in both arms, we measured different variables more than

once in order to define it. Moreover, we will try, as far as possible, that the patients come accompanied. Thus, we will verify the subjective variables by broadening the information source.
Contrasting morbidity subjective, our study presents a big strength, which is the kind of principal dependent variable (survival) as it is a hard, extremely objective and hardly impressionable measure that will minimize the possible detection bias that could exists in every not-completely blinded clinical trial.

Another of the strengths of our trial includes the prospective design, with consecutive recruitment of women within a publicly available healthcare system. Moreover, we are in front of a clinical trial, the unique study design able to demonstrate an innovative strategy, which will not only be controlled and randomized, but also will dispose a big sample in order to be more precise (less random error).

Lastly, we want to outline that the most important strength we dispose is the vast impact that will suppose for the patient, the physicians and the whole health department, our hypothesis acceptation. As we believe that the state-of-the-art technique proposed (SLNB) is not only easier, but also is faster than the LAD, involves less complications that decrease the quality-life of the patient and, furthermore, it could be more inexpensive. All aforementioned, with the same survival rates. So, it would offer a huge range of additional advantages that would alter the morbidity panorama that face patients in stage I EEC with intermediate / high-intermediate RF.

Regarding the external validity of our study, it should be said that from the beginning it could be presuppose that we have little, since we will only dispose patients treated in Catalonia. However, it would be worse if we only comprehend the patients of an only hospital and this is one of the reasons why we propose a multicentre trial. In addition, although the results of this study will not be extrapolated worldwide, as we are proposing a leading technique that needs advanced technology not available in all centres, we believe that this is the best way to achieve good results. We defend that this is not a big limitation since medicine is increasingly subspecialized and derived and we support that all cases such as the ones in our study should be treated in specialized and prepared centres and that when doing so, this practice could be generalized and the same results would be obtained.

10. ETHICAL AND JURIDICAL ASPECTS

First of all, we would like to emphasize that at all time the ethical principles for medical research with human beings included in the Helsinki Declaration of 1965 (respect for people or autonomy, beneficence, maleficence and justice) will be followed.

In order to an external body to corroborate it, this research protocol will be sent to the *Comitè Ètic d'Investigació (CEI) of Hospital Universitari de Girona Dr. Josep Trueta*, who will have to approve it so as to be able to start the study.

Currently, in a multicentre clinical trial such as ours, the single opinion is used and if approved by this committee, the decision is valid for all Spanish's State hospital committees. However, this protocol will be proposed to the other participating hospitable centres *(Hospital Universitari Vall d'Hebron, Hospital Universitari de Bellvitge, Hospital Clínic de Barcelona, Hospital Universitari de Tarragona Joan XXIII* and *Hospital Universitari Arnau de Vilanova de Lleida)* so that each centre's management gives us permission, since only when all the participating centres' management are satisfied will we start the study. Nevertheless, the ethical committee to which we will deliver this protocol will assess whether these centres actually meet the requirements, as we affirm.

To further evaluate the ethics of this study, we have enclosed the protocol information sheet of the study and all the ICs *(see point 16. Annexes, page 56)* that should be signed voluntarily by the patient in order to participate (one to accept the study and 3 to accept the surgical techniques that could imply). All these documents are available in both official languages of the centres where the trial will be undertaken, Catalan and Spanish. However, this protocol will only encircle one of the versions.

Despite this, we want to outline that this study is regulated by the "*Ley Orgánica 3/2018, de 5 de diciembre, de Protección de Datos Personales y garantía de los derechos digitales. (BOE núm. 294, de 6 de diciembre de 2018)"* and by the *"Real Decreto-ley 5/2018, de 27 de julio, de medidas urgentes para la adaptación del Derecho español a la normativa de la Unión Europea en materia de protección de datos"* which assures the confidentiality and anonymously of the patient's data.

Moreover, as a clinical trial is addressed, we will follow the "*Ley 14/2007, de 3 de julio, de Investigación biomédica"* and the *"Real Decreto Legislativo 1/2015, de 24 de julio"*, and since we consider that we are investigating with invasive procedures, also the "*Real Decreto 1090/2015, de 4 de diciembre"* which, among other things, establishes that we will contract a policy insurance for the study patients.

Nevertheless, it will be the CEI who will decide whether or not this is actually an invasive intervention. If it is emphatically concluded that it is an invasive procedure, we will request permission to do this study at Catalonia's health department (the autonomous community where it will be undertaken).

Lastly, and authorization to conduct the study will be demanded at *Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)*, bearing in mind that heretofore the registration number must be requested, the information putted in the AEMPS portal and the fee payed.

Besides, we commit to send the curriculum of the researchers that will take part on this study, so as to demonstrate that they are all experts selected for the topic that occupies them.

Not forgetting other ethical aspects, we compromise to communicate the results of this study, although they are unfavourable to our hypothesis, and not to exclude any type of population without an explanation, since all patients have the right to benefit from our study.

Therefore, we ensure that we have ethical integrity and that our research will respect the legal requirements.

11. WORK PLAN AND CHRONOGRAM *(Table 7, page 46)*

Subsequently, we will detail the sequence of activities developed during the project, which are organized in five phases:

PHASE 1) PROTOCOL PREPARATION, DESIGN AND APPROVATION.

- **Initial approach and scientific research**: expert gynaecology oncology physicians of *Hospital Universitari de Girona Dr. Josep Trueta* have been experimenting for a while with the da Vinci robot ® and the SLNB in stage I EEC with low RF surgery. Confirming the promising results that are increasingly being supported by many studies, they thought that another step should be taken and investigate this technique in stage I EEC with intermediate / high-intermediate RF. To commence entering the subject, during the months of May and June 2019 they decided to make a review of the bibliography published about this topic in PubMed data base, Embase, Cochrane... and they were aware of the current lack of consensus in the treatment of this tumour and the necessity of doing a large-scale study in order to solve the gap of knowledge.

- **Protocol elaboration:** with the previous intention, during the months of July, August and September this protocol was designed, with the help of expert gynaecology oncology doctors from the other hospitals in Catalonia that met the requirements and wanted to get involved.

  During the following months the project will be suggested to the organisms in charge of giving the allowance so as to be able to proceed. Therefore, their approval will be waited.

- **Protocol approbation** by *Hospital de Girona's CEI* and by the directors of all the participating hospitals during the month of October, by AEMPS and, if necessary, since the CEI says that is an invasive procedure, also by the health department of the *Generalitat de Catalunya* during the month of October or November.

PHASE 2) ORGANIZATION AND CORDINATION during the month of December.

- **Researchers meetings**: the first Monday of December, each hospital's gynaecology oncological service will gather at their centre and will decide who will be the representative (the manager) of the service for this investigation. During the Mondays and Thursdays of the following two weeks, the representatives of each centre will gather in Barcelona in order to

reach an agreement and standardize the different centre protocols that participate in the trial, likewise hiring the non-medical personnel needed in this trial (an statistic, an external person in charge of the coordination between the centres and a data manager who note the data and controls their quality) and organise a formative course for all the professionals involved.

Therefore, each participating centre will dispose a representative (who will be one of the investigating doctors) and an external person not related with the hospitals will be in charge of organizing and ensuring the optimum communication among centres by visiting and phone calling in order to assure that the agreed protocols are being followed, collect patient's data, which will be facilitated by each representative, and supply the data to the data manager and subsequently to the statistic. Moreover, from now on, he or she will be the person who will organize the coming meetings and will be entrusted with the bureaucracy.

- **Training course for research surgeons:** the two remaining Mondays of December, all the investigating physicians of all centres will assist in a course in Barcelona, which will be done in order that all specialists follow the same objective practices.

PHASE 3) STUDY CONDUCT

- **Patient recruitment, sample collection:** we would need 2 years (from January 2020 to January 2022) in order to recruit the 768 required patients for the study.

  As we will follow a consecutive sampling, during these two years we will progress with the following sections, while each patient is being recruited:

- **Intervention:** for a few hours of a morning.

- **Patient evaluation; follow up routine:** during the post-operative 5 years.

- **Data collection:** from the patient entrance at the oncologic gynaecology service to the last monitoring visit 5 years after the surgery.

  Thus, we estimate all required data to be collected in January 2027, as it will be then when the last patient who completes the study' sample will finalize the 5 monitoring years.

PHASE 4) DATA MONITORIZATION, ANALYSIS AND INTERPRETATION

- **Data monitorization and quality control:** 3 months of work, distributed during the study: one month in January 2021, another month in January 2023 and a final control in February 2027, when all the variables of the study have been collected.
  Thus, in March 2027 we will have finished the data monitorization and control.

- **Statistical analysis:** 1 month of work in February 2023 (because, as we have explained, an intermediate analysis will be undertaken in the first 3 years of the study in order to verify that, from the moment, the collected data are in accordance with our hypothesis and, therefore, it is convenient to continue with the study) and 2 months of work after 5 years of recruiting the last patient and after data control, in March and April 2027.

- **Interpretation and discussion of the results:** on May Mondays.

  One first meeting between the centre representatives in order to expose the provided results by the statistic, another between the investigators of each oncologic gynaecology service to interpret them and submit them for debate, one other meeting between the representatives in order to explain each centre's interpretation, contrasting opinions and reaching an unanimous conclusion, one other between investigators of each centre in order that the responsible translates the conclusion which each service has reached and 1 last meeting for all investigators on 31st May to contemplate and/or resolve doubts and encourage new investigations.

- **Final report elaboration:** the maximum responsible person among all centre's responsible people, who is presented voluntarily and is elected by the investigators on a voting, which will be undertaken in the last meeting, will redact a scientific article exposing the interpreting results during the months of June and July 2027. During August 2027, it will be read by the other investigators, who will propose possible modifications and/or give their approval.

PHASE 5) PRESENTATION AND DIVULGATION OF THE RESULTATS

- **Report publication** in September or October 2027.
- **Dissemination** in national and international (the European of ESMO-ESGO) congresses.
  During November and December 2027.

Table 7: Chronogram

STEPS		2019								2020 to 2022		2022 to 2027				2027											
		May	June	July	A	S	O	N	D							J	F	M	A	M	J	J	A	S	O	N	D
1) PROTOCOL PREPARATION, DESIGN AND APPROVATION																											
Scientific research																											
Protocol elaboration																											
Protocol approbation	Ethical authorization by Trueta's committee																										
	Authorization by directors of hospitals																										
	By AEMPS																										
	By Catalonia's health department																										
2) ORGANIZATION AND CORDINATION																											
Researchers meetings																											
Training course for research surgeons																											
3) STUDY CONDUCT																											
Patient recruitment, sample collection																											
Surgery intervention																											
Patient evaluation, follow up routine																											
Data collection; during all the study																											
4) DATA ANALYSIS AND INTERPRETATION																											
Data monitorization and quality control										J		J															
Statistical analysis												F															
Interpretation and discussion of the results																											
Final report elaboration																											
5) PRESENTATION AND DIVULGATION OF THE RESULTATS																											
Report publication																											
Dissemination in congresses																											

Intermediate analysis in 2023

12. BUDGET

Firstly, we would like to clarify that we will not budget for the da Vinci robot ® with whom we will perform the surgery, as it is already available in all the hospital centres involved in the study.
Likewise, neither the budget for the pre-operative tests, the surgical approach material, the adjuvant treatment nor the monitoring visits are included, since all these procedures will be the same as the current clinical practice. Regarding the post-operative tests, it must be said that they will be the same, except from the TV US that we would do in addition after 5 years provided that during this time the neoplasia has not given signs nor symptoms of reappearance.
*As our sample is of 768 patients and according to (39) the DFS of the stage I EEC with intermediate / high-intermediate RF is of 93% in 5 years, we have estimated that 714 patients would be in need of it.

On the other hand, as previously mentioned, we will use a quality scale called FACT-En, version 4, which will not be included in the budget as after consulting its copy-right policies we have noticed that the English version of the questionnaire is free for anyone and despite translations are not available and may require a fee depending on the details of the study, fees per language are typically waived for investigator-initiated studies like ours. Nevertheless, we will have to provide them with copies of any publication which come about as the result of collecting data with their questionnaire.

Furthermore, when counting the budget that we will spend printing we have not included neither the IC of the hysterectomy with BSO nor the complete lymphadenectomy one, as these two documents would be printed nonetheless in the clinical practice. We do have counted the information document of the study, the IC of the study, the IC of the SLNB and the quality-life survey sheet aforementioned.

Besides, we want to emphasize that we do not hire the investigating doctors of this study. These will not earn any commission to participate, but their travels and diets related with the meetings will be covered and their names will be published, from the most to the less collaborative.
Patients who participate in the clinical trial will not acquire any profit either, as it is not legal nor ethical.
Therefore, we only need money to pay to external people hired for the coordination of the study, for the quality control and for the analysis of data, as specified in Table 8.

Forthwith, what we need to carry out the study that we do not have will be therefore specified in the following table, including the fortune that we require and urge to achieve.

Table 8: Resources that we need for the study

	DESCRIPTION		COST PER UNIT	QUANTITY	SUBTOTAL
MATERIAL	**Printing** of: • Protocol information sheets for participants • Informed consents • Quality-surveys		0.01 €	7,680 sheets (10 per patient)	76.80 €
	Tape measures for lymphedema definition		1.45 €	6 tapes measures, 1 for each hospital	8.70 €
	Vials with 25 mg of **ICG**		68.15 €	384 vials (for patients of arm B)	26,169.60 €
TESTS	**TV USs**		32 €	*715 TV USs	22,855.68 €
STAFF	A **coordinating person** between hospital centers in charge of supplying data to the data manager and subsequently to the statistical		1 person who will spend a total of 181h organizing, making and answering calls, visiting the centres, the data manager and the statistic. He/she will charge 10 €/h, but we will cover his/her travels		2,650 €
	Data manager in charge of data monitory and quality control, verifying with high degree of exhaustiveness that table data concur with clinical history data		1 data manager who will work 768h, a total of 3 months, in order to dedicate 1h to each patient and earn 10 €/h		7,680 €
	Statistical expert for data analysis		1 statistic who will work 100h in 3 months and will collect 50 €/h		5,000 €
MEETINGS **(including travels and diets)**	Of hospital managers	For protocol standardization and hiring staff	40 € per person	4 meetings and 6 managers (6 centres)	960 €
		For results interpretation and discussion	40 € per person	2 meetings and 6 managers	480 €
	Of all the researchers to contemplate and/or resolve questions about the results and encourage new investigations		40 € per person	1 meeting and 3 surgeons per centre	720 €

PROFESSIONAL TRAINING	Surgeons training (including travel and diet)	40 € per person	2 meetings and 3 surgeons per centre	1,440 €
INSURANCE	Insurance policy	10,000 €	1	10,000 €
FEES	AEMPS	115 €	1	115 €
PUBLICATION	Publication in a journal	2,000 €	1	2,000 €
PRESENTATIONS	National Congress	1,400 €	1	4,400 €
	International Congress	3,000 €	1	
TOTAL COST				**84,555.70 €**

Although our awareness about the important economic resources that we ask, we understand that these are necessary to carry out a study of such magnitude. Maybe we could attempt to hire one and only person to coordinate between centres, organize the events and also do the monitorization and quality control of the data in order to economize the study or even maybe we could get by without a good coordinator and without data manager. However, we believe that this would compromise the validity of our multicentre clinical trial since we propose that every person has his exclusive and specialized job in order to reach the perfection.

Moreover, the 3 years intermediate analysis will prevent us to waste resources, as if it does not support our hypothesis, we would stop the study and this would save us from the 22,855.68 € that cost the TV USs and from the budget for posterior staff hours (1,115 € from the coordinating person, 5,120 € from data manager and 3,330 € from statistic expert). Thus, 32,420.68 € will be returned.

Furthermore, we probably will be made a discount or be forgiven of the AEMPS fees afterwards for proposing a non-commercial clinical investigation.

Finally, we should keep in mind that probably the technique we propose to use in group B (the SLNB with cervical injection of ICG) could minimize the costs of the LAD (according to previous literature) because despite the price of the ICG, it entails a shorter surgical time and we believe (although we have not verify it yet) that the SLNB in stage I EEC would have to budget less time for admission and health care due to the minor postoperative complications that would imply. Therefore, the new technique would be relatively cheaper than the conventional one and could save us resources.

13.FEASIBILITY

We determine that our study is feasible because we have the physical means to realize it (since the participating centres are reference hospitals with sufficient resources to be able to participate in this study). Moreover, for the time calculated, according to our previously mentioned estimations, we can recruit the necessary sample to obtain a good representation of the proposed study population.

Furthermore, we claim that all the members of the research team are perfectly qualified to carry out their work, as they have been carefully selected for their expertise in the field and trained to carry out the same practice.

The previously explained work plan itemizes the steps that make this trial feasible.

14. CONFLICT OF INTERESTS

Authors declare no conflict of interest. No funding sources supported this investigation.

15. BIBLIOGRAPHY

1. Cáncer de endometrio ESMO/ACF: una guía para pacientes [Internet]. Lugano (SW): Society for Medical Oncology, European Anticancer Fundation; 2012. Available from: www.fundacioncontraelcancer.orgwww.esmo.org
2. Holloway RW, Abu-Rustum NR, Backes FJ, Boggess JF, Gotlieb WH, Jeffrey Lowery W, et al. Sentinel lymph node mapping and staging in endometrial cancer: A Society of Gynecologic Oncology literature review with consensus recommendations. Gynecol Oncol. 2017;146(2):405–15.
3. Pölcher M, Rottmann M, Brugger S, Mahner S, Dannecker C, Kiechle M, et al. Lymph node dissection in endometrial cancer and clinical outcome: A population-based study in 5546 patients. Gynecol Oncol [Internet]. 2019;154(1):65–71. Available from: https://doi.org/10.1016/j.ygyno.2019.04.002
4. SEGO. Cáncer de Endometrio. Madrid: Sociedad Española de Ginecología y Obstetricia; 2016.
5. Candido EC, Rangel Neto OF, Toledo MCS, Torres JCC, Cairo AAA, Braganca JF, et al. Systematic lymphadenectomy for intermediate risk endometrial carcinoma treatment does not improve the oncological outcome. Eur J Obstet Gynecol Reprod Biol X [Internet]. 2019;3:100020. Available from: https://doi.org/10.1016/j.eurox.2019.100020
6. Leitao MJ. Sentinel Lymph Node Mapping in Patients with Endometrial Carcinoma: Less Can Be More. Curr Obs Gynecol Rep. 2016;5(4):279–2.
7. Bogani G, Raspagliesi F, Maggiore ULR, Mariani A. Current landscape and future perspective of sentinel node mapping in endometrial cancer. J Gynecol Oncol. 2018;29(6):1–10.
8. NIH. Dictionary of Cancer Terms [Internet]. Bethesda (MD): National Institutes of Health, National Cancer Institute; Available from: https://www.cancer.gov/publications/dictionaries/cancer-terms/def/transvaginal-ultrasound
9. Gastañaga Holguera T. Valor de la linfadenectomía en la supervivencia de las pacientes con adenocarcinoma de endometrio. Universidad Complutense de Madrid; 2013.
10. Instituto Nacional del Cáncer. Biopsia de ganglio linfático centinela. INH; 2011.
11. Lv S, Wang Q, Zhao W, Han L, Wang Q, Batchu N, et al. A review of the postoperative lymphatic leakage. Oncotarget. 2017;8(40):69062–75.
12. NIH. Lymphedema (PDQ®)–Health Professional Version [Internet]. Bethesda (MD): National Institutes of Health; 2019. Available from: https://www.cancer.gov/about-cancer/treatment/side-effects/lymphedema/lymphedema-pdq
13. Bogani G, Murgia F, Ditto A, Raspagliesi F. Sentinel node mapping vs. lymphadenectomy in endometrial cancer: A systematic review and meta-analysis. Gynecol Oncol [Internet]. 2019;153(3):676–83. Available from: https://doi.org/10.1016/j.ygyno.2019.03.254
14. IA A, M A-F, G Z, S S, B K, M S, et al. Sentinel Lymph Nodes in Endometrial Cancer Update 2018. Gynecol Minim Invasive Ther. 2019;(8):94–100.

15. Royal College of Obstetricians and Gynacologists. Sentinel lymph node biopsy in endometrial cancer. Scientific Impact Paper No. 51. 2016.

16. Barlin JN, Khoury-Collado F, Kim CH, Leitao MM, Chi DS, Sonoda Y, et al. The importance of applying a sentinel lymph node mapping algorithm in endometrial cancer staging: Beyond removal of blue nodes. Gynecol Oncol [Internet]. 2012;125(3):531–5. Available from: http://dx.doi.org/10.1016/j.ygyno.2012.02.021

17. Persson J, Geppert B, Lönnerfors C, Bollino M, Måsbäck A. Description of a reproducible anatomically based surgical algorithm for detection of pelvic sentinel lymph nodes in endometrial cancer. Gynecol Oncol [Internet]. 2017;147(1):120–5. Available from: http://dx.doi.org/10.1016/j.ygyno.2017.07.131

18. Wang T, Hu Y, He Y, Sun P, Guo Z. A retrospective validation study of sentinel lymph node mapping for high-risk endometrial cancer. Arch Gynecol Obstet. 2019;299(5):1429–35.

19. Multinu F, Casarin J, Cappuccio S, Keeney G, GE G, Clibly W, et al. Ultrastaging of Negative Pelvic Lymph Nodes to Decrease the True Prevalence of Isolated Paraaortic Dissemination in Endometrial Cancer. Gynecol Oncol. 2019;151(1):60–4.

20. Kumar S, Mariani A, Bakkum-Gamez JN, Weaver AL, McGree ME, Keeney GL, et al. Risk factors that mitigate the role of paraaortic lymphadenectomy in uterine endometrioid cancer. Gynecol Oncol. 2013 Sep 1;130(3):441–5.

21. May K, Bryant A, Ho D, Kehoe S, Morrison J. Lymphadenectomy for the management of endometrial cancer (Review). Cochrane Collab. 2010;(1):30.

22. Mariani A, Dowdy SC, Cliby WA, Gostout BS, Jones MB, Wilson TO, et al. Endometrial cancer : A paradigm shift in surgical staging. Gynecol Oncol. 2008;109(1):11–8.

23. Creasman WT, Morrow CP, Bundy BN, Homesley HD, Graham JE, Heller PB. Surgical Pathologic Spread Patterns of Endometrial Cancer. Cancer [Internet]. 1987;60:2035–41. Available from: http://incan-mexico.org/wp_ginecologia/wp-content/uploads/GOG-33.pdf

24. Tortorella L, Casarin J, Multinu F, Cappuccio S, McGree ME, Weaver AL, et al. Sentinel lymph node biopsy with cervical injection of indocyanine green in apparent early-stage endometrial cancer: predictors of unsuccessful mapping. Gynecol Oncol [Internet]. 2019;155(1):34–8. Available from: https://doi.org/10.1016/j.ygyno.2019.08.008

25. Persson J, Salehi S, Bollino M, Lönnerfors C, Falconer H, Geppert B. Pelvic Sentinel lymph node detection in High-Risk Endometrial Cancer (SHREC-trial)—the final step towards a paradigm shift in surgical staging. Eur J Cancer. 2019;116:77–85.

26. Hopp EE, Osborne JL, Schneider DK, Bojar CJ, Uyar DS. A prospective pilot study on the incidence of post-operative lymphedema in women with endometrial cancer. Gynecol Oncol Reports [Internet]. 2016;15:25–8. Available from: http://dx.doi.org/10.1016/j.gore.2015.12.002

27. T G. Cuidados personales con el linfedema [Internet]. Wellington (FD): National Institutes of Health; 2018. Available from: https://medlineplus.gov/spanish/ency/patientinstructions/000045.htm

28. Angeles MA, Meyrignac O, Martínez-Gómez C, Daboussi A, Segal J, Del M, et al. Aortic abdominal dissection after retroperitoneal laparoscopic paraaortic lymphadenectomy. Gynecol Oncol Reports [Internet]. 2019;29(March):25–8. Available from: https://doi.org/10.1016/j.gore.2019.05.001

29. Franchi M, Ghezzi F, Riva C, Miglierina M, Buttarelli M, Bolis P. Postoperative complications after pelvic lymphadenectomy for the surgical staging of endometrial cancer. J Surg Oncol. 2001;78:232–40.

30. Kennard JA, Stephens AJ, Ahmad S, Zhu X, Singh C, McKenzie ND, et al. Sentinel lymph nodes (SLN) in endometrial cancer: The relationship between primary tumor histology, SLN metastasis size, and non-sentinel node metastasis. Gynecol Oncol [Internet]. 2019;154(1):53–9. Available from: https://doi.org/10.1016/j.ygyno.2019.04.654

31. Body N, Grégoire J, Renaud MC, Sebastianelli A, Grondin K, Plante M. Tips and tricks to improve sentinel lymph node mapping with Indocyanin green in endometrial cancer. Gynecol Oncol [Internet]. 2018;150(2):267–73. Available from: https://doi.org/10.1016/j.ygyno.2018.06.001

32. Kilgore LC, Partridge EE, Alvarez RD, Austin JM, Shingleton HM, Noojin F, et al. Adenocarcinoma of the Endometrium: Survival Comparisons of Patients with and without Pelvic Node Sampling. Gynecol Oncol. 1995 Jan 1;56(1):29–33.

33. Picot J, Cooper K, Bryant J, Clegg AJ. The clinical effectiveness and cost effectiveness of bortezomib and thalidomide in combination regimens with an alkylating agent and a corticosteroid for the first-line treatment of multiple myeloma: A systematic review and economic evaluation. Health Technol Assess (Rockv). 2011;15(41).

34. Symptom Management Guidelines : Lymphedema [Internet]. Vancouver: BC CANCER; 2018. Available from: http://www.bccancer.bc.ca/nursing-site/Documents/9. Lymphedema.pdf

35. Brestcancer.org. Stages of Lymphedema [Internet]. BrestCancer.org; 2016. Available from: https://www.breastcancer.org/treatment/lymphedema/how/stages

36. Mayo Clinic. Deep vein thrombosis (DVT) [Internet]. Scottsdale (AZ): Mayo Clinic; 2018. Available from: https://www.mayoclinic.org/diseases-conditions/deep-vein-thrombosis/symptoms-causes/syc-20352557

37. Domingo-Salvany A, Bacigalupe A, Carrasco JM, Espelt A, Ferrando J, Borrell C. Propuestas de clase social neoweberiana y neomarxista a partir de la Clasificación Nacional de Ocupaciones 2011. Gac Sanit. 2013;27(3):263–72.

38. Colombo N, Creutzberg C, Amant F, Bosse T, González-Martín A, Ledermann J, et al. ESMO–ESGO–ESTRO consensus conference on endometrial cancer: Diagnosis, treatment and follow-up. Radiother Oncol. 2015;117(3):559–81.

39. Raventós Tato RM. Análisis de la afectación ganglionar, recurrencia y supervivencia en el cáncer de endometrio endometrioide [Internet]. Univeristat Autònoma de Barcelona; 2016. Available from: https://www.tdx.cat/handle/10803/399984

16. ANNEXES

16.1. PROTOCOL INFORMATION SHEET FOR PARTICIPANTS

We attach the Catalan version, but it is also available in Spanish.

Full d'informació per la pacient candidata a entrar en el nostre estudi d'investigació

Títol de l'estudi: LA BIÒPSIA DEL GANGLI SENTINELLA versus LA LIMFADENECTOMIA en el CÀNCER ENDOMETRIOIDE D'ENDOMETRI EN ESTADI I AMB RISC INTERMIG O INTERMIG-ALT

Investigador(a) principal: .....

Centre: .....

Benvolguda,

Si se li ha entregat aquest document és perquè creiem que és vostè la pacient ideal per a participar en aquest estudi realitzat per diferents serveis de Ginecologia Oncològica de diferents hospitals de Catalunya. Desitjaríem que ens prestés uns minuts per llegir-se detingudament aquest full informatiu, ja que és important que vostè estigui ben informada per considerar si li agradaria o no participar.

La convidem a preguntar qualsevol dubte o inquietud al respecte i a decidir lliurement si vol o no formar part del nostre projecte, tenint en compte que si accepta la proposta en qualsevol moment podrà fer-se enrere, sense necessitat de donar explicacions i sense que això tingui cap repercussió negativa en la seva assistència sanitària.

A continuació, intentarem resoldre-li els primers dubtes que es puguin haver originat.

PER QUÈ JO SÓC LA MILLOR CANDIDATA?

Perquè vostè ha estat diagnosticada d'un tumor de la capa interna de l'úter (o matriu) que per a poder ser tractat amb garanties requereix que se li treguin certes estructures perifèriques, anomenades ganglis limfàtics, ja que aquest tipus de tumor pot afectar-los i segons si ho fa o no s'afegirà un tractament o un altra a la cirurgia que se li realitzarà.

QUIN ÉS L'OBJECTIU D'AQUEST ESTUDI?

Volem comparar dues tècniques quirúrgiques d'extirpació de ganglis limfàtics (la **limfadenectomia**, que és l'extracció de tots els ganglis limfàtics de la pelvis i del voltant de l'aorta, i la **biòpsia del gangli**

sentinella, que consisteix en l'extracció explícita del gangli limfàtic pelvià dret i esquerra més proper al tumor) perquè creiem que ambdues ofereixen la mateixa supervivència lliure de malaltia. És a dir, pensem que les dues proporcionen el mateix percentatge de reaparició tumoral (recidiva), però per contra, recolzem que la tècnica que actualment es fa servir (la limfadenectomia) comporta moltes més complicacions i una pitjor qualitat de vida pel pacient que la nova tècnica que proposem utilitzar (la biòpsia del gangli sentinella).

QUÈ IMPLICA QUE JO ACCEPTI PARTICIPAR?

Implica acceptar que per atzar, a través d'un programa informàtic, se li assignaria una de les dues tècniques quirúrgiques d'extirpació ganglionar sense que vostè sàpigues quina, però gaudint de les mateixes altres mesures pre-operatòries, intra-operatòries i post-operatòries.

UNA TÈCNICA ÉS MILLOR QUE L'ALTRA?

Per intentar-ho respondre ens hem de plantejar què vol dir millor.

Per la majoria d'oncòlegs, millor significa més temps sense tumor, que implica més temps de vida. Però per la majoria de pacients, millor també significa que aquest temps de vida es pugui considerar de qualitat.

Així doncs, si per millor entenem supervivència i qualitat de vida, quina tècnica és millor?
No ho sabem del cert i és per això que és necessari realitzar estudis com el que es presenta en aquest document.

I SI AL FINAL RESULTA QUE UNA TÈCNICA ÉS MOLT MILLOR QUE L'ALTRA I A MI EM TOCA LA PITJOR?

Tot i que cada estudi té els seus riscos i beneficis, volem que sàpiga que hi ha molts estudis anteriors que han investigat les dues tècniques confirmant la seva eficàcia detectant malaltia ganglionar, i gràcies a aquestes investigacions podem sospitar que la supervivència que comporten és equivalent.

De fet, per aquest tipus i estadi de tumor, tot i que en països com Espanya en la pràctica habitual només es realitzin limfadenectomies, en altres centres d'arreu del món ja s'ha implantat la tècnica del gangli sentinella. Actualment, no hi ha un consens perquè no s'ha realitzat un bon estudi a gran escala amb un seguiment exhaustiu.

Sobretot li volem transmetre un missatge de tranquil·litat, seguretat i legalitat, ja que aquest estudi ha estat aprovat pel *Comitè d'Ètica i Investigació Clínica* i per *l'Agència Espanyola del Medicament i Productes Sanitaris*, seguint la legislació vigent sobre la realització d'assaigs clínics.

No obstant això, en cas que el fet de participar en l'estudi li produís algun dany o perjudici, disposem d'una pòlissa d'assegurança contractada que s'encarregaria de la seva compensació i indemnització.

COBRARÉ O EM SUPOSARÀ UNA DESPESA PARTICIPAR? HAURÉ DE VENIR MÉS SOVINT A L'HOSPITAL?

La resposta a totes aquestes preguntes és no. La participació ha de ser totalment voluntària i sense ànim de lucre. Ni participants ni investigadors rebran cap compensació econòmica, però tampoc els hi suposarà cap despesa. Es faran les mateixes visites de seguiment que es ferien fora de l'estudi i també les mateixes proves si no fos per l'ecografia transvaginal que es farà al cap de cinc anys de l'operació si durant aquest temps no ha tingut signes ni símptomes de recidiva tumoral.

PERÒ ALGO DE MÉS HAURÉ DE FER SI DECIDEIXO PARTICIPAR NO?

L'únic que vostè haurà de fer de més són tres coses.
Primer de tot, firmar el consentiment informat que se li entregarà si comunica al seu metge que vol participar en aquest estudi.
Segon, comprometre's a assistir (en la mesura de lo possible i contant amb les nostres facilitats per adaptar-nos) en les visites de seguiment que se li programaran, tenint en compte que potser serà necessari fer alguna prova per a valorar signes o símptomes.
Per últim, deixar-nos utilitzar les seves dades i mostres biològiques per fins d'investigació.

ES PUBLICARAN LES MEVES DADES PERSONALS O MÈDIQUES?

No. Totes les seves dades seran tractades amb la més absoluta confidencialitat segons l'establert a la *"Ley Orgánica 15/1999, de 13 de Diciembre, de Protección de Datos de Carácter Personal"* i en la seva última modificació *"Real Decreto-ley 5/2018, de 27 de julio, de medidas urgentes para la adaptación del Derecho español a la normativa de la Unión Europea en materia de protección de datos".*

I SI NO HI GUANYO RES I A SOBRE M'HE DE COMPROMETRE A VENIR I POTSER M'HE DE FER DOS PROVES MÉS, PERQUÈ HAURIA DE PARTICIPAR?

Perquè pot ajudar a aclarir un buit de coneixement de gran importància clínica, ja que si es confirmen les nostres sospites podríem començar a practicar una millor tècnica quirúrgica de la qual potser vostè mateixa se'n beneficiaria, així com altres dones que en un futur es trobin en la seva situació.

COM I AMB QUI PUC CONTACTAR SI TINC DUBTES O PROBLEMES?

Disposem d'una persona que s'encarregarà d'aclarir-li tots els dubtes que li puguin sorgir.

Responsable referent: .....
E-mail:.....
Telèfon: .....

Moltes gràcies per l'atenció i consideració.

16.2. INFORMED CONSENT DOCUMENTS

16.2.1. Study Informed consent

We attach the Catalan version, but it is also available in Spanish.

Document de consentiment informat de participació en estudi

Jo, …….. , amb DNI/NIE …….., accepto voluntàriament participar en l'assaig clínic "La biòpsia del gangli sentinella versus la limfadenectomia en el carcinoma endometrioide en estadi I amb risc intermig o intermig-alt" i confirmo que:

- He estat informada adientment per el/la Dr./Dra. ……
- He llegit i entès el full d'informació que se m'ha entregat.
- He pogut realitzar qualsevol pregunta relacionada amb l'estudi als responsables d'aquest i els meus dubtes han quedat resolts.
- Se m'han exposat les possibles alternatives a aquest estudi.
- Entenc el meu paper com a participant de l'estudi.
- Entenc els possibles beneficis i riscos que se'n deriven.
- Comprenc que la meva participació és voluntària i que podré revocar el consentiment prèviament signat en qualsevol moment, retirant-me de l'estudi sense haver de donar explicacions i sense que això repercuteixi en la meva atenció mèdica i els meus drets.

Així doncs, dono la meva conformitat per a participar en l'estudi.

Signatura de la pacient Signatura de l'investigador(a)

Lloc i data: …….. , …… de …….. del 20……

REVOCACIÓ (denegació del consentiment atorgat)

Firma i DNI de la pacient: .....

16.2.2. Surgery informed consent

Patients will have to sign 3 ICs: one for the hysterectomy and the BSO, one for the pelvic and para-aortic LAD and one for the SLNB, since they will not know to which of the two lymphatic techniques they will be submitted and therefore, they will have to accept both ICs, understanding that they agree with any of these.

We attach the Spanish version of the 3 ICs, but they are also available in Catalan.

Documento de consentimiento informado de la HISTERECTOMÍA + DOBLE ANEXECTOMÍA

Este consentimiento se formula de acuerdo con lo que establece la Ley 41/2002, de 14 de Noviembre, Básica Reguladora de la Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica.

CENTRO SANITARIO	SERVICIO DE
	GINECOLOGÍA ONCOLÓGICA

OBJETIVO DEL PROCEDIMIENTO

Se trata de extirpar el útero y los anejos (es decir, trompas de Falopio y ovarios).

En mi caso la indicación quirúrgica es: ADENOCARCINOMA ENDOMETRIOIDE

DESCRIPCIÓN DEL PROCEDIMIENTO

La histerectomía consiste en la extirpación del útero. Asimismo, esta lleva asociada la extirpación de los anejos (ovarios y trompas). Se puede practicar por vía laparoscópica, vaginal o laparotomía.

En mi caso se practicará preferentemente por vía: LAPAROSCÓPICA

Esta intervención precisa anestesia. El Servicio de Anestesia valorará su caso y le informará del tipo de anestesia más adecuada para usted.

CONSECUENCIAS DE LA CIRUGÍA

La histerectomía supone la no posibilidad de tener hijos, así como la ausencia de menstruaciones. La histerectomía con anexectomía bilateral conlleva la instauración de la menopausia en la mujer joven, pudiendo recibir terapia hormonal sustitutiva posteriormente, según indicación médica.

RIESGOS GENERALES

Toda intervención quirúrgica, tanto por la propia técnica, como por la situación vital de cada paciente (obesidad, edad avanzada, hipertensión, diabetes, anemia, etc.) lleva implícita una serie de posibles complicaciones comunes y potencialmente serias que podrían requerir tratamientos complementarios, tanto médicos como quirúrgicos, así como un mínimo porcentaje de mortalidad. Las complicaciones pueden aparecer en el mismo acto quirúrgico, en el periodo inmediato o a medio o largo plazo.

• **Complicaciones de la intervención:**

1. Infecciones con posible evolución febril (de cicatriz quirúrgica, pélvicas, urinarias…).
2. Hemorragias que precisen reintervención quirúrgica y/o transfusión sanguínea.
3. Lesiones intestinales, vesicales, uretrales, vasculares y/o neurológicas.
4. Fistulas.
5. Tromboembolismo venoso profundo o pulmonar.

• **Complicaciones a largo plazo:** prolapsos (descenso) de órganos pélvicos y hernias abdominales.

RIESGOS PERSONALIZADOS (explicar los riesgos según las características de la paciente):

.....

.....

ANATOMÍA PATOLÓGICA

Todas las piezas operatorias o materiales extirpados serán enviados para completar el estudio anatomopatológico definitivo, siendo la paciente y/o sus familiares o representante legal, en su caso, informados de los resultados del estudio.

Autorizo que el excedente de material biológico utilizado para pruebas diagnósticas y la información clínica asociada se pueda utilizar para investigación.

También autorizo a que se hagan fotos o vídeos para documentar el caso o con fines docentes de difusión del conocimiento científico, siempre que sea preservada mi identidad de forma confidencial.

ALTERNATIVAS

Si en el momento del acto quirúrgico surgiera algún imprevisto, el equipo médico podrá modificar la técnica quirúrgica programada.

Apellidos y nombre de la **paciente:** .....

.....

DNI de la **paciente:** .....

AUTORIZACIÓN

He comprendido las explicaciones que se me han facilitado en un lenguaje claro y sencillo, y el facultativo que me ha atendido me ha permitido realizar todas las observaciones **y me ha aclarado** todas las dudas que le he planteado.

Me han informado y he entendido plenamente los riesgos posibles. Si surge alguna complicación, doy mi consentimiento para que se haga lo que sea necesario y convenga.

También comprendo que, en cualquier momento y sin necesidad de dar ninguna explicación, puedo revocar el consentimiento que ahora presto.

Por ello, manifiesto que estoy **satisfecha** con la información recibida y que **comprendo** el alcance y los riesgos del tratamiento quirúrgico propuesto**.**

He recibido una copia de este documento.

Apellidos del **médico** que informa: .....

Nombre del **médico** que informa: .....

No de colegiado: .....

Fdo.: El/la **médico** que informa Fdo.: La **paciente**

Fecha y lugar: .....

REVOCACIÓN (denegación del consentimiento otorgado)

Firma y DNI de la **paciente:** .....

Documento de consentimiento informado de la LINFADENECTOMÍA PÉLVICA Y PARAÓRTICA

Este consentimiento se formula de acuerdo con lo que establece la Ley 41/2002, de 14 de Noviembre, Básica Reguladora de la Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica.

CENTRO SANITARIO	SERVICIO DE
	GINECOLOGÍA ONCOLÓGICA

OBJETIVO DEL PROCEDIMIENTO

La principal vía de diseminación de los tumores ginecológicos es a través de los ganglios linfáticos, sobretodo de la pelvis.

La linfadenectomía pélvica y paraórtica forma parte de la estadificación quirúrgica de los tumores ginecológicos como el de Endometrio; así, se realiza para valorar la extensión de la enfermedad. Los ganglios linfáticos se estudian mediante técnicas de Anatomía Patológica, con el objetivo de conocer la extensión tumoral. El objetivo es analizar si las células del tumor primario se han extendido a los ganglios, para poder planificar el tratamiento más adecuado para la paciente, con impacto en el pronóstico de la enfermedad.

DESCRIPCIÓN DEL PROCEDIMIENTO

La linfadenectomía consiste en la extirpación de los ganglios linfáticos que se encuentran situados en las cadenas pélvicas y/o paraórticas.

La linfadenectomía pélvica bilateral consiste en la extirpación de los ganglios pélvicos, tejido ganglionar y graso de la pelvis, en el territorio vascular ilíaco externo, interno, interilíaco y obturador. Identificando además el nervio obturador y los nervios genitofemoral y genitocrural.

La linfadenectomía paraórtica pretende la extirpación del tejido linfático que rodea a los grandes vasos (a nivel paraórtico) bajo anestesia general.

El Servicio de Anestesia valorará su caso y le informará del tipo de anestesia más adecuada para usted.

En mi caso el tipo de cirugía que se efectuará será: LAPAROSCÓPICA CON ASISTENCIA ROBÓTICA

La utilización de la laparoscopia persigue un menor dolor en el postoperatorio, disminuir las complicaciones relacionadas con la herida abdominal, una estancia hospitalaria más corta, así como la más rápida recuperación de la actividad habitual.

Es posible que una vez comenzada la cirugía por vía laparoscópica tenga que reconvertirse a cirugía abierta si las condiciones generales del paciente o del campo quirúrgico así lo requieren.

CONSECUENCIAS DE LA CIRUGÍA

Durante el acto quirúrgico, a la vista de los hallazgos, el cirujano puede tomar la decisión de no realizarla total o parcialmente, porque la enfermedad esté más avanzada de lo previsto o por dificultades técnicas.

La extirpación de los ganglios linfáticos supone una alteración importante del drenaje linfático de estas regiones anatómicas.

El análisis de los ganglios puede modificar la conducta terapéutica después de la cirugía, pudiendo ser necesario un tratamiento complementario con radioterapia y/o quimioterapia.

RIESGOS GENERALES

A pesar de la adecuada elección de la técnica y de su correcta realización pueden presentarse efectos indeseables, tanto los comunes a toda intervención y que pueden afectar a todos los órganos y sistemas, como otros específicos del procedimiento.

Frecuentes:

- No conseguir la extirpación de los ganglios o masas retroperitoneales o lograrlo solo parcialmente.

- Persistencia de la sintomatología previa total o parcialmente.

- **Complicaciones por alteración del drenaje linfático:** linforrea o pérdida de líquido linfático de duración imprevisible.

Infrecuentes:

- Complicaciones del procedimiento quirúrgico: Hemorragia incoercible tanto durante el acto quirúrgico como en el postoperatorio que puede obligar a reintervenir para solucionar la hemorragia; posible necesidad de transfusión; parálisis u obstrucción intestinal; lesión térmica intestinal; lesión uretral o vesical; lesiones nerviosas (nervio obturador, nervios genitofemoral y genitocrural); infecciones, abscesos y peritonitis; hematoma pélvico; fístulas intestinales o urológicas; tromboembolismo venoso profundo o pulmonar cuya gravedad depende de la intensidad del proceso.

- **Problemas y complicaciones derivadas de las incisiones de los puertos**: infección con diferente gravedad; dehiscencia de sutura; defectos estéticos derivados de algunas de las complicaciones anteriores o procesos cicatriciales anormales; intolerancia a los materiales de sutura que pueden llegar incluso a la necesidad de reintervención para su extracción; seroma; herniaciones; eventraciones; quemaduras; neuralgias -dolores nerviosos-; hiperestesias -aumento de la sensibilidad- o hipostesias -disminución de la sensibilidad-.

- **Complicaciones laparoscópicas por la entrada de gas CO2 - Dióxido de Carbono en el abdomen:** enfisema subcutáneo. Problemas pulmonares, cardiacos o renales. Implantes peritoneales o en puertos de entrada. Embolismo gaseoso. Dolor hombro.

- **Complicaciones por alteración del drenaje linfático:** Linfedema. Linfocele. Celulitis.

Estas complicaciones habitualmente se resuelven con tratamiento médico (medicamentos, sueros…) pero pueden llegar a requerir una reintervención, generalmente de urgencia, incluyendo un riesgo de mortalidad.

RIEGOS PERSONALIZADOS (explicar los riesgos según las características de la paciente): .....

.....

Urológicos, vasculares, digestivos, sangrado, hemoperitoneo, infecciones, transfusión, descompensación de las patologías de base de la paciente, fallo multiorgánico.

Toda intervención quirúrgica, tanto por la propia técnica como por el estado de salud de cada paciente (diabetes, cardiopatías, hipertensión, anemia, obesidad, edad avanzada...) lleva implícita una serie de posibles complicaciones comunes y potencialmente serias no exentas de un porcentaje mínimo de mortalidad, pero que podrían requerir tratamientos complementarios tanto médicos como quirúrgicos. Si en el momento del acto quirúrgico surgiera algún imprevisto, el equipo médico podrá modificar la técnica quirúrgica habitual o programada.

En caso de padecer problemas de salud relevantes o estar bajo los efectos de cierta medicación de riesgo concomitante (antiagregantes, anticoagulantes, etc.) la probabilidad de experimentar complicaciones puede aumentar.

Por mi situación actual (diabetes, obesidad, HTA, anemia, edad avanzada...) puede aumentar la frecuencia o la gravedad de riesgos o complicaciones.

ANATOMÍA PATOLÓGICA

Toda la pieza operatoria o material extirpado será enviado para completar el estudio anatomopatológico definitivo, siendo la paciente y/o sus familiares o representante legal, en su caso, informados de los resultados del estudio.

Autorizo que el excedente de material biológico utilizado para pruebas diagnósticas y la información clínica asociada se pueda utilizar para investigación. También autorizo a que se hagan fotos o videos para documentar el caso o con fines docentes de difusión del conocimiento científico, siempre que sea preservada mi identidad de forma confidencial.

ALTERNATIVAS

Me han explicado la existencia de otras posibles opciones terapéuticas como tratamiento quimioterápico, radioterápico, hormonoterápico con sus respectivas complicaciones.

Apellidos y nombre de la **paciente:** .....

.....

DNI de la **paciente:** .....

AUTORIZACIÓN

He comprendido las explicaciones que se me han facilitado en un lenguaje claro y sencillo, y el facultativo que me ha atendido me ha permitido realizar todas las observaciones **y me ha aclarado** todas las dudas que le he planteado.

Me han informado y he entendido plenamente los riesgos posibles. Si surge alguna complicación, doy mi consentimiento para que se haga lo que sea necesario y convenga.

También comprendo que, en cualquier momento y sin necesidad de dar ninguna explicación, puedo revocar el consentimiento que ahora presto.

Por ello, manifiesto que estoy **satisfecha** con la información recibida y que **comprendo** el alcance y los riesgos del tratamiento quirúrgico propuesto**.**

He recibido una copia de este documento.

Apellidos del **médico** que informa: .....

Nombre del **médico** que informa: .....

No de colegiado: ....

Fdo.: El/la **médico** que informa Fdo.: La **paciente**

Fecha y lugar .....

REVOCACIÓN (denegación del consentimiento otorgado)

Firma y DNI de la **paciente**: .....

Documento de consentimiento informado de la BIOPSIA SELECTIVA DEL GANGLIO CENTINELA

Este consentimiento se formula de acuerdo con lo que establece la Ley 41/2002, de 14 de Noviembre, Básica Reguladora de la Autonomía del Paciente y de Derechos y Obligaciones en Materia de Información y Documentación Clínica.

CENTRO SANITARIO	SERVICIO DE
	GINECOLOGÍA ONCOLÓGICA

OBJETIVO DEL PROCEDIMIENTO

El Ganglio Centinela es el primer ganglio al que llegarían las células tumorales en el caso de haberse extendido desde la lesión tumoral, a través de los vasos linfáticos, hasta la región pélvica o inguinal. En ocasiones el drenaje pélvico puede ser más alejado, llegando a nivel más superior o paraaórtico.

La técnica de ganglio centinela forma parte de la Estatificación Quirúrgica del tumor aparentemente confinado a su localización de origen, en este caso el CÁNCER DE ENDOMETRIO, y en ausencia de metástasis por técnicas de imagen y exploración clínica.

El o los ganglios centinelas se estudian mediante técnicas anatomopatológicas de Ultraestadificación. El objetivo es realizar un procedimiento selectivo, más exhaustivo y preciso de aquel/aquellos ganglios con mayor riesgo de albergar células tumorales, para poder aplicar el tratamiento más adecuado para la paciente, con impacto en el pronostico de la enfermedad.

DESCRIPCIÓN DEL PROCEDIMIENTO

La Biopsia Selectiva de Ganglio Centinela consiste en identificar y extirpar uno o más ganglios inguinales o pélvicos, de manera bilateral, a través de una incisión superficial en la piel.

En el cáncer de Endometrio, la técnica de detección, exéresis y análisis (diferido) del ganglio centinela se realiza con la indicación de enfermedad limitada al útero.

En mi caso el tipo de cirugía quirúrgica que se efectuará será: LAPAROSCÓPICA, CON ASISTENCIA ROBÓTICA

- **Realización**

  En mi caso, la técnica de localización del ganglio centinela requerirá de la inyección pericervical de un colorante (Verde de Indocianina) en el mismo acto quirúrgico, que permitirá su localización mediante captación por imagen durante la cirugía.

La pieza o piezas extirpadas en la intervención se someterán a estudio anatomopatológico, mediante ultraestadificación, realizando tres niveles de análisis: histológico, inmunohistoquímico y molecular.

Esta intervención precisa anestesia. El Servicio de Anestesia valorará su caso y le informará del tipo de anestesia más adecuada para usted.

CONSECUENCIAS DE LA CIRUGÍA

El análisis de los ganglios centinelas puede modificar la conducta terapéutica después de la cirugía, pudiendo ser necesario un tratamiento complementario con radioterapia i/o quimioterapia.

RIESGOS GENERALES

1. **Complicaciones Herida Quirúrgica:** Infección. Seroma. Dehiscencia. Herniaciones. Eventraciones. Quemaduras.

2. **Complicaciones Procedimiento Quirúrgico:** Hemorragias, posible necesidad de transfusión. Parálisis u obstrucción intestinal. Lesión térmica intestinal. Lesión uretral o vesical. Lesiones nerviosas (nervio obturador, nervios genitofermoral y genitocrural). Infecciones, abscesos y peritonitis. Hematoma pélvico. Fistulas intestinales o urológicas. Tromboembolismos venosos o pulmonares.

3. **Complicaciones laparoscópicas por la entrada de gas CO2-Dióxido de Carbono en el abdomen:** Enfisema subcutáneo. Problemas pulmonares, cardiacos o renales. Implantes peritoneales o en puertos de entrada. Embolismo gaseoso. Dolor hombro.

4. **En algunas ocasiones no se consigue localizar el ganglio centinela por lo que será preciso realizar la Linfadenectomía, siendo las complicaciones asociadas a alteración del drenaje linfático:** Linfedema. Linforrea. Linfocele. Celulitis.

5. **Otras complicaciones:** La sustancia inyectada como marcador del ganglio centinela emite una cantidad mínima de radiación, que no supone ningún riesgo añadido. Excepcionalmente reacción alérgica grave al colorante empleado.

RIESGOS PERSONALIZADOS (explicar los riesgos según las características de la paciente):
.....
.....

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Si en el momento del acto quirúrgico surgiera algún imprevisto, el equipo médico podrá modificar la técnica quirúrgica habitual o programada. Por otro lado, estas complicaciones habitualmente se resuelven con tratamiento médico (medicamentos, sueros) pero pueden llegar a requerir de reintervención con carácter urgente, no exento como se ha comentado, de un riesgo de mortalidad.

ANATOMÍA PATOLÓGICA

Toda la pieza operatoria o material extirpado será enviado para completar el estudio anatomopatológico definitivo, siendo la paciente y/o sus familiares o representante legal, en su caso, informados de los resultados del estudio.

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