Sentinel lymph nodes in endometrial carcinoma
- Mapping, diagnostic accuracy and oncologic outcome

Doctor philosophiae thesis

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“Nothing in life is to be feared, it is only to be understood. Now is the time to understand more, so that we may fear less.”

Marie Skłodowska Curie
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Oslo, March 5th Ane Gerda Zahl Eriksson
2. LIST OF PAPERS


### 3. ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>AJCC</td>
<td>American joint committee on cancer</td>
</tr>
<tr>
<td>BMI</td>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>BSO</td>
<td>Bilateral salpingo-oophorectomy</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>CAP</td>
<td>College of American pathologists</td>
</tr>
<tr>
<td>DFI</td>
<td>Disease free interval</td>
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<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
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<tr>
<td>EBRT</td>
<td>External beam radiotherapy</td>
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<tr>
<td>EBL</td>
<td>Estimated blood loss</td>
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<tr>
<td>EC</td>
<td>Endometrial carcinoma</td>
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<tr>
<td>EIC</td>
<td>Endometrial intraepithelial carcinoma</td>
</tr>
<tr>
<td>FDA</td>
<td>Federal drug agency</td>
</tr>
<tr>
<td>FDG PET</td>
<td>Fluorodeoxyglucose positron emission tomography</td>
</tr>
<tr>
<td>CT</td>
<td>Computerized tomography</td>
</tr>
<tr>
<td>FIGO</td>
<td>International federation of gynecology and obstetrics</td>
</tr>
<tr>
<td>H&amp;E</td>
<td>Hematoxylin and eosin</td>
</tr>
<tr>
<td>HER-2/neu</td>
<td>Human epidermal growth factor receptor 2</td>
</tr>
<tr>
<td>ICG</td>
<td>Indocyanine green</td>
</tr>
<tr>
<td>IHC</td>
<td>Immunohistochemistry</td>
</tr>
<tr>
<td>IQR</td>
<td>Interquartile range</td>
</tr>
<tr>
<td>ITC</td>
<td>Isolated tumor cells</td>
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<tr>
<td>IMRT</td>
<td>Intensity modulated radiotherapy</td>
</tr>
<tr>
<td>IVRT</td>
<td>Intravaginal radiotherapy</td>
</tr>
<tr>
<td>KRAS2</td>
<td>Kirsten rat sarcoma viral oncogene homolog</td>
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<tr>
<td>LN</td>
<td>Lymph node</td>
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<tr>
<td>LND</td>
<td>Lymph node dissection</td>
</tr>
<tr>
<td>LVSI</td>
<td>Lymphovascular space invasion</td>
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<tr>
<td>LVM</td>
<td>Low-volume metastasis</td>
</tr>
<tr>
<td>MI</td>
<td>Myometrial invasion</td>
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<tr>
<td>MM</td>
<td>Micrometastasis</td>
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<tr>
<td>MSI</td>
<td>Microsatellite instability</td>
</tr>
<tr>
<td>MSK</td>
<td>Memorial Sloan Kettering Cancer Center</td>
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<tr>
<td>NIR</td>
<td>Near infrared</td>
</tr>
<tr>
<td>NCCN</td>
<td>National comprehensive cancer network</td>
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<tr>
<td>NPV</td>
<td>Negative predictive value</td>
</tr>
<tr>
<td>OS</td>
<td>Overall survival</td>
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<tr>
<td>PALN</td>
<td>Para-aortic lymph nodes</td>
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<tr>
<td>PCOS</td>
<td>Polycystic ovary syndrome</td>
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<tr>
<td>PFS</td>
<td>Progression free survival</td>
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<tr>
<td>PLN</td>
<td>Pelvic lymph nodes</td>
</tr>
<tr>
<td>PLND</td>
<td>Pelvic lymph node dissection</td>
</tr>
<tr>
<td>POLE</td>
<td>DNA polymerase ε catalytic subunit</td>
</tr>
<tr>
<td>PTEN</td>
<td>Phosphatate and tensin homolog</td>
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<tr>
<td>QOL</td>
<td>Quality of life</td>
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<tr>
<td>RFS</td>
<td>Recurrence free survival</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>RT</td>
<td>Radiotherapy</td>
</tr>
<tr>
<td>SLN</td>
<td>Sentinel lymph node</td>
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<tr>
<td>TCGA</td>
<td>The cancer genome atlas</td>
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<tr>
<td>TP53</td>
<td>Tumor protein 53</td>
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<tr>
<td>WPRT</td>
<td>Whole pelvic radiotherapy</td>
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4. THESIS AT A GLANCE

**Study I - Papers I and II**

*Study question:* Does type of dye and BMI affect SLN intraoperative mapping in women with uterine-confined endometrial carcinoma?

*Observational period:* 2011-2013.

*Study population:* All women with clinical stage I endometrial carcinoma having undergone SLN mapping with either ICG or blue dye on the robotic platform. N=472

*Exposure:* ICG or blue dye.

*Main outcome:* SLN mapping rates.

**Study II – Papers III and IV**

*Study question:* Does nodal assessment approach influence detection of stage III disease and oncologic outcomes?


*Study population:* Women with clinically stage I endometrial carcinoma, who had undergone nodal assessment either by a SLN or comprehensive lymphadenectomy nodal approach. N=1345

*Exposure:* Nodal assessment approach.

*Main outcomes:* Detection of metastatic lymph nodes and disease specific survival.

**Study III – Paper V**

*Study question:* Is recurrence free survival time affected by size of nodal metastasis in women with endometrial carcinoma?

*Observational period:* 2005-2013

*Study population:* Women with endometrial carcinoma treated surgically in which SLN mapping was performed. N=844.

*Exposure:* Low-volume metastasis.

*Main outcome:* Recurrence free survival.
5. SUMMARY

Endometrial carcinoma (EC) is the most common cancer of the female genital tract in industrialized countries. More than 60,000 women are diagnosed with EC annually in the United States, and 779 women were diagnosed in Norway in 2015. The incidence of EC is on the rise worldwide, with the highest disease burden reported in Western Europe and North America. This is due, in part, to an aging population and a rise in obesity. Approximately 80% of patients present with assumed uterine-confined, or early-stage, disease, with a favorable prognosis.

EC is a surgically staged disease. It is well accepted that surgical staging should include a hysterectomy and bilateral salpingo-oophorectomy (BSO), but the role and extent of lymph node dissection is highly debated. After surgical staging, metastatic lymph nodes are identified in approximately 20% of patients. However, lymphadenectomy is associated with significant short- and long-term morbidity such as increased operating time, neurovascular injury, lymphocyst formation, and lymphedema. Two randomized clinical trials have failed to demonstrate a survival benefit following lymphadenectomy in EC. Nevertheless, the presence of lymph node metastasis is the single most important prognostic factor in this group of patients. Lymph node status also guides the determination for or against adjuvant therapy. Thus, there is an urgent need to replace lymphadenectomy with an accurate staging procedure that would ascertain lymph node status without inflicting the significant morbidities associated with lymphadenectomy.

Sentinel Lymph Node (SLN) mapping has emerged as a reasonable approach to lymphadenectomy in the surgical staging of patients with uterine-confined EC. Several retrospective studies have demonstrated a high sensitivity, specificity and negative predictive value (NPV) when applying an SLN algorithm along with a pathologic ultrastaging protocol (the latter involves additional sectioning and staining of the SLN tissue with hematoxylin and eosin (H&E) and immunohistochemistry (IHC)). These findings were recently confirmed by a large, multi-center, randomized, controlled study: the Fluorescence Imaging for Robotic EC Sentinel node mapping (FIRES) trial. Although the SLN technique and algorithm have evolved over the past few decades, there remain unanswered questions regarding the role of SLN biopsy in the management of EC. Optimal choice of dye, significance of low-volume metastasis, and long-term oncologic outcome are still undetermined.

The main aim of this thesis was to investigate the introduction of indocyanine green (ICG) as a novel dye in the detection of SLNs (Papers I and II). Another aim was to evaluate detection of metastatic lymph nodes, and oncologic outcome, when applying an SLN approach compared to a selective lymphadenectomy (LND) approach (Papers III and IV) in women with EC. We also sought to investigate the treatment patterns and oncologic outcome of patients with low-volume metastasis (Paper V). The investigations of ICG dye and low-volume metastasis were based on retrospective data from the Memorial Sloan Kettering Cancer Center (MSKCC) institutional SLN database. The retrospective comparisons of the MSK SLN algorithm with the Mayo Clinic selective LND approach were based on data from the MSK SLN database in addition to a historic LND cohort from the Mayo Clinic.
The novel findings of this thesis are, in summary:

- ICG is superior to blue dye in the overall and bilateral detection of SLNs in patients with assumed uterine-confined EC. It is also superior to the previously reported mapping rates of blue dye and radioactive tracers combined (Paper I).

- Increase in BMI correlates with decrease in the success of overall and bilateral SLN mapping. However, even in obese patients, ICG remains superior to blue dye with respect to mapping (Paper II).

- When adhering to an SLN algorithm and pathologic processing protocol with ultrasection, the SLN approach detects stage IIIIC disease in as many patients as does the selective LND approach. Furthermore, in the setting of endometroid adenocarcinoma with limited myometrial invasion, more patients will have assessment of lymph nodes and fewer lymph nodes will be removed per patient. The 2-year disease-free interval is similar with both approaches, and recurrences are distributed in similar anatomical locations in both groups. Importantly, we found a 3-year isolated node-free recurrence of 99.6% in both cohorts (Paper III).

- For patients with endometrioid adenocarcinoma and deep myometrial invasion, we noted that the detection rate of stage IIIIC disease was similar between the SLN and LND approaches; however, a higher rate of stage IIIIC1 disease was detected in the SLN cohort, and a higher rate of stage IIIIC2 disease was detected in the LND cohort. (Paper IV).

- For patients with serous and clear cell EC, pelvic lymph node sampling was performed in a greater percentage of patients using the SLN approach, and fewer nodes were removed. We observed a similar proportion of patients in each group with positive paraaortic nodes; however, a greater median number of positive paraaortic nodes were identified in the LND group. Overall, stage IIIIC disease was diagnosed at a similar rate with either approach. (Paper IV).

- Patients with low-volume nodal metastasis who received adjuvant therapy had a recurrence-free interval similar to that of patients who were node-negative. This is significantly superior to the recurrence-free interval of node-positive patients with macrometastasis who received adjuvant therapy (Paper V).

To fully benefit from the SLN approach, thus avoiding additional nodal extraction, bilateral mapping is key. As noted above, we found that ICG was superior to blue dye in bilateral and overall mapping. Importantly, ICG was superior to blue dye even in obese patients. Obesity is a major risk factor for uterine cancer. In our study, 53% of patients had a BMI >30. The high prevalence of obesity in the EC patient population makes it imperative to find reliable techniques for accurate surgical staging of obese and morbidly obese women. Based on our findings, we recommend the use of ICG dye in SLN mapping, across all weight classes, for women with EC.
In our retrospective study, we conclude that the detection of stage IIIC disease is not compromised by applying an SLN algorithm, compared to a selective LND approach. This held true for all risk groups. Prospective trials are needed to further evaluate the oncologic outcomes and potential benefits of implementing the SLN approach in women with EC—particularly in patients at intermediate and high risk of recurrence.

New challenges have emerged with the implementation of the SLN technique in EC, such as how to manage patients with low-volume metastasis detected on ultrastaging. Based on the current study, we cannot yet determine whether improved progression-free survival (PFS) for patients with low-volume metastasis is due to adjuvant therapy or to the fact that this group may have a more benign course inherently. Conducting a randomized prospective trial on this topic is not thought to be feasible, due to the low prevalence of low-volume metastasis. Pooling of data from multiple institutions may assist us in answering this question.
6. INTRODUCTION

6.1 Endometrial Carcinoma

6.1.1. Epidemiology

Endometrial carcinoma is the sixth most common cancer in women worldwide. The highest incidence of EC is in North America and Europe; the lowest incidence is in Africa and Asia (1).


In 2017 the estimated number of new cases of EC in the United States was 61,380, or an incidence of 25.7 per 100,000 women. In the US the cumulative risk of EC is estimated to be 2.8%. In 2017, the estimated number of deaths from EC were 10,920 (2). The overall incidence of type I ECs (endometrioid histology) is rising in all developed countries. In an analysis of 6,867 women with EC registered in a UK population-based cancer registry between 1994 and 2006, the age-standardized incidence rates (ASR) increased significantly from 12.0 per 100,000 in 1994 to 16.3 per 100,000 in 2006. The ASR of type II EC (serous or clear-cell histology) was nearly unchanged during the same period (3). Figure 2 shows differential trends in incidence across type I and type II EC (ASR and 95% confidence intervals (CIs) are shown). Based on observed trends, this increase is expected to continue, in part due to the increased life expectancy in industrialized regions, and also as a consequence of the obesity epidemic. In the US, if current trends continue, there will be a doubling in the number of women diagnosed with EC by the year 2030: to 122,000 cases per year (4).
Approximately 80% of women with EC present with uterine-confined disease. This is associated with a favorable prognosis, with 85-91% of stage I patients alive at 5 years (5). Women with advanced stage or recurrent disease have a poor prognosis, and the treatment options are limited. In the US, the median age at diagnosis is 62 years. Five-year survival is 81.3% (2007-2013). The 5-year survival by stage was 95.3% for localized disease, 68.5% for regional disease, 16.2% for distant disease, and 50.3% in unstaged patients (Figure 3) (2).
6.1.2. Pathophysiology and risk factors

**Histopathology**
EC is the most common malignancy of the uterine corpus, representing approximately 95% of cases (6). EC is defined as an epithelial tumor, usually with glandular differentiation, arising in the lining of the uterine cavity (endometrium) which has the potential to invade the myometrium and spread to distant sites. For the purpose of this thesis we will define EC as cancer of the lining of the uterus. Endometrioid histology is the most common type of EC (type I), accounting for approximately 80% of cases (6). These tumors are stimulated by estrogen, are typically preceded by endometrial hyperplasia, present at an early stage, and have a good prognosis. Type II EC often develops in non-obese, elderly women, and arises from an atrophic endometrium. These cancers are serous or clear-cell carcinomas (7, 8). Endometrial intraepithelial carcinoma (EIC) is reportedly a precursor lesion for serous EC, and is frequently found in association with extrauterine disease (9-11). This dualistic approach to EC, described by Bokhman in 1983, results in a very broad classification, and lacks the ability to categorize tumors for accurate, targeted adjuvant therapy.

**Molecular pathogenesis of type I and type II EC**
Distinct molecular changes are associated with type I and type II EC: Carcinomas of type I are associated with mutations in the KRAS2 oncogene, the PTEN tumor suppressor gene, and defects in DNA mismatch repair; type II carcinomas are associated with mutations in the tumor suppressor genes TP53 and ERBB-2 (HER-2/neu) expression (12-16). Microsatellite instability (MSI) is present in nearly 20% of sporadic type I EC cases (17, 18).

A classification system incorporating genomic and histopathologic features defining biological and clinically relevant subsets of EC could potentially be useful in tailoring adjuvant therapy (19). In-depth molecular characterization of EC has been performed by several groups, identifying mutation profiles that aid in discriminating EC subtypes (20-23). In 2013 The Cancer Genome Atlas (TCGA) research network published the most comprehensive molecular study of EC to date. This included a combination of whole-genome sequencing, whole-exome sequencing (sequencing all the protein-coding genes in a genome), MSI assays, copy number analyses, and proteomics (24). In the TCGA study, 232 patients with EC were classified into four groups based on molecular information: DNA polymerase ε catalytic subunit (POLE) ultramutated; MSI hypermutated; copy-number low; and copy-number high. The four groups correlated with PFS (24) Figure 4 (25).

The extensive genomic and molecular testing used in the TCGA study is not feasible in daily clinical practice. Researchers in Vancouver and Leiden have developed surrogate assays replicating the TCGA classification (26, 27), Figure 4 (25). In the future, these four major molecular subgroups, alone or with additional clinicopathologic and molecular criteria, may provide improved prognostication and guide targeted adjuvant therapy for women with EC.
Figure 4. TCGA, Leiden and Vancouver group characterizations.

"(A) The Cancer Genome Atlas (TCGA) performed in-depth characterization (genomic, transcriptomic, and proteomic) of ECs. Four subgroups were identified from 232 ECs and serous cancers: 1) DNA polymerase epsilon catalytic subunit (POLE) (ultramutated) through exome sequencing for POLE exonuclease domain (EDM) mutations and high C>A transversion frequencies; 2) microsatellite instability (MSI) (hypermutated) identified with an MSI assay; 3) copy-number low (endometrioid); 4) copy-number high (serous-like) subgroups. Kaplan-Meier survival curves and log-rank statistics for progression-free survival are shown. (B) Stelloo et al (“Leiden classification”) used more pragmatic tools, identifying: 1) a p53-mutant subgroup (immunohistochemical [IHC] or mutational analysis); 2) an MSI subgroup (MSI assay); 3) a POLE proofreading mutant subgroup; 4) a no specific molecular profile (NSMP) subgroup in 116 patients with high-risk EC. Recurrence-free survival (RFS) analysis is shown. (C) The Vancouver group’s classifier (ProMise) applied pragmatic tests to 143 ECs. The first assessment was IHC for the presence of mismatch-repair (MMR) deficiency proteins. Tumors with loss of expression (MMR IHC abnormal [abnl]) were designated MMR-deficient (MMR-D); those in which all proteins were present were termed MMR intact. Next focused sequencing (Fluidigm, digital PCR) for POLE EDM’s. Finally, cases were assessed with IHC for p53. IHC scores of 1 were consistent with p53 wild type (‘p53 wt’), and IHC scores of 0 or 2 considered abnormal (‘p53 abn’), indicating nonsense/loss of function mutations and missense/gain of function mutations respectively. Models, case allocation, and associated Kaplan-Meir survival curves are shown” (25).
**Risk factors**

Epidemiologic studies have found that the major risk factors for endometrioid EC are postmenopausal status, excessive fat consumption, BMI $\geq 25$ kg/m², and exposure to endogenous and exogenous estrogens. A large epidemiologic study has found this to be true for non-endometrioid EC as well (28). The global obesity epidemic is largely responsible for the increase in EC cases. Other factors are an aging population, a decline in the use of progesterone and estrogen hormone-replacement therapy, delay in childbearing, and an increased prevalence of diabetes (29-32).

In premenopausal women obesity causes insulin resistance, ovarian androgen excess, anovulation, and chronic progesterone deficiency. In postmenopausal women obesity causes higher circulating concentrations of bioavailable estrogens from extraglandular conversion of androgens (e.g. in adipose tissue). This hormonal alteration stimulates endometrial cell proliferation, inhibits apoptosis, and promotes angiogenesis (33). A BMI $>25$ kg/m² doubles a woman’s risk of EC, and a BMI $>30$ kg/m² triples the risk (34). Physical inactivity, high energy intake, blood pressure $>140/90$ mm Hg, and high serum glucose concentrations are BMI-independent risk factors (35-39). Increases in physical activity have been associated with decreased EC risk, possibly by lowering the levels of sex steroids, insulin resistance, and chronic inflammation (40-42). By maintaining a normal weight and being physically active, women may lower their bioavailable estrogens (43). A significant proportion of ECs could be eliminated through these inexpensive preventative measures.

Polycystic ovary syndrome (PCOS) is also associated with an increased risk of EC. This is due to lack of progesterone secretion in the luteal phase secondary to chronic anovulation, combined with relatively constant estrogenic stimulation of the endometrium. This combination may cause endometrial hyperplasia and EC (44). EC risk is also elevated in women with breast cancer, possibly in association with shared reproductive risk factors such as nulliparity or late age at menopause (45). The use of Tamoxifen in women with breast cancer triples the risk of EC, due to the opposite cellular growth effects of Tamoxifen on endometrial cells versus breast cells (46).

The increased placental production of progestagens during pregnancy is thought to be protective for EC. Nulliparity, however, is a risk factor for EC, as is infertility and late-onset menopause (47-49). Progesterone- and estrogen-containing oral contraceptive use lowers the risk of EC (50, 51). Smoking affects estrogen production and metabolism, and is thought to reduce the risk of EC (52, 53).

With the increased understanding of the molecular features of EC, novel concepts are emerging as to how metabolic illnesses influence cancer development and risk. These concepts warrant further investigation. Improved survival has been associated with loss of the tumor suppressor gene PTEN expression in obese women versus non-obese women with EC (54). Links have been established between PI3K signaling (which is frequently dysregulated in EC) and obesity, with its associated inflammation (55). Increased KRAS (a proto-oncogene) expression and decreased Stathmin 1 (STMN1) expression have been found in women with complex atypical hyperplasia and BMI $>30$ kg/m², compared to non-obese
women (56). Furthermore, an association between age, obesity, and MSI has been demonstrated, in which obesity is correlated with MLH1 promoter methylation in older patients with EC (57).

### 6.1.3. Diagnosis

Abnormal uterine bleeding is the cardinal symptom of EC and the presenting symptom in 90% of patients. Any vaginal bleeding in a postmenopausal woman warrants an evaluation for EC, as does abnormal uterine bleeding associated with risk factors for EC or hyperplasia such as polycystic ovaries, obesity, age >40 years, estrogen-only hormone-replacement therapy, and Tamoxifen use. The probability of EC in women presenting with postmenopausal bleeding (PMB) is 5-10% (58). In 20-40% of patients, PMB is caused by endometrial hyperplasia, endometrial polyps, or other miscellaneous pathology of the endometrium. In the remaining 50-70% no pathology is discovered, and the PMB is commonly attributed to endometrial or vaginal atrophy (59). Endometrial hyperplasia can be simple or complex, with or without atypia. Hyperplasia without atypia, whether simple or complex, has a low likelihood (1% and 3%, respectively) of progressing to carcinoma. However, atypical endometrial hyperplasia is believed to be a direct precursor to endometrioid EC (7, 60). Various investigations have demonstrated that endometrial biopsy specimens interpreted as atypical endometrial hyperplasia on preoperative examination frequently correspond to an invasive EC at the time of hysterectomy (60-62).

In postmenopausal women, transvaginal ultrasound (TVU) evaluation of endometrial thickness may be used as an initial investigation to evaluate for EC. Endometrial sampling is the gold standard. The accuracy of pipelle endometrial biopsy, which can be performed in any out- or in-patient setting, is comparable to that of dilatation and curettage (D&C) in women with PMB, up to an endometrial thickness of 6 mm (63). In patients with a thicker endometrial stripe and normal pipelle biopsy, hysteroscopy or saline infusion sonography (SIS) are reasonable options for further assessment. Ultimately D&C may be required. Combining endometrial biopsy and TVU increases the sensitivity in detecting EC to 100% (64). A study by Karlsson and colleagues reported on a multicenter, prospective study of 1168 women with PMB, in which all women underwent TVU followed by uterine curettage. A threshold of 5 mm or less was used, yielding a sensitivity of 94%, a specificity of 78%, and a positive predictive value (PPV) of 69%, with an NPV of 96%, and an 84% accuracy (59). The high NPV lends itself well to excluding a diagnosis of EC when endometrial biopsy is not feasible. However, these results are applicable only to women with PMB. TVU as a screening tool for EC in asymptomatic women is not sufficiently sensitive as a diagnostic tool, and is not recommended (65).

### 6.1.4. Staging

The first International Federation of Gynecology and Obstetrics (FIGO) staging system of EC was based on two criteria: 1) Stage I disease was clinically confined to the uterus; 2) Stage II disease had spread beyond the uterus (66). The staging system has since undergone multiple
revisions, most importantly the expansion to a four-stage system in 1962, and the change from clinical to surgical staging in 1988. Prior to 1988, the standard of treatment for EC was total hysterectomy and BSO with pre- or postoperative radiotherapy. In 1987 the Gynecologic Oncology Group (GOG) published a study (GOG 33) to determine the frequency of occult extrauterine disease in a cohort of surgically staged women with EC that was initially thought to be clinically confined to the uterus (67). The study demonstrated that 22% of women had extrauterine disease, with an 11% rate of nodal metastasis. Subsequently the FIGO staging system was revised to include systematic pelvic and para-aortic lymphadenectomy (68).

According to the 26th annual FIGO report, which pooled data on 9386 patients from 34 countries, treated between 1999 and 2001, surgical staging continued to show prognostication superior to that of clinical staging (69). It was noted that sub-groups within stage I had very similar prognosis, and a suggestion was made to combine these groups. This is reflected in the revised FIGO 2009 staging system (70).

**Carcinoma of the Endometrium, FIGO 2009**

<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>Tumor confined to the uterus, &lt;50% myometrial invasion</td>
</tr>
<tr>
<td>IB</td>
<td>Tumor confined to the uterus, ≥50% myometrial invasion</td>
</tr>
<tr>
<td>II</td>
<td>Cervical stromal invasion, but not beyond uterus</td>
</tr>
<tr>
<td>IIIA</td>
<td>Tumor invades serosa or adnexa</td>
</tr>
<tr>
<td>IIIB</td>
<td>Vaginal and/or parametrial involvement</td>
</tr>
<tr>
<td>IIIC1</td>
<td>Pelvic node involvement</td>
</tr>
<tr>
<td>IIIC2</td>
<td>Para-aortic involvement</td>
</tr>
<tr>
<td>IVA</td>
<td>Tumor invasion bladder and/or bowel mucosa</td>
</tr>
<tr>
<td>IVB</td>
<td>Distant metastases including abdominal metastases and/or inguinal lymph nodes</td>
</tr>
</tbody>
</table>

**Figure 5.** FIGO 2009 endometrial carcinoma stages. 
6.1.5. Predicting lymph node status and the significance of lymphadenectomy

Although nodal status forms an essential part of the FIGO staging system, there is ongoing debate about the clinical value of lymphadenectomy. GOG 33 demonstrated an overall risk of metastasis in the pelvic and para-aortic lymph nodes of 9% and 6%, respectively; however, in well-differentiated tumors the risk was 3% and 2%, respectively; and tumors confined to the endometrium had an even lower risk of metastasis, at 1% (67). Thus, the majority of patients are node-negative, but would nevertheless be subjected to the potential morbidities associated with lymphadenectomy. Additionally, there are no clear or widely accepted guidelines for selecting women who might truly benefit from comprehensive surgical staging. As a result, there are significant variations in staging practices between continents, countries, cities, and institutions (71, 72).

Predicting lymph node status

Intraoperative prediction: The landmark trial by Creasman established EC grade in combination with myometrial invasion as risk factors for nodal metastasis (67). Mariani and colleagues at the Mayo Clinic have suggested guidelines for management of women with EC based on uterine risk factors for lymph node dissemination. They demonstrated that primary tumor diameter, measured at time of surgery, together with histologic subtype, grade, and depth of myometrial invasion, facilitated the selection of “low-risk” women whose treatment could be safely managed with hysterectomy and BSO alone, avoiding lymphadenectomy (73). Among women who presented with endometrioid histologic subtype, histologic grade 1 or 2, myometrial invasion of ≤50%, tumor diameter ≤2 cm, and no evidence of macroscopic tumor beyond the uterine corpus, neither positive lymph nodes nor lymph node recurrences were identified. These women represented 27% of those who underwent surgery for EC at the Mayo Clinic during the study period (2004-2006) (74). In comparison, patients with high-grade histologies (endometrioid G3, clear cell, serous and carcinosarcoma) had a 20-40% risk of lymph node involvement (74, 75). The Mayo Clinic approach relies on dedicated pathologists with expertise in gynecologic oncology to assess frozen tumor sections based on the aforementioned criteria. Outside of tertiary care centers, however, the reliability of findings on frozen section are variable (76, 77), and may lead to under-staging in some high-risk cases.

Preoperative prediction: Many surgeons rely on preoperative prediction of nodal metastasis, by means of imaging studies and preoperative histology. It has been uniformly reported that preoperative tumor grade based on endometrial sampling does not accurately correlate with final pathologic grade. The overall Kappa statistics for level of agreement between pathologists assigning FIGO grade to EC range from 0.41 to 0.68, indicating moderate levels of interobserver agreement (78). Major disagreement or lack of consensus of histologic type assignment has been observed in one-third or more of high-grade ECs, and this holds true with the addition of IHC (79, 80). On final pathologic assessment, a higher FIGO grade is diagnosed in approximately 25% of patients who initially present with preoperative FIGO grade 1 disease (81, 82). A recent study from France demonstrated that a preoperative assessment by MRI and endometrial biopsy overestimated or underestimated the risk of recurrence in nearly 40% of cases, with errors in lesion type, grade or stage (83). Erroneous preoperative risk assessment leads to unsatisfactory initial surgical management. With
advances in imaging technology, several studies have proposed incorporating preoperative FDG-PET/CT to identify nodal metastasis. In high-risk clinical stage I EC, FDG PET/CT has demonstrated moderate sensitivity, high specificity and accuracy in assessing lymph node status (84). In women with EC who are found to be node-negative on preoperative MRI, FDG-PET/CT has low value in predicting lymph node metastasis (85).

Significance of lymphadenectomy
The knowledge obtained from comprehensive surgical staging is prognostic (67, 86), and guides the appropriate determination of adjuvant therapy (87, 88). It is also useful for stratification in randomized clinical trials, and for assessing treatments among patient groups. Although two prospective, randomized clinical trials have failed to show a survival advantage associated with lymphadenectomy (89, 90), there is ongoing debate regarding the therapeutic efficacy of comprehensive lymphadenectomy in patients with EC.

Various retrospective studies have shown a potential therapeutic role of pelvic and para-aortic lymphadenectomy in EC (91-94). The number of lymph nodes retrieved is a significant predictor of outcome in surgically staged patients. In retrospective studies based on patients registered with the National Cancer Institute (NCI) and the Surveillance, Epidemiology, and End Results (SEER) Program (95, 96), a more extensive node dissection remains a significant prognostic factor for improved survival in FIGO stage I patients who did not have nodal metastasis, but whose tumors showed “intermediate-/high-risk” uterine features (Stage IB, Grade 3; Stage IC, all grades). These studies may be affected by stage migration: the greater the number of LNs removed, the more likely it is to discover stage IIIC disease.

The Survival Effect of Para-Aortic Lymphadenectomy in endometrial cancer (SEPAL) study was a retrospective analysis of intermediate- and high-risk EC patients who had a complete, systematic pelvic lymph node dissection vs. combined pelvic and para-aortic lymph node dissection (94). SEPAL reported that overall survival was significantly improved in patients undergoing pelvic and para-aortic lymph node dissection. However, the pelvic and para-aortic dissection group had a median of 59 pelvic lymph nodes and 23 para-aortic lymph nodes removed. This is considerably higher than the number of nodes excised in most studies. It is also unclear whether the difference in overall survival reported in the SEPAL study was due to adjuvant therapy, rather than the actual removal of para-aortic lymph nodes. Forty-seven percent of patients in the pelvic and para-aortic lymphadenectomy group received adjuvant chemotherapy, compared to 27% in the pelvic lymphadenectomy group—a difference that is statistically significant.

In contrast to the aforementioned studies, a CART (classification and regression tree) analysis by Barlin and colleagues, evaluating the influence of various clinicopathologic factors on overall survival in EC, did not find that the number of lymph nodes removed, or the assessment of para-aortic lymph nodes, was a predictor of overall survival (97). These retrospective studies are all limited by selection bias, and one must use caution in drawing firm conclusions based on these results—particularly in light of the prospective randomized trials summarized below:
A Study in the Treatment of Endometrial Cancer (ASTEC) including more than 1400 patients randomized to pelvic lymph node dissection or no nodal assessment, with a second randomization to whole pelvic radiation therapy or observation for patients with intermediate- or high-risk features, found no difference in overall or progression-free survival (98). ASTEC has been heavily criticized as an intention-to-treat study, in which almost half of the patients in the pelvic lymph node dissection arm had no nodes or ≤9 nodes excised, suspicious nodes were sampled in 5% of the no-lymphadenectomy group, and para-aortic node dissection was not required. Furthermore, many patients were secondarily randomized to radiation without their surgical pathology being taken into account, and chemotherapy was not administered to patients with positive nodes.

The randomized trial by Panici et al. required a minimum of 20 excised lymph nodes and had similar adjuvant therapy in both groups but showed no difference in overall survival (90). Approximately 3% of patients in the no-lymphadenectomy arm had positive nodes, as the surgeon was permitted to remove suspicious lymph nodes. No para-aortic lymph node dissection was performed. Both studies included a large proportion of low-risk women, decreasing the probability of finding a therapeutic benefit to lymphadenectomy.

Regardless of their flaws and the subsequent criticism, the results of these two trials do cast doubt on the role of routine lymphadenectomy in EC. SLN mapping may provide a middle ground that spares most patients from unnecessarily undergoing complete bilateral pelvic lymph node dissection, thereby reducing risk of unwanted side effects while providing a reasonably low false negative rate.
6.1.6. Therapy and outcomes

Surgical treatment of EC is the mainstay initial management, and is curative in most cases of early-stage disease. This procedure was historically performed by laparotomy. However, minimally invasive techniques such as laparoscopy or robot-assisted surgery have become the new surgical standard. These less invasive surgical methods have non-inferior oncologic outcomes and favorable perioperative results, including fewer complications, shorter hospital stay, decreased postoperative use of opioids, improved quality of life (QOL), and cost-effectiveness (99-105). External pelvic radiotherapy and/or vaginal brachytherapy are used postoperatively for patients whose tumors pose a high risk of local recurrence (33, 106). During the past two decades, systemic chemotherapy has been incorporated into the treatment of stages III and IV EC (107-110), and it is also an important element in the management of high-risk early-stage patients. There is, however, a lack of consensus regarding adjuvant therapy for EC.

Adjuvant radiotherapy

Several studies have evaluated the role of postoperative adjuvant radiotherapy in women with uterine-confined EC. The PORTEC I and GOG 99 trials have compared pelvic radiation versus observation (111, 112). Although the populations varied in some characteristics, both studies showed similar 5-year survival rates (81% for the radiotherapy group (RT) vs. 85% for the observation group) demonstrating a decrease in local recurrences in the RT groups, but no difference in overall survival (92% for RT vs. 86% for the observation group). Subsequently, the PORTEC-II trial randomized women at high-to-intermediate risk of recurrence to pelvic RT versus vaginal brachytherapy after hysterectomy and BSO (113). The study demonstrated no difference in overall survival, and a similar rate of vaginal recurrence (1.9%) in both arms. QOL was significantly better in the brachytherapy group (113). These findings support the omission of pelvic RT for this group of EC patients. Results from the PORTEC series and GOG 99 have provided the following criteria for classification of high-/intermediate-risk of recurrence:

• PORTEC: Requires two of three factors: age >60, depth of myometrial invasion >50%, or grade 3 histology (113, 114).
• GOG 99: Age in conjunction with uterine factors: Age ≥70 + one risk factor, age ≥50 + two risk factors, age <50 + three risk factors. Risk factors: tumor grade 2 or 3, depth of myoinvasion >50%, presence of LVSI (112).

Adjuvant chemotherapy and chemoradiation

In the PORTEC I study, patients at high risk of recurrence (stage IB, grade 3) had a 14% risk of local or regional recurrence and a 31% risk of distant recurrence after initial surgery (hysterectomy and BSO) and adjuvant pelvic radiation (115). These data were suggestive of a need to explore novel strategies for adjuvant therapy to improve survival in this patient group. Studies comparing various chemotherapy regimens, chemotherapy versus radiotherapy, and chemoradiotherapy versus radiotherapy, are summarized in Table 1. The most active chemotherapeutic agents were anthracyclines, platinum compounds and taxanes, with modest response rates of 20-30% (116). As use of the SLN technique grows, chemotherapy with or without radiotherapy should be considered for patients with lymph node metastasis, due to the
possibility of residual microscopic nodal disease. Despite efforts to determine the optimal adjuvant treatment regimen for women with EC, there is lack of consensus and regional variation exists.

Table 1. Adjuvant radiochemotherapy for endometrial carcinoma

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient selection</th>
<th>Protocol/ Active agents</th>
<th>Year of publication</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GOG 34 Morrow</strong> (117)</td>
<td>High-risk (+LNs, +adnexa or ≥50% MI) stage I and occult stage II after staging</td>
<td>Pelvic RT +/- Doxorubicin q 3wks</td>
<td>1990</td>
<td>No difference in recurrence or OS. Due to protocol violations, small sample size, high loss to follow-up, this study was unable to draw firm conclusion.</td>
</tr>
<tr>
<td><strong>GOG 122 Randall</strong> (110)</td>
<td>≤2cm residual stage III/V WAP, N=202 AP, N=194</td>
<td>Whole abdominal RT vs AP</td>
<td>2006</td>
<td>5-year PFS: 38% vs 50% HR progression 0.71 (95% CI:0.55-0.91) 5-year OS: 42% vs 55% HR death 0.68 (95% CI:0.52-0.89) Recurrences: 54% vs 50% AP improved PFS and OS. AP more heme, cardiac, neuro toxic. WAR more hepato-toxic. Gross residual disease did worse than microscopic residual</td>
</tr>
<tr>
<td><strong>GOG 184 Holmsley</strong> (118)</td>
<td>≤2cm residual stage III/V initially, then only stage III LND not required AP, N=270 TAP, N=282</td>
<td>Tumor-volume directed RT then randomized to AP vs TAP, 6 cycles. Para-aortic RT if +nodes or &lt;2 LNs retrieved. IVRT boost optional</td>
<td>2009</td>
<td>RFS: 62% vs 64% HR recurrence or death 0.90 (95%CI: 0.69 - 1.17) TAP: 50% reduction of risk of recurrence in patients with residual disease. (95%CI: 0.26 - 0.92) TAP more toxic</td>
</tr>
</tbody>
</table>
### B. Measurable stage III/IV or recurrent disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient selection</th>
<th>Protocol/ Active agents</th>
<th>Year of publication</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>GOG 107 Thigpen (109)</td>
<td>≤2cm residual stage III/IV or recurrent disease</td>
<td>Doxorubicin vs Doxorubicin/Cisplatin q 3 weeks</td>
<td>2004</td>
<td>CR: 8% vs 19%. PR: 17% vs 23%. ORR: 25% vs 42%.* PFS: 3.8 vs 5.7 Adj HR recurrence 0.74 (95%CI: 0.56, 0.94) OS: 9.0 vs 9.2 Adj HR death 0.93 (95%CI: 0.73, 1.19) Doxo/Cis with better RR and PFS, but not OS, and with increased hem toxicities, nausea, renal toxicities.</td>
</tr>
<tr>
<td>GOG 163 Fleming (119)</td>
<td>≤2cm residual stage III/IV or recurrent disease</td>
<td>Doxorubicin/Cisplatin vs Doxorubicin/Paclitaxel/GCSF</td>
<td>2004</td>
<td>CR: 15% vs 17%. PR: 25% vs 26%. ORR: 40% vs 43%. PFS: 7.2 vs 6. OS: 12.6 vs 13.6 Doxo/taxol is not better.</td>
</tr>
<tr>
<td>GOG 177 Fleming (108)</td>
<td>≤2cm residual stage III/IV or recurrent disease</td>
<td>Doxorubicin/Cisplatin vs Doxorubicin/Paclitaxel/Cisplatin</td>
<td>2004</td>
<td>CR: 7% vs 22%. PR: 27% vs 35%. ORR: 34% vs 57%.* PFS: 5.5 vs 8.3* Adj HR recurrence 0.60 (95%CI: 0.46, 0.78) OS: 12.3 vs 15.3* Adj HR death 0.75 (95%CI: 0.57, 0.99) TAP demonstrated superior RR, PFS and OS (3 months) with 5 treatment-related deaths and more neurotoxicity.</td>
</tr>
<tr>
<td>GOG 209 (120)</td>
<td>≤2cm residual stage III/IV or recurrent disease If LVEF &lt;50% after randomization to TAP, then cross to Carbo/Taxol N=1381</td>
<td>TAP/GCSF vs Carboplatin/Paclitaxel q 3 wks 7 cycles</td>
<td>2004</td>
<td>Interim analysis PFS: 14 vs 14 HR 1.03 OS: 38 vs 32 HR 1.01 No difference between arms in outcomes. Less toxicities w Carbo/Taxol</td>
</tr>
<tr>
<td>EORTC 55872 Van Wijk (107)</td>
<td>stage III/IV or recurrent disease N=177</td>
<td>Doxorubicin vs Doxorubicin+Cisplatin q 4 wks</td>
<td>2003</td>
<td>RR: 17% vs 43% * Median OS 7 vs 9 Doxo/Cis had higher, but acceptable toxicity</td>
</tr>
</tbody>
</table>
### C. No residual disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient selection</th>
<th>Protocol/ Active agents</th>
<th>Year of publication</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSGO-EC-9501/EORTC-55991 and MaNGO ILIADe-III Hogberg (121)</td>
<td>Stage I-III with no residual tumor. High-risk features. Serous/clear cell included. LND optional.</td>
<td>Pelvic RT +/- chemotherapy (various regimens allowed)</td>
<td>2010</td>
<td>OS HR 0.69 (95%CI 0.46-1.03) CSS * HR 0.55 (95%CI: 0.35-0.88) Adjuvant RT + chemo improved PFS</td>
</tr>
<tr>
<td>PORTEC III De Boer (122)</td>
<td>Stage I high-intermediate risk per PORTEC criteria. Stage II or III, stage I-III serous/clear cell.</td>
<td>Pelvic RT w concomitant Cisplatin + Carboplatin/Paclitaxel 4 cycles vs pelvic RT alone</td>
<td>2018</td>
<td>5-year FFS: 75.5% vs 68.9% HR 0.77 (95%CI: 0.58-1.03) 5-year OS: 81.8% vs 76.7% HR 0.79 (95%CI: 0.57-1.12) Stage III: FFS improved by 11% at 5 years*</td>
</tr>
<tr>
<td>GOG 249 Randall</td>
<td>Stage I, endometrioid histology, high-intermediate-risk by GOG 99 criteria, stage II, or stage I-II serous or clear cell. LND optional.</td>
<td>Vaginal brachytherapy + Carboplatin/Paclitaxel q 3 wks 3 cycles vs pelvic RT</td>
<td>ASTRO 2017</td>
<td>3-year RFS 82% vs 82% 3-year OS 88% vs 91% Nodal recurrence 25% vs 12%* More tox in VCB/C arm.</td>
</tr>
<tr>
<td>GOG 258 Matei</td>
<td>Stage III/IVA, optimally debulked. Chemo-RT N=407 Chemo N= 406</td>
<td>RT/Cisplatin + Carbo/Taxol 4 cycles versus Carboplatin/Paclitaxel 6 cycles</td>
<td>ASCO 2017 ASCO abstract #5505</td>
<td>RFS HR 0.9 (95%CI: 0.74, 1.1) 5-year vag recur: 3% vs 7% HR 0.36 (95%CI: 0.16, 0.82)* 5-year nodal recur: 10% vs 19% HR 0.43 (95%CI: 0.28, 0.66)* 5-year distant recur: 27% vs 21% HR 1.36 (95%CI: 1.00, 1.86)* 5-year OS not mature for final analysis (70% vs 73%) Similar toxicities for both arms</td>
</tr>
</tbody>
</table>
### D. Radiotherapy versus Chemotherapy, no residual disease

<table>
<thead>
<tr>
<th>Trial</th>
<th>Patient selection</th>
<th>Protocol/ Active agents</th>
<th>Year of publication</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>JGOG Susumu (123)</td>
<td>Endometrioid only. IC-IIIC and &gt;50% MI, &lt;75 years. LND optional. RT: N=193 Chemo N=192</td>
<td>Pelvic RT +/- para-aortic RT +/- IVRT vs CAP q 28 days x ≥3 cycles</td>
<td>2008</td>
<td>5-year PFS: 83.5% vs 81.8% 5-year OS: 85.3% vs 86.7%</td>
</tr>
<tr>
<td></td>
<td>LIR (IC≤70 years and G1 or 2. N=190) HIR (IC&gt;70 years, or G3 or II or IIIA +washings). N=120 High-risk (IIIA other, IIIB, IIIC). N=75</td>
<td></td>
<td></td>
<td>Recurrences: Total: 15.5% vs 17.2% Pelvic: 6.7% vs 7.3% Extrapelvic: 13.5% vs 16.1% LIR group: 5-year PFS: 94.5% vs 87.6% 5-year OS: 95.1% vs 90.8% HIR group: 5-year PFS: 66.2% vs 83.8%* 5-year OS: 73.6% vs 89.7%* High-risk group 5-year PFS: 78.6% vs 64.4% 5-year OS: 75.8% vs 71.1% Similar rates of adverse effects in both groups</td>
</tr>
<tr>
<td>Maggi (124)</td>
<td>Excluded serous/clear cell. IC (G3), IIA/B (G3) if ≥50%MI, III (any) RT: N=166 Chemo= 174 LND optional.</td>
<td>Pelvic RT + para-aortic RT if+LNs vs CAP q 28d x 5 cycles</td>
<td>2006</td>
<td>5-year PFS: 63% vs 63% 5-year OS: 69% vs 66% No difference in survival, both arms were well tolerated.</td>
</tr>
</tbody>
</table>

*Statistically significant

Abbreviations: CAP= Cyclophosphamide + Doxorubicin + Cisplatin, TAP= Paclitaxel + Doxorubicin + Cisplatin, AP= Doxorubicin + Cisplatin, VBT= vaginal brachytherapy, RT= radiotherapy, LND= lymphadenectomy, LN= lymph nodes, CR= complete response, PR= partial response, ORR= overall response rate, PFS= progression free survival, OS= overall survival, CSS= cancer specific survival, FFS= failure free survival.
**Hormonal therapy**

Endocrine therapy can be considered in EC patients with advanced disease who are not able to tolerate other treatment options, or in the recurrent setting for patients presenting with distant metastasis. The presence of estrogen and progesterone receptors constitute an important positive predictive factor for endocrine treatment response in these cases (125).

**Outcomes**

The most important predictors of recurrence and death in patients with EC are advanced surgical stage, poorly differentiated histologic grade, non-endometrioid histology, deep myometrial invasion, presence of LVSI, primary tumor diameter >2 cm, and cervical stromal invasion (33, 67, 73, 86, 126-129). Recommendations for adjuvant therapy are based on the estimated risk for disease recurrence. The exact definition of risk categories varies between studies. The ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer new risk groups are presented in Table 2.

![Table 2](image)

Table 2. ESMO-ESGO-ESTRO Consensus Conference on Endometrial Cancer new risk groups.


**6.1.7. Quality of life**

As previously mentioned, a comprehensive lymphadenectomy is associated with peri- and postoperative complications such as injury to nearby nerves and vessels, lymphocyst formation, lymphedema, and cellulitis (131-133). By reducing the extent of surgery, and
reducing the number of lymph nodes extracted, one may observe a decrease in the above-mentioned complications. A major unwanted side effect of lymphadenectomy is post-treatment lymphedema of the lower extremities. Similarly, in the breast cancer setting, lymphedema of the upper extremities is a complication following axillary LND. It is well-documented that lymphedema is significantly reduced when an axillary SLN biopsy is performed, compared with an axillary LND, and QOL scores are superior for SLN patients (134, 135). Based on these findings, when applying the SLN approach rather than the more extensive LND for EC patients, we might expect a similar reduction in lower limb lymphedema. Ongoing trials evaluating lymphedema in women with EC will hopefully provide answers to these questions.

6.2. Sentinel lymph node biopsy

6.2.1. Definition of sentinel lymph node

The word “sentinel” is defined in the Oxford English Dictionary as “to stand guard over, to keep guard”. Sentinel lymph nodes (SLNs) are the first nodes to drain a tumor site; therefore, they are generally the first to demonstrate occult malignancy—prior to other regional and distant lymph nodes (Figure 6) (136).

Figure 6. Sentinel lymph node.
Modified and reprinted with permission from Terese Winslow LLC. U.S. Govt. has certain rights.

6.2.2. History of sentinel lymph nodes in solid tumors

The French anatomist Marie Philibert Constant Sappey explored cutaneous lymphatic systems in humans by injecting mercury into cadavers, enabling him to visualize routes of lymphatic drainage. He observed that lymphatic drainage was both orderly and predictable, an important
principle of the sentinel node theory (137). In 1874, he published an anatomical atlas that included a detailed study of lymphatic drainage. More than a century ago, the surgeons William Halsted and Herbert Snow also hypothesized that cancer spread in an orderly fashion, initially to regional lymph nodes and thereafter to more distant sites. They subsequently advocated for lymph node dissection in patients with melanoma and breast cancer (138-140). In the middle of the 20th century, surgeons recognized that cancer spread from a primary lesion to lymph nodes by tumor emboli, and not by progressive invasion of the lymphatic channels. These studies set the stage for the modern exploration of lymphatic mapping and sentinel lymph node detection in solid tissue malignancies.

Figure 7. Tumor emboli.

“Sentinel node” for cancer of the parotid gland was described in 1960 by Dr. Ernest Gould. Gould advocated that the “sentinel node” should be dissected and sent for frozen section. If the sentinel node was found to be without malignancy, a radical neck dissection could be omitted (141). The first report of successful SLN mapping was in 1977, for lymphangiography of the penis (142). Since then, the mapping of other solid malignancies such as cutaneous melanoma, and carcinoma of the breast, vulva, and cervix, has adopted this technique (Table 3). The evolution of the initiation and acceptance of SLN mapping has been unique to each disease site, due to multiple variations in demographic as well as clinicopathologic characteristics.

In gynecologic oncology, SLN mapping was first implemented in the setting of vulvar cancer. Vulvar tumors are easily accessible to injection of tracer, and the lymphatic drainage is well described: following lymphatic channels to one or both groins. Several trials have focused on the safety of SLN biopsy in replacing inguinofemoral lymphadenectomy in patients with vulvar cancer (143-146). The SLN approach is now accepted as standard of care in the management of clinically node-negative, T1-T2 (<4 cm) vulvar cancer. It is recognized that the procedure should be performed by experienced surgeons at high-volume institutions.
Table 3. Milestones of SLN approach in solid tumors. (141, 142, 147-151)

6.2.3. Techniques for SLN mapping in gynecologic cancer

Multiple studies have evaluated the detection rates of SLNs in EC using various tracers, alone and in combination (152-161).

Colorimetric SLN mapping: Colorimetric SLN mapping refers to detection of lymphatic channels with the “naked eye”, using colored dyes in white light. This technique is suitable for open surgery as well as for minimally invasive surgery, and does not require specialized equipment. The most common dye used is Isosulfan Blue (2-4 mL of a 1% solution is injected superficially into the cervix with subsequent uptake in the SLNs within 10-20 minutes). The disadvantages of Isosulfan Blue are its cost, limited availability, and risk of allergic reaction,
including anaphylaxis in 1.1% of cases (162). Risk factors for anaphylaxis include a history of bronchial asthma, multiple allergies, or allergies to triphenylmethane dyes. Isosulfan Blue may also cause falsely low oxygen saturation readings, due to interference, with measurement of O2 saturation in the patient’s peripheral blood.

**Radionuclear SLN mapping:** Radio-labeled colloid technetium 99 (Tc99) and detection with nuclear imaging and/or intraoperative gamma counters is one of the first techniques used in SLN mapping. Gamma probes are available for laparotomy and laparoscopy. One mL of 1 mCi of Tc99 is injected into the cervix preoperatively, followed by lymphoscintigraphy to detect the location of the SLNs. Radio-labeled isotopes have the capacity for signal penetration through tissues. Tc99 is commonly used in conjunction with Isosulfan Blue dye or ICG. However, radio-nuclear techniques are costly and cumbersome.

**Indocyanine green/near infra-red imaging (ICG/NIR):** ICG was developed in World War II as a photographic dye. It was tested in 1957 at the Mayo Clinic for use in human medicine. ICG subsequently received Federal Drug Agency (FDA) approval in 1959, and was initially used in hepatic function diagnostics and later in cardiology. ICG emits a fluorescent signal in the near-infrared light range and demonstrates peak absorption at about 800nm. Specialized NIR cameras are available for laparotomy and minimally invasive surgery. After the patient is prepped and draped, prior to placing a uterine manipulator, 2-4 mL of diluted dye is injected into the cervix. Optimal SLN detection occurs when the dye is diluted to a 0.5 mg/mL – 1.25 mg/mL concentration using sterile water (152, 163). ICG combines the qualities of radio-nuclear and colorimetric tracers, as it provides both signal penetration through tissues and real-time visualization. ICG is excreted by the liver, and should be avoided in patients with liver failure. It should also be avoided in patients with severe iodide allergies.

**Injection site in endometrial carcinoma**

The lymphatic drainage pattern of the endometrium has been established in several reports (164, 165). There are two major routes of lymphatic drainage from the uterus. The main drainage follows the uterine vessels through the parametria; the second route is more cephalad, along the gonadal vessels. Three main injection techniques have been evaluated for SLN mapping in EC: cervical, hysteroscopically guided sub-endometrial, and laparoscopic fundal injections (147, 158, 166-168). Cervical injection is preferable due to its higher technical success rate and greater feasibility. Some para-aortic lymph nodes may be reached only via the infundibulopelvic ligament channels, which are not commonly accessible via superficial cervical injection, and there is concern that some isolated para-aortic lymph node metastases are missed because of this. However, the incidence of isolated para-aortic nodes is low (3%) (169, 170). The common cervical injection sites for SLN mapping in EC are shown in Figure 8.
6.2.4. Sentinel lymph node mapping in endometrial carcinoma

The main goal of the SLN approach is to identify high-yield lymph nodes, limiting the need for a comprehensive lymphadenectomy. To achieve this, the technique must have a high bilateral SLN detection rate, a high sensitivity for detection of metastatic lymph nodes, and a low false-negative rate. The detection of SLNs is dependent on the surgeon’s experience, as well as injection site and choice of dye. Khoury-Collado and colleagues have described a learning curve, with an increase of 77% to 94% in SLN detection following a 30-case experience (171).

Adherence to an SLN algorithm significantly improves the sensitivity and decreases the false-negative rate of the SLN approach. Barlin and colleagues demonstrated this in 2012. In their study, an EC surgical algorithm was retrospectively applied to 498 patients who had received a blue dye cervical injection for SLN mapping. The surgical algorithm in this study was as follows: a survey of the peritoneal cavity and serosal surfaces is performed and peritoneal washings collected; thorough retroperitoneal evaluation is done, with excision of all mapped SLNs and removal of any enlarged, suspicious lymph nodes; if mapping fails, a side-specific lymph node dissection should be performed in the unmapped hemi-pelvis; para-aortic lymph node dissection is performed at the discretion of the attending surgeon (Figure 9). The algorithm demonstrated an improved performance compared to SLN alone: sensitivity, 98.1% vs. 85.1%; false-negative rate, 1.9% vs. 14.9%; NPV, 99.8% vs 98.1% (172). This algorithm was incorporated into the NCCN (National Comprehensive Cancer Network) guidelines for EC in 2014, and it has been validated by other investigators (157, 173, 174).
The prospective multicenter SENTI-ENDO trial sought to describe the accuracy of SLN mapping in patients with early-stage EC. Patients underwent pelvic SLN assessment with dual cervical injection of technetium and patent blue dyes, with subsequent pelvic lymphadenectomy and histopathologic examination. The authors demonstrated an overall detection rate of 89% and NPV of 97% (95% CI, 91-99) (175). These findings were affirmed in the aforementioned FIRES trial, another prospective multicenter trial designed to assess the sensitivity and NPV of SLN compared to lymphadenectomy. In this trial, patients with clinical stage I EC of all histologies and grades were included. They received a cervical injection of ICG with SLN mapping and extraction followed by a pelvic (340 cases) ± para-aortic (196 (55%) cases) lymphadenectomy, using the robotic platform. The study reported a sensitivity to detect node-positive disease of 97.2% (95%CI, 85-100) and an NPV of 99.6% (95% CI, 97.9-100) (176). These studies have established the safety of an SLN approach in EC.

Achieving a high SLN detection rate, and particularly a high bilateral detection rate, is key to a successful SLN approach in EC treatment. In a recent systemic review and meta-analysis by Smith et al, cervical injection with combination blue dye and radiotracer or ICG dye alone increased the overall detection rate (177). In the same study, the pooled sensitivity of SLN detection of metastatic disease was 96% (95% CI, 93-98; 47 studies). The pooled NPV was 99.7%, and in cases with SLN metastasis, SLNs were the only positive nodes identified in 66% of the patients (22 studies) (177). This meta-analysis suggests that the SLN detection rate and sensitivity in the setting of EC approach those observed in breast cancer and melanoma, malignancies for which SLN mapping is the standard of care (135).

Figure 9. MSKCC SLN surgical algorithm
Reprinted with permission from MSKCC (172)
6.3. Pathologic processing

6.3.1. Pathologic ultra-sectioning

There are currently no evidence-based guidelines for the pathologic assessment of SLNs in EC. There is considerable variation between institutions with respect to number of sections examined by routine H&E staining, depth of sectioning into the tissue block, the interval of microns (μm) between parallel sections, and the use of IHC to identify tumor cells not noted on H&E alone (178). The College of American Pathologists (CAP) guidelines for breast SLN processing are to slice along the long axis of the node at 2-mm intervals and examine all slices microscopically with at least 1 representative H&E level. Additional H&E parallel levels or IHC studies may be employed (179).

The MSK pathologic ultrastaging protocol for gynecologic malignancies is as follows: SLNs are initially examined by routine H&E staining, and subsequent ultrastaging is performed if the initial H&E assessment is negative; SLN ultrastaging is performed by cutting two adjacent 5-μm sections at each of 2 levels, 50-μm apart, from each paraffin block lacking metastatic carcinoma; at each level, one slide is stained with H&E and with IHC using the anticytokeratine AE1:AE3 for a total of 5 slides per block, Figure 10 (180).

In a study from MSKCC of 508 EC patients, with successful mapping and application of the above-mentioned pathologic processing protocol, 12.6% had positive nodes; 6.9% were detected by routine H&E, whereas ultrastaging detected an additional 4.5% who would otherwise have been missed (180). Ultrastaging can likely be omitted in cases of endometrioid adenocarcinoma with no myoinvasion, as a metastatic rate of 0.8% was found in this subgroup of patients (180).

Figure 10. MSKCC pathologic processing protocol
Reprinted with permission from MSKCC. (180).
6.3.2. Definition of low-volume metastasis

According to the American Joint Committee on Cancer (AJCC) staging guidelines for the staging of breast cancer, macrometastasis is defined as groups of malignant cells > 2.0mm. Micrometastasis is defined as tumors within a lymph node measuring >0.2mm and/or >200 cells, but ≤2.0mm. Isolated tumor cell (ITC) clusters are small clusters of cells ≤0.2mm, present either as single tumor cells or clusters of <200 cells (Figure 11) (181). These definitions have also been adopted for EC. ITC must be seen on both H&E and IHC, and cells seen only on IHC are designated as cytokeratin (CK)-positive cells, and are not considered to be metastatic tumor cells (although this is still a matter of debate).

![Figure 11. Nodal metastasis in endometrial carcinoma. Photos courtesy of Robert A. Soslow, MD.](image)

**Figure 11.** Nodal metastasis in endometrial carcinoma. Photos courtesy of Robert A. Soslow, MD.

6.3.3. Significance of low-volume metastasis

The clinical and prognostic significance of low-volume metastasis in EC is largely unknown. The controversy regarding the value of ultrastaging in EC likely reflects the general uncertainty surrounding the value of lymphatic assessment in this disease. The AJCC breast cancer guidelines do not include nodes containing ITCs as positive lymph nodes. The guidelines do, however, recommend including them in the total number of nodes evaluated (181). There is a need to further examine and better understand the significance of ITCs and MM in EC, and if, or how, these should guide adjuvant therapy.
7. OBJECTIVES OF THE THESIS

7.1. Background

Surgical treatment of clinically uterine-confined EC consists of total hysterectomy and removal of the adnexa. Assessment of nodal status is an integral part of the FIGO staging system for EC. However, there is ongoing debate and controversy regarding the value of a comprehensive pelvic and para-aortic lymph node dissection (LND) in patients with EC. There are no clear, widely accepted international or national guidelines for lymph node assessment in these patients. Thus, assessment of lymph nodes varies widely: from no lymph node dissection, to sampling, to systematic pelvic and para-aortic lymphadenectomy for all women. The anatomic extent of para-aortic nodal dissection also varies with respect to cranial limitation to the inferior mesenteric artery, or to the renal veins. SLN mapping has emerged as an alternative to comprehensive LND.

To derive full advantage from the SLN approach, bilateral mapping is key. The optimal choice of dye is still under investigation. Concern remains regarding the ability of an SLN mapping algorithm to detect nodal metastasis, particularly in the setting of higher-risk carcinomas. Oncologic outcomes in association with the SLN approach have not been well-studied. The clinical significance of low-volume metastasis detected on ultrastaging, and the role of adjuvant therapy in these cases, is unclear.

7.2. General aims

The main aim of this thesis was to investigate the various unanswered aspects of implementing an SLN mapping algorithm for EC. We aimed to study optimal dye choice, and the clinical significance of low-volume metastasis. We also sought to explore the accuracy of an SLN mapping algorithm in detecting metastatic nodes, and to assess the oncologic outcomes in comparison to a comprehensive LND approach.

7.3. Specific aims

1. To assess and compare the SLN detection rate with ICG and NIR fluorescence imaging versus blue dye, using the robotic platform in patients with EC (Paper I).

2. To determine the impact of obesity on the rate of successful SLN mapping in patients with EC undergoing robotic surgery, and compare SLN detection rates using ICG/NIR versus blue dye (Paper II).

3. To assess clinicopathologic outcomes between an SLN mapping algorithm and a selective, comprehensive LND approach in patients with low-risk EC (defined as endometrioid adenocarcinoma with myoinvasions <50%), and to compare oncologic outcomes (Paper III).
4. To determine the performance of an SLN mapping algorithm in detecting metastatic nodal disease in patients with intermediate- and high-risk EC, compared to a selective, comprehensive LND approach (Paper IV).

5. To characterize treatment patterns and oncologic outcome in patients with low-volume lymph node metastasis (ITCs and MM) discovered during SLN mapping for EC (Paper V).
8. MATERIALS AND METHODS

8.1. Study design and patient selection

This thesis utilizes data from several patient series; from Memorial Sloan Kettering Cancer Center, New York, NY, USA and from the Mayo Clinic, Rochester, MN, USA. A summary of the thesis populations is presented in Table 4, and is more briefly summarized in the section “THESIS AT A GLANCE” (on page 10).

Table 4. Summary of thesis populations

<table>
<thead>
<tr>
<th>Study population</th>
<th>Paper I</th>
<th>Paper II</th>
<th>Paper III</th>
<th>Paper IV</th>
<th>Paper V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study question</td>
<td>Does choice of dye affect SLN mapping in women with uterine-confined EC?</td>
<td>Does BMI affect SLN mapping in women with uterine-confined EC?</td>
<td>Does nodal assessment approach influence detection of stage III disease and oncologic outcomes in women with low-risk EC?</td>
<td>Does nodal assessment approach influence detection of stage III disease in women with intermediate- and high-risk EC?</td>
<td>Is RFS influenced by size of nodal metastasis in women with EC?</td>
</tr>
<tr>
<td>Main study outcome</td>
<td>SLN mapping</td>
<td>SLN mapping</td>
<td>Identification of metastatic LNs, RFS</td>
<td>Identification of metastatic LNs.</td>
<td>RFS</td>
</tr>
<tr>
<td>Main explanatory variable</td>
<td>Dye (ICG/NIR vs blue dye)</td>
<td>BMI</td>
<td>Mode of LN assessment; SLN vs LND</td>
<td>Mode of LN assessment; SLN vs LND</td>
<td>Low-volume metastasis</td>
</tr>
<tr>
<td>Study design</td>
<td>Retrospective cohort study</td>
<td>Retrospective cohort study</td>
<td>Retrospective cohort study</td>
<td>Retrospective cohort study</td>
<td>Retrospective cohort study</td>
</tr>
</tbody>
</table>

**Memorial Sloan Kettering (MSK) Cancer Center Institutional SLN database**

In our studies, we used data from the MSKCC Institutional SLN database. This is an institutional database of all surgical cases in which SLN mapping is performed. The MSK SLN algorithm was adhered to (Figure 9). Lymphatic mapping was performed by injecting Blue dye or ICG into the cervical stroma at superficial and deep levels at the 3- and 9-o’clock positions for a total of 4 mL. Identified SLNs were excised and evaluated by the institutional Pathologic Processing Protocol (Figure 10). We excluded patients who had received neoadjuvant chemotherapy, had another malignancy or synchronous cancer, or had visible gross metastatic disease.

**Mayo Clinic Institutional Endometrial Cancer database**

For Papers III and IV we also used data from the Mayo Clinic Institutional Endometrial Cancer database. The population from this database was a historic cohort in which all patients underwent the Mayo Clinic historical surgical algorithm (Figure 11): hysterectomy, BSO, peritoneal cytology, and bilateral pelvic and para-aortic lymphadenectomy up to the renal veins, were performed. A gynecologic oncology pathologist performed frozen section analysis of the uterine specimen to determine tumor size and depth of myometrial invasion. Lymphadenectomy was omitted in patients with disease of endometrioid histology of any grade or tumor size if there was no myometrial invasion, and in patients with disease of endometrioid histology, grade 1 or 2, with <50% myometrial invasion and tumor diameter ≤2 cm.

**Figure 11.** Mayo Clinic surgical algorithm


### 8.2. Data access and ethics

The studies were approved by the Institutional Review Board at Memorial Sloan Kettering Cancer Center, for all papers. No specific patient consent is required for retrospective data analysis of this form, per national regulations.
8.3. Treatment and follow-up
Adjuvant therapy for stage IIIC and high-risk patients remains controversial, with conflicting data for EC. As our cohort in Paper III was low-risk, the heterogeneity of adjuvant therapeutic approaches only affected women with extra-uterine disease, and was not corrected for, due to the low number of events (metastatic disease and recurrences). A variety of treatment modalities were administered, and varied from no therapy, IVRT only, EBRT ± IVRT, chemotherapy ± IVRT, chemotherapy and EBRT ± IVRT, and hormonal therapy. In Paper V, the MSK treatment algorithm for patients with stage IIIC disease called for cisplatin 50mg/m² on days 1 and 29 plus volume-directed radiation therapy, followed by paclitaxel and carboplatin for four cycles. Alternatively, patients could be treated with chemotherapy (paclitaxel and carboplatin for six cycles) with or without vaginal brachytherapy. The decision to proceed with one or the other depended on additional clinicopathologic features as well as patient and provider preference.

Follow-up was relevant for Papers III and V. Patients followed up with their provider at recommended 3- or 6-month intervals per SGO guidelines (183). The median follow-up for the various cohorts was as follows:
Paper III: Median follow-up of 2.1 years (IQR: 1.2, 3.3) in the MSK cohort, and 3.5 years (IQR: 2.5, 4.9) in the Mayo cohort.
Paper V: Median follow-up of 26 months (range 0-108).
Recurrence-free survival and disease-free survival rates were calculated from the date of surgery to recurrence, confirmed by clinical examination or imaging, or date of last follow-up.

8.4. Study variables
Demographic, clinicopathologic, nodal characteristics, and disease-specific parameters were collected from electronic medical records, including outpatient and inpatient notes, laboratory results and imaging, operative reports, pathology reports, and records detailing postoperative treatment, including chemotherapy and radiation therapy. Date and location of recurrence, and date of and disease status at last follow-up, including cause of death if deceased, were also retrieved from electronic medical records. All pathologic evaluations were performed by gynecologic oncology pathologists. All surgical procedures were performed by gynecologic oncologists.

Patient age was defined as age at date of surgery. BMI was calculated as weight divided by height squared (kg/m²). Height and weight were recorded from the patient chart at initial visit. Data were stratified by BMI as normal and overweight (BMI <30), obese (BMI ≥30-40), and morbidly obese (BMI ≥40), and were further broken down into the following categories for bilateral mapping rate in relation to BMI by dye: <20, 20-25, 25-30, 30-35, 35-40, 40-45 and ≥45 kg/m². Estimated blood loss (EBL) was noted in cubic centimeter (cc) per the operative report. Operative time was noted in minutes from incision to closure of the patient per the operative report. SLN operative time was noted in minutes, and this was extracted from the MSK Institutional Robotic Surgery database.

Mapping status: Bilateral mapping is defined as an SLN identified in both hemi-pelvises. Unilateral mapping is defined as an SLN identified in only one hemi-pelvis. Overall mapping is defined as the sum of cases with bilateral mapping and cases with unilateral mapping.
Side-specific lymphadenectomy: In the case of unilateral or bilateral unsuccessful mapping extraction of lymph nodes from the failed hemi-pelvis(es) is performed.

**Nodal status:** In the MSK cohort macrometastasis, micrometastasis (MM) and isolated tumor cells (ITCs) were all considered positive for the analysis. Metastatic disease was categorized and reported in a standardized fashion according to the American Joint Committee on Cancer, as described in section 1.3.1. When the tumor measurement was not delineated in the pathology report and the terms “isolated tumor cells” and “micrometastasis” were not used, a determination was made based on the pathology report, with clarification from a gynecologic pathologist when needed. Cytokeratin-positive-only cells not seen on H&E stained sections were considered to be node-negative.

**Histopathology:** Histologic type, grade and uterine features including LVSI, myometrial invasion (MI) and cervical stromal invasion were retrieved from the routine pathology reports in the MSK cohort; and from frozen section, which equals final pathology, for the Mayo cohort. Information regarding number of lymph nodes extracted was also retrieved from these reports. LVSI was defined by pathologists at both centers as tumor cells within or attached to the wall of a capillary-like space. The presence of artifactual tumor displacement was excluded. MI was measured as the distance the tumor invaded the uterine wall and recorded as either “no myoinvasion” or “myoinvasion present in x mm”, where the distance from the endometrial lining to the serosa was also noted in mm. Stage is reported per FIGO 2009 in all papers, and per FIGO 2009 and FIGO 1988 in paper III to highlight the cases with no myometrial invasion (FIGO 1988 stage IA).

Location of first recurrence of EC following initial surgery was recorded and defined as follows, in paper III: hematogenous included locations metastatic cells could only reach hematogenously (i.e. brain, bone, intraparenchymal liver); lymphatic included enlarged lymph nodes or masses in known lymph node basins; vaginal included disease involving any portion of the vagina including the vaginal cuff; and peritoneal included disease recurring anywhere in the peritoneal cavity or on a peritoneal surface. For paper V, recurrences were categorized into the following categories: Local, nodal, distant, multisite. Local included disease involving the vagina and pelvis; nodal included enlarged lymph nodes or masses in known lymph node basins; distant included single locations other than vaginal or nodal; and multisite included disease in more than one location.

**8.5. Statistical analysis**
In papers I and II, the Fisher exact test or Wilcoxon rank sum test was used to test the 2-way associations depending on whether a continuous variable was included or not, and the 3-way associations were tested using the Cochran-Manter-Haenszel test. In paper I, the Kruskal-Wallis test was used to investigate the relationship between EBL and BMI category, and the relationship between SLN time and SLN number was evaluated using Pearson correlation coefficient. All calculated p values were two-sided, and P-values <0.05 were considered statistically significant. The statistical analysis in papers I and II were performed by Qin Zhou, MA, at the Department of Epidemiology and Biostatistics at Memorial Sloan Kettering Cancer Center. Statistical analysis was performed using SAS 9.2 or R2.3.1 statistical software.
In papers III and IV, we compared patient-, treatment-, and disease-specific parameters between cohorts using the Chi-square or Fisher’s exact test for categorical variables, the two-sample t test for age and BMI, and the Wilcoxon rank-sum test for number of nodes removed and number of positive nodes. Survivorship was estimated using the Kaplan-Meier method and compared between cohorts using the Log-rank test. All calculated p values were two-sided, and P-values <0.05 were considered statistically significant. The statistical analyses in papers III and IV were performed by Michaela E. McGree, BS, and Amy L. Weaver, MS, at the Division of Biomedical Statistics and Informatics, Department of Health Sciences Research at the Mayo Clinic. Statistical analysis was performed using SAS version 9.3 software package (SAS Institute Inc., Cary, NC).

In paper V, we reported clinicopathologic data using median (range) for continuous variables, and number of patients (n) and percentage (%) for categorical variables. Survivorship was estimated using the Kaplan-Meier method and compared between cohorts using the Log-rank test. Statistical analysis was performed using IBM SPSS Statistics 22.0 (IBM Corporation, Armonk, NY).
9. SUMMARY OF RESULTS

The detailed results are presented in the five published papers (Paper I-V). Below is a brief summary of the results relevant to the specific thesis aims (Chapter 2).

9.1. Paper I
A comparison of the detection of sentinel lymph nodes using Indocyanine Green and Near-Infrared fluorescence imaging versus blue dye during robotic surgery in uterine cancer

We retrospectively assessed and compared the SLN detection rate using the novel dye ICG and near-infrared (NIR) fluorescence imaging versus blue dye at a single institution. Patients who had undergone an SLN mapping for EC with ICG or blue dye using the robotic platform from January 2011 to December 2013 were identified in our institutional database (n=472). This time period encompassed the transition from blue dye to ICG. ICG was used in 312 patients and blue dye in 160 patients. Overall mapping and bilateral mapping was achieved in a significantly higher proportion of cases where ICG was used, compared to blue dye. We also found that additional lymph node dissection beyond removal of SLNs was performed in a significantly lower number of cases with ICG, compared to blue dye. The majority (23/25: 92%) of identified aortic SLNs were detected using ICG.

Table 5. Mapping by dye used

<table>
<thead>
<tr>
<th></th>
<th>All, N = 472 (%)</th>
<th>ICG, n = 312 (%)</th>
<th>Blue Dye, n = 160 (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall mapping</td>
<td>425 (90%)</td>
<td>295 (95%)</td>
<td>130 (81%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bilateral mapping</td>
<td>352 (75%)</td>
<td>266 (85%)</td>
<td>86 (54%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Additional lymph node sampling</td>
<td>220 (47%)</td>
<td>122 (39%)</td>
<td>98 (61%)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>


9.2. Paper II
Impact of obesity on sentinel lymph node mapping in patients with newly diagnosed uterine cancer undergoing robotic surgery

Patients who had undergone an SLN mapping for EC with ICG or blue dye, using the robotic platform from January 2011 to December 2013, were identified (same population as in paper I, n=472). Data were stratified by BMI and dye used. Patients with successful bilateral mapping had a significantly lower BMI than patients with failed mapping: median BMI 29.8 kg/m2 (range 16.3-65.3 kg/m2) versus median BMI 43.7 kg/m2 (range 21.4-60.4 kg/m2), respectively. With increasing BMI, there was a significant decrease in successful bilateral mapping rates in both the ICG and blue-dye groups; however, the use of ICG resulted in improved bilateral and overall mapping rates compared to the use of blue dye in all BMI groups.
9.3. Paper III

Comparison of a sentinel lymph node and a selective lymphadenectomy algorithm in patients with endometrioid endometrial carcinoma and limited myometrial invasion

In this study we found that, for this low-risk cohort, the SLN algorithm resulted in significantly more patients undergoing pelvic nodes excision and evaluation, a lower number of lymph nodes removed per patient, and a higher detection rate of FIGO 2009 stage IIIC1 disease. With respect to para-aortic nodes, the SLN algorithm resulted in fewer patients having para-aortic nodes removed, a lower number of nodes excised per patient, and a similar detection rate in the setting of stage IIIC2 disease, compared with the Mayo Clinic LND algorithm. Significantly more patients in the SLN cohort received adjuvant therapy. Because of the higher number of patients with documented LVI in the SLN cohort, there was an increased administration of IVRT; the increased use of chemotherapy, with or without radiation therapy, corresponded to the higher number of patients with detected stage IIIC disease. There were two isolated lymph node recurrences within each cohort, yielding a three-year isolated nodal-free recurrence of 99.6% in both cohorts. The 3-year DFS rates were comparable for both groups.

Figure 13. Bilateral mapping by BMI.

Figure 14. Pelvic nodal extraction and status

Para-aortic nodal extraction and status
9.4. Paper IV
Comparison of a sentinel lymph node mapping algorithm and comprehensive lymphadenectomy in the detection of stage IIIC endometrial carcinoma at higher risk for nodal disease

Intermediate-risk cases: Endometrioid histology, any grade, and ≥50% myometrial invasion
Pelvic lymph node assessment was performed in the majority of patients in both groups. Significantly more PLNs were removed in the LND cohort; however, pelvic nodal metastasis was detected with similar frequency in both groups. Para-aortic lymph nodes were assessed more frequently in the LND cohort than the SLN cohort, with a significantly higher number of PALNs removed in the LND cohort. We noted a similar detection rate of stage IIIC disease between the SLN and LND cohorts; but more stage IIIC1 disease was detected in the SLN cohort and more stage IIIC2 disease in the LND cohort.

<table>
<thead>
<tr>
<th>FIGO stage 2009, N(%)</th>
<th>SLN cohort</th>
<th>LND cohort</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IIIC</td>
<td>29 (35.4)</td>
<td>30 (28.0)</td>
<td>0.28</td>
</tr>
<tr>
<td>Stage IIIC1</td>
<td>26 (31.7)</td>
<td>12 (11.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stage IIIC2</td>
<td>3 (3.7)</td>
<td>18 (16.8)</td>
<td>0.004</td>
</tr>
</tbody>
</table>

Figure 15. Stage distribution in both intermediate-risk cohorts. Figure courtesy of Jen Ducie, MD.

High-risk cases: Serous and clear cell histology with any degree of myometrial invasion
For the high-risk group, pelvic lymph node sampling was performed in a significantly greater percentage of patients in the SLN cohort, and significantly fewer nodes were removed. Positive pelvic lymph nodes were identified with similar frequency in each group. A similar number of metastatic nodes were extracted, per patient with positive nodes, in both cohorts. Para-aortic lymph nodes were assessed more frequently in the LND cohort than in the SLN cohort, with a significantly higher number of PALNs removed in the LND cohort. A greater median number of positive para-aortic lymph nodes per node-positive patient, were identified in the LND cohort. However, there was a similar percentage of patients in each group with
positive para-aortic nodes. Overall, stage IIIC disease was diagnosed at similar rates in each cohort (Figure 16).

![MSK: SLN (N=120) and Mayo: LND (N=103) Stage Distribution](image)

<table>
<thead>
<tr>
<th>FIGO stage 2009, N(%)</th>
<th>SLN cohort</th>
<th>LND cohort</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage IIIc</td>
<td>27 (22.5)</td>
<td>20 (19.4)</td>
<td>0.57</td>
</tr>
<tr>
<td>Stage IIIc1</td>
<td>18 (15.0)</td>
<td>9 (8.7)</td>
<td>0.15</td>
</tr>
<tr>
<td>Stage IIIc2</td>
<td>9 (7.5)</td>
<td>11 (10.7)</td>
<td>0.41</td>
</tr>
</tbody>
</table>

**Figure 16.** Stage distribution in both high-risk cohorts. Figure courtesy of Jen Ducie, MD.

**9.5. Paper V**  
**Low-volume lymph node metastasis discovered during sentinel lymph node mapping for endometrial carcinoma**

In this study, 89.2% of all patients were node-negative. Approximately 5% of patients had low-volume metastasis. The node-positive cases were distributed as follows: 2.7% had ITCs only, 2.5% had MM only, and 5.6% had macrometastasis. Postoperative treatment was recommended for all patients with low-volume metastasis; 4 patients, in total, declined any adjuvant therapy. Adjuvant chemotherapy was administered to 14% of node-negative patients, 83% of patients with ITCs, 81% of patients with MM, and 89% of patients with macrometastasis. With a median follow-up of 26 months, the 3-year RFS was similar for node-negative cases and cases with low-volume metastasis: 90% for node-negative patients, 86% for ITCs only, 86% for MM only. This was significantly better than for patients with macrometastasis, for whom the 3-year RFS was 71%.

When considering only cases with endometrioid histology (N=724)—as these are the patients whose adjuvant treatment may depend heavily on lymph node status—we again found a similar, and significantly superior, 3-year RFS for node-negative patients and patients with low-volume metastasis, compared to patients with macrometastasis: the 3-year RFS was 93% for patients with negative lymph nodes, 94% for ITCs, 92% for MM only, and 85% for those with macrometastasis. As only 4 patients declined any adjuvant therapy, we cannot comment
on the natural history of patients with untreated low-volume metastasis, and cannot make any inference as to whether adjuvant therapy was solely responsible for the improved oncologic outcome in this group.

10. DISCUSSION

10.1 Methodological considerations
The gold standard in research is the randomized controlled trial (RCT). For logistic, fiscal or ethical reasons, however, this design is not always feasible. Observational studies play a significant role in health research, particularly when evidence from randomized controlled experiments is not available. Observational, retrospective studies may be hypothesis-generating, and may serve as a foundation for creating RCTs; and the data from observational, retrospective studies constitute the basis of clinical decision-making until such time as an RCT may be conducted (if at all). All of the studies discussed in this thesis are retrospective in nature. Health records that had already, previously been collected and stored in an electronic institutional database were used to explore associations between one or more risk factors and a pre-defined outcome. We recognize that the use of two institutions does limit the ability to standardize or control for a variety of potentially confounding factors.

Retrospective studies are designed to analyze pre-existing data, and as a result are subject to numerous biases. Errors affecting the validity of a study may be due to chance (random error) or systematic error, usually explained by bias or confounding. A random error is known as variability. The impact of random error can be minimized by increasing sample size. Systematic error, or bias, creates an association that is not true. Random error corresponds to imprecision, whereas bias corresponds to inaccuracy (Figure 18).

Bias: The two most relevant forms of bias are selection bias and information bias. Patient recall bias, a form of selection bias, is not relevant for any of the papers used in this thesis because we did not rely on patient-reported information. We will discuss the various forms of bias that are relevant:

Selection bias: Selection bias occurs when selection, enrollment or continued participation in a study leads to a result that is different from what one would have gotten if the entire population was enrolled.
For papers I and II, we assessed the detection rates of lymph nodes based on dye. The study period was January 2011–December 2013. The transition in use of dye was related to time, as the patients were not randomly assigned to one dye or the other. There is no obvious reason why patients referred to our institution for surgical treatment of EC during the time period when blue dye was used should differ, in terms of demographic characteristics, from patients referred during the time-period when IGC was used. This is reflected in the finding that the demographic characteristics assessed (age, BMI, EBL, histologic type and grade, FIGO stage) did not differ significantly between cohorts (Table 1, Papers I and II). Follow-up was not required for these studies.

In Papers III and IV, we compared heterogenous groups from two institutions. We cannot exclude the possibility of a patient selection bias in these studies, which is a limitation. The LND cohort was older and had a higher BMI overall than the SLN cohort. This difference between cohorts may have influenced the disease-specific survival in favor of the SLN cohort. A significantly higher proportion of EC patients in the SLN cohort had no myometrial invasion, and a significantly higher proportion in the SLN cohort was found to have LVSI. The disproportionate number of patients without myometrial invasion may have played a favorable role in the SLN cohort. However, the presence of LVSI, in the same cohort is a negative predictive factor and may have influenced the recurrence rates or RFS negatively.

**Loss to follow-up bias** is relevant for Paper III. There is a possibility that EC patients who recurred, or those who did not recur, would be less likely to adhere to scheduled follow-up appointments. However, there is no plausible reason why women in one cohort should be more likely to behave this way, compared to the other cohort. We therefore believe that recurrences were identified equally often, in both cohorts. This belief is supported by the fact that our detected recurrence rates were similar to those reported in the literature. Median follow-up in the SLN cohort was shorter than in the LND cohort. However, both median follow-ups were greater than 2 years, in which time period the majority of EC recurrences occur.

In Paper V, we reviewed the treatment characteristics and oncologic outcomes of patients with low-volume metastasis. All women treated surgically at our institution, in whom an SLN approach was applied, were included in this study. This was a large study, with more than 800 women. There is no plausible reason why women treated at our institution should have a different rate and distribution of metastatic disease than other women with EC. We therefore conclude that, in this respect, our study population is representative of EC patients in general. However, this study could contain a loss-to-follow-up bias, as we relied on patients adhering to the follow-up schedule in order for us to record any recurrence. The recurrence rate in our study population is, however, similar to that reported in the literature. For this reason, we believe that we identified the majority of recurrences in our cohort.

**Information bias**: Information bias results from systematic differences in the way data are obtained. It may affect both independent and dependent variables. Systematic differences in registration of exposure according to the outcome, or in registration of outcome according to exposure, may result in information bias. In all five papers we collected information from electronic medical records; thus, there could be information bias due to errors in medical
records, or recording errors. In an attempt to limit the risk of information bias, the electronic databases were validated by cross-checking all fields related to nodal assessment; and pathology reports for all patients in the patient electronic medical record were re-reviewed.

**Misclassification:** Misclassification occurs when there is an incorrect categorization of subjects with respect to their exposure status or outcome. Non-differential misclassification occurs if the frequency of errors is approximately the same in the groups being compared. This results in a bias towards the null. Differential misclassification occurs when the information errors differ between groups; the bias is different for exposed and non-exposed.

**Differential misclassification bias** may be present in Papers III and IV due to institutional variation and diagnosis performed by two different groups of pathologists. As described earlier in this thesis, there is interobserver variation in assessing and grading pathology slides for EC. Institutional variation in evaluation may also partially explain the observed differences in rates of LVSI. A way to overcome this would be to conduct a central pathologic review. This would be time-consuming and costly, however, and was not feasible for this retrospective study. Central pathology review is not always implemented for prospective studies. The recent FIRES trial applied the following quality-control for pathologic processing: “The lead pathologist at each site received instruction on the standardized processing and reporting of specimens required by the protocol before enrollment of patients. Pathology reports from each site were audited on a quarterly basis by the principal investigator to ensure compliance with processing and reporting according to protocol specifications.” (186).

**Confounding:** Confounding occurs when the differences in baseline characteristics between study groups result in differences in outcomes between the groups (apart from those related to the exposure or intervention(s)). Adequate adjustment for potential confounders depends on two conditions that must be satisfied: (i) the association with the disease is known; (ii) the identified or suspected confounders can be measured with adequate validity and accuracy.

In Papers I and II there were no differences between groups in known baseline characteristics. We recognize that there may have been differences in unmeasured baseline characteristics, as this is a potential pitfall in retrospective studies. To our knowledge there is no data describing any known demographic characteristics that would influence the uptake and distribution of blue dye versus ICG in lymphatic channels and lymph nodes. It has been shown that high numbers of cancerous cells block the uptake of ICG (187); therefore, if one cohort had a higher number of patients with positive nodes this could have influenced our results. However, the SLN algorithm was applied. The algorithm calls for removal of any suspicious nodes, limiting this potential confounder. Since the change from blue dye to ICG occurred at a certain point in time, one could argue that the increased detection during the ICG period was due to an increase in the experience of the surgeons during the ICG period. We do not believe this to be the case because all the surgeons had already performed more than the 30-case learning curve, previously described, during the blue dye period.

In Papers III and IV there are known differences in baseline characteristics between cohorts, such as proportion of patients with no myometrial invasion, proportion of patients with LVSI,
patient age, and patient BMI. There is no known association between these characteristics and
the capacity of any surgical technique to detect metastatic lymph nodes. We are confident that
the capacity of both surgical approaches to detect stage IIIC disease was not significantly
influenced by these differences. Paper III compares oncologic outcomes between cohorts.
Previous studies have shown that uterine factors are less accurate predictors of recurrence than
lymph node status (188). Older age and higher BMI in the LND cohort may have influenced
survival negatively. The lack of standardized adjuvant therapy is also a potential confounder.
However, disease-specific survival was excellent in both cohorts. Adjusting for other factors
was not possible due to the low number of deaths (0 vs. 5).

In Paper V, the primary outcome was recurrence-free survival by nodal status. Due to small
sample size (89 node-positive cases; 23 ITCs, 21 MM, 47 macrometastasis) and small number
of recurrences (2/23 ITCs, 2/21 MM and 16/46 macrometastasis) we did not adjust for other
factors in the survival analysis. We did estimate RFS for cases with endometrioid EC (type I)
separately, as type II EC is known to have a poorer prognosis. The use of adjuvant therapy (in
85% of the low-volume node-positive cases) is a confounder, and precludes us from drawing
conclusions regarding the natural course of disease in these women.

**Statistical power:** A type II error is defined as failure to reject the null hypothesis, given that
the alternative hypothesis is actually true. A type II error frequently occurs when sample size
is too small, restricting statistical power. Although EC is the most common gynecologic
malignancy in the developed world, it remains a relatively rare disease. The majority of
women with uterine cancer have an excellent prognosis; therefore, the number of events
(recurrence and/or death) will be low. This is reflected in papers III and V, which are limited
by the small number of events and small cohorts. Because the lack of power does not allow us
to confidently assess a type II error, any potential difference is not fairly assessed. We
acknowledge the lack of power in our analysis, which is partially due to its retrospective
nature. Retrospective studies cannot determine causation, only association.

**Validity:** External validity and internal validity are essential components in the design of
clinical trials. External validity reflects the extent to which the study results can be
generalized to the population that the sample is intended to represent. Internal validity reflects
the extent to which observed treatment effects can be ascribed to differences in treatment (not
confounding), thereby allowing inference of causality to be ascribed to a treatment.

**External validity:** In terms of clinicopathologic and prognostic factors, the patients included in
a study may differ from those who were eligible but not included. As the proportion of
eligible patients not included in a trial increases, external validity decreases. In our studies, all
patients who were referred to two major cancer centers for surgical treatment of EC were
included. Because of the way the US health system is currently organized, and based on the
vicissitudes of healthcare insurance, patients may self-select to a certain extent. There may be
differences in socioeconomic status between the patients referred to these institutions, and the
general patient population, as well as differences in EC populations in other regions and
countries. However, the research described in papers I, II and IV would not necessarily be
influenced by such differences. We believe the results from these papers are generalizable,
and can be applied to EC patients in the general population. The survival analysis in papers III
and V may be influenced by variations in socioeconomic status, which could affect the external validity of our results. Finally, our results may not be applicable outside high-volume centers or major cancer centers, especially in the case of surgeons inexperienced in the SLN technique.

**Patient satisfaction:**
A weakness in our retrospective studies is that patients were not evaluated beyond oncological endpoints. However, we do not believe that quality of life is influenced by the use of one dye versus another. Comparison of an SLN approach to a selective LND approach, with respect to peri- and postoperative complications, was omitted from our study because patients in the SLN cohort underwent minimally invasive surgery, whereas patients in the selective LND cohort underwent laparotomy. It would not be possible to assess which outcomes were affected by surgical modality versus nodal assessment approach. Lymphedema assessment is currently being done for our study population.

10.2. Discussion of results and clinical implications

10.2.1 Sentinel lymph node mapping (Papers I and II)

As implementation of an SLN algorithm is gaining acceptance in the surgical staging of women with clinical uterine-confined EC, it is imperative to ensure optimal choice of dye to achieve successful mapping. One of the advantages of an SLN approach is to reduce the number of lymph nodes removed during primary surgery, thus minimizing the surgical trauma and potential morbidity associated with a comprehensive lymphadenectomy (131-133). Previous studies have demonstrated similar or lower detection rates of SLNs as were described in our study, when combining ICG and radioisotope (technetium-99m), or ICG and blue dye (153, 155, 189). The use of radioisotope commonly inflicts pain and discomfort to the patient during injection. It also presents a logistic challenge, additional cost, and risk of radiation exposure.

Successful mapping is done bilaterally. In our study we found that overall and bilateral mapping was achieved in a significantly higher proportion of cases were ICG was used, compared to cases where blue dye was used. We also found that additional lymph node sampling, beyond removal of SLNs, was performed in significantly fewer cases where ICG was used. Based on our findings, we recommend implementing ICG/NIR as the dye of choice for surgeons who are incorporating SLN mapping into their practice. For surgeons who do not have the imaging tools required for ICG, we recommend a combination of blue dye and radioisotope to improve SLN detection rates. As with any surgical procedure, quality control is paramount. We recommend that each surgeon record their SLN mapping efforts, become familiar with his or her own mapping rates, and continuously strive to improve these rates.

One concern in adopting an SLN approach has been the omission of para-aortic lymph node assessment, and a subsequently increased risk of “missing”, or failing to identify, isolated para-aortic metastasis. However, nodal metastasis in the para-aortic area, in the absence of metastatic nodes in the pelvis, is rare (190, 191). Our findings also support the use of ICG.
over blue dye with respect to the detection of para-aortic SLNs: 92% of para-aortic SLNs in our study were detected when ICG/NIR was applied.

When investigating clinicopathologic factors that influence mapping rates, we discovered that patients who underwent unsuccessful mapping in the ICG group had a significantly higher median BMI and higher EBL than those with successful mapping (Paper I). When examining the relationship between BMI and EBL, we found that these were not independent factors for unsuccessful mapping. It is possible that, in patients with a higher BMI, and in the presence of well-vascularized visceral fat, there is more bleeding during dissection of the pelvic sidewall when opening of the anatomic spaces is required to locate lymphatic channels and lymph nodes. This bleeding may obscure the surgical field, compromising the ability to detect SLNs.

In our study, the median SLN time was the same for ICG as for blue dye. When stratified by BMI, SLN time significantly correlated with BMI. This may reflect the additional challenge of navigating the visceral fat during EC surgery, when identifying the lymphatic channels. Based on our experience and findings, we recommend that this part of the procedure be done carefully and methodically, as the goal is to detect uninterrupted lymphatic channels leading to the SLN.

In patients with successful bilateral mapping, median BMI was significantly lower than in patients with unsuccessful mapping. When stratified by BMI, we noted a significant decrease in the rate of bilateral mapping for both the ICG and blue dye cohorts. However, the superior bilateral detection rates of ICG compared to blue dye remained for all BMI groups. This finding is clinically significant, especially in light of the fact that an increased BMI increases the risk of developing EC (34). A large proportion of women who present with EC will be obese, and will benefit from the superior detection afforded by ICG over blue dye.

10.2.2 Sentinel lymph node diagnostic accuracy and oncologic outcomes (Papers III and IV)

As mentioned in section 5.2.1, one of the advantages of a SLN approach, compared with a comprehensive lymphadenectomy, is to reduce the number of lymph nodes extracted, minimizing surgical trauma and potential subsequent peri- and post-operative complications. Achieving successful mapping, and adhering to an SLN algorithm, is fundamental when this approach of surgical staging is applied. Once this fundament is established, the patient and surgeon can benefit from the added advantages of the SLN approach; namely, the aspects of precision medicine achieved by image-guided surgery and the addition of pathologic ultrastaging (180). In our study, use of the SLN approach resulted in a higher proportion of patients undergoing nodal assessment, and detection of a similar number of patients with stage IIIC disease. Since preoperative risk stratification is known to be inaccurate (78), and true risk category can only be known once final pathology is available, the SLN approach lends itself well to surgical staging in EC. Implementation of this approach may render some pre- and peri-operative examinations obsolete (such as MRI and frozen section to evaluate myoinvasion) and at the same time reduce the costs incurred by these tests.
Short-term oncologic outcome was not inferior for the SLN approach compared to comprehensive lymphadenectomy in low-risk EC patients, further supporting the implementation of SLN in the surgical staging of women EC. Some may argue that, as the recurrence risk is low in this group of patients, longer follow-up is required before convincing statements can be made with respect to oncologic outcome. We appreciate this criticism and will continue to monitor recurrence rates in this group of patients. Recently, Buda and colleagues published findings with a median follow-up of 30 months, supporting our conclusions (192).

We are currently analyzing results from the intermediate- and high-risk EC cohorts regarding oncologic outcomes. Recent retrospective studies comparing detection of stage IIIC disease and survival of patients with high-risk histology, managed by the SLN approach versus lymphadenectomy, have shown similar 2-year PFS in both cohorts (193, 194). Studies with longer follow-up are needed to confirm these findings.

Concern remains about the SLN approach with respect to residual metastatic nodes. Studies have shown that, beyond a positive SLN, metastatic nodes are present in approximately 40% of patients (195, 196). There is evidence that residual microscopic disease can be controlled by adjuvant therapy (194, 197). As per the SLN algorithm, it is important to evaluate for and remove any suspicious nodes. Patients at high risk for nodal metastasis should also undergo pre- or postoperative imaging to identify any enlarged nodes, guiding the initial surgery and tailoring adjuvant therapy.

Recent breast cancer studies have evaluated oncologic outcome in SLN biopsy alone versus axillary LND (ALND) in cases with negative SLNs and in cases with positive SLNs. The Swedish Multicenter Cohort Study reported on axillary recurrence after negative SLN biopsy with a 10-year follow-up (198). SLN was performed in 3518 women with clinically negative axilla, and ALND was thereafter performed in patients with demonstrated SLN metastasis. Isolated axillary recurrences were found in only 1.6% of cases, supporting the assertion that there is no role for ALND in patients with SLN-negative breast cancer. The American College of Surgeons Oncology Group (ACOSOG) Z0011 trial prospectively examined overall survival of patients with SLN metastases undergoing breast-conserving therapy, randomized to ALND after SLND or to no further axillary-specific treatment. Ten-year regional recurrence did not differ significantly between the two groups. These findings do not support routine use of ALND in this patient population (women with clinical T1 or T2 invasive breast cancer, no palpable axillary adenopathy, and 1 or 2 sentinel lymph nodes containing metastases) (199). While breast cancer and EC are distinct entities with unique pathophysiology, these results nevertheless lend support to omitting completion lymphadenectomy in SLN-positive patients demonstrating no grossly enlarged nodes preoperatively or on imaging.

There may never be a randomized controlled trial investigating oncologic outcomes of SLN versus lymphadenectomy in EC. Some will argue that the results from a retrospective study, should not drive a change in clinical practice. However, as clinicians we must be pragmatic, and when RCTs are not feasible, retrospective series may be the best available evidence to further enhance patient survival and wellbeing.
### 10.2.3 Low-volume metastasis (Paper V)

When applying enhanced pathology to extracted SLNs by means of ultra-sectioning, low-volume nodal EC metastasis are detected in an additional 25-60% of cases (180, 189, 200). In our study, approximately half of the detected nodal metastases were low-volume (MM or ITC). This cohort had a 3-year RFS similar to that of node-negative patients, and significantly improved 3-year RFS compared with node-positive patients. Very few patients with low-volume metastasis did not receive adjuvant therapy, so we are unable to comment on the natural progression of disease.

There is a paucity of data regarding the significance of low-volume metastasis in EC—its impact on prognosis, and its role in guiding adjuvant therapy. Marie Plante’s group recently published a series of 519 patients, investigating the significance of adjuvant therapy in women with ITCs (201). In this group, approximately half of the metastatic nodes were low-volume disease. ITCs were not considered node-positive, and only 35% of cases with ITCs received adjuvant therapy, based on uterine factors. Patients with low-volume metastasis, irrespective of receiving adjuvant therapy or not, had a similar oncologic outcome to node-negative patients, and did significantly better than patients with macrometastatic lymph nodes. Based on these findings, one could argue that, in the absence of high-risk uterine factors, patients with endometrioid histology and ITCs derive limited benefit from adjuvant therapy. However, administration of adjuvant therapy in women with low-volume metastasis and high-risk features is supported by the findings of Todo et al, who retrospectively performed ultrastaging of previously-determined, macroscopically-negative lymph nodes in a high-risk population that had undergone LND (202). They demonstrated that ITCs and MM were an independent risk factor for extrapelvic recurrence in this population, and that patients with ITC or MM who did not receive adjuvant therapy recurred at a higher rate than those who did receive adjuvant therapy (although this finding was not statistically significant). Similar studies with similar findings exist (203-205). However, these are retrospective studies involving small numbers of patients with metastatic disease. Conclusions based on these results should be drawn with caution.

The study from Plante’s group differs from ours in that the patients underwent SLN mapping followed by PLND ± PALND, whereas our study adhered to the SLN algorithm. However, both studies demonstrated similar, excellent oncologic outcome for women with low-volume EC metastasis, leading us to question the therapeutic benefit of LND in patients with ITCs. The role of completion LND in patients with low-volume metastasis has been investigated in the breast cancer literature. The multicenter, randomized, non-inferiority, phase 3 IBCSG trial 23-01 was designed to determine whether no axillary dissection was non-inferior to axillary dissection in patients with one or more micrometastatic (≤2 mm) sentinel nodes and primary tumor of maximum 5 cm (134). The authors concluded that axillary dissection could be avoided in patients with early breast cancer and limited SLN involvement, with no adverse effect on survival. This concurs with the finding in Plante’s study that additional positive LNs were not detected in any cases of low-volume metastasis (201), and it also concurs with previously published findings from the same group demonstrating that only 5% of patients with SLN metastasis ≤2mm had additional metastatic LNs (196). Extrapolation of results from one disease site to another should be done with caution. However, the findings from the
IBCSG trial 23-01, in addition to our findings and the findings from Plante’s group, support the omission of a completion LND for EC patients with low-volume metastasis.

Our study of low-volume nodal metastasis (Paper V) in more than 800 women is the largest series published on this topic. Due to the low prevalence of low-volume metastasis it is not realistic to conduct a sufficiently powered prospective randomized trial comparing adjuvant therapy versus surveillance in this group. This question is further complicated by variability in practice and lack of consensus regarding the use of adjuvant therapy in EC. Collaborative registry studies may help answer these questions, and facilitate therapeutic decision-making in the future.
11. CONCLUSIONS

The management of EC is complex and challenging, highlighted by longstanding debate, and lack of consensus regarding surgical staging and adjuvant therapy regimens. In this era of personalized medicine and targeted therapies, the SLN approach is being incorporated into the surgical staging paradigm of EC in an effort to tailor treatment. The conclusions of this thesis are as follows:

- ICG and NIR are superior to blue dye alone in SLN mapping and detection, and should be preferred for use in the SLN approach, when available (Paper I).
- Increasing BMI results in poorer SLN detection for both ICG and blue dye. ICG provides a superior mapping rate across all BMI categories, further supporting its use in EC (Paper II).
- In the low-risk setting, application of an SLN algorithm increases the number of patients undergoing LN assessment, compared to a comprehensive LND approach. Fewer nodes are removed per patient via the SLN approach, with a detection rate of stage IIIC disease similar to that of the LND approach. Three-year survival rates are comparable between the two approaches (Paper III). These findings support the incorporation of an SLN approach in the surgical staging of this patient cohort.
- In intermediate-risk EC patients, fewer nodes are removed when an SLN approach is applied; however, a similar number of positive nodes are identified. Therefore, stage IIIC disease is diagnosed with similar frequency in both approaches, although more patients are diagnosed with stage IIIC2 via the LND approach (Paper IV). We conclude that identification of stage IIIC is not compromised when implementing a SLN approach. The significance of the fact that more patients were diagnosed with stage IIIC2 in the LND cohort is undetermined, and warrants further investigation.
- For EC patients with serous or clear-cell carcinoma (high-risk), pelvic nodes are assessed in a higher proportion of patients, and para-aortic nodes are assessed in a lower proportion of patients, with the SLN approach versus the LND approach. In this patient population, fewer nodes are removed per patient via the SLN approach, with a similar rate of stage IIIC disease (Paper IV). These findings support the incorporation of an SLN approach in the surgical staging of this patient cohort.
- In our study, the vast majority of EC patients with low-volume metastasis received adjuvant therapy. We are therefore unable to comment on the natural course of patients with untreated low-volume disease (Paper V).
- EC patients with low-volume metastasis, receiving adjuvant therapy, had similar oncologic outcomes as node-negative patients, and improved oncologic outcomes compared to patients with nodal macrometastasis (Paper V). Future collaborative efforts are underway to determine how the presence of low-volume metastasis should influence management of patients with EC.
- In conjunction with other studies, these studies have contributed to the evidence supporting adoption of ICG-only dye for staging of EC in major institutions in the US. This technique is being introduced in other countries.
12. FUTURE PERSPECTIVES

The results from several retrospective studies, and the prospective SENTI-ENDO and FIRES trials, have established the safety of applying an SLN algorithm in the surgical staging of EC, and demonstrate the high sensitivity and NPVs of this technique. As we move forward in further refining the SLN approach, we acknowledge the need for further investigation. We must continue to explore the significance of low-volume metastasis, particularly ITCs, to determine if, and how, this finding should guide adjuvant therapy. Multi-institutional registry studies are one way in which such determinations can be made. Such registries would also be useful for benchmarking, ensuring that a sufficient standard is achieved as an increasing number of practitioners and institutions implement the SLN approach.

Exciting advances in imaging technology and molecular markers may one day provide us with dyes and cameras capable of detecting metastatic nodes and tissue in real time. Another field of promise lies beyond histopathology—in the molecular assessment of SLNs. There may be prognostic molecular information within the SLNs. Such information can be incorporated into algorithms for adjuvant therapy and surveillance. As this field evolves, and we gain a better understanding of molecular classification in EC, new risk stratifications will likely emerge, allowing us to enhance care of patients with this disease.
13. RELATED PUBLICATIONS DURING THE PhD PERIOD

Data from the following abstracts were presented during the 2016 annual meeting of the Society of Gynecologic Oncology. Further statistical analysis and manuscript preparation are ongoing.

1. Multicenter study comparing survival outcomes between two nodal assessment methods in patients with deeply invasive endometrioid endometrial carcinoma: A sentinel lymph node algorithm versus a comprehensive pelvic and paraaortic lymphadenectomy

**Objectives:** We compared survival outcomes of patients with deeply invasive endometrioid endometrial cancer (EEC) staged using an SLN algorithm to those staged with a comprehensive pelvic and paraaortic nodal dissection to the renal veins. We also compared outcomes specifically in node-negative cases.

**Methods:** Patients diagnosed with deeply invasive (≥50% myoinvasion) EEC of any grade and surgically staged at 2 collaborating institutions were reviewed. The historical approach (2004-2008) at one institution was comprehensive pelvic and paraaortic lymphadenectomy to the renal veins (LND cohort). This other institution used an SLN algorithm and ultra-staging from 2006-2013 (SLN cohort). FIGO stage IV cases were excluded. Follow-up was limited to 3 years post-surgery. Outcomes were compared using inverse-probability weighting (IPW) derived from propensity scores to adjust for covariate imbalance between the 2 cohorts. IPW-adjusted Kaplan-Meier rates are reported. Cox proportional hazards models were fit.

**Results:** 186 patients were identified—82 in the SLN cohort and 104 in the LND cohort. Patient characteristics are listed in the table. Overall, 3-yr progression-free survival (PFS) for the SLN cohort was 77% (95%CI:67.1-88.3) vs 70% (95%CI:39.2-82.5) for the LND cohort (P=0.65). The 3-yr overall survival (OS) was 91% (95%CI:83-98.7) vs 78% (95%CI:69.5-88.5), respectively (P=0.06). On multivariate analysis, grade 3 vs 1/2 (HR 3.78, 95% CI 1.72–8.34), stage III vs I/II (HR 7.84, 95% CI 3.44–17.87), adjuvant chemotherapy ± brachytherapy (HR 0.26, 95% CI 0.09–0.75), and adjuvant chemotherapy with external beam radiation ± brachytherapy (HR 0.04, 95% CI <0.01–0.27) were associated with OS. Nodal assessment method was not independently associated with OS. In node-negative cases, 3-yr PFS was 74% vs 81%, respectively (P=0.26). 3-yr OS was 91% vs 85%, respectively (P=0.4). The use of adjuvant therapy in node-negative cases was not statistically associated with either PFS or OS.

**Conclusions:** Survival is not impaired by using an SLN algorithm to stage patients with deeply invasive endometrioid endometrial adenocarcinoma. Survival is excellent in node-negative cases regardless of nodal assessment method. The role of adjuvant therapy in these node-negative cases does not seem to impact survival.
Multicenter study comparing oncologic outcomes in patients with serous and clear cell endometrial carcinoma between two nodal assessment methods: A sentinel lymph node algorithm versus a comprehensive pelvic and paraaortic lymphadenectomy

**Objectives:** To compare survival with nodal assessment using a sentinel lymph node (SLN) algorithm compared to comprehensive pelvic and paraaortic lymph node dissection in patients diagnosed with serous and clear cell endometrial carcinoma, and to compare survival in the node-negative cases (NN).

**Methods:** Patients with newly diagnosed serous and clear cell endometrial cancer and surgically staged at two collaborating institutions were reviewed. The historical approach (2004-2008) at one institution was a comprehensive pelvic and paraaortic lymphadenectomy to the renal veins (LND cohort). An SLN algorithm and ultra-staging was used at the other institution from 2006-2013 (SLN cohort). FIGO stage IV cases were excluded. Overall survival (OS) and progression-free survival (PFS), restricted to the first 3 years after surgery, were compared between cohorts using inverse-probability weighting (IPW) derived from propensity scores to adjust for covariate imbalance between cohorts. IPW-adjusted Kaplan-Meier rates are reported. Cox models were fit using the IPW pseudo-cohorts with additional covariate adjustment.

**Results:** 214 patients were identified (118 SLN cohort, 96 LND cohort; Table). The 3-yr PFS rates were 69% and 80% in the SLN and LND cohorts, respectively. The 3-yr OS rates were 88% and 77%, respectively. The adjusted hazard ratio (aHR) for the association of surgical approach (LND vs SLN) with progression and death was 0.72 (0.32-1.59; p=0.41) and 2.35 (0.96-6.00; p=0.07), respectively. In NN cases, adjuvant therapy differed between the 2 cohorts, with 82% and 29% in the SLN and LND cohorts receiving chemotherapy ± some form of radiotherapy. In these NN cases, 3-yr PFS rates were 73% and 91% in the SLN and LND cohorts, respectively. The 3-yr OS rates were 89% and 86%, respectively. Among the NN cases, the aHR for the association of surgical approach (LND vs SLN) with progression and death was 0.32 (0.09-1.15; p=0.08) and 1.40 (0.45-4.33; p=0.56), respectively.

**Conclusions:** Survival does not appear to be compromised when using an SLN algorithm to evaluate patients with serous or clear cell endometrial carcinomas overall. However, SLN may be associated with a decreased PFS but similar OS in NN cases despite the majority receiving chemotherapy. Continued investigation is needed to further explain this finding.
Role of lymphadenectomy and adjuvant treatment in high-risk endometrial cancer with positive lymph nodes: Comparison of an historical series with comprehensive surgical staging and a contemporary series with sentinel lymph nodes

**Objectives:** To compare survival outcomes with systematic lymphadenectomy vs sentinel lymph node (SLN) mapping in patients with high-risk (HR) endometrial cancer and positive lymph nodes.

**Methods:** All patients treated for endometrial cancer at 2 different institutions were reviewed. At one institution, a historical series (2004–2008) was treated with systematic pelvic and para-aortic lymphadenectomy (LND cohort). At the second institution, patients were treated using an SLN mapping algorithm from 2006-2013 (SLN cohort). “HR” was defined as endometrioid adenocarcinoma with myometrial invasion ≥50% or non-endometrioid histology. Lymph node metastases >0.2 mm were considered node-positive. Patients with isolated tumor cells (ITCs), stage IV disease, synchronous cancer, or who underwent neoadjuvant therapy were excluded. Associations with OS and PFS were evaluated using Cox models. Outcomes were compared using inverse-probability weighting (IPW) derived from propensity scores to adjust for covariate imbalance between the 2 cohorts. IPW-adjusted Kaplan-Meier rates are reported.

**Results:** 388 patients with HR endometrial cancers were identified (200 LND and 188 SLN). Of these, 93 had positive lymph nodes (50 [25%] and 43 [23%], respectively). Chemoradiation (CT+RT) was used in 22% of LND vs 49% of SLN patients (p=0.007). At univariate analysis, SLN, grade 1-2, negative washings, and postoperative CT+RT were significantly predictive of better OS (p<0.05), while grade 1-2 and postoperative CT+RT predicted PFS (p<0.05). On multivariate analysis, independent predictors of OS and PFS were FIGO grade 3 and adjuvant therapy (p<0.05). OS and PFS at 3-years were 81% and 72% in patients who had CT+RT, and 45% and 61% in patients with no adjuvant therapy. 3-year OS was 61% (95% CI 46-80.2) in the LND cohort vs 87% (95% CI 74.9-100) in the SLN cohort (HR 3.09; 95%CI 0.96, 9.94; p=0.06). 3-year PFS was 49% (95% CI 33.7-71.4) and 70% (95% CI 53.8-90.3), respectively (HR 1.68; 95%CI 0.70, 4.01; p=0.25).

**Conclusions:** Our results suggest that using an SLN mapping algorithm in patients with node-positive HR endometrial cancer provides similar survival outcomes and lymphatic recurrence compared to extensive lymphadenectomy. Moreover, adjuvant CT+RT seems to be instrumental in improving postoperative outcome.
14. REFERENCE LIST


https://link.springer.com/content/pdf/10.1245%2Fs10434-017-5825-3.pdf


PAPERS
Comparison of a sentinel lymph node and a selective lymphadenectomy algorithm in patients with endometrioid endometrial carcinoma and limited myometrial invasion

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HIGHLIGHTS

• SLN algorithm in low-risk endometrial carcinoma allows for lymph node assessment in more patients.
• Fewer lymph nodes are removed in patients undergoing an SLN approach vs selective lymphadenectomy.
• Oncologic outcomes are similar for SLN algorithm compared to selective lymphadenectomy.

Abstract

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Objective. To assess clinicopathologic outcomes between two nodal assessment approaches in patients with endometrioid endometrial carcinoma and limited myoinvasion.

Methods. Patients with endometrial cancer at two institutions were reviewed. At one institution, a complete pelvic and para-aortic lymphadenectomy to the renal veins was performed in select cases deemed at risk for nodal metastasis due to grade 3 cancer and/or primary tumor diameter \( N \leq 2 \) cm (LND cohort). This is a historic approach at this institution. At the other institution, a sentinel lymph node mapping algorithm was used per institutional protocol (SLN cohort). Low risk was defined as endometrioid adenocarcinoma with myometrial invasion \( b 50\%\). Macrometastasis, micrometastasis, and isolated tumor cells were all considered node-positive.

Results. Of 1135 cases identified, 642 (57%) were managed with an SLN approach and 493 (43%) with an LND approach. Pelvic nodes (PLNs) were removed in 93% and 58% of patients, respectively (\( P < 0.001 \)); para-aortic nodes (PANs) were removed in 14.5% and 50% of patients, respectively (\( P < 0.001 \)). Median number of PLNs removed was 6 and 34, respectively (both \( P < 0.001 \)). Metastasis to PLNs was detected in 5.1% and 2.6% of patients, respectively (\( P = 0.03 \)), and to PANs in 0.8% and 1.0%, respectively (\( P = 0.75 \)). The 3-year disease-free survival rates were 94.9% (95% CI, 92.4–97.5) and 96.8% (95% CI, 95.2–98.5), respectively.

Conclusions. Our findings support the use of either strategy for endometrial cancer staging, with no apparent detriment in adhering to the SLN algorithm. The clinical significance of disease detected on ultrastaging and the role of adjuvant therapy is yet to be determined.

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A B S T R A C T

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1. Introduction

The value of surgical staging in endometrial carcinoma is a subject of debate; as such, there is no uniform approach to lymph node assessment in clinically uterine-confined disease. Staging strategies range from no lymphadenectomy, with the use of preoperative imaging or
Intraoperative frozen section to guide management, to comprehensive lymphadenectomy. The results of two randomized trials showed no improvement in disease-free or overall survival for patients with early-stage endometrial carcinoma who had undergone systematic pelvic lymphadenectomy [1,2]. However, in a recent Classification and Regression Tree (CART) analysis, surgical staging, but not the total number of lymph nodes removed, was found to be the most important prognostic factor for overall survival in endometrial cancer [3]. Uterine factors have been shown to be less accurate predictors of recurrence than lymph node status [4,5]. Taken together, assessing nodal status at the time of initial staging in these patients is imperative.

In the landmark study by Creasman et al., pelvic nodal metastasis was found in 5% of patients with superficial myometrial invasion [6]. When taking into consideration the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system, Chi et al. found that 5.5% of patients with disease of endometrioid histology, all grades and myometrial invasion ≤50%, had nodal metastasis [7]. Despite the low incidence of nodal disease in these low-risk patients, omitting lymphadenectomy from their surgical management would result in inadequate staging, and consequently either preclude administration of adjuvant therapy when warranted or lead to the overtreatment of certain patients. Comprehensive lymphadenectomy is associated with intraoperative complications, such as increased operating time, nerve and vessel injury, higher blood loss, and postoperative morbidity [8]. The rate of long-term lymphedema directly attributed to lymphadenectomy was recently reported to be 23% [9]. The morbidity associated with comprehensive lymphadenectomy is of particular concern in the low-risk population.

Sentinel lymph node (SLN) mapping is emerging as an acceptable approach for nodal assessment in endometrial carcinoma. This is reflected by the inclusion of an SLN algorithm in the 2014 National Comprehensive Cancer Network (NCCN) guidelines for the management of endometrial cancer [10]. However, when introducing a novel management strategy, we must take great care not to compromise oncologic outcome or inflict harm on our patients. With this in mind, we conducted the following study, in which we sought to assess and compare the clinicopathologic outcomes between two nodal assessment approaches in patients with "low-risk" endometrial carcinoma as defined by endometrioid histology and limited myoinvasion.

2. Materials and methods

Patients with low-risk endometrial cancer at two institutions were identified using the uterine cancer institutional databases at the Mayo Clinic (Mayo) and Memorial Sloan Kettering Cancer Center (MSK). Low risk was defined as endometrioid adenocarcinoma of any grade with myometrial invasion ≤50%. At one of the institutions, tumor size is not routinely assessed intra- or postoperatively. Therefore, tumor size was not included in our risk classification. From the Mayo Clinic, the historic lymph node dissection (LND) cohort encompassed the years 2004 through 2008. The SLN cohort from MSK encompassed the years 2006 through 2013.

The Mayo Clinic historical surgical algorithm for the study period was to perform a hysterectomy, bilateral salpingo-oophorectomy (BSO), peritoneal cytology, and bilateral pelvic and para-aortic lymphadenectomy. A gynecologic oncology pathologist performed frozen section of the uterine specimen to determine tumor size and depth of myometrial invasion. Lymphadenectomy was omitted in patients with disease of endometrioid histology with grade 1 disease in which there was no myometrial invasion, and in patients with disease of endometrioid histology, grade 1 or 2, with ≤50% myometrial invasion and tumor diameter ≤2 cm (Supplementary Fig. 1) [11]. At MSK, a previously published SLN algorithm was used per institutional protocol (Supplementary Fig. 2) [12]. Lymphatic mapping was performed by injecting blue dye or indocyanine green (ICG) into the cervical stroma at superficial and deep levels at the 3- and 9-o’clock positions for a total of 4 mL. Identified SLNs were excised and evaluated by the institutional SLN Pathologic Processing Protocol [13]. Any suspicious nodes were removed regardless of mapping. In cases with no mapping on a hemi-pelvis, a side-specific LND was performed. Para-aortic LND was performed at the surgeon’s discretion.

Macrometastasis, micrometastasis, and isolated tumor cells (ITCs) were all considered node-positive for this analysis. ITCs were defined as cells measuring ≤0.2 mm, as seen on corresponding hematoxylin and eosin (H&E) sections and not just immunohistochemical (IHC) staining. Micrometastasis was defined as tumor within a lymph node larger than 0.2 mm but less than 2.0 mm in greatest diameter. Notably, when the tumor measurement was not delineated in the pathology report and the terms “isolated tumor cells” and “micrometastasis” were not used, a determination was made based on the pathology report, with clarification from a gynecologic pathologist when needed. For example, “rare scattered tumor cells” were classified as ITCs, whereas “diffuse clusters of cells” were defined as micrometastases. Lymph nodes with a tumor burden ≥2.0 mm were reported as metastatic lymph nodes without further delineation of number or cells or the size of the metastasis. Cytokeratin-positive cells not seen on H&E were considered node-negative. Adjuvant therapy was administered per recommended institutional guidelines.

We compared patient-, treatment-, and disease-specific parameters between cohorts using the chi square or Fisher exact test for categorical variables, the two-sample t test for age and body mass index (BMI), and the Wilcoxon rank-sum test for number of nodes removed and number of positive nodes. Disease-free survival, disease-specific survival, and overall survival were evaluated within the first 3 years after surgery. Survivalship was estimated using the Kaplan-Meier method and compared among the cohorts using the log-rank test. All calculated P values were two-sided, and P values < 0.05 were considered statistically significant.

3. Results

A total of 1135 cases were identified: 642 in the SLN cohort and 493 in the selective LND cohort. Patient and tumor characteristics are shown in Table 1. Patients in the SLN cohort were significantly younger (mean age, 59.6 vs 63.1 years), had an overall lower mean BMI (31.7 vs 35.4 kg/m²), and more likely to not have myometrial invasion (57.0% vs 29.4%) compared with patients in the LND cohort (P < 0.001 for each characteristic). The distribution of FIGO grade was similar in the two cohorts. In the SLN cohort, 15.2% of patients had lymphovascular space invasion (LV1) compared with 3.0% in the LND cohort (P < 0.001). There are institutional differences in the diagnostic criteria for the presence of LV1. Pelvic lymph nodes were excised in 92.8% of the patients in the SLN cohort compared with 57.8% in the LND cohort (P < 0.001; Table 2). Among those who underwent pelvic nodal assessment, the median number of pelvic lymph nodes excised per patient was 6 (interquartile range [IQR]: 3.11) in the SLN cohort versus 34 (IQR: 26.45) in the LND cohort (P < 0.001). Positive pelvic lymph nodes were detected in 5.1% (33/642; 95% CI, 3.4–6.9%) and 2.6% (13/493; 95% CI, 1.2–4.1%) of patients, respectively (P = 0.03). These last percentages are not identical to the detection rate of stage IIIC1 since some patients with positive pelvic lymph nodes also had positive para-aortic lymph nodes and belong in stage IIIC2. The median number of positive pelvic nodes per patient among those patients with positive pelvic nodes was 1 (IQR: 1.2) for both groups.

Para-aortic lymph nodes were excised in 14.5% of the patients in the SLN cohort compared with 49.7% in the LND cohort (P < 0.001). Among those who underwent para-aortic nodal assessment, the median number of para-aortic lymph nodes excised was 5 (IQR: 3.8) in the SLN cohort versus 16 (IQR: 11.23) in the LND cohort (P < 0.001). Positive para-aortic lymph nodes were detected in 0.8% (5/642; 95% CI, 0.1–1.5%) and 1.0% (5/493; 95% CI, 0.1–1.9%) of patients, respectively (P = 0.75). Among the patients with positive para-aortic nodes (5 in each cohort), 4 in
the SLN cohort had a single positive node and 1 had 2 positive nodes; in the LND cohort, 2 patients had 1 positive node, 1 had 3 positive nodes, and 2 had 5 positive nodes. Of the 36 cases with positive pelvic or para-aortic nodes in the SLN cohort, 11 were positive by macrometastasis, 2 by micrometastasis, and 23 by ITCs (Supplementary Table 1).

Adjuvant therapy was administered to 27.1% of patients in the SLN cohort and 10.8% of patients in the LND cohort ($P < 0.001$). Intravaginal brachytherapy (IVRT) alone was administered to 17.6% of patients in the SLN cohort vs 6.1% in the LND cohort ($P < 0.001$). The various combinations of adjuvant therapy are shown in Table 3.

The median follow-up time was 2.1 years (IQR: 1.2, 3.3) in the SLN cohort compared with 3.5 years (IQR: 2.5, 4.9) in the LND cohort (Fig. 1).

Table 1

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SLN cohort</th>
<th>LND cohort</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>59.6 (9.9)</td>
<td>63.1 (11.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Mean BMI, kg/m$^2$ (SD)</td>
<td>31.7 (8.4)</td>
<td>35.4 (9.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Final FIGO grade, N (%)</td>
<td>450 (70.1)</td>
<td>336 (68.2)</td>
<td>0.69</td>
</tr>
<tr>
<td>1</td>
<td>146 (22.7)</td>
<td>123 (24.9)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>46 (7.4)</td>
<td>34 (6.9)</td>
<td></td>
</tr>
<tr>
<td>Myometrial invasion, N (%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td>None</td>
<td>366 (57.0)</td>
<td>145 (29.4)</td>
<td></td>
</tr>
<tr>
<td>$&lt; 0$ or $&gt; 50$%</td>
<td>276 (42.0)</td>
<td>348 (70.6)</td>
<td></td>
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<tr>
<td>Lymphovascular space invasion, N (%)</td>
<td>&lt;0.001</td>
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<tr>
<td>No</td>
<td>523 (81.7)</td>
<td>478 (97.0)</td>
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<tr>
<td>Yes</td>
<td>94 (14.2)</td>
<td>15 (3.0)</td>
<td></td>
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<tr>
<td>Cervical invasion, N (%)</td>
<td>0.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No invasion</td>
<td>624 (97.2)</td>
<td>485 (98.4)</td>
<td></td>
</tr>
<tr>
<td>Mucosa</td>
<td>13 (2.0)</td>
<td>5 (1.0)</td>
<td></td>
</tr>
<tr>
<td>Cervical stroma</td>
<td>5 (0.8)</td>
<td>3 (0.6)</td>
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<td>Peritoneal cytology, N (%)</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
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<tr>
<td>Negative</td>
<td>550 (85.7)</td>
<td>370 (75.1)</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>68 (10.6)</td>
<td>30 (6.1)</td>
<td></td>
</tr>
<tr>
<td>Not sampled</td>
<td>24 (3.7)</td>
<td>93 (18.9)</td>
<td></td>
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<tr>
<td>1988 FIGO stage, N (%)</td>
<td>&lt;0.001</td>
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<tr>
<td>IA</td>
<td>341 (53.1)</td>
<td>139 (28.2)</td>
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<tr>
<td>IB</td>
<td>192 (29.9)</td>
<td>308 (62.5)</td>
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</tr>
<tr>
<td>IC</td>
<td>–</td>
<td>–</td>
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<tr>
<td>IIA</td>
<td>2 (0.3)</td>
<td>4 (0.8)</td>
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<tr>
<td>IIB</td>
<td>6 (0.9)</td>
<td>1 (0.2)</td>
<td></td>
</tr>
<tr>
<td>IIA/B</td>
<td>65 (10.1)</td>
<td>25 (5.1)</td>
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<tr>
<td>IIB/C</td>
<td>36 (5.6)</td>
<td>14 (2.8)</td>
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<tr>
<td>IVC</td>
<td>–</td>
<td>2 (0.4)</td>
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<tr>
<td>2009 FIGO stage, N (%)</td>
<td>0.02</td>
<td></td>
<td></td>
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<tr>
<td>IA</td>
<td>595 (92.7)</td>
<td>471 (95.5)</td>
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<tr>
<td>IB</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>8 (1.2)</td>
<td>2 (0.4)</td>
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<tr>
<td>IIB/B</td>
<td>3 (0.5)</td>
<td>4 (0.8)</td>
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<td>31 (4.8)</td>
<td>9 (1.8)</td>
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<tr>
<td>IIB/C2</td>
<td>5 (0.8)</td>
<td>5 (1.0)</td>
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</tr>
<tr>
<td>IV</td>
<td>–</td>
<td>2 (0.4)</td>
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</tbody>
</table>

SLN, sentinel lymph node; LND, lymph node dissection; BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; SD, standard deviation.

Table 2

<table>
<thead>
<tr>
<th>Lymphadenectomy characteristics and adjuvant therapy.</th>
<th>SLN cohort</th>
<th>LND cohort</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic LND, N (%)</td>
<td>–</td>
<td>–</td>
<td>&lt;0.001</td>
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<tr>
<td>No</td>
<td>46 (7.2)</td>
<td>208 (42.2)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>596 (92.8)</td>
<td>285 (57.8)</td>
<td></td>
</tr>
<tr>
<td>Median number of pelvic nodes removed among patients undergoing pelvic LND (IQR)</td>
<td>6 (3, 11)</td>
<td>34 (26, 45)</td>
<td>&lt;0.001</td>
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<tr>
<td>Positive pelvic nodes, N (%)</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No or pelvic LND not performed</td>
<td>609 (94.9)</td>
<td>480 (97.4)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33 (5.1)</td>
<td>13 (2.6)</td>
<td></td>
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<tr>
<td>Positive pelvic nodes among patients undergoing pelvic LND, N (%)</td>
<td>0.54</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>563 (95.4)</td>
<td>272/285 (95.4)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>33/596 (5.5)</td>
<td>13/285 (4.6)</td>
<td></td>
</tr>
<tr>
<td>Para-aortic LND, N (%)</td>
<td>&lt;0.001</td>
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<td></td>
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<tr>
<td>No</td>
<td>549 (85.5)</td>
<td>248 (50.3)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>93 (14.5)</td>
<td>245 (49.7)</td>
<td></td>
</tr>
<tr>
<td>Median number of para-aortic nodes removed among patients undergoing para-aortic LND (IQR)</td>
<td>5 (3, 8)</td>
<td>16 (11, 22)</td>
<td>&lt;0.001</td>
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<tr>
<td>Positive para-aortic nodes, N (%)</td>
<td>0.75</td>
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<tr>
<td>No or para-aortic LND not performed</td>
<td>637 (99.2)</td>
<td>488 (99.0)</td>
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<tr>
<td>Yes</td>
<td>5 (0.8)</td>
<td>5 (1.0)</td>
<td></td>
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<tr>
<td>Positive para-aortic nodes among patients undergoing para-aortic LND, N (%)</td>
<td>0.15</td>
<td></td>
<td></td>
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<tr>
<td>No</td>
<td>88/93 (4.8)</td>
<td>240/245 (98.0)</td>
<td></td>
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<tr>
<td>Yes</td>
<td>5/93 (5.4)</td>
<td>5/245 (2.0)</td>
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</tbody>
</table>

SLN, sentinel lymph node; LND, lymph node dissection; IQR, interquartile range.
Recurrences.

<table>
<thead>
<tr>
<th>Disease progression/recurrence within 3 years, N (%)</th>
<th>SLN cohort N = 642</th>
<th>LND cohort N = 493</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-year disease-free survival, % (95% CI)</td>
<td>94.9 (92.4–97.5)</td>
<td>96.8 (95.2–98.5)</td>
<td>0.35</td>
</tr>
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<td>Route of first recurrence, N</td>
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<tr>
<td>Hematogenous only</td>
<td>4 (2.5)</td>
<td>3 (3.1)</td>
<td>0.41</td>
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<tr>
<td>Hematogenous and lymphatic</td>
<td>1 (0.6)</td>
<td>2 (2.0)</td>
<td></td>
</tr>
<tr>
<td>Hematogenous and peritoneal</td>
<td>1 (0.6)</td>
<td>1 (0.8)</td>
<td></td>
</tr>
<tr>
<td>Lymphatic only</td>
<td>1 (0.6)</td>
<td>2 (2.0)</td>
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<tr>
<td>Lymphatic and peritoneal</td>
<td>1 (0.6)</td>
<td>1 (0.8)</td>
<td></td>
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<tr>
<td>Vaginal only</td>
<td>7 (4.3)</td>
<td>9 (6.9)</td>
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<tr>
<td>Vaginal and peritoneal</td>
<td>–</td>
<td>1 (0.8)</td>
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<tr>
<td>Peritoneal only</td>
<td>1 (0.6)</td>
<td>4 (4.1)</td>
<td></td>
</tr>
</tbody>
</table>

SLN, sentinel lymph node; LND, lymph node dissection.

In most institutions, low-risk endometrial cancer is a postoperative diagnosis based on final pathology. The goal of staging women with uterine-confined endometrial cancer is to do as little harm as possible intraoperatively while evaluating nodal status adequately. Such evaluation is important to allow for the tailoring of adjuvant therapy, as uterine factors have been shown to be less accurate predictors of recurrence compared with lymph node status [45]. The Mayo Clinic has published extensively on their approach to intraoperative frozen section to triage patients to no lymphadenectomy or comprehensive lymphadenectomy [14,15]. In particular, the intraoperative utilization of tumor diameter, in combination with frozen section, can help select patients (27% of the total endometrial cancer population) who can potentially avoid surgical staging [14]. Moreover, even in the absence of frozen section, the intraoperative use of tumor diameter may select those patients with preoperative endometrioid grade 1 or 2 cancer who may not benefit from surgical staging [16]. A French prospective multicenter study has shown that SLN biopsy can accurately diagnose lymph node involvement in patients with low-risk or intermediate-risk endometrial cancer [17], as have other prospective and retrospective studies [18–20]. It is of great importance to adhere to a surgical SLN algorithm to minimize the false-negative rate when applying the SLN technique [20]. The SENTI-ENDO study’s long-term results support the relevance of SLN biopsy on surgical management, as well as on indications for adjuvant therapies [5].

In our study, we were able to retrospectively compare the historical Mayo LND algorithm to the MSK institutional SLN algorithm [12]. We found that for this low-risk cohort, the SLN algorithm results in significantly more patients having pelvic nodes excised, a lower number of lymph nodes removed per patient, and a higher detection rate in FIGO 2009 stage IIB1 disease. Theoretically, SLN mapping should reduce the risk of lower extremity lymphedema, but this has not yet been objectively assessed. When looking at para-aortic nodes, the SLN algorithm results in fewer patients having nodes removed from this anatomic basin, a lower number of nodes excised per patient, and a similar detection rate in stage IIB2 disease compared with the Mayo LND algorithm. Interestingly, the median number of positive pelvic nodes was the same with both approaches (1; IQR: 1.2), suggesting that the SLN approach is able to identify the positive pelvic nodes in cases with FIGO 2009 stage IIB1 disease, and that it is an adequate method for surgical staging. In fact, isolated para-aortic metastases, with negative pelvic lymph nodes, are extremely rare in patients with endometrioid cancer and limited myometrial invasion [21]. For the para-aortic nodes, the median number of positive nodes was 1 versus 3, respectively, suggesting that in those patients with a positive para-aortic lymph node, there may be residual nodal metastasis with the
SLN approach. The importance of this latter finding on disease-free survival and overall survival is unclear, as these patients will receive tailored adjuvant therapy.

The differences between cohorts in age and BMI may have influenced the disease-specific survival in disfavor of the LND cohort. The disproportion of patients without myometrial invasion between the groups may also have played a favorable role for the SLN cohort. However, the SLN cohort had a significantly higher number of patients with LVI, which is a negative predictive factor. There is institutional variation in the pathologic criteria for the presence of LVI, which limits the interpretation of this finding. Regardless, disease-specific survival was excellent in both cohorts, with a small number of patients dying from their disease. Adjusting for other factors was not possible because of this low number of deaths. At a minimum, this favorable disease-specific survival outcome in the SLN cohort provides additional reassurance that an SLN mapping algorithm will not lead to unnecessary deaths due to false-negative staging. This finding would have to be proven in a randomized trial.

The SLN cohort received significantly more adjuvant therapy, mainly IVRT, but also more chemotherapy with or without radiation therapy, compared with the LND cohort. When we excluded the use of IVRT, however, differences in adjuvant treatment were minimal. There may be institutional differences in guiding the administration of adjuvant therapy. Irrespective of this, the higher number of patients with documented LVI in the MSK cohort was responsible for the increased administration of IVRT, and the increased use of chemotherapy with or without radiation therapy corresponds to the higher number of patients with detected stage IIIC disease. It is extremely important to consider the potential added morbidity of any adjuvant therapies, especially in the presence of low-volume metastases in a low-risk cohort of endometrial cancer patients.

Twenty-five of 36 patients with stage IIIC disease in the SLN cohort were staged based on findings of low-volume metastasis. The clinical significance of low-volume metastasis and how it should guide adjuvant therapy remains uncertain. However, in a retrospective case-control surgicopathological study of women with early-stage cervical cancer, low-volume metastases were found to be an important risk factor of tumor recurrence in patients with no apparent lymph node metastasis [22]. In other studies, immunohistochemical expression of cyto keratin in lymph nodes with undetected metastasis predicted occult metastasis and was a risk factor for recurrence in early-stage endometrial cancer [23,24]. These findings, though limited in numbers, support the removal of low-volume metastasis and adjuvant treatment for these patients. However, in all these reported cases with micrometastases, recurrences occurred when the primary cancers presented with high-risk characteristics and may not specifically apply to our series of low-risk patients [23,25]. The optimal management of patients with ITCs and micrometastasis in endometrial cancer remains to be determined.

There are limitations to this retrospective study. It is a comparison between two institutions with two sets of pathologists evaluating the specimens; this may have influenced the discrepancy in reported uter ine characteristics, such as the large difference in the number of tumors with LVI. Tumor size was not available in the SLN cohort, and subsequently the comparison of this subgroup could not be performed. Another limitation is the lack of standardized postoperative treatment approaches both between the two institutions and within each one. This heterogeneity could likely have affected our survival outcomes. The median follow-up of the SLN cohort was significantly shorter than that of the LND cohort. However, both follow-up times were >24 months, and the majority of recurrences will occur during this period, and the evaluation of outcomes in this analysis was limited to the first 36 months [25,26].

It is important to recognize that the Mayo Clinic algorithm described here is historical, and it has evolved since the study time period in this report. In 2009, the Mayo Clinic modified their protocol, leading to fewer patients requiring a para-aortic lymphadenectomy. In brief, a pelvic and para-aortic lymphadenectomy is performed in patients with either deep (>50%) myoinvasion or Type 2 carcinoma. In cases without either of these features, a pelvic lymphadenectomy is performed if any one of 3 other features are found (cervical invasion, FIGO grade 3 (any myoinvasion), or tumor diameter >2 cm). A para-aortic lymphadenectomy is reserved only in these cases if they are found to have pelvic nodal metastases. SLN mapping has been increasingly incorporated since 2013 [27].

In conclusion, when comparing these two approaches to surgical staging of low-risk endometrial carcinoma, we found that pelvic lymph nodes were excised in a larger proportion of patients when applying an SLN algorithm versus a selective LND algorithm; however, fewer lymph nodes were removed per patient with the SLN algorithm, the algorithm yielded a higher detection rate in stage IIIC1 disease, and the median number of positive pelvic nodes per patient was the same. For stage IIIC2 disease, both algorithms achieved the same detection rate. The application of an SLN algorithm does not appear to compromise oncologic outcomes within this short follow-up. Our findings strongly support the use of an SLN mapping algorithm, instead of a comprehensive lymphadenectomy, in patients with endometrioid
endometrial cancer and myometrial invasion <50%. Of note, patients with grade 1 or 2 cancer and tumor diameter of 2 cm or less may be able to avoid any type of nodal assessment if they can be reliably identified pre- and intraoperatively. The clinical significance of disease detected on ultrastaging and the role of adjuvant therapy in these cases is yet to be determined. Prospective assessment of the SLN algorithm is needed and currently underway [28].

Conflict of interest statement
The authors have no conflicts of interest to disclose.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.ygyno.2015.12.028.

References
Comparison of a sentinel lymph node mapping algorithm and comprehensive lymphadenectomy in the detection of stage IIIC endometrial carcinoma at higher risk for nodal disease

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HIGHLIGHTS
• The SLN algorithm does not compromise overall detection of higher-risk Stage IIIC EC
• Stage IIIC2 is detected more frequently by LND than by SLN in deeply invasive EC
• Use of an SLN algorithm may be considered in the detection of nodal metastasis

Objective. To determine if a sentinel lymph node (SLN) mapping algorithm will detect metastatic nodal disease in patients with intermediate−high-risk endometrial carcinoma.

Methods. Patients were identified and surgically staged at two collaborating institutions. The historical cohort (2004−2008) at one institution included patients undergoing complete pelvic and paraaortic lymphadenectomy to the renal veins (LND cohort). At the second institution an SLN mapping algorithm, including pathologic ultrastaging, was performed (2006−2013) (SLN cohort). Intermediate-risk was defined as endometrioid histology (any grade), ≥50% myometrial invasion; high-risk as serous or clear cell histology (any myometrial invasion). Patients with gross peritoneal disease were excluded. Isolated tumor cells, micro-metastases, and macro-metastases were considered node-positive.

Results. We identified 210 patients in the LND cohort, 202 in the SLN cohort. Nodal assessment was performed for most patients. In the intermediate-risk group, stage IIIC disease was diagnosed in 30/107 (28.0%) (LND), 29/82 (35.4%) (SLN) (P = 0.28). In the high-risk group, stage IIIC disease was diagnosed in 20/103 (19.4%) (LND), 26 (21.7%) (SLN) (P = 0.68). Paraaortic lymph node (LN) assessment was performed significantly more often in intermediate−/high-risk groups in the LND cohort (P < 0.001). In the intermediate-risk group, paraaortic LN metastases were detected in 20/96 (20.8%) (LND) vs. 3/28 (10.7%) (SLN) (P = 0.23). In the high-risk group, paraaortic LN metastases were detected in 13/82 (15.9%) (LND) and 10/56 (17.9%) (SLN) (%; P = 0.76).

Conclusions. SLN mapping algorithm provides similar detection rates of stage IIIC endometrial cancer. The SLN algorithm does not compromise overall detection compared to standard LND.

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1. Background

Endometrial cancer is the most common gynecologic malignancy in the United States. Approximately 60,050 women were diagnosed with endometrial cancer in 2016 [1]. Surgical staging has been the standard modality for evaluation of metastatic disease since 1968, when the International Federation of Gynecology and Obstetrics (FIGO) changed the staging system for endometrial cancer from clinical to surgical-pathologic [2]. Important prognostic information can be obtained from surgical staging, facilitating identification of patients who stand to benefit from adjuvant therapy.

An important component of surgical staging in endometrial cancer includes pelvic and paraaortic lymphadenectomy (LND). Conventionally, systematic LND includes dissection of the pelvic and paraaortic lymph nodes up to the renal veins; however, the extent of LND is the subject of ongoing debate [3]. It is known that complete LND poses significant risks to the patient, and is associated with high rates of morbidity [3]. Rates of complications vary in the literature, but a significant proportion of patients who undergo a completion LND sustain procedure-related complications, including chronic lymphedema, lymphocysts, infection, and nerve and vascular injuries [4–10]. Complication rates increase in patients who receive adjuvant radiation therapy after LND [7,11]. Despite these risks, surgical assessment of lymph nodes is considered important in patients with endometrial cancer, especially in those with high-risk pathologic features, because the presence of nodal metastasis is highly prognostic and will influence decision-making with respect to adjuvant therapy.

The rate of nodal metastasis in patients with endometrial carcinoma clinically confined to the uterus was determined by landmark studies from the Gynecologic Oncology Group in the 1980s [12,13]. Tumor grade and depth of myometrial invasion were associated with a risk of nodal metastasis, but this finding was based on final uterine pathology. It is important to note that these were surgically-pathologic studies focused on assessing patterns of spread, and the authors did not intend to support routine LND. A study from the Mayo Clinic found that, despite skepticism evident in the published literature, intraoperative frozen section was a reliable tool for use in surgical staging and intraoperative decision-making. However, it is unclear whether this can be used as reliably outside of major specialty institutions that bring significant pathologic expertise and experience to bear [14]. Multiple algorithms have been suggested to determine the need for nodal assessment [15].

There is ongoing controversy about the utility of a systematic pelvic and paraaortic LND in patients at risk for lymphatic dissemination [16] vs. no LND at all [17,18]. The major criticism of the “PORTEC” [17] approach was its inability to identify patients with lymphatic dissemination, whereas a comprehensive LND provides accurate nodal assessment and, some argue, a therapeutic benefit. However, the procedure requires extensive surgery, with associated morbidity. Furthermore, in recent randomized trials, pelvic LND alone was not associated with survival [18,19].

SLN mapping has emerged as an alternative to comprehensive LND in the surgical assessment of lymph nodes [20]. Recently, we reported our comparison of an SLN mapping algorithm vs. a selective, comprehensive LND approach in patients at low risk for nodal metastases (i.e., endometrioid histology of any grade and size with limited myoinvasion (<50%) [21]. In these “low-risk” patients, the detection of nodal metastasis was at least similar to, if not better than, patients in the SLN cohort. More importantly, recurrence rates and survival were the same, supporting the use of an SLN mapping algorithm in “low-risk” patients who are nevertheless at some risk of lymphatic dissemination. There may even be a group of extremely low-risk patients for whom SLN mapping is unnecessary.

Compared to this “low-risk” group, the risk of nodal metastasis is greater in patients with deeper myometrial invasion (≥50%), and in patients with serous and clear cell carcinomas with any invasion [22]. Concern remains about the ability of the SLN algorithm to detect nodal metastasis in the setting of these higher-risk carcinomas, particularly because of the greater risk of paraaortic dissemination, and possibly isolated paraaortic metastases, in select subgroups [22].

We sought to retrospectively compare the rate of detection of lymph node-positive disease in patients with deeply invasive (≥50%) endometrioid cancer and patients with serous and clear cell endometrioid cancer, who were historically treated at one institution using a selective yet comprehensive, pelvic and paraaortic LND to the renal veins, compared to patients at another institution who were treated with a contemporary SLN mapping algorithm approach.

2. Methods

Institutional Review Board approval and data-transfer permission were obtained at both collaborating institutions. Patients who were surgically staged for endometrial cancer were identified at each center. In this study, we limited our analysis to patients with deeply invasive endometrioid endometrial cancer and serous or clear cell carcinoma. Patients were stratified into two risk groups. Intermediate-risk disease was defined as endometrioid histology, of any grade, with ≥50% myometrial invasion. High-risk disease was defined as serous or clear cell carcinoma, with any degree of myometrial invasion. Patients with carcinosarcoma were excluded from the analysis. We also excluded patients who received neoadjuvant chemotherapy, had another malignancy or synchronous cancer, or had visible gross metastatic disease. Preoperative imaging is only performed for grade 3 endometrioid, serous or clear cell histologies at both institutions. Imaging is also performed if there are any symptoms or signs of possible metastatic disease. Computer-assisted tomography (CT) scan of the chest, abdomen and pelvis is most commonly used. Routine positron emission tomography (PET) and pelvic magnetic resonance (MRI) imaging are not done at either institution. Preoperative imaging is used merely to identify obvious metastatic disease which would exclude these cases from a staging algorithm and refer them instead to a discussion of the role of surgical cytoreduction.

Patients who underwent complete pelvic and paraaortic LND as part of an historical surgical algorithm at the Mayo Clinic between the years 2004–2008 (LND cohort) were identified. Patients who underwent surgical staging with an SLN algorithm and pathologic ultra-staging at Memorial Sloan Kettering Cancer Center (MSKCC) between the years 2006–2013 (SLN cohort) were also identified. Pertinent clinical and pathologic data were collected from electronic medical records, operative notes and pathology reports. Staging was defined according to the 2009 FIGO surgical staging system. All surgical procedures at both centers were performed by trained gynecologic oncologists. At the Mayo Clinic, patients in the LND cohort underwent comprehensive surgical staging with complete pelvic and paraaortic lymph node dissection to the renal veins bilaterally, and intraoperative assessment of tumor characteristics. Frozen section evaluation of the uterine specimen was performed by a gynecologic pathologist to determine depth of invasion and tumor size. LND was not performed in cases meeting all of the following criteria: grade 1 or 2 endometrioid histology, ≤50% myometrial invasion, tumor size ≤2 cm, and no evidence of gross disease at time of operation [6]. Pelvic and paraaortic LND was performed in all other patients. Frozen section is performed on all hysterectomy specimens as part of a standard process decided upon at the Mayo Clinic.

At MSKCC, SLNs were removed in accordance with a previously published institutional algorithm [23]. According to this algorithm, a survey of the peritoneal cavity and serosal surfaces is performed and peritoneal washings collected. Thorough retroperitoneal evaluation is done, with excision of all mapped SLNs and removal of any enlarged, suspicious lymph nodes. If mapping fails, a side-specific lymph node dissection should be performed in the unmapped hemi-pelvis. Paraaortic lymph node dissection is performed at the discretion of the attending surgeon. This side-specific dissection and discretionary paraaortic dissection was
included in the total nodal counts in addition to the SLNs. Lymphatic mapping is performed by first injecting either blue dye (methylene blue or isosulfan blue) or indocyanine green (ICG) into the cervical stroma at the 3- and 9-o’clock positions. One milliliter (1 ml) of dye is injected both superficially and 1 ml deep in the cervical stroma (total injection of 4 ml). The injection is performed at the start of the operative case.

At MSKCC, pathologic ultra-staging is a standard part of the SLN algorithm [24]. All SLNs are assessed by trained gynecologic pathologists. Pathologic ultra-staging includes standard lymph node assessment, which involves sectioning the SLN once along the longitudinal axis and staining it with hematoxylin and eosin (H&E) to determine if it contains metastatic tumor cells. If tumor cells are identified, the lymph node is considered positive and no additional sectioning or staining is performed. However, if the initial H&E is negative, enhanced pathologic assessment—which entails additional sectioning and staining of the SLN with H&E and immunohistochemistry (using cytokeratin stains AE1:AE3)—is performed to examine the SLN for low-volume metastatic disease. Micrometastases are defined as a focus of metastatic tumor cells measuring >0.2 mm and ≤2 mm, whereas isolated tumor cells (ITCs) are defined as microscopic clusters and single cells measuring ≤0.2 mm. For the purposes of this analysis, isolated tumor cells (ITCs), micrometastases, and macrometastases in the SLN cohort were all considered node-positive. At both institutions, lymphovascular space invasion (LVSI) was considered to be present if tumor cells were within or attached to the wall of a capillary or lymphatic vessel.

Demographic, clinicopathologic, and nodal characteristics were compared between the SLN and LND cohorts using the Chi-square test or Fisher’s exact test for categorical variables, the two-sample t-test for age and body mass index (BMI), and the Wilcoxon rank-sum test for the number of LNs removed. All calculated P values were two-sided, and we considered P values <0.05 to be statistically significant. Statistical analysis was performed using the SAS version 9.3 software package (SAS Institute Inc., Cary, NC).

3. Results

We identified 412 surgically staged patients at the two participating institutions who met the inclusion criteria. Two-hundred and two patients were in the SLN cohort, and 210 were in the LND cohort. Tables 1 and 2 summarize the demographic and pathologic information for patients with endometrioid histology (“intermediate-risk”). Tables 3 and 4 summarize data for patients with serous and clear cell carcinoma of the endometrium (“high-risk”).

3.1. Intermediate-risk cases: Endometrioid histology, any grade, and ≥50% myometrial invasion

We identified 82 patients in the SLN cohort and 107 patients in the LND cohort meeting the criteria for intermediate risk of LN metastases. Mean age was 64.3 years in the SLN cohort and 68.2 in the LND cohort (P = 0.02). Mean BMI was different between the groups (Table 1, P = 0.046). Data on demographic, clinicopathologic, and nodal characteristics are summarized in Tables 1 and 2. Of note, LVS1 was detected more frequently among patients in the SLN cohort than in the LND cohort [N = 61 (32.7%) vs. N = 35 (16.8%), P = 0.001]. Patients who underwent SLN mapping were more frequently diagnosed with stage IIIC1 disease [N = 26 (31.7%) vs. N = 12 (11.2%) (P = 0.001), but were less likely to be diagnosed with stage IIIC2 disease [N = 3 (3.7%) vs. N = 18 (16.8%) (P = 0.004).

Pelvic lymph node assessment was performed in most of the patients in both cohorts (Table 2). Eighty-one (98.8%) patients in the SLN cohort and 101 (94.4%) patients in the LND cohort underwent removal of some pelvic lymph nodes (P = 0.14). The total number of pelvic lymph nodes removed differed significantly, with a median number of 10 (IQR: 4, 14) lymph nodes removed from patients in the SLN cohort and 35 (IQR: 27, 45) in the LND cohort (P < 0.001).

Among patients with deeply-invasive (≥50%) endometrioid carcinoma, pelvic nodal metastases were detected with similar frequency in both groups (Table 2). Among patients who had any pelvic lymph nodes removed, 27/81 (33.3%) in the SLN cohort and 25/101 (24.8%) in the LND cohort had pelvic nodal metastasis (P = 0.20). Among patients with positive pelvic lymph nodes, the median number of total positive lymph nodes was 1 (IQR: 1, 3) in the SLN cohort and 2 (IQR: 1, 5) in the LND cohort.

Paraortic lymph nodes were assessed more frequently in the LND cohort than in the SLN cohort (P < 0.001). Most patients (N = 96, 89.7%) in the LND cohort had a paraaortic LND, while only 28 (34.1%) patients in the SLN cohort had any paraaortic lymph nodes removed (P = 0.001). Among patients who had paraaortic lymph nodes removed, 3 (10.7%) in the SLN cohort and 20 (20.8%) in the LND cohort had positive paraaortic lymph nodes (P = 0.23), with a median number of 1 (IQR: 1, 1) and 2 (IQR: 1, 3) positive paraaortic lymph nodes in the SLN and LND cohorts, respectively. Among all patients, including those in whom paraaortic nodes were not removed, the rate of detected paraaortic lymph node metastasis was 3 (3.7%) vs. 20 (18.7%) patients in the SLN and LND cohort, respectively (P = 0.002). Among the 20 patients with positive paraaortic nodes in the intermediate-risk LND cohort, 2 had positive nodes below the inferior mesenteric artery (IMA), 6 had positive nodes above the IMA, and 7 had positive nodes above and below the IMA. Information regarding the location of the positive nodes was unavailable for 5 of the patients.

The overall number of patients with stage IIIC disease was 29 (35.4%) in the SLN cohort and 30 (28.0%) in the LND cohort (P = 0.28). However, FIGO stage IIIC2 (presence of paraaortic nodal metastasis +/− pelvic metastasis) was noted in only 3 (3.7%) cases in the SLN cohort compared to 18 (16.8%) in the LND cohort (P = 0.004).

Table 1 Select clinicopathologic characteristics of the “intermediate-risk” cases (endometrioid histology of any grade with myometrial invasion ≥50%).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SLN (N = 82)</th>
<th>LND (N = 107)</th>
<th>P value</th>
</tr>
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<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>64.3 (10.2)</td>
<td>68.2 (11.3)</td>
<td>0.02</td>
</tr>
<tr>
<td>BMI (kg/m²), mean (SD)</td>
<td>29.8 (6.8)</td>
<td>32.0 (8.0)</td>
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<td>FIGO grade, N (%)</td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>29 (35.4)</td>
<td>35 (32.7)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>31 (37.8)</td>
<td>46 (43.0)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>22 (26.8)</td>
<td>26 (24.3)</td>
<td></td>
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<tr>
<td>Lymphovascular space invasion, N (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>21 (25.6)</td>
<td>72 (67.3)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>61 (74.4)</td>
<td>35 (32.7)</td>
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<tr>
<td>Cervical stromal invasion, N (%)</td>
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</tr>
<tr>
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<td>87 (81.3)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>11 (13.4)</td>
<td>20 (18.7)</td>
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<tr>
<td>Peritoneal cytology, N (%)</td>
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<tr>
<td>Negative</td>
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<td></td>
</tr>
<tr>
<td>Positive</td>
<td>12 (14.6)</td>
<td>22 (21.8)</td>
<td></td>
</tr>
<tr>
<td>Not sampled</td>
<td>–</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>FIGO stage (2009), N (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IB</td>
<td>46 (56.1)</td>
<td>60 (56.1)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>5 (6.1)</td>
<td>10 (9.3)</td>
<td></td>
</tr>
<tr>
<td>IIIA/B</td>
<td>2 (2.4)</td>
<td>4 (3.7)</td>
<td></td>
</tr>
<tr>
<td>IIIC1</td>
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<td>12 (11.2)</td>
<td></td>
</tr>
<tr>
<td>IIIC2</td>
<td>3 (3.7)</td>
<td>18 (16.8)</td>
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</tr>
<tr>
<td>IV</td>
<td>–</td>
<td>3 (2.8)</td>
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<tr>
<td>FIGO stage (2009) any IIIC, N (%)</td>
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<td>Nodal metastasis classification</td>
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<tr>
<td>Micrometastasis</td>
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</tr>
<tr>
<td>Macrometastasis</td>
<td>16</td>
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</tr>
</tbody>
</table>

Abbreviations: BMI, body mass index; FIGO, International Federation of Gynecology and Obstetrics; SD, standard deviation; ITC, isolated tumor cells.  
† t-test P value presented for age and BMI and chi-square or Fisher’s exact test P value reported for categorical variables.
3.2. High-risk cases: Serous and clear cell histology with any degree of myometrial invasion

We identified 223 patients with serous and/or clear cell histology at our two participating institutions: 120 patients in the SLN cohort and 103 in the LND cohort. Tables 3 and 4 summarize pertinent demographic, clinicopathologic, and nodal characteristics. Mean age (P = 0.80) and BMI (P = 0.43) were similar between the two groups. Depth of myometrial invasion varied significantly between the groups (P = 0.01). More patients in the SLN cohort had disease limited to the endometrium, with no myometrial invasion (N = 56, 46.7%), compared to the LND cohort (N = 29, 28.2%). Deep (≥50%) myometrial invasion was noted in 30 (25.0%) and 28 (27.2%) patients in the SLN and LND cohorts, respectively, LVSI (P = 0.15) and positive peritoneal cytology (P = 0.32) were observed in a similar number of patients in each cohort.

Pelvic lymph node assessment was performed in most patients in both cohorts (Table 4). In the SLN cohort, 97.5% had pelvic nodes removed compared to 85.4% in the LND cohort (P = 0.001). Patients in the SLN cohort had fewer lymph nodes removed, with a median 11 (IQR: 5, 16) total pelvic lymph nodes removed, compared to 30 (IQR: 26, 41) in the LND cohort (P < 0.001).

Positive pelvic LNs were identified at a similar frequency in each group (Table 4). Among all patients analyzed, including those who had no pelvic nodes removed at all, 27 (22.5%) and 20 (19.4%) in the SLN and LND cohorts, respectively, were noted to have pelvic nodal metastases (P = 0.57). In patients who had at least one pelvic lymph node removed, pelvic nodal metastases were identified in 27 (23.1%) in the SLN cohort and 20 (22.7%) in the LND cohort (P = 0.95). Among patients with nodal metastasis, the median number of metastatic pelvic lymph nodes was similar between the two cohorts (Table 4).
However, no difference in survival was observed between patients who had multi-site vs. limited-site pelvic LND [26]. Chan and colleagues also reported a survival advantage in patients undergoing more extensive LND at time of surgical staging for endometrioid endometrial cancer [27]. Specifically, these authors noted an improved 5-year disease-specific survival in patients with intermediate- and high-risk disease (defined as stage IB, grade 3; stage IC and II-IV, all grades) undergoing a more extensive lymph node dissection. Among patients with stage IIIC disease, the authors showed that the extent of lymph node resection improved survival significantly [27]. Mahdi and colleagues reported that LND was associated with improved survival in patients with uterine serous cancer (hazard ratio [HR] 0.59; 95% CI 0.54–0.64; P < 0.001). The authors emphasized that more extensive LND correlated positively with survival. Women with >10 nodes removed were 26% less likely to die (HR 0.74; 95% CI 0.67–0.83; P < 0.001) compared to women with only 1–10 nodes removed [28]. Mahdi and colleagues observed a similar survival advantage in patients with clear cell carcinoma of the uterus undergoing LND [29]. However, it is important to note that these series are all retrospective in nature, and subject to associated inherent biases.

Two randomized, controlled trials failed to demonstrate an improvement in survival after LND, compared to hysterectomy alone [17,19]. However, these trials have been heavily criticized [30–32]. No paraaortic lymphadenectomy was performed in either of the studies; both included many low-risk patients; in many of the cases in which nodal metastasis was identified, adjuvant therapy was not administered; the only adjuvant treatment used was pelvic radiation without any systemic therapy.

SNL mapping and biopsy certainly has its advantages. Although not yet objectively reported, we anticipate that SNL mapping will be shown to result in decreased morbidity compared to lymphadenectomy. SNL mapping can also improve the detection of lymph node metastases through pathologic ultra-staging [24]. However, the actual significance of low-volume metastases remains unknown. It has been shown that patients with ITCs and micro-metastases have survival comparable to that of patients with node-negative disease [33]. The limitations of this study were its retrospective design, and the fact that a large proportion (~80%) of patients with low-volume metastases received adjuvant therapy. In the current series, of course, ultra-staging was not done in the Mayo Clinic cohorts. It is quite plausible that, upon review, some of the nodal metastases noted in the Mayo Clinic cohorts could be reclassified as ITCs and micro-metastases using SNL criteria and terminology.

We have recently reported our experience comparing the SNL algorithm to systematic pelvic and paraaortic LND in patients with "low-risk" endometrioid endometrial cancer [21]. In this study, the SNL algorithm did not compromise detection of stage IIIC disease and did not impact 3-year disease-free survival. However, the patients included in the current study are at an increased risk of lymph node spread due to greater depth of myometrial invasion and higher tumor grade. Does the SNL algorithm compromise detection of lymphatic spread in these higher-risk patients? If so, will this impact survival? In fact, the current study demonstrates that the detection of lymph node metastases in patients with "intermediate- and high-risk" endometrial carcinoma is not compromised by the utilization of an SNL mapping algorithm. FIGO stage IIIC disease (presence of any nodal metastasis) was identified with similar frequency in both risk groups, using both surgical staging approaches, despite the fact that fewer total lymph nodes and fewer paraaortic nodes were sampled in the SNL cohort. In the endometrioid group with deep myometrial invasion, FIGO stage III was diagnosed in 31 (37.8%) and 34 (31.8%) patients in the SNL and LND cohorts, respectively (Table 1). FIGO stage IIIC1 disease was identified in 26 (31.7%) and 12 (11.2%) patients in the SNL and LND cohorts, respectively. FIGO stage IIIC2 disease was diagnosed more frequently in the LND cohort.

The importance of detecting more paraaortic nodal involvement, rather than merely any nodal involvement, remains unclear. Many have expressed concern that if only SNLs are removed and systematic paraaortic LND omitted in these higher-risk populations, isolated aortic lymph node metastases may be missed, and this could significantly impact oncologic outcome. Creasman and colleagues [12] showed that, when pelvic nodes were negative, only 2% of patients had isolated positive paraaortic lymph nodes alone. Abu-Rustum and colleagues also demonstrated a 1.6% risk of isolated paraaortic nodal metastases in the setting of negative pelvic nodes [34].

On the other hand, Creasman et al. identified 22 (3%) patients with positive pelvic lymph nodes who also had positive paraaortic lymph nodes [12]. Thus, positive pelvic lymph nodes could be considered a surrogate for assessing the risk of paraaortic lymph node spread. A Mayo Clinic series confirmed that isolated paraaortic metastases overall are rare, as expected [22]. However, the authors observed that there is a small group of patients in which the risk of isolated paraaortic metastases is higher than 10%. This group is characterized by all of the following: endometrioid tumor, myometrial invasion >50%, and grade 2 or 3 histology. Interestingly, these patients are all part of the "intermediate-risk" group described in this series.

Today, multimodal therapy (chemotherapy and radiotherapy) is more frequently considered for patients with FIGO stage IIIC disease. Several single-institution, multi-institution, and large observational
Abbreviations: IQR, interquartile range; LND, lymphadenectomy.

IIIC1 endometrial cancer who were treated with radiation alone [40]
paraaortic control and improved outcome in patients with FIGO stage
Oncology Group reported that paraaortic LND provided excellent
none of the patients had received chemotherapy. The Korean Radia-
tion therapy did not effectively control disease in the paraaortic region, and it suggests that chemotherapy alone is not sufficient to sterilize paraaortic
disease [42]. However, no postoperative radiation therapy was uti-
ized in this retrospective cohort.

It is noteworthy that the rate of paraaortic nodal metastasis in the current study was higher in the endometrioid LND group than in the se-
rous/clear cell LND group (20.8% vs. 15.9%, Tables 2 and 4). The reason
for this is not entirely clear. A possible explanation is that patients with serous or clear cell histology had more extensive nodal assessment
of the paraaortic region. Thus it appears as though more of the
endometrioid cases had positive paraaortic nodes, when, in fact, fewer
patients overall had sampling of paraaortic nodes; thus, the proportion
of patients with positive nodes is higher. However, as shown in Tables 2
and 4, 89.7% of patients in the endometrioid group underwent paraaortic LND compared to 79.6% of patients in the “high-risk” group.
The median number of paraaortic lymph nodes removed was 18 (12,
23) and 17 (11, 23) in the endometrioid and serous/clear cell groups, re-
spectively. Additionally, positive nodes were removed from, and detec-
ted both above and below, the IMA.

Patients in the endometrioid “intermediate-risk” group were older.
LVI was identified more frequently in the SLN population, but we be-
lieve this is due to institutional variation in detection and diagnosis,
and not to actual differences in patient characteristics. In the “high-
risk” or non-endometrioid cases, we observed that more patients in
the SLN group had only endometrial involvement, or no myometrial in-
vasion. However, both groups had similar rates of deep (≥50%) myometrial invasion.

Certainly, an important next step would be to compare the outcomes
between these two groups (SLN vs. LND). This is the focus of active anal-
ysis by our group, but is not addressed in the current study. Other limi-
tations include its retrospective design, and the fact that it compares
heterogeneous groups from two institutions. Furthermore, we cannot comment on the rate of lymphedema between the two cohorts.

### Table 4
Nodal assessment patterns in the “high-risk” group.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>SLN N = 120</th>
<th>LND N = 103</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pelvic lymphadenectomy, N (%)</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>No</td>
<td>1 (2.5)</td>
<td>15 (14.6)</td>
<td>0.001</td>
</tr>
<tr>
<td>Yes</td>
<td>117 (97.5)</td>
<td>88 (85.4)</td>
<td></td>
</tr>
<tr>
<td>Number of pelvic nodes removed median (IQR) *</td>
<td></td>
<td></td>
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<tr>
<td>Right</td>
<td>5 (2, 8)</td>
<td>15 (12, 21)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Left</td>
<td>5 (2, 8)</td>
<td>16 (13, 20)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total</td>
<td>11 (5, 16)</td>
<td>30 (26, 41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive pelvic nodes, N (%)</td>
<td></td>
<td></td>
<td>0.57</td>
</tr>
<tr>
<td>No or pelvic LND not done</td>
<td>93 (77.5)</td>
<td>83 (80.6)</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27 (22.5)</td>
<td>20 (19.4)</td>
<td></td>
</tr>
<tr>
<td>Positive pelvic nodes, N (%) *</td>
<td></td>
<td></td>
<td>0.95</td>
</tr>
<tr>
<td>No</td>
<td>90 (76.9)</td>
<td>68 (77.3)</td>
<td></td>
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<tr>
<td>Yes</td>
<td>27 (23.1)</td>
<td>22 (22.7)</td>
<td></td>
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<tr>
<td>Number of positive pelvic nodes among those with positive nodes, median (IQR)</td>
<td></td>
<td></td>
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<tr>
<td>Left</td>
<td>1 (0.1)</td>
<td>2 (1.5)</td>
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<tr>
<td>Total</td>
<td>1 (1.2)</td>
<td>2 (1.10)</td>
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<tr>
<td>Paraaortic lymphadenectomy, N (%)</td>
<td></td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>No</td>
<td>64 (53.3)</td>
<td>21 (20.4)</td>
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<tr>
<td>Yes</td>
<td>56 (46.7)</td>
<td>82 (79.6)</td>
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<tr>
<td>Number of paraaortic nodes removed, median (IQR) *</td>
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<tr>
<td>No or paraaortic LND not done</td>
<td>4 (3, 8)</td>
<td>17 (11, 23)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Positive paraaortic nodes, N (%)</td>
<td></td>
<td></td>
<td>0.29</td>
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<tr>
<td>No</td>
<td>110 (91.7)</td>
<td>90 (87.4)</td>
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<tr>
<td>Yes</td>
<td>10 (8.3)</td>
<td>13 (12.6)</td>
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<td>Positive paraaortic nodes, N (%) *</td>
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<td>0.76</td>
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<tr>
<td>No</td>
<td>46 (82.1)</td>
<td>60 (84.1)</td>
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<tr>
<td>Yes</td>
<td>10 (17.9)</td>
<td>13 (15.9)</td>
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<tr>
<td>Number of positive paraaortic nodes among those with positive nodes, median (IQR)</td>
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<tr>
<td>Pelvic</td>
<td>2 (1, 3)</td>
<td>5 (2, 7)</td>
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<tr>
<td>No or pelvic LND not done</td>
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<tr>
<td>Yes</td>
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<tr>
<td>Positive paraaortic nodes, N (%)</td>
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<td>No or pelvic LND not done</td>
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<td>Positive paraaortic nodes, N (%)</td>
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<td>No or pelvic LND not done</td>
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Abbreviations: IQR, interquartile range; LND, lymphadenectomy.

* Only includes cases in which nodal tissue was obtained.
† Wilcoxon rank-sum P value reported for continuous variables and chi-square P value reported for categorical variables.
However, the large number of patients lends strength to this study. Another strength is the fact that these patients were treated by trained gynecologic oncologists and pathologists at two cancer specialty centers. Firm recommendations based on a retrospective series must be taken with caution and put into context. Surgeons must interpret these results in the context of other published results and then decide how best to incorporate SLN mapping into their practice. It is not possible to make "standard" recommendations on how these data should change each surgeon's practice. SLN mapping is considered an acceptable option to LND in the NCCN guidelines. We can state that both MSKCC and the Mayo Clinic have fully adopted the SLN algorithm and no longer perform routine staging lymphadenectomy.

In summary, we have demonstrated that use of an SLN algorithm does not compromise the detection of stage IIIC disease in patients with deeply invasive endometrioid (any grade) endometrial cancer, or in patients with serous and clear cell cancers with any degree of myometrial invasion. However, the higher rate of stage IIIC1 in patients with serous and clear cell cancers with any degree of change each surgeon's practice. SLN mapping is considered an acceptable option to LND in the NCCN guidelines. We can state that both MSKCC and the Mayo Clinic have fully adopted the SLN algorithm and no longer perform routine staging lymphadenectomy.

Conflict of interest statement
None of the authors declare conflicts of interest.

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References
[7] N. Biglia, A. Librino, M.C. Ottino, E. Panuccio, A. Daniele, A. Chahin, Lower limb pelvic and/or paraaortic LND in the setting of SLN metastasis is unknown. These issues, and the comparison of oncologic outcomes, are topics of ongoing analysis, the results of which will be reported in the future.

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