SENTINEL LYMPH NODE IN ENDOMETRIAL CANCER: Validation of the selective sentinel lymph node biopsy technique

FINAL DEGREE PROJECT

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Agraeixo al servei de Ginecologia Oncològica del Hospital Universitari Dr. Josep Trueta de Girona i en especial a la Dra. Elena Álvarez Castaño, tutora del meu treball de final de grau. També m'agradaria agrair a la meva família, amics i sobretot a la Sally Palet. Gràcies.

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1. ABBREVIATIONS

BT	Brachytherapy
CKPT	Cytokeratin-positive cells
EC	Endometrial Cancer
FIGO	International Federation of Gynaecology and Obstetrics
H&E	Hematoxylin and Eosin
ICG	Indocyanine Green
IHC	Immunohistochemistry
ITC	Isolated Tumour Cells
LN	Lymph Node
LND	Lymph node dissection / Lymphadenectomy
LVSI	Lymph Vascular Space Invasion
mM	Micrometastasis
MM	Macrometastasis
NPV	Negative Predictive Value
ParaAo	Para-aortic
PLN	Pelvic Lymph Nodes
QT	Chemotherapy
RT	Radiotherapy
SLN	Sentinel Lymph Node
SPECT	Single Photon Emission Computed Tomography
SS	Surgical Staging
Tc99	Technetium colloid
TUMIR	Transvaginal ultrasound-guided myometrial injection of radiotracer

2. ABSTRACT

TITLE	*Sentinel lymph node in Endometrial cancer: validation of the selective sentinel lymph node biopsy technique*
BACKGROUND	Surgical staging of the endometrial cancer includes lymphadenectomy. Lymphadenectomy is associated with high earlier morbidity. Though, there is still an inability to predict which patients have lymph nodes affected and would benefit from lymphadenectomy, it continues to be the only accurate way to provide the lymphatic status of the disease, prognosis and the needing of adjuvant treatment to the patient. Sentinel lymph node mapping is a promising technique to validate and apply in the routine performance to avoid the lymphadenectomy to the patients that do not need it.
AIM	The goal of the study is to evaluate the validation of the selective sentinel lymph node biopsy technique in endometrial cancer in Hospital Universitari Dr. Josep Trueta of Girona, including sensitivity, specificity and negative predictive value.
METHODS	A cross-sectional design carried out within Gynaecology Oncologic Unit at Hospital Universitari Dr. Josep Trueta in Girona, in a period of time of three years and four months.
PARTICIPANTS	A total of 95 patients with EC diagnosis will be included in the study.
KEYWORDS	Sentinel Lymph Node Biopsy, Endometrial Cancer, Technetium, Blue dye, Cervical injection, Transvaginal ultrasound-guided myometrial injection radiotracer.

3. INTRODUCTION

3.1. MAGNITUDE OF THE PROBLEM

It is known that sentinel lymph node (SLN) is a standard of care in breast cancer, melanoma and vulvar cancer to assess lymphatic spread (1–6). In select cervical cancer cases, SLN is performed in some places world-wide and may soon emerge as a part of the daily practice. Endometrial cancer (EC) SLN is more controversial. EC SLN was proposed pioneering by Burke et al. in 1996 and it is still in a preliminary stage of evaluation. EC SLN has been suggested to minimize both the rate of unnecessary lymph node dissection (LND) in low risk women, as well as the risk of under-staging and under-treating (1,4,7–10).

The biggest problem is because of the midline position of the uterus and its bilateral lymphatic drainage consisting of pelvic and para-aortic (paraAo) drainage. For these reasons, SLN mapping is really difficult to define (1,2,4,10). It is known that firstly occurs pelvic lymph nodes (PLN) metastasis and secondly to the paraAo regions, but we did not always find this, not in type II cancers (1,2). Those cases are known as isolated paraAo SLN and it occurs when a SLN is found in paraAo regions and there is an absence of mapping in the pelvic regions, but it is extremely rare, reporting more cases each study (1,2,11). The drain is not always bilateral either (2).

Systematic lymph node (LN) assessment has been recommended to do in surgical staging (SS) since 1988, but the role and extention of the LND has been discussed from the beginning (1,7,12–14). Mostly in EC early stages the recommendations ranged from no LND to systematic complete pelvic and paraAo lymphadenectomy across institutions. Both approaches risk under or over-treatment of the EC (7,11,15,16). LND is still the only procedure that provides a proper evaluation of the lymphatic spread of the EC, its prognosis, the risk of recurrence and the need of adjuvant therapies. We must see LND for all of these and not for their supposed therapeutic approach, because it is still questionable (5,7,9,13,17,18).

SLN biopsy could be an attractive and cost-effective possible solution to the controversies on lymphadenectomy in low and intermediate risk patients of EC who will not benefit from complete lymphadenectomy. SLN would correctly stage EC avoiding aggressive surgical procedures. The SLN information would determine likewise the prognostic and adjuvant therapy (2,8,12).

The technique is very practical: An intraoperative assessment is done and if the SLN is negative, LND could be avoided reducing morbidity and optimizing resources. And, if it is

positive, LND would be held (15,17,19). Obviously, the SLN detection, dissection and removal increase the duration of the surgery (2).

SLN search the adequate information about the extension of LN involvement avoiding potential complications of LND as lymphoedema, lymphocysts, deep vein thrombosis, associates pressure symptoms, vessels and nerves damage (11,12,20,21). Other drawbacks of LND are that can be risky and difficult in people with comorbidities as obesity, hypertension or diabetes (2).

SLN has been an object of study in EC because:

- Lymphatic system is the principal route of tumorous dissemination.
- Prevalence of LN involvement is low in early stages.
- Surgical complications of LND are currently present.
- Negative results about the therapeutic role of lymphadenectomy (8,22).

Until now, the relatively low detection rate and nuclear medicine requirements have made the SLN biopsy more difficult to spread (17). Another huge problem is the search for the injection site and the tracer that best represents the drainage of the tumour (2,5,7,8,10,15).

Since 1996 there are many groups reporting their experience on EC SLN technique (23). Although the experience reported in literature is promising, it is to date, scarce. In most centres this technique is not a part of the routine management of these tumours, yet. Most of the studies agree that SLN in EC deserves further evaluation because it is a technique with a great future (4,5,10,18,22).

3.2. BACKGROUND

3.2.1. ENDOMETRIAL CANCER

Endometrial cancer (EC) is the sixth most common malignancy cancer in women (24). As well, EC is the most common malign gynaecologic cancer in industrialized countries of Europe and North America (5,10,18,25–29). This is, also, the second gynaecologic cancer with higher mortality after ovarian cancer (25). And the seventh most common cause of cancer death in women, accounting for 1-2% of all deaths from cancer (26,27).

According to “Oncoguia SEGO: Cáncer de Endometrio 2010” the adjusted incidence by age in Spain is 10.4 per 100.000 women/year (lower than the European Union incidence, that is 13.6 cases/100000 women/year in 2012 according European Society for Medical Oncology) and mortality is 2.4 per 100.000 women/year (the European is of 4-5 per 100.000 women/year). The incidence has been increasing in recent years, mostly due to the aging and obesity(2,18,22,25,27,30).

The mean age of presentation is 63 years old and in general EC is more frequent after 50 years old (more than 90%), if it appears before 40 years old (4% of women), we have to take in to account the possibility of having a family cancer syndrome such as Lynch syndrome or hereditary non-polyposis colorectal cancer (18,25,27,28).

Some risk factors are: exposure to exogenous oestrogens, hyperinsulinism, family cancer syndrome, tamoxifen, obesity (BMI >30), advanced age, polycystic ovarian syndrome, late menopause and early menarche, sterility history, nulliparity, diabetes mellitus, hypertension... (14,18,25,27,29).

It is known that hormonal contraceptive exercises a protect action against EC, smoking do it too, but not advisable (18,25).

There is not a population screening test useful on EC patients, not even in patients in treatment with tamoxifen or oestrogens. It is necessary to alert women with the principal symptoms and signs to consult and encourage them to adopt an active lifestyle to reduce the risk factors. The only screening made is to do a gynaecological examination, transvaginal ultrasound and aspiration biopsy in women with family cancer syndrome annually from 35 years old, considering hysterectomy from 40 years old (18,25).

- **Types of EC tumours** *(Annex 1)*

WHO pathological classification differentiates between:

I. Endometrioid adenocarcinoma (80%). It is composed of malignant glandular epithelial elements. This type is hormone-dependent caused by an excess of oestrogenism without progesterone counteract. Sometimes is developed from atypical hyperplasia. It is not usually very aggressive and it is slow to spread (14,18,25,27,28).

II. Not-endometrioid cancer. It includes serous (5-10%), clear cells cancers (1-5%), mucinous, mixed, squamous cell, transitional cell, carcinosarcoma[1] and undifferentiated carcinomas are some types. Those are not related with oestrogens exposure and are more frequent in post-menopausal women. This type is more aggressive and it has worse prognosis, because of the advanced stage on the diagnostic (14,18,25–27,30).

Histological grade:

The histological grade can be determined by uterine biopsy or by the final pathological evaluation of the hysterectomy specimen. We can divide the type 1 EC in three grades of differentiation as follows:

HISTOLOGICAL GRADE
- **G1:** Well differentiated, it represents less than 5% of solid tumour. - **G2:** Moderately differentiated, it represents between 6 – 50% of solid tumour - **G3:** Poorly differentiated, it represents more than 50% of solid tumour. We can consider that all the type II EC diagnosed is G3.

(4,14,25,28,30)

- **Diagnose**

SIMPTOMS

- Post-menopausal bleeding or pink flow. EC associated in 20% of the cases.
- Inter-menstrual bleeding or anomalous and/or excessive menstruation (around 45 -55 years old).
- Purulent genital secretion in elderly women (18,25,28,29).

[1] Carcinosarcoma: It is a metaplastic carcinoma containing both sarcomatous and carcinomatous elements. It is rare and aggressive: at diagnosis more than 35% presents extra-uterine disease and a 5-year surveillance of 50% (18).

SUSPECTED DIAGNOSIS

If there is a suspected sign of EC it is necessary to do a transvaginal ultrasound. The transvaginal ultrasound allows us to rule out organic pathology and measure endometrial thickness in longitudinal section (25,28,30).

DIAGNOSTIC CONFIRMATION

If there are clinical and ultra-sonographic suspicion (thickness of more than 4 mm in postmenopausal women and 16 mm in premenopausal) an endometrial aspiration biopsy outpatient is recommended. If the endometrial biopsy is not satisfactory or negative and the clinic persists, it will be necessary to do a hysteroscopy diagnosis and a directed biopsy or curettage. The EC diagnosis requires histopathological confirmation (25,28,30).

- **FIGO Staging**

In 1987, the Gynaecologic Oncology Group Protocol 33, did a prospective study to demonstrate the limitation of clinical assignment of stage compared with surgical-pathological evaluation. In this study 22% of patients with clinical stage I were found to have metastatic extra-uterine disease. The metastatic pattern vas defined. They also found that the probability of finding metastasis was correlated with final tumour grade using hysterectomy specimens. With that data, it was possible to determine how necessary it was to do a SS instead of clinical (4,28).

The staging of the EC is surgical since 1988 (4,13,29,31). The staging system used most widely is the one designed by Féderation Internationale de Gynécologie et d'Obstétrique (FIGO), which it was created in 1958, updated in 1988 and most recently revised in 2009 (28) (see Table).

Table . (28)
FIGO Staging of Endometrial Carcinoma

Stage	Description
I	Tumor confined to the uterus
IA	<50% invasion of the myometrium
IB	≥50% invasion of the myometrium
II	Tumor invades the cervical stroma but does not extend beyond the uterus
III	Local or regional spread of tumor
IIIA	Serosal or adnexal invasion
IIIB	Vaginal or parametrial involvement
IIIC	Metastasis to pelvic or paraaortic lymph nodes
IIIC1	Pelvic lymph node involvement
IIIC2	Paraaortic lymph node involvement (with or without pelvic nodes)
IV	Extension to the pelvic wall, lower one-third of the vagina, or hydronephrosis or nonfunctioning kidney
IVA	Invasion of bladder or bowel mucosa
IVB	Distant metastases, including abdominal, or involvement of inguinal lymph nodes

About 75% of patients are presented with stage I and have a good prognosis with an inherently low risk of LN metastasis. Many of those patients can be cured only by surgery (5,7,13,18,30,31).

The correlation between preoperative tumour and final SS is only modest. The histological diagnosis (including stage and grade) is changed at final SS in up to 25% of cases (4,13–15,30).

- **Metastasis**

The most frequent via metastasis is the lymphatic system through pelvic and paraAo LNs. The risk of metastasis is determined by the depth of myometrial invasion, lymph vascular space invasion (LVSI) and histological grade as well as the histological subtype. In general, the endometrioid adenocarcinoma with invasion <50% of myometrial thickness (stage IA) and with histological grade I or II, metastasis is infrequent (in G1, the risk of node metastasis is approximately 2.8% for pelvic metastasis and 2% for paraAo metastasis; while G3 is 18% for pelvic and 11 for paraAo nodes metastasis). Direct extension and hematogenic dissemination it also happens (4,22,29).

If there is infiltration of PLN, around 50% of these patients will have affected the paraAo chain. Isolated paraAo LNs affects just 1% of these patients (22).

- **Management and treatment.**

The EC management has been heterogeneous between different countries and institutions (13,17).

- *Surgical management:*

Surgery has two main goals: removal of the cancer and accurate documentation of the extent of the disease (staging) (4).

Prior to the SS , patients should have a chest X-ray, clinical and gynaecological examination (transvaginal ultrasound), blood count, liver and renal function profile and a CT-scan of the abdomen and retroperitoneal nodes, to determine the therapeutic strategy (18,27,30). FIGO is doing some research to also implement the magnetic resonance imaging (MRI) to accurately limit the extension of EC at diagnosis (depth of myometrial invasion, cervical stromal invasion and metastatic spread) and help to stratify the risk and determine the therapeutic strategy. But this is not completely implemented, yet (28).

According to “Oncoguia SEGO: Cáncer de Endometrio 2010”, the treatment is based principally on the SS (25)

SS TYPE 1	**SS TYPE 2**
▪ Total hysterectomy ▪ Bilateral annexectomy ▪ Pelvic and paraAo lymphadenectomy [2] (it depends on the risk groups, LND is not routinely performed in low risk patients because its clinical benefit remain uncertain)	• Peritoneal washing for oncologic cytology (it is not longer considered mandatory(18)) • Total hysterectomy • Bilateral annexectomy • Pelvic and paraAo lymphadenectomy (always it is necessary) • Omentectomy • Appendicectomy
(18,25,27,28,30) *(Annex 2)*	(25,27,28,30)*(Annex 3)*

Type II cancers are more aggressive in the early stages and are high grade lesions. For this reason the surgery is more extensive. Type II tumours demonstrate a pattern of metastatic spread in a similar way as ovarian carcinoma (4,25–30)

The traditional approach is surgery via an open, laparotomy incision. Laparoscopic surgery in EC has the same outcomes than laparotomy but with laparoscopic advantages. Laparoscopic surgery will be preferred because of being a less invasive procedure, their disease-free survivals and reduced postoperative morbidity, hospital stay and cost. Especially it will be done in patients with comorbidities (16–18,25,31).

Surgery is recommended only if optimal cytoreduction can be achieved (18).

- *Lymphadenectomy:*

A controversial issue is whether to perform or not lymphadenectomy because of the inability to predict which patients would benefit from LND. LND is associated with a higher earlier morbidity and complications. Nevertheless, it continues to be the only accurate way to provide the lymphatic status of the disease, the prognosis, the needing of adjuvant therapy and is the standard of care to do the EC SS (10,17,22,24,26,29).

[2] Pelvic lymphadenectomy includes complete resection of the fatty and LN of the common, external and iliac vessels above and below the obturator nerve (10,17,26,34).

Paraortic lymphadenectomy landmarks should be presacral area as the lower borderline and right ovarian vein insertion to vena cava and left renal vessels as upper boundary (the LND anatomical borders are still controversial, the Gynecologic Oncology Group guideline consider the upper borderline as inferior mesenteric artery) (7,9,10,16–18).

The European Society of Medical Oncology (EMSO) has subdivided the patients with early stages of EC into risk groups according to survival and relapse:

RISK GROUPS
- **Low risk** (<1%): IA G1-2 type 1 EC - **Intermediate risk:** IA G3, IB G1-2, II G1-2 type 1 EC - **High risk** (17%): IB G3 and II G3 type 1 EC; any type 2 EC

(17,25,28,30)

Risks groups have been determined to guide the needing of LND. Those risk groups indicate that low risk patients should not need LND, while intermediate and high risk do need it to guide adjuvant therapy (17,22).

The Medical Research Council and the National Cancer Research Institute in the UK found no evidence of therapeutic benefit for LND in low risk because they present negative LNs and favourable prognosis. So, it cannot be recommended as routine procedure for therapeutic purposes in low risk patients. But it is still doubtful because there are dates that approximately 10% of the patients in stage I have LN micrometastasis (mM) (4,6,22,25,27). Instead of that it is mandatory in advanced stages or in risk to relapse (4,25).

Another issue to deal with LND is how we can detect affected LN. Palpation and direct vision of the nodes are inaccurate methods of determining which LN requires to be removed. Fewer than 30% of LN metastases are identified through palpation and nearly a half of metastatic LNs measure less than 1 cm. For this reason, there are certain areas already described where the nodes are mostly affected (pelvic and paraAo area with their borders) and then the surgeon also removes any suspicious or enlarged nodes (4,32).

Besides, there is still no defined number of LNs to remove to ensure the elimination of all possible disease unlike colonic cancers in which it is recommended to remove more than 12 LN. The Gynaecologic Oncology Group Surgical Procedures Manuals suggests a minimum of 10 PLN be retrieved to evaluation. But there is no consensus; different centres admit that the pelvic lymphadenectomy is adequate from 20 LN or more. The resection of around 21-25 LN provided an 80% of probability to detect 1 LN positive, but removing more than 25 LN did not significantly increase that probability. The surgeon is the only one who can ensure that the lymphadenectomy executed was complete (4,15,17,18).

Many complications are found in patients with EC because most of them suffer from morbid obesity and are over 75 years of age with other comorbidities; it makes SS problematic, because the surgery is highly aggressive. Sometimes paraAo lymphadenectomy is more risky in patients with serious health conditions such as obesity, diabetes and hypertension. In those cases paraAo LND is not performed (2,5,29).

Lymphadenectomy complications as we have mentioned before are lower-limb lymphoedema[3] (in around 11%), lymphocysts[4] (appear in about 8% of EC), deep vein thrombosis, associated pressure symptoms, vessels and nerve damage. Those complications are relatively uncommon, but when they appear they impair the patients' quality of life. Lymphoedema is the most concerning complication (6,11–13,20,21). Todo et al. determined that pelvic lymphadenectomy and the resection of more than 31 nodes increases the risk of develop a lower-limb lymphoedema unlike A. Achouri et al. that have not found any relation with the number of nodes removed (21,33). Some studies suggest that some LND drawbacks might be dependent on the surgical approach and would be avoided by laparoscopy (17).

- *<u>Adjuvant treatment:</u> (see Annex 2) (see Annex 3)*

The adjuvant treatment is based on the histopathology of the cancer. One of the most important factors to determine if the patients are going to benefit from the adjuvant therapy in EC is the status of regional node. It also depends on risk factors such as: patient's age (>60 years old), lesion size (> 20 mm), positive lymph vascular space invasion (LVSI) and lower third uterine involvement (4,10,16,17,24,25).

In the first place, the adjuvant treatment consists of radiotherapy (RT), because it is effective improving local disease control; can be use as brachytherapy (BT) or external RT. RT is associated with important late complications such as stenosis of the vagina and intestinal lesions. After RT we can consider the chemotherapy (QT). The QT is considered in patients with high risk of recurrence (IB G3, II G3, IIIA and IIIB). Even so, in IIIC, IV and type II we consider firstly QT as adjuvant post-surgery and after that RT may be an option (14,17,18,25,27,30).

[3] Lower-limb lymphoedema: Pitting edema that is first detectable over the dorsum of the foot and it can be extended along the limb up to the pelvis. Lymphoedema can be asymptomatic or associated with pain erythema and/or heaviness sensation (21).

[4] Lymphocysts: Organized collections of lymph that are usually asymptomatic and identified only upon routine imaging studies performed during follow-up. Sometimes can cause symptoms if they become very large, putting pressure on neighboring structures, or if it become infected (21).

QT used is 4 cycles of Carboplatine AUC 5 plus Paclitaxel 175 mg/m^2, every 21 days. Adriamicine 60 mg/m^2 plus cisplatine 50 mg/m^2, every 21 days is an alternative (18,25).

Neoadjuvant QT or RT can be considered for advanced tumours or inoperable (27).

Another primary treatment option in an inoperable condition, relapsed well-differentiated tumour or with hormone receptors are the progestins; megestrol acetate 160 mg/d, medroxyprogesterone acetate 200 mg/day or tamoxifen 20 mg/day (18,25,30).

- **Prognostic**

Age (over 60 years old), race, type II histological cancer, higher grade tumours (G3), increased depth myometrial invasion (over 50%), tumoural size, invasion of the lower third of the uterus, endocervical stromal invasion, extrauterine extension, LVSI and LN metastasis are factors associated to low survival. The latter being the most important and strongest prognostic factor for recurrences (1,2,5,16–18,25,30).

Most recurrences occur within the first three years after treatment. The mainly local relapses are located in vagina or pelvis. Vaginal BT has a big role, because it is the main place where it relapses and it has a loco-regional effect. Pregnancy seems to reduce the risk for EC recurrence (4,13,16,18,27,30). The more common metastatic sites are lungs, bone and liver (14).

- **Survival**

Survival is stage related. Most patients are diagnosed on an early-stage disease, approximately in 75% of the cases (stage I). The survival for 5 years of those patients, with negative LNs, is about 85-91%. Nonetheless, advanced-stage disease with unfavourable risk factors has a small chance for improvement; decreasing to 84-74% in stage II, 66.2-49.9% in stage III and 25.5-20.1% in stage IV. Furthermore, descends until 75% with positive PLNs and to 38% with positive paraAo LNs (5,14,17,18,22,27).

EC histotypes are also a prognostic factor. Endometrioid tumour has a five-year survival of 83% compared with 62% for clear cell and 53% for papillary carcinomas (the last two, are in more advanced stage) (14). (*Annex 4*)

3.2.2. SENTINEL LYMPH NODE BIOPSY

SLN mapping is a form of image-guided surgery with the ability to find the more important nodes to test (8). The procedure consists of detecting and removing selectively SLN to evaluate regional lymphatic status and select the patients that would need a lymphadenectomy. SLN was first described by Cabanas in 1977 as the first LN in a lymphatic chain that receives drainage from a primary tumour. SLN is the most likely beginning site for lymphatic spread. The histopathologic status of this LN would be representative of the other remaining LNs, so it may predict the node status of the patient. If there is a negative SLN it is unlikely that the tumoural cells will have spread beyond. In those cases, lymphadenectomy could be avoided resulting in a reduction of the surgical invasiveness, morbidity and resources optimization (2,11,13,15,17,29). SLN has been reported to improve the detection of LN metastasis; even so micrometastasis (mM) (34).

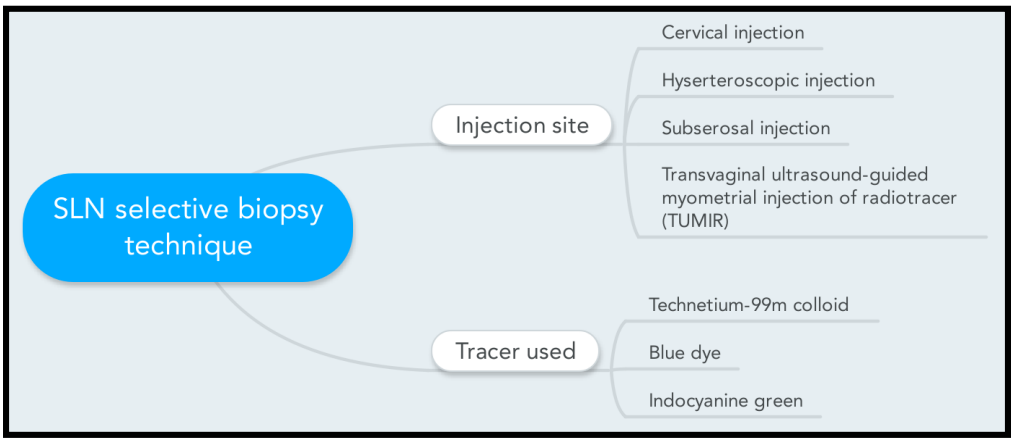
SLN in EC was first proposed in a study by Burke et al. in 1996, since then many investigators have explored the concept of SLN mapping in EC (6–8). As we have, already, mentioned the lymphatic drainage of the uterus is complex to define, because of its midline position and its bilateral lymphatic drainage, so it has several anatomical areas at risk of metastasis (1,2,4).

The main sites where the SLN in EC is detected are: pelvic region (around 55%) (in order from more typically located to less: obturator area, internal iliac, external iliac, common iliac), localized in the paraAo and pelvic regions (around 35%) and also can be detected isolated in the paraAo area mainly above the origin of the inferior mesenteric artery (not much common, around 10%) (5,7,10,14,15,29)**.**

The finality of SLN biopsy is to stage EC correctly and to guide the adjuvant treatment, not to cytoreduct the tumour extension (8).

- **Selective SLN biopsy technique**

Best site of injection and the most appropriate tracer materials are still being investigated (4).



- Injection site:

While melanoma, vulvar and cervical cancer all allow a direct peri-tumoural injection, EC is more challenging and can only be achieved by hysteroscopy, transvaginal ultrasound or laparotomy/laparoscopic. The injection site has been debated over the years. The different injection sites tested are: in the cervix (it might not be appropriate for all EC, but is the most common injection site practice among the studies(12)), peri-tumoural, myometrial and subserosal (1,5,7–10,15).

- Cervical injection: Easily carried out, reproducible, does not increase the overall cost and time very much, needs no particular ability, good results in detection rates (around 90%) but sometimes is not able to detect the whole lymphatic drainage of the uterus (paraAo area may not be mapped appropriately because the lymphatic drainage of the cervix and uterine fundus are different). However, in general frequency of isolated paraAo in EC is reported to be low: in Abu-Rustum et al. Study was only 2% (3,5,6,9,15,22).
- Hysteroscopic injection: The migration of the tracer in this injection through the internal uterine mucosa is the most similar to which the tumour would do. It is more cumbersome and demanding, has lower tolerance, requires experienced personnel in hysteroscopy, because of the long learning curve of the technique, and it has a high variability in SLN detection rates (ranged from 44 to 100%). On the other side it is more likely to highlight the complete lymphatic drainage of the uterus. Hysteroscopic route is the technique that seems more closely as the techniques performed in other solid tumours (breast, melanoma). General anaesthesia is not needed (3,5,6,9,10,15).
- Subserosal injection: It is the first technique described. This technique, also, can cover the lymphatic drainage from the whole uterus. The main approach is by laparotomy doing direct injections in different sites; it is easy to learn and manage. Some drawbacks are that it is impossible to do a surgical planning before surgery and minimally invasive surgery is technically problematic. The detection rate is low (around 55-65%), but increases with the number of injections (5,6,10,15).
- Transvaginal ultrasound-guided myometrial injection of radiotracer (TUMIR): It is a new method similar to the embryo transfer method used in assisted reproduction in cervical stenosis. It allows the exact visualization of the injection site. A. Torné et al, shows in his study that the technique is safe and feasible with good SLN detection rates (82%). The migration of the tracer, also detects paraAo SLNs. It is a promising technique (10).

No significant differences are found on comparing the detection rate between techniques although the detection of paraAo LN is lower in cervical approach (9,22). An association between the injection site and SLN location has been observed in Laios A. et al. study (12).

- Tracer used:

- Technetium colloid (Tc99): It consists of albumin nanocolloid particles (5 to 80 nm) labelled with technetium-99m (2). The focal site where the Tc99 is first accumulated is considered the SLN. This tracer could be detected for a long period of time and thus is often injected pre-operatively (minimum two hours before surgery or the day before). It is detected through pre-operative lymphoscintigraphy (a gammagraphy of the lymphatic system) or by SPECT-CT taking dynamic and static images of the entire pelvis and abdominal cavity by the nuclear medicine physician. The correlation of the findings between the image done the day before and the intra-operative detection facilitates their localization during the intervention. The intraoperative detection is with a handheld gamma probe. This gamma probe localizes the hot spot detected by lymphoscintigraphy because of the radiation emitted (ten times above background radiation level). The studies who tested Tc99 lasted 15 minutes (range from 10 to 20 min) to SLN detection with dissection and removal (1,2,7,22). Another drawback is that the equipment required for SLN mapping is uncomfortable, challenging, costly and is not available for all the hospitals and surgeons (1,7,12,23).

- Blue dye: It has been used in SLN mapping for many different cancers, so it is well known (7). Blue dye is a much cheaper and more widely available product than the others tracers. It is injected intraoperatively, so it is not necessary to come prior to surgery as Tc99 needs for the lymphoscintigraphy. It is very simple and it is visualized directly because of the blue coloured LN that can differentiate them from the surrounding tissues. Otherwise it is unreliable based on low detection rates. Moreover, it is more difficult to detect especially in obese patients. A few allergic reactions have been met, but not many severe (instead of life threating anaphylaxis reactions that it is known that is a potential risk). The studies not recommended managing it alone, it is better in combination with other tracers (1,3,7,17,23,31).

- Indocyanine green (ICG): ICG is a new injection agent that it is based on near-infrared imaging (appears green when it is excited by light in the near infrared

range) and has a very high SLN detection rates and an excellent safety profile (1,6,7). Unlike blue dye, it has the potential advantage of being visible through visceral fat (7). ICG has to be injected immediately before the surgery. No adverse reactions are known since now (12). However, it is really expensive and it requires the use of specialized high-tech equipment (1).

There is no consensus about the best technique for detecting SLNs (11,17). The concurrent use of two tracers increases the detection rate of SLN (5,6,12,22). How. J et al. has done a study using a mixture of blue dye, ICG and Tc99. This study determined that blue dye may not be essential to SLN detection in EC because ICG is comparable to Tc99 and can reach a high detection rate of SLN (11). Indeed, blue dye provides a greater SLN detection than direct view, but it is also the tracer with more potential allergic reactions (12,23).

Sometimes, more than one SLN is detected, in those cases it is necessary to analyse all of them. The median of nodes detected per person in the different studies are of 3 (ranged from 0 to 9) (3,10,13,15).

Then, a LND has to be performed to compare the SLN with the gold standard (2,15,19).

- Lymph node histological analysis and ultrastaging

Histopathology is used to determine the SLN affection and the tumour metastasis in the LND (12). Metastatic cells from EC are three times more likely to be detected in SLN than randomly LN (3,13,32).

The SLN found intraoperatively is sent to Department of Anatomic Pathology for study. It will be fixed in neutral buffered formaldehyde and processed in paraffin blocks according to standard protocol. Then, it has to be sliced and stained with Hematoxylin and Eosin (H&E) using standard techniques. Sometimes H&E do not detect mM and yes it does immunostaining for anti-cytokeratin[5] (immunohistochemistry (IHC)). So, when a SLN is negative in H&E stain, a serial cut of the SLN is needed at intervals of 200µm (the studies ranges between 50-500 µm) and staining ones with H&E and others with IHC using anti-cytokeratin antibody AE1/AE3 in order to examine the mM of the SLN (it is called ultrastaging). The ultrastaging detects an additional 3-50% of mM or ITC. So alone or combined are needed to analyze LN (3,5,11,13,15,19,26,32,34).

[5] Cytokeratin: a constituent of the cytoskeleton of normal and malignant epithelial cells, is usually only present in tumour metastasis.(26)

Non-SLN status is determined by routine H&E staining after ultrastaging the SLN. It is not necessary do ultrastaging because it is a costly and durable technique (5–7,19,26,32).

According to the American Joint Committee on Cancer (AJCC): Macrometastasis (MM) are considered as a focus of metastatic tumour cells larger than 2 mm, whereas micrometastasis (mM) between 0.2 – 2 mm. Isolated tumour cells (ITC) are defined as microscopic clusters and single cells measuring less than 0.2 mm (3,9,11,13,26,32).

Another concept is isolated cytokeratin-positive cells (CKPCs), those cells may be benign mesothelial cells and are not considered diagnostic of carcinoma. These cells are not stained with H&E. The clinical significance of finding CKPCs is not certain. Some studies have noted that CKPCs may represent artificial displacements of benign epithelial cells during manipulation or biopsy, whereas others have demonstrated that the instrumentation alone is not the cause (13,32).

- Limitations:

The SLN detection may fail, then it would be necessary to perform the complete lymphadenectomy (17). The detection rate found in the studies with different techniques ranged from 77% to 100% and the reason is not fully understood (2,4,7,10,15,22,23,26,29)**.** One of the causes can be due to proximity of injection site to the lymphatic basin which can mask the SLN on lymphoscintigraphy images. This problem can be overcome by SPECT/CT. Also, it may be caused for the complex lymphatic drainage of the uterus and possibly due to the delay between the injection and the intervention. Another explanation could be in part a consequence of blockage of the LN by neoplastic cells, but that cannot be applied to patients with mM (13,22,23,29).

Bilateral drainage in EC is very important in the pelvic area. However, not all patients have bilateral drainage during surgery. Only in less than 30% of cases, bilateral SLN detection is not possible (6,10,23).

3.3. JUSTIFICATION

EC is one of the most prevalent gynaecologic cancers in women, and its management has been controversial from the beginning in 1988. Nowadays EC is surgically staged and treated in an aggressive way. This surgically approach include in some stages (except IA G1-G2) pelvic and para-aortic lymphadenectomy, because LN invasion is a prognostic factor and it is used to guide the adjuvant treatment, too. LNs are not always affected, so in those cases, patients are undergoing an excessive surgical procedure. Lymphadenectomy leads a high morbidity, so in recent years there have been some studies trying to validate the SLN in EC, an application which is already used in other cancers as melanoma, breast or vulva.

The main difficulty to validate the SLN mapping in EC is its anatomical lymphatic drainage, that it is bilateral (because of its midline position) and includes pelvic and paraAo LNs. Nowadays, there is still no consensus or validation of the best SLN mapping technique. Studies have been using different tracers and injection sites. Some studies have had good results but in general they have been heterogeneous and the best technique to map the SLN has yet to be found. The application of the SLN in EC is promising because with SLN will be possible to avoid lymphadenectomy when the SLN have no metastatic cells, reducing the morbidity of the lymphadenectomy and improving the quality of life after treatment. SLN would solve the debate on the performance of the lymphadenectomy. Despite all of this and although it is included as an optional treatment in some clinical guidelines, it is not yet applied in the routine management.

The majority of the studies published so far have used the cervical injection knowing that it is not a good approximation of the paraAo drainage. The tracers mainly studied are blue dye and Tc99, so they are well known and they have better results in combination than alone. ICG is still in investigation.

Recent studies have included mostly patients with low-grade, early-stages EC, in which the baseline risk of having nodal metastasis is low. In this study we have decided to exclude a significant proportion of women in early stage (IA G1-G2) because it does not indicated the need for a lymphadenectomy according to FIGO and we have also included patients with high-risk who are more likely to present nodal metastasis.

The aim of the study is to show the applicability of the SLN biopsy in EC at Hospital Universitari Dr. Josep Trueta of Girona adjusting the different limitations that we have detected in other studies and the different results that the studies have shown of the different techniques to perform SLN mapping. According to this information and the

resources that are available in our institution we will use TUMIR procedure with Tc99 and the injection of blue dye into the cervix.

In order to show the applicability we will determine the sensitivity, specificity and negative predictive value (NPV) of the technique in order to evaluate the accordance of the SLN with the regional LN status and thereby improve the diagnosis and treatment in patients with EC in Hospital Universitari Dr. Josep Trueta's Gynaecology Oncologic unit.

We expect that this study will give more information about the applicability of the TUMIR in SLN mapping and will be applied to future studies because we believe that it may be the most feasible and appropriate one for this type of cancer.

4. HYPOTHESIS

Based on the preliminary results of endometrial cancer sentinel lymph node studies our main hypothesis of this study is:

Selective sentinel lymph node biopsy allows establishing the correct lymph node affectation in endometrial cancer.

5. OBJECTIVES

Main objective:

The principal aim of this project is:

- To evaluate the validation of the selective sentinel lymph node biopsy technique in endometrial cancer in Hospital Dr. Josep Trueta of Girona, including sensitivity, specificity and negative predictive value.

Secondary objectives:

- To identify the amount of patients with lymphatic metastasis.

- To determine which the detection rate is of the sentinel lymph node technique used.

- To ascertain where the SLN are mainly located depending on the EC type.

6. MATERIAL AND METHODS

6.1. Study Design

The endometrial SLN will be validated by a diagnostic test cross-sectional study. This would be executed in a tertiary referral hospital in Girona within the Gynaecological Oncology Unit integrated by gynaecologists, nuclear medicine physicians, pathologists and oncologists.

6.2. Participants

The study population is based in women diagnosed with EC type I and II and with indication of SS

- **Inclusion criteria**

- Endometrial biopsy confirming the diagnosis of EC
- Stages IA-G3, II, IIIA and IIIB of type I or type II according to the 2009 FIGO classification requiring SS with SLN mapping
- Detection of at least one SLN
- Patients over 18 years old
- Patients referred to Hospital Universitari Dr. Josep Trueta de Girona.
- Informed consent signed to do the procedure *(Annex 6)*

- **Exclusion criteria**

- Patients with EC cancer IA G1-G2: That is because in order to determine whether SLN biopsy is applicable we need to compare it with lymphadenectomy and in those cases the LND is not routinely performed. It would be not ethically correct to submit those patients to this surgical process, because we would over-treat the disease and the morbidity would increase.
- Patients with EC cancer IIIC or IV: Because it already implies PLN and paraAo LN involvement and metastasis respectively.
- Contraindication for surgical treatment
- Impossibility to perform a transvaginal ultrasound exam
- Patients who received neoadjuvant treatment: Can make the nodes become negative.
- Prior cancers (except in situ of cervix and squamous of the skin)
- Patients with allergic reactions history of blue dye and Tc99

6.3. Setting

All the study will be performed in the Gynaecologic Oncologic Unit in Hospital Dr. Josep Trueta of Girona integrated by gynaecologists, nuclear medicine physicians, pathologists and oncologists.

6.4. Sample selection

The selection of the population will be performed as a consecutive non-probabilistic sampling of women diagnosed of EC, whatever the type and stage diagnosed, tributary of SS to biopsy the SLN. We will select the patients who fulfil the criteria as they consult to the doctor. Patients will be given all the information and the information sheet (Annex 5), and then they will be asked to participate in the study and will have to sign the informed consent (Annex 6).

6.5. Sample size

Sample size is calculated by "Calculadora de Tamaño mostral GRANMO" Version 7.12 Abril 2012. The research team accepts an alpha risk of 0.05 and a beta risk of 0.2 in a two-sided test. In several studies the sensitivity and specificity of SLN ranges from 75 to 100% (2,4,6,9–11,15,17,19,29)**.** We accept a sensitivity of 90% for SLN in front of a sensitivity of 99% for LND. 95 subjects are needed to recognize a statistically significant difference between both techniques. We predict a drop-out rate of 15%, including the subjects which we will not detect SLN because of technical problems.

We do not need to calculate the sample size necessary to cover specificity because the specificity target is less than the sensitivity necessary to validate the technique. So, if we assume that we need a specificity of 80% to consider valid this technique, we will need just 35 patients, that are included into the 95 subjects necessary to achieve the sensitivity.

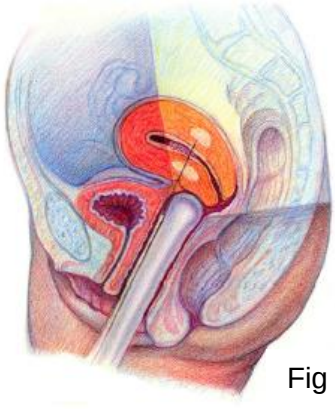
In Hospital Universitari Dr. Josep Trueta about 50 patients of EC are diagnosed per year of whom final IA G1-G2 FIGO stage are in about 10% of the patients because it is a referral hospital and the cancers derived are more advanced. We have not taken into consideration stages IIIC and IV because the number of patients in those stages at the moment of diagnosis is very low.

We will diagnose about 45 patients per year that fulfil our inclusion criteria. We will need 2 years and 2 months to recruit them.

6.6. Surgical procedure

According to the literature and the equipment availability in our centre; the SLN technique chosen is the use of Tc99 injected by TUMIR procedure[6] and blue dye injected into the cervix:

All the subjects included in the study will need an extra procedure during the SS. First of all, the patients will be asked to empty their bladder. The day before of the surgery the surgeon will be responsible for doing the identification of the outer two thirds of the myometrium trough ultrasound-imaging equipment (Toshiba Nemio XG SSA-580A). Then a transvaginal puncture of 3mCi of Tc99 into the myometrial with a 16-gage needle (COOK. K-OSN-1730-B-60) will be performed**.** Always a nuclear medicine physician must be present to ensure that there is no problem. Afterwards a static and dynamic lymphoscintigraphy will be carried out at 30 minutes and 4 hours after the tracer injection to detect where the SLNs are located. The day of the surgery, surgeons will inject 2 ml (10mg/ml) of blue dye to the cervix in four quadrants to a depth of 0.5 cm. From here, depending on the surgical indication, a laparoscopy or laparotomy approach will be performed. The tracers are going to be accumulated inside the SLN. Blue dye will be seen directly by the surgeon but the Tc99 is detected by a handheld gamma probe. Once the SLN is detected the surgeon will remove it and send it to Pathology Department to submit the specimen to frozen section examination staining it with H&E, but if it not stains the SLN it will be necessary to ultrastage with IHC. Meanwhile the surgeons can continue the SS doing the pelvic and paraAo lymphadenectomy, when it is needed according to the protocol. One pathologist will study the SLN and other the non-SLN of the lymphadenectomy (assuming the last one as the gold standard), so we will minimize the verification bias. SLN findings will be compared to complete lymphadenectomy findings for an analysis of sensitivity, specificity and NPV for detecting metastatic disease.



Fig

We estimate a surgery time increase of the 30-35 minutes. We have to add an extra time of 15 minutes of Tc99 injection the previous day.

[6] According to Torné et al. **TUMIR procedure** consists in ultrasound-guided injection of the tracer in two preselected targets of the myometrium (anterior and posterior myometrial wall). Tracer injection will be performed half-way between the internal opening and the fundus. When the tumour is identified by ultrasound, the puncture can be performed according the location of the tumour. When the needle passes through the anterior vaginal fornix to the anterior uterine wall, a half-dose of the tracer is injected in the outer two-thirds of the myometrium (where the lymph vessels are abundant). After the initial injection, the needle crosses the endometrial cavity to the outer two-thirds of the myometrium of the posterior wall of the uterus, where the remaining volume of the tracer has to be injected. Caution to accidental puncture and spill tracer into the peritoneal cavity (10).
Fig: *Image of TUMIR procedure* (10)

6.7. Variables

- **Main variable**
  - **Sentinel lymph node (SLN)**

SLN invasion by malignant cells constitutes a dichotomic qualitative variable.

When SLN is removed, it is sent to the pathology service where it is evaluated and processed by the pathologist. The pathologist is the one who is in charge of determining when the SLN is positive or not. We will consider a positive SLN when metastasis appears; no matters if it is a MM, a mM or if the pathologist just find ITC.

Detection of malignant cells will be defined according the American Joint Committee on Cancer (AJCC) as follows:

- Macrometastasis (MM): a focus of metastatic tumour cells larger than 2 mm.
- Micrometastasis (mM): a focus of metastatic tumour cells between 0.2 - 2 mm.
- Isolated tumour cells (ITC): microscopic clusters and single cells measuring less than 0.2 mm (3,9,11,13,19,26,32,34)

The pathologist will use H&E to detect MM and IHC to find mM and ITCs at SLNs

The pathologist evaluation of the lymphadenectomy is considered to be the gold standard for LN status assessment. The non-SLNs, of the lymphadenectomy, have to be analysed to compare with the SLN. Those LN will be stained just with H&E, because the principal site to find mM is the SLN, so it is no necessary to use IHC.

The two different situations that we can find are:

A) NEGATIVE: no tumour cells (non-MM, non-mM, non-ITC) are found in SLNs or non-SLNs. We include normal, atypical endometrial hyperplasia and CKPT.
B) POSITIVE:
    a. MM: macroscopic tumour cells are found on H&E SLNs or non-SLNs stained.
    b. mM or ITCs: mM or ITCs are found by histological ultrastaging in SLNs and all non-SLNs do not contain them.

With this procedure, we will be able to calculate the sensitivity, specificity and NPV of the SLN, comparing the ability for detecting metastatic disease of it with our current gold standard: the lymphadenectomy pathologic study.

- **Covariables**

These variables are included because we want to take them into account in our population. We will make a multivariate analysis because we believe that all of them can influence and change the LN affectation:

- Age: in years

- Socio-economic level

- Comorbidities

- Obesity: >30 / ≤30, SLN is more readily identified in thin persons than obese (7).

- Professionals' experience: surgeon's experience is an essential factor for having good results in lymphatic mapping in other solid tumours (breast, melanoma, vulva). The study will be restricted to surgeons with demonstrated proficiency in the technique of pelvic and para-aortical lymphadenectomy and to pathologist's with experience in ultrastaging SLN of other kind of tumours and non-SLN. We will measure this in number of surgeries with lymphadenectomy performed and number of SLN ultrastaging performed, respectively.

- EC type: I (endometrioid adenocarcinoma) or II (non-endometrioid cancer: clear cells, serous or carcinosarcoma) according to WHO classification (*Annex 1)*

- EC histological grade: G1, G2 or G3

- EC stage: According FIGO (see table)

- LVSI: presence or absence

- Surgical approach: laparoscopic or laparotomic.

- Number of SLN detected

6.8. Methods of data collection

For data collection, the first step required will be the acquisition of the informed consent signed *(Annex 6)* after the patient has read the informative sheet (*Annex 5*). Once the patient has read and understood the procedure of the study where she is participating, the SLN detection will begin.

The research team will inform the rest of the members of the Gynaecology Oncologic Unit about such study. A special requirement will be asked to nuclear medicine and pathology departments due to the fact that they represent important parts of the study concerning firstly the detection of the SLN and after that the SLN affection.

Most of the data will be collected from the clinical history of the participating women and this data will be recorded into the general database. The principal investigator will not have access to the personal information in order not to identify the patient. We will create an anonymization method to codify the patient's information. The information will be obtained from:

- Nuclear medicine (NM) report: lymphoscintigraphy and the verification of the SLN by handed gamma sonda (after surgeon removes it) report will be used for obtaining information about the presence and the localisation of SLN.
- Surgeon (SG) report: Intraoperative handed gamma sonda will guide the surgery and also will do the blue dye previously injected. Once SLN is detected, the surgeon will excise it. After that the surgeon will follow the protocoled management and will do the lymphadenectomy, hysterectomy, double annexectomy and what it is indicated depending on the cancer type and stage.
- Pathologist (AP) report: the removed SLN will provide information about the presence or absence of MM, mM or ITCs. Additionally, another different pathologists will proceed to do the non-SLN pathological analysis, as a goal standard. It will provide us with the sensitivity, specificity and NPV of the SLN. All the data from histological variables have been collected from pathology reports during the routine diagnostic of pathological oncologic samples.

	PRE SURGERY		**DURING SURGERY**	**POST SURGERY**
	Day before	**Day of the surgery**		
NM	Tc99 dosification and lymposcintigraphy		Verification of SLN after remove	
SG	Transvaginal Ultrasound-guided injection of the Tc99	Blue dye injection into the cervix.	SLN detection by handed gamma sonda, removal and LND	
AP				SLN and non-SLN pathologic analysis

7. STATISTICAL ANALYSIS

Data will be introduced in the database (Access 2014) and statistical analysis will be performed using the Statistical Package for the Social Sciences programme version 12.0 (SPSS Inc, Chicago, Illinois).

A p value <0,05 will be considered statistically significant.

UNIVARIANT DESCRIPTION:

The results will be expressed as percentages or absolute frequencies for categorical variables. Quantitative continuous variables will be described by means and standard deviation or median and percentiles, depending on whether or not they were normally distributed.

BIVARIANT DESCRIPTION:

Categorical variables will be analysed using the Chi-square test.

For continuous normally distributed variables, the t-student will be used; and for continuous non-normally distributed variables, the Mann-Whitney test will be used.

MULTIVARIANT DESCRIPTION:

To adjust confusion and analyse the relationship between our primary endpoint with other covariates in our study, a logistic regression analysis will be performed. We will see how our covariates (age, socio-economic level, comorbidities, obesity, professionals' experience, EC type, EC histological grade, EC stage, LVSI, surgical approach and the number of SLN detected) contribute in the study.

8. ETHICAL ASPECTS

CEIC (Clinical Research Ethical Committee) of Hospital Universitari Dr. Josep Trueta will evaluate the study. It will decide if it meets all the criteria required for approval. The committee recommendations will be taken into account and applied to the study.

The patients included in the study will be informed orally and with an information sheet. The participants will be asked to sign a written informed consent before entering into the study.

This study protocol follows the Ethical Principles for Medical Research Involving Human Subjects in accordance with Helsinki Declaration developed by the World Medical Association (revised in 64th WMA General Assembly Fortaleza, Brazil, October 2013).

It will be carried out under the normative framework of The Spanish Organic Law 14/2007, 3 de Julio, de Investigación Biomédica. In Spain, this is the law that regulates investigations which involve humans.

Moreover, according to “Real Decreto Legislativo 1/2015, de 24 de julio” por el que se aprueba el texto refundido de la Ley de garantías y uso racional de los medicamentos y productos sanitarios, “BOE” núm. 177”, we will guarantee the rational use of medical devices.

All the patient information involved in the study will be confidential. All the collecting data and results will be treated in total anonymity. The confidentiality and anonymity will be guaranteed according to Organic Law 15/1999, 13 de Diciembre, de Protección de Datos Personales.

All the patients will have right to access and consult their own information. All data will be managed anonymously.

Every investigator will have to declare no conflict of interests.

9. LIMITATIONS OF THE STUDY

- Verification/detection bias: To minimize this bias, as we have to do the SLN and the lymphadenectomy to the same patient, two different pathologists will analyse the SLN and the lymphadenectomy respectively.

- Information bias: Along with the method of anonymisation of data, we avoided this bias, making the principal investigator not being the same person who performs the technique and recruit the information.

- We assume a technique to detect the SLN through TUMIR and the injection of blue dye to the cervix. However some studies are evaluating the use of ICG for the detection rate and they are having very good results compared with blue dye. Tc99 and blue dye are the only option that we dispose in our country because of the availability and the cost. ICG is still in investigation. This can lead to potential selection bias.

- Confusion bias: It is possible to produce confusion with covariables that we have not considered in the multivariate analysis.

- Spectrum bias: We are not including all the EC population: we may be missing information. It is possible that by excluding the patients with EC IA G1 or G2 we will lose information, because they are an important amount of patients who are diagnosed of EC. If it was ethically correct to perform a lymphadenectomy, they will be the subjects who will benefit the most from the SLN, because with just a little procedure we will know if they have LN invasion and be treated correctly.

- SLN technique is an operator-dependent technique that requires trained nuclear medicine physicians, gynaecologists' surgeons and pathologists. Even though the enrolled specialist will be trained in the procedure, a learning curve will be observed as it uses to happen with all technician dependent methods.

- The results will be from a single institution with a new adopted EC SLN program, as a consequence the results might not be generalizable to the general population or to other institutions. But we expect to help other institutions to use this technique to detect the SLN and end up being a reference method.

10. WORK PLAN

STUDY TEAM:

The study team will be composed by the research team (RT) (who will coordinate the study, will evaluate if the study procedure is well performed and will analyze all the data; this team will be composed by investigators different from who will recollect the information and patient data), the surgeons (SG) (who will recruit the participants, perform the transvaginal puncture through TUMIR and to the cervix, detecting the SLN and do the surgery), the nuclear medicine physician (MN) (who will detect by lymphoscintigraphy the SLN and will verificate by handed gamma sonda the SLN after remove it), the pathologists (AP) (who will analyse the SLN and the LNs of the lymphadenectomy), and the statistical specialist (SS).

PREPARATION AND COORDINATION PHASE: (3 months)

- Bibliographic research and protocol elaboration: The protocol will be written by the Research Team after a deep literature review.
- Ethical Committee evaluation and approval: We will present the protocol to the Ethical Committee (CEIC) to evaluate and accept the protocol to start the study.
- Coordination of the team: We will organise a first meeting between the researchers and the rest of collaborators before start the study to be sure that everyone knows which role he has. It will be discussed, also, the project design and execution plan, the patient recruitment, anonymization method, the chronogram and data collection.

FIELD WORK AND DATA COLLECTION: (26 months)

- Sampling recruitment and SLN intervention: At least twenty-six months are required to select all the patients who will participate into the study: 95 patients are necessary and they must fulfil the inclusion and exclusion criteria. Then the intervention can be performed. Patients will be included until the sample size will be achieved.
- Data collection: Whilst procedure it is performed, the patient's clinical history and the results of every intervention will be collected into the database.
- Quality control of the data: Each investigator is responsible for ensuring that all data is complete, exact, in an accurate manner, collect following the anonymization method and guarantee the availability for the research team. So the quality control will be done at the same time as data collection.

- Meetings: two meetings, one in the middle and another at the final of the recruitment, will be necessary to be sure that the protocol is followed correctly.

DATA ANALYSIS: (8 months)

- Statistical analysis: Three months are needed to perform the statistical analysis exposed.
- Analysis, interpretation and discussion of the results: All the research team will meet with the statistics to interpret and discuss the results and get conclusions.
- Final report elaboration: Three months are required to write the article. The article will be written by the researchers.
- Final report evaluation: It will be exposed to the collaborators who will deeply evaluate it.

PUBLICATIONS AND SCIENTIFIC DISSEMINATION: (3 months)

- Scientific publication: We will send the article to magazines, journal articles and reports for its official publication as Gynaecologic Oncology and Progresos en Ginecología i Obstetricia.
- Congress attendance: We will present the results of our study at annual state and also international conferences: Congreso Sección de Ginecología Oncológica y Patología Mamaria de la SEGO, ESGO Congress and we will attend to all conferences that we will be invited.

Therefore, the total estimated duration of the study would be of 3 years and 4 months.

11. TIME SCHEDULE

TASKS	TIME																		STAFF
	2015		2016		2017	2018												2019	
	N	D	J	F – D		J	F	M	A	M	J	J	A	S	O	N	D		
PREPARATION AND COORDINATION PHASE																			
Bibliographic research and protocol elaboration																			RT
Ethical Committee evaluation and approval																			RT, CEIC
Coordination of the team																			RT, SG, MN, AP, SS
FIELD WORK AND DATA COLLECTION																			
Sampling recruitment and SLN intervention																			SG, MN
Data collection																			SG, AP
Quality control of the data																			RT, SG, AP
Meetings																			RT
DATA ANALYSIS																			
Statistical analysis																			SS
Analysis, interpretation and discussion of the results																			SS, RT, SG, MN, AP
Final report elaboration																			RT
Final report evaluation																			RT, SS, SG, MN, AP
PUBLICATION AND SCIENTIFIC DISSEMINATION																			
Scientific publication																			RT
Congress attendences																			RT

12. AVAILABLE RESOURCE TO CARRY OUT THE PROJECT

This project will take place at Hospital Universitari Dr. Josep Trueta in Girona, where the centre will provide all means for developing the study: operating rooms, transvaginal ultrasound, stretchers, handheld gamma probe and sanitary devices to monitor the patient.

The Gynaecology Oncologic Unit will coordinate with Nuclear Medicine service because of the use of the Tc99 and the imaging by lymphoscintigraphy. The gynaecologic service will do the data extraction and collection and will perform the SLN remove and the lymphadenectomy and the pathologic service the analysis of the SLN and the non-SLNs. Additionally, the hospital will provide the informatics equipment suitable for processing the database for the study development without additional cost.

No additional hiring will be necessary due to the fact that all health workers will be trained with the procedure.

The supplementary costs include:

- The use of tracers: Tc99 and blue dye.
- Lymphoscintigraphy imaging.
- Plastic sleeves for ultrasound
- Needles to inject the tracer.
- IHC
- The statistician will be paid by the project.

13. BUDGET

		Cost	Time/Quantity	SUBTOTAL (€)
STAFF	INVESTIGATION GROUP	0€/person	12	0€
	COLLABORATING STAFF	0€/person	6	0€
	STATISTICAL	35€/hour	25 h	875€
MATERIAL	ARTICLES, LITERATURE MATERIAL, PRINTING AND PAPER PACKS	100€	-	100€
	Tc99-LYMPHOSCINTIGRAPHY	650€/unit	95	61,750€
	BLUE DYE	10€/unit	95	950 €
	PLASTIC SLEEVE FOR ULTRASOUND	1.20/unit	95	114€
	NEEDLES	53€/unit	95	5,035 €
	ANTI-CYTOKERATIN ANTIBODY AE1/AE3	175€/unit	75	13,125€
PUBLICATION	ARTICLE PUBLICATION (PUBLISHING FEES)	1500€	2	3,000€
DISSEMINATION	*Congreso Sección de Ginecología Oncológica y Patología Mamaria de la SEGO*	500€/person	1	500€
	ESGO Congress	460€/person	1	460€
	TRAVEL EXPENSES (TRANSPORT, ACCOMMODATION AND DIETS)	500€/person	2	1,000€
			TOTAL COST (IVA included)	86,909 €

Neither the investigation group nor the collaborating staff will receive any financial compensation for their contribution to the study; it will be a part of their daily routine in the hospital and a part of their work.

The material is the most expensive part, because of the nuclear medicine resources and the IHC that it is needed. We calculate that not all the SLN will need IHC, and some of them will be detected with just H&E, which is already part of the standardized protocol.

It is necessary an extra money for the conferences where we will expose the results of the study, and apart from the price of the congress, it has been taken into account the indirect costs (travel expenses, publishing fees…) that will be distributed depending on where it will be placed.

14. CLINICAL AND HEALTHCARE IMPACT

As we have already mentioned, lymphadenectomy have been always deeply discussed from the beginning of the EC staging in 1988 by the FIGO. This is because, in some cases, patients have been over and under-treated and they do not know how to determine when lymphadenectomy is needed. A few years ago some authors thought about the SLN application in EC, unfortunately not always had good outcomes. The majority of the authors agree that it is a promising technique and so do we.

It is a fact that it is necessary to continuously check a technique to know if it is still valid and if it is valid in different centres. And it is especially necessary with a technique as SLN in EC that it is not applied in the routine procedure because it is still debated the lymphatic drainage of the EC. The main debated topic is through which technique we can detect the SLN, and after a deep literary review we conclude that the cheapest, widely available and easily manageable is the one that we apply in that study: ultrasound vaginal-guided myometrial injection of Tc99 combined with a injection of blue dye to the cervix.

In our protocol we have tried to avoid the limitations of similar studies in the design and sample size. If we reach a sensitivity and specificity up to 90% (we will consider as optimal) in Hospital Universitari Dr. Josep Trueta, it would mean that this technique is valid in this centre and probably in other centres. We want to give evidence to other institutions to use this technique to detect the SLN and end up being a reference method. So, if we have enough information about regional LN with just the SLN, the staging protocol might change in a future and the lymphadenectomy will just be applied if the SLN is positive. This will save them from doing lymphadenectomies with their own morbidity previously exposed (lymphoedema, lymphocysts, deep vein thrombosis, vessels and nerves damage...) when SLN is negative.

Even though the total study will be a little bit expensive (because you need to perform both lymphadenectomy and SLN mapping), eventually we will reduce health resources, especially surgical time (some patients will not need lymphadenectomy).

Moreover, we know that lymphadenectomy gives us information about the LN status, the prognostic factor most important about how to manage the adjuvant therapy, which also would do the SLN.

This protocol can be reported by other future studies and can increase the pool of data available for analysis to compare the different techniques (combining the best tracer and the foremost injection site) to reach the maximum detection rate.

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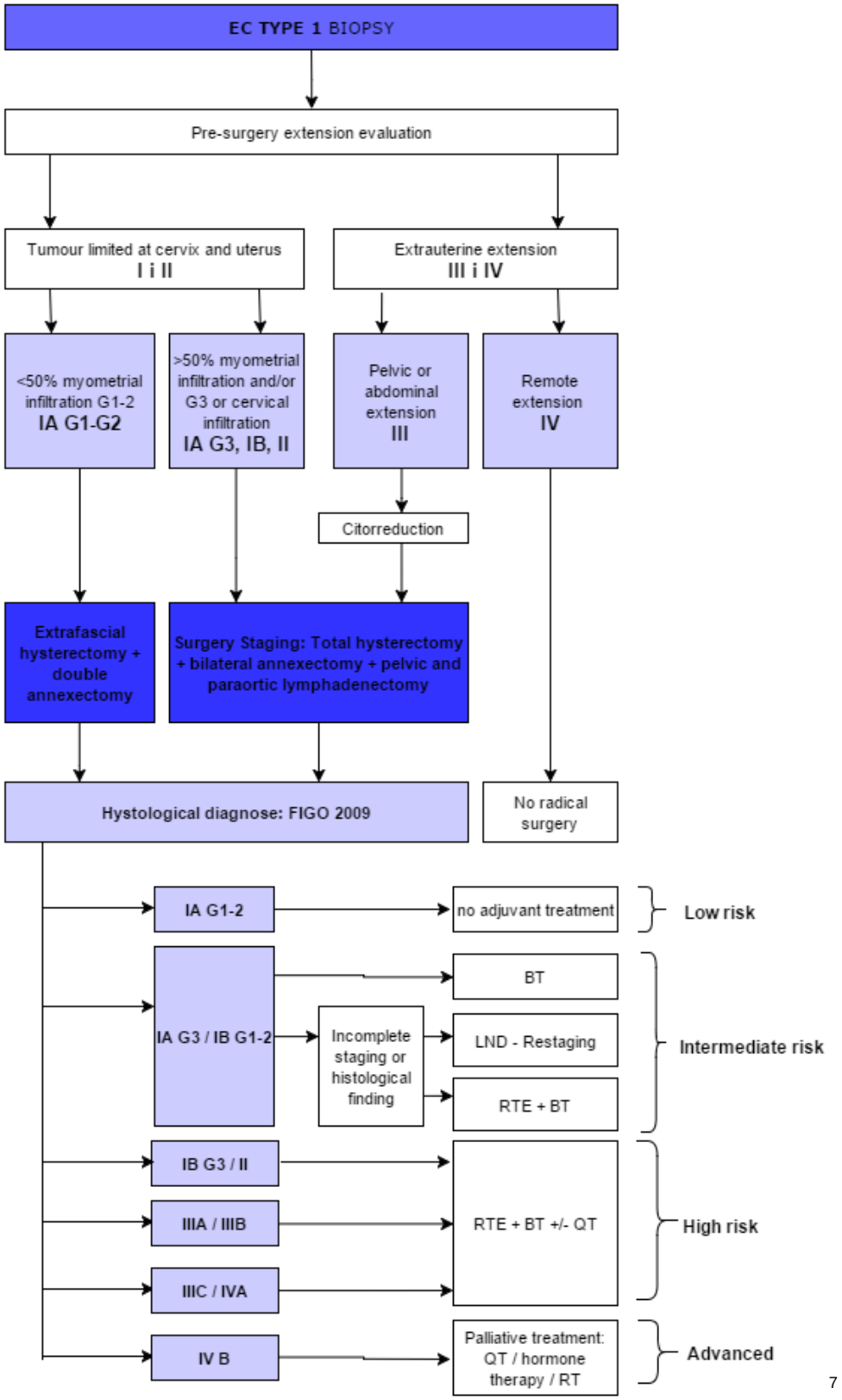
16. ANNEXES

Annex 1: Types of EC tumours

WHO HISTOLOGICAL CLASSIFICATION OF ENDOMETRIAL CARCINOMA(35)		
Endometrioid adenocarcinoma		8380/3
	Variant with squamous differentiation	8570/3
	Villoglandular variant	8262/3
	Secretory variant	8382/3
	Ciliated cell variant	8383/3
Mucinous adenocarcinoma		8480/3
Serous adenocarcinoma		8441/3
Clear cell adenocarcinoma		8310/3
Mixed cell adenocarcinoma		8323/3
Squamous cell carcinoma		8070/3
Transitional cell carcinoma		8120/3
Small cell carcinoma		8041/3
Undifferentiated carcinoma		8020/3
Others		

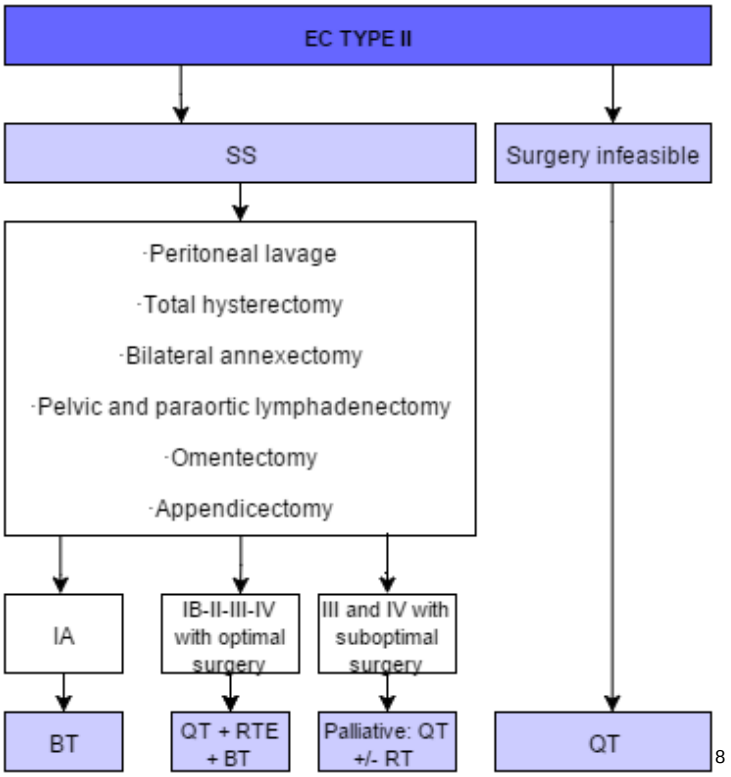
Annex 2: EC type I management



[7]

[7] *Adapted from SEGO and ESMO consensus conference*(18,25)

Annex 3: EC type II management



[8]

Annex 4: Overall survival tables

	Overall survival (%) at[9]	
Histotype	**Two years**	**Five years**
Endometrioid	91.2	83.2
Adenosquamous	87.3	80.6
Mucinous	90.4	77.0
Papillary	69.8	52.6
Clear cell	76.1	62.5
Squamous	74.2	68.9
Other	70.9	57.7

	Overall survival (%) at[10]	
Stage	**Two years**	**Five years**
IA	96.6	90.8
IB	96.6	91.1
IC	93.7	85.4
IIA	93.2	83.3
IIB	85.3	74.2
IIIA	79.9	66.2
IIIB	61.6	49.9
IIIC	74.5	57.3
IVA	46.7	25.5
IVB	37.0	20.1

[8] *Adapted from SEGO and ESMO consensus*(18,25)

[9] *Adapted from FIGO 26th Annual Report. Survival by histological type in SS patients. Data obtained from patients treated in 1999-2001*(14).

[10] *Adapted from FIGO 26th Annual Report and UptoDate 2016. Survival by FIGO surgical stage in Endometrioid carcinoma. Data obtained from patients treated in 1999-2001 using the original 1988 FIGO SS.* (14)

Annex 5: Information sheet
FULL D'INFORMACIÓ AL PACIENT[11]

TITOL DE L'ESTUDI**:** ***Gangli sentinella en càncer d'endometri: Validació de la tècnica de biòpsia selectiva del gangli sentinella.***

Agraïm el seu interès pel que fa a la seva col·laboració en l'estudi que estem realitzant en persones que, com vostè, pateixen càncer d'endometri i estem duent-lo a terme des de la Unitat de Ginecologia Oncològica (GONC) de l'Hospital Universitari Dr. Josep Trueta de Girona sense rebre compensació econòmica. La nostra intenció és que rebi la correcta informació perquè pugui avaluar si vol o no participar-hi. A continuació, li expliquem en què consisteix l'estudi. L'equip que en forma part li respondrà qualsevol dubte o qüestió que li pugui sorgir.

La legislació espanyola i els principis ètics de confidencialitat exigeixen que vostè conegui els detalls de l'estudi i doni el seu consentiment a participar-hi.

A continuació l'informarem sobre la raó de ser de l'estudi i de les preguntes més comunes:

Quin és l'objectiu d'aquest estudi?

Aquest estudi té com a principal objectiu avaluar si la detecció del gangli sentinella seria una bona eina per establir l'afectació locoregional ganglionar real que presenta, en dones amb càncer d'endometri candidates a participar a l'estudi.

Actualment, el tractament d'elecció per les pacients diagnosticades de càncer d'endometri s'inicia amb una cirurgia d'estadificació que varia segons el tipus de càncer i que consta de histerectomia (extirpació del úter), doble annexectomia (extirpació dels dos ovaris), limfadenectomia pèlvica i aortica (extirpació dels ganglis) i en cas que fos necessari: omentectomia (extirpació del greix que cobreix els intestins), apendicectomia (si precisa) i resecció de tot allò sospitós de malignitat. Els ganglis limfàtics són la principal via de disseminació del càncer en qüestió, així que fins al moment es recomanen treure per sistemàtica. Hi ha casos en què un cop analitzats els ganglis, no se'n troben d'afectats, així, doncs, es vol comprovar si amb la tècnica de gangli sentinella podem ser menys agressius amb la tècnica quirúrgica i detectar quines pacients es poden lliurar de la limfadenectomia.

[11] *Adapted from Exemple de full d'informació al pacient proporcionat per els Serveis de Salut Integrats. Baix Empordà*

Quines característiques han de reunir els pacients per participar en el estudi?

Tenint en compte la informació que anteriorment els hem aportat, els pacients que participaran han de tenir, com vostè, un diagnòstic clar de càncer d'endometri indiferentment del tipus, estadi o grau amb indicació de estadificació quirúrgica. A més és necessari que sigui major d'edat i que signi el consentiment informat si està conforme.

L'estudi es realitzarà al Hospital Universitari Dr. Josep Trueta aconseguint reunir les dades d'uns 95 pacients com vostè.

En què consisteix participar-hi?

Vostè seguirà el procediment terapèutic habitual segons el protocol establert per la Unitat de Ginecologia Oncològica de l'Hospital Universitari Dr. Josep Trueta, però es farà un procediment diagnòstic addicional. El que pretenem es detectar el gangli sentinella previ i durant la cirurgia, per a estudiar-lo un cop extret.

D'acord amb l'objectiu del nostre estudi, realitzarem una injecció de Tecneci99 al úter guiada per ecografia transvaginal el dia previ a la cirurgia seguida d'una prova d'imatge per a detectar on es situen els ganglis sentinella: limfoescintigrafia. El dia de la cirurgia es farà una segona injecció amb blau de metilè i aquesta vegada al cèrvix. Llavors es procedirà a realitzar l'acte quirúrgic d'estadificació i es procurarà detectar els ganglis sentinella per visió de la coloració blava, i per una gamma sonda el Tecneci99 acumulat als ganglis sentinella. S'extirparan aquests ganglis sentinella detectats i a continuació es farà la linfadenectomia protocol·litzada. S'estudiaran independentment els ganglis sentinelles i la resta de linfadenectomia per valorar si coincideix l'afectació.

Es farà el seguiment reglat del post-operatori, ja no objecte d'estudi de l'estudi.

És obligatori participar?

La participació a l'estudi és totalment voluntària. Si decideix participar-hi, se li demanarà que signi el consentiment informat segons el qual vostè ha entès tot el que concerneix participar en aquest estudi. Abans i després de firmar pot preguntar tot el que cregui convenient als metges i personal sanitari responsable de l'estudi.

Contràriament, si decideix no participar-hi, això no afectarà ni modificarà el pla assistencial que ha de rebre.

Si decideix canviar d'opinió, és lliure d'abandonar-lo, si així ho desitja. Per suposat, encara que vostè abandoni l'estudi, rebrà el mateix procediment terapèutic protocol·litzat.

Quins inconvenients té l'estudi?

El principal inconvenient de l'estudi és haver d'assistir el dia anterior a la cirurgia per a realitzar la injecció de Tecneci99 i la realització de la limfoescintigrafia. Accessòriament també se li realitzarà una injecció d'un altre tinció: blau de metilè, a la mateixa cirurgia.

Puc tenir alguna reacció adversa al procediment?

Els traçadors utilitzats, són traçadors ja utilitzats en altres circumstàncies i pocs efectes adversos s'han detectat, en alguns casos s'han detectat reaccions al·lèrgiques. No recomanem participar al estudi a pacients amb reaccions al·lèrgiques relacionades conegudes.

Les meves dades s'utilitzaran de forma confidencial?

Sí. Per a la realització de l'estudi hem de conèixer algunes de les seves dades mèdiques relacionades amb la seva malaltia. Aquestes es registraran a una base de dades codificada a través d'una sèrie numèrica aleatoritzada. Només seran registrades aquelles dades de la història clínica que estiguin relacionades amb l'estudi. La informació recollida per aquest estudi serà tractada i regulada segons la Llei Orgànica de Protecció de Dades de Caràcter Personal (15/1999) segons la qual, les seves dades seran manejades de forma confidencial i només seran utilitzades amb finalitat d'investigació per el grup d'investigació.

Què se'n farà de la informació obtinguda a partir de l'estudi?

Els resultats seran publicats en revistes d'interès científic relacionades amb l'àrea de coneixement corresponent a la patologia ginecològica oncològica per tal que altres centres i pacients puguin aprofitar les troballes del nostre estudi en un futur. Recordi que totes les seves dades de caràcter personal són confidencials i, per tant, seran manejades de forma anònima.

Amb qui he de contactar davant qualsevol dubte o problema que sorgeixi?

En cas de necessitar informació podrà posar-se en contacte amb la Unitat de Ginecologia Oncològica de l'Hospital Universitari Dr. Josep Trueta de Girona.

Moltes gràcies per la seva atenció,

Unitat de Ginecologia Oncològica de l'Hospital Universitari Dr. Josep Trueta de Girona

Annex 6: Informed consent

CONSENTIMENT INFORMAT [12]

TITOL DE L'ESTUDI: ***Gangli sentinella en càncer d'endometri: Validació de la tècnica de biòpsia selectiva del gangli sentinella.***

Jo,_____ declaro que he estat correctament informat per el membre responsable de l'equip investigador a sota esmentat, sobre els objectius de l'estudi així com sobre el procés de selecció de les dades personals, així com que puc formular les preguntes que consideri oportunes; també declaro que he estat informat que la meva participació és voluntària i que puc retirar-me de l'estudi sense haver de donar explicacions sense que això repercuteixi en les meves cures mèdiques.

Conforme amb el que estableix la L.O. 15/1999, de 13 de desembre, de Protecció de Dades de Caràcter Personal (article 3, punt 6 del Reial Decret 223/2004), declaro haver estat informat: De l'existència d'un fitxer de dades de caràcter personal, de la finalitat de la seva recollida i dels destinataris de la informació. De la disponibilitat d'exercir els drets d'accés, rectificació, cancel·lació i oposició dirigint-me al titular del fitxer de dades. Consenteixo que les dades clíniques referents a la meva malaltia siguin emmagatzemades en un fitxer automatitzat, la informació del qual podrà ser utilitzada exclusivament per finalitats de caire científic ara i en un futur.

De rebre una còpia d'aquest mateix document.

Dono lliurement la meva conformitat per participar a l'estudi.

Accepto ☐

Rebutjo ☐

Signatura del participant:	
NOM, COGNOMS i DNI _____	
FIRMA	Data:_____

Signatura del investigador:	
NOM, COGNOMS _____	
FIRMA	Data:_____

[12] *Adaptat del Exemple de Consentiment Informat proporcionat per els Serveis de Salut Integrats. Baix Empordà*