PhD in Oncology; XXX Cycle
Curriculum "Gynecological and Obstetric Sciences"
Doctoral School of Experimental and Clinical Medical Sciences
Department of Medical and Surgical Sciences and Translational Medicine

DOCTORAL THESIS:

Laparoscopic Sentinel Lymph Node mapping in Endometrial Cancer

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To my Mentors,

ardent supporters and strong source of inspirations.

SCIENTIFIC ACHIEVEMENTS OF THE CANDIDATE, DURING HER PhD:

During the 3 years of PhD, the candidate was active in various research projects that ranged from clinical to translation and basic science research. Altogether, during this period, the candidate published 48 scientific papers, including 24 original research manuscripts, 5 meta-analysis as first author, 11 review articles, 5 case reports, and 3 letters to Editor (one in *Jama Oncology* and two in *The Lancet*). She also edited 3 chapters for Translational Medicine books edited by Spinger.

Alongside, she was awarded with 4 prizes from international scientific societies for the goals achieved with the results of her projects, presented at international meeting conferences. She also won 3 grants to found part of her PhD research activity, in Italy and abroad.

She worked, and still cooperates, with two laboratories of the Sapienza University of Rome, the Oncogenomic Unit of the Department of Molecular Medicine directed by Prof. E. Ferretti and the Laboratory of Cellular and Molecular Immunology and Laboratory of Proteomics, directed by Prof. V. Barnaba. With the former, she investigates the clinical application of the miRNAs from biologic fluids as biomarkers in gynecological malignancies. So far, she published two papers and one book chapter on this topic edited by Springer, and the analysis of one prospective trial is ongoing (the accrual was recently completed). The project of the candidate in this lab has partially been founded by the Ministero dell'Istruzione, dell'Università e della Ricerca (MIUR), through a grant that the candidate won in 2015.

In cooperation with the lab of Prof. V. Barnaba, she was involved in two projects in the field of Immuno-oncology. During her PhD, the candidate published on this topic 9 papers and 1 book chapter, 8 of which as first author, and she was the invited Guest Editor of the special issue of "Immunobiology of solid cancer" published in *BioMed Research International Journal* (IF2.4). She has recently concluded one of her projects on this topic, and the final results were recently awarded in "18th Gyn. Endocrin. World Congress of ISGE". The final draft of the manuscript on this project has been recently submitted for publication.

For 16 months of her PhD, the candidate experienced a research fellow PhD period in the Department of Gynecology and Obstetrics of the University of Bern, Switzerland, under the supervision of the Full Professor MD Mueller, Chief of the Department. During this period, she authored/co-authored 26 papers in different areas of Gynecology. In the same period, the candidate participated at the "Bernische Krebsliga" Grant competition with a project in cooperation with the Laboratory of Tumor Immunology of the University of Bern (Prof. A. Ocsenbein), awarded for 25.000 CHF.

Multiple international collaborations were carried out by the candidate, such as the one with the international prospective Tumor Bank for Ovarian Cancer (TOC Network), which led to a recently submitted publication. The results of this collaboration trial were selected as abstract at the ASCO Annual Meeting 2017, in Chicago.

In order to better interact with the colleagues in the german part of Switzerland, where she spent part of her PhD, the candidate attended several certified German language courses achieving the B2 certification in German language.

To complete her statistical skills, she attended an Advanced Training Courses in Biostatistics certified by the "Centro Studi Gorgia", in Florence.

In May 2017, the candidate was the youngest gynecologist achieving the National academic competence qualification as Associate Professor.

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1. PREFACE:

The sentinel lymph node mapping represents one of the research lines of the candidate during her PhD activity at the Department of Gynecology and Obstetrics, at the University of Bern, under the supervision of Prof. MD Mueller.

During this period, the candidate authored/coauthored 16 articles in the field of sentinel lymph node mapping in uterine cancers; part of them were multicentric trials, edited in cooperation with several other European Academic Institutions.

In this thesis, the candidate focused the main results achieved in this period, in the setting of the clinical application of lymph node mapping in endometrial cancer.

2. INTRODUCTION:

In the management of endometrial cancer patients, the staging lymphadenectomy has been controversial since 30 years. In 1988, following the results of a seminal Gynecologic Oncology Group (GOG) study, the GOG#33 trial, FIGO transitioned from a clinical to a surgical staging [1, 2]. This surgical-pathologic study conducted on 621 patients with Stage I carcinoma of the endometrium showed that an appreciable number of patients with clinical early stage cancer present with disease outside of the uterus.

Despite this change in FIGO staging, a low adherence to the staging procedure among physicians was recorded. In particular, only 54% of the centers of reference for gynecologic cancers in North America and 25% of those in Western Europe routinely performed a pelvic and para-aortic lymphadenectomy in endometrial cancer patients [3, 4]. The relatively indolent biological behavior of endometrial cancer, the surgical complexity of a pelvic and para-aortic lymphadenectomy and the typical clinical characteristics (obese, affected by multiple comorbidities including diabetes and hypertension) of these patients can probably explain the low adherence to a full surgical staging with pelvic and para-aortic lymphadenectomy. In the attempt to reduce the risk of lymphoceles and lymphatic complications occurring after a systematic lymphadenectomy, the prophylactic use of fibrin sealant patches have been investigated with promising results [5]

Different methods have been proposed to identify the patient that benefit the most from a full surgical staging. The most widespread method to triage patients to a full lymphadenectomy is based on intrauterine risk factors identification at frozen section analysis. However, this methodology does not seem to be accurate and reproducible since different series have led to different results [6-10]. This approach is limited in that a large number of patients with negative

lymph nodes has to undergo a full lymphadenectomy in order to keep the false negative rate of the triage low. Furthermore, in patients not undergoing a full lymphadenectomy no pathologic information on lymph node status is provided.

In 2008 and 2009, two large randomized prospective clinical trials were published: the CONSORT and the ASTEC trial [11, 12]. Despite the fact that these two large prospective trials failed to show any survival benefit from the surgical staging, these data did not translate in clinical practice: the lymphadenctomy has not been abandoned, still represents the cornerstone of FIGO staging and is a recommended procedure by the major guidelines [13-15]. Although a systematic lymphadenectomy does not have a direct effect on survival it provides important pathologic information that define prognosis and can help determine the most appropriate adjuvant treatment. Although at times adjuvant therapy is already indicated based on uterine risk factors, the postoperative management of high intermediate and high risk endometrial cancer patients changes, according to the ESMO-ESGO-ESTRO consensus conference, based on the availability of a pathologically proven negative lymph nodal status [14-16]. It has been proven that patients with pathologically negative lymph nodes are subjected less often to adjuvant radiotherapy as compared to patients in whom the lymph nodal status is unknown [17, 18]. Interestingly, in a large multicenter retrospective study on patients with high intermediate and high-risk endometrial cancer patients the worst survival was recorded for those patients in whom the lymph nodal status was unknown. Both patients with negative and positive lymph nodal status had better overall survival than those in whom the lymph nodal status was unknown [19].

In this setting, if proven reliable and safe, the sentinel lymph node mapping may represent a balanced alternative to an “all or nothing at all” approach. The overall aim of this research was to assess the clinical applicability of the sentinel lymph node mapping of endometrial cancer in different settings.

To this purpose, several analyses with the following aims were performed:

1. Validation analysis of the sentinel lymph node mapping in endometrial cancer
2. Comparison of sentinel lymph node detection rate based on adopted tracers
3. Assessment of the optimal number of retrieved sentinel lymph nodes
4. Influence of indocyanine green (ICG) dose on the sentinel lymph node mapping
5. Efficacy of sentinel lymph node mapping in low risk endometrial cancer
6. Efficacy of sentinel lymph mapping in high risk endometrial cancer
7. Oncologic outcome of sentinel node lymph node mapping as compared to full lymphadenectomy

3. MATERIAL AND METHODS:

3.1 Patients' cohort

The analysis was conducted on prospectively collected data on patients with complex atypical hyperplasia and endometrial cancer. Various cohorts of patients were enrolled based on the aim of the study. Patients with a preoperative diagnosis of complex atypical hyperplasia were included in the cohort because of their inherent risk of harboring an endometrial cancer at final pathological analysis of the uterus [20]. Women were included if they underwent surgery including sentinel lymph node mapping for the aforementioned diagnosis at the following Institutions:

- Department of Obstetrics and Gynecology, University of Berne, Bern, Switzerland.
- Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, San Gerardo Hospital, University of Milano-Bicocca, Monza, Italy.
- Gynaecologic Oncology Unit, La Paz University Hospital - IdiPAZ, Madrid, Spain.
- Department of Oncological Surgery, Gynecologic Oncologic Unit, "Regina Elena" National Cancer Institute, Rome, Italy.
- Department of Obstetrics and Gynecology, Gynecologic Oncology and Minimally-Invasive Pelvic Surgery International School of Surgical Anatomy Sacred Heart Hospital, Negrar, Verona, Italy.
- Department of Obstetrics and Gynecology, "Regina Montis Regalis" Hospital, Mondovi, Italy.
- Department of Gynecology and Obstetrics, Santa Chiara Regional Hospital, Trento, Italy.

It should be noted that for one specific analysis (the assessment of the optimal number of retrieved sentinel lymph nodes, see in Results 4.3.a, 4.3.b, 4.3.c), 39 cervical cancer/84 patients were also included. The decision to include these patients was taken because the technique of the sentinel lymph node mapping is the same as for endometrial cancer. The assumption was that the intracervical injection of the tracer is the relevant variable for the distribution of the sentinel lymph nodes rather than the location of the tumor. In order to avoid bias, in the uni-multivariate analysis, the site of tumor (cervical vs endometrial) was included and it was demonstrated to be not significant for the outcome.

3.2 Surgical technique

The sentinel lymph node mapping is performed via intracervical injection of the tracer. The cervix is injected submucosally and deep in the stroma. Depending on the tracer used the timing of the injection is different.

3.2.1 Tracers:

Tc-99m is the most commonly used medical radioisotope in diagnostic procedures [21, 22]. It short half-life of 6 hours is ideal for diagnostic procedures such as the sentinel lymph node mapping. After injection, the radioactive signal is identified with a gamma probe. Since Tc-99m is colorless the sentinel lymph node detection relies only on the audiometric signal of the gamma probe that identifies the emitted –rays. Prior to surgery a lymphoscintigraphy or a SPECT-CT are performed to detect the number and location of sentinel lymph nodes. Tc-99m is usually injected the day prior to surgery in a radio-protected setting. This allows enough time to acquire the preoperative radiologic imaging. The relatively short decay time of this tracer can jeopardize the

effectiveness of the planned sentinel lymph node mapping should the scheduled procedure be delayed.

Various blue dyes including methylene blue, isosulfan blue and patent blue have been used as tracers for sentinel lymph node mapping. Following interstitial administration, they travel fairly through the lymphatic channels to the sentinel lymph nodes that become blue. This methodology is therefore simple and user friendly. However, the visual signal only lasts approximately 20 minutes and the amount of time available to detect the sentinel lymph nodes is limited. Furthermore, it exacerbates allergic reactions in up to 2% of the cases [23].

In our series, Tc-99m and patent blue were always used in combination. Two-hundred –300 µCi radiolabeled filtered technetium Tc-99m albumin nanocolloid were injected into the four quadrants of the cervix on the day before surgery. A Lymphoscintigraphy was performed to preoperatively locate the sentinel lymph node. A SPECT/CT study was performed if deemed necessary by the treating physicians. In the operating room on the day of surgery, the patient was intracervically injected with 5 ml of patent blue dye in the four cervical quadrants. Under gamma probe (Navigator; Autosuture, Norwalk, CT, USA) guidance and patent blue-dye visual guidance, the sentinel lymph nodes were laparoscopically located and excised.

Indocianine green (ICG) is a dye that shows diffuse fluorescence when excited by near-infrared light (NIR) (700–900 nm). ICG is FDA approved for intravenous administration since over 50 years and has been widely employed in ophthalmology for retinal fluorangiographies. In the past few years it has been adopted as tracer for sentinel lymph node mapping. Its ease of use has been detrimental in accelerating the development and clinical acceptance of the sentinel lymph node mapping in gynecological oncology. ICG is considered to be a safe tracer, it should however be avoided in patients with iodine allergies as it contains iodine. Allergic reactions to ICG have been

described even in absence of iodine allergy [24]. ICG has been injected both intracervically and peritumorally under hysteroscopic guidance [23, 25].

The amount of ICG injected differed in concentration and volume based on institutional protocol. Concentration of ICG varied between 1.25 mg/ml and 5 mg/ml. At the Department of Obstetrics and Gynecology, University of Berne, Bern, Switzerland one vial of 25 mg ICG powder (Pulsion®) was diluted with 10 ml sterile water. An amount of 8 ml of the resulting solution was then injected in the four cardinal points of the cervix. In different centers, a concentration of ICG of 1.25 mg/ml and a volume of 4 ml were used.

3.2.2. Sentinel lymph node mapping:

When ICG is used, the tracer is injected after the general anesthesia is obtained and the laparoscopy is started. In case of combined use of Tc-99m and blue dye, Tc-99m is injected on the day prior to surgery and followed by a lymphoscintigraphy or by a SPECT/CT, whereas the blue dye is injected in the operating room on the day of surgery, after a general anesthesia has been obtained, at the beginning of the laparoscopy.

For the laparoscopic surgery, two 5 mm trocars are placed in the right and left lower quadrants of the abdomen, approximately 2 cm medial and cranial from the anterior superior iliac spine, laterally of the inferior deep epigastric vessels. A 12 mm trocar is inserted suprapubically in the midline.

For the mapping performed via ICG, the camera mode is switched on the near infrared (NIR) mode to detect a fluorescent signal coming from the lymphatic vessels or from a sentinel lymph node prior to accessing the retroperitoneal space. Often, the green color of the ICG solution can already be

seen through the peritoneum prior to switching the NIR mode on; after activation of the NIR mode, the visual signal becomes stronger and fluorescent.

The retroperitoneum is accessed after opening of the pelvic side wall peritoneum and the retroperitoneal areolar tissue is developed bluntly. The retroperitoneal structures are identified (ureter, iliac vessels, superior vescical artery) and the retroperitoneal space is gently dissected. A gentle tissue dissection is necessary to reduce the spill of ICG from disrupted lymphatics, as this may result in a non-specific diffuse fluorescent signal in the anatomic region. Once a fluorescent lymphatic vessel is identified, its course is followed until the sentinel lymph node is identified (Figure 1). The sentinel lymph node is then excised, removed and sent for pathological analysis.

A similar procedure, without the need to switch the camera to the NIR mode, is adopted when the blue dye is used. On the contrary, Tc-99m gives an audiometric signal and the identification of the sentinel lymph node relies on the identification of a radioactive signal that is detected with a gamma probe. The laparoscopic gamma probe is inserted via the suprapubic 12 mm trocar. Hence, during the detection of the radioactive signal, only the two 5-mm ancillary trocars can be adopted for the use of other laparoscopic instruments such as graspers, bipolar cautery or scissors.

3.2.3 Pelvic and paraaortic Lymphadenectomy

Both the pelvic (Figure 2A and 2B) and paraaortic (Figure 2 C) lymphadenectomies are performed laparoscopically.

For an adequate pelvic lymphadeenctomy, all the lympho-fatty tissue located between the following boundaries is removed:

Cranially: the common iliac vessels

Caudally: the deep circumflex iliac vessels

Laterally: the psoas muscle

Medially: the ureter and the superior vescical artery

Dorsally: the obturator nerve

For an adequate paraaortic lymphadeenctomy, all the lympho-fatty tissue located between the following boundaries is removed:

Cranially: the ovarian vein on the right side and the renal vein on the left side

Caudally: the common iliac vessels (or the upper landmark of the pelvic lymphadenectomy)

Laterally: the psoas muscle and the ureters

3.3 Pathological analysis.

3.3.1 Sentinel lymph node pathological analysis with ultrastaging

The sentinel lymph nodes were processed according to an ultrastaging protocol. After an initial examination by routine Hematoxylin and Eosin (H&E) staining, an ultrastaging is performed on metastases free sentinel lymph nodes. This is performed by cutting 2 adjacent 5-µm sections at each of 2 levels, 200- µm apart, from each paraffin block lacking metastatic carcinoma. At each level, one slide is stained with H&E and with immunohistochemistry (IHC) using the anticytokeratin AE1:AE3 (Ventana Medical Systems, Inc, Tucson, AZ) for a total of 5 slides per block. According to the definition of the American Joint Committee on Cancer, metastatic disease to the sentinel lymph nodes is then classified as follows (26):

-macrometastases if the identified tumor deposits are larger than 2.0 mm;

-micrometastases if the identified tumor deposits are larger than 0.2 mm and up to 2 mm;

-isolated tumor cells if the identified tumor deposits do not exceed 2 mm in size.

3.3.2 Frozen section analysis of the uterus:

At the Department of Obstetrics and Gynecology, University of Berne, Bern, Switzerland, patients with complex atypical hyperplasia, grade 1 and 2 endometrial cancer on preoperative endometrial biopsy undergo an intraoperative microscopic analysis of the uterus at frozen section after the sentinel lymph nodes have been excised and the uterus removed. Uterine risk factors are assessed, and based on these and on clinical judgment, a completion of the surgical staging is performed. Usually, patients with grade 3 endometrial cancer or deep myometrial invasion undergo a pelvic and paraaortic lymphadenectomy; patients with grade 1 endometrial cancer and superficial myometrial invasion undergo a sentinel lymph node biopsy only. In the other cases, a pelvic lymphadenectomy is usually performed.

3.4 Statistics

3.4.1 Definitions

The overall detection rate defines the number of patients undergoing a sentinel lymph node mapping in whom at least one sentinel lymph node is detected; whereas, the bilateral detection rate defines the number of patients having detectable sentinel lymph nodes in both hemipelvises. A true positive sentinel lymph node was defined as a positive sentinel lymph node identified with histopathological techniques, independent of regional lymph node status. The sensitivity was defined as the proportion of actual positives that are correctly identified as such. A false negative sentinel lymph node mapping was defined as a bilateral negative sentinel lymph nodes in combination with a metastatic not-sentinel lymph node. The false negative rate (FN) of the sentinel

lymph node mapping was calculated for patients who underwent at least a pelvic lymphadenectomy after the sentinel lymph node biopsy. The false positive rate was defined as zero.

Overall survival was defined as the interval of time between the date of surgery and the date of death, whereas Disease Free Survival (DFS) was defined as the time between date of surgery (or the end adjuvant therapy if present) and recurrence.

3.4.2 Statistical methods

Clinicopathologic characteristics were evaluated using the basic descriptive statistics. Surgical data were compared among the group of patients undergoing sentinel lymph node mapping only and those undergoing a full lymphadenectomy after the sentinel lymph node biopsy, using the unpaired t test. Overall and bilateral detection rates, sensitivity, and FN rate of the sentinel lymph node mapping were calculated using Fisher's exact test.

The K statistics was used to measure the agreement between indication to lymphadenectomy based on frozen section analysis of the uterus and lymph nodal metastasis, and the agreement between sentinel lymph node metastasis and lymph nodal metastasis. K results were interpreted as follows: values <0 as indicating no agreement, 0.01–0.20 as none to slight (very mild concordance), 0.21–0.40 as fair (mild concordance), 0.41–0.60 as moderate, 0.61–0.80 as substantial and 0.81–1.00 as almost perfect agreement.

Univariate and multivariate analyses were performed in order to identify factors associated with bilateral detection rate and number of removed sentinel lymph nodes. Univariable and multivariable proportional hazard Cox regression models were also applied to estimate the odds ratio and the p-values for association of the oncologic outcomes and risk factors. Multivariable

models were carried out for variables with a p-value ≤0.5 at the univariate analysis but only p-values ≤0.05 were considered statistically significant.

3.4.3 Software

Statistical analyses were performed using the R software version 3.1.0, Stata software 9.0 (Stata Corporation, College Station, Texas, USA), GraphPad version 5 for Mac (GraphPad Software, San Diego CA) and IBM-Microsoft SPSS version 22.0.

4. RESULTS:

4.1 Validation analysis of the sentinel l mapping in endometrial cancer

4.1.a Clinicopathologic characteristics of the patients

Seventy-five patients fulfilled inclusion criteria and were included in this analysis; their clinicopathologic characteristics are reported in Table 1.1

4.1.b Anatomic distribution of sentinel lymph nodes

The 55% of sentinel lymph nodes were detected in the Obturator fossa, 32% in the external iliac artery, 8% in the common iliac artery, 4% in the aortic bifurcation, 1% in the para-aortic area. This distribution of the sentinel lymph nodes is summarized in Fig. 3.

4.1.c Detection rates

Overall and bilateral sentinel lymph nodes detection rates were 96 % (72/75) and 88% (66/75), respectively. In two of the three patients in whom the sentinel lymph nodes mapping failed, the pelvis had been previously irradiated, secondary to bladder cancer and pelvic lymphoma, respectively. By excluding these patients from the analysis, these rates rise to 98.6 % (72/73) and 90.4 % (66/73), respectively.

4.1.d False negative (FN) rate

Of the 42 patients in whom a pelvic/paraortic lymphadenectomy was performed, one FN mapping occurred: both the bilateral sentinel lymph nodes in the pelvis and all the pelvic lymph nodes were negative, whereas two para-aortic non- sentinel lymph nodes had metastatic disease. In another patient, four of five sentinel lymph nodes were true positive in the right hemipelvis, whereas one sentinel lymph node in the left pelvis was FN as one Non- sentinel lymph node had metastatic disease. The calculated sensitivity of the sentinel lymph nodes mapping was 91.7 %; the FN rate was 8.3 %.

4.1.e Lymph node data

The median number of sentinel lymph nodes removed was 3 (range 0–11), and in 5% (4/75) of cases, additional sentinel lymph nodes were identified in the para-aortic region; no isolated para-aortic sentinel lymph node was detected. Complete data on sentinel lymph nodes are summarized in Table 1.2.

4.2 Comparison of sentinel lymph node detection rate based on adopted tracers

4.2.a Clinicopathologic characteristics of the patients

342 patients fulfilled inclusion criteria and were included in this analysis (one hundred and forty-seven in the Tc99m + BD group and 195 in the ICG group). Patients characteristics are reported in Table 2.1.

4.2.b Detection rates based on adopted tracers for sentinel lymph node mapping

The overall detection rate of the sentinel lymph nodes mapping was 97.3 and 96.9% in Tc99m+BD and ICG, respectively (p = 0.547). A statistically significant difference was recorded for the bilateral

detection rate in favor of ICG group (73.5 vs 84.1%; p=0.007). The differences of sentinel lymph nodes mapping between the two groups are shown in Figure 4.

4.2.c Sentinel lymph node mapping and lymph node pathological characteristics according to the tracer used.

The anatomical distribution of the sentinel lymph nodes was similar in both groups, and the vast majority of mapped nodes were located in the external iliac area and the obturator fossa. On final pathology, 320 women (92%) were node negative. Overall, 22 patients presented nodal involvement (8%). Metastases were discovered in 12/147 women (8.1%) in the Tc99m + BD group and in 10/195 women (5.1%) of the ICG group (p = 0.181). Among 993 sentinel lymph nodes removed, 71 lymph nodes presented metastasis (7.1%). Low volume metastases were identified in 20/38 of the sentinel lymph nodes in the Tc99m + BD group (16 MM and 4 ITC) and in 9 sentinel lymph nodes in the ICG group (8 MM and 1 ITC). Patients with MM or ITC only in the lymph nodes were 18/43 (41.8%), including 13/25 in the Tc99m + BD group and 5/18 in the ICG group. Surgical characteristics are displayed in Table 2.2. The overall sensitivity (OS) and overall false negative rate were not statistically significant between patients underwent sentinel lymph node mapping with lymphadenectomy and patients who received sentinel lymph node mapping algorithm (p value = 0.311). The NPV was in favor of the sentinel lymph node algorithm group (p value = 0.030).

4.3 Assessment of the optimal number of retrieved sentinel lymph nodes

4.3.a Clinicopathologic characteristics of the patients

131 patients fulfilled inclusion criteria and were included in this analysis. The patients characteristics are reported in Table 3.1.

4.3.b Impact of the number of sentinel lymph nodes removed on the false negative rates

The median number of sampled sentinel lymph nodes was 3.5 (range: 2-18). Based on this result, two groups of patients were created. Group 1 consisted of 42 patients with a sentinel lymph nodes count of up to 3 lymph nodes and Group 2 consisted of 42 patients with a sentinel lymph nodes count of 4 or more. The sentinel lymph node false-negative rate was 4.8 and 0 % for Group 1 and Group 2, respectively and did not differ significantly between the two groups (Table 3.2).

4.3.c Univariate and multivariate analysis on factors influencing sentinel lymph nodes count.

When patient characteristics (age, BMI), disease characteristics (type of tumor, presence of positive sentinel lymph nodes), and characteristics of the surgeon (experience of up to or over 20 ICG sentinel lymph node mappings and gynecologic oncology certification) were evaluated for influence on the sentinel lymph nodes count in the univariate analysis, the BMI of the patient, type of uterine cancer (cervical vs endometrial), positive sentinel lymph nodes, surgical experience (up to 20 procedures vs over 20 procedures), and gynecologic oncology certification were considered significant and further analyzed at multivariate analysis. Only surgical expertise maintained significance as an independent prognostic factor for number of sentinel lymph nodes removed. Data on univariate and multivariate analysis are presented in Table 3.3.

4.4. Influence of ICG dose on the sentinel lymph node mapping

4.4.a Clinicopathologic characteristics of the patients

168 patients fulfilled inclusion criteria and were included in this analysis. The patients characteristics are reported in Table 4.1

4.4.b Influence of ICG dosage on detection rates at Uni and Multivariate analysis

In the univariate analysis, for bilateral detection rate ICG dose, BMI and tumor diameter were considered significant and further analyzed at multivariate analysis. No independent factors were associated with the bilateral detection rate (Table 4.2).

4.4.c Influence of ICG dosage on sentinel lymph nodes number at Uni and Multivariate analysis

In the univariate analysis for number of removed sentinel lymph nodes, ICG dose, tumor diameter, and LVSI were considered significant and further analyzed at multivariate analysis. At multivariate analysis, ICG dose was the only factor associated with number of removed sentinel lymph nodes (OR 4.8 (2.31, 9.97); p=0.0001) (Table 4.3).

4.5 Efficacy of sentinel lymph node mapping in low risk endometrial cancer

4.5.a Clinicopathologic characteristics of the patients

116 patients fulfilled inclusion criteria and were included for this analysis. The patients characteristics are reported in Table 5.1

4.5.b Surgical data

Six (9.5%) patients presented with metastatic lymph nodes. In five cases, these were macrometastasis and in one case micrometastasis. Metastatic lymph nodes were located in the pelvis in every case, additionally; three (4.8%) patients also had metastatic paraaortal lymph nodes. Complete surgical data are reported in Table 5.2.

4.5.c Performance of frozen section of the uterus versus sentinel node lymph node mapping in identifying low-risk endometrial cancer patients with lymph nodal metastases

After frozen section, 23 (36.5%) and 14 (22.2%) patients underwent a pelvic lymphadenectomy and a paraortic lymphadenectomy, respectively. In 5 (80%) of the 6 patients with metastatic lymph nodes, a pelvic lymphadenectomy or a paraortic lymphadenectomy was performed based on intrauterine risk factors identified at frozen section analysis of the uterus. In one case, frozen section of the uterus failed to identify a small clear cell carcinoma that had already metastasized to the lymph nodes. After the identification of metastatic disease to one sentinel lymph node at permanent section, the patient underwent a completion paraortic lymphadenectomy that revealed 23 additional metastatic paraaortic lymph nodes. The false negative rate of the frozen section in identifying metastatic lymph nodes was 16.7% with a NPV and a PPV of 97.6 and 27.3%, respectively. Based on intrauterine risk factors identified at frozen section, 6 patients have to be staged to identify one with lymph node metastases. Additionally, if surgical staging had been performed based only on intrauterine risk factors 16.7% of the patients with lymph node metastasis would have been missed. Correlation between indication to lymph node dissection at frozen section and metastatic disease to the lymph nodes was mild (K = 0.244). For the sentinel lymph node mapping, overall and bilateral detection rates were 100 and 93.7%, respectively. sentinel lymph nodes were positive in 6 patients. In this cohort of patients, the FN rate of the sentinel lymph node mapping was 0%, with a NPV and a PPV of 100% in both cases. Correlation between metastatic sentinel lymph nodes and metastatic disease to the lymph nodes was excellent (K= 1). The performance of the two surgical methods is presented in Table 5.3 and figurally depicted in Figure 5.

4.6 Efficacy of sentinel lymph node mapping in High risk endometrial cancer

4.6.a Clinicopathologic characteristics of the patients

42 patients fulfilled inclusion criteria and were included in this analysis. Clinicopathologic characteristics of the patients Table 6.1.

4.6.b Lymph nodal characteristics

Overall and bilateral detection rates were 100 and 90.5%, respectively. Ten patients had lymph node metastases for a disease prevalence of 23.8% (95% CI 12–39%). Nine of the patients with lymph node metastases could be correctly identified with the sentinel lymph node mapping. In eight cases and one case were the sentinel lymph node metastases macro- and micrometastases, respectively. The positive sentinel lymph nodes were located predominantly in the pelvis (8 out of 9) and in only one case in the para-aortic region only. A single FN case was recorded in a patient who mapped bilaterally in the pelvis and in whom three sentinel lymph nodes were retrieved. The positive not-sentinel lymph node was located in the para-aortic region. This metastatic not- sentinel lymph node was considered clinically suspicious and intraoperatively sent for frozen section analysis. This revealed a macrometastasis of 9 mm. Data on sentinel lymph nodes and not- sentinel lymph nodes are summarized in Table 6.2.

4.6.c Sensitivity, NPV, and FN rate of the sentinel lymph node mapping and of the MSKCC sentinel lymph node mapping algorithm

Sensitivity and NPV for the sentinel lymph node mapping were 90% (95% CI 76–96%) and 97.1%(95% CI 85–99%), respectively. The FN rate was 10%. However, by applying the MSKCC sentinel lymph node mapping algorithm in which every sentinel lymph node is excised along with every suspicious node, a side-specific lymphadenectomy is performed in case of unilateral detection rate and a paraaortic lymphadenectomy is performed based on surgeons choice, the sensitivity, NPV, and FN rate are 100% (95% CI 89–100%), 100% (95% CI 89–100%), and 0%, respectively. Data are summarized in Table 6.3

4.7 Oncologic outcome

4.7.a Clinicopathologic characteristics of the patients

171 patients fulfilled inclusion criteria and were included in this analysis. The patients characteristics are reported in Table 7.1

4.7.b *Surgical data and Lymph nodal characteristics*

Overall outcomes including overall sensitivity, overall false-negative rate, overall negative predictive value were 85.2%, 14.7%, 93%, respectively. Algorithm-specific outcomes including overall sensitivity, algorithm false-negative rate, and algorithm negative predictive value were 91.2%, 8.8%, 96%, respectively. Complete data are summarized in Table 7.2.

4.7.c Survival data

The median follow-up time was 20 months (range 5-80) in sentinel lymph node mapping group and 16 months (range 6-88) in the lymphadenectomy group, respectively. Recurrence and death were similar in both groups. The Kaplan-Meier curves of disease-free survival were not significantly different between the two groups with a p value = 0.86 and are reported in Figure 6.

4.7.d Univariate and Multivariate analysis of disease free survival

In the univariate analysis, the stage, hystotype and adjuvant therapy were considered significant and further analyzed at multivariate analysis. Only stage and histology maintained significance as an independent prognostic factor for number negative disease-free survival in the multivariate analysis (p=0.007 and p=0.03, respectively). Table 7.3 summarizes these results.

5. DISCUSSION:

In medicine, the false negative rate is defined as the rate of occurrence of negative test results in subjects known to have the disease for which an individual is being tested. When applied to the sentinel lymph node mapping, the false negative rate represents the amount of patients with non-affected sentinel lymph nodes who do actually harbor metastatic disease to other lymph nodes. This is probably the most critical characteristic of a sentinel lymph node mapping. For the procedure to be safe, the false negative rate has to be low in order to avoid under-staging patients. In the clinical settings in which the sentinel lymph node mapping is considered standard of care, such as breast or vulvar cancer and melanoma, the false negative rate is approximately 3% [27, 28].

In our series, we recorded a false negative rate of 8.3% [29]. This result correlates well with those reported by other series [30]. In order to improve the false negative rate and to take into account that the uterus is a midline structure that requires bilateral lymph nodal sampling a sentinel lymph node mapping algorithm has been proposed (MSKCC algorithm) and should be adopted whenever performing a sentinel lymph node mapping instead of a full lymphadenectomy [13, 30]. This algorithm recommends to remove, in addition to the sentinel lymph nodes, every lymph node that appears clinically suspicious and to perform a side specific pelvic lymphadenectomy when the detection of a sentinel lymph node fails on one side; a para-aortic lymphadenectomy should be performed on physicians' discretion. With the adoption of this algorithm, Barlin et al were able to reduce the false negative rate of the sentinel lymph node mapping in their cohort of endometrial cancer patients from 15% to 1.5%. Since their publication in 2011, their algorithm has been incorporated in the majority of the centers [30]. In 2017, the largest prospective validation trial on sentinel lymph node mapping in endometrial cancer, the FIRES trial, was published [31]. Three

hundred and forty patients with endometrial cancer underwent a robotic ICG sentinel lymph node mapping followed by a systematic pelvic lymphadenectomy in every case and by a para-aortic lymphadenectomy in 58% of the cases. In this trial, the sentinel lymph node mapping algorithm as described by Barlin et al was applied and a false negative rate of 3% was recorded confirming the data derived by the previously published retrospective analysis [30, 31].

Another aspect that defines a successful sentinel lymph node mapping is a high detection rate. As previously mentioned, in order to have a complete and successful mapping, sentinel lymph nodes need to be detected on both sides. This will reduce the number of side specific lymphadenectomies performed when the sentinel lymph node mapping algorithm is applied [30].

Probably, the single most important variable affecting bilateral detection rate is the type of tracer used. The most commonly used traces for sentinel lymph node mapping in endometrial cancer patients include Tc-99m, blue dyes and ICG, alone or in combination. In our first series, in which all the patients underwent an ICG laparoscopic sentinel lymph node mapping, the overall and bilateral detection rates were 96% and 88% respectively [29]. We had previously reported a comparison of detection rates with different tracers in cervical cancer patients [30]. This model is very similar to that adopted in endometrial cancer since, in both cases, the tracer is injected intracervically. In our experience, the bilateral detection rate was higher after intracervical injection of ICG as compared to a combination of Tc-99 and blue dye. These results were later confirmed by several other series [23, 33-36].

Among these, our multicenter experience is the largest, so far, confirming the higher bilateral detection rates seen when ICG is adopted as compared to a combination of blue dye and Tc-99 (84.1% versus 73.5%; p=0.007) [37]. Similar data have been recorded in the robotic setting, where mappings performed with ICG have consistently higher bilateral detection rates as compared

to those performed with other tracers [36-41]. In the FIRES trial, overall and bilateral detection rates were 86% and 52% respectively [31].

Overall, these results suggest that NIR-ICG sentinel lymph node mapping has higher bilateral detection rates as compared to those recorded with the combination of Tc-99m and blue dye and have higher overall and bilateral detection rates as compared to blue dye alone. Finally, three meta-analyses (including ours) have confirmed these results [42-44].

Although the sentinel lymph node is defined as the first lymph node draining the tumor, most of the times, multiple sentinel lymph nodes are identified. These can be sentinel lymph nodes draining independent lymphatic pathways or echelon lymph nodes situated downstream of a real sentinel lymph node. Differentiating between these two entities is not easy. Although echelon lymph nodes are often removed during a sentinel lymph node mapping, the removal of additional lymph nodes other than the sentinel ones may, at least in part, reduce the benefit of the sentinel lymph node mapping. On the other hand, removing all the lymph nodes draining the tracer, regardless if they are sentinel or echelon lymph nodes, may reduce the false-negative rate thus increasing the safety of the mapping

Interestingly, in our series, in which the median number of removed sentinel lymph nodes was 3,5, the false negative rate did not differ significantly based on sentinel lymph node count [45]. The two patients with false negative sentinel lymph nodes had isolated para-aortic lymph nodal metastases, in one and two lymph nodes, respectively, with negative pelvic sentinel and non-sentinel lymph nodes. These results are concordant with the risk of isolated para-aortic lymph nodal metastasis reported by Mariani el al in fully staged high-risk endometrial cancer patients [46]. We believe, that, in our series, given the peculiar distribution of the metastases, sampling a larger number of lymph nodes would not have led to the identification of the isolated par-aortic lymph

node metastases. Some authors suggest that a hysteroscopic peritumoral tracer injection increases the identification of sentinel lymph nodes located in the para-aortic region [25, 47]. However, so far, the cervix remains the preferred site of injection of the tracer because of its ease of use, reproducibility and overall good results.

ICG is drained relatively quickly through the lymphatic vessels to the sentinel lymph nodes. However, as compared to blue dyes, the signal of which disappears after 30 min, the fluorescent signal of ICG persists in the lymph nodes for a long time. These characteristics allow for a ”pressure-free” interval of time during which the sentinel lymph nodes can be located and most likely is the reason why detection rates are higher when this tracer is adopted. On the other hand, however, the same characteristic may be responsible for the removal of a higher number of fluorescent lymph nodes (sentinel and echelon lymph nodes) that have stained during the surgery, especially in those cases in which a significant amount of time elapses between tracer injection and retroperitoneal exploration.

As of now, ours is the only series addressing this issue in uterine cancer. In breast cancer surgery, this topic has been investigated with heterogeneous results. Martin et al, suggest to remove every sentinel lymph node that has a count per minute (CPM) of 10% of the hottest sentinel lymph node removed, when Tc-99m is adopted as tracer [48]. Other authors suggested that, excising more than four sentinel lymph nodes does not significantly improve the accuracy of the mapping, when a combination of Tc-99m and blue dyes is used [49-54]. Excising a larger number of sentinel lymph nodes does not come without a price since the incidence of complications increases with the number of removed sentinel lymph nodes. In breast cancer surgery, for example, Wilke et al showed that the removal of five or more sentinel lymph nodes is associated with higher rates of axillary seroma and wound infection [55].

The identification of multiple sentinel lymph nodes, as previously stated, is a common event. In melanoma, for example, in a multicenter validation trial, the average number of removed sentinel lymph nodes removed from axilla, groin and neck were 2.8, 2.3 and 2.6 respectively [56]. Our results show that removing more than 3 sentinel lymph nodes does not significantly improve the false negative rate of the sentinel lymph node mapping. Although we do not believe that a sentinel lymph node mapping should necessarily be stopped once three sentinel lymph nodes are removed, we do believe that the surgeon performing the sentinel lymph node mapping should be aware of these data and of the peculiarities of the tracers used for the mapping in order to avoid an extensive and non useful dissection. ICG has a long half-life and remains in the lymphatic system for a long time. If this tracer is adopted, a long interval of time between the tracer injection and the sentinel lymph node detection will allow the tracer to travel though the lymphatic system leading to a diffuse fluorescent signal. In these cases, an sentinel lymph node mapping may translate easily into a focused sampling or even into a complete lymphadenectomy.

In our series, we also tried to assess the influence of patient (age, BMI) and tumor characteristics (type of tumor, presence of metastatic sentinel lymph nodes) and the surgeon's expertise (gynecologic oncology certification, number of procedures performed) on the number of removed sentinel lymph nodes using univariate and multivariate analysis. We determined that the only factor associated with the number of removed sentinel lymph nodes at multivariate analysis was the expertise of the surgeon. Surgeons who had performed more than 20 laparoscopic ICG sentinel lymph node mappings were those who retrieved a smaller number of sentinel lymph nodes without increasing the false negative rate of the procedure. With greater specific experience in ICG sentinel lymph node mapping, surgeons may be more confident in their ability to correctly detect and differentiate between sentinel and echelon lymph nodes. These data are in agreement with

those of McMasters et al, which identified 20 cases as the cases needed to be performed in breast cancer surgery to be proficient in sentinel lymph node mapping [57].

Other factors that may influence the number of sentinel lymph nodes identified are the tracer adopted and the concentration and volume of tracer injected. In our institution, we inject a volume of 6 ml of ICG solution at a concentration of 5 mg/ml for a total of 40 mg of ICG. This dose is significantly higher than the dose adopted at different institutions, where a volume of 2 ml at a concentration of 1.25 mg/ml is typically adopted [33, 42].

ICG is FDA approved for intravenous but not for interstitial injection, hence the dose adopted at different institutions is empirical. A meta-analysis on ICG sentinel lymph node mapping on different solid tumors showed that larger volumes and small concentration of ICG were associated with better results [58]. We tried to study the influence of the dose and concentration of ICG injected by comparing series from two Institutions using different ICG protocols.

We found that ICG concentration does not affect bilateral detection rate at multivariate analysis, however the amount of ICG injected was the only factor affecting the number of removed sentinel lymph nodes. Ours is the first study investigating this topic in the endometrial cancer setting. Injecting too much dye may lead to an overload of tracer in the lymphatics and in the lymph nodes. This may result in a diffused signal, especially when ICG is adopted, that makes the differentiation of sentinel and echelon lymph nodes difficult. Sampling too many lymph nodes, that are not true sentinel lymph nodes, may lead to an increased surgical related morbidity and to an unnecessary increased work load for the pathology department that has to process with ultrastaging lymph nodes that are not true sentinel lymph nodes. Given these results, we recommend to use low concentrations of ICG. It is well known that, the success of the sentinel lymph node mapping decreases with BMI [59, 60]. Interestingly, in our series the dose of ICG used did not affect bilateral detection rate, regardless the BMI. The thickness of the adipose tissue interferes with the visual

and audiometric signals thus reducing the detection rate and this effect does not seem to be attenuated by a larger volume and/or concentration of tracer.

So far, we have demonstrated that the sentinel lymph node mapping in endometrial cancer is feasible and reliable given the excellent results in terms of false negative and detection rates. Furthermore we have demonstrated how to optimize it by defining the best tracer to use, the ideal number of sentinel lymph node to strive for and the optimized volume and concentration of ICG to inject. However, the most important question that remains unanswered is if the sentinel lymph node mapping is of clinical benefit for the patients and in which scenario.

It could be argued that a pathological lymph nodal assessment is unnecessary in low risk endometrial cancer patients. However, the definition of low risk endometrial cancer occurs postoperatively after permanent pathological examination of the uterine specimen and patient considered to be at low risk preoperatively or intraoperatively at frozen section analysis of the uterus may end up having a high risk endometrial carcinoma with a risk of lymph nodal metastases that can reach 40% [19]. Lack of pathological information of lymph nodal status in these patients will result in a more generous indication to an adjuvant radiotherapy that may otherwise have been safely omitted and potentially to a survival disadvantage [14, 17-19].

In our series of patients with a preoperative diagnosis of complex atypical hyperplasia or grade 1 or 2 endometrial cancer, we show that a strategy based on sentinel lymph node mapping is more accurate in detecting patients with lymph nodal metastases as compared to a strategy based on triage to a systematic lymphadenectomy based on intraoperative frozen section analysis of the uterus [61]. All the patients with lymph nodal metastases were correctly identified with the strategy based on sentinel lymph node mapping, whereas one out of six patients with nodal metastases were missed with the “traditional” strategy that relies on a full lymphadenectomy when uterine risk factors are identified at frozen section. The latter strategy has a false negative rate of 16.7% at the

cost of performing a systematic lymphadenectomy in approximately one third of patients considered to be at low risk preoperatively. The sentinel lymph node mapping had an excellent correlation with final FIGO stage IIIC whereas the system adopting the frozen section as a triage to a systemic lymphadenectomy had only a mild correlation with final FIGO stage IIIC.

Accordingly, Sinno et al recommend to perform a sentinel lymph node mapping in patients who are preoperatively considered to be at low risk [62]. A frozen section of the uterus is performed only in those cases in which the sentinel lymph node mapping fails bilaterally and a side specific pelvic lymphadenectomy (according to the algorithm proposed by Barlin et al) is performed only in case the frozen section analysis of the uterus defines the endometrial cancer as a high risk one [30, 62].

In patients with these pathological characteristics, a large multicenter retrospective comparison among the patients treated at Mayo Clinic and at the Memorial Sloan Kettering Cancer Center was performed [63]. Patients were subjected to a systematic lymphadenectomy at the first institution and to a sentinel lymph node mapping at the second and an excellent and comparable 3-year survival was reported for both groups, suggesting that the sentinel lymph node mapping does not jeopardize survival in this setting.

Recently, several series have assessed the validity of the sentinel lymph node mapping in high risk endometrial cancer patients such as grade 3 endometrioid endometrial carcinomas, uterine papillary serous carcinomas, clear cell carcinomas and carcinosarcomas. As opposed to patients with low risk endometrial cancer, patients presenting with these characteristics (high grade and high risk histology) have a high incidence of lymph nodal metastases. Consequently, there is concern that the result recorded in the low risk setting may not be easily translated in this setting,

as the reported high negative predictive value reported may be the result of high proportion of true negatives in a population with a low prevalence of metastatic disease to the lymph nodes.

In our series of high risk endometrial cancer patients, we recorded a prevalence of lymph node metastases of 23.8% [64]. Additionally, in the majority of the cases the lymph node metastases were not isolated but several lymph nodes were affected and in the majority of the cases the metastases were macrometastases. In our series, we recorded a single patient with a false negative mapping, accounting for a negative predictive value of 97.1% and a false negative rate of 10% [64]. This specific case had an isolated paraortic lymph node metastasis. Interestingly, during the surgery, the affected para-aortic lymph node appeared clinically suspicious and was sent for frozen section pathology that confirmed the presence of disease. It could be argued, that given its intraoperative detection, the false negative rate would drop to 0% for the sentinel lymph node mapping algorithm [30]. Given these results, we strongly believe that a thorough exploration of the pelvic and para-aortic area is mandatory in this subset of patients when a sentinel lymph node mapping is adopted as opposed to a systematic lymphadenectomy. This is crucial as, often, the para-aortic area is explored with less accuracy than the pelvic region.

With the exception of one retrospective multicenter French series that reports a false negative rate of 20% in this setting, all the other series and validation studies report reasonably low false negative rates that improve with the application of the sentinel lymph node mapping algorithm and are roughly comparable to those reported in the low risk setting [65-70]. In the FIRES trial, in which 100 patients presented with high-risk histologies and in which the sentinel lymph node mapping algorithm was adopted, the reported false negative rate is 5% [30, 31].

Finally, considering the oncologic outcome in these patients, we did not record any differences in patients with high-intermediate risk endometrial cancer undergoing sentinel lymph

node mapping algorithm or a sentinel lymph node mapping followed by a systematic lymphadenectomy (RFS: SLN-A vs S-LND: 79.2 vs 81.6; p=0.831) [71]. Of note, that stage and histotype were predictors of recurrence-free survival at multivariate analysis, whereas adjuvant therapy was not. These data suggest that the completion lymphadenectomy may be omitted even in this subset of patients without jeopardizing oncological outcome given that a sentinel lymph node mapping is adopted.

In high risk endometrial cancer patients the risk of para-aortic lymph nodal metastases in absence of pelvic lymph nodal involvement exceeds the reported rate of 2% and can be as high as 27% [17, 46]. Possible strategies may include a systematic paraarotic lymphadenectomy in patients with poorly differentiated and deeply invasive tumors, the integration of a corporal or peritumoral hysteroscopic tracer injection in conjunction to the cervical one or the inclusion of a preoperative PET/CT scan in the preoperative work-up. It is our believe that, a thorough inspection of the para-aortic region is the first, easy step, that may help detect patients with isolated para-aortic lymph nodal metastases.

6. CONCLUSIONS:

In conclusion, we have demonstrated that:

1. the sentinel lymph node mapping in endometrial cancer is an effective procedure characterized by an acceptable false negative rate,
2. the adoption of indocyanine green as a tracer and of the NIR-technology improves the detection rate as compared to the use of a combination of Tc-99m and patent blue as tracer,
3. the excision of every fluorescent lymph node does not improve the false negative rate and that therefore caution should be used in the differentiation between sentinel and echelon lymph nodes,
4. a smaller volume and concentration of ICG may be helpful in achieving the goal of reducing the number of sentinel lymph nodes removed,
5. the use of the sentinel lymph node mapping in patients preoperatively considered to be at low risk is a better strategy is compares to on in which patients are triaged to a systematic lymphadenectomy based on intraoperative identification of risk factors at frozen section analysis of the uterus,
6. even in the setting of high-risk endometrial cancer patients, in which the rate of lymph node metastasis is significantly higher, the sentinel lymph node mapping maintains a reasonable false negative rate,
7. a strategy that adopts a sentinel lymph node mapping algorithm as opposed to a systematic lymphadenectomy in intermediate-high risk endometrial cancer patients does not jeopardize the oncologic outcome.

In 2014 the National Comprehensive Cancer Network (NCCN) guidelines first recognized the sentinel lymph node mapping as an acceptable alternative to a systematic lymphadenectomy in selected case of endometrial cancer [72]. Since then the NCCN guidelines have extended the indication to a sentinel lymph node mapping algorithm even in high-risk endometrial cancer patients [13]. On the contrary the ESMO-ESGO-ESTRO guidelines, recommend the adoption of the sentinel lymph node mapping in endometrial cancer patients only within controlled trials [14]. These consensus guidelines have been last update in 2015 and we are confident that, given the additional scientific evidence produce since then, a new revision of these guidelines may lead to a different recommendation, more in line with those produced by the NCCN. As oppose to a dual "everything or nothing at all" system in which a lymphadenectomy is either omitted or performed in a radical manner, we believe that the sentinel lymph node mapping represents a solomonic solution that allows to obtain relevant pathologic information on the status of the lymph nodes without subjecting the patients to an extensive surgical procedure and its related morbidity [74].

7. LEGEND TO FIGURES:

Figure 1 Sentinel lymph node mapping with ICG

Figure 2A Laparoscopic pelvic lymphadenectomy (part 1)

Figure 2B Laparoscopic pelvic lymphadenectomy (part 2)

Figure 2C Laparoscopic paraaortic lymphadenectomy

Figure 3 Anatomical distribution of sentinel node lymph nodes detected by ICG

Figure 4 Detection rates based on adopted tracers for sentinel lymph node mapping (ICG vs Tc99+ blu)

Figure 5 Figural depicted performance of frozen section of the uterus versus sentinel node lymph node mapping in identifying low-risk endometrial cancer patients with lymph nodal metastases

Figure 6 Kaplan-Meyer curves for recurrence-free survival (RFS)

8. LEGEND TO TABLES:

Table 1. Validation analysis of the sentinel l mapping in endometrial cancer

Table 1.1 Clinicopathologic characteristics of the patients

Table 1.2. Lymph node data

Table 2. Comparison of sentinel lymph node detection rate based on adopted tracers

Table 2.1. Clinicopathologic characteristics of the patients

Table 2.2 sentinel lymph node mapping and lymphnode pathological characteristics according to the tracer used (Table 2.2)

Table 3. Assessment of the optimal number of retrieved sentinel lymh nodes

Table 3.1 Clinicopathologic characteristics of the patients

Table 3.2 Impact of the number of sentinel lymph nodes removed on the false negative rates

Table 3.3 Univariate and multivariate analysis on factors influencing sentinel lymph nodes count

Table 4. Influence of ICG dose on the sentinel lymph node mapping

Table 4.1 Clinicopathologic characteristics of the patients

Table 4.2 Influence of ICG dosage on detection rates at Uni and Multivariate analysis

Table 4.3 Influence of ICG dosage on sentinel lymph nodes number at Uni and Multivariate analysis

Table 5. Efficacy of sentinel lymph node mapping in low risk endometrial cancer

Table 5.1 Clinicopathologic characteristics of the patients

Table 5.2 Surgical data

Table 5.3 Performance of the two surgical strategies in identifying low-risk endometrial cancer patients with lymph nodal metastases

9. FIGURES:

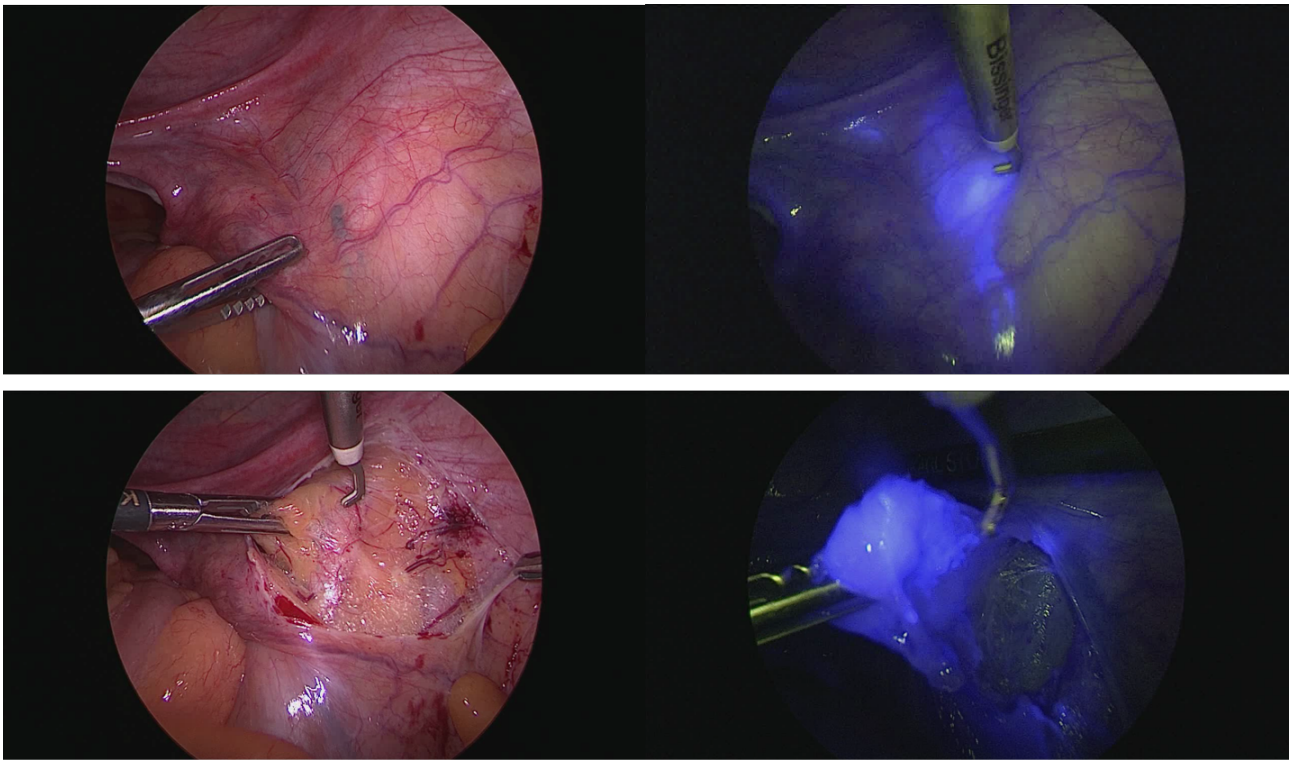


Figure 1: Sentinel lymph node mapping with ICG

Laparoscopic view of the right hemipelvis after intracervical ICG injection.

The green color of the tracer can already been seen transperitoneally prior to activation of the NIR mode. After activation of the NIR, with the fluorescent signal, an afferent and efferent lymphatic vessel draining to and from the sentinel lymph node can easily be visualized. The sentinel lymph node, located in the typical anatomic region of the obturator fossa, can be easily identified.

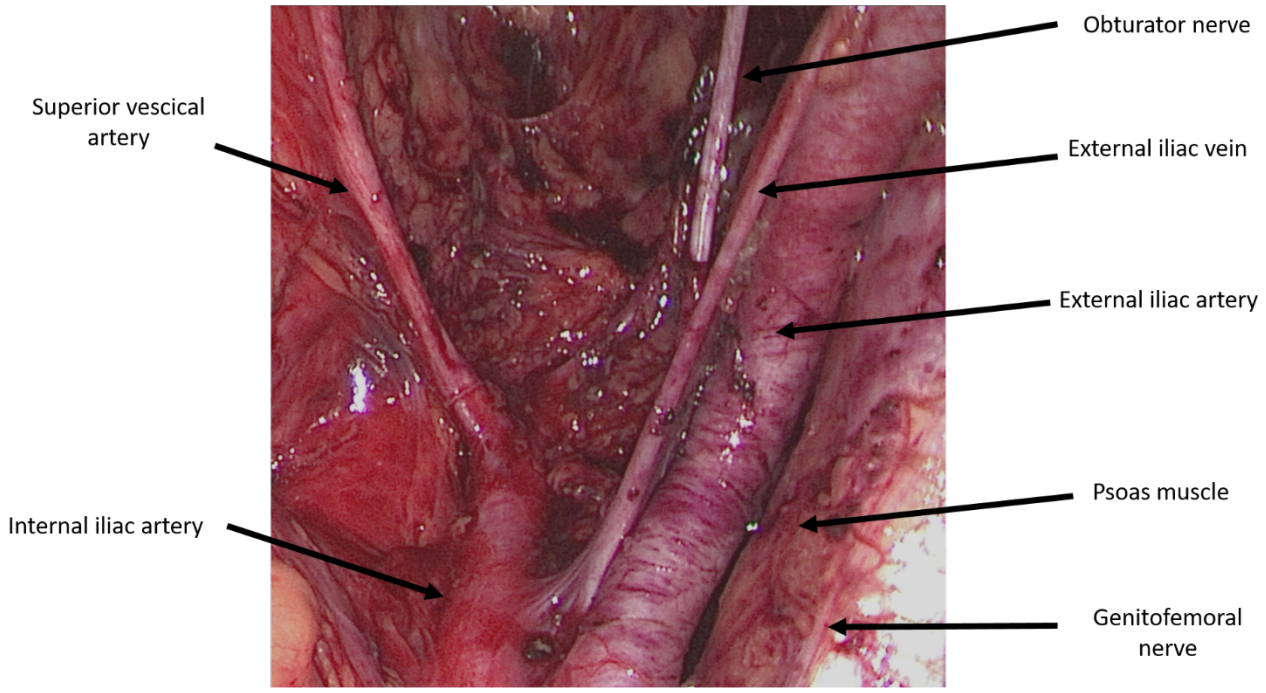


Figure 2 A: Laparoscopic pelvic lymphadenectomy (part 1)

Anatomic view of the right hemipelvis after completion of a laparoscopic systematic lymphadenectomy

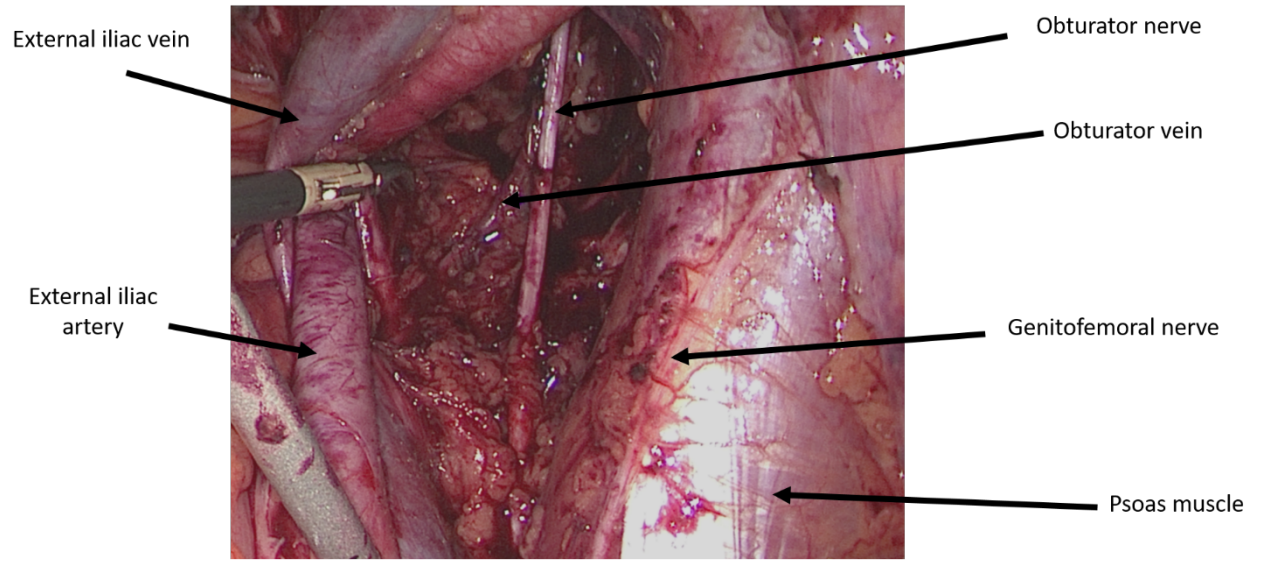


Figure 2 B: Laparoscopic pelvic lymphadenectomy (part 2)

Anatomic view of the right hemipelvis after completion of a laparoscopic systematic lymphadenectomy. The external iliac vessels are retracted medially to fully expose the obturator fossa.

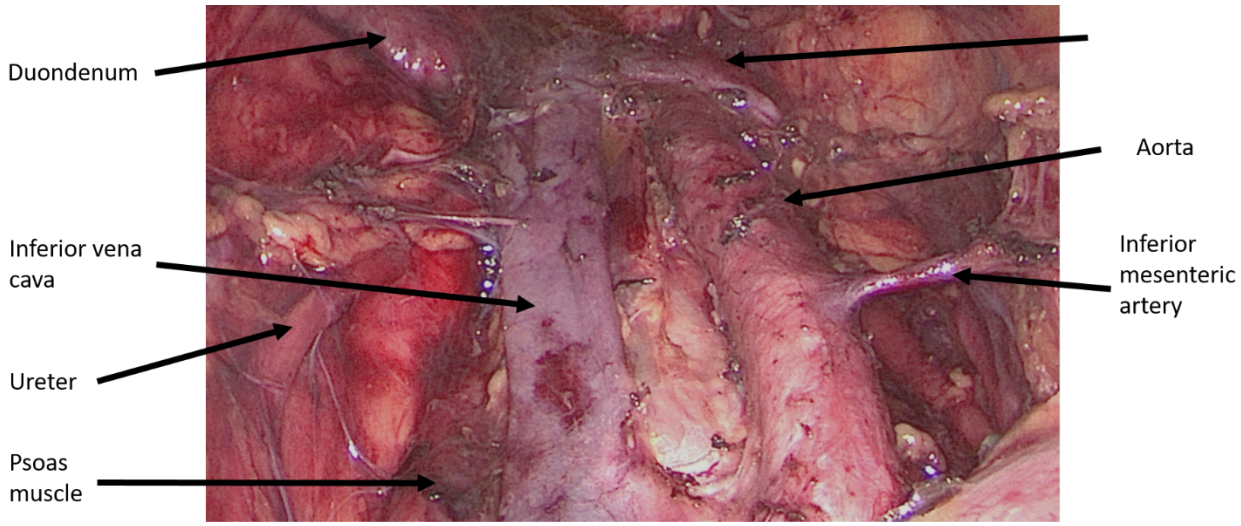


Figure 2 C: Laparoscopic paraaortic lymphadenectomy

Anatomic view of the paraaortic region after completion of a laparoscopic systematic lymphadenectomy

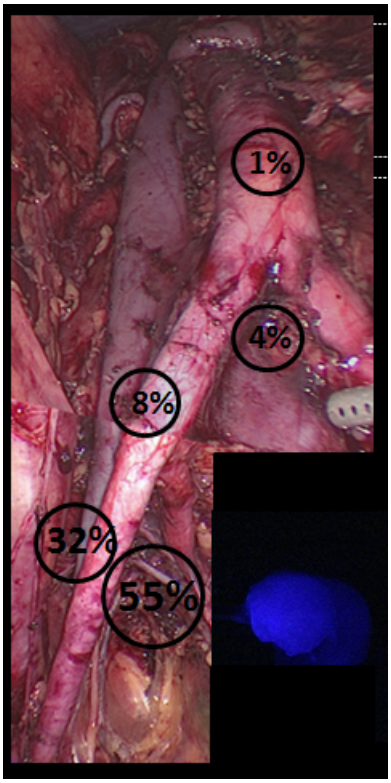


Figure 3. Anatomical distribution of sentinel node lymph nodes detected by ICG

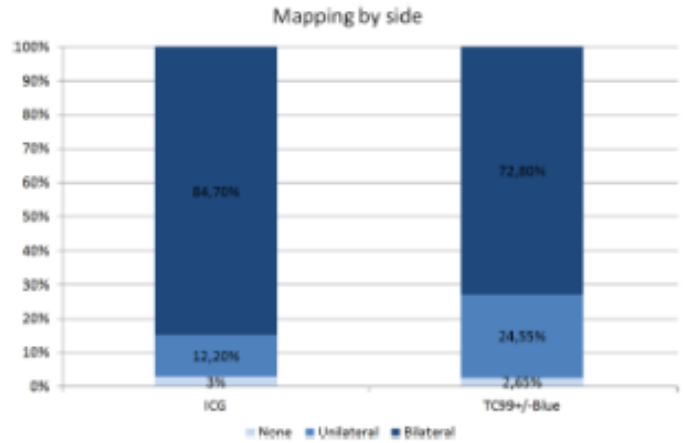
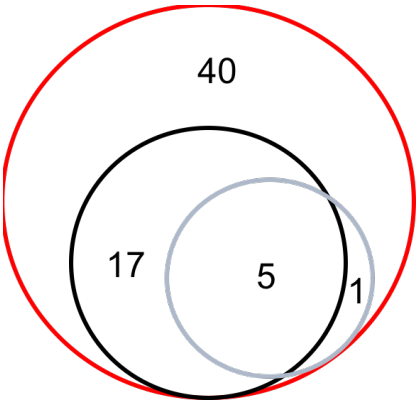


Figure 4. Detection rates based on adopted tracers for sentinel lymph node mapping (ICG vs Tc99+ blu)



Total	**63**	
Stage IIIC	6	9.5%
LND	22	34.9%
Stage IIIC detected with LND	5	83.3%

Figure 5: Figural depicted performance of frozen section of the uterus versus sentinel node lymph node mapping in identifying low-risk endometrial cancer patients with lymph nodal metastases

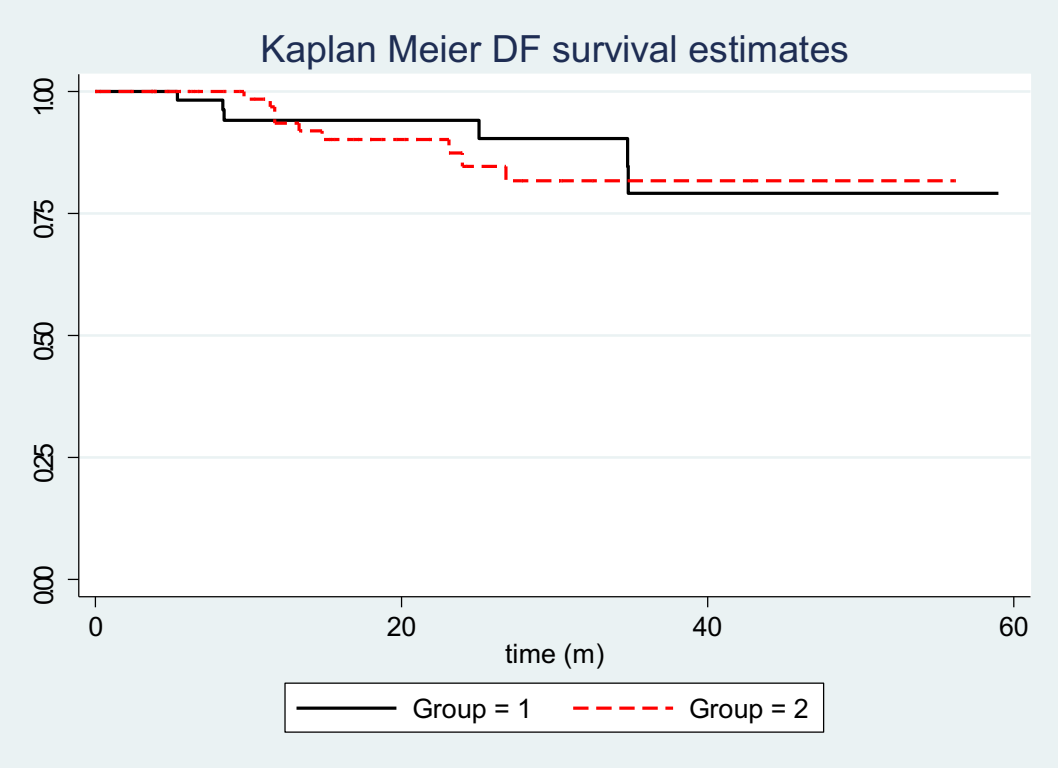


Figure 6. Kaplan-Meyer curves for Disease-free survival (N=171). The DFS observed was 79.2% (CI 95%: 56-91) for patients in SLN-A group, and 81.6% (CI 95%: 67 -90) in S-LND group (p value = 0.831). Group 1: LSN-A group; group 2: S-LND group.

10. TABLES:

Patients	**Number (%) Total 75 patients**
Median age (range)	65 (38-89)
Median BMI (range)	27.2 (17.4-47)
Stage	
FIGO 0 (intraepithelial neoplasia, complexe hyperplasia)	2 (2.7%)
FIGO I	53 (70.7%)
FIGO II	5 (6.6%)
FIGO III	14 (18.7%)
FIGO IV	1 (1.3%)
Histology	
Complex atypical hyplerplasia/intraepithelial neoplasia	2 (2.7%)
Endometroid	66 (88.0%)
Serous	2 (2.7%)
Clear cell	1 (1.3%)
Carcinosarcoma	4 (5.3%)
Grade	
-1	24 (32.9%)
-2	30 (41.1%)
-3	19 (26.0%)
Lympho vascular space invasion	
-present	17 (22.7%)
-absent	58 (77.3%)
Myometrial invasion	
-absent	2 (2.7%)
-< 50%	46 (61.3%)
->50%	27 (36.0%)
Patients with lymph node metastases	11 (14.7%)
Surgical lymph node assessment	
SLN biopsy only	33 (44.0%)
SLN biopsy +PLND	13 (17.3%)
SLN biopsy +PLND +PALND	29 (38.7%)
Median number PLN (range)	27 (10-48)
Median number PALND (range)	19 (9-56)
Operations performed	
Hysterectomy + BSO	33 (44.0%)
Hysterectomy + BSO + PLND	13 (17.4%)
Hysterectomy + BSO + PLND + PALND	26 (34.7%)
Radical hysterectomy + radical colpectomy + BSO + PLND + PALND	1 (1.3%)
Radical hysterectomy + hemicolectomy + BSO + PLND + PALND	1 (1.3%)
Radical hysterectomy + BSO + PLND + PALND	1 (1.3%)
+laparotomy	1 (1.3%)
+omentectomy	2 (2.6%)

Table 1.1 Clinicopathologic characteristics of the patients (included in the validation analysis of the sentinel lymph node mapping in endometrial cancer). PLND: pelvic lymphadenectomy, PALND: paraortic lymphadenectomy, BSO: bilateral salpingo-oophorectomy, SLN: sentinel lymph node

Median number sentinel lymph nodes / Patient (range)	**3 (0-11)**
Patients with lymph node metastasis	11/75 (14.7%)
Macrometastasis	7/11 (63.6%)
Micrometastasis	4/11(36.4%)
ITC (Isolated tumor cells)	0

Table 1.2: Lymph node data

	TC99 + blu (n=147)	**ICG (n=195)**	P value
Age, Median (range)	66 (39-87)	65 (29-89)	>0.05
BMI, Median (range)	27.5 (17-50)	28.1 (15-56)	>0.05
FIGO IA	80 (54.4%)	123 (63.1%)	>0.05
FIGO IB	29 (19.7%)	27 (13.9%)	
FIGO II	8 (5.4%)	10 (5.1%)	
FIGO IIIA	1 (0.7%)	5 (2.6%)	
FIGO IIIB	1 (0.7%)	1 (0.5%)	
FIGO IIIC1	20 (13.6%)	11 (5.6%)	
FIGO IIIC2	5 (3.4%)	8 (4.1%)	
FIGO IV	3 (2%)	2 (1%)	
ENDOMETRIOID HISTOLOGY	116 (78.9%)	165 (84.6%)	>0.05
G1	56 (38.1%)	68 (35.2%)	>0.05
G2	47 (32%)	70 (35.7%)	
G3	23 (15.6%)	49 (25%)	
LVSI +	53 (36.1%)	34 (17.4%)	<0.0001
LVSI -	94 (63.9%)	149 (76.5%)	
LVSI NA	-	12 (6.1%)	

Table 2.1. Clinicopathologic characteristics of the patients (included in the comparison analysis of sentinel lymph node mapping detection rate based on adopted tracers)

	TC99 + blu (n=147)	**ICG (n=195)**	**P value**
Standard laparoscopy	127 (86.4%)	186 (95.4%)	0.003
Open surgery	20 (13.6%9	9 (4.6%)	
Median SLN per patient	3 (0-9)	3 (0-18)	0.596
No mapping	4 (2.7%)	6 (3.1%)	0.547
Overall detection rate	143 (97.3%)	189 (96.9%)	
Unilateral detection rate	35 (23.8%)	25 (12.8%)	0.007
Bilateral detection rate	108 (73.5%)	164 (84.1%)	<0.005
Pts with +lymphnodes	12 (8.2%)	10 (5.1%)	0.181
Pts with +SLN	38/400 (9.5%)	25/593(5.6%)	0.013
Macrometastasis	18/38 (47.4%)	24/33 (72.7%)	0.105
Micrometastasis	16/38(42.1%)	8/33 (24.2%)	
Isolated tumor cells	4/38 (10.5%)	1/33 (3.1%)	

Table 2.2 Sentinel lymph node mapping and lymphnode pathological characteristics according to the tracer used

Characteristics	Group 1 (n=42)	Group 2 (n=42)	p
Age (years)	54.5 (34-89)	55 (28-83)	0.6
BMI (kg/m2)	25.6 (17.4-43.6)	44.9 (19-40.2)	0.8
Histologic Diangosis			0.01
Endometrial cancer	25 (1 CS)	20	
Cervical cancer	17	22	
Median number of SLNs	3 (2-3)	5 (4-18)	<0.001
Patients with metastatic SLNs	9 (21.4%)	12 (28.6%)	0.3
Median number of pelvic LN	27	36	0.2
Median number of paraaortic LN	12 (21 pts)	20.5 (28 pts)	0.21
Pts with metastatic pelvic NSLN	8 (19%)	12 (28.6%)	0.17
Metastatic paraarotic NSLN	6 (14.3%)	4 (9.5%)	0.24

Table 3.1 Clinicopathologic characteristics of the patients (included in the analysis of the assessment of the optimal number of retrieved sentinel lymph nodes)

SLNs removed (n)	Patients with SLNs identified (n)	Patients with true positive SLNs (n)	Patients with false negative SLNs (n)	False negative rate (%)
≤3	42	9	2	4.8
>3	42	12	0	0

Table 3.2 Impact of the number of sentinel lymph node removed on the false negative rates

	P at UNIVARIATE ANALYSIS	P at MULTIVARIATE ANALYSIS
Age	0.261	-
BMI	0.130	0.421
Type of cancer	0,091	0.486
Surgical expertise	**0,005**	**0.041**
Positive SLN	0.793	-
Age of the surgeon	0.141	0.480
Gyn Onc Certification	0.042	0.823

Table 3.3 Univariate and multivariate analysis on factors influencing sentinel lymph nodes count

	N = 168 (%)
Median Age (range)	64 years (29-89)
BMI (range)	26 kg/m2 (15.4-50.8)
Grade n.a.	3 (1.8)
Grade 1	58 (34.5)
Grade 2	64 (38.1)
Grade 3	43 (25.6)
LVSI	
No	137 (81.5)
Yes	31 (18.5)
Histology	
CAH	3 (1.8)
Endometrioid	145 (86.3)
UPSC	9 (5.4)
CCC	5 (3)
Carcinosarcoma	5 (3)
Neuroendocrine	1 (0.5)
Tumor Diameter	
< 2 cm	77 (45.8)
≥ 2 cm	91 (54.2)
FIGO stage	
n.a.	3 (1.8)
IA	109 (64.9)
IB	21 (12.5)
II	9 (5.4)
IIIA	7 (4.2)
IIIB	1 (0.6)
IIIC1	10 (6)
IIIC2	7 (4.1)
IV	1 (0.5)

Table 4.1 Clinicopathologic characteristics of the patients (included in the analysis on the Influence of ICG dose on the sentinel lymph node mapping)

	Bilateral Detection (yes / no)			
	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
	OR (95% CI)	P	OR (95% CI)	P
Age (<64 vs ≥64)	1.37 (0.54, 3.45)	0.49		
BMI (≥ 35 vs <35)	0.44 (0.15, 1.29)	0.13	0.34 (0.11, 1.07)	0.06
Tumor volume (≥2 vs < 2 cm)	1.34 (0.54, 3.33)	0.52		
LVSI (positive vs negative)	0.73 (0.15, 3.45)	0.69		
ICG dose (5 vs 1.25mg/ml)	2.2 (0.88, 5.52)	0.09	2.64 (0.81, 6.92)	0.08

Table 4.2 Influence of ICG dosage on detection rates at Uni and Multivariate analysis

	Number of Lymph Nodes (≥3 vs < 3)			
	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
	OR (95% CI)	P	OR (95% CI)	P
Age (<64 vs ≥64)	1.46 (0.76, 2.81)	0.25	1.65 (0.81, 3.39)	0.16
BMI (≥ 35 vs <35)	0.78 (0.32, 1.87)	0.58		
Tumor volume (≥2 vs < 2 cm)	1.26 (0.65, 2.42)	0.48	1.39 (0.66, 2.95)	0.37
LVSI (positive vs negative)	1.88 (0.67, 5.26)	0.22	2.4 (0.74, 7.72)	0.14
ICG dose (5 vs 1.25 mg/ml)	**4.75 (2.32, 9.72)**	**0.0001**	**4.8 (2.31, 9.97)**	**0.0001**

Table 4.3 Influence of ICG dosage on sentinel lymph nodes number at Uni- and Multivariate analysis

	N=63 (%)
Median age (range)	62 (38-83)
Median BMI (range)	28 (18.8-47)
Preoperative Diagnosis	
-complex atypical hyperplasia	2 (3.2%)
-endometrial cancer	61 (96.8%)
Grading	
-n.a.	2 (3.2%)
-G1	23 (36.5%)
-G2	38 (60.3%)
Frozen section analysis	
-no tumor	10 (15.9%)
-complex atypical hyperplasia	1 (1.6%)
-endometrial cancer	52 (82.5%)
Grading	
-n.a.	0 (3.2%)
-G1	21 (33.3%)
-G2	28 (44.4%)
-G3	2 (3.2%)
FIGO stage at frozen section	
-IA	38 (60.3%)
-IB	12 (19%)
-II	2 (3.2%)
Permanent section analysis	
-complex atypical hyperplasia	1 (1.6%)
-endometrial cancer	62 (98.4%)
Grading	
-n.a.	1 (1.6%)
-G1	28 (44.4%)
-G2	32 (50.8%)
-G3	2 (3.2%)
FIGO stage IA	43 (68.3%)
FIGO stage IB	11 (17.5%)
FIGO stage II	2 (3.2%)
FIGO stage IIIC1	3 (4.8%)
FIGO stage IIIC2	3 (4.8%)

Table 5.1 Clinicopathologic characteristics of the patients (included in the analysis of efficacy of sentinel lymph node mapping in low risk endometrial cancer)

	N (%)
Pelvic lymph node dissection	22((34.9%)
Median number pelvic lymph nodes	21 (2-60)
Paraaortic lymph node dissection	14 (22.2%)
Median number paraaortic lymph nodes	13 (1-56)
Median number sentinel lymph nodes	3 (1-11)
Overall detection rate	63 (100%)
Bilateral detection rate	59 (93.7%)
Patients with positive pelvic lymph nodes	6
Patients with positive paraaortic lymph nodes	3 (4.8%)
Type of metastasis to the sentinel lymph nodes	
Micrometastasis	1
Macrometastasis	5

Table 5.2: surgical data on the two proposed strategies

	FN-rate	PPV	NPV	Correlation κ
Triage to lymphadenectomy based on frozen section of the uterus	17.7% (1/6)	27.3%	97.6%	0.244
sentinel lymph node mapping	0%	100%	100%	1

Table 5.3 Performance of the two surgical strategies in identifying low-risk endometrial cancer patients with lymph nodal metastases

	N=42 (100%)
Median age in years (range)	65 (43-83)
Median BMI (range)	26.8 (19-46.3)
Histology -Endometrioid -UPSC -Clear cell carcinoma -Carcinosarcoma -Neuroendocrine	 24 (57.1%) 9 (21.4%) 3 (7.1%) 5 (11.9%) 1 (2.4%)
Myometrial infiltration -< 50% ->50%	 25 (59.5%) 17 (40.5%)
Tumor size -< 2 cm - > 2 cm - n.a.	 10 (23.8%) 30 (71.4%) 2 (4.8%)
LVSI -Negative -Positive	 32 (76.2%) 10 (23.8%)
FIGO stage -IA -IB -II -IIIA -IIIC1 -IIIC2	 17 (40.5%) 11 (26.2%) 1 (2.4%) 3 (7.1%) 2 (4.8%) 8 (19%)

Table 6.1 Clinicopathologic characteristics of the patients (included in the analysis on the efficacy of sentinel lymph node mapping in High risk endometrial cancer)

	N= 42 (100%)
Pelvic LND -No -Yes	 0 42 (100%)
Paraaortic LND -No -Yes	 0 42 (100%)
Median number of LN (range)	54 (21-83)
sentinel lymph node mapping -no mapping -Monolateral mapping -Bilateral mapping	 0 4 (9.5%) 38 (90.5%)
Median number of sentinel lymph nodes (range)	3 (1-18)
Patients with positive sentinel lymph node	9 (21.4%)
Median number of positive sentinel lymph nodes	2 (1-7)
Location of positive sentinel lymph nodes -pelvis -paraaortal	 8 (19%) 1 (2.4%)
Type of positive sentinel lymph nodes -micrometastases -macrometastases	 1 (2.4%) 8 (19%)
Patients with positive not-sentinel lymph nodes	8 (19%)
Median number of positive not-sentinel lymph nodes (range)	4 (1-66)
Location of positive not- sentinel lymph nodes -pelvic -paraaortic -pelvic and paraaortic	 3 (7.1%) 4 (9.5%)

Table 6.2 Lymph nodal characteristics

	sentinel lymph node mapping	sentinel lymph node mapping algorithm
Sensitivity	90% (95%CI: 76%-96%)	100% (95%CI: 89% - 100%)
NPV	97.1% (95%CI: 85%-99%)	100% (95%CI: 89% - 100%)
FN rate	10%	0%
Prevalence of lymph node metastases	23.8% (95%CI: 12%-39%)	23.8% (95%CI: 0.12%-0.39%)

Table 6.3 Sensitivity, NPV, and FN rate of the sentinel lymph node mapping and of the MSKCC sentinel lymph node mapping algorithm

	SLN-A (N=66)	S-LND (N=105)	P value
Age *median (range)*	65.5 (29 -86)	67.0 (43-86)	0.564
BMI *median (range)*	26.4 (15.4- 50)	26.0 (18.0 – 46.2)	0.350
Stage *I* *II* *III*	42 (63.6%) 6 (9.1%) 18 (27.3%)	64 (61.0%) 6 (5.7%) 34 (33.3%)	0.551
Grade *1* *2* *3*	17 (25.8%) 25 (37.9%) 24 (36.4%)	4 (3.8%) 37 (35.2%) 64 (60.0%)	<0.0001
Histotype *Endometrioid* *Others*	54 (83.1%) 11 (16.9%)	79 (74.3%) 26 (15.7%)	0.156
Myometrial invasion *No* *< 50%* *> 50%*	0 24 (48.0%) 26 (52.0%)	2 (2.1%) 40 (42.6%) 52 (55.3%)	0.698
LVSI *No* *Yes*	37 (59.7%) 25 (40.3%)	56 (53.9%) 48 (46.1%)	0.285

Table 7.1 Clinicopathologic characteristics of the patients (included in the Survival analysis)

SLN-A: sentinel lymph node group; S-LND: lymphadenectomy group

	SLN-A (N=66)	S-LND (N=105)	P value
Pelvic LND, N (%)			
No	56 (84.9)	0	
Yes bilateral	5 (7.6)	105 (100)	
Yes unilateral	5 (7.6)	0	
Aortic LND, N (%)			
No	66 (100)	51 (48.6)	
Yes	0	54 (51.4)	
Pts with positive nodes, N (%)	18 (27.3)	34 (32.4)	0.297
Pts with positive aortic nodes, N (%)	-	13/54 (24)	
SLN positivity location, N (%)			0.421
External iliac	17 (68)	25 (48.1)	
Obturator	7 (28)	23 (44.2)	
Common iliac	1 (4)	3 (5.8)	
Aortic	-	1 (1.9)	
Type of SLN metastasis, N (%)			
MAC	11 (44)	40 (76.9)	0.013
MM	11 (44)	10 (19.2)	
ITC	3 (12)	2 (3.9)	
Follow-up time			
median (range)	20 (5-80)	16 (6-88)	0.327
N° of death	3	10	
N° of recurrence	6	9	
Site of recurrence			
vaginal	2	1	
nodal	0	2	
nodal+peritoneal	1	0	
peritoneal+distant	1	2	
peritoneal	2	3	
distant	0	1	
Adjuvant therapy, N (%)			
None	34 (51.5)	25 (23.8)	0.001
RT + CHT	11 (16.7)	37 (35.2)	
RT	5 (7.6)	11 (10.5)	
CHT	9 (13.6)	10 (9.5)	
BRT	7 (10.6)	22 (21)	

Table 7.2. Surgical data and Lymph nodal characteristics

	UNIVARIATE ANALYSIS		MULTIVARIATE ANALYSIS	
	OR (95% CI)	P value	OR (95% CI)	P value
Age	0.98 (0.93-1.03)	0.406		
Stage	2.02 (1.13-3.59)	0.016	2.32 (1.25 – 4.30)	**0.007**
Grade	2.17 (0.84-5.61)	0.111		
Histotype	2.85 (0.94-8.64)	0.064	3.69 (1.13 – 12.0)	**0.030**
LVSI	1.48 (0.51-4.28)	0.473		
Group	0.93 (0.32-2.75)	0.898		
Type of metastasis	1.94 (0.99-3.81)	0.055		
Adjuvant therapy	0.94 (0.71-1.26)	0.684	0.85 (0.60 – 1.22)	0.385

Table 7.3 Univariate and Multivariate analysis of disease free survival

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67. Naoura I, Canlorbe G, Bendifallah S et al. Relevance of sentinel lymph node procedure for patients with high-risk endometrial cancer. Gynecol Oncol 2015; 136: 60–64.

68. Soliman PT, Westin SN, Dioun S et al. A prospective validation study of sentinel lymph node mapping for high-risk endometrial cancer. Gynecol Oncol2017; 146: 234–239.

69. Ballester M, Dubernard G, Lécuru F et al. Detection rate and diagnostic accuracy of sentinel-node biopsy in early stage endometrial cancer: a prospective multicentre study (SENTI-ENDO). Lancet Oncol 2011; 12:469–476

70. Touhami O, Grégoire J, Renaud MC et al. Performance of sentinel lymph node (SLN) mapping in high-risk endometrial cancer. Gynecol Oncol 2017; 147: 549–55.
71. Buda A, Gasparri ML, Puppo A, Mereu L, De Ponti E, Di Martino G, Novelli A, Tateo S, Muller MD, Landoni F, Papadia A. Lymph node evaluation in high-risk early stage endometrial cancer: a multi-institutional retrospective analysis comparing the sentinel lymph node (SLN) algorithm and SLN with selective lymphadenectomy. Gynecol Oncol, accepted for pubblication.
72. NCCN Clinical Practice Guidelines in Oncology. Uterine Neoplasms. Version 2.2014. Available online: http://www. nccn.org/professionals/physician_gls/pdf/uterine.pdf
73. Papadia A., Gasparri M.L., Mueller M.D. Is it time to consider the sentinel lymph node mapping the new standard in endometrial cancer? Translational Cancer Research 2017; 6: S547-S552.

Curriculum Vitae

Maria Luisa Gasparri

PERSONAL INFORMATION

Maria Luisa Gasparri,
Born in Rome, Italy, October 12, 1983

DEGREES:
Medical Doctor, Specialist in Obstetrics and Gynecologist

Number of publications indexed in PubMed and Scopus: 71
Impact Factor: 369.5; H-Index: 13; Citations on Scopus: 504
Orcid Id: https://orcid.org/0000-0002-9482-9527

CURRENT POSITION:

- PhD in Gynecology and Obstetrics at the Department of Medical and Surgical Sciences and Translational Medicine, Sapienza University of Rome
- Member of Medical Faculty Academic Board, "Sapienza" University of Rome
- ObGyn Consultant at the IAMAT Clinic "*Doctors in Italy*", and for the Food and Agriculture Organization of the United Nations (FAO/ONU)
- Since May 2017, National (Italian) academic competence qualification as Associate Professor

LANGUAGES: Italian (native language), English (CEFR C1), German (CEFR B2)

EDUCATION:

2009	Graduated *summa cum laude* (110/110lode) at the Medical School Sapienza University of Rome (Chairman: Prof. Pierluigi Benedetti Panici).
2010	Registration within the "Ordine dei Medici di Roma", Rome, Italy
2015	Graduated *summa cum laude (70/70lode)* from the Residency program in Obstetrics and Gynecology at Sapienza University of Rome (Chairman: Prof. Pierluigi Benedetti Panici
2015-2018	Enrolled in the PhD program in Gynecology and Obstetrics at the Surgical and Medical Department of Translational Medicine, Sant'Andrea Hospital and Sapienza University of Rome, Italy
2016-2018	Fulfilled Eighteen months mobility-PhD Program at the Department of Gynecology and Obstetrics, University Hospital of Berne, Berne, Switzerland
2018	Master in Senology at the Humanitas Cancer Center, Rozzano, Milano

PRIZES AND AWARDS

2005-2006 Winner of the Cooperation in Didactic Award from the Department of Human Anatomy and Cardiovascular Respiratory and Morphologic Sciences at Sapienza University of Rome, Italy (Chief. Prof. C. Cavallotti)

2008 Winner of the Best Medical School students award at Sapienza University, Rome, Italy

2013 Winner of the Best Oral Presentation prize for the study "Pregnancy rate and fertility outcome after monolateral adnexaetomy" , XXV Congresso Nazionale della Società Polispecialistica Italiana Giovani Chirurghi (SPIGC)

2014 Winner of the Best Researcher selection under 35, Associazione Italiana Ginecologia Endocrinologica (AIGE)

2016 Winner of the AIGE (Associazione Italiana Ginecologia Endocrinologica) young researcher selection for the 5th National Course of AIGE, Firenze 4-5 Nov 2016

2016 Winner of the AGUI (Associazione Ginecologi Universitari Italiani) 2016 award for best abstract (title of the study: IIIC FIGO stage identification among low risk endometrial cancer patients: laparoscopic indocyanine green sentinel lymph node mapping versus frozen section of the uterus)

2017 First Prize winner project in Obstetrics at the swiss annual meeting conference for SGGG (Schweizerische Gesellschaft für Gynäkologie und Geburtshilfe). Project "Misoprostol vaginal insert vs vaginal tablet", Losanna, il 29.06.2017

2018 Winner of the FCP Scholarship of the International Society of Gynecological Endocrinology (ISGE) for trainees and postDoc under 35 at the 18th Gynecological Endrocrinology World Congress, Florence, 7-10 March 2018

WORK EXPERIENCES:

Laboratory activities:

2009-2012 Cooperation with the Cancer Immunotherapy Lab, University Sapienza of Rome, (Chief. Prof.ssa M. Nuti)

2015 –ong Medical supervisor of the gynecologic scientific projects at the laboratory of Cellular and Molecular Immunology and the Laboratory of Proteomics at the Department of Internal Medicine, Sapienza University of Rome (Chief. Prof. V. Barnaba)

2016-ong Medical Supervisor of the gynecologic scientific projects at the Lab of Oncogenomic of the Department of Experimental Medicine, "Sapienza" University of Rome (Chief. Prof. E. Ferretti)

Clinical activities:

2010-2015 Residency in Obstetrics and Gynecology at the Department of Gynecology and Obstetrics, Sapienza University of Rome, Italy (Chief. Pierluigi Benedetti Panici)

2010 Internship at the Department of Obstetrics Santa Maria Goretti Hospital, Sapienza University, Polo Pontino (Chief Prof.F.Maneschi)

2013-2014 Research and Clinical training at the Department of Gynecologic Oncology of the IRCCS Foundation, "National Cancer Institute" of Milan, Italy (Chief Prof. Francesco Raspagliesi)

2015-ong Consultant at the IAMAT Clinic "*Doctors in Italy*" for English Speaking patients (Via Frattina, 48 Rome) *(see patients reviews at docita.ly/g)*

2017-ong Inclusion in the Food and Agriculture Organization of the United Nations (FAO/ONU) Medical Providers' list as Ob-Gyn consultant, after successful selection panel decision by FAO Health Service

2018 Master in Senology at the Humanitas Cancer Center, Rozzano, Milano

Training activities:

2008 Scholarship from the "Waterford Institute of Technology", Ireland

2011 'Roche Clinical Trial' training and certification

2013 Training Course at the International School of Gynecological and Reproductive Endocrinology in Malta (directed by prof. A.Genazzani)

2014 Six months Training Course certification in Gynecologic Oncology by ESGO (European Society of Gynaecological Oncology) and EBCOG (European Board & College of Obstetrics and Gynaecology)

2018 Advanced Training Course in Biostatistics at the "Centro Studi Gorgia", in Florence (March 2018)

Didactic activities:

2006 Scientific manager of the didactic web site of Human Anatomy at Sapienza University of Rome, (w3.uniroma1.it/anat3b/anat

2013-ong Member of Medical Faculty Academic Board, "Sapienza" University of Rome

2015-ong Tutor of several Medical Students candidates for thesis in Gynecology and Obstetrics at the Department of Gynecology and Obstetrics, Sapienza University of Rome

2016-ong "Cultore della materia" in Gynecology and Obstetrics, Faculty of Medicine (CCL-A) Sapienza University of Rome (the didactic activity consists in frontal classes, seminars for medical students and residencies, and final examinations)

WINNER OF FOUNDED GRANTS

May 2009 Sapienza University Awards "*Progetti di Ricerca di Università*" as sub-investigator on the project "MGL receptor expressed by Dendritic Cells: new targeting mechanisms to antitumor vaccine" (PI. Prof.ssa M.Nuti, sub-inv: dott.ssa Gasparri ML), founded by MIUR for 61, 500 euro (cod.Cineca:C26A09HECZ)

May 2015 Sapienza University Awards "*Progetti Avvio alla Ricerca*" as Principal Investigator on the project: "Urinary Metabolomic Profiling as potential Marker in Ovarian Cancer" (P.I.: Dott.ssa Maria Luisa Gasparri), founded by "Sapienza" University of Rome for 2000 euro.

Nov 2015 Sapienza University Awards "*Progetti AWARDS di Università*" presenting the project "KGFR expression in ovarian cancer: correlation with responsiveness to systemic therapy and potential use as target to enhance the efficacy of treatment with PARP inhibitors" (PI: Prof. Pierluigi Benedetti Panici, sub-invest. Dott.ssa Maria Luisa Gasparri), Founded for 21, 000 euro (prot. C26H15ZYKR)

March 2017 "Bernische Krebsliga" Grant. Title of the project: "Redirecting the natural history of HPV infection through immune check point inhibitors" (PI: Prof. Andrea Papadia, sub-invest. Dott.ssa Maria Luisa Gasparri), Founded for 25,000,00 CHF.

SOCIETY MEMBERSHIP

2010- present	Associazione Universitaria Ginecologi in Formazione (AGIF)
2010- present	Associazione Universitaria Ginecologi Italiani (AGUI)
2011	International Gynecological Cancer Society (IGCS)
2011	European Society of Gynecological Oncology (ESGO)
2011- present	Multicenter Italian Trials in Ovarian Cancer and Gynecologic Malignancies (MITO) (active member of the "MITO work group-website" from 2011 to 2018 https://www.mito-group.it/it/consiglio-direttivo)
2011- present	Società Italiana Giovani Chirurghi) (SPIGC)
2011- present	Società di Ginecologia Oncologica Italiana (SIGO)
2016	Society of Gynecologic Oncology (SGO)
2016	American Association of Gynecologic Laparoscopists (AAGL)
2018	International Society of Gynecological Endocrinology (ISGE)
2018	Associazione Italiana Ginecologia Endocrinologica (AIGE)

REFEREE AND EDITORIAL ACTIVITY

2012	Invited Referee for *BMC Cancer Journal*
2015	Editorial Board of *Advance in Modern Oncology Research Journal, Current Trends in Gynecologic Oncology, Journal of Neoplasm*
2016	Referee for several scientific journals including *Green Journal (Obstetrics and Gynecology), Oncotarget, Gynecologic Oncology, BMC Cancer Journal, Cellular Physiology and Biochemistry, PLOS ONE, and British Journal of Cancer*
2018	Guest Editor of the Special Issue "Immunobiology of Solid Cancers: Cellular and Molecular Pathways as Potential Diagnostic and Therapeutic Targets", published on *BioMed Research International Journal* (IF 2.476)

MULTICENTER INTERNATIONAL CURRENT RESEARCH COOPERATIONS:

Department of Gynecology, Campus Virchow Clinic, Charité Medical University, Berlin, Germany

Gynaecologic Oncology Unit, La Paz University Hospital - IdiPAZ, Madrid, Spain

Department of Obstetrics and Gynecology, University Hospital of Berne and University of Berne, Berne, Switzerland

Laboratory for Translational Oncology and Personalized Medicine, Rashid Latif Medical College, Lahore, Pakistan

INVITED SPEAKER AND ORAL PRESENTATIONS:

- Invited Speaker at the scientific meeting "MEDICINA SPERIMENTALE E GINECOLOGIA: ATTUALITA' E PROSPETTIVE"; Title of presentation: "EFFETTO IMMUNOMODULATORIO DELLA CHIRURGIA IN PAZIENTI CON TUMORE DELL'OVAIO".
  Sapienza University, Latina 18th November 2009

- Oral Presentation "VALUTAZIONE DEL POTENZIALE RIPRODUTTIVO FEMMINILE DOPO ANNESSECTOMIA MONOLATERALE" (awarded the price of best oral presentation)
  Montecatini 12th-15th April 2012, II Congresso Nazionale FIOG

- Oral Presentation "CHEMIOTERAPIA NEOADIUVANTE E TUMORE DELLA CERVICE: VALUTAZIONE DELLE PAZIENTI NON RESPONDERS"
  Montecatini 12th-15th April 2012, II Congresso Nazionale FIOG

- Oral Presentation "FERTILITY OUTCOME AFTER MONOLATERAL OVARIECTOMY" Rome 24th-26th January 2013, II Focus Meeting di Ginecologia, Medicina della Riproduzione e Ostetricia

- Oral Presentation "PREGNANCY RATE AND FERTILITY OUTCOME AFTER MONOLATERAL ANNESSECTOMY: OUR SERIES"
  Bari, 13th-15th July 2013; XXV Congresso Nazionale della Società Italiana Giovani Chirurghi

- Invited Speaker at the XXVII Congresso SPIGC 2015, title of presentation "Conservative surgery in Cervical Cancer patients"
  Brescia, 11th-13th June 2015 XXVII Congresso Nazionale della Società Italiana Giovani Chirurghi

- Oral Presentation "FEASIBILITY AND ONCOLOGIC OUTCOME OF CYTOREDUCTIVE SURGERY IN PRIMARY AND RECURRENT OVARIAN CANCER WITH LIVER INVOLVEMENT"
  Brescia, 11th-13th June 2015 XXVII Congresso Nazionale della Società Italiana Giovani Chirurghi

- Invited Speaker on "Sexually Transmitted Disease and Contraception" at the High School "Vincenzo Pallotti Institute". Rome, 30th October 2015

- Workshop speaker on "Sexually Transmitted Disease" at John Cabot American University. Rome, 11th November 2015

- Invited presentation "The Immunobiology of Cancer: from Tumor Immunosurveillance to Cancer Immunoediting", seminar at the Department of Gynecology and Obstetrics, Medical and Surgical Sciences and Translational Medicine, Sant'Andrea Hospital, Sapienza University of Rome, Rome 15th April, 2016

- Speaker at the workshop on "Sexual Health Education" at John Cabot American University, Rome, 13th February, 2017

- Oral Presentation: "Immune response to Chemotherapy-Associated Antigens as preoperative predictor of oncologic outcome in Ovarian Cancer patients: a pilot study". 18th Gynecological Endrocrinology World Congress, Florence, 7-10 March 2018 (awarded the price of the ISGE competition for trainees and postDoc under 35)

- Invited speaker at the "3rd Global Insight Conference of Breast Cancer", title of presentation: "Neoadjuvant versus Adjuvant chemotherapy in Triple Negative Breast Cancer". Valencia, Spain, 16-18 July 2018.

AUTHOR OF BOOKS CHAPTERS:

- **Maria Luisa Gasparri**, Ilary Ruscito, Katayoun Taghavi, Ammad Farooqi, Andrea Papadia, Chiara Focaccetti, Vincenzo Barnaba, Pierluigi Benedetti Panici, Michael D Mueller. *Chapter Title*: THE IMMUNOBIOLOGY OF CANCER. From tumor escape to cancer immunoediting towards immunotherapy in gynecologic oncology. *e-Book*: Molecular Oncology: Underlying Mechanisms and Translational Advancements. *Edited by:* Springer. ISBN: 978-3-319-53082-6

- Rukset Attar, **Maria Luisa Gasparri**, Talha Abdul Halim, Dana Al Hamwi, Ilknur Ucak, Ammad Ahmad Farooqi. *Chapter Title:* Legacy of Vitamin D: Role of Vitamin D in Prevention of Gynecological Cancers. *e-Book:* Molecular Oncology: Underlying Mechanisms and Translational Advancements. *Edited by*: Springer. ISBN: 978-3-319-53082-6

- **Gasparri Maria Luisa,** Besharat Zein Mersini, Besharat Raad Aris, Ruscito Ilary, Nirgianakis Konstantinos, Farooqi Ammad Ahmad,Papadia Andrea, Ferretti Elisabetta, Benedetti Panici Pierluigi, Mueller David Michael. *Chapter's title:* Current knowledge of miRNAs as biomarkers in Breast Cancer. *E-Book*: Recent Trends in Cancer Biology: Spotlight on Signaling Cascades and microRNAs. Book Subtitle: Cell Signaling Pathways and microRNAs in Cancer Biology. *Edited by* Springer. ISBN:978-3-319-71552-0

- Ghazala Butt, Durray Shahwar, Muhammad Zahid Qureshi, Rukset Attar, Misbah Malik, Yelda Birinci, Gokce Seker Karatoprak, **Maria Luisa Gasparri**, Ammad Ahmad Farooqi. *Chapter's title:* Role of mTORC1 and mTORC2 in Breast Cancer: Therapeutic Targeting of mTOR and its Partners to Overcome Metastasis and Drug Resistance *E-Book*: II edition of Breast Cancer Metastasis and Drug Resistance *Edited by* Springer. In press.

CONGRESSES ORGANIZER

- Member of the Scientific Program Committee of the "*Roma Focus Meeting on Gynecology, Reproductive Medicine and Obstetrics"*, Complesso Monumentale di Santo Spirito in Saxia, Rome 19-21 January 2012

- Multidisciplinary Workshop on "Sexually Transmitted Disease" at John Cabot American University, Via della Lungara 233 Rome, 11 November, 2015

- Multidisciplinary Workshop on "Sexual Health Education" at John Cabot American University, Via della Lungara 233 Rome, 13 February, 2017

LIST OF SCIENTIFIC PUBLICATIONS

Number of publications indexed in PubMed and Scopus: 71
Impact Factor: 369.5; H-Index: 13; Citations on Scopus: 504

- **Gasparri ML,** Nirgianakis K, Taghavi K, Papadia A, Mueller MD. Placenta previa and placental abruption after assisted reproductive technology in patients with endometriosis: a systematic review and meta-analysis. *Arch Gynecol Obstet*. 2018 (IF 2.09)

- Bolla D, Weissleder SV, Radan AP, **Gasparri ML,** Raio L, Müller M, Surbek D. Misoprostol vaginal insert versus misoprostol vaginal tablets for the induction of labour: a cohort study. *BMC Pregnancy Childbirth. 2018* (IF 2.72)

- **Gasparri ML,** Besharat ZM, Farooqi AA, Khalid S, Taghavi K, Besharat RA, Sabato C, Papadia A, Panici PB, Mueller MD, Ferretti E. MiRNAs and their interplay with PI3K/AKT/mTOR pathway in ovarian cancer cells: a potential role in platinum resistance. *J Cancer Res Clin Oncol*. 2018 (IF 3.5)

- Ruscito I, Braicu E.I, **Gasparri ML,** Zizzari I. Immunobiology of solid cancer: Cellular and Molecular pathways as potential diagnostic and therapeutic targets. *BioMed Research International* 2018 (IF 2.58)

- Gasparri ML, **Mueller MD**, Papadia A. Instead of feeling blue, go green. *Lancet Oncol* 2018 (IF 36.42)

- Farooqi AA, Desai NN, Qureshi MZ, Librelotto DRN, **Gasparri ML**, Bishayee A, Nabavi SM, Curti V, Daglia M. Exosome biogenesis, bioactivities and functions as new delivery systems of natural compounds. *Biotechnol Adv*. 2018 (IF 11.45)

- Taghavi K, **Gasparri ML**, Bolla D, Surbek D. Predictors of cerclage failure in patients with singleton pregnancy undergoing prophylactic cervical cerclage. *Arch Gynecol Obstet*. 2018 (IF 2.09)

- Buda A, **Gasparri ML,** Puppo A, Mereu L, De Ponti E, Di Martino G, Novelli A, Tateo S, Muller M, Landoni F, Papadia A. Lymph node evaluation in high-risk early stage endometrial cancer: A multi-institutional retrospective analysis comparing the sentinel lymph node (SLN) algorithm and SLN with selective lymphadenectomy. *Gynecol Oncol* 2018 (IF 4.96)

- **Gasparri ML,** Mueller MD, Taghavi K, Papadia A. Conventional versus Single Port Laparoscopy for the Surgical Treatment of Ectopic Pregnancy: A Meta-Analysis. *Gynecol Obstet Invest.* 2018 (IF 1.42)

- Papadia A, **Gasparri ML,** Radan AP, Stämpfli CAL, Rau TT, Mueller MD. Retrospective validation of the laparoscopic ICG SLN mapping in patients with grade 3 endometrial cancer. *J Cancer Res Clin Oncol.* 2018 (IF 3.5)

- Papadia A, Buda A, **Gasparri ML,** Di Martino G, Bussi B, Verri D, Mueller MD. The impact of different doses of indocyanine green on the sentinel lymph-node mapping in early stage endometrial cancer. *J Cancer Res Clin Oncol*. 2018 (IF 3.5)

- **Gasparri ML,** Ruscito I, Bolla D, Benedetti Panici P, Mueller MD, Papadia A. The Efficacy of Fibrin Sealant Patches in Reducing the Incidence of Lymphatic Morbidity After Radical Lymphadenectomy: A Meta-Analysis. *Int J Gynecol Cancer. 2017* (IF 2.37)

- Papadia A, **Gasparri ML,** Mueller MD. Are allergic reactions to indocyanine green really that uncommon? A single institution experiences. *Obstetrics and Gynecology reports* 2017

- **Gasparri ML**, Bardhi E, Ruscito I, Papadia A, Farooqi AA, Marchetti C, Bogani G, Ceccacci I, Mueller MD, Benedetti Panici P. PI3K/AKT/mTOR Pathway in Ovarian Cancer Treatment: Are We on the Right Track? *Geburtshilfe Frauenheilkd.* 2017 (IF 1.18)

- Buda A, Papadia A, Di Martino G, Imboden S, Bussi B, Guerra L, De Ponti E, Reato C, **Gasparri ML,** Crivellaro C, Mueller M. Real-Time Fluorescent Sentinel Lymph Node Mapping with ICG in Women with Previous Conization Undergoing Laparoscopic Surgery for Early Invasive Cervical Cancer: Comparison with Radiotracer +/- Blue Dye. *J Minim Invasive Gynecol. 2017* (IF 2.39)

- Papadia A, **Gasparri ML,** Buda A, Mueller MD. Sentinel lymph node mapping in endometrial cancer: comparison of fluorescence dye with traditional radiocolloid and blue. *J Cancer Res Clin Oncol. 2017* (IF 3.5)

- **Gasparri ML**, Casorelli A, Bardhi E, Besharat AR, Savone D, Ruscito I, Farooqi AA, Papadia A, Mueller MD, Ferretti E, Benedetti Panici P. Beyond circulating microRNA biomarkers: Urinary microRNAs in ovarian and breast cancer. *Tumor Biol. 2017* (IF 3.7)

- Di Martino G, Crivellaro C, De Ponti E, Bussi B, Papadia A, Zapardiel I, Vizza E, Elisei F, Diestro MD, Locatelli L, **Gasparri ML**, Di Lorenzo P, Mueller M, Buda A. Indocyanine Green versus Radiotracer with or without Blue Dye for Sentinel Lymph Node Mapping in Stage >IB1 Cervical Cancer (>2 cm). *J Minim Invasive Gynecol.* 2017 (IF 2.39)

- Bellati, F., Papadia, A., Gasparri, M.L., Scanagatta P, Carriero F, Benedetti Panici, P., Raspagliesi, F. Tertiary cytoreduction for recurrent endometrial cancer. *European Journal of Gynaecological Oncology* 2017 (IF 0.6)

- Papadia A, **Gasparri ML,** Mueller MD. Is time to consider the sentinel lymph node mapping the new standard in endometrial cancer? *Translational Cancer Research 2017* (IF 1.76)

- Papadia A, Nirgianakis K, **Gasparri ML**, Grandi G, Bolla D, Klaeser B, Mueller MD. PET/CT guided surgical excision of small abdominal wall metastases in morbidly obese endometrial cancer patients. *Minerva Ginecol. 2017* (IF 1.07)

- Bolla D, **Gasparri ML,** Badir S, Bajka M, Mueller MD, Papadia A, Raio L. Cervical length after cerclage: comparison between laparoscopic and vaginal approach. *Arch Gynecol Obstet. 2017* (IF 2.09)

- **Gasparri ML**, Mueller MD, Papadia A. Self-responsibility for our good health. *Jama Oncol 2016* (IF 16.56)

- Andrea Papadia, Daniele Bolla, **Maria Luisa Gasparri**, Luigi Raio. CORONIS trial on caesarean section. *Lancet 2016* (IF 45.2)

- Papadia A, Imboden S, **Gasparri ML**, Siegenthaler F, Fink A, Mueller MD. Endometrial and cervical cancer patients with multiple sentinel lymph nodes at laparoscopic ICG mapping: How many are enough? *J Cancer Res Clin Oncol 2016* (IF 3.5)

- Ilary Ruscito and **Maria Luisa Gasparri** · Elena Ioana Braicu · Filippo Bellati · Luigi Raio · Jalid Sehouli · Michael D. Mueller · Pierluigi Benedetti Panici · Andrea Papadia. Sentinel Node Mapping in Cervical and Endometrial Cancer: Indocyanine Green Versus Other Conventional Dyes—A Meta-Analysis. *Annals of Surgical Oncology 2016* (IF 3.9)

- Andrea Papadia· Ignacio Zapardiel · Beatrice Bussi · Fabio Ghezzi · Marcello Ceccaroni · Elena De Ponti ·Federica Elisei · Sara Imboden · Begoña Diaz de la Noval · **Maria Luisa Gasparri**· Giampaolo Di Martino · Javier De Santiago · Michael Mueller · Francesca Vecchione · Federica Dell'Orto · Alessandro Buda. Sentinel lymph node mapping in patients with stage I endometrial carcinoma: a focus on bilateral mapping identification

by comparing radiotracer Tc99m with blue dye versus indocyanine green fluorescent dye. *J Cancer Res Clin Oncol 2016* (IF 3.5)

- Alessandro Buda · Andrea Papadia · Ignacio Zapardiel · Enrico Vizza · Fabio Ghezzi · Elena De Ponti · Andrea Alberto Lissoni · Sara Imboden · Maria Dolores Diestro · Debora Verri · **Maria Luisa Gasparri** · Beatrice Bussi · Giampaolo Di Martino · Begoña Diaz de la Noval · Michael Mueller · Cinzia Crivellaro. From Conventional Radiotracer Tc-99m with Blue Dye to Indocyanine Green Fluorescence: A Comparison of Methods Towards Optimization of Sentinel Lymph Node Mapping in Early Stage Cervical Cancer for a Laparoscopic Approach. *Annals of Surgical Oncology 2016* (IF 3.9)

- Andrea Papadia, Sara Imboden, Franziska Siegenthaler, **Maria Luisa Gasparri**, Michael D Mueller. Laparoscopic indocianine green sentinel lymph node mapping in endometrial cancer. *Annals of Surgical Oncology 2016* (IF 3.9)

- Sundas Fayyaz • Tuba Aydin • Ahmet Cakir • **Maria Luisa Gasparri** • Pierluigi Benedetti Panici • Ammad Ahmad Farooqi. Oleuropein mediated targeting of signaling network in cancer. *Current topics in medicinal chemistry 2016* (IF 3.37)

- Andrea Papadia · **Maria Luisa Gasparri**· Franziska Siegenthaler · Sara Imboden · Stefan Mohr · Michael D. Mueller. FIGO stage IIIC endometrial cancer identification among patients with complex atypical hyperplasia, grade 1 and 2 endometrioid endometrial cancer: laparoscopic indocyanine green sentinel lymph node mapping versus frozen section of the uterus, why get around the problem? *J Cancer Res Clin Oncol 2016* (IF 3.5)

- **Gasparri ML**, Grandi G, Bolla D, Gloor B, Imboden S, Panici PB, Mueller MD, Papadia A. Hepatic resection during cytoreductive surgery for primary or recurrent epithelial ovarian cancer. *J Cancer Res Clin Oncol. 2015* (IF 3.5)

- Papadia A, Imboden S, Fink A, **Gasparri ML,** Bolla D, Mueller MD. Accuracy of Sentinel Lymph Node Mapping After Previous Hysterectomy in Patients with Occult Cervical Cancer. *Ann Surg Oncol. 2016* (IF 3.9)

- **Gasparri ML**, Panici PB, Papadia A. Primary chemotherapy versus primary surgery for ovarian cancer. *Lancet 2015* (IF 45.2)

- Marchetti C, De Felice F, Palaia I, Musella A, Di Donato V, **Gasparri ML,** Musio D, Muzii L, Tombolini V, Panici PB. Efficacy and toxicity of bevacizumab in recurrent ovarian disease: an update meta-analysis on phase III trials. *Oncotarget. 2015* (IF 5.17)

- Ruscito I, **Gasparri ML,** Marchetti C, De Medici C, Bracchi C, Palaia I, Imboden S, Mueller MD, Papadia A, Muzii L, Panici PB. Cediranib in ovarian cancer: state of the art and future perspectives. *Tumour Biol. 2016* (IF 3.7)

- Panici PB, Di Donato V, Palaia I, Visentin VS, Marchetti C, Perniola G, Musella A, **Gasparri ML,** Lecce F, Sabatucci I, Monti M, Muzii L. Type B versus Type C Radical Hysterectomy After Neoadjuvant Chemotherapy in Locally Advanced Cervical Carcinoma: A Propensity-Matched Analysis. *Ann Surg Oncol. 2015* (IF 3.9)

- Musella A, Marchetti C, **Gasparri ML,** Salerno L, Casorelli A, Domenici L, Imperiale L, Ruscito I, Abdul Halim T, Palaia I, Di Donato V, Pecorini F, Monti M, Muzii L, Panici PB. PARP inhibition: A promising therapeutic target in ovarian cancer. *Cell Mol Biol (Noisy-le-grand). 2015* (IF 1.37)

- **Gasparri ML**, Savone D, Besharat RA, Farooqi AA, Bellati F, Ruscito I, Panici PB, Papadia A. Circulating tumor cells as trigger to hematogenous spreads and potential biomarkers to predict the prognosis in ovarian cancer. *Tumour Biol. 2015* (IF 3.7)

- Papadia A, Bellati F, Bogani G, Ditto A, Martinelli F, Lorusso D, Donfrancesco C, **Gasparri ML**, Raspagliesi F. When Does Neoadjuvant Chemotherapy Really Avoid Radiotherapy? Clinical Predictors of Adjuvant Radiotherapy in Cervical Cancer. *Ann Surg Oncol. 2015* (IF 3.9)

- **Gasparri ML,** Bellati F, Brunelli R, Perrone G, Pecorini F, Papadia A, Meloni G, Trisolini SM, Gozzer M, Domenici L, Lecce F, Benedetti Panici P. Thrombotic thrombocytopenic purpura during pregnancy versus imitator of preeclampsia. *Transfusion. 2015* (IF 3.23)

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