Universitat Autònoma de Barcelona

The Sentinel Lymph Node Mapping in Endometrial Carcinoma: "Past, Present and Future"

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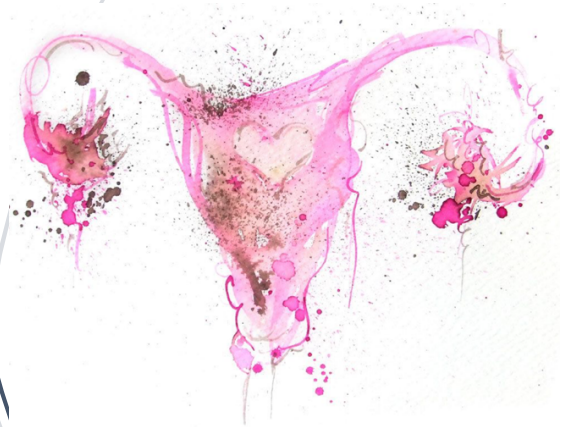

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The Sentinel Lymph Node Mapping in Endometrial Carcinoma:

"Past, Present and Future"

A PhD program by Natalia Rodríguez Gómez-Hidalgo, MD

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Barcelona 2021

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“Porque la vida es tango, y hay que seguir bailando “

Una de mis pacientes,
antes de entrar a quirófano.

Contents

Abstract

Abstract

Objective: The treatment for endometrial cancer is an hysterectomy and bilateral salpingo-oophorectomy with or without lymphadenectomy (depending on uterine risk factors). One of the documented complications of lymphadenectomy is the development of lymphedema of the lower extremities. Sentinel lymph node biopsy has been shown to be safe and feasible in various gynecological cancers.
The aim of this study is to show that sentinel node mapping technique in early-stage endometrial carcinoma is safe, decreases the associated morbidity of complete lymphadenectomy, particularly the rate of lymphedema, and it also provides with prognostic information.

Methods: The proposed research is a PhD program composed by 4 published from February 2016 to August 2020.
The first study is a systematic review regarding the use of indocyanine green in cervical or endometrial cancer. We searched in Medline, PubMed, and BioMed Central for all English-language literature using the terms "'indocyanine green," "cervical cancer," "endometrial cancer," and "sentinel lymph node" between 1994 and 2014. We included all publications reporting sentinel lymph node mapping performed by open or robotic surgery.
The second study is a meta-analysis about the rate of micrometastases and isolated tumor cells after lymphatic mapping. Literature search of Medline and PubMed was done using the terms: micrometastases, isolated tumor cells, endometrial cancer, and sentinel lymph node. Inclusion criteria were English-

language manuscripts, retrospective or prospective studies published between January 1999 and June 2019.

The third article is a transversal study including patients who underwent primary surgery for endometrial cancer from 01/2006-12/2012. Patients included were mailed a survey that included a validated 13-item lymphedema screening questionnaire in 08/2016. Patients diagnosed with lymphedema prior to surgery and those who answered ≤6 survey items were excluded.

The four study is a retrospective cohort from National Cancer Database (NCDB) including patients who underwent lymphadenectomy, sentinel lymph node mapping and who did not undergo nodal assessment from 2013–2014. The NCDB is a hospital-based registry developed by the American College of Surgeons and American Cancer Society.

Results: The first study reports that different tracers have been shown to be useful, including technetium-99 and blue dye, with a detection reported in 66% to 86%. Recently, there has been increasing interest in the use of fluorescent dies such as indocyanine green. The second study included 45 manuscripts, and 8 studies met inclusion criteria. We found that the total number of patients with micrometastases/isolated tumor cells was 286 (187 and 99, respectively). The micrometastases/isolated tumor cells group has a higher relative risk of recurrence of 1,34 (1,07-1,67) than the negative group, even if the adjuvant therapy was given.

In the third study, 623 (49%) patients responded to the survey and 599 were evaluable (180 sentinel lymph node, 352 lymphadenectomy, 67 hysterectomy alone). Self- reported lymphedema prevalence was 27% (49/180) and 41% (144/352), respectively (OR=1.85; 95% CI, 1.25-2.74; p=0.002). Patients with self-reported lymphedema had significantly worse quality of life compared to those without self-reported lymphedema.

In the last study, we analyzed 54,039 women, including 38,453 (71.2%) who underwent lymphadenectomy, 1929 (3.6%) who underwent sentinel lymph node mapping, and 13,657 (25.3%) who did not undergo nodal assessment. Sentinel lymph node mapping increased from 2.8% in 2013 to 4.3% in 2014 (p<0.001). There was no association between use of sentinel lymph node biopsy and use of radiation (aRR=0.92; 95% CI, 0.82–1.05).

Conclusion: Sentinel node mapping represents an attractive mid-way between the omission of lymph node dissection and full lymphadenectomy. Accumulating evidence suggested that sentinel node mapping is safe and effective in Endometrial cancer patients, avoiding unnecessary morbidity. Further long-term experiences are needed to dilucidate the standards techniques of sentinel node mapping in Endometrial cancer patients.

Keywords: Endometrial carcinoma, early stage, sentinel lymph node mapping, low volume disease, lymphedema, green indocyanine.

Resumen

Objetivo: El tratamiento estándar para el cáncer de endometrio es la histerectomía, salpingooforectomía bilateral con o sin linfadenectomía (según factores de riesgo uterino). Una de las posibles complicaciones documentadas de la linfadenectomía es el desarrollo de linfedema de las extremidades inferiores. Se ha demostrado que la biopsia de ganglio linfático centinela es segura y factible en varios cánceres ginecológicos. Por ello, el objetivo de este estudio es demostrar que la técnica de ganglio centinela en el carcinoma de endometrio en estadios iniciales es segura, disminuye la morbilidad asociada a la linfadenectomía y proporciona además, información pronóstica.

Métodos: La investigación propuesta está compuesta por 4 articulos publicados. durante Febrero de 2016 a Agosto de 2020.

El primer estudio es una revisión sistematica sobre el uso de verde de indocianina en el cáncer de cuello uterino o de endometrio. Buscamos en Medline, PubMed y BioMed las siguientes “Mesh”: "verde de indocianina", "cáncer de cervix", "cáncer de endometrio" y "ganglio centinela" entre 1994 y 2014. Se incluyeron estudios mediante cirugía abierta o minimamente invasiva.

El segundo articulo es un metaanálisis sobre las micrometástasis y células tumorales aisladas en ganglio centinela en cáncer de Endometrio. La búsqueda bibliográfica en Medline y PubMed se realizó utilizando los términos: micrometástasis, células tumorales aisladas, cáncer de endometrio y ganglio

centinela. Los criterios de inclusión fueron: idioma inglés, estudios retrospectivos o prospectivos publicados entre Enero de 1999 y Junio de 2019.

El tercer artículo es un estudio transversal que incluye a pacientes sometidas a cirugía primaria por cáncer de endometrio entre Enero 2006 a Diciembre 2012. A las pacientes se les envió por correo una encuesta que incluía un cuestionario validado de detección de linfedema de 13 ítems.

El cuarto estudio es una cohorte retrospectiva de la Base de Datos Nacional de EE.UU que incluye pacientes que se sometieron a linfadenectomía, ganglio centinela y aquellas que no se sometieron a evaluación ganglionar entre 2013 y 2014. Se evaluó el incremento del uso de la técnica, así como, su asociación a la terapia adyuvante radioterápica.

Resultados: El primer estudio demuestra el uso de trazadores fluorescentes como el verde de indocianina, alcanza tasas de detección bilateral de un 95 % en el cáncer de Endometrio. El segundo estudio incluyó un número total de pacientes con micrometástasis y células tumorales aisladas de 286 (187 y 99, respectivamente). Las pacientes con enfermedad de bajo volumen tuvieron un riesgo relativo más alto de recurrencia de 1,34 (1,07-1,67) que las pacientes negativas, incluso si se administró terapia adyuvante.

En el tercer estudio, 623 (49%) pacientes respondieron a la encuesta y 599 fueron evaluables (180 ganglio centinela, 352 linfadenectomía, 67 histerectomía sola). La prevalencia de linfedema fue de un 27% (49/180) para el grupo de ganglio centinale y 41% (144/352) para la linfadenectomia, respectivamente (OR = 1,85; IC

del 95%, 1,25-2,74; p = 0,002). Los pacientes con linfedema tenían una calidad de vida significativamente peor en comparación con aquellos sin linfedema.
En el último estudio analizamos 54.039 mujeres, incluidas 38.453 (71,2%) que se sometieron a linfadenectomía, 1.929 (3,6%) a ganglio centinela y 13.657 (25,3%) sin evaluación ganglionar. El mapeo de ganglios centinelas aumentó del 2,8% en 2013 al 4,3% en 2014 (p <0,001). No hubo asociación entre el uso de biopsia de ganglio centinela y el uso de radioterapia (aRR = 0,92; IC del 95%, 0,82–1,05).

Conclusión: La evidencia sugiere que la técnica de ganglio centinela es segura y efectiva en pacientes con cáncer de endometrio, evitando morbilidad innecesaria.

Keywords: Cáncer de Endometrio, estadios iniciales, ganglio centinela, enfermedad de bajo volumen, linfedema, verde indocianina.

Introduction

Introduction

Endometrial carcinoma

Endometrial cancer is the fourth most common cancer in women in developed countries and the sixth in terms of mortality (1). Unlike other cancers, endometrial cancer has been rising in both incidence and associated mortality in the last years and are expected to increase in 23% and 33% worldwide, respectively, by 2040 (2). Even most women diagnosed with endometrial cancer have early-stage disease and favorable outcomes, the mortality increases dramatically for women with recurrent or advanced disease and for women diagnosed with a clinically aggressive tumor (3).

Epidemiology

Endometrial cancer is typically a disease of the peri-post-menopause period, with a median age at diagnosis of 63 years, and more than 90 % of cases occurring in women older than 50 years. (4) However, approximately 4% of women with endometrial cancer are younger than 40 years, with obvious implications regarding the wish to preserve fertility. (5)

Familial endometrial carcinoma has been consistently described in the literature and it is now well-accepted that approximately 5% of all endometrial carcinomas are caused by an inherited susceptibility. Lynch syndrome, also known as

hereditary nonpolyposis colorectal carcinoma (HNPCC) syndrome accounts for most hereditary cases. (6)

Endometrial carcinoma was traditionally classified as type I and type II in accordance with its histological characteristics. Type I Endometrial carcinomas account for 80% to 90% of Endometrial carcinomas cases and have endometrioid (ie, adenosquamous, mucinous, and villoglandular) histological features. Type II Endometrial carcinomas represent 10% to 20% of all cases and have papillary serous or clear-cell features (7). These differences in histologic features reflect the differences in clinical characteristics. Almost 80% of type I endometrial carcinomas are diagnosed when the tumor is confined to the uterus (8), but this percentage is reduced to 50% and 37% when the analysis is limited to clear-cell (4) or serous (9) endometrial carcinomas, respectively.

Consequently, survival is also heavily affected by histologic subtype. The 5-year progression-free and overall survivals are about 80% and more than 85%, respectively, when all types of endometrial carcinoma are considered (7,8). They decrease to about 36% to 46% and 45% to 55%, respectively, when solely type II endometrial carcinoma are considered. (4,9)

Regarding etiologic factors, a large epidemiologic study from the Epidemiology of Endometrial Cancer Consortium on 14.069 endometrial cancer patients (7) has shown many: obesity, parity, oral contraceptives use, cigarette smoking, age at menarche, and diabetes were associated with both type I and Type II endometrial

carcinomas. Other well-known risk factors include hypertension, anovulation, estrogen therapy unopposed by progesterone treatment, polycystic ovary, and tamoxifen therapy.

Furthermore, different types of endometrial carcinoma have specific histological and molecular features, precursor lesions and natural histories. There is overwhelming evidence that traditional pathologic features, such as histopathologic type, grade, myometrial invasion, and lymphovascular space invasion (LVSI), are important in assessing prognosis, as recommended in the ISGyP guidelines. (10)

Regarding classification, histopathologic typing should be performed according to the WHO Classification of Tumors (5th edition). (11) A binary International Federation of Gynecology and Obstetrics (FIGO) grading is recommended, which considers grade 1 and grade 2 carcinomas as low-grade and grade 3 carcinomas as high-grade. (12) For the assessment of myometrial invasion, account needs to be taken of the endo-myometrial junction which is undulating. (13) In addition, focal LVSI is defined by the presence of a single focus around the tumor, substantial LVSI as multifocal or diffuse arrangement of LVSI or the presence of tumor cells in five or more lymphovascular spaces.

Moreover, the molecular classification adds another layer of information to the conventional morphologic features and therefore should be integrated in the pathologic report. Indeed, the new ESGO-ESTRO-ESP guidelines in endometrial

carcinoma recommends incorporating the molecular classification into the endometrial cancer classification, Table 1. (12) This diagnostic algorithm requires testing of three immunohistochemical markers (p53, MSH-6, PMS-2) and somatic mutation analysis of POLE (exons 9, 11, 13, 14) to identify prognostic groups analogous to the TCGA molecular-base classification. (14-17) In addition, endometrial carcinoma should only be classified as POLE-mutated (POLEmut) when pathogenic variants of POLE are identified in the gene's exonuclease domain. (18,19)

Five categories of tumors are recognized: (1) ultramutated/with pathogenic POLE mutations; (2) hypermutated with MSI/MMRd (loss of MMR protein immunoreactivity); (3) high copy number/ p53abn (p53 mutant immunoreactive pattern); (4) low copy number/NSMP (retained MMR protein immunoreactivity, and p53 wild type immunoreactive pattern); (5) multiple classifier (any combination of markers included in the previous categories).

Application of the molecular classification in high-grade and/or high-risk endometrial carcinomas shows that there is a group of patients with an excellent prognosis—that is, the POLEmut tumors—and a group with a poor prognosis—that is, the p53-abnormal (p53abn) tumors. Hence, the new ESGO Guidelines recommends that POLE mutation analysis may be omitted in low-risk and intermediate-risk endometrial carcinoma with low-grade histology. (12)

Risk group	Molecular classification unknown	Molecular classification known*†
Low	► Stage IA endometrioid + low-grade‡ + LVSI negative or focal	► Stage I–II ***POLEmut*** endometrial carcinoma, no residual disease ► Stage IA **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal
Intermediate	► Stage IB endometrioid + low-grade‡ + LVSI negative or focal ► Stage IA endometrioid + high-grade‡ + LVSI negative or focal ► Stage IA non-endometrioid (serous, clear cell, undifferentiared carcinoma, carcinosarcoma, mixed) without myometrial invasion	► Stage IB **MMRd/NSMP** endometrioid carcinoma + low-grade‡ + LVSI negative or focal ► Stage IA **MMRd/NSMP** endometrioid carcinoma + high-grade‡ + LVSI negative or focal ► Stage IA **p53abn** and/or non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) without myometrial invasion
High–intermediate	► Stage I endometrioid + substantial LVSI regardless of grade and depth of invasion ► Stage IB endometrioid high-grade‡ regardless of LVSI status ► Stage II	► Stage I **MMRd/NSMP** endometrioid carcinoma + substantial LVSI regardless of grade and depth of invasion ► Stage IB **MMRd/NSMP** endometrioid carcinoma high-grade‡ regardless of LVSI status ► Stage II **MMRd/NSMP** endometrioid carcinoma
High	► Stage III–IVA with no residual disease ► Stage I–IVA non-endometrioid (serous, clear cell, undifferentiated carcinoma, carcinosarcoma, mixed) with myometrial invasion, and with no residual disease	► Stage III–IVA **MMRd/NSMP** endometrioid carcinoma with no residual disease ► Stage I–IVA **p53abn** endometrial carcinoma with myometrial invasion, with no residual disease ► Stage I–IVA **NSMP/MMRd** serous, undifferentiated carcinoma, carcinosarcoma with myometrial invasion, with no residual disease
Advanced metastatic	► Stage III–IVA with residual disease ► Stage IVB	► Stage III–IVA with residual disease of any molecular type ► Stage IVB of any molecular type

*For stage III–IVA *POLE*mut endometrial carcinoma and stage I–IVA MMRd or NSMP clear cell carcinoma with myometrial invasion, insufficient data are available to allocate these patients to a prognostic risk group in the molecular classification. Prospective registries are recommended.
†See text on how to assign double classifiers (eg, patients with both *POLE*mut and p53abn should be managed as *POLE*mut).
‡According to the binary FIGO grading, grade 1 and grade 2 carcinomas are considered as low-grade and grade 3 carcinomas are considered as high-grade.
LVSI, lymphovascular space invasion; MMRd, mismatch repair deficient; NSMP, non-specific molecular profile; p53abn, p53 abnormal; *POLE*mut, polymerase-mutated.

Table 1: The new definition of prognostic risk groups according to molecular classification: Concin N, Matias-Guiu X, Vergote I, Cibula D, Mirza MR, Marnitz S et al. ESGO/ESTRO/ESP guidelines for the management of patients with endometrial carcinoma. *Int J Gynecol Cancer. 2021 Jan;31(1):12-39.*

Pathogenic germline variant in a Lynch syndrome associated gene

Approximately 3% of all endometrial carcinomas and about 10% of mismatch repair deficient (MMRd)/microsatellite unstable endometrial carcinomas are causally related to germline mutations of one of the MMR genes MLH1, PMS2, MSH2 and MSH6. (20) The preferred approach (widely available and cost-effective) to identifying patients with a higher chance of having Lynch syndrome is by MMR-immunohistochemistry (IHC) on well preserved tumor tissue. MMR-IHC is a reliable method to assess MMR status, and in addition provides information on the altered gene/protein. ISGyP guidelines therefore recommend MMR-IHC as the preferred test. (10) MMR-IHC consists of the assessment of the expression of four MMR proteins (MLH1, PMS2, MSH6, and MSH2).

The cumulative incidences for cancer depend on the specific mutation in women with Lynch syndrome. For endometrial carcinoma, the cumulative incidences at 70 years are 34%, 51%, 49%, and 24% for MLH1, MSH2, MSH6, and PMS2 mutation carriers, respectively, and for ovarian cancer 11%, 15%, 0%, and 0%, respectively. (21) Furthermore, the age of cancer onset in Lynch syndrome varies among specific mutated genes and types of mutations. Ryan et al. (22) suggests gynecological surveillance to be appropriate from age 30 years for those with MSH2 mutations, from age 35 years for those with no truncating MLH1 mutations, and from age 40 years for those with MSH6 and truncating MLH1 mutations.

Symptoms

Abnormal vaginal bleeding is present in approximately 90% of endometrial carcinoma cases, and when it occurs in postmenopausal women, it should be always regarded as a suspicious symptom, warranting an initial evaluation to rule out malignancy. (8) Other abdominal symptoms could be appeared once the advanced disease is presented.

Pre-operative work-up

An endometrial biopsy is needed to diagnose or exclude malignancy. In addition, imaging for the detection of extra-abdominal spread is usually limited to chest radiography and abdominal tomographic scan (CT) is indicated when extra-pelvic disease is suspected, however, is more commonly used when poorly differentiated or type II cancer is discovered in the endometrial biopsy.

Pelvic magnetic resonance (MRI) is a reliable tool to assess myometrial invasion and to tailor the extent of surgery, particularly for the decision as to whether to perform pelvic or para-aortic lymphadenectomy.

The diagnostic performance of transvaginal ultrasound and MRI for detecting myometrial invasion in endometrial carcinoma are quite similar. (23-26) Of note, pre-operative ultrasound assessment of deep myometrial and cervical stromal invasion in endometrial carcinoma is best performed by an expert sonographer as, compared with gynecologists, they show a greater degree of agreement with histopathology and greater inter-observer reproducibility, but RMI is better in carcinomatosis or lymph node involvement. (27) Hence, positron emission tomography (PET) scanning has an excellent specificity for the pre-operative

assessment of lymph node metastases in patients with endometrial carcinoma. Its moderate sensitivity for detecting lymph node metastases during pre-operative staging probably reflects the need for enough neoplastic cells to induce 18F-fluoro- 2-deoxy- D- glucose hypermetabolism. (28-39) The usefulness of maximal standardized uptake value in classifying patients into pre-defined risk groups is limited.

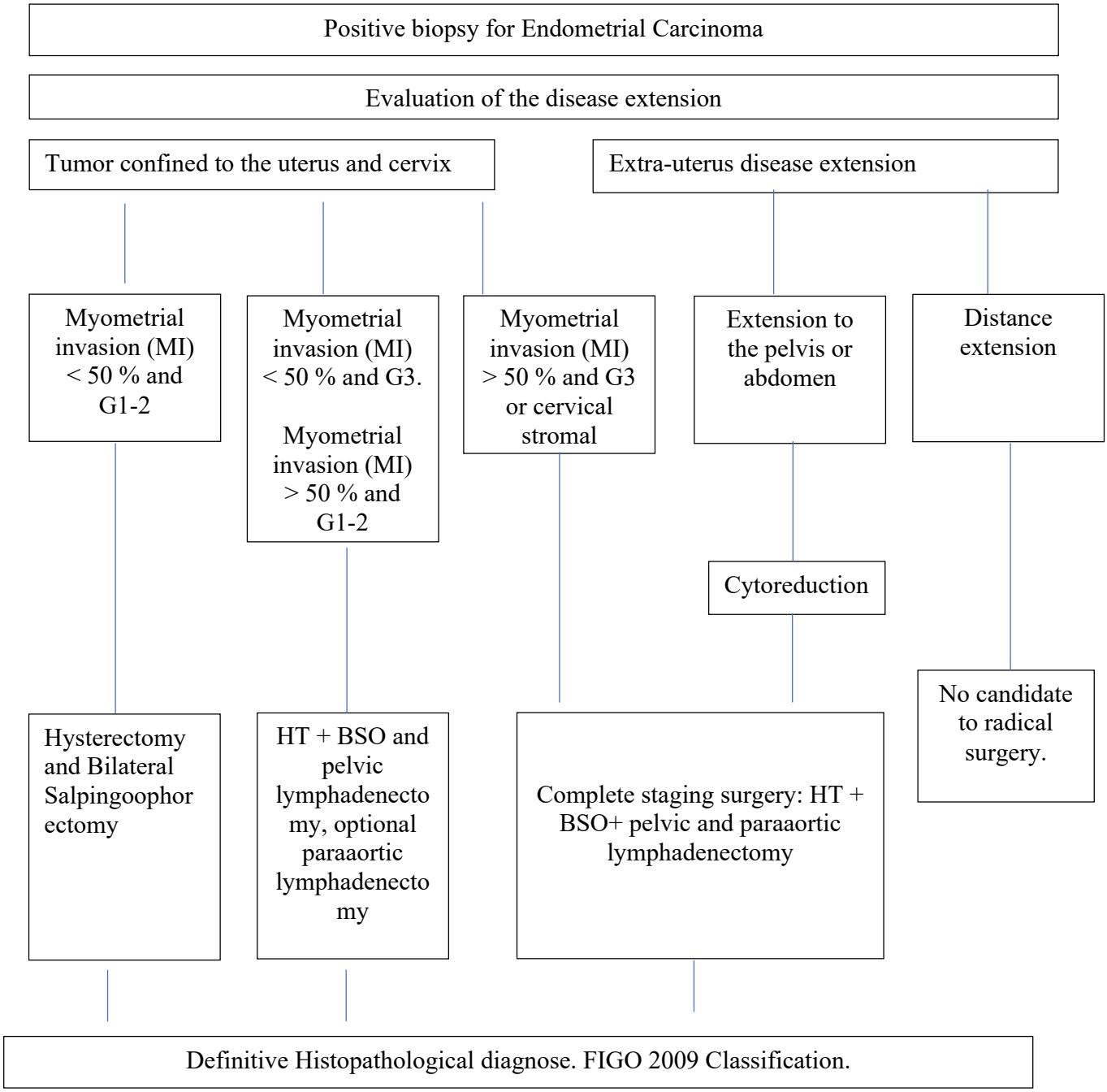
Treatment

The standard treatment for endometrial cancer is a simple hysterectomy and a bilateral salpingo-oophorectomy (BSO) with or without lymphadenectomy (depending on uterine risk factors). Table 2

In patients with intermediate or high-risk factors, a pelvic and para-aortic lymphadenectomy is routinely performed. In addition, according to what extend the endometrial cancer is, the International Federation of Gynecology and Obstetrics (FIGO) classify the tumor in different stages and the treatment is based on that. Table 3.

Furthermore, patients with possible spread of disease outside the uterus may benefit of further surgical and/or adjuvant treatment. Hence, before deciding the optimal therapeutic management for endometrial cancer patients, it is crucial to stratify patients based on clinical, histopathological characteristics and even more, the molecular classification. Table 1

Table 2. Treatment Algorithm.



SEGO Treatment protocols for Endometrial cancer. 2016

Table 3. FIGO staging of Endometrial Carcinoma.

FIGO Stage	
I[a]	Tumor confined to the corpus uteri
IA[a]	No or less than half myometrial invasion
IB[a]	Invasion equal to or more than half of the myometrium
II[a]	Tumor invades cervical stroma, but does not extend beyond the uterus[b]
III[a]	Local and/or regional spread of the tumor
IIIA[a]	Tumor invades the serosa of the corpus uteri and/or adnexae[c]
IIIB[a]	Vaginal involvement and/or parametrial involvement[c]
IIIC[a]	Metastases to pelvic and/or para-aortic lymph nodes[c]
IIIC1[a]	Positive pelvic nodes
IIIC2[a]	Positive para-aortic nodes with or without positive pelvic lymph nodes
IV[a]	Tumor invades bladder and/or bowel mucosa, and/or distant metastases
IVA[a]	Tumor invasion of bladder and/or bowel mucosa
IVB[a]	Distant metastasis, including intra-abdominal metastases and/or inguinal nodes)

[a]Either G1, G2, or G3.
[b]Endocervical glandular involvement only should be considered as Stage I and no longer as Stage II.
[c]Positive cytology has to be reported separately without changing the stage.

Amant F, Mirza M, Koskas M, et al. Cancer of the corpus uteri. FIGO Cancer Report 2018.

Early-stage disease

Surgical management of apparent stage I/II endometrial carcinomas

The recommended procedure for early-stage endometrial carcinoma is a hysterectomy and bilateral salpingo-oophorectomy by minimally invasive surgery. However, patients with grade 1 endometrioid carcinoma without myometrial invasion should be considered for fertility-sparing treatments. (40-46)

Two randomized prospective studies comparing minimally invasive with open surgeries showed similar survival with quicker recovery with the minimally invasive approach. (47-49) Regarding the type of hysterectomy, in a randomized controlled trial comparing modified radical (Piver– Rutledge class II) hysterectomy to the standard extrafascial (Piver– Rutledge class I) or simple total hysterectomy in stage I endometrial carcinoma, Signorelli et al (49) showed no differences in locoregional control and survival.

Regarding omentectomy, the low rate of omental metastases in apparent clinical stage I endometrioid and clear cell carcinoma does not justify the procedure. (50) However, omentectomy should be part of staging surgery in stage I serous and undifferentiated endometrial carcinoma and in carcinosarcoma patients. (51) Furthermore, positive peritoneal cytology correlates with poor prognostic factors and poor survival; however, it is not part of FIGO staging and unclear if this should influence treatment decisions. (52-54)

Hence, to assess the nodal status lymph node staging is an integral part of the FIGO staging system for endometrial cancer. However, performing pelvic node assessment in all cases leads to a low rate of patients with positive lymph nodes (9%) (55), with a high risk of procedure-related short- and long-term complications. The challenge is to identify patients who are at high-risk of nodal metastases and performing nodal assessment only on them, thus sparing unnecessary procedures.

The 2009 update of FIGO staging system clearly distinguishes two subtypes of stage IIIC disease, i.e., stage IIIC1, with only pelvic nodes positivity, and stage IIIC2 with positive para-aortic nodes. Due to that, sentinel node biopsy has been introduced as an alternative to lymph node dissection for lymph node staging and, if done according to state-of- art principles, a negative sentinel node is accepted to confirm pN0. (56)

Recently, sentinel lymph node mapping has been described as an alternative to lymphadenectomy that allows for nodal assessment while minimizing the risks of lymphadenectomy including prolonged operative times, intraoperative injury, blood loss, and lymphedema. (56)

The sentinel lymph node mapping technique

The sentinel lymph node technique entails the injection of a radioactive tracer and colored dye to locate hot nodes in order to visualize the lymphatic drainage of the uterus. Sentinel lymph node are considered positive if they

contain macrometastasis (tumor clusters larger than 2 mm), micrometastasis (tumor cluster between 0.2-2 mm in size), or isolated tumor cells, single cells, or tumor clusters smaller or equal to 0.2 mm in size). (57,58)

In terms of the technique, different methods have been described depending on the tracer and the site of injection used. There are three different types of sentinel lymph node mapping techniques exist based on site of injection: 1) uterine subserosal, 2) cervical and 3) endometrial via hysteroscopy. (57,58)

The lymphatic drainage of the uterus is complex and can be directed towards multiple lymphatic regions, Image 1. It extends along the obturator, iliac (external, internal, or common), cava, and aortic pathways, and into the parametrial tissue and presacral space. There are three possible routes for lymphatic drainage:

1. Through the hypogastric and obturator regions: they drain into the common iliac chains.
2. Along the round ligaments: drain the inguinal chains.
3. Through the ovarian vessels: they drain directly into the para-aortic chains

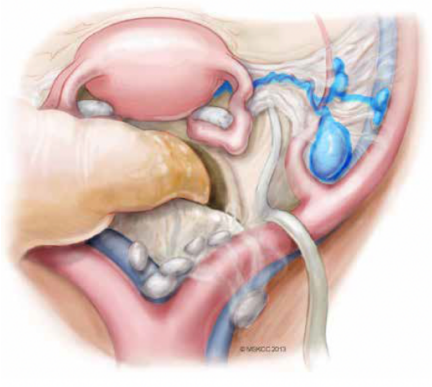


Image 1A: The most common drainage routes, usually when the lymphatic trunks cross over the obliterated umbilical ligament. The most common locations of sentinel lymph nodes after a cervical injection are medial to the external iliac, ventral to the hypogastric, or in the superior part of the obturator space.

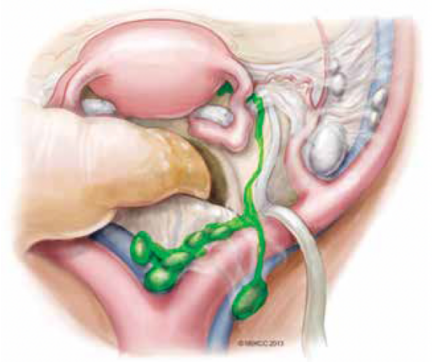


Image 1B: The less common locations of sentinel lymph nodes, usually seen when lymphatic trunks do not cross over the umbilical ligament but follow the mesoureter cephalad to the common iliac and presacral sentinel lymph nodes.

Abu-Rustum NR. Sentinel Lymph Node Mapping for Endometrial Cancer: A Modern Approach to Surgical Staging. Review. Journal of the National Comprehensive Cancer Network. *NCCN.org. Vol 2. Number 12. Feb 2014.*

More than a decade, in 2007, Ballester et al. (59) published a prospective, multicenter study using dual cervical injection of radiolabeled colloid with Tc99 and blue dye in patients with early-stage endometrial cancer. A total of 133 patients were included. The cases with previous lymphadenectomy and those with a history of any previous type of surgery (i.e., conization, myomectomy) were excluded. Four 0.2 ml cervical injections (20 MBq each) of radiolabelled colloid were administered at the 3, 6, 9, and 12 o'clock positions the day before or the morning of surgery. Subsequently, images were obtained by lymphogammagraphy, first 2 hours after the injection and then every 30 minutes to guide the location of the sentinel lymph node preoperatively. The day of the surgery, after anesthetic induction, the blue dye was injected at cervical 3 and 9 hours (1 ml per injection). The lymphatic pathways were subsequently tracked with a portable gamma probe to localize the sentinel lymph node before accessing the retroperitoneum. After removing the lymph nodes stained, a systematic pelvic lymphadenectomy was performed in all patients. Paraaortic lymphadenectomy was only performed in those patients with type II endometrial carcinoma or in those who showed metastatic disease in any of the removed nodes (including sentinel lymph nodes). The sentinel lymph nodes and non-sentinel lymph nodes were considered positives in the presence of macrometastasis, micrometastasis or isolated tumor cell. Paraaortic sentinel lymph nodes were detected in 5 patients. The authors stated that the low overall detection rate (89%) was due to the long time between the radiocolloid injection and the procedure (22 hours on average). After the histopathological analysis, a negative predictive value, and a sensitivity of both 100% were obtained for each

hemipelvis. There were 3 false negative cases: 2 patients presented metastases in the contralateral hemipelvis (where sentinel lymph was not detected) and another in paraaortic lymphadenectomy. The authors concluded that the sentinel lymph node technique using dual cervical injection of blue dye and radiolabeled colloid could be an alternative to complete lymphadenectomy in patients with low or medium risk endometrial cancer.

In addition, at Memorial Sloan Kettering Cancer Center, (58) they found that a cervical injection is adequate for effective sentinel lymph node mapping, the rationale for using a cervical injection includes the following: as above, the main lymphatic drainage to the uterus is from the parametria, therefore, a combined superficial (1-3mm) and deep (1-2cm) cervical injection is adequate; the cervix is easily accessible, the cervix in women with endometrial carcinoma is rarely distorted by anatomic variations, such us myomas, scarred, the majority of early stage endometrial carcinoma do not have disease infiltrating and ulcerating the uterine fundal serosa (60). The colored dye, such as isosulfan blue 1%, (lymphazurin), Methilene blue 1%, Patente-blue 2.5% sodium (Bleu Patente V sodique) or Indocyanine green is injected while the patient is under anesthesia in the operating room. The dye is injected in a similar fashion to that of the radiotracer. The 4 mL can be divided into four separate injections, one into each quadrant of the cervix (1 mL each). The injections also can be given at the 3 and 9 o'clock positions, which correspond to the parametria. (61)

In 2012, once again, the Memorial Sloan Kettering Cancer Center in New York (USA) published a study including 498 patients with early-stage endometrial carcinoma, based on their experience since 2005. They suggest a standardized surgical algorithm for the sentinel lymph node technique to increase the detection rate and decrease the false negative rate. (62)

The proposed algorithm is below, regardless of the tracer and site of injection:

1. Evaluation and washing of peritoneum and serosa
2. Retroperitoneal evaluation
3. Excision of all identified sentinel lymph nodes
4. Excision of any macroscopically suspicious lymph node (regardless of not being considered sentinel)
5. If a sentinel node cannot be identified in any hemipelvis, complete lymphadenectomy should be performed on that side.
6. Dissection of paraaortic lymph nodes according to the surgeon's criteria

They concluded that, using the sentinel lymph node mapping technique, the percentage of lymphadenectomies performed had decreased from 65 to 23%, the average surgical operative time had been reduced by one hour, the median number of lymph nodes removed had decreased from 20 to 7, and the detection rate of metastases had increased by 4%. The detection rate was 81%, and the false negative rate was 1.9% with a negative predictive value of 99.8%.

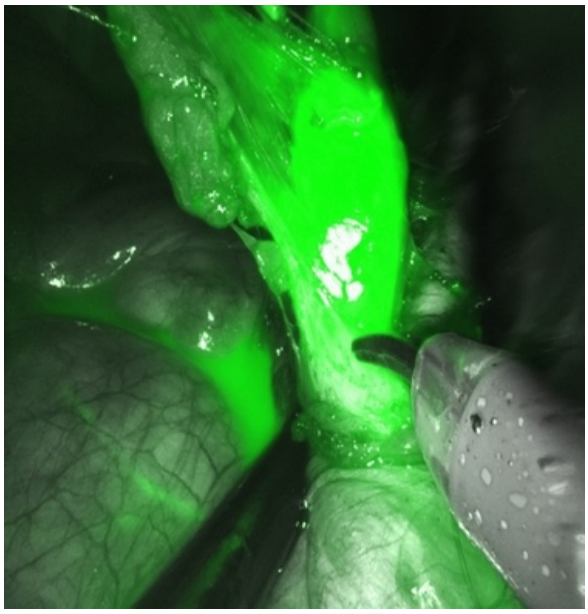
Regarding the tracers, various tracers have been tested during sentinel node mapping. The most utilized tracers included: 1) technetium-99 radiocolloid (Tc-99m),2) blue dyes (including methylene, isosulfan, and patent blues), and 3) indocyanine green. Tc-99m should be injected prior to surgery (generally the day before). Tc-99m has a half-life of about 6 hours. A gamma-probe is needed to detect the signal emitted by Tc-99m. The detection of sentinel nodes thorough Tc-99m is based on audiometric signal (no visualization of colors). However, the execution of single-photon-emission computed tomography (SPECT-CT) might be useful to obtain more precise information regarding the location of sentinel nodes. Elisei et al. (63) observed that the execution of SPECT-CT is associated with a highest detection rate and bilateral mapping when compared with audiometric signal only. Blue dyes are injected into interstitial spaces. They bind serum proteins and are picked up by lymphatic vessels. The major advantage in the utilization in blue tracers is that they do not require dedicated and often costly equipment.

Indocyanine green is composed by small particles that show florescence after they are visualized thorough a near infrared light (range, 700–900 nm). A dedicated optical system is needed to visualize drainage of indocyanine green into the lymphatic vessels.

Several studies compared the effectiveness of various tracers in terms of detection rates and bilateral mapping (64). Overall, these studies agree that indocyanine green is characterized by a higher overall and bilateral detection rate

in comparison to other methods (even when are combined [Tc-99m plus blue dye]) (64). Moreover, the detrimental effects of body mass index (BMI) in sentinel node mapping are softened when indocyanine green is used as a tracer (63-65). In fact, although accumulating data underlined that higher BMI reduce sentinel node detection rate the fluorescent signal observed with indocyanine green might overcome the shielding effect of the adipose tissue on the colorimetric signal (64-66). Two independent studies published by Tanner et al. (65) and Eriksson et al. (66) suggested the detrimental effect of an increased BMI on sentinel node detection and the better sentinel nodes visualization when indocyanine green was used in comparison to blue dye.

Another point deserving attention is that current literature agrees that indocyanine green is characterized by a better safety profile in comparison to Tc-99m (that is a radioactive drug and blue dyes (various adverse events are reported including skin necrosis). (67) On the light of this evidence, although costly, indocyanine green should be considered the preferred tracer for sentinel node mapping (especially in the setting of minimally invasive surgery).



Sentinel lymph node mapping with ICG by Robotic Surgery. Vall d´Hebron Hospital.

The site of injection

Related to the site of injection, three possible techniques have been proposed: the uterine body (subserosa intra-myometrial), the cervix and peritumoral using hysteroscopy. The tracer drainage appears different depending on the site of injection.

The myometrial injection

In 1996, Burke et al. (68) published an important study regarding the identification of sentinel lymph node mapping in endometrial cancer. In their series of 15 patients, at the time of laparotomy, the vessels were occluded with hemoclips and blue isosulfan was injected into the uterine fundus myometrium at 3 midline sites.

Stained lymph nodes were identified and removed, followed by the standard lymphadenectomy. Dye uptake was observed in at least one node in 67% of cases. Of the 31 identified sentinel lymph nodes, 12 (39%) were found in the para-aortic region. Two of the four lymph nodes that were metastatic did not take blue dye (false negative rate of 50%). In 2002, Holub et al. (69) and Gien et al. (70) in 2005, reported similar detection rates of 61.5% and 56%, respectively, using a similar technique.

Moreover, in 2007, Lopes L et al. (71) reported the results of the sentinel lymph node biopsy in 40 patients with endometrial carcinoma confined to the uterus. After accessing the abdominal cavity, intramyometrial blue dye was injected at a point equidistant from both uterine horns, on the anterior and posterior walls. The sentinel lymph node was identified in 31 patients (77%): in the paraaortic region in 7 cases, in the pelvic region in 17, and in both regions in 7.

At the same time, Altgassen et al. (72) tried to obtain better detection rates. They used 8 sub-serosal injection points (4 ventral and 4 dorsal) and they obtained the highest detection rate of 92%. These data indicate that the detection rate may increase with the number of injections, at different locations in the uterine body and increase the paraaortic detection.

The Cervical Injection

The uterus is a midline structure and has bilateral lymphatic drainage. Therefore, it is important to define the bilateralism of the technique. If not, sentinel lymph

node is detected in one side, a complete hemipelvis lymphadenectomy should be perform, regardless of what was detected in the opposite hemipelvis.
Several studies used the cervix as a site of injection, either alone or in combination with subserous myometrium injection. The sentinel lymph node detection rates ranged from 80% to 100%.

In 2003, Pelosi E et al. (73) evaluated a combined cervical injection of radiocolloid and blue dye in patients with early-stage endometrial cancer. All detected sentinel lymph nodes were iliac, different from the previous study. Furthermore, in 2007, Delpech Y et al. (74) reported the results of the sentinel lymph node biopsy in 23 patients with endometrial cancer. Four injections of 99m-Tc were injected into the cervix the day before surgery followed by two intraoperative injections of blue dye. A detection rate of 83% was obtained. The 47 detected sentinel lymph nodes were found in the pelvic region. No sentinel lymph nodes were found in the para-aortic region.

Regarding detection rates, the overall detection rate published by Ballester et al. in the SENTI-ENDO study (59) was 89% and the bilateral detection rate was 69%. It should be noted that the main problem was the low rates of bilateral detection (enhanced by indocyanine green) and low rates of paraaortic detection (enhanced by corporal site of injections). On the other hand, several authors criticize the cervical injection since the patterns of lymph node spread are somewhat different between cervix and uterus.

Therefore, in 2009, Abu-Rustum et al. (75) in a prospective study reported a total of 42 patients diagnosed preoperatively with endometrial carcinoma type I were included. (Image 2) The day before surgery, 2 doses of radiolabeled colloid with Tc99 were injected into the cervical stroma at the 3 and 9 o'clock positions.

Afterwards, a lymphogammagraphy was performed to identify the sentinel lymph nodes. Intraoperatively, the blue dye was injected, applying 2 intracervical doses in all patients at 3 and 9 o'clock, and another 2 extra doses in the uterine fundus (one on the anterior side and one on the posterior side). This study obtained a detection rate of 86% and the lymph node pattern of spreading was as follow: internal iliac (36%), external iliac (30%), obturators (23%), iliac common (8%) and 5 paraaortic (3%). Therefore, the negative predictive value and the sensitivity were 100% for stage I patients. The addition of 2 injections into the uterine fundus did not appear to improve detection rates, with 4 out of 21 failed detections in the cervical injection group vs. 2 out of 21 combined cervical and fundic ($p = 0.4$).

They concluded that deep cervical injections at the 3 and 9 o'clock positions (corresponding to the lymphatic vessels paracervical and parametria) showed an accurate distribution of the tracer to the parauterine lymphatic vessels (the main route of lymphatic drainage from the uterus).

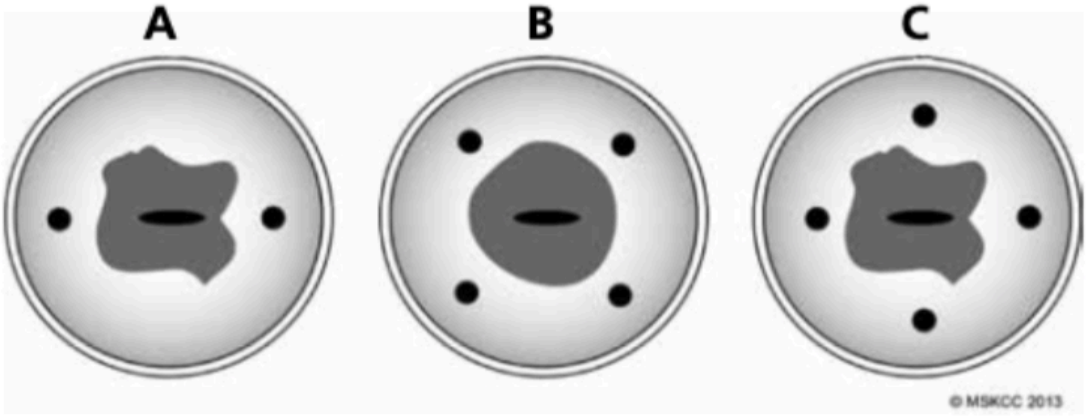


Image 2: Three different options for cervical injections: a 2-sided option (A) and the 4 – quadrant options (B and C). *Abu-Rustum NR, Levine DA, Barakat RR, eds. Atlas of procedures in Gynecologic Oncology, 3rd ed. London: informa Healthcare. 2013.*

Peritumoral injection by hysteroscopy

In 2006, Niikura et al. (76) published a series of 28 patients in whom the radioactive tracer was injected around the tumor under direct hysteroscopic visualization the day before surgery. The injections were made at 4 endometrial points around the lesion, and the blue dye was used to ensure the absence of leaks and not to identify the sentinel lymph nodes. Patients with multiple lesions, 5 injection points covering the entire uterine cavity were used. The scintigraphy was first, performed 10 min after injection and was repeated the following day, just before surgery. During surgery, the sentinel lymph nodes were identified by scanning with a gamma camera and subsequently, excised. Both, pelvic and para-

aortic lymphadenectomies were performed. The detection rate obtained was 82%, with a sensitivity of 100% and 100% of specificity.

Lastly, Maccauro M et al. (77) and Raspagliesi F et al. (78) evaluated the injection of radioactive tracer and blue dye by hysteroscopy. Both studies have some differences from the previous one. First, both tracers were injected to identify the sentinel lymph node. The scintigraphy was performed 15 min after the hysteroscopic injection. The surgery was performed within the first 3-4 hours after the hysteroscopic injection. The intraoperative identification of sentinel lymph nodes was performed by a gamma camera and by direct visualization of the blue-stained nodes. Subsequently, a pelvic lymphadenectomy was performed in all patients, and patients with type II tumors underwent an aortic lymphadenectomy. The authors reported a detection rate of 100% with the radiocolloid, while the identification of blue dye by direct visualization was only 30% in both studies. Additionally, a 100% of negative predictive value was reported for metastatic disease, and there were no false negatives.

Later, in 2008, Perrone et al. (79) published a study comparing cervical and hysteroscopic injection in terms of detection rates and location of sentinel lymph nodes. The study included 54 patients with stage I and II endometrial cancer, who were randomly assigned to the cervical injection or hysteroscopy group. Only radiocolloid was used as a tracer. In the cervical group, 4 injections (3, 6, 9, and 12 h) were administered the night before surgery, while in the hysteroscopy group the dose was infiltrated at the endo-myometrial junction around the tumor, 2 h

before surgery. Both groups received the same dose (4 ml), and both underwent lymphogammagraphy, 30 min after injection. Finally, the detection rate for the cervical injection group was 70% while for the hysteroscopy group was 65%. For the cervical group, the location of the sentinel lymph node was pelvic in all cases, while for hysteroscopy group, 2 paraaortic sentinel lymph nodes were found. No false negatives were found for both groups. The authors concluded that the hysteroscopic technique offered a better representation of the complete drainage of the uterus, but both techniques were equally effective in practice.

One of the main limitations of the hysteroscopic technique is the technical difficulty of the procedure compared to the cervical or subserosal techniques, and the risk of retrograde transtubal spread of cancer cells into the abdominal-pelvic cavity due to increased pressure in the uterine cavity during hysteroscopy. Related to this, Ben-Arie et. al (80) showed no differences in recurrence rates or overall survival after hysteroscopy compared to other diagnostic procedures for endometrial carcinoma. Furthermore, Solima E et. al (81) published a prospective study, using Tc99 radiolabeled albumin colloid alone and performing a systematic paraaortic and pelvic dissection. Eighty patients were included. The same day of the surgery (no more than 6 h) they underwent a hysteroscopy without cervical dilation. The pressure applied by saline solution to distend the uterine cavity was always less than 70 mmHg to avoid the possible risk of reflux. The site of subendometrial injections depended on the characteristics of the tumor; If it was a single localized lesion, the radiopharmaceutical was applied at 3, 6, 9, and 12 h peritumorally, while, in tumors involving the entire cavity, injections were applied

to the fundus and the four endometrial walls. After administration, the lymphogammagraphy was obtained for 15 minutes. During the surgery, a gamma camera scan was performed on the pelvic and para-aortic lymphatic drainage routes. After sentinel lymph node sampling, lymphadenectomy was performed systematically in all patients with stage II or greater and selectively in patients with stage I. Finally, a sentinel lymph node detection rate of 95% was obtained, and of these, 56% presented some sentinel lymph node in the para-aortic area. A sensitivity of 90% and a negative predictive value of 98% were obtained. This high detection rates compared to previous studies could be explained by the short time interval between injection and surgery (which never exceeded 6 hours), and by the accumulated team's experience. Indeed, para-aortic nodes are important part of lymphatic drainage of the uterus. However, only 2 paraaortic sentinel lymph nodes were positive, one was associated with another positive pelvic sentinel lymph node, and the other one was found in a patient with a high-grade tumor, making the hysteroscopic technique less reproducible than cervical injection.

The low volume disease

The advantages of the sentinel lymph node technique are the possibility of avoiding unnecessary lymphadenectomy and to have a more precise lymphatic diagnostic precision due to the application of more complex techniques than those of classical cutting and staining. The classic cutting techniques with subsequent impregnation in hematoxylin-eosin (H&E) involve only a small fraction

of the total tissue and have limited sensitivity with high observer dependence, which can lead to a high percentage of false negatives. For this reason, the analysis of the sentinel lymph node should be made by ultrastaging and immunohistochemical (IHC) techniques, which provide a more accurate staging.

Currently, the preparation of at least one section (three or four sections in the case of large nodes) in the longitudinal or transverse plane is recommended for histological study after macroscopic identification of nodes. In addition, IHC cytokeratin (CK) and polymerase chain reaction (RT-PCR) techniques are added to routine H&E staining. Each half of the sentinel lymph node is sectioned at 3 mm and each section is analyzed at four additional 150 micro mm levels before being examined by IHC with a mix of anti-CK antibodies.

The antibodies against epithelial specific antigens have provided a less laborious approach to the detection of micrometastases. Cytokeratins, which comprise a multigenic family of 20 related polypeptides, are constituents of the intermediate filaments of epithelial cells that are expressed in various combinations depending on the epithelial type and the degree of differentiation. The AE1 / AE3 monoclonal antibody mix is reactive with a broad spectrum of human keratins and has been found to work well in both mesothelial and epithelial cells, even in poorly differentiated epithelial neoplasms.

The greater the number of sections, the lower the volume of the lymph node that is not analyzed and, therefore, the higher the detection rate of metastasis, with

fewer false negatives. In addition, IHC techniques facilitate the identification of tumor cells due to the amplification of the signal immunodetection.

Lymphatic mapping by sentinel lymph node biopsy analyzes the lymphatic status by studying a single node, or a small number of them, which allows the application of ultrastaging histological techniques, making possible to detect low volume disease than those visualized by conventional techniques. Such cell clusters are called micrometastases or isolated tumor cells, depending on the size.

The micrometastases are defined as metastases that are between 0.2 and 2 mm in size. The cell clusters that are less than 2 mm are defined as an isolated tumor cells. (Image 3) Isolated tumor cells are usually not considered metastasis in other pathologies, considering the node negative. For example, the presence of micrometastases in breast cancer is associated with an increased risk of recurrence, however, in endometrial cancer there are still controversial. (82)

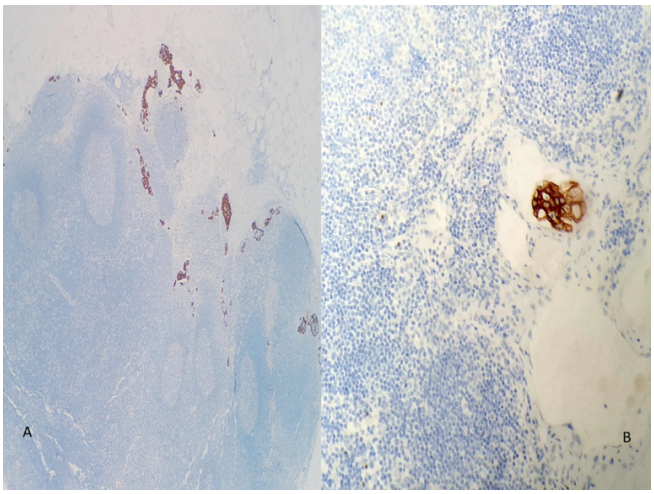


Image 3: Microscopic features of micrometastasis and isolated tumor cells.

Bogani G, et al. Low-volume disease in endometrial cancer: The role of micrometastasis and isolated tumor cells. *Gynecol Oncol. 153 (2019) 670–675.*

Recently, the New ESGO Guidelines recommends, if sentinel lymph node biopsy is performed: Indocyanine green with cervical injection is the preferred detection technique, side-specific systematic lymphadenectomy should be performed in high–intermediate-risk/ high-risk patients if sentinel lymph node is not detected on either pelvic side and pathologic ultrastaging of sentinel lymph nodes is recommended. (12)

The Lymphedema

Surgical lymphadenectomy and radiation are common components of therapy for women with endometrial cancer and are thought to increase the risk of developing lower-extremity lymphedema. These patients may also have comorbid conditions such as obesity that further increase their risk. Once present, the symptoms and local effects of lymphedema can only be managed, not cured. The resulting disability may lead to severe lifelong morbidity including pain, skin breakdown, impaired mobility, difficulty with self-care, psychosocial morbidity, and impaired quality-of-life. (83-85)

Moreover, signs and symptoms are often ignored or unrecognized, and the diagnosis may be challenging because the condition is frequently bilateral,

prohibiting comparison with an uninvolved contralateral limb (in contrast to upper extremity lymphedema in the context of axillary lymphadenectomy for breast cancer). (86) Strategies to reduce lymphedema include omission of lymphadenectomy in low-risk patients. (87-89) Sentinel lymph node mapping (90) has also been utilized, but preliminary data suggest it may be unacceptably high for patients at high risk (59, 91), and according to the most accepted algorithm 35–50% of patients who undergo sentinel lymph node dissection will nevertheless require unilateral or even bilateral lymphadenectomy.

Adjuvant Treatment

Adjuvant treatment recommendations for endometrial carcinoma strongly depend on the prognostic risk group, Table 1. The new ESGO Guidelines recommendations are as follows:

Low risk patients: No adjuvant treatment is recommended based on data from multiple randomized trials. (92-95)

Intermediate risk patients: Adjuvant brachytherapy provides excellent vaginal control and high survival rates, similar to those after adjuvant external beam radiation therapy. (96-104) The intermediate-risk category only includes those with none or only focal LVSI and p53wt. Therefore, no adjuvant treatment is an option in this group, especially for patients aged <60 years who have a lower risk of relapse. (12)

High- Intermediate risk patients: In view of the recent randomized trials GOG-249 (for stage I and II endometrioid endometrial carcinomas with high-risk factors or serous or clear cell histology), the PORTEC-3 trial, and the older GOG-99 trial, adjuvant external beam radiation therapy is recommended in case of substantial LVSI or stage II. (92,105,106) Additional chemotherapy can be considered, especially for high-grade carcinomas, based on the PORTEC-3 trial, but the question remains whether the benefit outweighs the toxicity for stage I–II endometrioid carcinomas, and multi-disciplinary shared decision-making is needed. (105)

High risk patients: High-risk carcinomas are now either stage III–IVA without residual disease or stage I–IVA p53abn or non-endometrioid carcinomas without residual disease with myometrial invasion, Table 1. In 2019, the PORTEC -3 trial comparing combined chemotherapy and radiotherapy (two cycles of cisplatin during radiotherapy followed by four cycles of carboplatin-paclitaxel) with radiotherapy alone was published. (105,106) A statistically significant 5% overall survival benefit at 5 years and a 7% failure-free survival benefit was seen in the combined therapy group compared with radiotherapy alone. Moreover, the greatest overall survival difference was seen in stage III carcinomas and in serous carcinomas regardless of stage. Hence, external beam radiation therapy with concurrent and adjuvant chemotherapy (I, A) or alternatively sequential chemotherapy and radiotherapy is recommended. Therefore, chemotherapy alone is an alternative option. (12)

Advanced disease

Surgery for clinically overt stage III and IV disease

In stage III and IV endometrial carcinoma (including carcinosarcoma), maximal cytoreduction should be considered only if macroscopic complete resection is feasible with acceptable morbidity. (107-111)
Regarding lymph node assessment, suspicious enlarged lymph nodes should be resected if complete resection is possible. (112,113) A full systematic pelvic and para-aortic lymphadenectomy of non-suspicious lymph nodes is not recommended because there is no evidence of a therapeutic impact. In case upfront surgery is not feasible or acceptable and therefore primary systemic therapy is given, delayed surgery can be considered in case of a meaningful response to chemotherapy. (114-121)

Furthermore, patients with unresectable locally advanced disease and no evidence of multiple distant metastases, treatment options include definitive radiotherapy or neoadjuvant chemotherapy followed by surgery or definitive radiotherapy, depending on response. (116,117,122,123) Definitive radiotherapy comprises external beam radiation therapy to the pelvis followed by image-guided brachytherapy and concurrent chemotherapy may be considered to enhance the radiation effect

Moreover, adjuvant chemotherapy should also be considered following primary local treatment (surgery or radiotherapy) to reduce the risk of distant metastases, even more, chemotherapy treatment reduces the risk of distant metastases for patients with lymph node involvement. (105, 115,119,124)

Recurrent Disease

Treatment of patients with recurrent endometrial carcinoma involves a multi-disciplinary approach with surgery, radiotherapy, and/or systemic therapy depending on the fitness and wishes of the patient, the tumor dissemination patterns, and prior treatment. A decision about surgery needs to take account of patient morbidity and wishes, available non-surgical treatments, and resources. The interval between primary treatment and recurrence should also be taken into consideration. Patients with recurrent disease, including resectable peritoneal and lymph node relapse, should be considered for surgery only if it is anticipated that complete resection of macroscopic disease can be achieved with a reasonable morbidity profile. (125-131).

Indeed, radiotherapy has become the treatment of choice in previously non-irradiated patients with isolated vaginal recurrence or locoregional recurrence. (132,133)

However, in patients who have previously received external beam radiation therapy or brachytherapy, radical surgery with the intention of complete resection with clear margins should be considered in specialized centers after ruling out metastatic disease with modern imaging. And other option is pelvic

exenteration for central local relapse. (133,134) Otherwise, further radiation should be considered as radical therapy with or without systemic therapy.

Regarding systemic therapy, low-grade, slowly progressing, hormone receptor-positive tumors appear to gain the greatest benefit from hormonal treatment. However, clinical benefit has also been observed in patients with hormone receptor-negative tumors. (136) Hormonal treatment results in a response rate of up to 55% in advanced/recurrent endometrial carcinoma (137) and progestogens are generally recommended. (136) Alternative options include aromatases inhibitors, tamoxifen, and fulvestran

Rationale for this study

Many questions on sentinel node in endometrial carcinoma remain unanswered, however the technique is promising and is gaining more credibility.
One of the possible documented complications of treatment-related is the development of lymphedema of the lower extremities. For this reason, the development of techniques for the evaluation of lymph nodes is essential, without the need to over-treat patients. This is how sentinel node biopsy arises, which has been shown to be safe and feasible in various gynecological cancers such as vulvar cancer, cervical cancer, and endometrial cancer. (138-142).

The goal of the sentinel lymph node technique is to reduce the associated morbidity of a complete lymphadenectomy, particularly the rate of lymphedema, providing prognostic information related to the lymph node involvement. In fact,

not performing a lymphadenectomy in low and intermediate risk cases would mean underestimating a 10-15% of these patients. Moreover, they would be managed as FIGO stages I instead of stage III, receiving less adjuvant treatment. (55)

In addition, in terms of survival, there are two randomized studies that did not show any increase in overall survival when performing a systematic lymphadenectomy in this group of patients.

The first prospective trial studying the benefit of lymph node dissection in endometrial cancer was published in 2009. It is an international multicenter study ASTEC ("A Study about Treatment of Endometrial Cancer"), in which 1408 patients diagnosed with endometrial carcinoma were randomized to lymphadenectomy vs and they were followed for 3 years. After analyzing the data, they did not observe that lymphadenectomy provided therapeutic benefit in early-stage endometrial cancer (FIGO stage I and II) in terms of overall or disease-free survival. However, the study had many limitations and not everyone is willing to abandon the lymphatic evaluation, arguing the need to obtain the real staging to plan an optimal adjuvant treatment. (55)

In the second prospective trial about this topic, published in 2008, Benedetti et al. (143) randomized 514 patients for pelvic lymphadenectomy vs non-lymphadenectomy, diagnosed with stage I Endometrial carcinoma. At 5-year follow-up, no differences were observed in both groups, in terms of overall

survival and disease-free survival. However, in the lymphadenectomy group, 13% of the patients presented lymph node metastases, requiring specific adjuvant treatment. The authors concluded that lymphadenectomy did not provide any therapeutic benefits in stage I endometrial cancer patients, but it is needed to prescribe the adjuvant treatment due to high frequency of upstaging from stage I to IIIC1 in supposedly low-risk patients.

The sentinel lymph node mapping technique offers an intermediate solution to this conflict, allowing information on the patient's nodal status in a less invasive and safer way than lymphadenectomy. (144) However, there is a continuous debate on the site of injection and what type of tracer is the most suitable for performing the sentinel lymph node mapping technique in endometrial carcinoma.

On the other hand, due to the development of histopathological diagnostic techniques, the concept of low-volume disease appears, and its prognostic significance in terms of survival is still unclear. For its detection, ultrastaging and immunohistochemical techniques are necessary, much more laborious than the traditional techniques of cutting and staining with hematoxylin and eosin (H&E). (145) Since the use of such techniques is possible in a reduced number of nodes, the sentinel node concept becomes more interesting, increasing the detection rate of lymphatic metastases and decreasing the percentage of under-treated patients. Therefore, ultrastaging could be included in the endometrial cancer staging algorithm.

Finally, in patients with early stages endometrial carcinoma, it is important to weight the risk of recurrence as a consequence of not undergoing treatment or the risk of complications due to excessive treatment, which is also costly. The availability of molecular biology, as standardized and reliable prognostic markers, would make possible to stratify patients according to the risk of recurrence, giving a more personalized treatment.

Hypothesis and objectives

Hypothesis

Selective sentinel node biopsy is a valid and effective lymphatic assessment technique in cases of endometrial adenocarcinoma in early stages I and II, reflecting the true tumor status of the rest of the regional nodes and decreasing the rate of lymphedema.

Objectives

Objective 1 To summarize the experience reported in the literature regarding indocyanine green for sentinel lymph node biopsy in cervical and endometrial cancer.

Objective 2 To explore the clinical significance of micrometastases and isolated tumor cells in endometrial cancer and summarize the reported literature on the impact on post- operative management in patients with such findings.

Objective 3 To assess the prevalence of lymphedema among patients who underwent either sentinel lymph node mapping or lymphadenectomy during surgery for newly diagnosed endometrial cancer.

Objective 4 First, to determine the utilization and predictors of use of sentinel lymph node mapping and second, to examine whether the use of sentinel lymph node mapping was associated with changes in the prescription of adjuvant therapy for women with early-stage tumors.

Chapter 1

Role of Indocyanine Green in Sentinel Node Mapping in Gynecologic Cancer: Is Fluorescence Imaging the New Standard?

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Abstract

Sentinel lymph node biopsy has proven safe and feasible in a number of gynecologic cancers such as vulvar cancer, cervical cancer, and endometrial cancer. The proposed aim of lymphatic mapping and sentinel node identification is to decrease the associated morbidity of a complete lymphadenectomy, particularly the rate of lymphedema, while also increasing the detection of small tumor deposits in the node. Different tracers have been shown to be useful, including technetium-99 and blue dye, with a detection reported in 66% to 86%. Recently, there has been increasing interest in the use of fluorescent dies such as indocyanine green (ICG). In this report we provide a review of the existing literature regarding the use of ICG in cervical or endometrial cancer with the goal to provide details on its utility and compare it with other tracers.

Keywords: Indocyanine green; Laparoscopy; Lymphatic mapping; Robotics

Introduction

The concept of sentinel lymph node (SLN) biopsy was first introduced by Cabanas in 1977 in patients with penile cancer [1]. Sentinel node detection has proven feasible and safe in select cancers such as vulvar cancer, breast cancer, early gastric cancer, and melanoma [2,3]. In gynecologic cancers, the first report on SLN detection in patients with vulvar cancer was published by Levenback et al in 1994 [4]. Two prospective studies then confirmed the utility of sentinel node in vulvar cancer (Table 1). In the first, the GROINSS I study [5], the investigators concluded that the SLN procedure in the management of early-stage vulvar cancer performed by a quality-controlled multidisciplinary team resulted in decreased morbidity without compromising groin recurrence or survival rates. The second study, GOG-173 [6], evaluated SLN in 452 patients with squamous cell carcinoma. All women underwent intraoperative lymph node mapping, sentinel node biopsy, and inguinofemoral lymphadenectomy. A total of 418 patients had at least 1 SLN identified. There were 132 node-positive women, including 11 (8.3%) with false-negative nodes. The sensitivity was 91.7% and the false-negative predictive value 3.7%. In women with tumor less than 4 cm, the false- negative predictive value was 2.0% (90% upper confidence bound, 4.5%). The authors concluded that SLN biopsy was a reasonable alternative to inguinal femoral lymphadenectomy in selected patients with squamous cell carcinoma of the vulva.

In cervical cancer, 2 prospective trials have demonstrated the safety and feasibility of SLN mapping (Table 2). The AGO Study Group trial [7] evaluated the detection rate of SLN. The detection rate of pelvic SLN was significantly higher for the combination of technetium-99 and patent blue (93.5%; 95% confidence interval, 90.3–96.0%).

Unfortunately, the overall sensitivity of the procedure was only 77%. However, when limiting the procedure to tumors, 2 cm in size, the sensitivity was 91%. The second trial, the SENTICOL I study by Lécuru et al [8], evaluated the sensitivity and negative predictive value (NPV) of SLN. Of the 139 patients involved, intraoperative radioisotope blue dye mapping detected at least 1 SLN in 136 patients, 23 of whom had true-positive results (sensitivity 92%; 95% confidence interval, 74–99%) and 2 had false- negative results. No false-negative results were observed in the 104 patients (76.5%) in whom SLN were identified bilaterally. The authors concluded that combined labeling for node mapping was associated with high rates of SLN detection and with high sensitivity and NPV for metastases detection. However, SLN biopsy was fully reliable only when SLNs were detected bilaterally. A recently completed trial, SENTICOL II [9], will hopefully shed light on whether sentinel node alone is safe and feasible in patients with early-stage cervical cancer.

The feasibility of lymphatic mapping in endometrial cancer was first introduced in 1996 by Burke and colleagues [10]. In that study, the authors evaluated SLN mapping by injecting isosulfan blue (ISB) into the subserosal myometrium, with a detection rate of 67%. In 2011, the SENTI-ENDO [11] study published the results of a prospective trial evaluating the accuracy of the SLN procedure in patients with early-stage endometrial cancer using cervical dual injection of technetium-99 and patent blue. Their overall detection rate was 89%, concluding that SLN biopsy alone can accurately diagnose lymph node involvement in patients with low-risk or intermediate-risk endometrial cancer.

There has been recent increasing interest in the use of the fluorescent dye, indocyanine green (ICG). Briefly, ICG is a tricarbocyanine dye that fluoresces in the

near-infrared (NIR) spectrum when illuminated with 806 nm light. The fluorescent light is then captured using a special video cam- era device that enables the ICG to be displayed in the visible light spectrum. ICG is highly water-soluble and rapidly binds to albumin and therefore has a propensity for lymphatic tissue [12]. ICG may be used for SLN detection in the setting of open, laparoscopic, or robotic surgery.

In 2005 Kitai et al [13] investigated the use of ICG for SLN mapping in breast cancer and were the first to propose that the use of ICG could improve both detection rate and NPV of SNL detection. This technique has proven feasible both in breast and skin cancer patients, with comparable or slightly better detection rates than conventional techniques like technetium-99 [14,15]. The aim of this current article is to summarize the experience reported in the literature regarding ICG for SLN biopsy in cervical or endometrial cancer.

Methods

We searched in Medline, PubMed, and BioMed Central for all English-language literature using the terms "'indocyanine green," "cervical cancer," "endometrial cancer," and "sentinel lymph node" between 1994 and 2014. We included all publications reporting SLN mapping per- formed by open or robotic surgery. We included all reviews, retrospectives or prospective studies, and case reports published on the use of ICG. Two authors (MCD and NRGH) independently reviewed the titles and abstracts of publications searched and excluded all unrelated articles. Publications that fulfilled selection criteria were included in the study. For each eligible study the following information was obtained: study design (randomized controlled trial, prospective trial, retrospective review), year of

publication, time period of study accrual, number of study subjects, type of cancer diagnosis, location of the injection of the ICG dye, SLN detection rate, and the false-negative rate.

Technique of ICG Mapping in Cervical or Endometrial Cancer

The technique used by our team for ICG SLN mapping is as follows: The cervix is prepped and the ICG is injected before laparotomy or insertion of the uterine manipulator (in minimally invasive cases). The concentration used is 1.25 mg/mL. For each patient a 25-mg vial with ICG powder is diluted in 20 mL of sterile water. We routinely inject 4 mL of the ICG solution into the cervix divided in the 3- and 9 o'clock positions, with 1-mL deep into the stroma and 1 mL submucosally on the right and the left of the cervix. This is performed before laparotomy, laparoscopy, or robotic surgery. Of note, ICG is not US Food and Drug Administration approved for interstitial injection and is currently only approved for intravenous use.

The appropriate dosing of ICG, has been previously ad- dressed in a study by Levinson et al [12], where the authors used 4 concentrations of ICG (1000, 500, 250, and 175 microg/.5 mL). The investigators concluded that an ICG dose of 250 to 500 mg enables identification of a SLN with more distinction from the surrounding tissues.

Table 1

Studies of sentinel lymph node detection in vulvar cancer

Clinical Trial	Eligible Patients	No. of patient's	Primary endpoint
GROINSS I	• Squamous cell carcinoma • T1 or T2 lesions • ¸4 cm in size • Depth of invasion. 1 mm • Clinically nonsuspicious lymph nodes	403	Groin recurrence
GOG 173	• Squamous cell carcinoma • Limited to the vulva • -2 to ¸6 cm in size • Depth of invasion R 1 mm • Clinically nonsuspicious lymph nodes	452	Negative predictive value

Table 2

Studies of sentinel lymph node detection in cervical cancer

Clinical Trial	Eligible patients	No. of patients	Labeling substance	Detection rate (%)	Sensitivity (%)
AGO study group	• Invasive cervical cancer all stages • With intention of surgical staging	507	Technetium–99 (45) Patent blue (159) Combined (303)	81.8 82 93.5	71.4 72.7 80.3
SENTICOL I	• Early-stage cervical cancer (IA1–IB1)	139	Technetium–99 and patent blue		95

Results

Use of ICG in Cervical or Endometrial Cancer

The first study describing the role of ICG in patients with a gynecologic cancer was published in 2010 by Furukawa et al [16] (Table 3). Twelve patients with early-stage cervical cancer underwent lymphatic mapping after injection of .2 mL of 5 mg/mL of ICG in 4 sites of the cervix. SLNs were identified in 10 patients (83%), and all were identified bilaterally. The median number of SLNs was 7 (range, 3–10). Lymph node metastases were found in 2 patients, and all were found in the SLNs. There were no false-negative lymph nodes. The site of the SLN was the right external iliac

node in 8 patients, the right obturator node in 8 patients, the left external iliac node in 9 patients, and the left obturator in 8 patients. There were no adverse events noted with ICG. This was an important study because it was the first to use ICG in gynecologic cancer patients, and ICG was found to have a similar rate of detection as blue dye and radioisotope, when comparing it with previous reports, and to be easier to use.

In 2011, Van der Vorst et al [17] also described the technique of mapping with NIR fluorescence imaging in early- stage cervical cancer patients. A total of 1.6 mL of ICG was injected in 4 sites of the cervix. SLNs were identified in all 9 patients and bilateral SLNs were identified in 8 of 9 patients with a total of 31 SLN's. All SLNs were pelvic no- des. After histologic confirmation, 3 positive SLNs were found in 2 patients. No false-negative SLNs were identified. This study was also relevant because it evaluated different doses of ICG concentration (500, 750, and 1000 mm) to determine what was the optimal dose.

That same year, Crane et al [18] published the first study in gynecology to evaluate the applicability of NIR imaging with ICG for the detection of the SLN in cervical cancer, using it in a combination with patent blue. In that study a mixture of patent blue and ICG was injected into the cervix of 10 patients. A total of 9 SLNs (90%) were detected in 6 patients, of which 1 (11%) contained metastases. All SLNs were pelvic nodes. Bilateral SLNs were detected in 3 of 6 patients (50%). Ex vivo fluorescence imaging revealed the remaining fluorescent signal in 11 of 197 non-SNLs (5%), of which 1 contained metastatic tumor. None of the nonfluorescent lymph nodes contained metastases. The authors concluded that lymphatic mapping and detection of the SLN in cervical cancer using

intraoperative NIR imaging is technically feasible. This study was also particularly useful because it showed that detection rates in tumors smaller than 2 cm were 80% in comparison with only 40% in patients with tumors >2 cm. They also showed that the ability to detect bilateral sentinel nodes was limited by tumor size. In addition, the study also showed that the penetration depth of ICG does not exceed 1 cm.

Up to this point all the published studies were in the setting of open surgery. The first study to evaluate the use of ICG in patients with endometrial cancer and in the setting of minimally invasive surgery was Rossi et al [19]. A total of .5 mg ICG was injected into the cervical stroma at the 3 o'clock and 9 o'clock positions. At least 1 SLN was identified in 17 patients (85%) with a median of 4.5 nodes identified per patient (range, 0–9). The median number of non-SLNs removed in each patient was 23.5 (range, 4–56). Bilateral SLNs were identified in 12 patients (60%) with no false-negative nodes. SLNs were not detected in 3 patients. Three patients had node-positive disease. Later, Holloway et al [20] aimed to compare the ability of ICG and standard colorimetric analysis of ISB dye for the detection of SLN in endometrial cancer. A total of 1 mL of ISB was injected in cervix, followed by .5 mL ICG immediately before placement of a uterine manipulator. Twenty-seven (77%) and 34 (97%) patients had bilateral pelvic or aortic SLN detected by colorimetric and fluorescence, respectively (p=0.03). Using both methods, bilateral detection was 100%. Ten patients (28.6%) had lymph node metastasis, and 9 of these had SLN metastasis (90% sensitivity, 1 false- negative SLN biopsy). Seven of 9 (78%) SLN metastases were ISB positive and 100% were ICG positive. Twenty- five patients had negative SLN biopsies (100% specificity).

In 2013 Rossi et al [21] compared the detection rates be- tween cervical and endometrial injection and patterns of nodal distribution. Seventeen patients underwent a cervical injection of 1 mg ICG, and 12 patients received hysteroscopic endometrial injections of .5 mg ICG. The SLN detection rate was 82% (14/17) for the cervical injection group and 33% (4/12) for the hysteroscopic injection group ($p<.027$). SLNs were seen bilaterally in 57% (8/14) of the cervical injection group and 50% (2/4) of the hysteroscopic group (nonsignificant). There was 1 false-negative SLN in the cervical injection group; no false negative was identified in the endometrial injection group. There was a significant improvement in detection rate with cervical injection (82% vs 33%) with similar rates of bilateral nodes identified (57% vs 50 %). No difference in the anatomic distribution of SLNs was seen for the 2 injection sites. This was also an important study because the authors showed that cervical injection of ICG allowed for excellent detection of para- aortic nodes in up to 71% of cases, including 3 cases above the inferior mesenteric artery.

The most recent and largest study to date using the robotic platform is the study published by Jewell et al in 2014 [22]. This retrospective study aimed to assess the detection rate of SLNs using ICG and NIR fluorescence imaging. In that study, 1.25 mg ICG was injected into the cervix of 227 patients. Blue dye was concurrently injected in 30 cases. The median SLN count was 3 (range, 1–23). The overall detection rate of the SLN (unilateral or bilateral) for this cohort of patients was 95% (216/227). When ICG was used alone, 95% of patients (188/197) mapped either unilateral or bilaterally compared with 93% (28/30) in cases in which both dyes were used (nonsignificant). The bilateral detection rate

was 79% (179/227) overall. The bilateral SLN detection rate for ICG alone was 79% (156/197) compared with 77% (23/30) for ICG and blue dye (nonsignificant). In that study the authors also showed that 10% of patients had SLNs identified in the aortic region. The study concluded that intracervical injection of ICG has a high bilateral detection rate and appears to offer an advantage over using blue dye alone. The authors stated that combined use of ICG and blue dye appeared to be unnecessary.

In 2014, Sinno et al [23] compared the ability to detect SLNs in women with endometrial cancer or complex atypical hyperplasia using ICG versus ISB. They observed that ICG mapped bilaterally in 78.9% and 42.4% with ISB (p 5 .02), concluding that ICG may be superior to colorimetric imaging. This study also provided important information regarding the impact of body mass index (BMI) on patients undergoing mapping with ICG. The authors found that increasing BMI was negatively associated with successful mapping only in the blue dye group but not in the ICG group. Recently, Plante et al [24] published the first reported experience about the use of ICG with NIR in endometrial and cervical cancer using the Pinpoint endoscopic system. Their overall detection rate was 96% and bilateral, 88%. Sensitivity, specificity, and NPV were 93.3%, 100%, and 98.7%, respectively, per side. The authors concluded that NIR imaging with ICG is an excellent, simple, and safe tracer modality for SLN mapping that should be the agent of choice if SLN mapping ever becomes standard of care.

Finally, a recent abstract was presented at the Annual Meeting of the Society of Gynecologic Oncology in 2015 [25]. The study presented 472 patients with uterine cancer undergoing SLN mapping using either ICG or blue dye. ICG was

used in 312 patients (66%) and blue dye in 160 (32%). Successful mapping occurred in 425 patients (90%). Mapping was bilateral in 352 patients (75%), unilateral in 73 patients (15%), and in 47 patients (10%) the investigators were not able to detect the SLN. Successful mapping occurred in 295 patients (95%) in which ICG was used compared with 130 patients (81%) in which blue dye was used (p <.001). Additional lymph node dissection beyond removal of SLNs occurred in 122 patients (39%) with ICG versus 98 patients (61%) with blue dye (p <.001). Regarding the anatomic distribution of SLNs, 490 of 1374 SLNs (36%) were located in the hypogastric basin, 453 (33%) in the external iliac basin, 313 (23%) in the obturator basin, 83 (6%) in the common iliac basin, and 25 (2%) in the aortic basin. There were 25 paraaortic SLNs detected, and 23 (92%) of these were detected using ICG. These authors concluded that SLN detection rate is superior when using ICG rather than blue dye. Bilateral mapping is significantly improved using ICG, resulting in a lower rate of additional lymphadenectomy.

Discussion

Limitations of ICG

Although there are many suggested benefits of ICG over other tracers for performing SLN identification and lymphatic mapping, one must also recognize that there are certain potential limitations. Jewell et al [22] found that BMI appeared to impact the success rate of SLN mapping. In their report, the median BMI of patients in whom an SLN was detected was 30.1 kg/m^2 (range, 17.7–59.6) compared with 41.2 kg/m^2 (range, 25.1–60.4) for patients who did not map (p =.01). Median BMI appeared to impact bilateral mapping, with the median BMI of unilaterally and bilaterally mapped cases being 34 kg/m^2 (range, 17.9–49) and 29.6 kg/m^2 (range, 17.7–59.6), respectively (p= .02). Tanner et al [26] evaluated patient, tumor, and surgeon fac- tors associated with successful bilateral mapping in patients with endometrial cancer using ISB or ICG. In that study the authors found that the rate of successful bilateral mapping decreased with a BMI R 30 kg/m^2 and that although the rate of success with ICG is superior to ISB, the variability is more pronounced at higher BMIs.

Another subject of particular interest with any tracer is that such dyes can be associated with an allergic reaction. Patients with iodine allergy should not be exposed to ICG because it contains 5% sodium iodide [19]. The risk of an allergic reaction to ICG has been estimated at 1 per 42,000 uses [27]. In addition, it is not recommended that patients with liver compromise be exposed to ICG because it is metabolized in the liver.

Areas for Further Research

One of the areas of active debate for all cases of SLN identification in endometrial cancer is the issue pertaining to the ideal site of injection for the tracer. Abu Rustum et al [28] described 3 different sites for SLN mapping for cervical and uterine malignancies for the already known dyes, not specifically ICG: uterine subserosal, cervix, or endometrium via hysteroscopy. These authors concluded that the preferred strategy was cervical injection. They argued that because the main lymphatic drainage of the uterus is from the parametria, a combined superficial (1–3 mm) and deep (1–2 cm) cervical injection is adequate. Moreover, it is easily accessible and rarely distorted by uterine anatomy variations such as myomas that make serosal mapping more difficult. Uterine fundal serosa mapping does not reflect the parametrial lymphatic drainage.

Only 2 articles have addressed location of injection in the setting of ICG use. The first was reported by Rossi et al [21], who evaluated the rate of SLN identification be- tween cervical and hysteroscopic injection of ICG. The authors supported the use of cervical injections because there was a significant improvement in detection rate with cervical injection (82% vs 33%) with similar rates of bilaterally identified nodes (57% vs 50%). No difference in the anatomic distribution of SLNs was seen for the 2 injection sites.

The second article was by Ditto et al [29], who presented a case managed by hysteroscopic injection of ICG and laparoscopic NIR fluorescence imaging in endometrial cancer staging. Sentinel node mapping was performed using a hysteroscopic injection of ICG followed by laparoscopic sentinel node detection via NIR fluorescence. A right-side obturator sentinel node was detected and

removed. No sentinel node was detected on the left side. The authors suggested that although there is growing evidence that cervical injection is effective in detecting lymphatic drainage of the uterus, hysteroscopy allows for injection in the proximity of the lesion.

Ongoing Trials

Currently, there are 2 ongoing trials evaluating SLN map- ping using ICG, among other tracers, in patients with endometrial cancer by the group at MD Anderson Cancer Center. The first study is evaluating the prediction of recurrence among low-risk endometrial cancer population. The primary objective of this trial is to validate the use of a molecular panel of estrogen-induced genes to predict recurrence in low-risk endometrial cancer. A secondary objective is to calculate the positive predictive value and NPV, sensitivity, and specificity of lymph node mapping to predict pelvic node involvement. The inclusion criteria for this study are histologically confirmed low-grade (1–2) endometrioid type adenocarcinoma and no evidence of deep invasion or peritoneal disease in preoperative imaging. All patients undergo hysterectomy and SLN mapping. Bilateral salpingo-oophorectomy may be performed based on discretion of the primary gynecologic oncologist and performance of pelvic and para-aortic lymphadenectomy are based on intraoperative findings and frozen section pathology. Intraoperative lymphatic mapping is performed with blue dye, radioactive colloid, or ICG by an injection in the cervix. The expected number of patients to accrue on this trial is 500.

The second trial is a prospective evaluation of lymph node metastasis in patients

with high-risk endometrial cancer. The inclusion criteria for this trial are as follows: histologically confirmed high grade endometrial cancer, including grade 3 endometrioid, serous, clear cell, mixed malignant mullerian tumors, or any mixed tumor containing 1 of these cell types; grade 1/2 and evidence of deep myometrial invasion or cervical involvement; and patient must be a candidate for surgery, have no evidence of peritoneal dis- ease, and have no preoperative treatment for endometrial cancer including radiation or chemotherapy. The primary objective is to estimate the false-negative rate of positron emission tomography/computed tomography and/or SLN mapping in the detection of positive lymph nodes in women with high-risk endometrial cancers. The secondary objective is to estimate the sensitivity, specificity, positive predictive value, and NPV of positron emission tomography/computed tomography and/or SLN mapping. Intraoperative lymphatic mapping is also performed with blue dye, radioactive colloid, and/or ICG. The estimated number of patient accrual is 100. The following is a list of other ongoing trials and their primary objectives using ICG in the detection of SLNs: Determining the sensitivity of SLNs identified with robotic fluorescence imaging (Indiana University, IN).

To estimate the sensitivity of the SLN in the determination of lymph node metastases in patients with invasive carcinoma of the cervix and uterus using ICG and robotic- assisted NIR imaging. Detection of SLNs in patients with endometrial cancer undergoing robotic-assisted staging: a comparison of ISB and ICG dyes with fluorescence imaging (Ohio State University, Columbus, OH).

The primary objective of this trial is to estimate the NPV of pelvic SLN in endometrial cancer to predict nodal metastasis. The feasibility and benefits of

using ICG and NIR fluorescence imaging to detect SLNs in patients with endometrial cancer (Lahey Hospital & Medical Center, Burlington, MA). To determine whether SLNs are accurately visualized using ICG and NIR imaging. Study of instillation technique using the modified intra- uterine manipulator catheter with methylene blue, ISB, or ICG dyes compared with cervical injection for SLN detection in endometrial carcinoma (Southeastern Regional Medical Center, Newnan, GA). The primary outcome of this study is an evaluation of the number of sentinel nodes detected by each method. Lymph node mapping in patients with newly diagnosed endometrial cancer undergoing surgery (Cleveland Clinic Case Comprehensive Cancer Center, Cleveland, OH). The primary objectives of this trial are to determine sensitivity of SLN biopsy, detection rate, and false-negative rate in patients undergoing lymphatic mapping. Accuracy of SLN biopsy in nodal staging of high-risk endometrial cancer (EndoSLN) (University Health Network, Toronto, CA). The primary objective is to evaluate the sensitivity, specificity, and predictive accuracy of mapping and detection of SLNs with metastatic disease. The Kelly Gynecologic Oncology Service Endometrial Cancer SLN Study (Johns Hopkins, Baltimore, MD). The primary objective is to determine the utility of per- forming SLN evaluation in women with apparent early-stage (grades 1–2) endometrioid tumors compared with grade 3 (type II) tumors.

Conclusion

ICG offers a novel tool to identify SLNs and can be used in real time, avoiding radioactivity, and demonstrating superior rates for identifying unilateral and bilateral SLN, even in obese patients. SLN mapping using ICG does not add significant time in the operating room. Although the most common site for SLN detection is the pelvic region, ICG has the potential to identify SLN in areas that are unlikely to be explored using the traditional approach to lymphadenectomy. Further studies evaluating the cost-effectiveness of ICG in comparison with other tracers is warranted.

Table 3

Studies of SLN mapping with ICG

Source, year	Cancer type	Stage	Surgery	No. of patients	Technique	Injection site	Detection rate (%)	Location of SLN
Furukawa et al (2010)	Cervical	IA1 (1) IB1 (5) IIA (1) IIB (5)	Radical hysterectomy and lymphadenectomy by laparomy	12	ICG	Cervical	83	Right external iliac (9) Left external iliac (9) Right obturator (8) Left obturator (8)
Van der Vorst et al (2011)	Cervical	IB1	Radical trachelectomy or radical hysterectomy by laparotomy	9	ICG	Cervical	100	Right external iliac (6) Left external iliac (8) Right common iliac (4) Left common iliac (5) Right obturator (4) Left obturator (2) Parametria (2)
Crane et al (2011)	Cervical	IA1-IIA	Radical hysterectomy and pelvic lymphadenectomy by laparotomy	10	ICG/ISB	Cervical	ICG 97 ISB 77	Right external iliac (2) Left external iliac (2) Right obturator (1) Left obturator (3) Right common iliac (1)
Rossi et al (2012)	Cervical (4) Endometrial (16)	I	Robotic-assisted bilateral pelvic and para-aortic lymphadenectomy in endometrial cancer	20	ICG	Cervical	85	Para-aortic (65%) Pelvic (85%)
Holloway et al (2012)	Endometrial	Low risk (9) High risk (26)	Robotic-assisted lymphadenectomy and hysterectomy	35	ICG/ISB	Cervical	ICG 97 ISB 77	Pelvic (22.5 ± 10.9) Aortic (10.3 ± 6.6)
Rossi et al (2013)	Endometrial	I	Robotic-assisted lymphadenectomy and hysterectomy	17 12	ICG	Cervical Hysteroscopic	82 33	Pelvic (17.5 vs 17.3, NS) Para-aortic (10.3 vs 10.6, NS)
Jewell et al (2014)	Cervical (89) Endometrial (138)			227	ICG/ISB	Cervical	ICG 95 ICG/ISB 93	Right external iliac (15.7%) Left external iliac (19.1%) Right obturator (10.9%) Left obturator (10.7%) Right common iliac (5.4%) Left common iliac (2.9%) Para-aortic (10%) Presacral (.004%)
Sinno et al (2014)	Endometrial	I (53) II (3) III (7) IV (1) Complex hyperplasia (7)	Robotic-assisted SLN mapping and hysterectomy	71	ICG/ISB	Cervical	ICG 78.9 ISB 42.4	Hypogastric (76.8%) External iliac (14.2%) Common iliac (4.5%) Para-aortic (4.5%)
Plante et al (2015)	Cervical (8) Endometrial (42)	IA2/IB1 I	Robotic/laparoscopic lymphadenectomy	50	ICG	Cervical	96	External iliac (71.3%) Obturator (17.8%) Common iliac (5.7%) Para-aortic (3.2%) Presacral (1.3%) Parametrial .6%
Ditto et al (2014)	Endometrial	II		1	ICG	Hysteroscopic	100	Right obturator (1)

ICG = indocyanine green; ISB = isosulfan blue; NS = nonsignificant; SNL = sentinel lymph node.

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Chapter 2

Oncologic Impact of Micrometastases or Isolated Tumor Cells in Sentinel Lymph Nodes of Patients with Endometrial Cancer: A Meta-Analysis

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Abstract

Purpose There is a gap in knowledge regarding the impact of micrometastases (MIC) and isolated tumor cells (ITCs) found in the sentinel lymph nodes of patients with endometrial cancer. Here, we present a meta-analysis of the published literature on the rate of MIC and ITCs after lymphatic mapping and determine trends in postoperative management.

Methods Literature search of Medline and PubMed was done using the terms: micrometastases, isolated tumor cells, endometrial cancer, and sentinel lymph node. Inclusion criteria were English-language manuscripts, retrospectives, or prospective studies published between January 1999 and June 2019. We removed manuscripts on sentinel node mapping that did not specify information on micrometastases or isolated tumor cells, non-English-language articles, no data about oncologic outcomes, and articles limited to ten cases or less.

Results A total of 45 manuscripts were reviewed, and 8 studies met inclusion criteria. We found that the total number of patients with MIC/ITCs was 286 (187 and 99, respectively). The 72% of patients detected with MIC/ITCs in sentinel nodes received adjuvant therapies. The MIC/ITCs group has a higher relative risk of recurrence of 1.34 (1.07, 1.67) than the negative group, even if the adjuvant therapy was given.

Conclusion We noted that there is an increased relative risk of recurrence in patients with low-volume metastases, even after receiving adjuvant therapy. Whether adjuvant therapy is indicated remains a topic of debate because there are other uterine factors implicated in the prognosis. Multi-institutional tumor registries may help shed light on this important question.

Keywords: Micrometastases, Isolated tumor cells, Endometrial cancer, Sentinel lymph node.

Introduction

Endometrial carcinoma is the most common gynecologic cancer in developed countries. In 2019, an estimated 61,880 new cases and 12,160 deaths from uterine cancer were diagnosed in the USA [1]. The standard management of patients diagnosed with endometrial cancer has changed in the last few years, the current recommendation is total hysterectomy and bilateral salpingo-oophorectomy along with sentinel lymph node mapping alone, to avoid full lymphadenectomy. Sentinel nodes are considered positive for disease if they contain macrometastases (MAC > 2 mm), micrometastases (MIC 0.2–2 mm), or isolated tumor cells (ITC ≤ 0.2 mm) [2, 3]. The relationship between MIC or ITCs and increased risk of recurrence, as well as prognosis, has been demonstrated in a number of cancers such as breast cancer [4, 5], vulva cancer [6–8], gastric cancer [9], esophageal cancer [10], colon cancer [11, 12], prostate cancer [13], and cervical cancer [14, 15].

In endometrial carcinoma, the clinical impact of low- volume metastasis remains unknown. Cibula et al. [16] published a study on the impact of MIC and ITCs in the sentinel lymph nodes (SLNs) and non-SLNs of cervical cancer patients. The patients selected for that study (17 patients in total) had cervical cancer and were at high risk of lymph node (LN) positivity (stage IB–IIA, biggest diameter ≥ 3 cm). A total of 573 pelvic LNs were examined through ultrastaging protocol (5762 slides). Meta- static involvement was detected in SLNs of eight patients (1 × MAC; 4 × MIC; 3 × ITCs) and in non-SLNs in two patients (2 × MIC). The authors found that using pathologic ultrastaging, there were no false-negative cases of positive non-SLN (MAC or MIC) and negative SLN. The presence of MAC and MIC was associated

with a decrease in overall survival, but no difference in survival was found between patients with negative LN and ITCs.

It is hypothesized that MIC represents a truly small meta- static involvement, while ITC can be a different entity with a limited potential for the development of distant disease spread. Furthermore, there is a gap in knowledge regarding the prognosis impact and the ideal management of patients with endometrial cancer who have MIC or ITCs in the sentinel lymph nodes. The aim of this review is to explore the clinical significance of MIC or ITC in endometrial cancer and summarize the reported literature on the impact on post- operative management in patients with such findings.

Methods

Search strategy and selection criteria

Keywords including “micrometastases”, “isolated tumor cells”, “endometrial cancer”, and “sentinel lymph node” were used for literature searches in MEDLINE and PubMed. The search spanned from January 1999 to June 2019 and included all articles that contained information regarding “endometrial cancer” and “micrometastases and isolated tumor cells” in the titles and abstracts.

Articles had to meet the following inclusion criteria: English-language manuscripts limited to endometrial cancer, patients who had micrometastases and/or isolated tumor cells in the sentinel lymph nodes, studies that report oncologic outcomes, articles including ≥ 10 patients, patients who underwent open, laparoscopic or robotic surgery, and studies that did not present duplicated data. We included all

retrospective and prospective studies. Two authors (NRGH and BN) reviewed the titles and abstracts of publications and excluded all unrelated articles (Fig. 1).

We collected information on study design, year of publication, time of study accrual, number of patients included, median age of patients, histological type, myometrial invasion (MI), lymphovascular invasion (LVI), grade, MIC/ITCs detection rate, and technique of detection (Table 1). We report the articles that compared the recurrences among patients with micrometastases, isolated tumor cells, and negative patients and studies that pro- vided information on adjuvant therapy (Table 2).

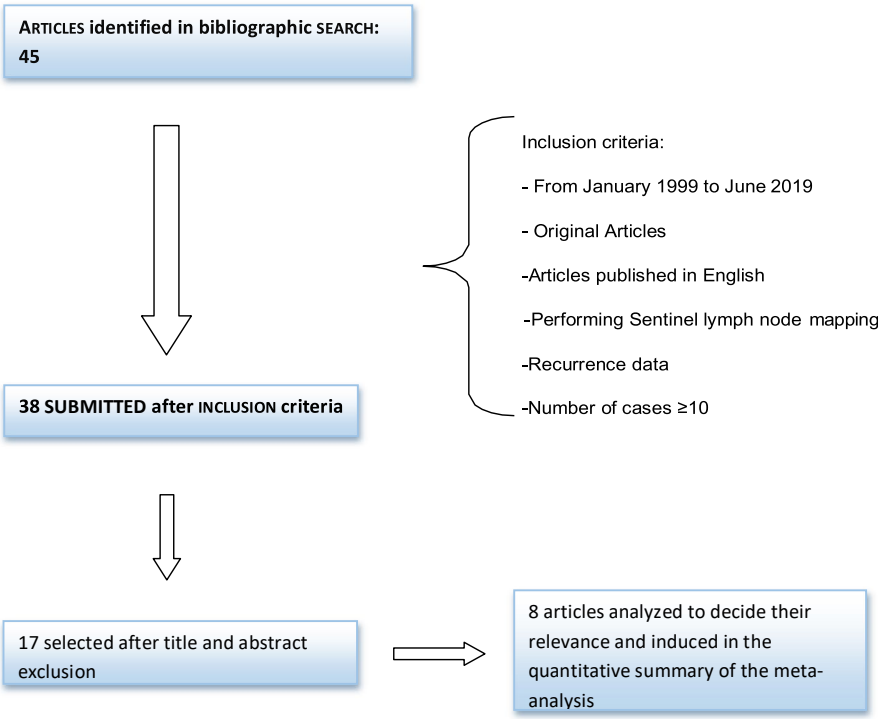


Fig. 1 Flowchart of studies retrieved and finally included in the meta-analysis

Statistical analysis

From each study, several cases and recurrences for each group of patients were extracted to calculate recurrence incidence. Relative risk and 95% confidence interval were calculated for each group number of cases. A random-effects meta-analysis was carried out for each comparison. Using the data, we created tables and forest plot was drawn. For each comparison, combined relative risk, given more weight for those studies with more cases, was calculated using DerSimonian–Laird random-effects mode, which accounts for both intra- and inter-study variability. All analyses were carried out with Stata 15.1

Results

We collected a total of 45 manuscripts, and 8 studies met our inclusion criteria (Fig. 1). Study characteristics are shown in Table 1. Studies totaled 2873 patients (range 41–508) among patients with MAC, negative lymph nodes, and MIC or ITCs. The median age was 62 years (range 54–69). Most of the patients (88%) reported an endometrioid histology on the final pathology, but 61% of total patients had more than 50% of myometrial invasion, 19% presented positive lymphovascular invasion, and Grade 3 was reported in the 20% of total patients. The median detection rate for MIC/ITCs was 17% (range 3–56). The ultrastaging technique was used in all the included studies. Among all the studies which report data about onco- logic outcomes, the total number of negative patients for MIC and ITCs was 2415, and the total number of patients with MIC/ITCs was 286 (187 and 99, respectively) (Table 2).

A total of 284 negative patients and 28 patients with either MIC or ITCs recurred. Table 3 shows the relative risk of recurrence between negative and MIC/ITCs patients.

Considering only studies with clear data about the administration of adjuvant therapy (Tables 4 and 5), in the MIC/ ITCs patients who did not receive adjuvant therapy, com- pared to negative patients and to MIC/ITCs patients who did receive adjuvant therapy, the relative risk of recurrence was similar in both groups not depending on adjuvant therapy.

Discussion

Our findings suggest that there is a higher relative risk of recurrence in patients with low-volume metastases, even after receiving adjuvant therapy.

As previously noted, the incidence of MIC can differ according to the histological and biological technique used. Several studies proved that CK 20 is more sensitive than traditional histopathologic method with H&E (sensitivity was 94.5 and 91%, respectively) [17, 18]. Table 1 shows different ultrastaging techniques used in all the studies. Moreover, the SLN mapping with pathologic ultrastaging identified MIC or ITCs in 4.5% patients with endometrial cancer in whom no metastatic disease would have otherwise been detected by conventional pathologic processing [19, 20].

In terms of oncologic outcomes, the findings of low- volume metastases might have a negative impact on prognosis. Erlanki et al. [21] found that 2/7 (28%) of patients with micrometastases recurred and died of disease: both were of high

risk—one had no adjuvant therapy, and the other one had both chemotherapy and radiotherapy. They reported a 36-month recurrence-free survival of 100% in patients who did not have micrometastases. Furthermore, Clair et al. [22] described a recurrence-free survival (RFS) of 86% for both MIC and ITCs patients. They observed that adjuvant therapy improves the survival rates in patients with low-volume metastasis compared to patients with macrometastasis. On the other hand, Todo et al. [23] reported that 28.6% of patients with ITC or MIC who received adjuvant therapy recurred ($p = 0.17$). Moreover, they found a higher rate of deep myometrial invasion in the ITCs or MIC patients than in node-negative patients ($p = 0.028$). However, this study presents some limitations: most of the patients had an early-stage carcinoma, received adjuvant therapy, or were patients with high-risk factors. In fact, histological grade, stage, and high-risk status are all important prognostic factors predicting disease recurrence. In addition, although we found that the 88% of the patients had an endometrioid histology on the final pathology, 61% of patients had more than 50% of myometrial invasion and 19% presented positive lympho- vascular invasion.

Interestingly, Plante et al. [24] published a study on ITCs in patients with endometrial cancer, including 519 patients with a median follow-up of 29 months (range 0–67), and the progression-free survival (PFS) at 3 years for the ITC patients was 95.5%, like node- negative (87.6%) and micrometastasis patients (85.5%), but statistically better than patients with macrometastasis (58.5%) ($p = 0.0012$). Moreover, the latest prospective study to assess the association between treatment and recurrence-free survival in stage I–II endometrioid endometrial cancer patients with ITCs was published by Backes et al. [25]. They found that in a

total of 175 patients with ITCs, 49% had stage IA, 39% stage IB, and 12% stage II disease (all with ITCs). Fifty-one percent underwent SLN assessment only, and the remainder underwent SLN and lymphadenectomy. A total of 76 (43%) received either no adjuvant therapy or vaginal brachytherapy only; 21 (12%) had external beam radiation; and 78 (45%) received chemotherapy + / − radiation. Patients who received chemotherapy more often had tumors with deep myometrial invasion, LVI, and higher grade. Nine (5.1%) patients recurred: 5 distant, 3 retroperitoneal, and 1 vaginal. After controlling for stage, LVI, and grade, chemotherapy was not associated with recurrence (HR = 0.63, 95% CI 0.11–3.52, p= 0.39). They concluded that the risk of retroperitoneal and/or distant recurrence is low (4.6%) for patients with stage I–II endometrioid EC and ITCs in SLNs regardless of adjuvant treatment or observation. The preliminary data suggest that adjuvant therapy does not appear to affect RFS.

The most recent publication is a multicenter, retrospective registry-based study of 2392 patients with endometrial cancer with and without MIC [26]. Without adjuvant therapy, the disease-free survival in the cohort of patients with MIC was reduced as compared with disease-free survival in the node-negative cohort, even after adjustment for age at diagnosis, myometrial invasion, histological grade and type, and performance status.

Although most of the studies recommended that the presence of isolated tumor cells should not drive the need for adjuvant treatments, the 72% of MIC/ITCs patients received adjuvant therapies. We could conclude that the benefit by giving additional treatments to ITCs patients depends on the presence of other high-risk uterine factors.

However, we recognize several important limitations. First, the number of the studies is small, given to the analysis a small power to make any conclusion. Second, in some studies, there were ITCs patients who received adjuvant therapy (chemotherapy or radiation) because of high-risk uterine factors or more advanced disease, and probably the prognosis could change. Lastly, given the favorable prognosis of endometrial cancer, our study is underpowered to detect small differences in survival.

In summary, when considering the association of MIC and ITCs with recurrence, we noted that patients with low- volume metastases had an increase relative risk of recurrence compared to negative patients, even if the adjuvant therapy was given. Further studies are needed in order to determine whether adjuvant therapy is indicated for both MIC and ITCs or only for those patients with MIC and to elucidate the specifics uterine factors that could change the indication of adjuvant therapy.

Conclusion

The current data show a higher sensibility and specificity of ultrastaging technique to detect MIC and ITCs; however, when we find these low-volume metastases, the clinical implications on adjuvant therapy remain a controversy. Currently, whether adjuvant therapy (chemotherapy or radiation) should be recommended in patients, at least, with MIC in regional LNs remains a topic of debate. In the near future, with the growing incorporation of SLN mapping and the initiatives of multi-institutional tumor registries, more data will elucidate the true clinical impact of MIC and ITCs on prognosis.

Table 1 Baseline characteristics of the included studies in the meta-analysis

Authors	Design	Year	Study period	Number of patients	Median age	Endometrioid histology	Non endometrioid	MI	LVI	Grade 1	Grade 2	Grade 3	Total MIC/ITCs patients	MIC/ITC (%)	Technique
Kim et al. [19]	Prospective cohort	2013	2005–2011	425	58	415	10	None: 241; < 50%: 184	Yes: 58; no: 367	302	108	15	12 (9 ITCs) (3 MIC)	3	Ultrastaging (H&E + IHC: Anticytokeratin AE1/AE3)
Kim et al. [20]	Retrospective cohort	2013	2005–2011	508	61	413	Serous: 62; clear cell: 12; carcinosarcoma: 21	None: 242; < 50%: 198; ≥ 50%:68	Yes: 132; no: 376	261	116	131	23 (19 ITCs) (4 MIC)	5	Ultrastaging (H&E + IHC: Anticytokeratin AE1/AE3)
Erlanki et al. [21]	Retrospective cohort	2010	2003–2006	47	60	37	Adenosquamous: 7; serous papillary: 2; clear cell: 1	None: 9; < 50%: 19; > 50%: 19	Yes: 4; no: 40; no data: 3	15	21	8	7(MIC)	15	Ultrastaging (H&E + IHC: Standard ABC + Anticytokeratin AE1/AE3)
Clair et al. [22]	Retrospective cohort	2015	2005–2013	844	61	724	Serous: 104; clear cell: 16	None: 422; < 50%: 310; ≥ 50%:112	Yes: 201; no: 618; no data: 25	479	177	188	44 (23 ITCs) (21 MIC)	5	Ultrastaging (H&E + IHC: Anticytokeratin AE1/AE3)
Todo et al. [23]	Retrospective cohort	2016	1997–2014	61	57	52	9	< 50%: 29; ≥ 50%:32	Yes: 15; no: 46	28	7	17	9 (6 ITCs) (3 MIC)	15	Ultrastaging (H&E + IHC: AE1/AE3 monoclonal antibody staining using an automated immunostainer)
Plante et al. [24]	Prospective cohort	2017	2010–2015	519	64	448	Serous: 36; carcinosarcoma: 25; clear cell: 7; other: 3	None: 125; < 50%: 234; ≥ 50%:160	Yes: 142; no: 362; no data: 15	260	150	109	42 (31 ITCs) (11 MIC)	8	Ultrastaging (H&E + IHC: Cytokeratin AE1/AE3)
Piedimonte et al. [27]	Retrospective case–control	2018	2012–2018	41	64	41	0	> 50%:16	17	No data	No data	No data	23 (11 ITCs) (12 MIC)	56	Ultrastaging (H&E + IHC: Cytokeratin-based)
Ignatov et al. [26]	Prospective cohort	2019	2000–2017	428	69	399	26	> 50%: 152; < 50%: 240	No data	145	174	100	126 (MIC)	29	Ultrastaging
Summary	Meta-analysis			2873	62	2529				1490	753	568		17	

SLN sentinel lymph node, *MM* micrometastases, *ITCs* isolated tumor cells, *RT-PCR* reverse transcription polymerase chain reaction, *H&E* hematoxylin and eosin; *IHC* immunohistochemistry, *MI* myometrial invasion, *LVI* lymphovascular space invasion, *ABC* avidin–biotin–peroxidase complex

Table 2 Number of patients with adjuvant therapy and recurrences

	Total patients	Total negative patients			Total MIC/ITCs patients		
			Adjuvant therapy	No adjuvant therapy		Adjuvant therapy	No adjuvant therapy
Total patients							
Kim et al. [19]	425	400	94	306	12 (9 ITCs) (3 MIC)	9	3
Kim et al. [20]	413	355	No data	No data	23 (19 ITCs) (4 MIC)	No data	No data
Erlanki et al. [21]	47	40	12	28	7 (MIC)	5	2
Clair et al. [22]	844	753	No data	No data	44 (23 ITCs) (21 MIC)	40	4
Todo et al. [23]	61	52	34	18	9 (6 ITCs) (3 MIC)	2	1
Plante et al. [24]	519	434	No data	No data	42 (31 ITCs) (11 MIC)	39	3
Piedimonte et al. [27]	41	18	3	15	23 (11 ITCs) (12 MIC)	16	2
Ignatov et al. [26]	428	302	0	302	126 (MIC)	95	31
Summary	2778	2354	143	669	286	206	46
Recurrences							
Kim et al. [19]	11	8	3	5	3 (2 ITCs). (1 MIC)	2(ITCs)	1(MIC)
Kim et al. [20]	2	No data	No data	0	2 (ITCs)	2 (ITCs)	0
Erlanki et al. [21]	2	0	0	0	2 (MIC)	1(MIC)	1(MIC)
Clair et al. [22]	51	47	No data	No data	4 (2 ITCs) (2 MIC)	4 (2 ITCs) (2 MIC)	0
Todo et al. [23]	12	8	No data	0	4 (ITCs/MIC)*	2(ITCs/MIC)*	2(ITCs/MIC)*
Plante et al. [24]	1	0	No data	No data	1 (ITCs)	1 (ITCs)	0
Piedimonte et al. [27]	2	0	0	0	2	2 (MIC)	0
Ignatov et al. [26]	231	221	No data	No data	10 (MIC)	No data	No data
Summary	312	284	3	5	28	15	4

*There is no difference between MIC and ITCS reported in the study

Table 3 Comparative recurrences between negative patients and MIC/ITC patients

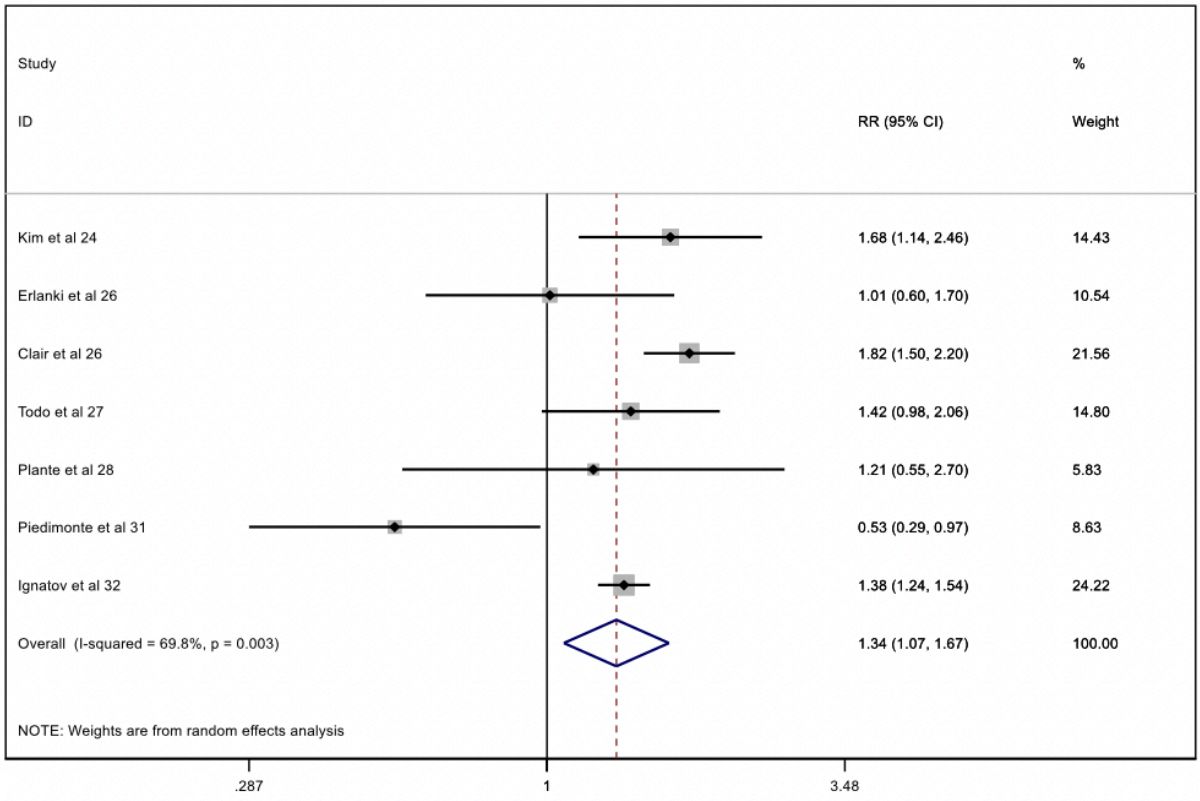


Table 4 Comparative recurrences between non-adjuvant negative patients and MIC/ITC non-adjuvant patients

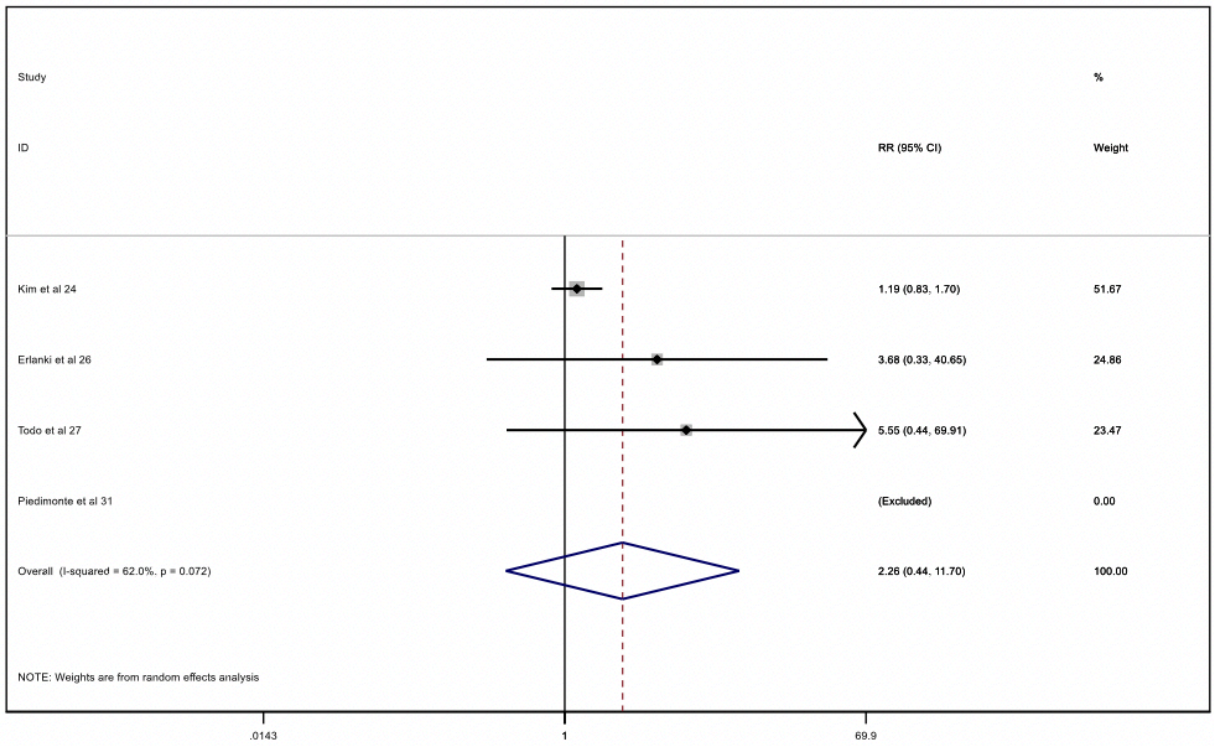
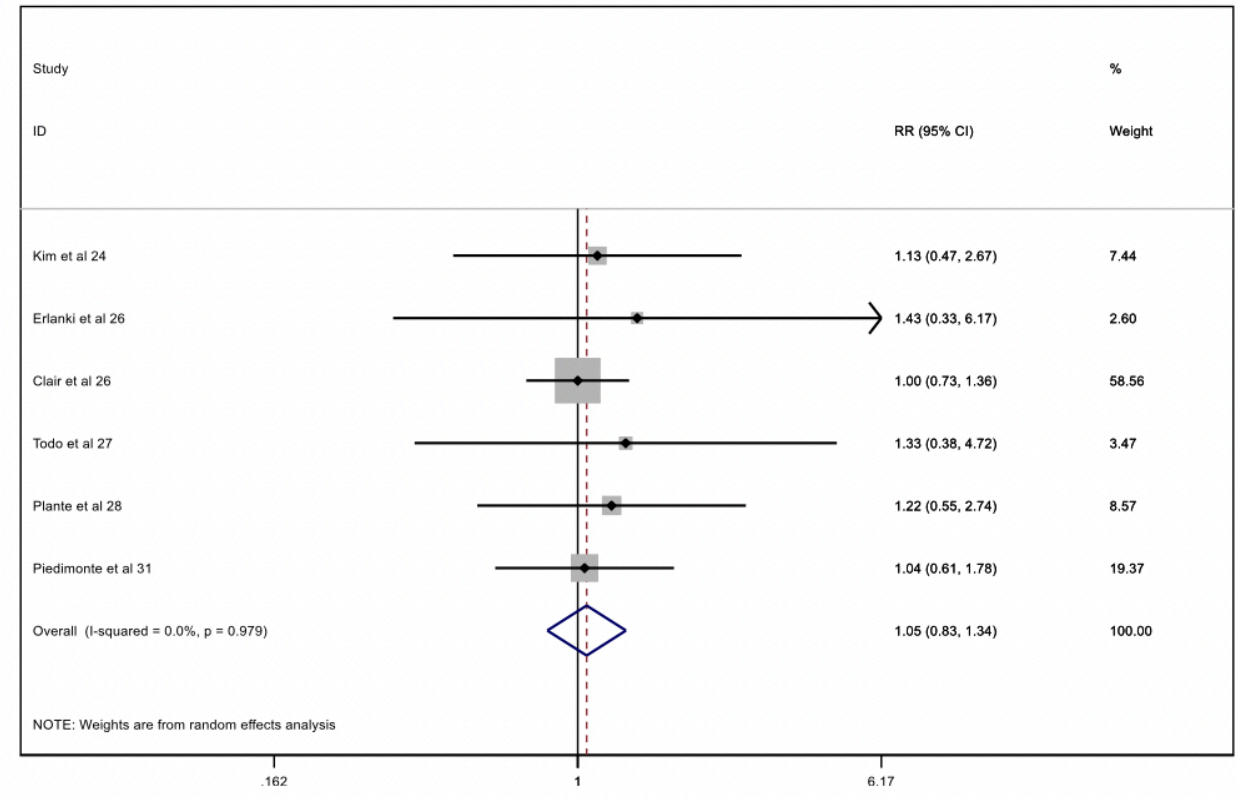


Table 5 Comparative recurrences between MIC/ITC patients with adjuvant therapy and MIC/ITC non-adjuvant patients



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Chapter 3

Patient-reported outcomes after surgery for endometrial carcinoma: Prevalence of lower-extremity lymphedema after sentinel lymph node mapping versus lymphadenectomy

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Abstract

Objective To compare the prevalence of patient-reported lower-extremity lymphedema (LEL) with sentinel lymph node (SLN) mapping versus comprehensive lymph node dissection (LND) for the surgical management of newly diagnosed endometrial carcinoma.

Methods Patients who underwent primary surgery for endometrial cancer from 01/2006-12/2012 were mailed a survey that included a validated 13-item LEL screening questionnaire in 08/2016. Patients diagnosed with LEL prior to surgery and those who answered ≤6 survey items were excluded.

Results Of 1275 potential participants, 623 (49%) responded to the survey and 599 were evaluable (180 SLN, 352 LND, 67 hysterectomies alone). Median BMI was similar among cohorts (p= 0.99). External-beam radiation therapy (EBRT) was used in 10/180 (5.5%) SLN and 35/352 (10%) LND patients (p=0.1). Self- reported LEL prevalence was 27% (49/180) and 41% (144/352), respectively (OR, 1.85; 95% CI, 1.25-2.74; p=0.002). LEL prevalence was 51% (23/45) in patients who received EBRT and 35% (170/487) in those who did not (OR, 1.95; 95% CI, 1.06-3.6; p=0.03). High BMI was associated with increased prevalence of LEL (OR, 1.04; 95% CI, 1.02-1.06; p=0.001). After controlling for EBRT and BMI, LND retained independent association with an increased prevalence of LEL over SLN (OR, 1.8; 95% CI, 1.22-2.69; p= 0.003).

Patients with self-reported LEL had significantly worse QOL compared to those without self-reported LEL.

Conclusions This is the first study to assess patient reported LEL after SLN mapping for endometrial cancer. SLN mapping was independently associated with a significantly lower prevalence of patient- reported LEL. High BMI and adjuvant EBRT were associated with an increased prevalence of patient- reported LEL.

Keywords: Endometrial cancer, sentinel lymph node, sentinel lymph node mapping, lymphadenectomy, lymphedema, patient reported outcomes.

Introduction

Pelvic and para-aortic lymphadenectomy (LND) has been considered standard of care for patients with newly diagnosed endometrial carcinoma [1]. The role of comprehensive LND, however, is debatable. In 2 randomized trials, pelvic LND did not result in improved survival [2,3], but it was associated with the identification of nodal disease and more accurate staging, which many clinicians consider necessary to guide adjuvant treatment. Despite the potential therapeutic value of LND, the procedure is associated with an increased risk of lower-extremity lymphedema (LEL) [4].

Most lymphedema patient-reported outcome (PRO) assessment tools have been designed for the upper extremity, in the context of breast cancer. There are now at least 2 validated LEL PRO tools. Investigators at the Mayo Clinic developed and validated one of these tools [5] and showed that 23% of women who underwent a comprehensive LND compared to hysterectomy alone reported LEL attributable to the LND [6]. Those who reported LEL also had significantly diminished quality of life (QOL) as assessed by validated QOL tools [6].

The National Comprehensive Cancer Network (NCCN) guidelines now allow for SLN mapping for the surgical staging of endometrial carcinomas [7]. Prospective trials have shown low false-negative predictive values with SLN mapping in the detection of nodal disease in these patients, including those with “high-risk” endometrial carcinoma [8,9]. The therapeutic superiority of LND over SLN mapping alone, especially in high-risk cases and those with SLN metastasis, is still highly debatable. Retrospective analyses, however, have

suggested that using SLN mapping over LND does not compromise oncologic outcome in such cases [10,11]. Furthermore, SLN mapping compared with LND is associated with a much lower risk of LEL development in patients with vulvar or endometrial cancer [12,13].

LEL assessment methods have varied in prior studies, ranging from physician assessment to the use of leg measurements, but no study has used LEL PRO tools to compare SLN mapping with LND. Here, we used a validated LEL PRO tool to assess the prevalence of LEL among patients who underwent either SLN mapping or LND during surgery for newly diagnosed endometrial cancer. We also assessed whether patient reported LEL was associated with QOL.

Methods and materials

After Institutional Review Board (IRB) approval, we identified all patients who had undergone primary surgery for newly diagnosed endometrial cancer at our institution (Memorial Sloan Kettering Cancer Center [MSK]) between 1/1/06 and 12/31/12. We excluded patients who had died or had a "do not contact" notation in the electronic medical record (EMR). The included patients were mailed a questionnaire that included a validated 13-item LEL screening survey and validated QOL assessment tools (Appendix 1) in August 2016 - a minimum of 44 months after surgery. The original questionnaire [6] was modified and used with permission. The 13-item LEL PRO survey (Items 9-21 of Appendix 1), validated by investigators from the Mayo Clinic [5], results in a score of 0-52, with a total score ≤5 indicative of LEL (primary endpoint).

The tool's sensitivity and specificity for detecting LEL is 95.5% and 86.5%, respectively, in all patients, and 94.8% and 76.5%, respectively, in obese patients [5]. The mailed questionnaire also included validated QOL assessment tools - EORTC QLQ-C30 (Items 22-49 of Appendix 1) and EORTC QLQ-EN24 (Items 50-75 of Appendix 1) [14-16]. Item 8 was included to identify patients who had LEL prior to surgery; these patients were subsequently excluded.

We used a highly proven 2-phase mail-first recruitment design to yield higher coverage and garner a higher response rate at a lower cost compared to phone-first design [17,18]. After the first mailing, a second mailing went out to non-respondents 1 month later. A month after that, the remaining non-respondents were called and reminded to complete the questionnaire using an IRB- approved phone script. Potential participants were called a maximum of 2 times. Questionnaire responses and clinicopathologic data were abstracted from the EMR and entered into the Web- based Research Electronic Data Capture (REDCap) platform. Those who reported preoperative LEL, had answered 6 or fewer of the 13 items on the LEL PRO survey, or reported having undergone a radical orthopedic resection of the pelvis and/or extremities since their hysterectomy were excluded.

The primary endpoint was the prevalence of patient reported LEL among those who had undergone hysterectomy with SLN mapping alone (SLN cohort) and those who had undergone hysterectomy with standard LND, with or without SLN mapping (LND cohort). We also assessed the prevalence of patient reported LEL in those who had undergone hysterectomy alone (HYST cohort). The HYST cohort included patients who had undergone hysterectomy alone with or without

bilateral salpingo-oophorectomy, as well as those in whom 1 or 2 “enlarged/suspicious” lymph nodes were removed without intent for LND or SLN mapping. The SLN cohort included those in whom only SLN mapping was performed and SLNs excised, with at least one SLN identified both clinically and pathologically. Those who had a unilateral side-specific LND of an unmapped hemi-pelvis were included in the SLN cohort, as per our algorithm. The LND cohort included those in whom a bilateral LND was performed alone or as a “backup” after SLN mapping, and in those who had a failed bilateral SLN mapping.

The statistical design assumed a two-sided type I error of 5% and power of 95% with an expected sample size of 413 LND and 260 SLN patients in order to detect a 10% difference in the rate of LEL be- tween the LND and SLN cohorts of 5-15%. The final sample size was 352 LND and 180 SLN patients.

The rate of LEL in each cohort and the 95% confidence interval (CI) was estimated assuming binomial distribution. A two-sample binomial proportions test was used to compare LEL prevalence between the 2 groups. As a secondary analysis, time to development of LEL was analyzed as a time-to-event variable from surgery date to questionnaire date while considering the interval censored data (LEL exact event date is not known). A type I interval censoring method was applied to compare LEL incidence between the cohorts [19].

Descriptive statistics were provided for all baseline variables for the entire cohort and subgroups (i.e., SLN/LND/HYST or LEL/No LEL). The Fisher exact test and Wilcoxon rank sum test were used to compare the distribution of prespecified covariates between the groups. Univariate logistic regression was used to investigate the effect of baseline covariates on the presence of patient reported

LEL. A multivariate logistic model was built based on significant variables ($p < 0.05$) in univariate setting, except the number of lymph nodes was excluded as a covariate since it was highly correlated with whether LND was performed or not.

QOL questionnaire scoring was calculated according to the EORTC QLQ-C30 and EORTC QLQ-EN24 scoring manuals [15,16]. The QLQ-C30 summary score is calculated from the mean of 13 of the 15 QLQ-C30 scales [20]. The Wilcoxon rank sum test is applied to compare the scores' distribution between patients who developed LEL and those who did not. Multiple comparisons adjustment is applied to the QOL analysis using Bonferroni correction.

Results

Of 1275 potential participants, 623 (49%) responded to the survey, an acceptable response rate for our study design. Twenty- four were excluded for either having answered 6 or fewer of the 13 items on the LEL PRO survey (n 11) or for indicating preoperative LEL (n 13). There were 599 evaluable patients (180 SLN, 352 LND, 67 HYST) (Fig. 1). The median time from date of surgery to date of filling out the questionnaire was 63.2 months (range, 44.3-101.2 months) in the SLN cohort, 93.1 months (range, 44.4-131.3 months) in the LND cohort, and 84.5 months (range, 45.1-127.9 months) in the HYST cohort ($P < 0.001$ for SLN vs LND). Clinicopathologic characteristics for the entire cohort and each sub-cohort are listed in Table 1. Median age and body mass index (BMI) did not differ between the SLN and LND cohorts. The differences noted in International Federation of Gynecology and Obstetrics (FIGO) stage, grade, and histology reflect the evolution of patient selection for SLN mapping during the selected time period.

Overall, 220 (37%) of 599 patients were noted to have LEL based on the 13-item LEL PRO questionnaire. Forty-nine (27.2%; 95% CI, 20.7-33.7%) of 180 patients in the SLN cohort screened positive for self-reported LEL compared with 144 (40.9%; 95% CI, 35.8-46.1%) of 352 patients in the LND cohort (p=0.002 using two-sample binomial proportion test and p=0.039 using interval censoring method), representing an absolute difference of approximately 14%, which we interpret to mean that LND contributed to the development of LEL in 14% of women compared to SLN mapping alone. Patient-reported LEL was also noted in 27 (40.3%; 95% CI, 28.6-52.0%) of the 67 patients in the HYST cohort.

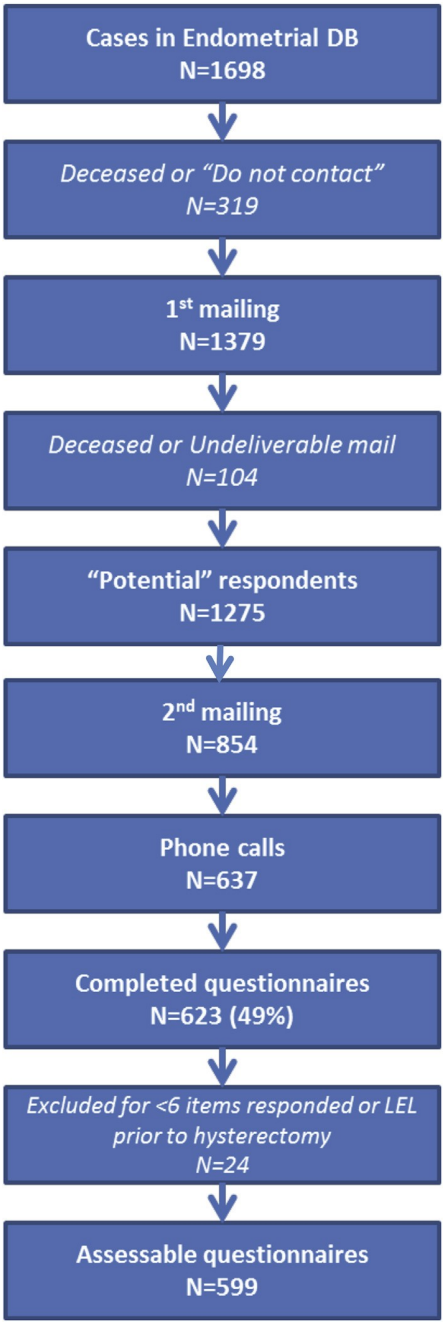
The pre-trial statistical design assumed a two-sided type I error of 5% and power of 94% with an expected sample size of 413 LND and 260 SLN patients in order to detect a 10% absolute difference in the rate of LEL between the LND (20%) and SLN (10%) cohorts. The post-hoc power calculation confirms that the study has 88% power to detect a difference in LEL rate from 27% (SLN cohort) to 41% (LND cohort) in the two arms with n 532 (352 LND 180 SLN) (two-sided Type I error=0.05).

Table 2 describes the association of patient-reported LEL with various factors such as BMI, hypertension, diabetes, and use of external-beam radiation therapy (EBRT). Three patients had congestive heart failure and were not included in our univariate analysis. We did not include FIGO stage, grade or histology, as these were likely to be correlated with the need for additional therapies. Furthermore, at earlier time points, tumor grade and histology would have been correlated with the decision to perform an LND. In addition to LND, increasing BMI and the use of EBRT were also associated with patient reported LEL on univariate analysis. The

distribution of total lymph node counts was skewed to the right, so we performed the log transformation, which resulted in a significant association with patient reported LEL. Limiting analysis to only the SLN cohort, the median number of nodes removed was 4 (range, 1-14) in those without LEL and 4 (range, 1-21) in those with LEL (p=0.6). The total number of lymph nodes removed was also not associated with the risk of LEL on univariate logistic regression (p=0.3). However, only 8 (4.4%) of the 180 patients in the SLN cohort had more than 10 nodes removed, limiting the interpretation of this specific analysis.

LND retained an independent association with patient reported LEL compared to SLN after adjusting for BMI and EBRT (Table 3). Increasing BMI was also independently associated with patient- reported LEL. Independent statistical significance was not achieved for the use of EBRT, but the cohort that received EBRT was small. Number of lymph nodes removed was not included in the multivariate model, as it is directly related to whether LND was performed or not. Total and global QOL scores were significantly worse in patients with patient reported LEL, and these patients had worse scores on all subscales (see Table 4).

Fig. 1. Study recruitment flow.



Discussion and conclusions

To our knowledge, there are no other published reports using LEL PRO tools comparing SLN mapping to LND. We are reassured this tool is valid and reflects a true correlation, since we also found an association of patient reported LEL with both BMI and EBRT. Of note, our 27% LEL prevalence rate in the SLN cohort may seem high; however, age and the associated comorbidities of age are also associated with LEL development. As the median age of our SLN cohort was 61 years, with an upper range of 85 years, a 27% prevalence rate gives further credence to the validity of our LEL PRO instrument.

Our findings are consistent with those of the Mayo Clinic, in which the same LEL PRO tool showed an LEL prevalence rate of 52% in patients who underwent an LND compared with 37% in those who underwent a hysterectomy alone [6]. Despite the differences in individual rates between our study and theirs, the absolute difference was similar (14% and 15%, respectively). This may indicate that SLN mapping does not contribute to the development of LEL beyond the hysterectomy itself and/or aging.

Nodal assessment in patients with newly diagnosed endometrial carcinoma is an important aspect of the initial management of these patients. The therapeutic value of comprehensive LND, however, is debatable [2,3]. Two randomized trials that showed no survival benefit have been highly criticized for the lack of para- aortic lymphadenectomy, the inclusion of mostly low-risk cases, and inconsistencies or a lack of adjuvant therapy in those with nodal disease. The addition of a para-aortic lymphadenectomy likely would

not impact survival considering that the nodal chains do not end at the level of the renal vessels. Those with para-aortic metastases will likely have nodal disease above the renal vessels, and there are no data to support extending lymphadenectomy to the mediastinum and scalenes in endometrial cancer. The comprehensive removal of both clinically and pathologically normal lymph nodes, which is the case in most patients with endometrial carcinoma, is not beneficial. Neither the number of lymph nodes removed, nor the performance of a para-aortic lymphadenectomy were predictive of survival in a classification and regression tree (CART) analysis [21]. The first branching point, meaning the most important factor, was stage of disease [21].

The exclusion of any nodal assessment is also not recommended in our opinion, as this would lead to improper staging and under or over-treatment, with adjuvant therapy decisions based on patient and uterine features alone. For example, adjuvant chemotherapy has been shown to provide a significant improvement in overall survival in patients with extrauterine disease, including nodal involvement. In a randomized trial, doxorubicin and cisplatin therapy compared with whole abdominal radiation resulted in significantly greater progression-free and overall survival in patients with FIGO stage III or IV endometrial carcinoma [22]. The number of lymph nodes removed was not associated with survival outcomes in an ancillary analysis of the study [23]. The NCCN guidelines recommend some form of adjuvant therapy for patients with FIGO stage III or IV disease, although the optimal regimen has not been determined [7].

SLN mapping has evolved as a viable alternative to comprehensive LND since its introduction in endometrial cancer in 1996 [24]. The MSK SLN algorithm, which is endorsed by the NCCN, has a false- negative predictive value (FNPV) of 0.5% [25]. In short, the algorithm requires the removal of any suspicious nodes, irrespective of dye uptake, as well as a side-specific lymph node dissection in hemi- pelvises that do not map. The FIRES trial demonstrated an FNPV of 0.4% in mapped SLNs in patients with clinical stage I endometrial cancer who underwent SLN mapping followed by an immediate LND [8]. In another prospective trial, the FNPV was 1.4% in patients with high-risk endometrial carcinoma [9].

Based on our study results and those of others, the benefit of SLN mapping over comprehensive LND lies in the reduction of lymphatic morbidity and subsequent improvement in QOL. The GROINSS V1 study in vulvar cancer reported an LEL rate of 25% in patients who had undergone SLN mapping followed by an inguinofemoral LND compared to only 2% in those who had undergone SLN mapping of the groin alone [26], although LEL diagnoses were based on physician assessment. In a prospective study of 188 patients with endometrial cancer, the incidence of LEL after SLN mapping alone was 1.3% compared with 18.1% after pelvic and para- aortic LND (P 0.0003). Lymphedema diagnoses in the study were based on the assessment of a physiotherapist using the Common Toxicity Criteria (CTC) version 3.0 [13]. Currently, there are no agreed upon standard guidelines for the diagnosis of LEL, and the use of PRO instruments in this setting is lacking.

The Gynecologic Cancer Lymphedema Questionnaire (GCLQ) is another LEL PRO tool, which was modified from the Lymphedema Breast Cancer Questionnaire

(LBCQ). The 20-item GCLQ has acceptable reported sensitivity and specificity (85.7% and 90%, respectively) [27]. We decided to use the Mayo Clinic LEL PRO tool for our study, because of the reduced patient burden of answering only 13 items as opposed to 20. However, both instruments are acceptable, and it would be interesting to see them assessed in a head-to-head study.

We recognize the limitations of our study. Varying cutoff points among studies may alter baseline rates of LEL. Recall bias is a concern in all studies of this design. Even though we feel that the survey response rate was acceptable, half of the potential respondents did not return the survey, which may impact the generalizability of our findings. We could only assess prevalence rates at the time patients received the questionnaires, and the time since surgery varied. We cannot assess the incidence rates over time as this was not a prospective study and the exact timing of LEL development is unknown. We would ideally like to conduct a study in a cohort of patients who present with newly diagnosed endometrial cancer and assess patient reported LEL and QOL before surgery and then at timed intervals for some years after surgery in order to better capture the timing of LEL after surgery. We also recognize that the median time since surgery was different be- tween the SLN and LND cohorts, which may impact the rate of patient-reported LEL, especially as patients continue to age. The minimum time from surgery was 44 months in both cohorts, which seems to be a reasonable amount of time to assess for the possible development of surgery-related, patient-reported LEL.

The noted range of 1-21 lymph nodes removed in the SLN cohort is due to multiple reasons. One of the reasons is related to the learning curve of surgeons

as they adopted SLN mapping. Surgeons tend to remove more “SLNs” early on in their experience, and the number removed decreases with increased experience and understanding of true SLN mapping. Also, there may be a few nodes within a packet that are removed as the “SLN”. The other reasons are related to the use of our algorithm, which includes the removal of any “suspicious” nodes irrespective of mapping, performance of a paraaortic LND at the surgeon’s discretion, and the performance of a unilateral LND in cases with an unmapped hemi-pelvis. The number of cases with true unilateral LND of unmapped hemi-pelvis was low, limiting any meaningful analysis comparing those with only SLN mapping to those with unilateral LND. Additionally, the PRO LEL questionnaire cannot differentiate laterality of LEL.

Our results demonstrate that SLN mapping over LND is independently associated with a significantly lower prevalence of patient reported LEL in patients who have undergone surgery for endometrial carcinoma. Our data also may inform discussions regarding the risks and benefits of adjuvant radiation therapy. These data provide additional support for SLN mapping in women with endometrial carcinoma. SLN mapping provides accurate surgical staging, as well as decreased morbidity and improved QOL.

Table 1
Select clinicopathologic characteristics. P value refers to the comparison between SLN and LND groups only.

Characteristic	Whole Cohort	SLN	LND	HYST	P value for SLN vs LND only
N	599	180	352	67	
Age at surgery (years)					0.37
Median	61	61	61	61	
Range	27–85	34–85	27–83	31–85	
BMI (kg/m^2)					0.99
Median	29	29.1	29.0	33.0	
Range	17.9–68.6	17.9–67.6	18.2–59.1	19.5–68.6	
FIGO stage					0.01
I	492 (82.3)	159 (88.3)	271 (77)	62 (93.9)	
II	15 (2.5)	2 (1.1)	12 (3.4)	1 (1.5)	
III	78 (13)	18 (1.0)	59 (16.8)	1 (1.5)	
IV	13 (2.2)	1 (0.6)	10 (2.8)	2 (3)	
FIGO tumor grade					<0.001
1	305 (51)	122 (67.8)	135 (38.4)	48 (72.7)	
2	132 (22.1)	34 (18.9)	88 (25)	10 (15.2)	
3	161 (26.9)	24 (13.3)	129 (36.6)	8 (12.1)	
Histology					<0.001
Endometrioid	472 (78.8)	162 (90)	256 (72.7)	54 (80.6)	
Non-endometrioid	60 (10)	8 (4.4)	47 (13.4)	5 (7.5)	
Carcinosarcoma	25 (4.2)	2 (1.1)	23 (6.5)	0 (0)	
Sarcoma	8 (1.3)	1 (0.6)	2 (0.6)	5 (7.5)	
Other[a]	34 (5.7)	7 (3.9)	24 (6.8)	3 (4.5)	
Hypertension					0.17
No	281 (46.9)	96 (53.3)	165 (46.9)	20 (29.9)	
Yes	318 (53.1)	84 (46.7)	187 (53.1)	47 (70.1)	
Diabetes					0.01
No	495 (82.6)	161 (89.4)	285 (81)	49 (73.1)	
Yes	104 (17.4)	19 (10.6)	67 (19)	18 (26.9)	
CHF					0.27
No	592 (98.8)	178 (98.9)	351 (99.7)	63 (94)	
Yes	7 (1.2)	2 (1.1)	1 (0.3)	4 (6)	
Renal disease					1.0
No	588 (98.2)	178 (98.9)	347 (98.6)	63 (94)	
Yes	11 (1.8)	2 (1.1)	5 (1.4)	4 (6)	
EBRT					0.1
No	550 (91.8)	170 (94.4)	317 (90.1)	63 (94)	
Yes	49 (8.2)	10 (5.6)	35 (9.9)	4 (6)	
Total LNs removed					<0.001
Median	11	4	19	0	
Range	0–80	1–21	1–80	0–1	

Values are N(%) except where noted otherwise.
SLN = sentinel lymph node mapping cohort; LND = lymphadenectomy cohort; HYST = hysterectomy alone cohort.
BMI = body mass index; FIGO=International Federation of Gynecology and Obstetrics; CHF = congestive heart failure; EBRT = external beam radiotherapy (postoperative); LN = lymph nodes.
[a] Other histology includes: adenocarcinoma NOS, carcinoma NOS, atypical hyperplasia, mixed histologies, squamous cell carcinoma, undifferentiated carcinoma, yolk sac tumor.

Table 2
Univariate analysis of the association of various clinicopathologic characteristics with patient-reported lower-extremity lymphedema. OR: odds ratio for developing LEL.

Characteristic	No patient-reported LEL	Patient-reported LEL	OR	95% CI	P value
Surgery Cohort					
LND	208 (59.1)	144 (40.9)			0.002
SLN	131 (72.7)	49 (27.2)	1.85	1.25-2.74	
BMI (kg/m^2)					
One unit increase	–	–	1.04	1.02-1.06	0.001
Hypertension					
Yes	174 (64.2)	97 (35.8)	0.96	0.67-1.36	0.8
No	165 (63.2)	96 (36.8)			
Diabetes					
Yes	48 (55.8)	38 (44.2)	1.49	0.93-2.37	0.1
No	291 (65.2)	155 (34.8)			
Renal disease					
Yes	4 (57.1)	3 (42.9)			
No	335 (63.8)	190 (36.2)	1.32	0.29-5.97	0.7
EBRT					
Yes	22 (48.9)	23 (51.1)	1.95	1.06-3.6	0.03
No	317 (65.1)	170 (34.9)			
Number LNs removed					
Total LNs	–	–	1.01	0.997-1.03	0.1
Log (total LNs)[a]	–	–	1.25	1.04-1.52	0.02

% is for the total in row.
LEL = lower-extremity lymphedema; SLN = sentinel lymph node mapping cohort; LND = lymphadenectomy cohort; EBRT = external beam radiotherapy (postoperative); LN = lymph nodes.
[a] Log transformation also shown as the distribution of lymph nodes removed was skewed.

Table 3
Multivariate model assessing independent association with patient-reported lower-extremity lymphedam. OR: odds ratio for developing LEL.

Characteristic	OR	95% CI	P value
Surgery cohort: LND vs SLN	1.81	1.22-2.69	0.003
EBRT: Yes vs No	1.85	0.99-3.46	0.05
BMI: one unit increase	1.04	1.02-1.06	<0.001

Total N of cases included in model = 532.
LEL = lower-extremity lymphedema; SLN = sentinel lymph node mapping cohort; LND = lymphadenectomy cohort; EBRT = external beam radiotherapy (post-operative); BMI, body mass index.

Table 4
EORTC QLQ-C30 and -EN24 scores between patients with and without patient-reported lower-extremity lymphedema.

	No patient-reported LEL	Patient-reported LEL	P value[a]
EORTC QLQ-C30			
Overall Score			
QLQ Total Score	94.9/91.8 (27.6–100)	84.7/79 (19.6–100)	<0.001
Global QOL	83.3/83.6 (0–100)	66.7/66.8 (0–100)	<0.001
Functional Scales			
Physical functioning	100/90.4 (0–100)	86.7/75.8 (0–100)	<0.001
Role functioning	100/95 (0–100)	83.3/80 (0–100)	<0.001
Emotional functioning	91.7/86.3 (0–100)	75/73.2 (0–100)	<0.001
Cognitive functioning	100/89.4 (16.7–100)	83.3/77.4 (0–100)	<0.001
Social functioning	100/93.8 (0–100)	83.3/77.3 (0–100)	<0.001
Symptom Scales			
Fatigue	0/12.9 (0–100)	22.3/31.7 (0–100)	<0.001
Nausea and vomiting	0/2.3 (0–100)	0/7.3 (0–100)	<0.001
Pain	0/7.7 (0–100)	16.7/28.5 (0–100)	<0.001
Dyspnea	0/6.4 (0–100)	0/17.5 (0–100)	<0.001
Insomnia	0/16.1 (0–100)	33.3/31.1 (0–100)	<0.001
Appetite loss	0/3.3 (0–100)	0/9.9 (0–100)	<0.001
Constipation	0/7.8 (0–100)	0/17.8 (0–100)	<0.001
Diarrhea	0/5.4 (0–100)	0/15.9 (0–100)	<0.001
Financial difficulties	0/5 (0–100)	0/19.5 (0–100)	<0.001
EORTC QLQ-EN24			
Functional Scales			
Sexual interest[b]	33.3/23.3 (0–100)	0/19.5 (0–100)	0.035
Sexual activity[c]	0/19.5 (0–100)	0/12.7 (0–100)	0.01
Sexual enjoyment[d]	33.3/49.2 (0–100)	33.3/33.3 (0–100)	<0.001
Symptom Scales			
Lymphedema	0/3 (0–100)	33.3/38.3 (0–100)	<0.001
Urologic symptoms	8.3/15.1 (0–75)	25/29.9 (0–100)	<0.001
Gastrointestinal symptoms	6.7/7.8 (0–100)	13.3/20.7 (0–86.7)	<0.001
Poor body image	0/9.1 (0–100)	16.7/25.6 (0–100)	<0.001
Sexual/vaginal problems[e]	22.2/35.3 (0–100)	44.4/48.5 (0–100)	0.019
Pain in back and pelvis	0/14.4 (0–100)	33.3/36.4 (0–100)	<0.001
Tingling/numbness	0/17.8 (0–100)	33.3/38.6 (0–100)	<0.001
Muscular pain	0/21.4 (0–100)	33.3/43.2 (0–100)	<0.001
Hair loss	0/12.4 (0–100)	0/25 (0–100)	<0.001
Taste change	0/4.4 (0–100)	0/10.1 (0–100)	<0.011

LEL = lower-extremity lymphedema; QOL = quality of life.
Data are reported as Median/Mean (range).
[a] P-value obtained using Wilcoxon Rank Sum Test and all except "sexual interest" and "sexual activity" remain significant using Bonferroni correction for multiple comparisons adjustment.
[b] Data missing from 56.
[c] Data missing from 62.
[d] Data missing from 321.
[e] Data missing from 317.

Appendix A. The questionnaire.

Memorial Sloan Kettering
Cancer Center

PREVALANCE OF SELF REPORTED LYMPHEDEMA IN PATIENTS WITH ENDOMETRIAL CANCER

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NAME:

DATE COMPLETED:

Memorial Sloan Kettering Cancer Center

INSTRUCTIONS: PLEASE CHECK THE APPROPRIATE BOX OR FILL IN THE BLANK AS INDICATED.

ABOUT YOU

This first set of questions is about you and your treatment for endometrial cancer.

1. **About how tall are you without shoes?**

   _____ Feet __ __ Inches

2. **About how much do you weigh without shoes?**

   __ __ __ Pounds

3. **Did you receive radiation treatment after your surgery for endometrial cancer?**

   ☐ No ☐ Yes ☐ Don't know

4. **Did you receive chemotherapy after your surgery for endometrial cancer?**

   ☐ No ☐ Yes ☐ Don't know

5. **Has a doctor, nurse, or other health professional ever told you that you have any of the following?** (Mark one response on each line.)

	NO	YES	DON'T KNOW
Diabetes or high blood sugar……	☐	☐	☐
Heart failure or congestive heart failure……	☐	☐	☐
Kidney disease or kidney failure……..	☐	☐	☐

6. **Has a doctor, nurse, or other health professional told you that your endometrial cancer has recurred?**

☐ No ☐ Yes ☐ Don't know

If Yes, when? ____ /_____
Month / Year

Lymphedema is swelling that can occur anywhere on a person's body. The swelling occurs when lymph fluid cannot drain properly because the lymphatic system is blocked or damaged.

The next few questions ask about lymphedema in your lower body, which includes anything below the navel (belly button).

7. **Before your surgery, did a doctor, nurse, or other health professional talk to you about the possibility of developing lymphedema in your lower body as a result of your surgery for endometrial cancer?**

☐ No ☐ Yes ☐ Don't know

8. **Has a doctor, nurse, or other health professional ever told you that you have lymphedema in your lower body?**

☐ No ☐ Yes ☐ Don't know

If Yes, when were you first told that you have lymphedema in your lower body?

☐ Before your surgery for endometrial cancer
☐ After your surgery for endometrial cancer
☐ Don't know

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Have you ever done any of the following to manage lymphedema in your lower body?	NO	YES	If yes, are you still doing this? NO	YES
Worn compression stockings……..	☐	☐	☐	☐
Worn bandages……	☐	☐	☐	☐
Done exercises such as "calf pumps"	☐	☐	☐	☐
Done self-massage, also called "manual lymphatic drainage"……	☐	☐	☐	☐
Other, please specify: _____	☐	☐	☐	☐

YOUR LOWER BODY

The following statements are about sensations you may have on one or both sides of your lower body.

Please mark one box for each statement that best describes how your lower body felt on average in the past 4 weeks. If you have one of these sensations on both sides of your lower body, describe the side that seems to be affected the most.

	Not at all	A Little bit	Somewhat	Quite a bit	Very much
9. The skin on my leg feels tight……..	☐	☐	☐	☐	☐
10. The skin above my ankle feels tight……	☐	☐	☐	☐	☐
11. My leg feels heavy……	☐	☐	☐	☐	☐
12. I have pain or discomfort in my leg……	☐	☐	☐	☐	☐
13. My leg is noticeably smaller when I get out of bed in the morning……	☐	☐	☐	☐	☐

I have swelling in my foot…….	☐	☐	☐	☐	☐
14. I have swelling around my ankle……	☐	☐	☐	☐	☐
15. I have swelling in my lower leg (including knee)……...	☐	☐	☐	☐	☐
16. I have swelling in my upper leg……...	☐	☐	☐	☐	☐
17. I have swelling in my buttocks……	☐	☐	☐	☐	☐
18. I have swelling in my hip (on the side below the waist)……	☐	☐	☐	☐	☐
19. I have swelling below my stomach (below the belly button)……	☐	☐	☐	☐	☐
20. I have swelling in my genital area……	☐	☐	☐	☐	☐

YOUR WELL-BEING

We are interested in some things about you and your health. Please answer all of the questions yourself by marking the box that best applies to you. There is no "right" or "wrong" answer. The information that you provide will remain strictly confidential.

	Not at all	A Little bit	Quite a bit	Very much
21. Do you have any trouble doing strenuous activities like carrying a heavy shopping bag or suitcase?.....……..	☐	☐	☐	☐
22. Do you have any trouble taking a long walk?.....	☐	☐	☐	☐
23. Do you have any trouble taking a short walk outside of the house?.....	☐	☐	☐	☐
24. Do you need to stay in bed or a chair during the day?.....	☐	☐	☐	☐

26. Do you need help with eating, dressing, washing yourself or using the toilet?.....… ☐ ☐ ☐ ☐

During the past week:

	Not at all	A Little bit	Quite a bit	Very much
27. Were you limited in doing either your work or other daily activities?.....	☐	☐	☐	☐
28. Were you limited in pursuing your hobbies or other leisure time activities?.....	☐	☐	☐	☐
29. Were you short of breath?.....	☐	☐	☐	☐
30. Have you had pain?.....	☐	☐	☐	☐
31. Did you need to rest?.....	☐	☐	☐	☐
32. Have you had trouble sleeping?.....	☐	☐	☐	☐
33. Have you felt weak?.....	☐	☐	☐	☐
34. Have you lacked appetite?.....	☐	☐	☐	☐
35. Have you felt nauseated?.....	☐	☐	☐	☐
36. Have you vomited?.....	☐	☐	☐	☐
37. Have you been constipated?.....	☐	☐	☐	☐
38. Have you had diarrhea?.....	☐	☐	☐	☐
39. Were you tired?.....	☐	☐	☐	☐
40.Did pain interfere with your daily activities?.....	☐	☐	☐	☐

During the past week:

	Not at all	A Little bit	Quite a bit	Very much
40. Have you had difficulty in concentrating on things like reading a newspaper or watching television?.....	☐	☐	☐	☐
41. Did you feel tense?.....	☐	☐	☐	☐
42. Did you worry?.....	☐	☐	☐	☐
43. Did you feel irritable?.....	☐	☐	☐	☐
44. Did you feel depressed?.....	☐	☐	☐	☐
45. Have you had difficulty remembering things?.....	☐	☐	☐	☐
46. Has your physical condition or medical treatment interfered with your <u>family</u> life?.....	☐	☐	☐	☐
47. Has your physical condition or medical treatment interfered with your <u>social</u> activities?.....	☐	☐	☐	☐
48. Has your physical condition or medical treatment caused you financial difficulties?.....	☐	☐	☐	☐

For the following items, please mark the number between 1 and 7 that best applies to you.

49. How would you rate your overall <u>health</u> during the past week?

☐ ☐ ☐ ☐ ☐ ☐ ☐

1 2 3 4 5 6 7

Very poor Excellent

50. How would you rate your overall quality of life during the past week?

☐ ☐ ☐ ☐ ☐ ☐ ☐

1 2 3 4 5 6 7
Very poor Excellent

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems.

During the past week:

	Not at all	A Little bit	Quite a bit	Very much
51. Have you had swelling in one or both legs?.....	☐	☐	☐	☐
52. Have you felt heaviness in one or both legs?.....	☐	☐	☐	☐
53. Have you had pain in your lower back and/or pelvis?.....	☐	☐	☐	☐
54. When you felt the urge to pass urine, did you have to hurry to get to the toilet?.....	☐	☐	☐	☐
55. Have you passed urine frequently?.....	☐	☐	☐	☐
56. Have you had leaking of urine?.....	☐	☐	☐	☐
57. Have you had pain or a burning feeling when passing urine?.....	☐	☐	☐	☐
58. When you felt the urge to move your bowels, did you have to hurry to get to the toilet?.....	☐	☐	☐	☐
59. Have you had any leakage of stools?.....	☐	☐	☐	☐
60. Have you been troubled by passing wind?.....	☐	☐	☐	☐
61. Have you had cramps in your abdomen?.....	☐	☐	☐	☐
62. Have you had a bloated feeling in your abdomen?..	☐	☐	☐	☐

63. Have you had tingling or numbness in your hands or feet?	☐	☐	☐	☐
64. Have you had aches or pains in your muscles or joints?	☐	☐	☐	☐

During the past week:

	Not at all	A Little bit	Quite a bit	Very much
65. Have you lost hair?	☐	☐	☐	☐
66. Has food and drink tasted differently from usual?	☐	☐	☐	☐
67. Have you felt physically less attractive as a result of your disease or treatment?	☐	☐	☐	☐
68. Have you felt less feminine as a result of your disease or treatment?	☐	☐	☐	☐

During the past 4 weeks:

	Not at all	A Little bit	Quite a bit	Very much
69. To what extent were you interested in sex?	☐	☐	☐	☐
70. To what extent were you sexually active?	☐	☐	☐	☐

Answer these questions only if you have been sexually active during the past 4 weeks:

71. Has your vagina felt dry during sexual activity?	☐	☐	☐	☐
72. Has your vagina felt short and/or tight?	☐	☐	☐	☐
73. Have you had pain during sexual intercourse or other sexual activity?	☐	☐	☐	☐

THANK YOU!

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Chapter 4

Trends in Sentinel Lymph Node Mapping and Adjuvant Therapy in Endometrial Carcinoma

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Abstract

We analyzed 54,039 women with uterine cancer in the National Cancer Database from 2013–2014 including 38,453 (71.2%) who underwent lymphadenectomy, 1929 (3.6%) who underwent sentinel lymph node (SLN) mapping, and 13,657 (25.3%) who did not undergo nodal assessment. SLN mapping increased from 2.8% in 2013 to 4.3% in 2014 ($p<0.001$). Patients treated in 2014 and those at community centers were more likely to undergo SLN biopsy, while women with advanced-stage disease, sarcomas, and grade 3 tumors were less likely to undergo SLN mapping ($p<0.05$). There was no association between use of SLN biopsy and use of radiation (aRR=0.92; 95% CI, 0.82–1.05).

Keywords: Uterine cancer; endometrial cancer; sentinel lymph node; lymphadenectomy; hysterectomy.

Introduction

Endometrial carcinoma is the most common gynecologic cancer in developed countries (1). The standard treatment for patients diagnosed with endometrial cancer is hysterectomy and bilateral salpingo-oophorectomy. The role of lymph node assessment remains controversial. While lymphadenectomy may provide prognostic information and help tailor adjuvant therapy, universal nodal assessment subjects a large number of women with uterine-confined disease to the procedure (2–4). Lymphadenectomy increases operative time and is associated with long-term sequelae such as lymphedema (5). Further, prospective trials have shown that lymphadenectomy is not associated with improved survival further calling into question the value of the procedure (6,7).

Sentinel lymph node (SLN) mapping has been proposed as an alternative to lymphadenectomy (8). SLN mapping relies on removal of a small number of lymph nodes that are the first drainage sites from a tumor and thus the most likely to harbor tumor cells (9,10). SLN mapping has the potential to reduce the morbidity of lymphadenectomy and has been extensively validated for several other solid tumors and is now in the standard of care in breast cancer, vulvar cancer, and melanoma (11–13).

Despite the potential benefits of SLN mapping, data describing the performance of the procedure in women with endometrial cancer is limited. We performed a population-based analysis of women with endometrial cancer to first determine

the utilization and predictors of use of SLN mapping and second, to examine whether use of SLN mapping was associated with changes in the prescription of adjuvant therapy for women with early-stage tumors.

Methods

Data source

The National Cancer Database (NCDB) Participant Use Data File (PUF) was used for the analysis (14). The NCDB is a hospital-based registry developed by the American College of Surgeons and American Cancer Society. It contains data on all patients with malignant tumors from over 1,500 Commission on Cancer (CoC)-accredited hospitals and represents more than 70% of newly diagnosed cancer cases across the United States. Incident tumor cases are collected by trained registrars and the data is examined and verified regularly to ensure quality. The data fields include patient demographics, tumor characteristics, treatment, survival, and hospital characteristics (14). The study was deemed exempt by the Columbia University Institutional Review Board.

Patient Selection

We identified women who had malignant uterine cancers diagnosed as their first or only cancer and confirmed with positive histology from 2013 to 2014. Women who had radiation before surgery or intraoperative radiation therapy were excluded. Women who did not have hysterectomy, or whose performance of

nodal assessment was unknown were excluded. Women who had stage IV cancer or unknown stage were also excluded.

Patients were classified based on nodal assessment codes as having undergone sentinel lymph node (SLN) mapping, lymphadenectomy (LND), or no nodal assessment (no LND). Among patients who had a code for SLN mapping, additional non-sentinel nodes could be taken and discovered by the pathologist. We determined if they had a concurrent lymphadenectomy when review of the operative report confirmed that a regional lymph node dissection followed the SLN. In cases of failed SLN mapping, lymphadenectomy was usually performed, and patients were classified as having SLN with concurrent lymphadenectomy. If no further regional lymph nodes were dissected, patients were classified as having SLN mapping only. The number of nodes removed was recorded for each group of patients.

Demographic data included age (<50, 50–59, 60–69, 70–79, ≥80 years), race (white, black, Hispanic, other, unknown), year of diagnosis, and insurance status (private, Medicaid, Medicare, uninsured, other governmental/unknown). Income was measured by median household income in the patients' zip code and was classified as <$38,000, $38,000- $47,999, $48,000-$62,999, $63,000+, or unknown. Education was measured by the percentage of adults in a patient's zip code who did not graduate from high school, and classified as ≥21%, 13–20%, 7.0–12.9%, <7%, or unknown. Location was estimated by matching the patients' state and country FIPS code to rural-urban continuum codes from the United States Department of Agriculture Economic Research Service, and classified as

metropolitan, urban, rural, and unknown. Comorbidity was measured using the Deyo adaptation of the Charlson's comorbidity score, and grouped as 0, 1, or ≥2 comorbid conditions (15).

Tumor stage was derived from the American Joint Committee on Cancer (AJCC) pathologic staging groups, and classified as IA, IB, I NOS, II, IIIA, IIIB, IIIC, and III NOS (not otherwise specified). Other tumor characteristics included histology (endometrioid, serous, clear cell, carcinosarcoma, sarcoma, and endometrial cancer not otherwise specified [NOS]/ other) and grade (well, moderate, poorly, unknown). Hospital characteristics included facility region (northeast, midwest, south, west, unknown) and facility type defined by the American Cancer Society's Commission on Cancer Accreditation program (academic/ research, community cancer, comprehensive community cancer, integrated network cancer, other/unknown). Radiation therapy was classified as combination, external beam, brachytherapy, or none/unknown.

Statistical Analysis

Frequency distributions between demographic and clinical characteristics of the patients and the scope of lymph node dissection were compared using $\chi 2$ tests. The number of lymph nodes removed in the SLN group was reported descriptively as means (standard deviation [SD]), and medians (interquartile range [IQR]). To examine predictors of having undergone SLN mapping, we fit mixed-effect models adjusting for age, race, year of diagnosis, insurance status, income, location, comorbidity, facility type, region, stage, histology and grade to compare patients

who underwent SLN mapping to those who underwent lymphadenectomy and to compare patients who underwent SLN mapping to who had no nodal assessment. The treating facility was included as random effect to account for hospital-level clustering.

To examine predictors of any type of radiation (external beam, brachytherapy or combination) among stage I patients who had SLN mapping or LND, we fit mixed-effect models adjusting for all demographic and clinical characteristics and scope of lymphadenectomy. A similar model was fit for predictors of external beam or combination radiation. To account for the data quality concerns in the accuracy of treatment data collected from more than one hospital in the NCDB, sensitivity analyses were performed limiting to patients who were reported from only one CoC-accredited hospital. All analyses were conducted using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina). All hypothesis testing was two-sided and a P-value of <0.05 was considered statistically significant.

Results

A total number 54,039 women were identified including 38,453 (71.2%) who underwent lymphadenectomy, 1929 patients (3.6%) who underwent sentinel lymph node (SLN) biopsy and 13,657 (25.3%) who did not undergo nodal assessment (Figure 1, Table 1). Among women treated in 2013, 2.8% underwent SLN biopsy, while 4.3% of those treated in 2014 underwent SLN biopsy (p<0.001). When limited to women who underwent some form of nodal assessment, either

SLN biopsy or lymphadenectomy, 3.8% in 2013 and 5.8% in 2014 underwent SLN biopsy.

In the cohort of women who had SLN biopsy, 863 (45.4%) were coded as having only undergone SLN biopsy while 1038 (54.6%) underwent concurrent lymphadenectomy (Table 2). The median number of lymph nodes removed was 3 (IQR, 2–4) in those who underwent SLN biopsy alone and 14 (IQR, 9–21) in patients who had a concurrent nodal dissection.

Among women who underwent nodal assessment (either SLN biopsy or lymphadenectomy), a patient treated in 2014 was 60% more likely to undergo SLN biopsy than if that patient had been treated in 2013 (aRR=1.60; 95% CI, 1.46–1.76) (Table 3). Likewise, a patient treated at a community cancer center was 72% more likely to undergo SLN biopsy than if she was treated at an academic center (aRR=1.72; 95% CI, 1.04–2.86). In contrast, women with more advanced stage disease, sarcomas or carcinosarcomas, and those with poorly differentiated tumors were less likely to undergo SLN biopsy ($p<0.05$ for all). Similarly, compared to women treated in the northeast, those who received care in the Midwest and south were less likely to undergo SLN biopsy ($p<0.05$ for both).
When the analysis was limited to women who either underwent SLN biopsy or no nodal evaluation, women with 2 or more comorbidities (versus none) and those in the south (versus northeast) were less likely to undergo SLN biopsy ($p<0.05$ for both) (Table 3). Patients with moderate and poorly differentiated neoplasms (versus well differentiated) were more likely to undergo SLN biopsy.

Among women with stage, I tumors who underwent nodal assessment, there was no association between use of SLN biopsy (compared to lymphadenectomy) and use of radiation (aRR=0.92; 95% CI, 0.82–1.05). Likewise, SLN biopsy was not associated with either external beam radiation alone or in combination with brachytherapy (aRR=0.98; 95% CI, 0.70–1.36) use. These results were unchanged in models limited to patients who received all care at only one facility.

Discussion

This study suggests that the use of sentinel lymph node biopsy for women with endometrial cancer is increasing. While a number of non-clinical factors contribute to uptake of SLN biopsy, women with non-endometrioid, poorly differentiated, and more advanced stage tumors are less likely to undergo SLN biopsy and are still more likely to have lymphadenectomy. Performance of SLN biopsy in lieu of lymphadenectomy is not associated with a higher rate of use of adjuvant radiation.

Sentinel lymph node biopsy techniques have been developed to reduce the morbidity of nodal assessment for a variety of solid tumors and the procedure has recently been utilized for endometrial cancer. Initial data for the procedure was largely based on institutional case series, but more recently, multicenter prospective clinical trials have also reported the performance characteristics of SLN biopsy (9,16,17). The SENTI-ENDO study included 133 patients and reported a sensitivity of 84% and negative predictive value of 97% for sentinel lymph node

sentinel lymph node mapping in 86% of subjects. The sensitivity for detection of nodal metastases was 97% with a negative predictive value of over 99% (19).

The role of any form of nodal assessment in endometrial cancer remains controversial. Two large, randomized trials both demonstrated that lymphadenectomy was not associated with improved survival (6,7). However, proponents of lymphadenectomy argue that the procedure allows not only prognostication but also allows more tailored adjuvant therapy (4,20). In the United States, many practitioners have shifted from universal lymphadenectomy to performance of the procedure in women with higher risk features (21).

In 2014, the National Comprehensive Cancer Network guidelines (22) included SLN biopsy as part of their accepted algorithm for staging. We noted that women with lower risk tumors (grade 1, superficially invasive) were more likely to undergo SLN biopsy and those with higher risk features preferentially underwent lymphadenectomy. While the value of nodal assessment in such low-risk patients is questionable, surgeons may have been hesitant to apply a new technology to women biopsy (18). More recently, the FIRES trial enrolled 385 patients with endometrial cancer and reported successful at higher risk for nodal disease. While based on limited data, some studies have suggested that SLN mapping may also be used in higher risk histologic subtypes (23–25).

Encouragingly, these findings suggest that there was no association between use of SLN mapping and use of radiation in women with stage I tumors. A concern

with implementation of SLN mapping is that clinicians may lack confidence in the ability of the technique to detect metastatic spread and prescribe adjuvant radiation therapy (4,26) These findings suggest that this is not the case. Women with stage I tumors who underwent SLN biopsy were no more likely to receive radiation therapy than those who underwent full lymphadenectomy.

In addition to clinical factors, we noted substantial regional variation in performance of SLN biopsy; patients in the northeast were much more likely to undergo the procedure than women in other parts of the U.S. Prior work have also demonstrated that patients undergoing robotic-assisted surgery are substantially more likely to undergo SLN mapping (27). SLN mapping is not unlike other new techniques and technologies in which non-clinical factors influence diffusion (28).

While the study benefits from the inclusion of a large cohort of patients, we recognize several important limitations. First, coding for sentinel lymph node biopsy for endometrial cancer in the NCDB is relatively new. As such, we cannot exclude the possibility of misclassification of a small number of women. Second, we are unable to capture women who had an attempted sentinel node biopsy but for technical reasons underwent only full lymphadenectomy. Technical considerations are an important consideration for any new surgical technique. Third, while we can account for a number of clinical and demographic characteristics, there are undoubtedly unmeasured confounding factors that influenced treatment choice and outcomes. Lastly, given the favorable prognosis

of endometrial cancer, our study is underpowered to detect small differences in survival or use of radiation. Further work is clearly needed to further monitor the association between sentinel lymph node biopsy and use of adjuvant therapy and survival.

In conclusion, the use of sentinel lymph node mapping in endometrial cancer is increasing rapidly. There does not appear to be an association between use of sentinel lymph node dissection and use of adjuvant radiation. To date, most of the patients who underwent SLN mapping had low risk, early-stage tumors and more data is clearly needed among women with higher risk cancers. With increasing surgeons experience, improvements in detection rates and developing technology, SLN mapping will likely play a more prominent role in lymph node evaluation.

Figure 1. Flowchart of cohort selection

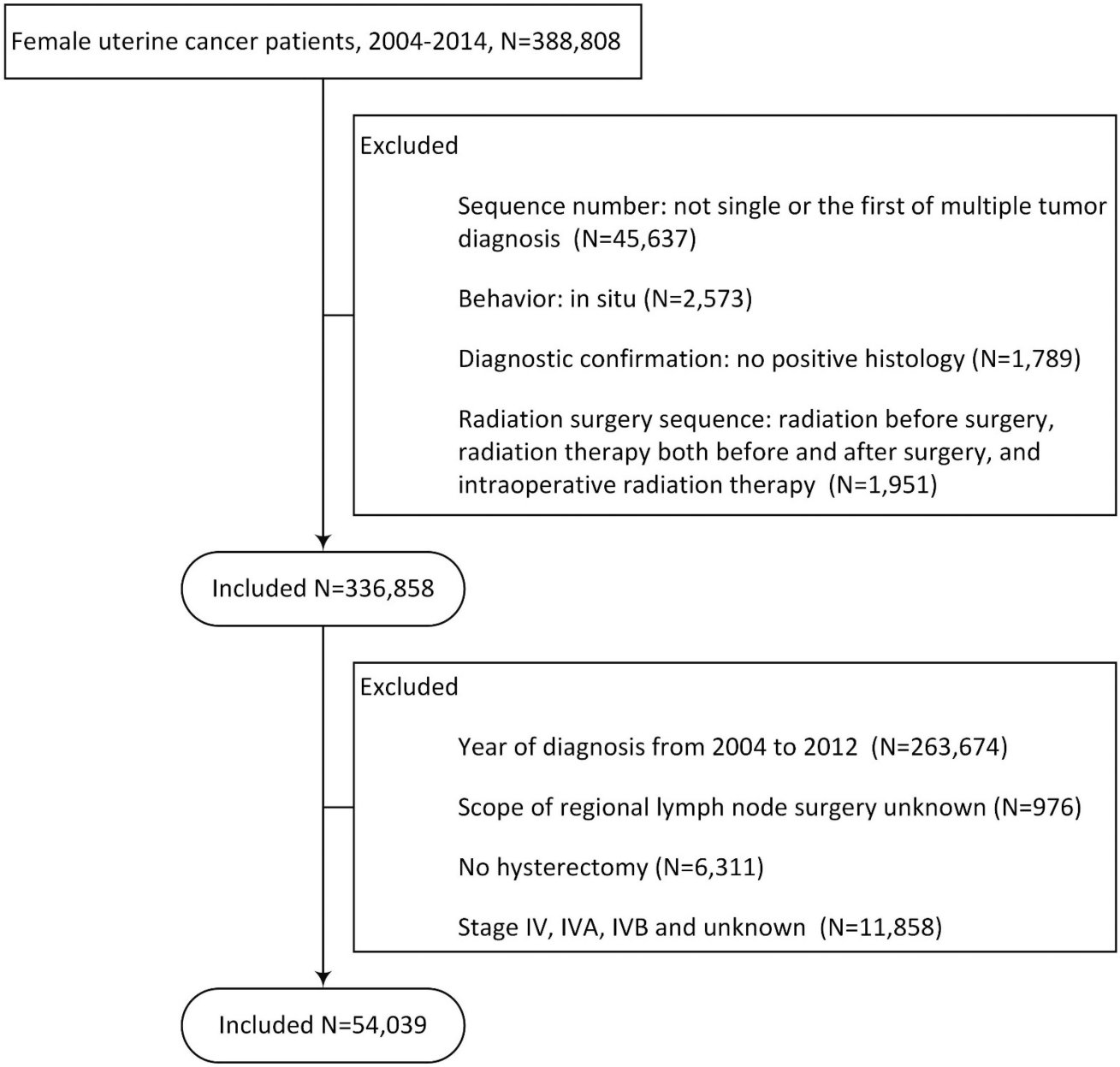

Table 1

Demographic and clinical characteristics of the patients by scope of lymph node dissection.

	No LND		Sentinel LN		LND		
	N	%	N	%	N	%	*P*-value
All	13,657	(25.3)	1,929	(3.6)	38,453	(71.2)	
Age							<0.001
<50	2,165	(15.9)	187	(9.7)	3,704	(9.6)	
50–59	4,201	(30.8)	565	(29.3)	10,499	(27.3)	
60–69	4,584	(33.6)	741	(38.4)	14,968	(38.9)	
70–79	1,758	(12.9)	342	(17.7)	7,233	(18.8)	
≥80	949	(6.9)	94	(4.9)	2,049	(5.3)	
Race							<0.001
White	10,716	(78.5)	1,508	(78.2)	30,167	(78.5)	
Black	1,269	(9.3)	126	(6.5)	3,894	(10.1)	
Hispanic	1,018	(7.5)	103	(5.3)	2,316	(6.0)	
Other	539	(3.9)	175	(9.1)	1,759	(4.6)	
Unknown	115	(0.8)	17	(0.9)	317	(0.8)	
Year of diagnosis							<0.001
2013	6,675	(48.9)	751	(38.9)	19,260	(50.1)	
2014	6,982	(51.1)	1,178	(61.1)	19,193	(49.9)	
Insurance status							<0.001
Private	7,134	(52.2)	1,045	(54.2)	18,820	(48.9)	
Medicare	4,711	(34.5)	728	(37.7)	15,234	(39.6)	
Medicaid	938	(6.9)	94	(4.9)	2,126	(5.5)	
Uninsured	545	(4.0)	28	(1.5)	1,314	(3.4)	
Other government/unknown	329	(2.4)	34	(1.8)	959	(2.5)	
Income							<0.001
<$38,000	2,348	(17.2)	163	(8.4)	6,210	(16.1)	
$38,000–$47,999	3,066	(22.5)	314	(16.3)	8,670	(22.5)	
$48,000–$62,999	3,684	(27.0)	471	(24.4)	10,536	(27.4)	
$63,000+	4,535	(33.2)	978	(50.7)	12,967	(33.7)	
Unknown	24	(0.2)	*	*	70	(0.2)	
Education							<0.001
≥21%	2,587	(18.9)	231	(12.0)	6,172	(16.1)	
13–20%	3,544	(26.0)	402	(20.8)	9,792	(25.5)	
7.0–12.9%	4,297	(31.5)	717	(37.2)	12,718	(33.1)	
<7%	3,211	(23.5)	576	(29.9)	9,715	(25.3)	
Unknown	18	(0.1)	*	*	56	(0.1)	
Location							<0.001
Metropolitan	11,108	(81.3)	1,642	(85.1)	31,225	(81.2)	
Urban	1,919	(14.1)	154	(8.0)	5,616	(14.6)	
Rural	224	(1.6)	*	*	701	(1.8)	

	No LND		Sentinel LN		LND		
	N	%	N	%	N	%	*P*-value
Unknown	406	(3.0)	127	(6.6)	911	(2.4)	
Comorbidity							<0.001
0	9,776	(71.6)	1,413	(73.3)	28,780	(74.8)	
1	3,068	(22.5)	458	(23.7)	7,941	(20.7)	
≥2	813	(6.0)	58	(3.0)	1,732	(4.5)	
Facility type							<0.001
Academic/research	5,501	(40.3)	1,027	(53.2)	16,204	(42.1)	
Community cancer	744	(5.4)	97	(5.0)	1,505	(3.9)	
Comprehensive community cancer	5,253	(38.5)	640	(33.2)	15,266	(39.7)	
Integrated network cancer	1,594	(11.7)	122	(6.3)	4,581	(11.9)	
Other/unknown	565	(4.1)	43	(2.2)	897	(2.3)	
Facility region							<0.001
Northeast	2,691	(19.7)	876	(45.4)	8,171	(21.2)	
Midwest	3,321	(24.3)	272	(14.1)	10,101	(26.3)	
South	4,546	(33.3)	460	(23.8)	12,637	(32.9)	
West	2,534	(18.6)	278	(14.4)	6,647	(17.3)	
Unknown	565	(4.1)	43	(2.2)	897	(2.3)	
Stage							<0.001
IA	9,682	(70.9)	1,271	(65.9)	20,588	(53.5)	
IB	1,531	(11.2)	276	(14.3)	7,447	(19.4)	
I NOS	1,175	(8.6)	63	(3.3)	1,470	(3.8)	
II	529	(3.9)	71	(3.7)	2,330	(6.1)	
IIIA	460	(3.4)	46	(2.4)	1,417	(3.7)	
IIIB	183	(1.3)	16	(0.8)	438	(1.1)	
IIIC	58	(0.4)	184	(9.5)	4,686	(12.2)	
III NOS	39	(0.3)	*	*	77	(0.2)	
Histology							<0.001
Endometrioid	10,900	(79.8)	1,519	(78.7)	27,578	(71.7)	
Serous	345	(2.5)	110	(5.7)	2,957	(7.7)	
Clear Cell	74	(0.5)	18	(0.9)	561	(1.5)	
Carcinosarcoma	284	(2.1)	51	(2.6)	1,794	(4.7)	
Sarcoma	547	(4.0)	12	(0.6)	550	(1.4)	
Other	1,507	(11.0)	219	(11.4)	5,013	(13.0)	
Grade							<0.001
Well	7,006	(51.3)	738	(38.3)	11,364	(29.6)	
Moderate	2,447	(17.9)	493	(25.6)	9,397	(24.4)	
Poorly	1,244	(9.1)	309	(16.0)	9,220	(24.0)	
Unknown	2,960	(21.7)	389	(20.2)	8,472	(22.0)	
Radiation							<0.001
None/unknown	11,963	(87.6)	1,405	(72.8)	25,720	(66.9)	
Combination	292	(2.1)	46	(2.4)	2,063	(5.4)	

	No LND		Sentinel LN		LND		
	N	%	N	%	N	%	*P*-value
External beam	518	(3.8)	112	(5.8)	3,086	(8.0)	
Brachytherapy	884	(6.5)	366	(19.0)	7,584	(19.7)	

* Cell size<10. NOS: not otherwise specified

Table 2

Number of sentinel lymph nodes removed in patients that had sentinel lymph nodes mapping.

	SLN only		SLN with LND	
Number of sentinel LN removed				
N	863		1,038	
Mean (SD)	4	(5)	16	(10)
Median (IQR)	3	(2–4)	14	(9–21)

1,901 patients in the sentinel LN group were included in the analysis. 28 patients, including 14 having SLN only, and 14 having SLN and LND) with unknown number were excluded.

SD: standard deviation.

IQR: interquartile range.

Table 3

Multivariable models for predictors of sentinel lymph node mapping.

	Sentinel LN vs LND	Sentinel LN vs No LND
	aRR	aRR
Age		
<50	Referent	Referent
50–59	1.08 (0.90–1.30)	1.06 (0.88–1.27)
60–69	1.11 (0.92–1.34)	1.12 (0.93–1.35)
70–79	1.04 (0.83–1.29)	1.18 (0.95–1.48)
≥80	1.14 (0.86–1.51)	0.80 (0.60–1.06)
Race		
White	Referent	Referent
Black	0.84 (0.69–1.02)	0.88 (0.72–1.07)
Hispanic	1.04 (0.84–1.28)	1.02 (0.82–1.27)
Other	0.88 (0.72–1.08)	1.04 (0.84–1.29)
Unknown	0.68 (0.42–1.10)	0.84 (0.52–1.38)
Year of diagnosis		
2013	Referent	Referent
2014	1.60 (1.46–1.76)*	1.36 (1.24–1.50)*
Insurance status		
Private	Referent	Referent
Medicare	1.02 (0.90–1.15)	0.94 (0.83–1.07)
Medicaid	0.98 (0.79–1.22)	0.95 (0.76–1.19)
Uninsured	0.74 (0.51–1.10)	0.69 (0.47–1.03)
Other government/unknown	0.96 (0.67–1.36)	0.86 (0.61–1.23)
Income		
<$38,000	Referent	Referent
$38,000–$47,999	1.18 (0.97–1.43)	1.08 (0.89–1.32)
$48,000–$62,999	1.12 (0.92–1.35)	1.06 (0.88–1.28)
$63,000+	1.18 (0.97–1.42)	1.13 (0.93–1.37)
Unknown	1.39 (0.44–4.46)	0.81 (0.25–2.63)
Location		
Metropolitan	Referent	Referent
Urban	0.87 (0.72–1.04)	0.90 (0.75–1.08)
Rural	0.56 (0.25–1.26)	0.59 (0.26–1.34)
Unknown	1.04 (0.80–1.34)	1.12 (0.87–1.45)
Comorbidity		
0	Referent	Referent
1	1.08 (0.97–1.20)	0.97 (0.87–1.09)
≥2	0.77 (0.59–1.01)	0.68 (0.52–0.88)*
Facility type		
Academic/research	Referent	Referent

	Sentinel LN vs LND	Sentinel LN vs No LND
	aRR	aRR
Community cancer	1.72 (1.04–2.86)*	1.07 (0.65–1.75)
Comprehensive community cancer	1.11 (0.79–1.57)	1.05 (0.75–1.47)
Integrated network cancer	0.92 (0.51–1.66)	0.91 (0.51–1.64)
Other/unknown	_≠	_≠
Facility region		
Northeast	Referent	Referent
Midwest	0.65 (0.43–0.99)*	0.72 (0.48–1.10)
South	0.58 (0.39–0.86)*	0.63 (0.42–0.93)*
West	0.64 (0.40–1.01)	0.66 (0.42–1.04)
Unknown	_≠	_≠
Stage		
IA	Referent	Referent
IB	0.78 (0.68–0.90)*	1.25 (1.09–1.44)*
I NOS	1.01 (0.77–1.32)	0.80 (0.60–1.05)
II	0.67 (0.53–0.86)*	1.04 (0.81–1.33)
IIIA	0.72 (0.54–0.97)*	0.90 (0.66–1.22)
IIIB	0.86 (0.52–1.43)	0.77 (0.46–1.28)
IIIC	0.69 (0.59–0.81)*	1.56 (1.32–1.84)*
III NOS	1.18 (0.29–4.85)	0.49 (0.12–2.00)
Histology		
Endometrioid	Referent	Referent
Serous	0.96 (0.77–1.19)	1.24 (0.99–1.54)
Clear Cell	0.74 (0.46–1.19)	1.15 (0.71–1.86)
Carcinosarcoma	0.74 (0.55–0.99)*	0.89 (0.66–1.21)
Sarcoma	0.54 (0.30–0.95)*	0.22 (0.13–0.40)*
Other	1.01 (0.87–1.17)	1.13 (0.98–1.32)
Grade		
Well	Referent	Referent
Moderate	0.91 (0.81–1.02)	1.35 (1.20–1.53)*
Poorly	0.70 (0.60–0.82)*	1.44 (1.23–1.69)*
Unknown	0.91 (0.79–1.04)	1.18 (1.02–1.35)*

aRR: adjusted risk ratio.

*P-value < 0.05.

≠Unestimable due to multicollinearity between the unknown groups of facility type and facility region.

82.4% of all patients were reported from only one CoC-accredited hospital. Sensitivity analysis was performed limiting to those cases and showed similar results.

Table 4

Multivariable models for predictors of any type of radiation and external beam or combination among stage I patients who had sentinel lymph node mapping or lymphadenectomy.

	Any Radiation aRR	External Beam/Combination aRR
Age		
<50	Referent	Referent
50–59	1.32 (1.17–1.49) *	1.04 (0.80–1.34)
60–69	1.42 (1.25–1.60) *	1.08 (0.83–1.39)
70–79	1.46 (1.28–1.67) *	1.09 (0.82–1.44)
≥80	1.01 (0.86–1.18)	0.57 (0.40–0.82) *
Race		
White	Referent	Referent
Black	1.05 (0.97–1.15)	1.27 (1.08–1.51) *
Hispanic	1.02 (0.91–1.14)	1.14 (0.92–1.43)
Other	1.04 (0.93–1.17)	1.40 (1.11–1.77) *
Unknown	0.88 (0.68–1.15)	0.88 (0.49–1.58)
Year of diagnosis		
2013	Referent	Referent
2014	1.02 (0.98–1.07)	1.00 (0.90–1.10)
Insurance status		
Private	Referent	Referent
Medicare	1.05 (0.99–1.11)	1.02 (0.89–1.17)
Medicaid	0.99 (0.89–1.11)	1.17 (0.93–1.46)
Uninsured	0.97 (0.84–1.13)	1.15 (0.87–1.52)
Other government/unknown	0.94 (0.80–1.11)	1.02 (0.71–1.46)
Income		
<$38,000	Referent	Referent
$38,000–$47,999	1.01 (0.94–1.10)	0.91 (0.77–1.08)
$48,000–$62,999	0.99 (0.91–1.07)	0.87 (0.74–1.03)
$63,000+	1.03 (0.95–1.12)	0.85 (0.71–1.01)
Unknown	0.74 (0.39–1.39)	0.33 (0.05–2.40)
Location		
Metropolitan	Referent	Referent
Urban	1.00 (0.93–1.08)	0.88 (0.74–1.04)
Rural	1.18 (1.00–1.40)	1.01 (0.68–1.51)
Unknown	1.03 (0.88–1.21)	0.93 (0.63–1.37)
Comorbidity		
0	Referent	Referent
1	0.96 (0.90–1.01)	0.87 (0.76–1.00) *
≥2	0.88 (0.78–0.98) *	0.97 (0.76–1.24)

	Any Radiation	External Beam/Combination
	aRR	aRR
Facility type		
Academic/research	Referent	Referent
Community cancer	1.04 (0.88–1.22)	2.17 (1.67–2.81) *
Comprehensive community cancer	1.06 (0.96–1.18)	1.44 (1.21–1.72) *
Integrated network cancer	1.11 (0.94–1.32)	1.38 (1.04–1.83) *
Other/unknown	_≠	_≠
Facility region		
Northeast	Referent	Referent
Midwest	0.86 (0.75–0.97) *	1.25 (1.01–1.56) *
South	0.64 (0.56–0.72) *	0.89 (0.71–1.11)
West	0.68 (0.59–0.79) *	0.93 (0.72–1.18)
Unknown	_≠	_≠
Stage		
IA	Referent	Referent
IB	2.93 (2.80–3.07) *	5.98 (5.33–6.71) *
I NOS	0.98 (0.85–1.13)	1.79 (1.34–2.39) *
Histology		
Endometrioid	Referent	Referent
Serous	1.11 (1.02–1.20) *	1.01 (0.83–1.23)
Clear Cell	1.21 (1.01–1.44) *	1.46 (1.00–2.13) *
Carcinosarcoma	1.10 (0.99–1.22)	1.78 (1.48–2.14) *
Sarcoma	0.31 (0.23–0.40) *	0.71 (0.51–0.99) *
Other	1.10 (1.03–1.17) *	1.16 (1.00–1.35) *
Grade		
Well	Referent	Referent
Moderate	1.90 (1.77–2.03) *	2.08 (1.72–2.50) *
Poorly	3.01 (2.80–3.23) *	5.39 (4.52–6.44) *
Unknown	1.86 (1.72–2.01) *	2.57 (2.12–3.12) *
Scope of lymph node dissection		
Lymphadenectomy	Referent	Referent
Sentinel lymph node mapping	0.92 (0.82–1.05)	0.98 (0.70–1.36)

aRR: adjusted risk ratio.

* *P*-value < 0.05.

≠ Unestimable due to multicollinearity between the unknown groups of facility type and facility region.

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Discussion

Discussion

Our findings suggests that the sentinel lymph node mapping in early-stage endometrial carcinoma is a safe, valid, and effective technique for lymphatic assessment, reflecting the real tumor status of the rest of the regional nodes and avoiding the consequences of an extended lymphadenectomy. Hence, this technique allows to improve the quality of life of our patients.

Role of sentinel lymph node mapping

In the present study, we performed a systematic review on series evaluating the experience reported in the literature regarding indocyanine green for sentinel lymph node biopsy in cervical or endometrial cancer. The technique used for indocyanine green sentinel lymph node mapping is as follows: The cervix is prepped and the indocyanine green is injected before laparotomy or insertion of the uterine manipulator (in minimally invasive cases). The concentration used is 1.25 mg/mL. For each patient a 25-mg vial with indocyanine green powder is diluted in 20 mL of sterile water. We routinely inject 4 mL of the indocyanine green solution into the cervix divided in the 3- and 9 o'clock positions, with 1-mL deep into the stroma and 1 mL submucosally on the right and the left of the cervix. Using this technique with indocyanine green, we found that bilateral mapping is significantly improved using indocyanine green, reaching rates of 95%.

Regarding the indocyanine green use, the appropriate dosing of indocyanine green, has been previously addressed in a study by Levinson et al (146), where the authors used 4 concentrations of indocyanine green (1000, 500, 250, and 175 mg/.5 mL) and they concluded that an indocyanine green dose of 250 to 500 mg enables identification of a sentinel lymph node with more distinction from the surrounding tissues.

In terms of sensitivity and negative predictive value of the sentinel-lymph-node mapping technique compared with the gold standard of complete lymphadenectomy in detecting metastatic disease, the FIRES trial was published. (147) A total of 385 patients with clinical stage I endometrial cancer of all histologies and grades undergoing robotic staging. Patients received a standardized cervical injection of indocyanine green and sentinel-lymph-node mapping followed by pelvic lymphadenectomy with or without para-aortic lymphadenectomy. Two hundred and ninety-three (86%) patients had successful mapping of at least one sentinel lymph node, forty-one (12%) patients had positive nodes, 36 of whom had at least one mapped sentinel lymph node. Nodal metastases were identified in the sentinel lymph nodes of 35 (97%) of these 36 patients, yielding a sensitivity to detect node-positive disease of 97,2% (95% CI 85,0–100), and a negative predictive value of 99,6% (97,9–100). The authors stated that sentinel lymph nodes identified with indocyanine green have a high degree of diagnostic accuracy in detecting endometrial cancer metastases and can safely replace lymphadenectomy in the staging of endometrial cancer.

Moreover, the first study to evaluate the use of indocyanine green in patients with endometrial cancer and in the setting of minimally invasive surgery was published by Rossi et al. (148). A total of 0.5 mg indocyanine green was injected into the cervical stroma at the 3 o'clock and 9 o'clock positions. At least one sentinel lymph node was identified in 17 patients (85%) with a median of 4.5 nodes identified per patient (range: 0–9). The median number of non-sentinel lymph nodes removed in each patient was 23,5 (range: 4–56). Bilateral sentinel lymph nodes were identified in 12 patients (60%) with no false-negative nodes. sentinel lymph nodes were not detected in 3 patients. Three patients had node-positive disease.

Later, Holloway et al (149) aimed to compare the ability of indocyanine green and standard colorimetric analysis of isosulfan blue dye for the detection of sentinel lymph node in endometrial cancer. A total of 1 mL of isosulfan blue was injected in cervix, followed by 0.5 mL indocyanine green immediately before placement of a uterine manipulator. Twenty-seven (77%) and 34 (97%) patients had bilateral pelvic or aortic sentinel lymph node detected by colorimetric and fluorescence, respectively (p=0.03). Using both methods, bilateral detection was 100%. Ten patients (28.6%) had lymph node metastasis, and 9 of these had sentinel lymph node metastasis (90% sensitivity, one false- negative sentinel lymph node biopsy). Seven of 9 (78%) sentinel lymph node metastases were isosulfan blue positives and 100% were indocyanine green positive. Twenty- five patients had negative sentinel lymph node biopsies (100% of specificity).

Regarding minimally invasive surgery, the most recent and largest study to date using the robotic platform is the study published by Jewell et al. in 2014. (150) This

retrospective study aimed to assess the detection rate of sentinel lymph nodes using indocyanine green and NIR fluorescence imaging. In that study, 1.25 mg indocyanine green was injected into the cervix of 227 patients. Blue dye was concurrently injected in 30 cases. The median sentinel lymph node count was 3 (range: 1–3). The overall detection rate of the sentinel lymph node (unilateral or bilateral) for this cohort of patients was 95% (216/227). When indocyanine green was used alone, 95% of patients (188/197) mapped either unilateral or bilaterally compared with 93% (28/30) in cases in which both dyes were used (non-significant). The bilateral detection rate was 79% (179/227) overall. The bilateral sentinel lymph node detection rate for indocyanine green alone was 79% (156/197) compared with 77% (23/30) for indocyanine green and blue dye (non-significant). In this study, the authors also showed that 10% of patients had sentinel lymph nodes identified in the aortic region. The study concluded that intracervical injection of indocyanine green has a high bilateral detection rate and appears to offer an advantage over using blue dye alone. The authors stated that combined use of indocyanine green and blue dye appeared to be unnecessary.

Furthermore, a meta-analysis published by Ruscito et al. (151) evaluating overall and bilateral detection rates for sentinel lymph node mapping in uterine cancer using different tracers, they observed that indocyanine green sentinel lymph node mapping increases both overall and bilateral detection rates by 27 % compared with blue dyes in 538 patients included in the study. No differences were recorded in overall and bilateral detection rates between indocyanine green and ^{99}TC. When comparing indocyanine green with the combination of blue dyes and ^{99}Tc, no differences in overall detection rate between the two groups were

recorded. Although non-significant, an improvement in bilateral detection rate for indocyanine green was noted. As far as false-negative rates, no differences were recorded between indocyanine green and other conventional tracers.

In terms of prospectives studies, a randomized phase III multicenter study was published by Frumovitz et al. (152) to determine whether indocyanine green, fluorescent dye is superior to isosulfan blue dye in detecting sentinel lymph nodes in women with cervical and uterine cancers. A total of 163 patients with clinical stage I endometrial or cervical cancer undergoing curative surgery were randomly assigned 1:1 to lymphatic mapping with isosulfan blue (visualized by white light) followed by indocyanine green (visualized by near infrared imaging) or indocyanine green followed by isosulfan blue. Laparoscopic surgery with the PINPOINT near infrared fluorescence imaging system (Stryker, Kalamazoo, MI) was used in all cases. A total of 517 sentinel nodes were identified. Of these, 478 (93%) were confirmed to be lymph nodes on pathologic processing: 92% (219/238) of nodes that were both blue and green, 100% (7/7) of nodes that were blue only, and 95% (252/265) of nodes that were green only (p=0,33). The conclusions of the study were that indocyanine green identifies more sentinel nodes than isosulfan blue in women with cervical and uterine cancers with no difference in the pathologic confirmation of nodal tissue between the two mapping substances.

Interestingly, Cabrera et al. (153) published a prospective, non-randomized, single-center trial including eighty-four patients with endometrial cancer (any grade or histology) in pre-operative early stage and operated on between February 2017 and July 2019; To compare the overall and bilateral detection rates for sentinel

lymph node biopsy using two combined techniques: technetium-99m-indocyanine green (Tc-99m- indocyanine green) versus technetium-99m-methylene blue (Tc-99m-methylen blue). All tracers were injected intracervically. Pelvic and aortic lymphadenectomy were performed on patients at intermediate or high risk of recurrence pre-operatively. All sentinel lymph nodes were sent for intra-operative frozen section and afterwards processed following an ultrastaging protocol. The overall detection rate was 93% and was not statistically different between the two groups and better bilateral detection rate was observed among Tc-99m- indocyanine green patients (69% vs 41%, p=0.012). In addition, a randomized controlled trial (154) highlighted that the use of indocyanine green alone instead of methylene blue dye resulted in a significant increase in sentinel lymph node detection rates per hemipelvis in women with endometrial carcinoma undergoing minimally invasive surgery with a detection rate of 90.9% using indocyanine green.

Hence, similar results are published by the COMBITEC study. (155) A multicentre retrospective study in which a total of 180 patients were included to compare the overall and bilateral pelvic detection rates of sentinel lymph nodes in two retrospective cohorts: indocyanine green exclusive vs. combined indocyanine green +99m-Tc. The overall detection rate was 92.8% without significant differences between groups (indocyanine green: 94.6% vs indocyanine green +99m-Tc: 90.9%, p= .34). It should be noted that no significant differences were observed neither in bilateral pelvic nor aortic mapping rate. The authors conclude that the use of 99m-Tc is not associate to a higher bilateral detections rate and even more, when 99m-Tc was used, surgical procedures were significantly longer.

Another consideration is the quality of life in regards of the type of sentinel lymph node technique. As far as we know, the cervical injection is the most convenience for surgeons as for patients. However, the type of tracers used has also influenced in our patients. For example, the study published by Buda et al. (156) 106 women with preoperative stage I endometrial cancer who underwent surgical staging with sentinel lymph node mapping (intracervical preoperative injection of Tc99m nanocolloid and intraoperative blue dye versus intraoperative cervical injection of indocyanine green or blue dye), were assessed using the European Organization for Research and Treatment of Cancer IN-PATSAT32 questionnaire. Curiously, the analysis of IN-PATSAT32 questionnaire scores showed a higher patient satisfaction score for patients in which cervical injection of indocyanine green was used (p= 0.001), which was independent of the physician and surgical outcomes evaluated. The scores were statistically better and in rating doctors (p= 0.0001), nurses (p= 0.006), and care and services organizations (p= 0.001).

On the other hand, in regards of high-intermediate risk patients, the prospective study SHREC (157) is published to assess the diagnostic accuracy of a pelvic sentinel lymph node mapping. Two hundred fifty-seven women with presumed FIGO stage I-II underwent robotic surgery, a cervical injection of indocyanine green was performed with reinjection of tracer in case of non-display of predefined lymphatic pathways. After removal of sentinel lymph nodes, a pelvic and infrarenal paraaortic lymphadenectomy was performed. Fifty-four had pelvic lymph node metastases, and 52 of those were correctly identified by the sentinel lymph node-indocyanine green algorithm. The sensitivity of the overall sentinel lymph node algorithm was 100% (95% CI 92-100) and the negative predictive value was 100%

(95% CI 98-100). The bilateral mapping rate was 95%. Two women (1%) had isolated paraaortic metastases. The conclusion of the study was as following: the described pelvic sentinel lymph node algorithm can, in the hands of experienced surgeons, exclude overall nodal involvement in 99% and thereby safely replace a full lymphadenectomy in high-risk endometrial carcinoma.

Consequently, Cusimano et al. (158) found the similar results in the SENTOR study. A prospective, multicenter cohort study which enrolled 156 patients with clinical stage I grade 2 endometrioid or high-grade endometrial carcinoma who underwent sentinel lymph node technique followed by lymphadenectomy. Patients with grade 2 endometrioid endometrial carcinoma underwent pelvic lymphadenectomy alone, and patients with high-grade endometrial carcinoma underwent pelvic lymphadenectomy and paraaortic lymphadenectomy. Sentinel lymph node detection rates were 97.4% per patient (95% CI, 93.6%-99.3%), 87.5% per hemipelvis (95% CI, 83.3%-91.0%), and 77.6% bilaterally (95% CI, 70.2%-83.8%). Of 27 patients (17%) with nodal metastases, 26 patients were correctly identified by the sentinel lymph node mapping, yielding a sensitivity of 96% (95% CI, 81%-100%), a false-negative rate of 4% (95% CI, 0%-19%), and a negative predictive value of 99% (95% CI, 96%-100%). The authors stated that sentinel lymph node mapping had acceptable diagnostic accuracy for patients with high-grade endometrial carcinoma at increased risk of nodal metastases and improved the detection of node-positive cases compared with lymphadenectomy.

Limitations of ICG

Although there are many suggested benefits of indocyanine green over other tracers for performing sentinel lymph node identification and lymphatic mapping, one must also recognize that there are certain potential limitations. Jewell et al. (159) found that BMI appeared to impact the success rate of sentinel lymph node mapping. In their report, the median BMI of patients in whom a sentinel lymph node was detected was 30,1 kg/m2 (range: 17,7–59,6) compared with 41,2 kg/m2 (range: 25,1–60,4) for patients who did not map (p=0,01). Median BMI appeared to impact bilateral mapping, with the median BMI of unilaterally and bilaterally mapped cases being 34 kg/m2 (range: 17,9–49) and 29,6 kg/m2 (range: 17,7–59,6), respectively (p=0.02). Tanner et al. (160) evaluated patient, tumor, and surgeon factors associated with successful bilateral mapping in patients with endometrial cancer using isosulfan blue or indocyanine green. In that study, the authors found that the rate of successful bilateral mapping decreased with a BMI more than 30 kg/m2 and that although the rate of success with indocyanine green is superior to isosulfan blue, the variability is more pronounced at higher BMIs.

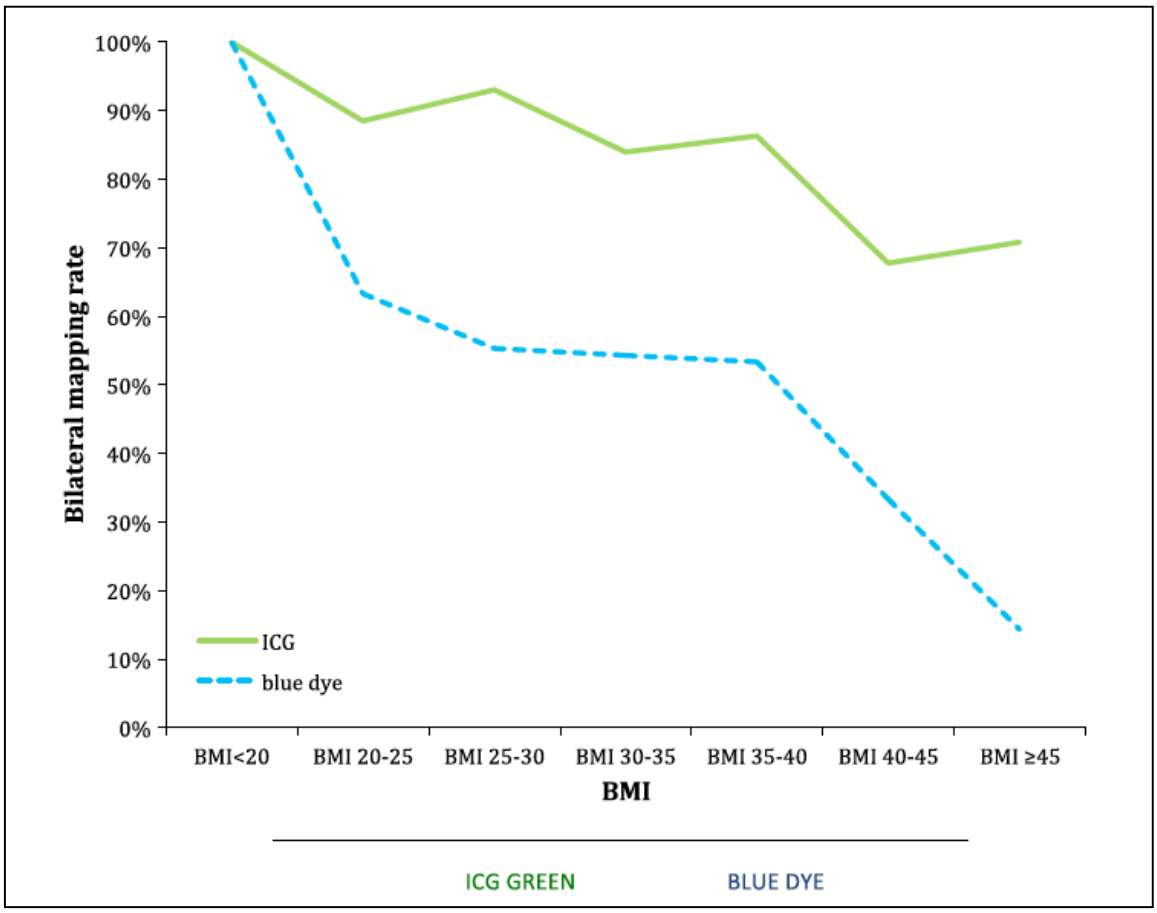

Image 4: Comparison of ICG vs blue dye with the increase of BMI. *Eriksson AG et al. Gynecol Oncol. 2016 Mar;140(3):394-9*

Interestingly, the learning curve seems to be important in order to obtain higher detection rates with indocyanine green. For instance, a prospective study published by Ianieri et al. (161) analyzes the factors associated with the possible failure of bilateral sentinel lymph node mapping with indocyanine green. A total of 110 patients with endometrial cancer apparently confined to the uterus underwent laparoscopic surgical staging with sentinel lymph node mapping with

indocyanine green. The bilateral detection rate for sentinel lymph nodes mapping was 72.7%, whereas at least one sentinel lymph node was detected in 79.1% of patients. No sentinel lymph nodes were identified in 6.3%. None of the patients or features related to tumor were associated with a risk of failure of the method. The only factor analyzed that was significantly associated with the success of bilateral mapping was the surgeon ($p = 0.003$).

Another subject of particular interest with any tracer is that such dyes can be associated with an allergic reaction. Patients with iodine allergy should not be exposed to indocyanine green because it contains 5% sodium iodide. (29) The risk of an allergic reaction to indocyanine green has been estimated at 1:42,000 uses. (28) In addition, it is not recommended that patients with liver compromise be exposed to indocyanine green because it is metabolized in the liver.

Besides these limitations, the new ESGO-ESMO-ESP guidelines published (12) recommends that sentinel lymph node biopsy can be considered for staging purposes in patients with low-risk/intermediate-risk disease and indocyanine green with cervical injection is the preferred detection technique.

In conclusion, given that other dye types and the combination of dye and radio-tracer demonstrated high overall sentinel lymph node detection rates but did not significantly improve bilateral mapping rates, indocyanine green could be considered as the preferred mapping agent for sentinel lymph node mapping of endometrial cancer. Additionally, the use of indocyanine green has several advantages compared with radiocolloids, including less pain with injection, lower

cost, fewer adverse effects. The good toxicity profile and ease of use of indocyanine green, which does not require the injection in a controlled environment and image acquisition before surgery, along with the availability of integrated platforms for minimally invasive approaches that make the sentinel lymph node mapping easy and intuitive, may favor the choice of this tracer over the combination of blue dyes and ^{99}Tc.

The low volume disease in sentinel lymph node mapping

Regarding the prognostic significance of low volume disease, the presence of lymphatic metastases has been found to have influence onto the prognosis of the disease. The 5-year disease-free survival in stage I patients with positive pelvic nodes is 54%, compared to 90% for those with negative nodes. (12)

Ultrastaging technique

The type of technique used for pathological assessment of sentinel lymph nodes is important since the incidence of micrometastases in the sentinel lymph nodes depends on the technique used and the patients' characteristics. Interestingly, immunohistochemistry staining has been associated with a higher detection rate of metastatic sentinel lymph nodes. For instance, Niikura et al. (76) and Pelosi et al. (73) reported, respectively, four and one patient with positive sentinel lymph

node for micrometastases, whom would have been considered negative with a standard H&E test.

In 2003, Gónzalez-Bosquet et. al (162) published a study to assess the sensitivity of cytokeratin staining in detecting occult nodal metastases. Twenty-five patients with high-risk endometrial cancer were included. All selected patients underwent complete pelvic lymphadenectomy. A total of 729 pelvic and paraaortic nodes were analyzed without using serial sectioning; Fourth of these nodes presented metastatic involvement in the H&E analysis. In the 16 patients with no lymph node involvement detected by classical techniques, immunohistochemistry techniques were subsequently performed, and micrometastases was reported in 2 of them (12.5%).

Furthermore, in the Solima et al. study (81), peritumoral radiocolloid hysteroscopic injection and immunohistochemistry techniques were used in those sentinel lymph nodes that had been negative for H&E. Due to the immunohistochemistry, six more positive sentinel lymph nodes were detected than with the traditional H&E. Two of them were paraaortic, one isolated and the other one was associated with another positive pelvic sentinel lymph node. The negative predictive value was 98% and the sensitivity was 90%. There was only a false negative case among the 49 negative sentinel lymph nodes, and this was high risk in the final pathological analysis, reinforcing the theory that the sentinel lymph node technique is less effective in these cases.

At the same time, Holloway et al. (149), investigated as a secondary endpoint to compare the detection of metastatic disease by ultrastaging followed by immunohistochemistry vs the traditional H&E. H&E staining of sentinel lymph nodes (at least six serial sections four microns thick at 40-micron intervals) before immunohistochemistry analysis, and then modified their reports based on the malignant cells identified. For immunohistochemistry analysis, an additional 4-micron section was cut between the third and fourth levels and stained with anti-AE1 / AE-3 cytokeratin mouse monoclonal antibody. Standard definitions derived from immunohistochemistry analysis of the breast cancer were used. In four of the 10 patients with lymph node involvement, metastasis was identified only by immunohistochemistry, representing an increase of 67% compared to routine H&E staining.

Later, in 2011, Khoury-Collado et al. (163) published a study to assess the incidence of metastasis in sentinel lymph nodes. They included 266 patients diagnosed with endometrial cancer regardless of their stage. Both, the tracer used, and the injection site varied throughout the study. Most received only two cervical blue dye intraoperative injections (3 and 9 hours), but some were also given cervical Tc99 the day before the operation and / or two extra-intraoperative blue dye injections were added to the uterine fundus. They obtained an overall detection rate of 84%, without distinguishing between injection sites or the tracer used. The sentinel lymph nodes obtained were analyzed. If the initial H&E examination was negative, two 5-micron sections were cut at each of the two levels 50 microns apart. At each level, one side was stained with H&E and the

other was stained by immunohistochemistry using anti-CK AE1: AE3 in a total of four sheets per block. Ultrastaging findings were reported as positive if isolated tumor cells or micrometastases were present. Positive sentinel lymph nodes were identified in 32 patients (12%), and of these, eight identified solely by ultrastaging. The results showed that sentinel lymph node biopsy, regardless of the tracer used, increases the detection of metastatic cells.

In fact, in the SENTI-ENDO study (59), metastases were observed in 20 of the 125 patients with stage I and II endometrial carcinoma included in the study (16%). Both, the sentinel lymph nodes, and the rest of the nodes were initially analyzed using classical techniques. Subsequently, ultrastaging was performed only on the sentinel lymph node. Each sentinel lymph node was sectioned at 3 mm intervals, and each section was analyzed in 4 parallel 200-micron subdivisions. H&E was used in each of these divisions, and the sections that were negative were subsequently subjected to immunohistochemistry using anti-CK AE1-AE3 antibodies. The sentinel lymph nodes were positive only in 16 patients of the 111 patients in whom a node was detected, that is, in 87.2% of the patients, lymphadenectomy could have been avoided. Staining with H&E was able to detect seven of the cases, while the other nine (47%) could only be detected by immunohistochemistry (one macrometastasis, seven micrometastases and one isolated tumor cell). None of the eight patients with micrometastases or isolated tumor cells reported in the sentinel lymph nodes presented metastases in the lymphadenectomy. None of the patients with low grade tumors (stage IA grade 1 or 2) or intermediate risk (IA G3 or IB G1 or 2) presented metastatic disease

beyond the sentinel lymph node. However, the sentinel lymph node, was positive in 11% of cases low risk and 15% of intermediate risk.

These results are in accordance with Bezu et al. (164) who showed that the detection rate of micrometastases varies between 0 and 15% combining H&E, serial sectioning, and immunohistochemistry. Among the 238 patients included in this review, 20% had lymph node metastases, including 6% with micrometastases.

On the other hand, Fishman et al. (165) was the first to use the RT-PCR method for the detection of micrometastases due to Cytokeratin 20 (CK 20) overexpression. After an initial abdominal-pelvic inspection, surgery was started with lymph node sampling from both sides of the pelvis and, in some selected paraaortic patients. Of the 18 patients with negative nodes with the standard technique, 6 (33%) were positive with CK 20 using RT-PCR. The results suggest that RT-PCR CK 20 is capable of diagnosing occult lymph node metastases that were negative on routine histological examination. RT-PCR can be more sensitive than immunohistochemistry, which, in addition, can associate a higher false positive rate. Therefore, this study show that metastases not detected by classical cutting and staining techniques are frequent in endometrial carcinoma. It is important to identify this subgroup of patients at the time of lymphatic staging to adapt the adjuvant therapy. However, perform immunohistochemistry or RT-PCR on the entire nodes of the lymphadenectomy would be too expensive and laborious.

Lastly, Yabushita et al. (166) investigated, in a case-control study, the immunohistochemistry expression of cytokeratin in the regional lymphatic nodes of endometrial cancer patients and the influence on disease recurrence. They did not perform sentinel lymph node biopsy or ultrastaging, the concept of micrometastases was used to refer to metastases in which tumor cells were detected only by the immunohistochemistry method and not by H&E, and the concept of occult metastasis referred to the presence of isolated tumor cells. They showed that removing of micrometastases from the analysis was associated with a significant increase in disease-free survival, and that the recurrence rate was 36% in patients with micrometastases after 40 months of follow-up. Multivariate analysis revealed that cytokeratin expression in lymph nodes was an independent risk factor for recurrence of the disease in early-stage endometrial cancer ($p = 0.0096$).

Based on these results, we could conclude that sentinel lymph node mapping with pathologic ultrastaging identified low volume disease in 4.5% patients with endometrial cancer in whom no metastatic disease would have otherwise been detected by conventional pathologic processing. (144,167)

Oncological impact of low volume disease

In terms of oncologic outcomes, the findings of low volume metastases might have a negative impact on prognosis. We found that the total number of patients with micrometastases and isolated tumor cells was 286 (187 and 99, respectively).

And although, the 72% of patients received adjuvant therapies, they have a higher relative risk of recurrence of 1,34 (1,07-1,67) than the negative group. However, one of the main limitations of the reported studies is the small number of patients, giving a small power to the analysis to make any conclusion. Second, in some studies, there were isolated tumor cells patients who received adjuvant therapy (chemotherapy or radiation) because of high-risk uterine factors or more advanced disease, and probably the prognosis could change.

Recently, a recent international retrospective multicenter study published by Ghoniem et al (168) shows that patients with isolated tumor cells and grade 1 endometrioid disease (no lymphovascular space invasion/ uterine serosal invasion) had favorable prognosis, even without adjuvant therapy. Of 247 patients included with endometrial cancer and low-volume metastasis in the sentinel lymph nodes, 132 patients had isolated tumor cells and 115 had micrometastasis. Overall, 4-year recurrence-free survival was 77.6% (95% CI, 70.2%-85.9%); the median follow-up for patients without recurrence was 29.6 (interquartile range, 19.2-41.5) months. Among 47 endometrioid isolated tumor cells patients without adyuvant therapy, 4-year recurrence free survival was 82.6% (95% CI, 70.1%-97.2). Considering 18 isolated tumor cells patients with endometrioid grade 1 disease, without lymphovascular space invasion, uterine serosal invasion, or adjuvant therapy, only 1 had recurrence (median follow-up, 24.8 months). Notably, further analysis (with more patients and longer follow-up) is needed to assess whether adjuvant therapy can be withheld in this low-risk subgroup.

In conclusion, the current data shows a higher sensibility and specificity of ultrastaging technique to detect micrometastases and isolated tumor cells; however, when we find these low-volume metastases, the clinical implications on adjuvant therapy remain a controversy. The new ESGO- ESMO-ESTRO guidelines recommend assessing the lymph nodes by pathologic ultrastaging and regards of oncologic impact, they consider the isolated tumor cells as negative lymph nodes. (12) Further research is still needed to dilucidate the real implication on prognosis for micrometastases lymph node.

Prevalence of lower-extremity lymphedema after sentinel lymph node mapping

Our findings suggest that sentinel lymph node mapping compared with lymphadenectomy is associated with a much lower risk of lymphedema development in patients with early-stage endometrial cancer. In addition, it should be noted that lymphedema may compromise the quality of life of our patients and screening tools for early diagnose are imperative needed.

Likewise, our study is the first to assess patient reported lymphedema after sentinel lymph node mapping for endometrial cancer. We included 623 patients who were mailed a questionnaire that included a validated 13-item lymphedema screening survey and validated quality of life assessment tools. Sentinel lymph node mapping was independently associated with a significantly lower prevalence of patient- reported lymphedema, 27% for sentinel lymph node group of patients and 41% for lymphadenectomy group (OR, 1.85; 95% CI, 1.25-2.74;

p=0.002). Therefore, high BMI and adjuvant external beam radiation were associated with an increased prevalence of patient- reported lymphedema. Hence, the benefit of sentinel lymph node mapping over comprehensive lymphadenectomy lies in the reduction of lymphatic morbidity and subsequent improvement in quality of life.

For instance, in a prospective study of 188 patients (169) with endometrial cancer who underwent surgery by robotic platform, to compare the rate of lymphatic complications, the lymphadenectomy was restricted to removal of sentinel lymph nodes in low risk whereas in high-risk patients also a full lymphadenectomy was performed. The bilateral detection rate of sentinel lymph nodes with indocyanine green was 96% after cervical tracer injection. Hence, the incidence of lymphedema after sentinel lymph node mapping alone was 1.3% compared with 18.1% after pelvic and para- aortic lymphadenectomy ($p<0.0003$), lower than our results.

Interestingly, Yost et al. (170) from Mayo Clinic found no relationship between the number of lymph nodes removed or the extent of lymphadenectomy (pelvic vs. pelvic and para-aortic dissection) with development of lymphedema after adjusting for other risk factors in a multivariable analysis. They performed a validated 13-item lymphedema screening questionnaire and two validated quality-of-life measures to estimate the prevalence of lower-extremity lymphedema in patients surgically treated for endometrial cancer, identify predictors of lymphedema, and evaluate the effects of lymphedema on quality of life. They report that lymphedema prevalence in patients treated with hysterectomy alone

compared with lymphadenectomy was 36.1% and 52.3%, respectively. The attributable risk was 23%. Furthermore, a self-reported diagnosis of lymphedema was made in 23.3% of patients who underwent lymphadenectomy compared to 5.2% who did not. However, despite the differences in individual rates between our study and Mayo Clinic (170), the absolute difference was similar (14% and 15%, respectively). This may indicate that sentinel lymph node mapping does not contribute to the development of lymphedema beyond the hysterectomy itself and/or aging. However, our study has some limitations: Varying cutoff points among studies may alter baseline rates of lymphedema and recall bias is a concern in all studies of this design.

Other point to be considered is that most patients (77%) responded that their surgeon had not discussed the possibility of developing lymphedema as a result of their endometrial cancer surgery. It should be noted that for an early detection of the lymphedema is important to let the patient know the main signs of lymphedema.

Currently, there are no agreed upon standard guidelines for the diagnosis of lymphedema. Actually, the Gynecologic Cancer Lymphedema Questionnaire is another lymphedema tool, which was modified from the Lymphedema Breast Cancer Questionnaire and it was used to determine the feasibility and efficacy for lymphedema of the lower extremity. (171) Twenty-eight gynecologic cancer survivors with documented lymphedema and 30 without a history or presence of lymphedema completed the questionnaire. The 20-item Gynecologic Cancer Lymphedema Questionnaire has acceptable reported sensitivity and specificity

(85.7% and 90%, respectively).

Finally, the largest prospective study to comprehensively assess lymphedema and its associated risk factors in a cohort of gynecologic cancer patient was published by Gynecologic Oncology Group LEG study (GOG 244, The Lymphedema and Gynecologic Cancer Study). They assessed quality of life in 1,300 patients with endometrial, vulvar, and cervical cancer. (172) Women undergoing a lymph node dissection for endometrial, cervical, or vulvar cancer were eligible for enrollment. Leg volume was calculated from measurements at 10-cm intervals starting 10 cm above the bottom of the heel to the inguinal crease. Measurements were obtained preoperatively and postoperatively at 4–6 weeks, and at 3-, 6-, 9-, 12-, 18-, and 24- months. Lymphedema was defined as a limb volume change (LVC) ≥10% from baseline and categorized as mild: 10–19% limb volume change; moderate: 20–40% limb volume change; or severe: >40% limb volume change. Seven hundred and thirty-four endometrial, 138 cervical, and 42 vulvar patients evaluable for limb volume change assessment. The incidence of limb volume change ≥10% was 34% (n=247), 35% (n=48), and 43% (n=18), respectively. The findings confirm that lymphedema is a common problem for these patients, and these are according to our results in where the self- reported lymphedema was 27 % even using the sentinel lymph node technique.

Indeed, these data provide additional support for sentinel lymph node mapping in women with endometrial carcinoma, providing accurate surgical staging, as well as decreased morbidity and improved quality of life.

Trends in Sentinel Lymph Node Mapping

Despite the potential benefits of sentinel lymph node mapping, our data describes that the performance of the procedure in women with endometrial cancer is limited. In 2014, the National Comprehensive Cancer Network guidelines (NCCN) (62) included the sentinel lymph biopsy as a part of their accepted algorithm for staging. We noted that women with lower risk tumors (grade 1, superficially invasive) were more likely to undergo sentinel lymph node biopsy and those with higher risk features preferentially underwent lymphadenectomy.

Moreover, in 2017, Wright J et al. (173) suggests that despite the unclear role of sentinel lymph node biopsy in endometrial cancer, the use of the procedure increased rapidly from 2011 to 2015. The increased use of the procedure was most notable in women who underwent a robotic-assisted hysterectomy. Currently available robotic technology is often equipped with near infrared fluorescence imaging to allow performance of sentinel lymph node biopsy with indocyanine green. (174,175) Given that use of sentinel lymph node biopsy increased much more rapidly in women undergoing robotic-assisted hysterectomy, the easy access of this technology with the robotic platform may be one factor driving the diffusion of sentinel lymph node biopsy. Interestingly, prior work has suggested that surgeons are often influenced to use technological advances when they are readily available even in the absence of data. (176,177)

Regarding cost-effectiveness, Wright J et al. (178) reported that compared to lymphadenectomy, sentinel lymph node biopsy was associated with lower costs.

Among women who underwent minimally invasive hysterectomy, the adjusted cost of sentinel lymph node biopsy was approximately $700 lower than for lymphadenectomy. The lower cost for sentinel lymph node biopsy is likely multifactorial; the currently available agents used for sentinel lymph node mapping are relatively inexpensive and the time to perform a sentinel node biopsy is likely substantially less than a full lymphadenectomy. Prior studies of breast cancer have also reported that the costs of sentinel lymph node biopsy are lower than axillary dissection both in the short and long-term. (179) On this basis, also thanks to technical and technological attempts and the growing and interesting experiences in other malignancies (e.g., breast cancer, melanoma) we assisted to a paradigm shift in our clinical practice. In fact, the adoption of sentinel node mapping represents the most important and innovative change in endometrial cancer surgical treatment over the recent decades.

Recently, Burg et al. (180) published the first study to compare the three lymph node assessment strategies in terms of costs and effects: 1) sentinel lymph node mapping; 2) post-operative risk factor assessment (adjuvant therapy based on clinical and histological risk factors); 3) full lymph node dissection, showing that sentinel lymph node mapping was the most effective strategy for lymph node assessment in patients with low- and intermediate-risk endometrial cancer.

Interestingly, Chambers et al. (181) published an online survey to assess the practice of sentinel lymph node mapping, including incidence, patterns of usage, and reasons for non-use among Society of Gynecologic Oncology members. A total of 198 responses were collected. In those using sentinel lymph node

mapping in endometrial carcinoma, the majority (86.6%) performed sentinel lymph node mapping in >50% of cases for all patients (56.3%), grade 1 (43.0%) and 2 (42.2%). Reported benefits of sentinel lymph node mapping in endometrial carcinoma were reduced surgical morbidity (89.6%), lymphedema (85.2%), and operative time (63.7%). Among the one-third, reporting non-use of sentinel lymph node mapping, the most common reasons were uncertainty of the data, concern for missing positive nodes, and efficacy of mapping. According to that, our findings certainly showed that the use of sentinel lymph node biopsy for women with endometrial cancer is increasing after 2014, right after NCCN guidelines were published.

On the other hand, our findings suggest that there was no association between use of sentinel lymph node mapping and use of radiation in women with stage I tumors. A concern with implementation of sentinel lymph node mapping is that clinicians may lack confidence in the ability of the technique to detect metastatic spread and prescribe adjuvant radiation therapy (182,183). However, we found that this was not the case since women with stage I tumors who underwent sentinel lymph node biopsy were no more likely to receive radiation therapy than those who underwent full lymphadenectomy.

In conclusion, the current information from sentinel lymph node mapping studies in endometrial cancer appear quite promising. Since 2014, in which Abu-Rustum et al (62) published the algorithm in the NCCN guidelines, the worldwide implementation was gaining acceptance. In fact, the use of the sentinel lymph node technique has been established in the guidelines of large societies such as

the European Society of Gynecologic Oncology (12) as the technique of choice for lymph node mapping in early-stage endometrial cancer patients.

Future perspectives and conclusions

Future perspectives

There is an increasingly use of the sentinel lymph node mapping in Endometrial carcinoma across many Spanish centers, using different tracers and injection techniques depending on the availability and expertise of each center. Furthermore, the patients diagnosed with low volume disease receive or not adjuvant therapy depending on an individualized decision- making since no clinical guideline's agreement was made for these types of patients. Due to the lack of a national consensus guidelines, we proposed the following study:

MULTISENT: Estudio MULTIcéntrico ambiespectivo de la biopsia de ganglio centinela (SENTinel lymph node biopsy) en cáncer de endometrio inicial.

The aim of this project is to create a national multicenter collaboration group to analyze the retrospective and prospective data related to patients who undergo sentinel lymph node mapping at early-stage endometrial carcinoma in the referral Spanish gynecologic oncology centers.

The final goal is to delineate future patterns of practice in the management of endometrial carcinoma patients at early stage, introducing the sentinel lymph node biopsy as a standard of care for the surgical staging of the endometrial carcinoma patients, avoiding lymph nodes dissections that outweigh the surgical and postoperative- morbidities and even the overall survival. Moreover, it is essential to develop appropriate screening tools and guidelines to reduce cancer

morbidity for these patients in our country. This new surgical technique adds a value regarding the lymph node status and decrease the risk of lymphedema related to lymphadenectomy. Even more, the evaluation of the perceived quality of life will be provide us the manner to assess of our patient complains in terms of quality of life. Lastly, the identification of molecular biomarkers that could predict the existence of preoperative lymph node involvement in patients with early-stage endometrial carcinoma could lead to determine which patients would have benefit from surgical management.

This project encompasses an integrative approach of endometrial carcinoma patients including the different patterns of work, with the objective to analyze the generated information of the past five years and the next 3 years prospective data.

The following are the different parts included in the MULTISENT project:

1. Sentinel lymph node detection technique performance: To analyze the most accurate technique of sentinel lymph node biopsy in endometrial cancer comparing the sites of injection, uterine vs cervical vs both (uterine + cervical), compare the tracers used by the different Spanish centers. Estimate the negative predictive value of pelvic sentinel lymph node in endometrial cancer to predict nodal metastasis.

   MAIN GOAL: Validation the sentinel lymph node mapping technique for early-stage endometrial cancer patients.

2. Prognostic impact of low-volume disease: Explore the clinical significance of micrometastases or isolated tumor cells in endometrial cancer.

   MAIN GOAL: Defining whether adjuvant therapy (chemotherapy or radiation) should be recommended in patients.

3. Quality of Life (QoL) Assessment: To estimate lower extremity lymphedema prevalence and assess the impact on patient's quality of life using specific postoperative questionnaires: EORTC QLQ-EN24. MAIN GOAL: To assess the impact of lymphedema on quality of life

4. Predictive Molecular Biomarkers of SLN disease: Detect biomarkers in the pre-operative biopsies of endometrial cancer patients that could lead to an early detection of patients with lymph node disease.

   MAIN GOAL: Tailor the surgery to the patient disease without over or under treating the patients by having the nodal involvement information before the surgery.

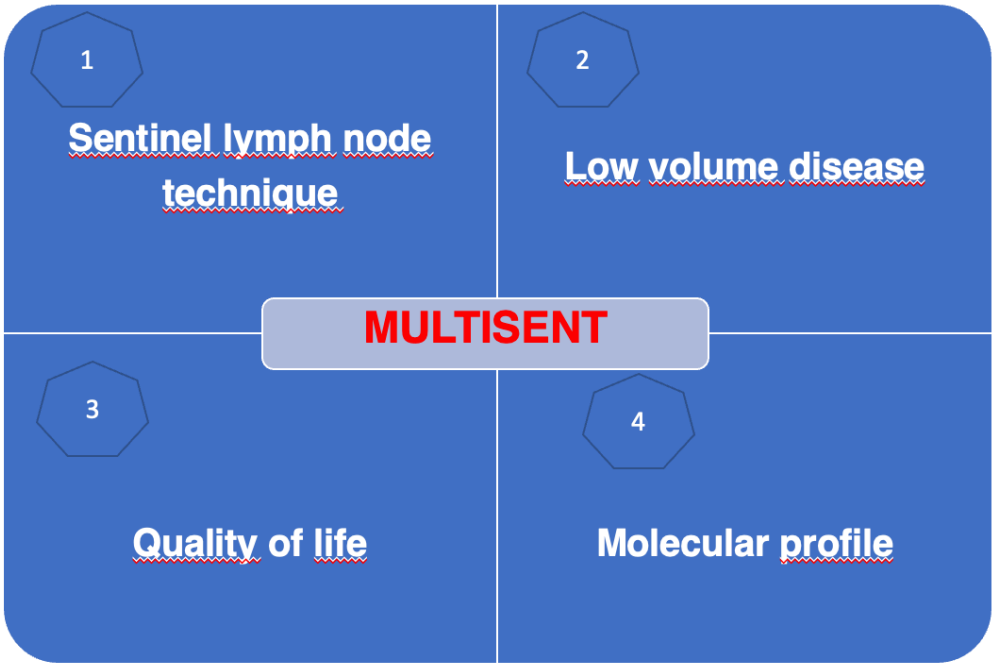

Image 5: Design of the MULTISENT study: Different parts of the study

Depending on the wishes and possibilities of each center, selected study parts will be chosen. New ideas will be developed to create new research papers after analyzing the results of the retrospective data.

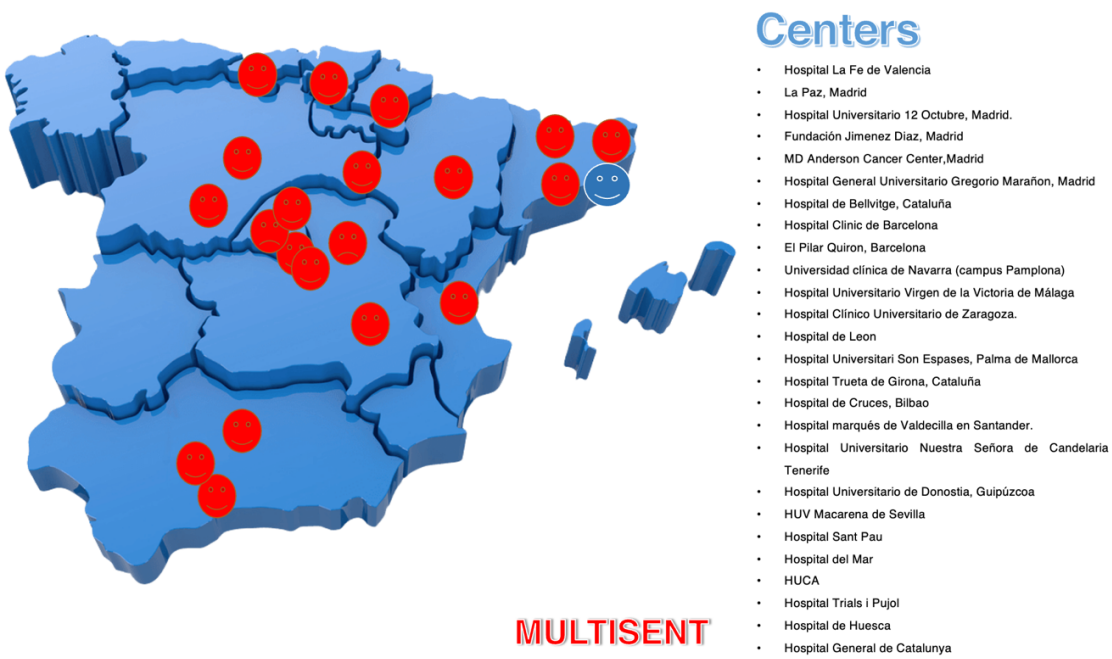

Image 6: MULTISENT Participating Centers

Conclusions

Conclusions 1 Indocyanine green sentinel lymph node technique is safe and valid, offering superior rates for identifying unilateral and bilateral sentinel lymph nodes, even in obese patients.

Conclusions 2 The findings of low volume metastases have a negative impact on prognosis. Patients with low volume disease have a higher relative risk of recurrence than patients with negative lymph nodes.

Conclusions 3 The prevalence of self-reported lymphedema is higher in patients who undergo a lymphadenectomy for endometrial cancer than patients who undergo a sentinel lymph node mapping technique.

Conclusions 4 The use of the sentinel lymph node technique has been established as the technique of choice for lymph node study in early-stage endometrial cancer patients. There does not appear to exist an association between use of sentinel lymph node dissection and use of adjuvant radiation.

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Tables and Figures

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Natalia

Publications

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Review Article

Role of Indocyanine Green in Sentinel Node Mapping in Gynecologic Cancer: Is Fluorescence Imaging the New Standard?

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ABSTRACT Sentinel lymph node biopsy has proven safe and feasible in a number of gynecologic cancers such as vulvar cancer, cervical cancer, and endometrial cancer. The proposed aim of lymphatic mapping and sentinel node identification is to decrease the associated morbidity of a complete lymphadenectomy, particularly the rate of lymphedema, while also increasing the detection of small tumor deposits in the node. Different tracers have been shown to be useful, including technetium-99 and blue dye, with a detection reported in 66% to 86%. Recently, there has been increasing interest in the use of fluorescent dies such as indocyanine green (ICG). In this report we provide a review of the existing literature regarding the use of ICG in cervical or endometrial cancer with the goal to provide details on its utility and compare it with other tracers. Journal of Minimally Invasive Gynecology (2016) 23, 186–193 © 2016 AAGL. All rights reserved.

Keywords: Indocyanine green; Laparoscopy; Lymphatic mapping; Robotics

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Introduction

The concept of sentinel lymph node (SLN) biopsy was first introduced by Cabañas in 1977 in patients with penile cancer [1]. Sentinel node detection has proven feasible and safe in select cancers such as vulvar cancer, breast cancer, early gastric cancer, and melanoma [2,3]. In gynecologic cancers, the first report on SLN detection in patients with vulvar cancer was published by Levenback et al in 1994 [4]. Two prospective studies then confirmed the utility of sentinel node in vulvar cancer (Table 1). In the first, the GROINSS I study [5], the investigators concluded that the SLN procedure in the management of early-stage vulvar cancer performed by a quality-controlled multidisciplinary team resulted in decreased morbidity without compromising groin recurrence or survival rates. The second study, GOG-173 [6], evaluated SLN in 452 patients with squamous cell carcinoma. All women underwent intraoperative lymph node mapping, sentinel node biopsy, and inguinofemoral lymphadenectomy. A total of 418 patients had at least 1 SLN identified. There were 132 node-positive women, including 11 (8.3%) with false-negative nodes. The sensitivity was 91.7% and the false-negative predictive value 3.7%. In women with tumor less than 4 cm, the false-negative predictive value was 2.0% (90% upper confidence bound, 4.5%). The authors concluded that SLN biopsy was a reasonable alternative to inguinal femoral lymphadenectomy in selected patients with squamous cell carcinoma of the vulva.

In cervical cancer, 2 prospective trials have demonstrated the safety and feasibility of SLN mapping (Table 2). The AGO Study Group trial [7] evaluated the detection rate of SLN. The detection rate of pelvic SLN was significantly

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Table 1

Studies of sentinel lymph node detection in vulvar cancer

Clinical Trial	Eligible patients	No. of patients	Primary endpoint
GROINSS I	• Squamous cell carcinoma • T1 or T2 lesions • <4 cm in size • Depth of invasion > 1 mm • Clinically nonsuspicious lymph nodes	403	Groin recurrence
GOG 173	• Squamous cell carcinoma • Limited to the vulva • >2 to <6 cm in size • Depth of invasion ≥ 1 mm • Clinically nonsuspicious lymph nodes	452	Negative predictive value

higher for the combination of technetium-99 and patent blue (93.5%; 95% confidence interval, 90.3–96.0%). Unfortunately, the overall sensitivity of the procedure was only 77%. However, when limiting the procedure to tumors < 2 cm in size, the sensitivity was 91%. The second trial, the SENTICOL I study by Lécuru et al [8], evaluated the sensitivity and negative predictive value (NPV) of SLN. Of the 139 patients involved, intraoperative radioisotope blue dye mapping detected at least 1 SLN in 136 patients, 23 of whom had true-positive results (sensitivity 92%; 95% confidence interval, 74–99%) and 2 had false-negative results. No false-negative results were observed in the 104 patients (76.5%) in whom SLN were identified bilaterally. The authors concluded that combined labeling for node mapping was associated with high rates of SLN detection and with high sensitivity and NPV for metastases detection. However, SLN biopsy was fully reliable only when SLNs were detected bilaterally. A recently completed trial, SENTICOL II [9], will hopefully shed light on whether sentinel node alone is safe and feasible in patients with early-stage cervical cancer.

The feasibility of lymphatic mapping in endometrial cancer was first introduced in 1996 by Burke and colleagues [10]. In that study, the authors evaluated SLN mapping by injecting isosulfan blue (ISB) into the subserosal myometrium, with a detection rate of 67%. In 2011, the SENTIENDO [11] study published the results of a prospective trial evaluating the accuracy of the SLN procedure in patients with early-stage endometrial cancer using cervical dual injection of technetium-99 and patent blue. Their overall detection rate was 89%, concluding that SLN biopsy alone can accurately diagnose lymph node involvement in patients with low-risk or intermediate-risk endometrial cancer.

There has been recent increasing interest in the use of the fluorescent dye, indocyanine green (ICG). Briefly, ICG is a tricarbocyanine dye that fluoresces in the near-infrared (NIR) spectrum when illuminated with 806 nm light. The fluorescent light is then captured using a special video camera device that enables the ICG to be displayed in the visible light spectrum. ICG is highly water-soluble and rapidly binds to albumin and therefore has a propensity for lymphatic tissue [12]. ICG may be used for SLN detection in the setting of open, laparoscopic, or robotic surgery.

In 2005 Kitai et al [13] investigated the use of ICG for SLN mapping in breast cancer and were the first to propose that the use of ICG could improve both detection rate and NPV of SNL detection. This technique has proven feasible both in breast and skin cancer patients, with comparable or slightly better detection rates than conventional techniques like technetium-99 [14,15]. The aim of this current article is to summarize the experience reported in the literature regarding ICG for SLN biopsy in cervical or endometrial cancer.

Methods

We searched in Medline, PubMed, and BioMed Central for all English-language literature using the terms

Table 2

Studies of sentinel lymph node detection in cervical cancer

Clinical Trial	Eligible patients	No. of patients	Labeling substance	Detection rate (%)	Sensitivity (%)
AGO study group	• Invasive cervical cancer all stages • With intention of surgical staging	507	Technetium–99 (45) Patent blue (159) Combined (303)	81.8 82 93.5	71.4 72.7 80.3
SENTICOL I	• Early stage cervical cancer (IA1–IB1)	139	Technetium–99 and patent blue		95

"indocyanine green," "cervical cancer," "endometrial cancer," and "sentinel lymph node" between 1994 and 2014. We included all publications reporting SLN mapping performed by open or robotic surgery. We included all reviews, retrospectives or prospective studies, and case reports published on the use of ICG. Two authors (MCD and NRGH) independently reviewed the titles and abstracts of publications searched and excluded all unrelated articles. Publications that fulfilled selection criteria were included in the study. For each eligible study the following information was obtained: study design (randomized controlled trial, prospective trial, retrospective review), year of publication, time period of study accrual, number of study subjects, type of cancer diagnosis, location of the injection of the ICG dye, SLN detection rate, and the false-negative rate.

Technique of ICG Mapping in Cervical or Endometrial Cancer

The technique used by our team for ICG SLN mapping is as follows: The cervix is prepped and the ICG is injected before laparotomy or insertion of the uterine manipulator (in minimally invasive cases). The concentration used is 1.25 mg/mL. For each patient a 25-mg vial with ICG powder is diluted in 20 mL of sterile water. We routinely inject 4 mL of the ICG solution into the cervix divided in the 3- and 9-o'clock positions, with 1-mL deep into the stroma and 1 mL submucosally on the right and the left of the cervix. This is performed before laparotomy, laparoscopy, or robotic surgery. Of note, ICG is not US Food and Drug Administration approved for interstitial injection and is currently only approved for intravenous use.

The appropriate dosing of ICG, has been previously addressed in a study by Levinson et al [12], where the authors used 4 concentrations of ICG (1000, 500, 250, and 175 μg/.5 mL). The investigators concluded that an ICG dose of 250 to 500 μg enables identification of a SLN with more distinction from the surrounding tissues.

Results

Use of ICG in Cervical or Endometrial Cancer

The first study describing the role of ICG in patients with a gynecologic cancer was published in 2010 by Furukawa et al [16] (Table 3). Twelve patients with early-stage cervical cancer underwent lymphatic mapping after injection of .2 mL of 5 mg/mL of ICG in 4 sites of the cervix. SLNs were identified in 10 patients (83%), and all were identified bilaterally. The median number of SLNs was 7 (range, 3–10). Lymph node metastases were found in 2 patients, and all were found in the SLNs. There were no false-negative lymph nodes. The site of the SLN was the right external iliac node in 8 patients, the right obturator node in 8 patients, the left external iliac node in 9 patients, and the left obturator in 8 patients. There were no adverse events noted with ICG. This was an important study because it was the first to use ICG in gynecologic cancer patients, and ICG was found to have a similar rate of detection as blue dye and radioisotope, when comparing it with previous reports, and to be easier to use.

In 2011, Van der Vorst et al [17] also described the technique of mapping with NIR fluorescence imaging in early-stage cervical cancer patients. A total of 1.6 mL of ICG was injected in 4 sites of the cervix. SLNs were identified in all 9 patients and bilateral SLNs were identified in 8 of 9 patients with a total of 31 SLN's. All SLNs were pelvic nodes. After histologic confirmation, 3 positive SLNs were found in 2 patients. No false-negative SLNs were identified. This study was also relevant because it evaluated different doses of ICG concentration (500, 750, and 1000 μm) to determine what was the optimal dose.

That same year, Crane et al [18] published the first study in gynecology to evaluate the applicability of NIR imaging with ICG for the detection of the SLN in cervical cancer, using it in a combination with patent blue. In that study a mixture of patent blue and ICG was injected into the cervix of 10 patients. A total of 9 SLNs (90%) were detected in 6 patients, of which 1 (11%) contained metastases. All SLNs were pelvic nodes. Bilateral SLNs were detected in 3 of 6 patients (50%). Ex vivo fluorescence imaging revealed the remaining fluorescent signal in 11 of 197 non-SNLs (5%), of which 1 contained metastatic tumor. None of the nonfluorescent lymph nodes contained metastases. The authors concluded that lymphatic mapping and detection of the SLN in cervical cancer using intraoperative NIR imaging is technically feasible. This study was also particularly useful because it showed that detection rates in tumors smaller than 2 cm were 80% in comparison with only 40% in patients with tumors $>$ 2 cm. They also showed that the ability to detect bilateral sentinel nodes was limited by tumor size. In addition, the study also showed that the penetration depth of ICG does not exceed 1 cm.

Up to this point all the published studies were in the setting of open surgery. The first study to evaluate the use of ICG in patients with endometrial cancer and in the setting of minimally invasive surgery was Rossi et al [19]. A total of .5 mg ICG was injected into the cervical stroma at the 3 o'clock and 9 o'clock positions. At least 1 SLN was identified in 17 patients (85%) with a median of 4.5 nodes identified per patient (range, 0–9). The median number of non-SLNs removed in each patient was 23.5 (range, 4–56). Bilateral SLNs were identified in 12 patients (60%) with no false-negative nodes. SLNs were not detected in 3 patients. Three patients had node-positive disease. Later, Holloway et al [20] aimed to compare the ability of ICG and standard colorimetric analysis of ISB dye for the detection of SLN in endometrial cancer. A total of 1 mL of ISB was injected in cervix, followed by .5 mL ICG immediately before placement of a uterine manipulator. Twenty-seven (77%) and 34 (97%) patients had bilateral pelvic or aortic SLN detected by colorimetric and fluorescence, respectively ($p < .03$). Using both methods, bilateral detection was 100%. Ten patients (28.6%) had lymph node metastasis,

Table 3

Studies of SLN mapping with ICG

Source, year	Cancer type	Stage	Surgery	No. of patients	Technique	Injection site	Detection rate (%)	Location of SLN
Furukawa et al (2010)	Cervical	IA1 (1) IB1 (5) IIA (1) IIB (5)	Radical hysterectomy and lymphadenectomy by laparomy	12	ICG	Cervical	83	Right external iliac (9) Left external iliac (9) Right obturator (8) Left obturator (8)
Van der Vorst et al (2011)	Cervical	IB1	Radical trachelectomy or radical hysterectomy by laparotomy	9	ICG	Cervical	100	Right external iliac (6) Left external iliac (8) Right common iliac (4) Left common iliac (5) Right obturator (4) Left obturator (2) Parametria (2)
Crane et al (2011)	Cervical	IA1-IIA	Radical hysterectomy and pelvic lymphadenectomy by laparotomy	10	ICG/ISB	Cervical	ICG 97 ISB 77	Right external iliac (2) Left external iliac (2) Right obturator (1) Left obturator (3) Right common iliac (1)
Rossi et al (2012)	Cervical (4) Endometrial (16)	I	Robotic-assisted bilateral pelvic and para-aortic lymphadenectomy in endometrial cancer	20	ICG	Cervical	85	Para-aortic (65%) Pelvic (85%)
Holloway et al (2012)	Endometrial	Low risk (9) High risk (26)	Robotic-assisted lymphadenectomy and hysterectomy	35	ICG/ISB	Cervical	ICG 97 ISB 77	Pelvic (22.5 ± 10.9) Aortic (10.3 ± 6.6)
Rossi et al (2013)	Endometrial	I	Robotic-assisted lymphadenectomy and hysterectomy	17 12	ICG	Cervical Hysteroscopic	82 33	Pelvic (17.5 vs 17.3, NS) Para-aortic (10.3 vs 10.6, NS)
Jewell et al (2014)	Cervical (89) Endometrial (138)			227	ICG/ISB	Cervical	ICG 95 ICG/ISB 93	Right external iliac (15.7%) Left external iliac (19.1%) Right obturator (10.9%) Left obturator (10.7%) Right common iliac (5.4%) Left common iliac (2.9%) Para-aortic (10%) Presacral (.004%)
Sinno et al (2014)	Endometrial	I (53) II (3) III (7) IV (1) Complex hyperplasia (7)	Robotic-assisted SLN mapping and hysterectomy	71	ICG/ISB	Cervical	ICG 78.9 ISB 42.4	Hypogastric (76.8%) External iliac (14.2%) Common iliac (4.5%) Para-aortic (4.5%)

(*Continued*)

Table 3

Continued

Source, year	Cancer type	Stage	Surgery	No. of patients	Technique	Injection site	Detection rate (%)	Location of SLN
Plante et al (2015)	Cervical (8)	IA2/IB1	Robotic/laparoscopic lymphadenectomy	50	ICG	Cervical	96	External iliac (71.3%)
	Endometrial (42)	I						Obturator (17.8%)
								Common iliac (5.7%)
								Para-aortic (3.2%)
								Presacral (1.3%)
								Parametrial .6%
Ditto et al (2014)	Endometrial	II		1	ICG	Hysteroscopic	100	Right obturator (1)

ICG = indocyanine green; ISB = isosulfan blue; NS = nonsignificant; SNL = sentinel lymph node.

and 9 of these had SLN metastasis (90% sensitivity, 1 false-negative SLN biopsy). Seven of 9 (78%) SLN metastases were ISB positive and 100% were ICG positive. Twenty-five patients had negative SLN biopsies (100% specificity).

In 2013 Rossi et al [21] compared the detection rates between cervical and endometrial injection and patterns of nodal distribution. Seventeen patients underwent a cervical injection of 1 mg ICG and 12 patients received hysteroscopic endometrial injections of .5 mg ICG. The SLN detection rate was 82% (14/17) for the cervical injection group and 33% (4/12) for the hysteroscopic injection group ($p < .027$). SLNs were seen bilaterally in 57% (8/14) of the cervical injection group and 50% (2/4) of the hysteroscopic group (nonsignificant). There was 1 false-negative SLN in the cervical injection group; no false negative was identified in the endometrial injection group. There was a significant improvement in detection rate with cervical injection (82% vs 33%) with similar rates of bilateral nodes identified (57% vs 50 %). No difference in the anatomic distribution of SLNs was seen for the 2 injection sites. This was also an important study because the authors showed that cervical injection of ICG allowed for excellent detection of para-aortic nodes in up to 71% of cases, including 3 cases above the inferior mesenteric artery.

The most recent and largest study to date using the robotic platform is the study published by Jewell et al in 2014 [22]. This retrospective study aimed to assess the detection rate of SLNs using ICG and NIR fluorescence imaging. In that study, 1.25 mg ICG was injected into the cervix of 227 patients. Blue dye was concurrently injected in 30 cases. The median SLN count was 3 (range, 1–23). The overall detection rate of the SLN (unilateral or bilateral) for this cohort of patients was 95% (216/227). When ICG was used alone, 95% of patients (188/197) mapped either unilateral or bilaterally compared with 93% (28/30) in cases in which both dyes were used (nonsignificant). The bilateral detection rate was 79% (179/227) overall. The bilateral SLN detection rate for ICG alone was 79% (156/197) compared with 77% (23/30) for ICG and blue dye (nonsignificant). In that study the authors also showed that 10% of patients had SLNs identified in the aortic region. The study concluded that intracervical injection of ICG has a high bilateral detection rate and appears to offer an advantage over using blue dye alone. The authors stated that combined use of ICG and blue dye appeared to be unnecessary.

In 2014 Sinno et al [23] compared the ability to detect SLNs in women with endometrial cancer or complex atypical hyperplasia using ICG versus ISB. They observed that ICG mapped bilaterally in 78.9% and 42.4% with ISB ($p = .02$), concluding that ICG may be superior to colorimetric imaging. This study also provided important information regarding the impact of body mass index (BMI) on patients undergoing mapping with ICG. The authors found that increasing BMI was negatively associated with successful mapping only in the blue dye group but not in the ICG group. Recently, Plante et al [24] published the first reported

experience about the use of ICG with NIR in endometrial and cervical cancer using the Pinpoint endoscopic system. Their overall detection rate was 96% and bilateral, 88%. Sensitivity, specificity, and NPV were 93.3%, 100%, and 98.7%, respectively, per side. The authors concluded that NIR imaging with ICG is an excellent, simple, and safe tracer modality for SLN mapping that should be the agent of choice if SLN mapping ever becomes standard of care.

Finally, a recent abstract was presented at the Annual Meeting of the Society of Gynecologic Oncology in 2015 [25]. The study presented 472 patients with uterine cancer undergoing SLN mapping using either ICG or blue dye. ICG was used in 312 patients (66%) and blue dye in 160 (32%). Successful mapping occurred in 425 patients (90%). Mapping was bilateral in 352 patients (75%), unilateral in 73 patients (15%), and in 47 patients (10%) the investigators were not able to detect the SLN. Successful mapping occurred in 295 patients (95%) in which ICG was used compared with 130 patients (81%) in which blue dye was used ($p < .001$). Additional lymph node dissection beyond removal of SLNs occurred in 122 patients (39%) with ICG versus 98 patients (61%) with blue dye ($p < .001$). In regard to the anatomic distribution of SLNs, 490 of 1374 SLNs (36%) were located in the hypogastric basin, 453 (33%) in the external iliac basin, 313 (23%) in the obturator basin, 83 (6%) in the common iliac basin, and 25 (2%) in the aortic basin. There were 25 para-aortic SLNs detected, and 23 (92%) of these were detected using ICG. These authors concluded that SLN detection rate is superior when using ICG rather than blue dye. Bilateral mapping is significantly improved using ICG, resulting in a lower rate of additional lymphadenectomy.

Discussion

Limitations of ICG

Although there are many suggested benefits of ICG over other tracers for performing SLN identification and lymphatic mapping, one must also recognize that there are certain potential limitations. Jewell et al [22] found that BMI appeared to impact the success rate of SLN mapping. In their report, the median BMI of patients in whom an SLN was detected was 30.1 kg/m^2 (range, 17.7–59.6) compared with 41.2 kg/m^2 (range, 25.1–60.4) for patients who did not map ($p = .01$). Median BMI appeared to impact bilateral mapping, with the median BMI of unilaterally and bilaterally mapped cases being 34 kg/m^2 (range, 17.9–49) and 29.6 kg/m^2 (range, 17.7–59.6), respectively ($p = .02$). Tanner et al [26] evaluated patient, tumor, and surgeon factors associated with successful bilateral mapping in patients with endometrial cancer using ISB or ICG. In that study the authors found that the rate of successful bilateral mapping decreased with a BMI $\geq$ 30 kg/m^2 and that although the rate of success with ICG is superior to ISB, the variability is more pronounced at higher BMIs.

Another subject of particular interest with any tracer is that such dyes can be associated with an allergic reaction. Patients with iodine allergy should not be exposed to ICG because it contains 5% sodium iodide [19]. The risk of an allergic reaction to ICG has been estimated at 1 per 42,000 uses [27]. In addition, it is not recommended that patients with liver compromise be exposed to ICG because it is metabolized in the liver.

Areas for Further Research

One of the areas of active debate for all cases of SLN identification in endometrial cancer is the issue pertaining to the ideal site of injection for the tracer. Abu Rustum et al [28] described 3 different sites for SLN mapping for cervical and uterine malignancies for the already known dyes, not specifically ICG: uterine subserosal, cervix, or endometrium via hysteroscopy. These authors concluded that the preferred strategy was cervical injection. They argued that because the main lymphatic drainage of the uterus is from the parametria, a combined superficial (1–3 mm) and deep (1–2 cm) cervical injection is adequate. Moreover, it is easily accessible and rarely distorted by uterine anatomy variations such as myomas that make serosal mapping more difficult. Uterine fundal serosa mapping does not reflect the parametrial lymphatic drainage.

Only 2 articles have addressed location of injection in the setting of ICG use. The first was reported by Rossi et al [21], who evaluated the rate of SLN identification between cervical and hysteroscopic injection of ICG. The authors supported the use of cervical injections, because there was a significant improvement in detection rate with cervical injection (82% vs 33%) with similar rates of bilaterally identified nodes (57% vs 50%). No difference in the anatomic distribution of SLNs was seen for the 2 injection sites.

The second article was by Ditto et al [29], who presented a case managed by hysteroscopic injection of ICG and laparoscopic NIR fluorescence imaging in endometrial cancer staging. Sentinel node mapping was performed using a hysteroscopic injection of ICG followed by laparoscopic sentinel node detection via NIR fluorescence. A right side obturator sentinel node was detected and removed. No sentinel node was detected on the left side. The authors suggested that although there is growing evidence that cervical injection is effective in detecting lymphatic drainage of the uterus, hysteroscopy allows for injection in the proximity of the lesion.

Ongoing Trials

Currently, there are 2 ongoing trials evaluating SLN mapping using ICG, among other tracers, in patients with endometrial cancer by the group at MD Anderson Cancer Center. The first study is evaluating the prediction of recurrence among low risk endometrial cancer population. The

primary objective of this trial is to validate the use of a molecular panel of estrogen-induced genes to predict recurrence in low risk endometrial cancer. A secondary objective is to calculate the positive predictive value and NPV, sensitivity, and specificity of lymph node mapping to predict pelvic node involvement. The inclusion criteria for this study are histologically confirmed low-grade (1–2) endometrioid type adenocarcinoma and no evidence of deep invasion or peritoneal disease in preoperative imaging. All patients undergo hysterectomy and SLN mapping. Bilateral salpingo-oophorectomy may be performed based on discretion of the primary gynecologic oncologist and performance of pelvic and para-aortic lymphadenectomy are based on intraoperative findings and frozen section pathology. Intraoperative lymphatic mapping is performed with blue dye, radioactive colloid, or ICG by an injection in the cervix. The expected number of patients to accrue on this trial is 500.

The second trial is a prospective evaluation of lymph node metastasis in patients with high-risk endometrial cancer. The inclusion criteria for this trial are as follows: histologically confirmed high grade endometrial cancer, including grade 3 endometrioid, serous, clear cell, mixed malignant mullerian tumors, or any mixed tumor containing 1 of these cell types; grade 1/2 and evidence of deep myometrial invasion or cervical involvement; and patient must be a candidate for surgery, have no evidence of peritoneal disease, and have no preoperative treatment for endometrial cancer including radiation or chemotherapy. The primary objective is to estimate the false-negative rate of positron emission tomography/computed tomography and/or SLN mapping in the detection of positive lymph nodes in women with high-risk endometrial cancers. The secondary objective is to estimate the sensitivity, specificity, positive predictive value, and NPV of positron emission tomography/computed tomography and/or SLN mapping. Intraoperative lymphatic mapping is also performed with blue dye, radioactive colloid, and/or ICG. The estimated number of patient accrual is 100.

The following is a list of other ongoing trials and their primary objectives using ICG in the detection of SLNs:

- Determining the sensitivity of SLNs identified with robotic fluorescence imaging (Indiana University, IN).

To estimate the sensitivity of the SLN in the determination of lymph node metastases in patients with invasive carcinoma of the cervix and uterus using ICG and robotic-assisted NIR imaging.

- Detection of SLNs in patients with endometrial cancer undergoing robotic-assisted staging: a comparison of ISB and ICG dyes with fluorescence imaging (Ohio State University, Columbus, OH).

The primary objective of this trial is to estimate the NPV of pelvic SLN in endometrial cancer to predict nodal metastasis.

- The feasibility and benefits of using ICG and NIR fluorescence imaging to detect SLNs in patients with endometrial cancer (Lahey Hospital & Medical Center, Burlington, MA).

To determine whether SLNs are accurately visualized using ICG and NIR imaging.

- Study of instillation technique using the modified intrauterine manipulator catheter with methylene blue, ISB, or ICG dyes compared with cervical injection for SLN detection in endometrial carcinoma (Southeastern Regional Medical Center, Newnan, GA).

The primary outcome of this study is an evaluation of the number of sentinel nodes detected by each method.

- Lymph node mapping in patients with newly diagnosed endometrial cancer undergoing surgery (Cleveland Clinic Case Comprehensive Cancer Center, Cleveland, OH).

The primary objectives of this trial are to determine sensitivity of SLN biopsy, detection rate, and false-negative rate in patients undergoing lymphatic mapping.

- Accuracy of SLN biopsy in nodal staging of high-risk endometrial cancer (EndoSLN) (University Health Network, Toronto, CA).

The primary objective is to evaluate the sensitivity, specificity, and predictive accuracy of mapping and detection of SLNs with metastatic disease.

- The Kelly Gynecologic Oncology Service Endometrial Cancer SLN Study (Johns Hopkins, Baltimore, MD).

The primary objective is to determine the utility of performing SLN evaluation in women with apparent early-stage (grades 1–2) endometrioid tumors compared with grade 3 (type II) tumors.

Conclusion

ICG offers a novel tool to identify SLNs and can be used in real time, avoiding radioactivity and demonstrating superior rates for identifying unilateral and bilateral SLN, even in obese patients. SLN mapping using ICG does not add significant time in the operating room. Although the most common site for SLN detection is the pelvic region, ICG has the potential to identify SLN in areas that are unlikely to be explored using the traditional approach to lymphadenectomy. Further studies evaluating the cost-effectiveness of ICG in comparison with other tracers is warranted.

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Oncologic impact of micrometastases or isolated tumor cells in sentinel lymph nodes of patients with endometrial cancer: a meta-analysis

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Abstract

Purpose—There is a gap in knowledge regarding the impact of micrometastases (MIC) and isolated tumor cells (ITCs) found in the sentinel lymph nodes of patients with endometrial cancer. Here, we present a meta-analysis of the published literature on the rate of MIC and ITCs after lymphatic mapping and determine trends in postoperative management.

Methods—Literature search of Medline and PubMed was done using the terms: micrometastases, isolated tumor cells, endometrial cancer, and sentinel lymph node. Inclusion criteria were: English-language manuscripts, retrospectives, or prospective studies published between January 1999 and June 2019. We removed manuscripts on sentinel node mapping that did not specify information on micrometastases or isolated tumor cells, non-English-language articles, no data about oncologic outcomes, and articles limited to ten cases or less.

Results—A total of 45 manuscripts were reviewed, and 8 studies met inclusion criteria. We found that the total number of patients with MIC/ITCs was 286 (187 and 99, respectively). The 72% of patients detected with MIC/ITCs in sentinel nodes received adjuvant therapies. The MIC/

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Author contributions NRGH and PTR contributed to conception and design of study. NRGH, BN, and NC collected the data. SPH and NRGH performed data analysis and interpretation. SPH performed statistical analysis. NRGH, PTR, JLSI, SC, SF, APB, and AGM prepared the manuscript.

Conflict of interest The authors declare no conflicts of interest.

Ethical approval The present study was approved by the local ethical committee.

Informed consent Informed consent was not applicable.

ITCs group has a higher relative risk of recurrence of 1.34 (1.07, 1.67) than the negative group, even if the adjuvant therapy was given.

Conclusion— We noted that there is an increased relative risk of recurrence in patients with low-volume metastases, even after receiving adjuvant therapy. Whether adjuvant therapy is indicated remains a topic of debate because there are other uterine factors implicated in the prognosis. Multi-institutional tumor registries may help shed light on this important question.

Keywords

Micrometastases; Isolated tumor cells; Endometrial cancer; Sentinel lymph node

Introduction

Endometrial carcinoma is the most common gynecologic cancer in developed countries. In 2019, an estimated 61,880 new cases and 12,160 deaths from uterine cancer were diagnosed in the USA [1]. The standard management of patients diagnosed with endometrial cancer has changed in the last few years, the current recommendation is total hysterectomy and bilateral salpingo-oophorectomy along with sentinel lymph node mapping alone, to avoid full lymphadenectomy.

Sentinel nodes are considered positive for disease if they contain macrometastases (MAC > 2 mm), micrometastases (MIC 0.2–2 mm), or isolated tumor cells (ITC ≤ 0.2 mm) [2, 3]. The relationship between MIC or ITCs and increased risk of recurrence, as well as prognosis, has been demonstrated in a number of cancers such as breast cancer [4, 5], vulvar cancer [6–8], gastric cancer [9], esophageal cancer [10], colon cancer [11, 12], prostate cancer [13], and cervical cancer [14, 15].

In endometrial carcinoma, the clinical impact of low-volume metastasis remains unknown. Cibula et al. [16] published a study on the impact of MIC and ITCs in the sentinel lymph nodes (SLNs) and non-SLNs of cervical cancer patients. The patients selected for that study (17 patients in total) had cervical cancer and were at high risk of lymph node (LN) positivity (stage IB–IIA, biggest diameter ≥ 3 cm). A total of 573 pelvic LNs were examined through ultrastaging protocol (5762 slides). Metastatic involvement was detected in SLNs of eight patients (1 × MAC; 4 × MIC; 3 × ITCs) and in non-SLNs in two patients (2 × MIC). The authors found that using pathologic ultrastaging, there were no false-negative cases of positive non-SLN (MAC or MIC) and negative SLN. The presence of MAC and MIC was associated with a decrease in overall survival, but no difference in survival was found between patients with negative LN and ITCs.

It is hypothesized that MIC represents a truly small metastatic involvement, while ITC can be a different entity with a limited potential for the development of distant disease spread. Furthermore, there is a gap in knowledge regarding the prognosis impact and the ideal management of patients with endometrial cancer who have MIC or ITCs in the sentinel lymph nodes. The aim of this review is to explore the clinical significance of MIC or ITC in endometrial cancer and summarize the reported literature on the impact on postoperative management in patients with such findings.

Methods

Search strategy and selection criteria

Keywords including “micrometastases”, “isolated tumor cells”, “endometrial cancer”, and “sentinel lymph node” were used for literature searches in MEDLINE and PubMed. The search spanned from January 1999 to June 2019 and included all articles that contained information regarding “endometrial cancer” and “micrometastases and isolated tumor cells” in the titles and abstracts.

Articles had to meet the following inclusion criteria: English-language manuscripts limited to endometrial cancer, patients who had micrometastases and/or isolated tumor cells in the sentinel lymph nodes, studies that report oncologic outcomes, articles including ≥ 10 patients, patients who underwent open, laparoscopic or robotic surgery, and studies that did not present duplicated data. We included all retrospective and prospective studies. Two authors (NRGH and BN) reviewed the titles and abstracts of publications and excluded all unrelated articles (Fig. 1).

We collected information on study design, year of publication, time period of study accrual, number of patients included, median age of patients, histological type, myometrial invasion (MI), lymphovascular invasion (LVI), grade, MIC/ITCs detection rate, and technique of detection (Table 1). We report the articles that compared the recurrences among patients with micrometastases, isolated tumor cells, and negative patients and studies that provided information on adjuvant therapy (Table 2).

Statistical analysis

From each study, a number of cases and recurrences for each group of patients were extracted to calculate recurrence incidence. Relative risk and 95% confidence interval were calculated for each group number of cases. A random-effects meta-analysis was carried out for each comparison. Using the data, we created tables and forest plot was drawn. For each comparison, combined relative risk, given more weight for those studies with more cases, was calculated using DerSimonian–Laird random-effects mode, which accounts for both intra- and inter-study variability. All analyses were carried out with Stata 15.1

Results

We collected a total of 45 manuscripts, and 8 studies met our inclusion criteria (Fig. 1). Study characteristics are shown in Table 1. Studies totaled 2873 patients (range 41–508) among patients with MAC, negative lymph nodes, and MIC or ITCs. The median age was 62 years (range 54–69). Most of the patients (88%) reported an endometrioid histology on the final pathology, but 61% of total patients had more than 50% of myometrial invasion, 19% presented positive lymphovascular invasion, and Grade 3 was reported in the 20% of total patients. The median detection rate for MIC/ITCs was 17% (range 3–56). The ultrastaging technique was used in all the included studies.

Among all the studies which report data about oncologic outcomes, the total number of negative patients for MIC and ITCs was 2415, and the total number of patients with MIC/ITCs was 286 (187 and 99, respectively) (Table 2).

A total of 284 negative patients and 28 patients with either MIC or ITCs recurred. Table 3 shows the relative risk of recurrence between negative and MIC/ITCs patients.

Considering only studies with clear data about the administration of adjuvant therapy (Tables 4 and 5), in the MIC/ITCs patients who did not receive adjuvant therapy, compared to negative patients and to MIC/ITCs patients who did receive adjuvant therapy, the relative risk of recurrence was similar in both groups not depending on adjuvant therapy.

Discussion

Our findings suggest that there is a higher relative risk of recurrence in patients with low-volume metastases, even after receiving adjuvant therapy.

As previously noted, the incidence of MIC can differ according to the histological and biological technique used. Several studies proved that CK 20 is more sensitive than traditional histopathologic method with H&E (sensitivity was 94.5 and 91%, respectively) [17, 18]. Table 1 shows different ultrastaging techniques used in all the studies. Moreover, the SLN mapping with pathologic ultrastaging identified MIC or ITCs in 4.5% patients with endometrial cancer in whom no metastatic disease would have otherwise been detected by conventional pathologic processing [19, 20].

In terms of oncologic outcomes, the findings of low-volume metastases might have a negative impact on prognosis. Erlanki et al. [21] found that 2/7 (28%) of patients with micrometastases recurred and died of disease: both were of high risk—one had no adjuvant therapy, and the other one had both chemotherapy and radiotherapy. They reported a 36-month recurrence-free survival of 100% in patients who did not have micrometastases. Furthermore, Clair et al. [22] described a recurrence-free survival (RFS) of 86% for both MIC and ITCs patients. They observed that adjuvant therapy improves the survival rates in patients with low-volume metastasis compared to patients with macrometastasis. On the other hand, Todo et al. [23] reported that 28.6% of patients with ITC or MIC who received adjuvant therapy recurred ($p = 0.17$). Moreover, they found a higher rate of deep myometrial invasion in the ITCs or MIC patients than in node-negative patients ($p = 0.028$). However, this study presents some limitations: the majority of the patients had an early-stage carcinoma, received adjuvant therapy, or were patients with high-risk factors. In fact, histological grade, stage, and high-risk status are all important prognostic factors predicting disease recurrence. In addition, although we found that the 88% of the patients had an endometrioid histology on the final pathology, 61% of patients had more than 50% of myometrial invasion and 19% presented positive lymphovascular invasion.

Interestingly, Plante et al. [24] published a study on ITCs in patients with endometrial cancer, including 519 patients with a median follow-up of 29 months (range 0–67), and the progression-free survival (PFS) at 3 years for the ITC patients was 95.5%, similar to node-negative (87.6%) and micrometastasis patients (85.5%), but statistically better than patients

with macrometastasis (58.5%) ($p = 0.0012$). Moreover, the latest prospective study to assess the association between treatment and recurrence-free survival in stage I–II endometrioid endometrial cancer patients with ITCs was published by Backes et al. [25]. They found that in a total of 175 patients with ITCs, 49% had stage IA, 39% stage IB, and 12% stage II disease (all with ITCs). Fifty-one percent underwent SLN assessment only, and the remainder underwent SLN and lymphadenectomy. A total of 76 (43%) received either no adjuvant therapy or vaginal brachytherapy only; 21 (12%) had external beam radiation; and 78 (45%) received chemotherapy + / − radiation. Patients who received chemotherapy more often had tumors with deep myometrial invasion, LVI, and higher grade. Nine (5.1%) patients recurred: 5 distant, 3 retroperitoneal, and 1 vaginal. After controlling for stage, LVI, and grade, chemotherapy was not associated with recurrence (HR = 0.63, 95% CI 0.11–3.52, $P = 0.39$). They concluded that the risk of retroperitoneal and/or distant recurrence is low (4.6%) for patients with stage I–II endometrioid EC and ITCs in SLNs regardless of adjuvant treatment or observation. The preliminary data suggest that adjuvant therapy does not appear to affect RFS.

The most recent publication is a multicenter, retrospective registry-based study of 2392 patients with endometrial cancer with and without MIC [26]. Without adjuvant therapy, the disease-free survival in the cohort of patients with MIC was reduced as compared with disease-free survival in the node-negative cohort, even after adjustment for age at diagnosis, myometrial invasion, histological grade and type, and performance status.

Although most of the studies recommended that the presence of isolated tumor cells should not drive the need for adjuvant treatments, the 72% of MIC/ITCs patients received some kind of adjuvant therapies. We could conclude that the benefit by giving additional treatments to ITCs patients depends on the presence of other high-risk uterine factors.

However, we recognize several important limitations. First, the number of the studies is small, given to the analysis a small power to make any conclusion. Second, in some studies, there were ITCs patients who received adjuvant therapy (chemotherapy or radiation) because of high-risk uterine factors or more advanced disease, and probably the prognosis could change. Lastly, given the favorable prognosis of endometrial cancer, our study is underpowered to detect small differences in survival.

In summary, when considering the association of MIC and ITCs with recurrence, we noted that patients with low-volume metastases had an increase relative risk of recurrence compared to negative patients, even if the adjuvant therapy was given. Further studies are needed in order to determine whether adjuvant therapy is indicated for both MIC and ITCs or only for those patients with MIC and to elucidate the specifics uterine factors that could change the indication of adjuvant therapy.

Conclusion

The current data show a higher sensibility and specificity of ultrastaging technique to detect MIC and ITCs; however, when we find these low-volume metastases, the clinical implications on adjuvant therapy remain a controversy. Currently, whether adjuvant therapy

(chemotherapy or radiation) should be recommended in patients, at least, with MIC in regional LNs remains a topic of debate. In the near future, with the growing incorporation of SLN mapping and the initiatives of multi-institutional tumor registries, more data will elucidate the true clinical impact of MIC and ITCs on prognosis.

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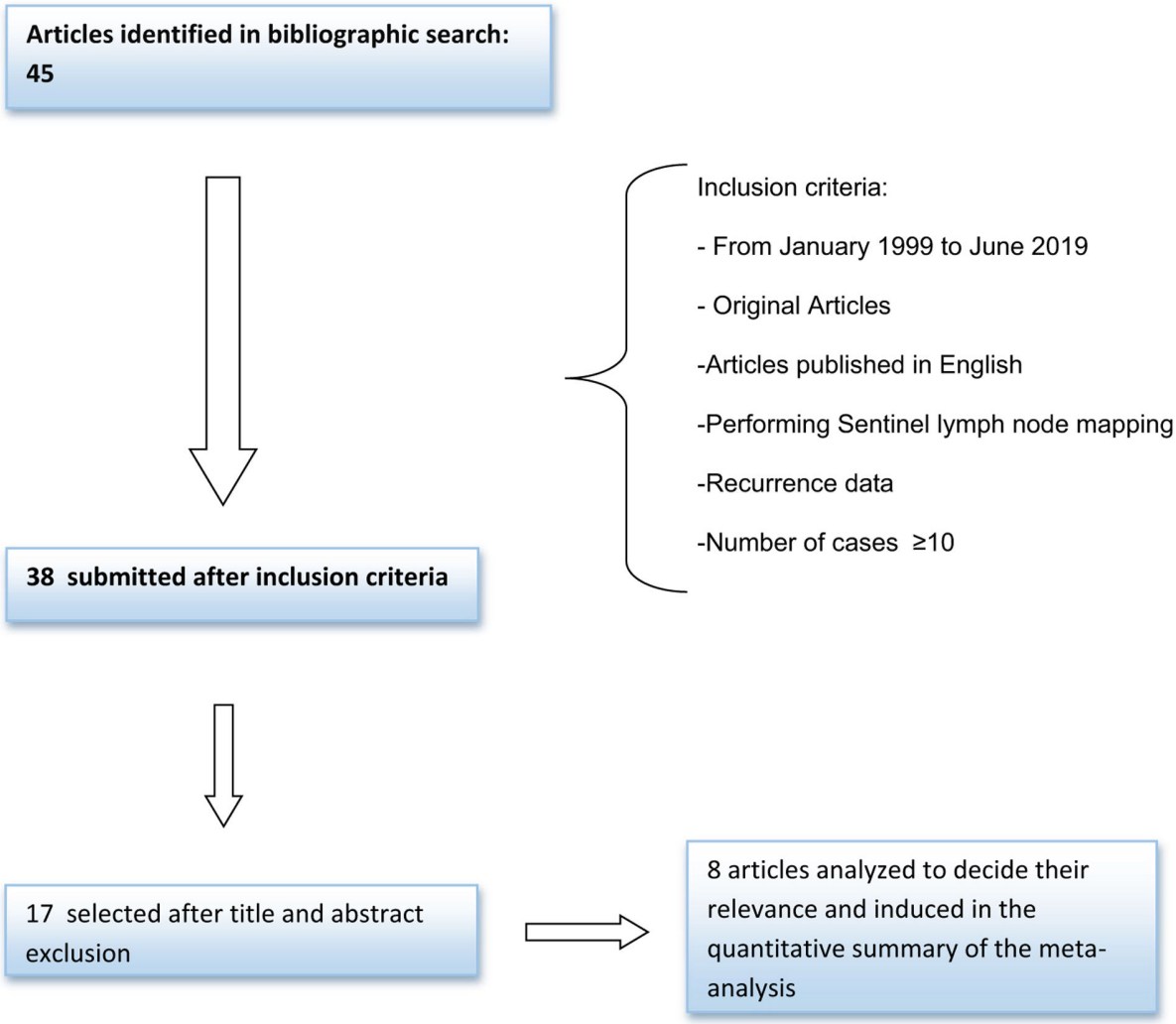

Fig. 1.
Flowchart of studies retrieved and finally included in the meta-analysis

Table 1

Baseline characteristics of the included studies in the meta-analysis

Authors	Design	Year	Study period	Number of patients	Median age	Endometrioid histology	Non endometrioid	MI	LVI	Grade 1	Grade 2	Grade 3	Total MIC/ ITCs patients	MIC/ ITC (%)	Technique
Kim et al. [19]	Prospective cohort	2013	2005–2011	425	58	415	10	None: 241; < 50%: 184	Yes: 58; no: 367	302	108	15	12 (9 ITCs) (3 MIC)	3	Ultrastaging (H&E + IHC: Anticytokeratin AE1/AE3)
Kim et al. [20]	Retrospective cohort	2013	2005–2011	508	61	413	Serous: 62; clear cell: 12; carcinosarcoma: 21	None: 242; < 50%: 198; ≥ 50%:68	Yes: 132; no: 376	261	116	131	23 (19 ITCs) (4 MIC)	5	Ultrastaging (H&E + IHC: Anticytokeratin AE1/AE3)
Erlanki et al. [21]	Retrospective cohort	2010	2003–2006	47	60	37	Adenosquamous: 7; serous papillary: 2; clear cell: 1	None: 9; < 50%: 19; > 50%: 19	Yes: 4; no: 40; no data: 3	15	21	8	7(MIC)	15	Ultrastaging (H&E + IHC: Standard ABC + Anticytokeratin AE1/AE3)
Clair et al. [22]	Retrospective cohort	2015	2005–2013	844	61	724	Serous: 104; clear cell: 16	None: 422; < 50%: 310; ≥ 50%:112	Yes: 201; no: 618; no data: 25	479	177	188	44 (23 ITCs) (21 MIC)	5	Ultrastaging (H&E + IHC: Anticytokeratin AE1/AE3)
Todo et al. [23]	Retrospective cohort	2016	1997–2014	61	57	52	9	< 50%: 29; ≥ 50%:32	Yes: 15; no: 46	28	7	17	9 (6 ITCs) (3 MIC)	15	Ultrastaging (H&E + IHC: AE1/AE3 monoclonal antibody staining using an automated immunostainer)
Plante et al. [24]	Prospective cohort	2017	2010–2015	519	64	448	Serous: 36; carcinosarcoma: 25; clear cell: 7; other: 3	None: 125; < 50%: 234; ≥ 50%:160	Yes: 142; no: 362; no data: 15	260	150	109	42 (31 ITCs) (11 MIC)	8	Ultrastaging (H&E + IHC: Cytokeratin AE1/AE3)
Piedimonte et al. [27]	Retrospective case–control	2018	2012–2018	41	64	41	0	> 50%:16	17	No data	No data	No data	23 (11 ITCs)	56	Ultrastaging (H&E + IHC:

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Authors	Design	Year	Study period	Number of patients	Median age	Endometrioid histology	Non endometrioid	MI	LVI	Grade 1	Grade 2	Grade 3	Total MIC/ ITCs patients	MIC/ ITC (%)	Technique
													(12 MIC)		Cytokeratin-based)
Ignatov et al. [26]	Prospective cohort	2019	2000–2017	428	69	399	26	> 50%: 152; < 50%: 240	No data	145	174	100	126 (MIC)	29	Ultrastaging
Summary	Meta-analysis			2873	62	2529				1490	753	568		17	

SLN sentinel lymph node, *MM* micrometastases, *ITCs* isolated tumor cells, *RT-PCR* reverse transcription polymerase chain reaction, *H&E* hematoxylin and eosin; *IHC* immunohistochemistry, *MI* myometrial invasion, *LVI* lymphovascular space invasion, *ABC* avidin–biotin–peroxidase complex

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Table 2

Number of patients with adjuvant therapy and recurrences

	Total patients	Total negative patients			Total MIC/ITCs patients		
			Adjuvant therapy	No adjuvant therapy		Adjuvant therapy	No adjuvant therapy
Total patients							
Kim et al. [19]	425	400	94	306	12 (9 ITCs) (3 MIC)	9	3
Kim et al. [20]	413	355	No data	No data	23 (19 ITCs) (4 MIC)	No data	No data
Erlanki et al. [21]	47	40	12	28	7 (MIC)	5	2
Clair et al. [22]	844	753	No data	No data	44 (23 ITCs) (21 MIC)	40	4
Todo et al. [23]	61	52	34	18	9 (6 ITCs) (3 MIC)	2	1
Plante et al. [24]	519	434	No data	No data	42 (31 ITCs) (11 MIC)	39	3
Piedimonte et al. [27]	41	18	3	15	23 (11 ITCs) (12 MIC)	16	2
Ignatov et al. [26]	428	302	0	302	126 (MIC)	95	31
Summary	2778	2354	143	669	286	206	46
Recurrences							
Kim et al. [19]	11	8	3	5	3 (2 ITCs). (1 MIC)	2(ITCs)	1(MIC)
Kim et al. [20]	2	No data	No data	0	2 (ITCs)	2 (ITCs)	0
Erlanki et al. [21]	2	0	0	0	2 (MIC)	1(MIC)	1(MIC)
Clair et al. [22]	51	47	No data	No data	4 (2 ITCs) (2 MIC)	4 (2 ITCs) (2 MIC)	0
Todo et al. [23]	12	8	No data	0	4 (ITCs/MIC) *	2(ITCs/MIC) *	2(ITCs/MIC) *
Plante et al. [24]	1	0	No data	No data	1 (ITCs)	1 (ITCs)	0
Piedimonte et al. [27]	2	0	0	0	2	2 (MIC)	0
Ignatov et al. [26]	231	221	No data	No data	10 (MIC)	No data	No data
Summary	312	284	3	5	28	15	4

* There is no difference between MIC and ITCS reported in the study

Table 3

Comparative recurrences between negative patients and MIC/ITC patients

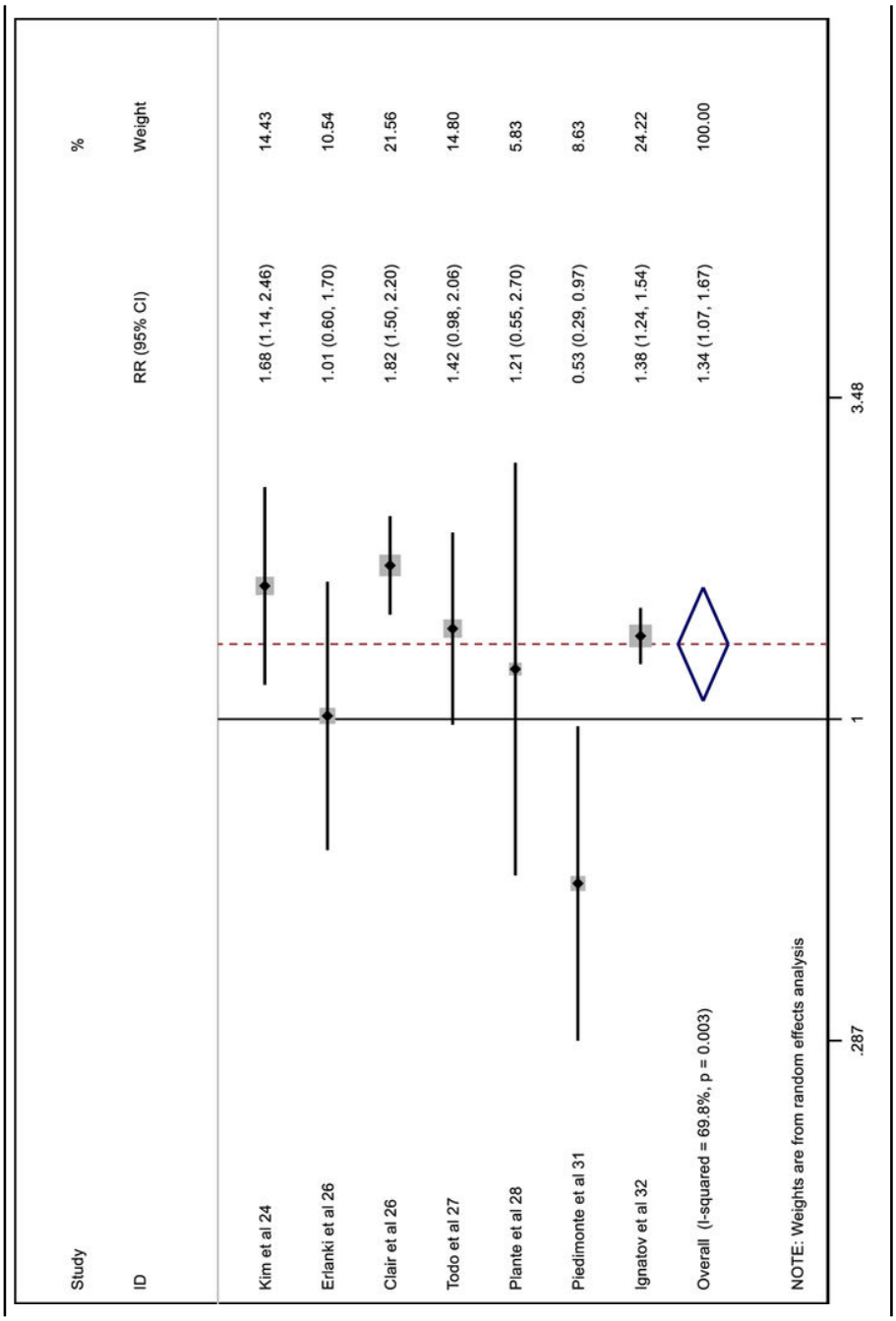


Table 4

Comparative recurrences between non-adjuvant negative patients and MIC/ITC non-adjuvant patients

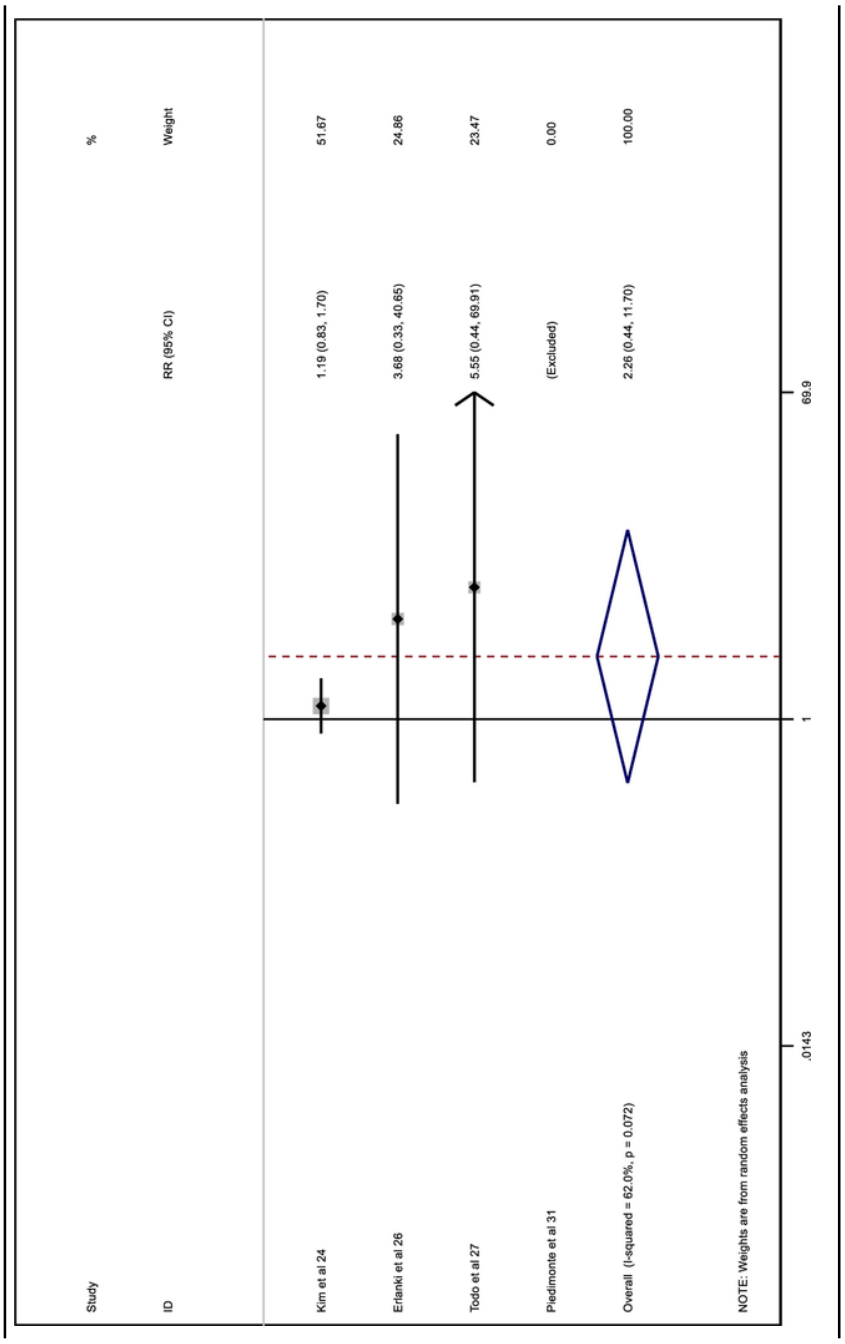
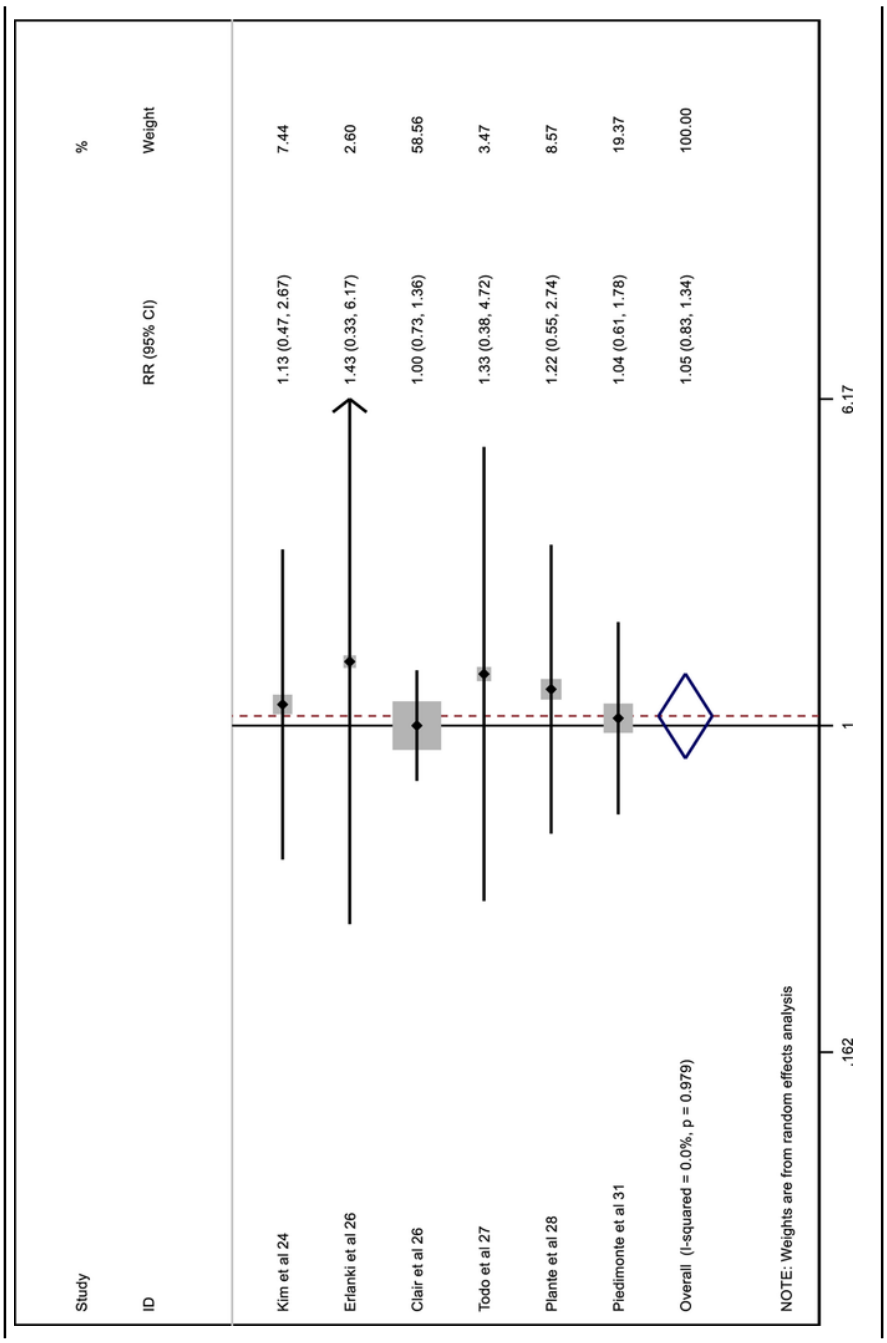


Table 5

Comparative recurrences between MIC/ITC patients with adjuvant therapy and MIC/ITC non-adjuvant patients



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Patient-reported outcomes after surgery for endometrial carcinoma: Prevalence of lower-extremity lymphedema after sentinel lymph node mapping versus lymphadenectomy

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HIGHLIGHTS

- SLN mapping was independently associated with significantly lower rate of patient-reported lower extremity lymphedema (LEL).
- Increasing BMI and use of adjuvant EBRT were associated with an increased prevalence of patient-reported LEL.
- SLN mapping in the surgical management of newly diagnosed endometrial cancer may spare these patients from LEL.
- Survival outcomes were similar between SLN mapping and comprehensive lymphadenectomy after endometrial cancer surgery.

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ABSTRACT

Objective: To compare the prevalence of patient-reported lower-extremity lymphedema (LEL) with sentinel lymph node (SLN) mapping versus comprehensive lymph node dissection (LND) for the surgical management of newly diagnosed endometrial carcinoma.
Methods: Patients who underwent primary surgery for endometrial cancer from 01/2006-12/2012 were mailed a survey that included a validated 13-item LEL screening questionnaire in 08/2016. Patients diagnosed with LEL prior to surgery and those who answered ≤6 survey items were excluded.
Results: Of 1275 potential participants, 623 (49%) responded to the survey and 599 were evaluable (180 SLN, 352 LND, 67 hysterectomy alone). Median BMI was similar among cohorts (P = 0.99). External-beam radiation therapy (EBRT) was used in 10/180 (5.5%) SLN and 35/352 (10%) LND patients (P = 0.1). Self-reported LEL prevalence was 27% (49/180) and 41% (144/352), respectively (OR, 1.85; 95% CI, 1.25–2.74; P = 0.002). LEL prevalence was 51% (23/45) in patients who received EBRT and 35% (170/487) in those who did not (OR, 1.95; 95% CI, 1.06–3.6; P = 0.03). High BMI was associated with increased prevalence of LEL (OR, 1.04; 95% CI, 1.02–1.06; P = 0.001). After controlling for EBRT and BMI, LND retained independent association with an increased prevalence of LEL over SLN (OR, 1.8; 95% CI, 1.22–2.69; P = 0.003). Patients with self-reported LEL had significantly worse QOL compared to those without self-reported LEL.
Conclusions: This is the first study to assess patient-reported LEL after SLN mapping for endometrial cancer. SLN mapping was independently associated with a significantly lower prevalence of patient-

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reported LEL. High BMI and adjuvant EBRT were associated with an increased prevalence of patient-reported LEL.

1. Introduction

Pelvic and para-aortic lymphadenectomy (LND) has been considered standard of care for patients with newly diagnosed endometrial carcinoma [1]. The role of comprehensive LND, however, is debatable. In 2 randomized trials, pelvic LND did not result in improved survival [2,3], but it was associated with the identification of nodal disease and more accurate staging, which many clinicians consider necessary to guide adjuvant treatment. Despite the potential therapeutic value of LND, the procedure is associated with an increased risk of lower-extremity lymphedema (LEL) [4].

Most lymphedema patient-reported outcome (PRO) assessment tools have been designed for the upper extremity, in the context of breast cancer. There are now at least 2 validated LEL PRO tools. Investigators at the Mayo Clinic developed and validated one of these tools [5], and showed that 23% of women who underwent a comprehensive LND compared to hysterectomy alone reported LEL attributable to the LND [6]. Those who reported LEL also had significantly diminished quality of life (QOL) as assessed by validated QOL tools [6].

Sentinel lymph node (SLN) mapping has emerged as an acceptable alternative to comprehensive LND in the staging of patients with endometrial cancer. The National Comprehensive Cancer Network (NCCN) guidelines now allow for SLN mapping for the surgical staging of endometrial carcinomas [7]. Prospective trials have shown low false-negative predictive values with SLN mapping in the detection of nodal disease in these patients, including those with “high-risk” endometrial carcinoma [8,9]. The therapeutic superiority of LND over SLN mapping alone, especially in high-risk cases and those with SLN metastasis, is still highly debatable. Retrospective analyses, however, have suggested that using SLN mapping over LND does not compromise oncologic outcome in such cases [10,11]. Furthermore, SLN mapping compared with LND is associated with a much lower risk of LEL development in patients with vulvar or endometrial cancer [12,13].

LEL assessment methods have varied in prior studies, ranging from physician assessment to the use of leg measurements, but no study has used LEL PRO tools to compare SLN mapping with LND. Here, we used a validated LEL PRO tool to assess the prevalence of LEL among patients who underwent either SLN mapping or LND during surgery for newly diagnosed endometrial cancer. We also assessed whether patient-reported LEL was associated with QOL.

1.1. Methods and materials

After Institutional Review Board (IRB) approval, we identified all patients who had undergone primary surgery for newly diagnosed endometrial cancer at our institution (Memorial Sloan Kettering Cancer Center [MSK]) between 1/1/06 and 12/31/12. We excluded patients who had died or had a “do not contact” notation in the electronic medical record (EMR). The included patients were mailed a questionnaire that included a validated 13-item LEL screening survey and validated QOL assessment tools (Appendix 1) in August 2016—a minimum of 44 months after surgery. The original questionnaire [6] was modified and used with permission.

The 13-item LEL PRO survey (Items 9–21 of Appendix 1), validated by investigators from the Mayo Clinic [5], results in a score of 0–52, with a total score $\geq$5 indicative of LEL (primary endpoint). The tool’s sensitivity and specificity for detecting LEL is 95.5% and 86.5%, respectively, in all patients, and 94.8% and 76.5%, respectively, in obese patients [5]. The mailed questionnaire also included validated QOL assessment tools—EORTC QLQ-C30 (Items 22–49 of Appendix 1) and EORTC QLQ-EN24 (Items 50–75 of Appendix 1) [14–16]. Item 8 was included to identify patients who had LEL prior to surgery; these patients were subsequently excluded.

We used a highly proven 2-phase mail-first recruitment design to yield higher coverage and garner a higher response rate at a lower cost compared to phone-first design [17,18]. After the first mailing, a second mailing went out to non-respondents 1 month later. A month after that, the remaining non-respondents were called and reminded to complete the questionnaire using an IRB-approved phone script. Potential participants were called a maximum of 2 times. Questionnaire responses and clinicopathologic data were abstracted from the EMR and entered into the Web-based Research Electronic Data Capture (REDCap) platform. Those who reported preoperative LEL, had answered 6 or fewer of the 13 items on the LEL PRO survey, or reported having undergone a radical orthopedic resection of the pelvis and/or extremities since their hysterectomy were excluded.

The primary endpoint was the prevalence of patient-reported LEL among those who had undergone hysterectomy with SLN mapping alone (SLN cohort) and those who had undergone hysterectomy with standard LND, with or without SLN mapping (LND cohort). We also assessed the prevalence of patient-reported LEL in those who had undergone hysterectomy alone (HYST cohort). The HYST cohort included patients who had undergone hysterectomy alone with or without bilateral salpingo-oophorectomy, as well as those in whom 1 or 2 “enlarged/suspicious” lymph nodes were removed without intent for LND or SLN mapping. The SLN cohort included those in whom only SLN mapping was performed and SLNs excised, with at least one SLN identified both clinically and pathologically. Those who had a unilateral side-specific LND of an unmapped hemi-pelvis were included in the SLN cohort, as per our algorithm. The LND cohort included those in whom a bilateral LND was performed alone or as a “backup” after SLN mapping, and in those who had a failed bilateral SLN mapping.

The statistical design assumed a two-sided type I error of 5% and power of 95% with an expected sample size of 413 LND and 260 SLN patients in order to detect a 10% difference in the rate of LEL between the LND and SLN cohorts of 5–15%. The final sample size was 352 LND and 180 SLN patients.

The rate of LEL in each cohort and the 95% confidence interval (CI) was estimated assuming binomial distribution. A two-sample binomial proportions test was used to compare LEL prevalence between the 2 groups. As a secondary analysis, time to development of LEL was analyzed as a time-to-event variable from surgery date to questionnaire date while considering the interval censored data (LEL exact event date is not known). A type I interval censoring method was applied to compare LEL incidence between the cohorts [19].

Descriptive statistics were provided for all baseline variables for the entire cohort and subgroups (i.e., SLN/LND/HYST or LEL/No LEL). The Fisher exact test and Wilcoxon rank sum test were used to compare the distribution of prespecified covariates between the groups. Univariate logistic regression was used to investigate the effect of baseline covariates on the presence of patient-reported

LEL. A multivariate logistic model was built based on significant variables ($P < 0.05$) in univariate setting, except the number of lymph nodes was excluded as a covariate since it was highly correlated with whether LND was performed or not.

QOL questionnaire scoring was calculated according to the EORTC QLQ-C30 and EORTC QLQ-EN24 scoring manuals [15,16]. The QLQ-C30 summary score is calculated from the mean of 13 of the 15 QLQ-C30 scales [20]. The Wilcoxon rank sum test is applied to compare the scores' distribution between patients who developed LEL and those who did not. Multiple comparisons adjustment is applied to the QOL analysis using Bonferroni correction.

2. Results

Of 1275 potential participants, 623 (49%) responded to the survey, an acceptable response rate for our study design. Twenty-four were excluded for either having answered 6 or fewer of the 13 items on the LEL PRO survey ($n = 11$) or for indicating preoperative LEL ($n = 13$). There were 599 evaluable patients (180 SLN, 352 LND, 67 HYST) (Fig. 1). The median time from date of surgery to date of filling out the questionnaire was 63.2 months (range, 44.3–101.2 months) in the SLN cohort, 93.1 months (range, 44.4–131.3 months) in the LND cohort, and 84.5 months (range, 45.1–127.9 months) in the HYST cohort ($P < 0.001$ for SLN vs LND). Clinicopathologic characteristics for the entire cohort and each subcohort are listed in Table 1. Median age and body mass index (BMI) did not differ between the SLN and LND cohorts. The differences noted in International Federation of Gynecology and Obstetrics (FIGO) stage, grade, and histology reflect the evolution of patient selection for SLN mapping during the selected time period.

Overall, 220 (37%) of 599 patients were noted to have LEL based on the 13-item LEL PRO questionnaire. Forty-nine (**27.2%**; 95% CI, 20.7–33.7%) of 180 patients in the SLN cohort screened positive for self-reported LEL compared with 144 (**40.9%**; 95% CI, 35.8–46.1%) of 352 patients in the LND cohort ($P = 0.002$ using two-sample binomial proportion test and $P = 0.039$ using interval censoring method), representing an absolute difference of approximately 14%, which we interpret to mean that LND contributed to the development of LEL in 14% of women compared to SLN mapping alone. Patient-reported LEL was also noted in 27 (**40.3%**; 95% CI, 28.6–52.0%) of the 67 patients in the HYST cohort.

The pre-trial statistical design assumed a two-sided type I error of 5% and power of 94% with an expected sample size of 413 LND and 260 SLN patients in order to detect a 10% absolute difference in the rate of LEL between the LND (20%) and SLN (10%) cohorts. The post-hoc power calculation confirms that the study has 88% power to detect a difference in LEL rate from 27% (SLN cohort) to 41% (LND cohort) in the two arms with $n = 532$ (352 LND+180 SLN) (two-sided Type I error = 0.05).

Table 2 describes the association of patient-reported LEL with various factors such as BMI, hypertension, diabetes, and use of external-beam radiation therapy (EBRT). Three patients had congestive heart failure and were not included in our univariate analysis. We did not include FIGO stage, grade or histology, as these were likely to be correlated with the need for additional therapies. Furthermore, at earlier time points, tumor grade and histology would have been correlated with the decision to perform an LND. In addition to LND, increasing BMI and the use of EBRT were also associated with patient-reported LEL on univariate analysis. The distribution of total lymph node counts was skewed to the right, so we performed the log transformation, which resulted in a significant association with patient-reported LEL. Limiting analysis to only the SLN cohort, the median number of nodes removed was 4 (range, 1–14) in those without LEL and 4 (range, 1–21) in those with

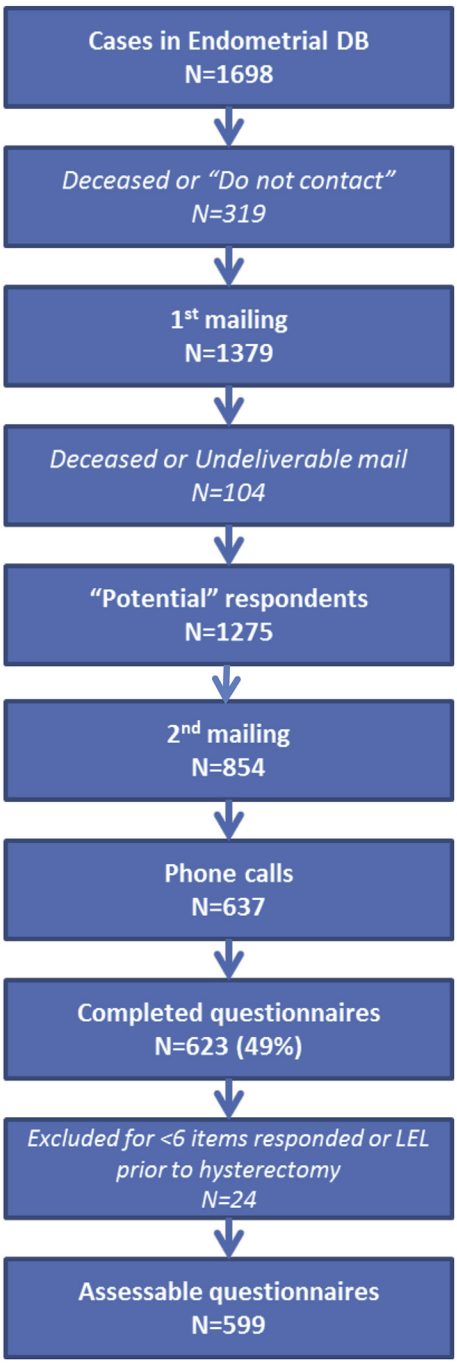

Fig. 1. Study recruitment flow.

LEL ($P = 0.6$). The total number of lymph nodes removed was also not associated with the risk of LEL on univariate logistic regression ($P = 0.3$). However, only 8 (4.4%) of the 180 patients in the SLN cohort had more than 10 nodes removed, limiting the interpretation of this specific analysis.

LND retained an independent association with patient-reported LEL compared to SLN after adjusting for BMI and EBRT (Table 3). Increasing BMI was also independently associated with patient-reported LEL. Independent statistical significance was not achieved for the use of EBRT, but the cohort that received EBRT was small. Number of lymph nodes removed was not included in the multivariate model, as it is directly related to whether LND was performed or not. Total and global QOL scores were significantly

Table 1
Select clinicopathologic characteristics. P value refers to the comparison between SLN and LND groups only.

Characteristic	Whole Cohort	SLN	LND	HYST	P value for SLN vs LND only
N	599	180	352	67	
Age at surgery (years)					0.37
Median	61	61	61	61	
Range	27–85	34–85	27–83	31–85	
BMI (kg/m^2)					0.99
Median	29	29.1	29.0	33.0	
Range	17.9–68.6	17.9–67.6	18.2–59.1	19.5–68.6	
FIGO stage					0.01
I	492 (82.3)	159 (88.3)	271 (77)	62 (93.9)	
II	15 (2.5)	2 (1.1)	12 (3.4)	1 (1.5)	
III	78 (13)	18 (1.0)	59 (16.8)	1 (1.5)	
IV	13 (2.2)	1 (0.6)	10 (2.8)	2 (3)	
FIGO tumor grade					<0.001
1	305 (51)	122 (67.8)	135 (38.4)	48 (72.7)	
2	132 (22.1)	34 (18.9)	88 (25)	10 (15.2)	
3	161 (26.9)	24 (13.3)	129 (36.6)	8 (12.1)	
Histology					<0.001
Endometrioid	472 (78.8)	162 (90)	256 (72.7)	54 (80.6)	
Non-endometrioid	60 (10)	8 (4.4)	47 (13.4)	5 (7.5)	
Carcinosarcoma	25 (4.2)	2 (1.1)	23 (6.5)	0 (0)	
Sarcoma	8 (1.3)	1 (0.6)	2 (0.6)	5 (7.5)	
Other[a]	34 (5.7)	7 (3.9)	24 (6.8)	3 (4.5)	
Hypertension					0.17
No	281 (46.9)	96 (53.3)	165 (46.9)	20 (29.9)	
Yes	318 (53.1)	84 (46.7)	187 (53.1)	47 (70.1)	
Diabetes					0.01
No	495 (82.6)	161 (89.4)	285 (81)	49 (73.1)	
Yes	104 (17.4)	19 (10.6)	67 (19)	18 (26.9)	
CHF					0.27
No	592 (98.8)	178 (98.9)	351 (99.7)	63 (94)	
Yes	7 (1.2)	2 (1.1)	1 (0.3)	4 (6)	
Renal disease					1.0
No	588 (98.2)	178 (98.9)	347 (98.6)	63 (94)	
Yes	11 (1.8)	2 (1.1)	5 (1.4)	4 (6)	
EBRT					0.1
No	550 (91.8)	170 (94.4)	317 (90.1)	63 (94)	
Yes	49 (8.2)	10 (5.6)	35 (9.9)	4 (6)	
Total LNs removed					<0.001
Median	11	4	19	0	
Range	0–80	1–21	1–80	0–1	

Values are N(%) except where noted otherwise.
SLN = sentinel lymph node mapping cohort; LND = lymphadenectomy cohort; HYST = hysterectomy alone cohort.
BMI = body mass index; FIGO=International Federation of Gynecology and Obstetrics; CHF = congestive heart failure; EBRT = external beam radiotherapy (postoperative); LN = lymph nodes.
[a] Other histology includes: adenocarcinoma NOS, carcinoma NOS, atypical hyperplasia, mixed histologies, squamous cell carcinoma, undifferentiated carcinoma, yolk sac tumor.

worse in patients with patient-reported LEL, and these patients had worse scores on all subscales (see Table 4).

3. Discussion and conclusions

To our knowledge, there are no other published reports using LEL PRO tools comparing SLN mapping to LND. We are reassured this tool is valid and reflects a true correlation, since we also found an association of patient-reported LEL with both BMI and EBRT. Of note, our 27% LEL prevalence rate in the SLN cohort may seem high; however, age and the associated comorbidities of age are also associated with LEL development. As the median age of our SLN cohort was 61 years, with an upper range of 85 years, a 27% prevalence rate gives further credence to the validity of our LEL PRO instrument.

Our findings are consistent with those of the Mayo Clinic, in which the same LEL PRO tool showed an LEL prevalence rate of 52% in patients who underwent an LND compared with 37% in those who underwent a hysterectomy alone [6]. Despite the differences in individual rates between our study and theirs, the absolute difference was similar (14% and 15%, respectively). This may indicate that SLN mapping does not contribute to the development of LEL beyond the hysterectomy itself and/or aging.

Nodal assessment in patients with newly diagnosed endometrial carcinoma is an important aspect of the initial management of these patients. The therapeutic value of comprehensive LND, however, is debatable [2,3]. Two randomized trials that showed no survival benefit have been highly criticized for the lack of para-aortic lymphadenectomy, the inclusion of mostly low-risk cases, and inconsistencies or a lack of adjuvant therapy in those with nodal disease. The addition of a para-aortic lymphadenectomy likely would not impact survival considering that the nodal chains do not end at the level of the renal vessels. Those with para-aortic metastases will likely have nodal disease above the renal vessels, and there are no data to support extending lymphadenectomy to the mediastinum and scalenes in endometrial cancer. The comprehensive removal of both clinically and pathologically normal lymph nodes, which is the case in the majority of patients with endometrial carcinoma, is not beneficial. Neither the number of lymph nodes removed nor the performance of a para-aortic

Table 2
Univariate analysis of the association of various clinicopathologic characteristics with patient-reported lower-extremity lymphedema. OR: odds ratio for developing LEL.

Characteristic	No patient-reported LEL	Patient-reported LEL	OR	95% CI	P value
Surgery Cohort					
LND	208 (59.1)	144 (40.9)			0.002
SLN	131 (72.7)	49 (27.2)	1.85	1.25-2.74	
BMI (kg/m^2)					
One unit increase	–	–	1.04	1.02-1.06	0.001
Hypertension					
Yes	174 (64.2)	97 (35.8)	0.96	0.67-1.36	0.8
No	165 (63.2)	96 (36.8)			
Diabetes					
Yes	48 (55.8)	38 (44.2)	1.49	0.93-2.37	0.1
No	291 (65.2)	155 (34.8)			
Renal disease					
Yes	4 (57.1)	3 (42.9)			
No	335 (63.8)	190 (36.2)	1.32	0.29-5.97	0.7
EBRT					
Yes	22 (48.9)	23 (51.1)	1.95	1.06-3.6	0.03
No	317 (65.1)	170 (34.9)			
Number LNs removed					
Total LNs	–	–	1.01	0.997-1.03	0.1
Log (total LNs)[a]	–	–	1.25	1.04-1.52	0.02

% is for the total in row.
LEL = lower-extremity lymphedema; SLN = sentinel lymph node mapping cohort; LND = lymphadenectomy cohort; EBRT = external beam radiotherapy (postoperative); LN = lymph nodes.
[a] Log transformation also shown as the distribution of lymph nodes removed was skewed.

Table 3
Multivariate model assessing independent association with patient-reported lower-extremity lymphedam. OR: odds ratio for developing LEL.

Characteristic	OR	95% CI	P value
Surgery cohort: LND vs SLN	1.81	1.22-2.69	0.003
EBRT: Yes vs No	1.85	0.99-3.46	0.05
BMI: one unit increase	1.04	1.02-1.06	<0.001

Total N of cases included in model = 532.
LEL = lower-extremity lymphedema; SLN = sentinel lymph node mapping cohort; LND = lymphadenectomy cohort; EBRT = external beam radiotherapy (postoperative); BMI, body mass index.

lymphadenectomy were predictive of survival in a classification and regression tree (CART) analysis [21]. The first branching point, meaning the most important factor, was stage of disease [21].

The exclusion of any nodal assessment is also not recommended in our opinion, as this would lead to improper staging and under- or over-treatment, with adjuvant therapy decisions based on patient and uterine features alone. For example, adjuvant chemotherapy has been shown to provide a significant improvement in overall survival in patients with extrauterine disease, including nodal involvement. In a randomized trial, doxorubicin and cisplatin therapy compared with whole abdominal radiation resulted in significantly greater progression-free and overall survival in patients with FIGO stage III or IV endometrial carcinoma [22]. The number of lymph nodes removed was not associated with survival outcomes in an ancillary analysis of the study [23]. The NCCN guidelines recommend some form of adjuvant therapy for patients with FIGO stage III or IV disease, although the optimal regimen has not been determined [7].

SLN mapping has evolved as a viable alternative to comprehensive LND since its introduction in endometrial cancer in 1996 [24]. The MSK SLN algorithm, which is endorsed by the NCCN, has a false-negative predictive value (FNPV) of 0.5% [25]. In short, the algorithm requires the removal of any suspicious nodes, irrespective of dye uptake, as well as a side-specific lymph node dissection in hemipelvises that do not map. The FIRES trial demonstrated an FNPV of 0.4% in mapped SLNs in patients with clinical stage I endometrial cancer who underwent SLN mapping followed by an immediate LND [8]. In another prospective trial, the FNPV was 1.4% in patients with high-risk endometrial carcinoma [9].

Based on our study results and those of others, the benefit of SLN mapping over comprehensive LND lies in the reduction of lymphatic morbidity and subsequent improvement in QOL. The GROINSS V1 study in vulvar cancer reported an LEL rate of 25% in patients who had undergone SLN mapping followed by an inguinofemoral LND compared to only 2% in those who had undergone SLN mapping of the groin alone [26], although LEL diagnoses were based on physician assessment. In a prospective study of 188 patients with endometrial cancer, the incidence of LEL after SLN mapping alone was 1.3% compared with 18.1% after pelvic and paraaortic LND (P = 0.0003). Lymphedema diagnoses in the study were based on the assessment of a physiotherapist using the Common Toxicity Criteria (CTC) version 3.0 [13]. Currently, there are no agreed upon standard guidelines for the diagnosis of LEL, and the use of PRO instruments in this setting is lacking.

The Gynecologic Cancer Lymphedema Questionnaire (GCLQ) is another LEL PRO tool, which was modified from the Lymphedema Breast Cancer Questionnaire (LBCQ). The 20-item GCLQ has acceptable reported sensitivity and specificity (85.7% and 90%, respectively) [27]. We decided to use the Mayo Clinic LEL PRO tool for our study, because of the reduced patient burden of answering only 13 items as opposed to 20. However, both instruments are acceptable, and it would be interesting to see them assessed in a head-to-head study.

We recognize the limitations of our study. Varying cutoff points among studies may alter baseline rates of LEL. Recall bias is a concern in all studies of this design. Even though we feel that the survey response rate was acceptable, half of the potential respondents did not return the survey, which may impact the generalizability of our findings. We could only assess prevalence rates at the time patients received the questionnaires, and the time since surgery varied. We cannot assess the incidence rates over time as this was not a prospective study and the exact timing of LEL development is unknown. We would ideally like to conduct a study in a cohort of patients who present with newly diagnosed endometrial cancer and assess patient-reported LEL and QOL before surgery and then at timed intervals for some years after surgery in order to better capture the timing of LEL after surgery. We also recognize that the median time since surgery was different between the SLN and LND cohorts, which may impact the rate of

Table 4
EORTC QLQ-C30 and -EN24 scores between patients with and without patient-reported lower-extremity lymphedema.

	No patient-reported LEL	Patient-reported LEL	P value[a]
EORTC QLQ-C30			
Overall Score			
QLQ Total Score	94.9/91.8 (27.6–100)	84.7/79 (19.6–100)	<0.001
Global QOL	83.3/83.6 (0–100)	66.7/66.8 (0–100)	<0.001
Functional Scales			
Physical functioning	100/90.4 (0–100)	86.7/75.8 (0–100)	<0.001
Role functioning	100/95 (0–100)	83.3/80 (0–100)	<0.001
Emotional functioning	91.7/86.3 (0–100)	75/73.2 (0–100)	<0.001
Cognitive functioning	100/89.4 (16.7–100)	83.3/77.4 (0–100)	<0.001
Social functioning	100/93.8 (0–100)	83.3/77.3 (0–100)	<0.001
Symptom Scales			
Fatigue	0/12.9 (0–100)	22.3/31.7 (0–100)	<0.001
Nausea and vomiting	0/2.3 (0–100)	0/7.3 (0–100)	<0.001
Pain	0/7.7 (0–100)	16.7/28.5 (0–100)	<0.001
Dyspnea	0/6.4 (0–100)	0/17.5 (0–100)	<0.001
Insomnia	0/16.1 (0–100)	33.3/31.1 (0–100)	<0.001
Appetite loss	0/3.3 (0–100)	0/9.9 (0–100)	<0.001
Constipation	0/7.8 (0–100)	0/17.8 (0–100)	<0.001
Diarrhea	0/5.4 (0–100)	0/15.9 (0–100)	<0.001
Financial difficulties	0/5 (0–100)	0/19.5 (0–100)	<0.001
EORTC QLQ-EN24			
Functional Scales			
Sexual interest[b]	33.3/23.3 (0–100)	0/19.5 (0–100)	0.035
Sexual activity[c]	0/19.5 (0–100)	0/12.7 (0–100)	0.01
Sexual enjoyment[d]	33.3/49.2 (0–100)	33.3/33.3 (0–100)	<0.001
Symptom Scales			
Lymphedema	0/3 (0–100)	33.3/38.3 (0–100)	<0.001
Urologic symptoms	8.3/15.1 (0–75)	25/29.9 (0–100)	<0.001
Gastrointestinal symptoms	6.7/7.8 (0–100)	13.3/20.7 (0–86.7)	<0.001
Poor body image	0/9.1 (0–100)	16.7/25.6 (0–100)	<0.001
Sexual/vaginal problems[e]	22.2/35.3 (0–100)	44.4/48.5 (0–100)	0.019
Pain in back and pelvis	0/14.4 (0–100)	33.3/36.4 (0–100)	<0.001
Tingling/numbness	0/17.8 (0–100)	33.3/38.6 (0–100)	<0.001
Muscular pain	0/21.4 (0–100)	33.3/43.2 (0–100)	<0.001
Hair loss	0/12.4 (0–100)	0/25 (0–100)	<0.001
Taste change	0/4.4 (0–100)	0/10.1 (0–100)	<0.011

LEL = lower-extremity lymphedema; QOL = quality of life.
Data are reported as Median/Mean (range).
[a] P-value obtained using Wilcoxon Rank Sum Test and all except "sexual interest" and "sexual activity" remain significant using Bonferroni correction for multiple comparisons adjustment.
[b] Data missing from 56.
[c] Data missing from 62.
[d] Data missing from 321.
[e] Data missing from 317.

patient-reported LEL, especially as patients continue to age. The minimum time from surgery was 44 months in both cohorts, which seems to be a reasonable amount of time to assess for the possible development of surgery-related, patient-reported LEL.

The noted range of 1–21 lymph nodes removed in the SLN cohort is due to multiple reasons. One of the reasons is related to the learning curve of surgeons as they adopted SLN mapping. Surgeons tend to remove more "SLNs" early on in their experience, and the number removed decreases with increased experience and understanding of true SLN mapping. Also, there may be a few nodes within a packet that are removed as the "SLN". The other reasons are related to the use of our algorithm, which includes the removal of any "suspicious" nodes irrespective of mapping, performance of a para-aortic LND at the surgeon's discretion, and the performance of a unilateral LND in cases with an unmapped hemi-pelvis. The number of cases with true unilateral LND of unmapped hemi-pelvis was low, limiting any meaningful analysis comparing those with only SLN mapping to those with unilateral LND. Additionally, the PRO LEL questionnaire cannot differentiate laterality of LEL.

Our results demonstrate that SLN mapping over LND is independently associated with a significantly lower prevalence of patient-reported LEL in patients who have undergone surgery for endometrial carcinoma. Our data also may inform discussions regarding the risks and benefits of adjuvant radiation therapy. These data provide additional support for SLN mapping in women with endometrial carcinoma. SLN mapping provides accurate surgical staging, as well as decreased morbidity and improved QOL.

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Declaration of competing interest

Outside the submitted work, Dr. Abu-Rustum reports grants from Stryker/Novadaq, Olympus, and GRAIL. Outside the submitted work, Dr. Leitao is an ad hoc speaker for Intuitive Surgical, Inc. Outside the submitted work, Dr. Chi reports personal fees from Bovie Medical Co., Verthermia Inc. (now Apyx Medical Corp.), C Surgeries, and Biom 'Up, as well as other from Intuitive Surgical, Inc. and TransEnterix, Inc. Outside the submitted work, Dr. Jewell reports personal fees from Covidien/Medtronic. The other authors have no potential conflicts to disclose.

Appendix A. Supplementary data

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Trends in Sentinel Lymph Node Mapping and Adjuvant Therapy in Endometrial Carcinoma

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Abstract

We analyzed 54,039 women with uterine cancer in the National Cancer Database from 2013–2014 including 38,453 (71.2%) who underwent lymphadenectomy, 1929 (3.6%) who underwent sentinel lymph node (SLN) mapping, and 13,657 (25.3%) who did not undergo nodal assessment. SLN mapping increased from 2.8% in 2013 to 4.3% in 2014 (P<0.001). Patients treated in 2014 and those at community centers were more likely to undergo SLN biopsy, while women with advanced-stage disease, sarcomas, and grade 3 tumors were less likely to undergo SLN mapping (P<0.05). There was no association between use of SLN biopsy and use of radiation (aRR=0.92; 95%CI, 0.82–1.05).

Keywords

Uterine cancer; endometrial cancer; sentinel lymph node; lymphadenectomy; hysterectomy

Introduction

Endometrial carcinoma is the most common gynecologic cancer in developed countries (1). The standard treatment for patients diagnosed with endometrial cancer is hysterectomy and bilateral salpingo-oophorectomy. The role of lymph node assessment remains controversial. While lymphadenectomy may provide prognostic information and help tailor adjuvant therapy, universal nodal assessment subjects a large number of women with uterine-confined

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disease to the procedure (2–4). Lymphadenectomy increases operative time and is associated with long-term sequelae such as lymphedema (5). Further, prospective trials have shown that lymphadenectomy is not associated with improved survival further calling into question the value of the procedure (6,7).

Sentinel lymph node (SLN) mapping has been proposed as an alternative to lymphadenectomy (8). SLN mapping relies on removal of a small number of lymph nodes that are the first drainage sites from a tumor and thus the most likely to harbor tumor cells (9,10). SLN mapping has the potential to reduce the morbidity of lymphadenectomy and has been extensively validated for a number of other solid tumors and is now in the standard of care in breast cancer, vulvar cancer, and melanoma (11–13).

Despite the potential benefits of SLN mapping, data describing the performance of the procedure in women with endometrial cancer is limited. We performed a population-based analysis of women with endometrial cancer to first determine the utilization and predictors of use of SLN mapping and second, to examine whether use of SLN mapping was associated with changes in the prescription of adjuvant therapy for women with early-stage tumors.

Methods

Data source

The National Cancer Database (NCDB) Participant Use Data File (PUF) was used for the analysis (14). The NCDB is a hospital-based registry developed by the American College of Surgeons and American Cancer Society. It contains data on all patients with malignant tumors from over 1,500 Commission on Cancer (CoC)-accredited hospitals, and represents more than 70% of newly diagnosed cancer cases across the United States. Incident tumor cases are collected by trained registrars and the data is examined and verified regularly to ensure quality. The data fields include patient demographics, tumor characteristics, treatment, survival, and hospital characteristics (14). The study was deemed exempt by the Columbia University Institutional Review Board.

Patient Selection

We identified women who had malignant uterine cancers diagnosed as their first or only cancer and confirmed with positive histology from 2013 to 2014. Women who had radiation before surgery or intraoperative radiation therapy were excluded. Women who did not have hysterectomy, or whose performance of nodal assessment was unknown were excluded. Women who had stage IV cancer or unknown stage were also excluded.

Patients were classified based on nodal assessment codes as having undergone sentinel lymph node (SLN) mapping, lymphadenectomy (LND), or no nodal assessment (no LND). Among patients who had a code for SLN mapping, additional non-sentinel nodes could be taken and discovered by the pathologist. We determined if they had a concurrent lymphadenectomy when review of the operative report confirmed that a regional lymph node dissection followed the SLN. In cases of failed SLN mapping, lymphadenectomy was usually performed and patients were classified as having SLN with concurrent lymphadenectomy. If no further regional lymph nodes were dissected, patients were

classified as having SLN mapping only. The number of nodes removed was recorded for each group of patients.

Demographic data included age (<50, 50–59, 60–69, 70–79, ≥80 years), race (white, black, Hispanic, other, unknown), year of diagnosis, and insurance status (private, Medicaid, Medicare, uninsured, other governmental/unknown). Income was measured by median household income in the patients' zip code and was classified as <$38,000, $38,000-$47,999, $48,000-$62,999, $63,000+, or unknown. Education was measured by the percentage of adults in a patient's zip code who did not graduate from high school, and classified as ≥21%, 13–20%, 7.0–12.9%, <7%, or unknown. Location was estimated by matching the patients' state and country FIPS code to rural-urban continuum codes from the United States Department of Agriculture Economic Research Service, and classified as metropolitan, urban, rural, and unknown. Comorbidity was measured using the Deyo adaptation of the Charlson's comorbidity score, and grouped as 0, 1, or ≥2 comorbid conditions(15).

Tumor stage was derived from the American Joint Committee on Cancer (AJCC) pathologic staging groups, and classified as IA, IB, I NOS, II, IIIA, IIIB, IIIC, and III NOS (not otherwise specified). Other tumor characteristics included histology (endometrioid, serous, clear cell, carcinosarcoma, sarcoma, and endometrial cancer not otherwise specified [NOS]/other) and grade (well, moderate, poorly, unknown). Hospital characteristics included facility region (northeast, midwest, south, west, unknown) and facility type defined by the American Cancer Society's Commission on Cancer Accreditation program (academic/research, community cancer, comprehensive community cancer, integrated network cancer, other/unknown). Radiation therapy was classified as combination, external beam, brachytherapy, or none/unknown.

Statistical Analysis

Frequency distributions between demographic and clinical characteristics of the patients and the scope of lymph node dissection were compared using χ^2 tests. The number of lymph nodes removed in the SLN group was reported descriptively as means (standard deviation [SD]), and medians (interquartile range [IQR]). To examine predictors of having undergone SLN mapping, we fit mixed-effect models adjusting for age, race, year of diagnosis, insurance status, income, location, comorbidity, facility type, region, stage, histology and grade to compare patients who underwent SLN mapping to those who underwent lymphadenectomy and to compare patients who underwent SLN mapping to who had no nodal assessment. The treating facility was included as random effect to account for hospital-level clustering.

To examine predictors of any type of radiation (external beam, brachytherapy or combination) among stage I patients who had SLN mapping or LND, we fit mixed-effect models adjusting for all demographic and clinical characteristics and scope of lymphadenectomy. A similar model was fit for predictors of external beam or combination radiation. To account for the data quality concerns in the accuracy of treatment data collected from more than one hospital in the NCDB, sensitivity analyses were performed limiting to patients who were reported from only one CoC-accredited hospital. All analyses

were conducted using SAS version 9.4 (SAS Institute Inc, Cary, North Carolina). All hypothesis testing was two-sided and a *P*-value of <0.05 was considered statistically significant.

Results

A total number 54,039 women were identified including 38,453 (71.2%) who underwent lymphadenectomy, 1929 patients (3.6%) who underwent sentinel lymph node (SLN) biopsy and 13,657 (25.3%) who did not undergo nodal assessment (Figure 1, Table 1). Among women treated in 2013, 2.8% underwent SLN biopsy, while 4.3% of those treated in 2014 underwent SLN biopsy (P<0.001). When limited to women who underwent some form of nodal assessment, either SLN biopsy or lymphadenectomy, 3.8% in 2013 and 5.8% in 2014 underwent SLN biopsy.

In the cohort of women who had SLN biopsy, 863 (45.4%) were coded as having only undergone SLN biopsy while 1038 (54.6%) underwent concurrent lymphadenectomy (Table 2). The median number of lymph nodes removed was 3 (IQR, 2–4) in those who underwent SLN biopsy alone and 14 (IQR, 9–21) in patients who had a concurrent nodal dissection.

Among women who underwent nodal assessment (either SLN biopsy or lymphadenectomy), a patient treated in 2014 was 60% more likely to undergo SLN biopsy than if that patients had been treated in 2013 (aRR=1.60; 95% CI, 1.46–1.76) (Table 3). Likewise, a patient treated at a community cancer center was 72% more likely to undergo SLN biopsy than if she was treated at an academic center (aRR=1.72; 95% CI, 1.04–2.86). In contrast, women with more advanced stage disease, sarcomas or carcinosarcomas, and those with poorly differentiated tumors were less likely to undergo SLN biopsy (P<0.05 for all). Similarly, compared to women treated in the northeast, those who received care in the Midwest and south were less likely to undergo SLN biopsy (P<0.05 for both).

When the analysis was limited to women who either underwent SLN biopsy or no nodal evaluation, women with 2 or more comorbidities (versus none) and those in the south (versus northeast) were less likely to undergo SLN biopsy (P<0.05 for both) (Table 3). Patients with moderate and poorly differentiated neoplasms (versus well differentiated) were more likely to undergo SLN biopsy.

Among women with stage I tumors who underwent nodal assessment, there was no association between use of SLN biopsy (compared to lymphadenectomy) and use of radiation (aRR=0.92; 95% CI, 0.82–1.05). Likewise, SLN biopsy was not associated with either external beam radiation alone or in combination with brachytherapy (aRR=0.98; 95% CI, 0.70–1.36) use. These results were unchanged in models limited to patients who received all care at only one facility.

Discussion

This study suggests that the use of sentinel lymph node biopsy for women with endometrial cancer is increasing. While a number of non-clinical factors contribute to uptake of SLN biopsy, women with non-endometrioid, poorly differentiated, and more advanced stage

tumors are less likely to undergo SLN biopsy and are still more likely to have lymphadenectomy. Performance of SLN biopsy in lieu of lymphadenectomy is not associated with a higher rate of use of adjuvant radiation.

Sentinel lymph node biopsy techniques have been developed to reduce the morbidity of nodal assessment for a variety of solid tumors and the procedure has recently been utilized for endometrial cancer. Initial data for the procedure was largely based on institutional case series, but more recently, multicenter prospective clinical trials have also reported the performance characteristics of SLN biopsy (9,16,17). The SENTI-ENDO study included 133 patients and reported a sensitivity of 84% and negative predictive value of 97% for sentinel lymph node biopsy (18). More recently, the FIRES trial enrolled 385 patients with endometrial cancer and reported successful sentinel lymph node mapping in 86% of subjects. The sensitivity for detection of nodal metastases was 97% with a negative predictive value of over 99% (19).

The role of any form of nodal assessment in endometrial cancer remains controversial. Two large, randomized trials both demonstrated that lymphadenectomy was not associated with improved survival (6,7). However, proponents of lymphadenectomy argue that the procedure allows not only prognostication but also allows more tailored adjuvant therapy (4,20). In the United States, many practitioners have shifted from universal lymphadenectomy to performance of the procedure in women with higher risk features (21).

In 2014, the National Comprehensive Cancer Network guidelines (22) included SLN biopsy as part of their accepted algorithm for staging. We noted that women with lower risk tumors (grade 1, superficially invasive) were more likely to undergo SLN biopsy and those with higher risk features preferentially underwent lymphadenectomy. While the value of nodal assessment in such low risk patients is questionable, surgeons may have been hesitant to apply a new technology to women at higher risk for nodal disease. While based on limited data, some studies have suggested that SLN mapping may also be used in higher risk histologic subtypes (23–25).

Encouragingly, these findings suggest that there was no association between use of SLN mapping and use of radiation in women with stage I tumors. A concern with implementation of SLN mapping is that clinicians may lack confidence in the ability of the technique to detect metastatic spread and prescribe adjuvant radiation therapy (4,26) These findings suggest that this is not the case. Women with stage I tumors who underwent SLN biopsy were no more likely to receive radiation therapy than those who underwent full lymphadenectomy.

In addition to clinical factors, we noted substantial regional variation in performance of SLN biopsy; patients in the northeast were much more likely to undergo the procedure than women in other parts of the U.S. Prior work has also demonstrated that patients undergoing robotic-assisted surgery are substantially more likely to undergo SLN mapping (27). SLN mapping is not unlike other new techniques and technologies in which non-clinical factors influence diffusion (28).

While the study benefits from the inclusion of a large cohort of patients, we recognize several important limitations. First, coding for sentinel lymph node biopsy for endometrial cancer in the NCDB is relatively new. As such, we cannot exclude the possibility of misclassification of a small number of women. Second, we are unable to capture women who had an attempted sentinel node biopsy but for technical reasons underwent only full lymphadenectomy. Technical considerations are an important consideration for any new surgical technique. Third, while we can account for a number of clinical and demographic characteristics, there are undoubtedly unmeasured confounding factors that influenced treatment choice and outcomes. Lastly, given the favorable prognosis of endometrial cancer, our study is underpowered to detect small differences in survival or use of radiation. Further work is clearly needed to further monitor the association between sentinel lymph node biopsy and use of adjuvant therapy and survival.

In conclusion, the use of sentinel lymph node mapping in endometrial cancer is increasing rapidly. There does not appear to be an association between use of sentinel lymph node dissection and use of adjuvant radiation. To date, the majority of the patients who underwent SLN mapping had low risk, early-stage tumors and more data is clearly needed among women with higher risk cancers. With increasing surgeons experience, improvements in detection rates and developing technology, SLN mapping will likely play a more prominent role in lymph node evaluation.

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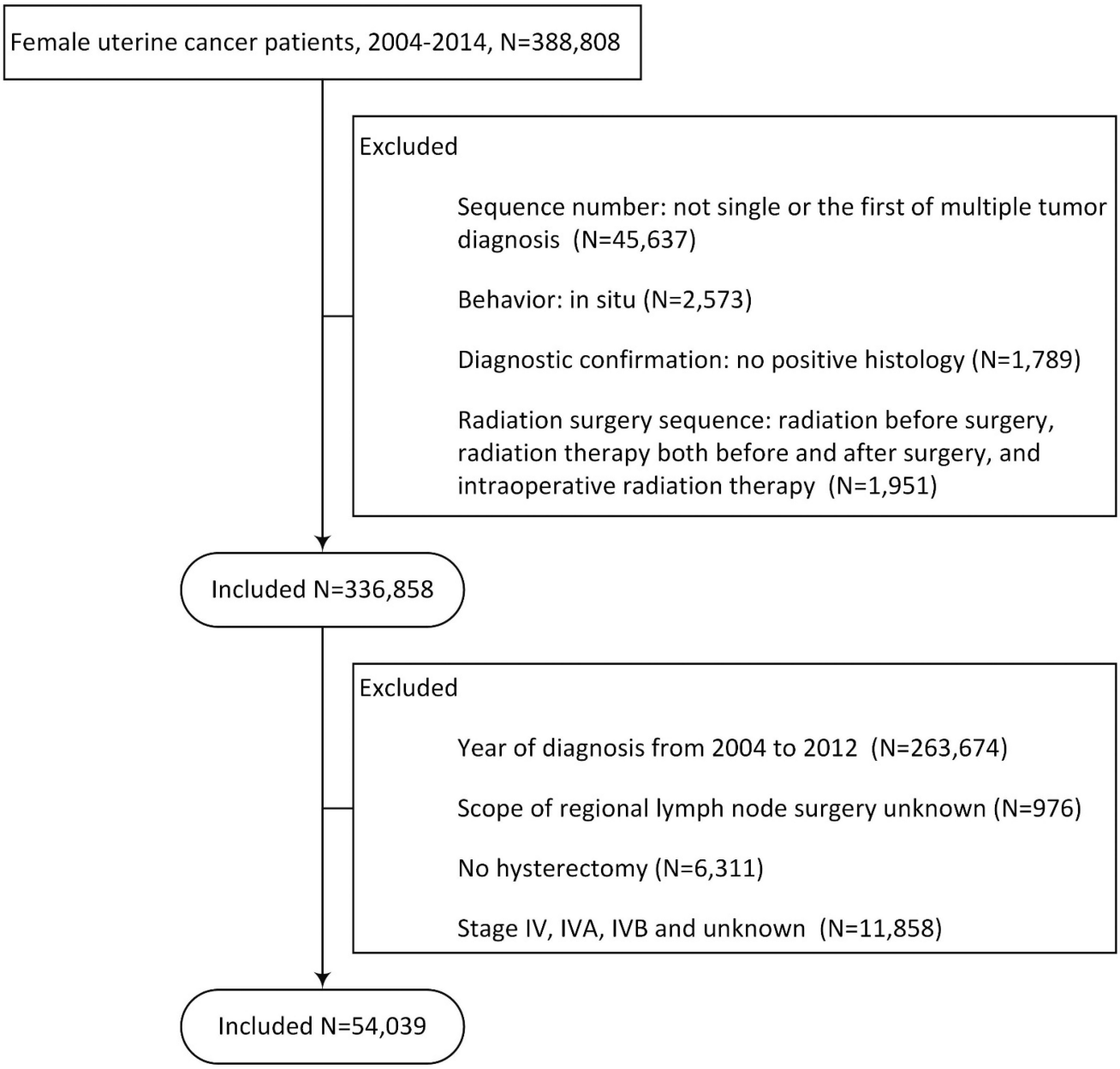

Figure 1.
Flowchart of cohort selection

Table 1

Demographic and clinical characteristics of the patients by scope of lymph node dissection.

	No LND		Sentinel LN		LND		
	N	%	N	%	N	%	*P*-value
All	13,657	(25.3)	1,929	(3.6)	38,453	(71.2)	
Age							<0.001
<50	2,165	(15.9)	187	(9.7)	3,704	(9.6)	
50–59	4,201	(30.8)	565	(29.3)	10,499	(27.3)	
60–69	4,584	(33.6)	741	(38.4)	14,968	(38.9)	
70–79	1,758	(12.9)	342	(17.7)	7,233	(18.8)	
≥80	949	(6.9)	94	(4.9)	2,049	(5.3)	
Race							<0.001
White	10,716	(78.5)	1,508	(78.2)	30,167	(78.5)	
Black	1,269	(9.3)	126	(6.5)	3,894	(10.1)	
Hispanic	1,018	(7.5)	103	(5.3)	2,316	(6.0)	
Other	539	(3.9)	175	(9.1)	1,759	(4.6)	
Unknown	115	(0.8)	17	(0.9)	317	(0.8)	
Year of diagnosis							<0.001
2013	6,675	(48.9)	751	(38.9)	19,260	(50.1)	
2014	6,982	(51.1)	1,178	(61.1)	19,193	(49.9)	
Insurance status							<0.001
Private	7,134	(52.2)	1,045	(54.2)	18,820	(48.9)	
Medicare	4,711	(34.5)	728	(37.7)	15,234	(39.6)	
Medicaid	938	(6.9)	94	(4.9)	2,126	(5.5)	
Uninsured	545	(4.0)	28	(1.5)	1,314	(3.4)	
Other government/unknown	329	(2.4)	34	(1.8)	959	(2.5)	
Income							<0.001
<$38,000	2,348	(17.2)	163	(8.4)	6,210	(16.1)	
$38,000–$47,999	3,066	(22.5)	314	(16.3)	8,670	(22.5)	
$48,000–$62,999	3,684	(27.0)	471	(24.4)	10,536	(27.4)	
$63,000+	4,535	(33.2)	978	(50.7)	12,967	(33.7)	
Unknown	24	(0.2)	*	*	70	(0.2)	
Education							<0.001
≥21%	2,587	(18.9)	231	(12.0)	6,172	(16.1)	
13–20%	3,544	(26.0)	402	(20.8)	9,792	(25.5)	
7.0–12.9%	4,297	(31.5)	717	(37.2)	12,718	(33.1)	
<7%	3,211	(23.5)	576	(29.9)	9,715	(25.3)	
Unknown	18	(0.1)	*	*	56	(0.1)	
Location							<0.001
Metropolitan	11,108	(81.3)	1,642	(85.1)	31,225	(81.2)	
Urban	1,919	(14.1)	154	(8.0)	5,616	(14.6)	
Rural	224	(1.6)	*	*	701	(1.8)	

	No LND		Sentinel LN		LND		
	N	%	N	%	N	%	*P*-value
Unknown	406	(3.0)	127	(6.6)	911	(2.4)	
Comorbidity							<0.001
0	9,776	(71.6)	1,413	(73.3)	28,780	(74.8)	
1	3,068	(22.5)	458	(23.7)	7,941	(20.7)	
≥2	813	(6.0)	58	(3.0)	1,732	(4.5)	
Facility type							<0.001
Academic/research	5,501	(40.3)	1,027	(53.2)	16,204	(42.1)	
Community cancer	744	(5.4)	97	(5.0)	1,505	(3.9)	
Comprehensive community cancer	5,253	(38.5)	640	(33.2)	15,266	(39.7)	
Integrated network cancer	1,594	(11.7)	122	(6.3)	4,581	(11.9)	
Other/unknown	565	(4.1)	43	(2.2)	897	(2.3)	
Facility region							<0.001
Northeast	2,691	(19.7)	876	(45.4)	8,171	(21.2)	
Midwest	3,321	(24.3)	272	(14.1)	10,101	(26.3)	
South	4,546	(33.3)	460	(23.8)	12,637	(32.9)	
West	2,534	(18.6)	278	(14.4)	6,647	(17.3)	
Unknown	565	(4.1)	43	(2.2)	897	(2.3)	
Stage							<0.001
IA	9,682	(70.9)	1,271	(65.9)	20,588	(53.5)	
IB	1,531	(11.2)	276	(14.3)	7,447	(19.4)	
I NOS	1,175	(8.6)	63	(3.3)	1,470	(3.8)	
II	529	(3.9)	71	(3.7)	2,330	(6.1)	
IIIA	460	(3.4)	46	(2.4)	1,417	(3.7)	
IIIB	183	(1.3)	16	(0.8)	438	(1.1)	
IIIC	58	(0.4)	184	(9.5)	4,686	(12.2)	
III NOS	39	(0.3)	*	*	77	(0.2)	
Histology							<0.001
Endometrioid	10,900	(79.8)	1,519	(78.7)	27,578	(71.7)	
Serous	345	(2.5)	110	(5.7)	2,957	(7.7)	
Clear Cell	74	(0.5)	18	(0.9)	561	(1.5)	
Carcinosarcoma	284	(2.1)	51	(2.6)	1,794	(4.7)	
Sarcoma	547	(4.0)	12	(0.6)	550	(1.4)	
Other	1,507	(11.0)	219	(11.4)	5,013	(13.0)	
Grade							<0.001
Well	7,006	(51.3)	738	(38.3)	11,364	(29.6)	
Moderate	2,447	(17.9)	493	(25.6)	9,397	(24.4)	
Poorly	1,244	(9.1)	309	(16.0)	9,220	(24.0)	
Unknown	2,960	(21.7)	389	(20.2)	8,472	(22.0)	
Radiation							<0.001
None/unknown	11,963	(87.6)	1,405	(72.8)	25,720	(66.9)	
Combination	292	(2.1)	46	(2.4)	2,063	(5.4)	

	No LND		Sentinel LN		LND		
	N	%	N	%	N	%	*P*-value
External beam	518	(3.8)	112	(5.8)	3,086	(8.0)	
Brachytherapy	884	(6.5)	366	(19.0)	7,584	(19.7)	

* Cell size<10. NOS: not otherwise specified

Table 2

Number of sentinel lymph nodes removed in patients that had sentinel lymph nodes mapping.

	SLN only		SLN with LND	
Number of sentinel LN removed				
N	863		1,038	
Mean (SD)	4	(5)	16	(10)
Median (IQR)	3	(2–4)	14	(9–21)

1,901 patients in the sentinel LN group were included in the analysis. 28 patients, including 14 having SLN only, and 14 having SLN and LND) with unknown number were excluded.

SD: standard deviation.

IQR: interquartile range.

Table 3

Multivariable models for predictors of sentinel lymph node mapping.

	Sentinel LN vs LND aRR	Sentinel LN vs No LND aRR
Age		
<50	Referent	Referent
50–59	1.08 (0.90–1.30)	1.06 (0.88–1.27)
60–69	1.11 (0.92–1.34)	1.12 (0.93–1.35)
70–79	1.04 (0.83–1.29)	1.18 (0.95–1.48)
≥80	1.14 (0.86–1.51)	0.80 (0.60–1.06)
Race		
White	Referent	Referent
Black	0.84 (0.69–1.02)	0.88 (0.72–1.07)
Hispanic	1.04 (0.84–1.28)	1.02 (0.82–1.27)
Other	0.88 (0.72–1.08)	1.04 (0.84–1.29)
Unknown	0.68 (0.42–1.10)	0.84 (0.52–1.38)
Year of diagnosis		
2013	Referent	Referent
2014	1.60 (1.46–1.76) *	1.36 (1.24–1.50) *
Insurance status		
Private	Referent	Referent
Medicare	1.02 (0.90–1.15)	0.94 (0.83–1.07)
Medicaid	0.98 (0.79–1.22)	0.95 (0.76–1.19)
Uninsured	0.74 (0.51–1.10)	0.69 (0.47–1.03)
Other government/unknown	0.96 (0.67–1.36)	0.86 (0.61–1.23)
Income		
<$38,000	Referent	Referent
$38,000–$47,999	1.18 (0.97–1.43)	1.08 (0.89–1.32)
$48,000–$62,999	1.12 (0.92–1.35)	1.06 (0.88–1.28)
$63,000+	1.18 (0.97–1.42)	1.13 (0.93–1.37)
Unknown	1.39 (0.44–4.46)	0.81 (0.25–2.63)
Location		
Metropolitan	Referent	Referent
Urban	0.87 (0.72–1.04)	0.90 (0.75–1.08)
Rural	0.56 (0.25–1.26)	0.59 (0.26–1.34)
Unknown	1.04 (0.80–1.34)	1.12 (0.87–1.45)
Comorbidity		
0	Referent	Referent
1	1.08 (0.97–1.20)	0.97 (0.87–1.09)
≥2	0.77 (0.59–1.01)	0.68 (0.52–0.88) *
Facility type		
Academic/research	Referent	Referent

	Sentinel LN vs LND	Sentinel LN vs No LND
	aRR	**aRR**
Community cancer	1.72 (1.04–2.86)*	1.07 (0.65–1.75)
Comprehensive community cancer	1.11 (0.79–1.57)	1.05 (0.75–1.47)
Integrated network cancer	0.92 (0.51–1.66)	0.91 (0.51–1.64)
Other/unknown	_≠	_≠
Facility region		
Northeast	Referent	Referent
Midwest	0.65 (0.43–0.99)*	0.72 (0.48–1.10)
South	0.58 (0.39–0.86)*	0.63 (0.42–0.93)*
West	0.64 (0.40–1.01)	0.66 (0.42–1.04)
Unknown	_≠	_≠
Stage		
IA	Referent	Referent
IB	0.78 (0.68–0.90)*	1.25 (1.09–1.44)*
I NOS	1.01 (0.77–1.32)	0.80 (0.60–1.05)
II	0.67 (0.53–0.86)*	1.04 (0.81–1.33)
IIIA	0.72 (0.54–0.97)*	0.90 (0.66–1.22)
IIIB	0.86 (0.52–1.43)	0.77 (0.46–1.28)
IIIC	0.69 (0.59–0.81)*	1.56 (1.32–1.84)*
III NOS	1.18 (0.29–4.85)	0.49 (0.12–2.00)
Histology		
Endometrioid	Referent	Referent
Serous	0.96 (0.77–1.19)	1.24 (0.99–1.54)
Clear Cell	0.74 (0.46–1.19)	1.15 (0.71–1.86)
Carcinosarcoma	0.74 (0.55–0.99)*	0.89 (0.66–1.21)
Sarcoma	0.54 (0.30–0.95)*	0.22 (0.13–0.40)*
Other	1.01 (0.87–1.17)	1.13 (0.98–1.32)
Grade		
Well	Referent	Referent
Moderate	0.91 (0.81–1.02)	1.35 (1.20–1.53)*
Poorly	0.70 (0.60–0.82)*	1.44 (1.23–1.69)*
Unknown	0.91 (0.79–1.04)	1.18 (1.02–1.35)*

aRR: adjusted risk ratio.

*P-value < 0.05.

≠Unestimable due to multicollinearity between the unknown groups of facility type and facility region.

82.4% of all patients were reported from only one CoC-accredited hospital. Sensitivity analysis was performed limiting to those cases and showed similar results.

Table 4

Multivariable models for predictors of any type of radiation and external beam or combination among stage I patients who had sentinel lymph node mapping or lymphadenectomy.

	Any Radiation aRR	External Beam/Combination aRR
Age		
<50	Referent	Referent
50–59	1.32 (1.17–1.49)*	1.04 (0.80–1.34)
60–69	1.42 (1.25–1.60)*	1.08 (0.83–1.39)
70–79	1.46 (1.28–1.67)*	1.09 (0.82–1.44)
≥80	1.01 (0.86–1.18)	0.57 (0.40–0.82)*
Race		
White	Referent	Referent
Black	1.05 (0.97–1.15)	1.27 (1.08–1.51)*
Hispanic	1.02 (0.91–1.14)	1.14 (0.92–1.43)
Other	1.04 (0.93–1.17)	1.40 (1.11–1.77)*
Unknown	0.88 (0.68–1.15)	0.88 (0.49–1.58)
Year of diagnosis		
2013	Referent	Referent
2014	1.02 (0.98–1.07)	1.00 (0.90–1.10)
Insurance status		
Private	Referent	Referent
Medicare	1.05 (0.99–1.11)	1.02 (0.89–1.17)
Medicaid	0.99 (0.89–1.11)	1.17 (0.93–1.46)
Uninsured	0.97 (0.84–1.13)	1.15 (0.87–1.52)
Other government/unknown	0.94 (0.80–1.11)	1.02 (0.71–1.46)
Income		
<$38,000	Referent	Referent
$38,000–$47,999	1.01 (0.94–1.10)	0.91 (0.77–1.08)
$48,000–$62,999	0.99 (0.91–1.07)	0.87 (0.74–1.03)
$63,000+	1.03 (0.95–1.12)	0.85 (0.71–1.01)
Unknown	0.74 (0.39–1.39)	0.33 (0.05–2.40)
Location		
Metropolitan	Referent	Referent
Urban	1.00 (0.93–1.08)	0.88 (0.74–1.04)
Rural	1.18 (1.00–1.40)	1.01 (0.68–1.51)
Unknown	1.03 (0.88–1.21)	0.93 (0.63–1.37)
Comorbidity		
0	Referent	Referent
1	0.96 (0.90–1.01)	0.87 (0.76–1.00)*
≥2	0.88 (0.78–0.98)*	0.97 (0.76–1.24)

	Any Radiation	External Beam/Combination
	aRR	aRR
Facility type		
Academic/research	Referent	Referent
Community cancer	1.04 (0.88–1.22)	2.17 (1.67–2.81)*
Comprehensive community cancer	1.06 (0.96–1.18)	1.44 (1.21–1.72)*
Integrated network cancer	1.11 (0.94–1.32)	1.38 (1.04–1.83)*
Other/unknown	_≠	_≠
Facility region		
Northeast	Referent	Referent
Midwest	0.86 (0.75–0.97)*	1.25 (1.01–1.56)*
South	0.64 (0.56–0.72)*	0.89 (0.71–1.11)
West	0.68 (0.59–0.79)*	0.93 (0.72–1.18)
Unknown	_≠	_≠
Stage		
IA	Referent	Referent
IB	2.93 (2.80–3.07)*	5.98 (5.33–6.71)*
I NOS	0.98 (0.85–1.13)	1.79 (1.34–2.39)*
Histology		
Endometrioid	Referent	Referent
Serous	1.11 (1.02–1.20)*	1.01 (0.83–1.23)
Clear Cell	1.21 (1.01–1.44)*	1.46 (1.00–2.13)*
Carcinosarcoma	1.10 (0.99–1.22)	1.78 (1.48–2.14)*
Sarcoma	0.31 (0.23–0.40)*	0.71 (0.51–0.99)*
Other	1.10 (1.03–1.17)*	1.16 (1.00–1.35)*
Grade		
Well	Referent	Referent
Moderate	1.90 (1.77–2.03)*	2.08 (1.72–2.50)*
Poorly	3.01 (2.80–3.23)*	5.39 (4.52–6.44)*
Unknown	1.86 (1.72–2.01)*	2.57 (2.12–3.12)*
Scope of lymph node dissection		
Lymphadenectomy	Referent	Referent
Sentinel lymph node mapping	0.92 (0.82–1.05)	0.98 (0.70–1.36)

aRR: adjusted risk ratio.

*P-value < 0.05.

≠Unestimable due to multicollinearity between the unknown groups of facility type and facility region.