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ROLE OF ROBOTIC-ASSISTED SURGERY FOR ENDOMETRIAL CANCER STAGING: comparison with open abdominal operations.

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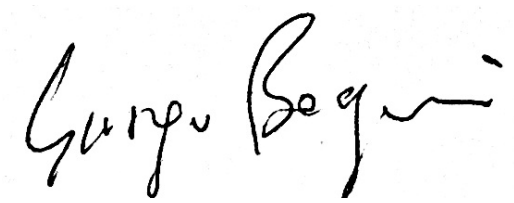

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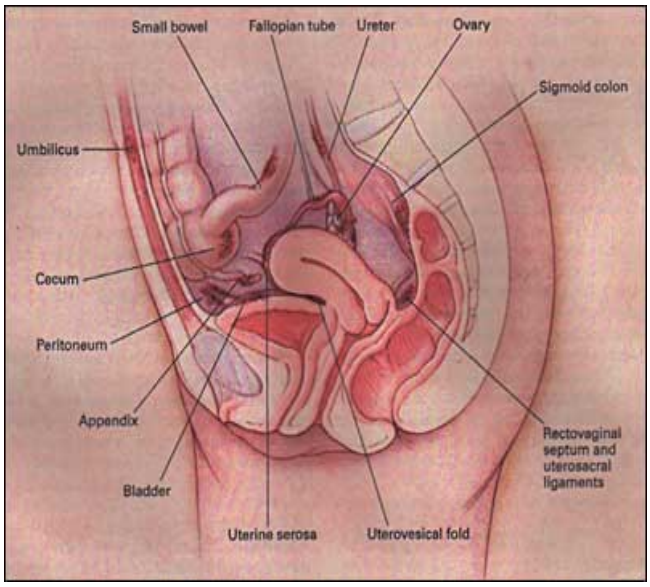
Endometrial cancer

Endometrial cancer (EC) is the most common gynecologic malignancy in developed countries. It is estimated that more than 52,000 new cases will be diagnosed in the United States during 2014 (1).

EC is a type of cancer that begins in the uterus. The uterus is the hollow, pear-shaped pelvic organ in women where fetal development occurs. EC begins in the layer of cells that form the lining (endometrium) of the uterus (Figure 1). EC is sometimes called uterine cancer. Other types of cancer can form in the uterus, including uterine sarcoma, but they are much less common than endometrial malignancies. EC is often detected at an early stage because it frequently produces abnormal vaginal bleeding, which prompts women to see their doctors. If EC is discovered early, removing the uterus surgically often cures EC. Hysterectomy plus salpingo-oophorectomy is the cornerstone for treatment of EC, but the use of lymphadenectomy, especially in early-stage disease, is a matter of debate (2,3).



Role of Surgical Staging

Despite the high incidence of EC, many features of its management remain unresolved. The main controversial topic in EC treatment concerns the therapeutic role of lymphadenectomy (3). Definitions of the adequacy and extent of lymphadenectomy have not been fully established.

In 1988, the International Federation of Gynecology and Obstetrics (FIGO) introduced the concept of surgical staging of EC (4), and in 2005, the American College of Obstetricians and Gynecologists (ACOG) recommended surgical staging as an important part of EC management. The ACOG committee suggested that "adjuvant therapy" should be limited to patients with positive nodes, while "the use of adjuvant radiation therapy in women with disease limited to the uterus based on systematic surgical staging is controversial" (5). Theoretically, the removal of lymph nodes has several potential advantages. Complete surgical staging may allow the identification of patients with documented lymphatic dissemination, thus targeting postoperative treatment and potentially reducing the morbidity related to unnecessary radiation therapy. Moreover, lymph node dissection may eradicate metastatic lymphatic disease.

The major criticisms of lymphadenectomy are based on the results of 2 independent randomized trials that evaluated the role of pelvic and limited para-aortic lymph node dissection in early-stage EC (6,7). Overall, a total of 1,922 patients were randomly assigned to evaluate whether the addition of pelvic (and para-aortic, in selected cases) lymphadenectomy to standard hysterectomy with bilateral salpingo-oophorectomy may improve survival outcomes. The cumulative results of these studies reported that lymphadenectomy did not improve disease-free survival (pooled hazard ratio [HR], 1.23; 95% confidence interval [CI], 0.96-1.58) and overall survival (pooled HR, 1.07; 95% CI, 0.81-1.43) (6,7).

These findings should be interpreted with caution, however, because of several pitfalls in the study design of both trials. First, they included a large proportion of low-risk women, which diluted the possible therapeutic effects of lymphadenectomy. Given the low rate of lymphatic spread in the early stage of disease (9%-13%), it is not surprising that the 2 trials failed to find any therapeutic role for pelvic lymphadenectomy in the low-risk population. Second, no clear indication was given for postoperative adjuvant therapy. One of the main goals of lymphadenectomy is to tailor adjuvant treatment to decrease radiation-related morbidity in patients with negative nodes. However, the adjuvant therapy administration rate was similar in both study arms; this result obviously influenced postoperative outcomes. Third, neither trial evaluated appropriately the role of para-aortic lymphadenectomy. In patients with lymphatic spread, para-aortic node involvement occurs in 60% of patients with endometrioid EC and 70% of those with nonendometrioid EC (8). Therefore, the performance of pelvic lymphadenectomy alone represents an incomplete surgical effort because of the partial removal of metastatic nodes.

Additionally, in the ASTEC trial (7), the number of pelvic nodes yielded was low in many of the patients. The median number of pelvic nodes harvested was 12 (range, 1-59); moreover, in the lymphadenectomy arm, 241 women (35%) had 9 or fewer nodes and 72 women (12%) had 4 or fewer nodes.

Recently, in response to the current evidence that pelvic lymphadenectomy alone did not provide any significant benefit on EC, Todo et al (9) designed a retrospective cohort analysis (the SEPAL study) aimed at assessing the role of para-aortic lymphadenectomy. The authors compared outcomes of patients undergoing systematic pelvic lymphadenectomy or combined pelvic and para-aortic lymphadenectomy in intermediate- and high-risk EC patients. The SEPAL study showed that high-risk patients who had pelvic and para-aortic lymph node dissection experienced a longer overall survival than patients who had pelvic lymphadenectomy alone (HR, 0.53; 95%

CI, 0.38-0.76; *P*<.001). Interestingly, in accordance with our previous comments, the authors found that survival was not influenced by the performance of para-aortic lymphadenectomy in the low-risk group (grade 1 and 2 endometrioid tumor limited to the inner half of the myometrium, without lymphovascular space invasion), while it was an independent prognostic factor in intermediate-risk EC patients (grade 1 and 2 tumor limited to the inner half of the myometrium with lymphovascular space invasion, grade 3 and/or nonendometrioid stage IA and IB tumor, stage IC and II) and high-risk EC patients (stage III and IV) (*P*<.001) (9). However, only 8% of patients in the SEPAL trial had nonendometrioid EC (13.5% of the intermediate- and high-risk group). Therefore, results of the SEPAL trial may not be fully applicable to patients with nonendometrioid EC. Also, the median age of patients in the SEPAL trial was relatively young (56 years), and those results may not be applicable to elderly patients (9).

Clinical Considerations

In light of the current evidence, it is not possible to draft definitive conclusions regarding the role of lymphadenectomy in EC patients. In this article, we will address the most important questions regarding the role of lymphadenectomy in EC:

1. Which is the population at risk of lymphatic spread?
2. How can we select patients at risk of lymphatic spread?
3. Which are the patterns of para-aortic lymphatic spread?
4. What is the role of sentinel lymph node (SLN) mapping?
5. How does lymphadenectomy impact morbidity, quality of life (QOL), and costs?
6. If lymph node metastases are identified, do we have adequate treatment?

7. How can we design a study to test the diagnostic and therapeutic role of lymphadenectomy?

1. Which Is the Population at Risk of Lymphatic Spread?

According to a risk stratification system in use at Mayo Clinic, Rochester, MN (Table 1), low-risk patients can be adequately treated with removal of the uterus and adnexa alone, without significantly compromising survival. In this subgroup, lymphadenectomy carries only potential adjunctive morbidity (10,11). In fact, we previously demonstrated that tumor diameter significantly influences the risk of lymph node dissemination. In an analysis of more than 300 endometrioid EC patients with FIGO grade 1 or 2 and myometrial invasion limited at the inner half, we found that no patients with tumor diameter of 2 cm or less had positive lymph nodes or lymph node recurrences or died of disease (11). This finding has been recently prospectively validated by our group (10) and others (12,13).

Based on the surgical protocol currently in use at Mayo Clinic, all patients with primary epithelial EC undergo hysterectomy with or without bilateral salpingo-oophorectomy. The need to perform lymphadenectomy is based on the tumor characteristics (histologic type, FIGO grade, tumor diameter, and depth of myometrial invasion) determined at frozen-section analysis. Systematic pelvic and para-aortic lymphadenectomy is performed when patients have myometrial invasion greater than 50%, nonendometrioid histology, or both. If patients do not match these characteristics, the choice to perform pelvic node dissection (with para-aortic lymphadenectomy only in those patients with documented pelvic lymph node metastases) is based on cervical involvement, FIGO grade, and tumor diameter (Figures 1 and 2). Para-aortic lymphadenectomy is therefore limited to patients with at least one of the following: 1) positive pelvic nodes (assessed at frozen section); 2) type 2 EC; or 3) deep myometrial invasion (>50%) (Figure 1) (14). In fact, we have recently observed that isolated para-

aortic dissemination (in the absence of pelvic lymph node involvement) is generally very uncommon (£5%), with the exception of patients with endometrioid grade 2 or 3 cancer and myometrial invasion greater than 50% (15). Also, para-aortic metastases are uncommon in patients with endometrioid grade 3 cancer with early myometrial invasion (£50%) (14).

When type II EC omentectomy is performed (Figure 1), random peritoneal biopsies, in the absence of macroscopic visible disease, are of limited diagnostic benefit (16).

Interestingly, in a large analysis among high-risk and ultra-high-risk (grade 3 endometrioid, serous, and clear cell) uterine cancers, we showed that lymphadenectomy as well as extensive surgery did not provide survival advantages in patients with advanced-stage disease (17).

In light of these findings, patients with a preoperative diagnosis of FIGO grade 1 or 2 endometrioid EC confined to the endometrium or with myometrial invasion less than 50% and tumor diameter of 2 cm or less do not undergo lymph node dissection at our institution. Moreover, from a practical standpoint, lymphadenectomy may be omitted also in ultra-high-risk patients with stage IV disease (Figure 2).

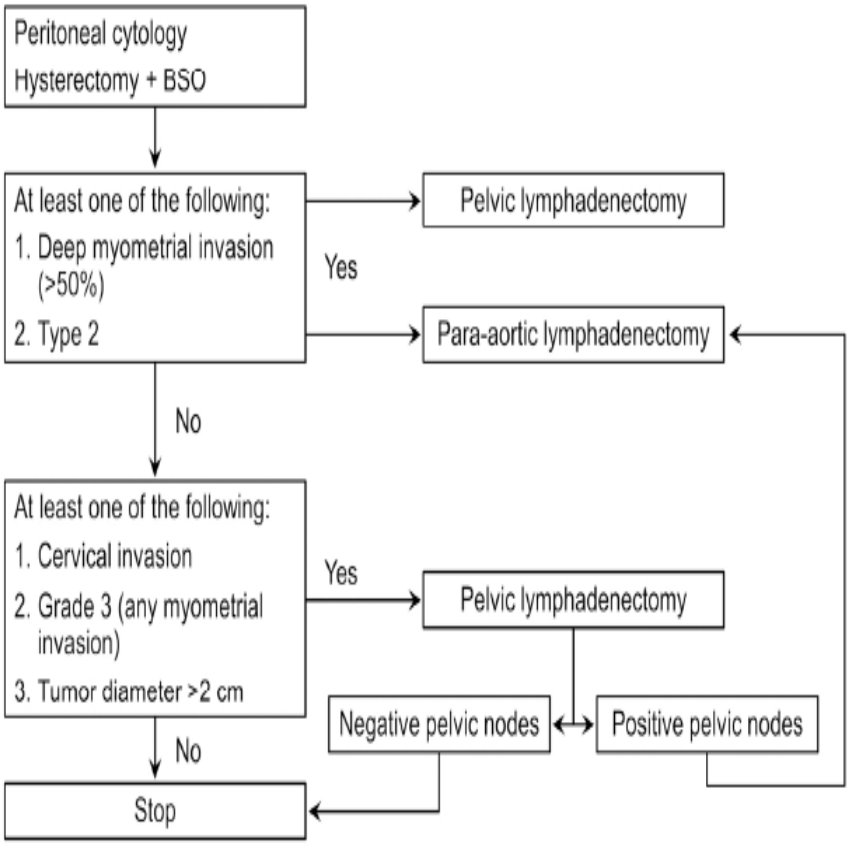


Figure 2. Algorithm for surgical management of endometrial cancer at our institution. In the case of type 2 endometrial cancer, omentectomy is required. No lymphadenectomy is done in the patients with stage IV cancer. BSO indicates bilateral salpingo-oophorectomy

2. How Can We Select Patients at Risk of Lymphatic Spread?

A scoring system based on preoperative and operative parameters should be used to tailor surgery and reduce the rate of unnecessary lymphadenectomy. Several models have been described (18-24). Decision making at Mayo Clinic is traditionally based on 4 variables during intraoperative frozen-section analysis: primary tumor diameter, FIGO grade, histologic type, and depth of myometrial invasion. An investigation by our group, aimed at determining the reliability of frozen-section analysis, suggested a high rate of clinical accordance (98.7%), with definitive pathologic findings (permanent paraffin sections). Among 784 patients included, 10 women (1.3%) had a potential change in operation plan due to deviation in pathologic results from frozen-section to permanent-paraffin analysis. This included changes in histologic subtypes (n=6, 0.7%), FIGO grade (n=1, 0.12%), and myometrial invasion (n=3, 0.38%) (18). Although different studies from other institutions report a similarly high accuracy rate of intraoperative frozen section (25,26), a survey of the Society of Gynecologic Oncologists revealed that only 31% of gynecologic surgeons use frozen section in their decision making for EC management (27). For this reason, we recently showed that, in the absence of an accurate frozen section, preoperative biopsy (which is consistently available) and intraoperative tumor diameter (easily measured on fresh tissue and unchanged on final pathology) may reliably predict lymph node tumor spread. We observed that low-risk women (patients with preoperative diagnosis of grade 1 or 2, endometrioid EC and tumor diameter £2.0 cm) have less than 1% risk of lymphatic spread, while patients with tumor diameter greater than 2.0 cm or with preoperative diagnosis of endometrioid grade 3 or nonendometrioid EC had a substantial risk of lymphatic involvement greater than 10% (Figure 3) (19).

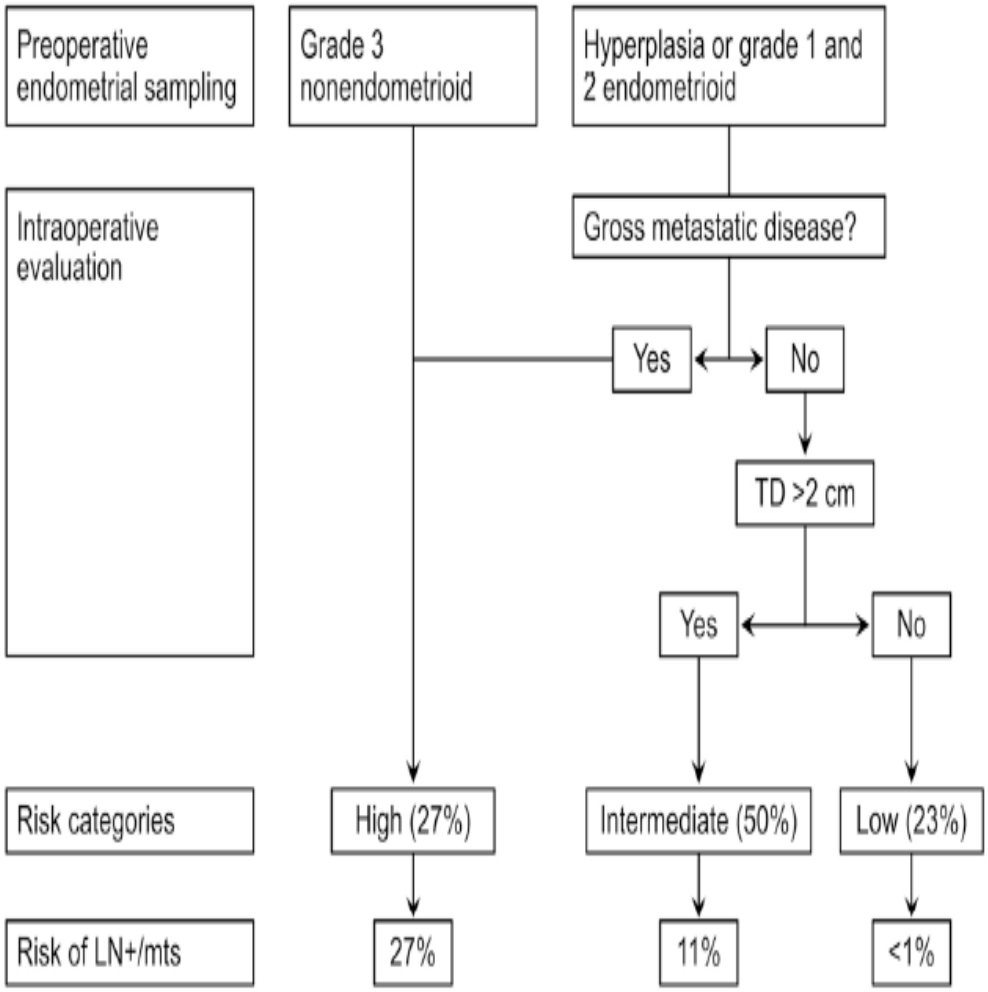


Figure 3: Risk of lymph node metastasis and lymph node recurrence according to preoperative and operative findings. LN indicates lymph node; mts, metastases; TD, tumor diameter. (Data from AlHilli et al [19].)

Other authors have used preoperative imaging and serum markers, suggesting that tumor volume (measured with magnetic resonance imaging), positron-emission tomographic scan findings (28), and preoperative cancer antigen 125 or human epididymis protein 4 levels may be useful in tailoring the indications for lymphadenectomy (20,21,29).

Our experience suggests that frozen-section analysis may represent a safe and effective method to direct the operative plan in selected medical centers. However, if frozen-section analysis is not available or if it is not reliable, findings of preoperative endometrial sampling associated with intraoperative tumor size, imaging studies, and serum markers are alternative methods to identify patients who may benefit from comprehensive surgical staging.

3. Which Are the Patterns of Para-aortic Lymphatic Spread?

Traditional imaging, node palpation through the peritoneum, and node sampling are inaccurate in predicting lymph node positivity (5). In 2005, ACOG recommended that "retroperitoneal lymph node assessment is a critical component of surgical staging" because it "is prognostic and facilitates targeted therapy to maximize survival and to minimize the effect of undertreatment and potential morbidity associated with overtreatment" (5). Nevertheless, in clinical practice a high variation of procedures reflects the lack of standardization of lymphadenectomy: techniques vary from elective omission to simple lymph node sampling, to systematic pelvic lymphadenectomy with or without para-aortic lymphadenectomy.

One investigation at Mayo Clinic illustrated the prevalence and site of pelvic and para-aortic lymphatic metastases. We reported that, among patients with lymphatic spread, 84% and 62% had pelvic and para-aortic node metastases, respectively. In particular, 46%, 38%, and 16% had involvement of both pelvic and aortic nodes, pelvic nodes only, and aortic nodes only, respectively (8).

Para-aortic lymph nodes can be classified based on their location above and below the inferior mesenteric artery (IMA). At Mayo Clinic, we evaluated para-aortic metastatic site frequency relative to the IMA and found that aortic nodes above the IMA were involved in 77% of cases (8,30). Fotopoulou and coworkers (31) corroborated

these results; they reported that metastatic disease above the IMA was recorded in 54% and 70% patients with stage IIIC and IIIC2 EC, respectively. Recently, a prospective study by our department suggested that, considering patients with aortic node involvement, high para-aortic lymph node metastases were detected in 88% of them, with no discernible difference between endometrioid (89%) and nonendometrioid (88%) histologic subtypes. Interestingly, 35% of patients with high para-aortic lymph node metastases had negative nodes below the IMA (39% endometrioid; 31% nonendometrioid). Furthermore, in the rare cases with para-aortic lymph node metastases and negative pelvic nodes, cancer dissemination is most commonly confined to the high para-aortic area (67%) (15).

Also, patients with pelvic node metastases may have occult aortic node involvement, with a rate of para-aortic dissemination higher than commonly reported. Todo et al (32) investigated the occurrence of occult metastases (ie, micrometastases and isolated tumor cells) in the para-aortic area in patients with stage IIIC1 EC who underwent pelvic and para-aortic lymphadenectomy. Ultra-staging was performed by multiple slicing, staining, and microscopic inspection of the specimens. The authors found that 73% of these patients had occult aortic node involvement. Although the role of micrometastases is not fully understood, the presence of microscopic occult disease in the para-aortic area should be considered even in stage IIIC1 EC or in those patients with documented pelvic lymph node invasion and no known information regarding the para-aortic area.

These findings indicate that para-aortic lymph node invasion is very common when pelvic lymph node metastases are demonstrated. Also, in the majority of patients with para-aortic lymph node invasion, the area above the IMA is involved. Table 2 shows the overall risk of para-aortic and high para-aortic lymph node metastasis in EC.

4. What Is the Role of SLN Mapping?

SLN mapping is an accepted way to assess lymphatic spread in several solid tumors (ie, breast cancer, vulvar cancer, and melanoma) and is gaining ground in cervical cancer and EC (33-35). SLN biopsy can be considered a compromise between comprehensive surgical staging and the complete omission of lymphadenectomy. In an ideal world, SLN mapping should be as good as a systematic lymphadenectomy in the identification of patients with lymph node dissemination, while reducing the morbidity associated with an extensive surgical procedure.

Although the complexity of uterine lymphatic drainage may discourage use of this procedure, the estimated accuracy rate is, in general, reasonably good (36-39). The prospective multi-institutional SENTI-ENDO study suggested that in stage I and II EC patients, SLN biopsy has a sensitivity of 84% (40). Moreover, ultra-staging of the SLN may be even more sensitive than a full lymphadenectomy, with lymph nodes evaluated by conventional pathology (35,41). However, we still do not know the clinical importance of isolated tumor cells discovered in a lymph node that is negative by traditional histologic analysis. Recently, a paper from the Memorial Sloan-Kettering Cancer Center, describing one of the largest prospective single-institution cohorts, showed that applying an SLN mapping algorithm may be a safe and effective alternative to systematic lymphadenectomy (38). The study pointed out that satisfactory SLN mapping requires adherence to a surgical algorithm and the removal of any “suspicious node” (38). However, the definition of a suspicious node was unclear. Also, identification of suspicious lymph nodes without fully opening the retroperitoneal spaces and without palpation (not possible with the minimally invasive approach) is limited and unreliable.

Like every effort aimed at decreasing the amount of surgery and the morbidity of EC treatment, we look at the experimental results on the use of SLN sampling with great interest. Ideally, SLN biopsy could be an effective alternative to systematic

lymphadenectomy. However, available data are still insufficient to define its role in clinical practice.

5. How Does Lymphadenectomy Impact Morbidity, QOL, and Costs?

Patients undergoing systematic pelvic and para-aortic lymphadenectomy experience longer operative times and are exposed to greater risk of intraoperative and postoperative complications than patients who have hysterectomy and bilateral salpingo-oophorectomy alone (6). While some investigations showed that lymph node dissection did not significantly influence complication rates among EC patients (42,43), at Mayo Clinic, we observed that retroperitoneal staging, including para-aortic lymphadenectomy, increases morbidity in patients with EC (44). Similarly, results from the ASTEC trial and the Italian collaborative trial indicated that women who underwent lymphadenectomy had a significantly higher risk of surgically related morbidity and lymphatic complications than those who had hysterectomy plus bilateral salpingo-oophorectomy alone (relative risk [RR], 3.72; 95% CI, 1.04-13.27, and RR, 8.39; 95% CI, 4.06-17.33, for risk of surgical and lymphatic complications, respectively) (6,7,45). However, it is important to note that the introduction of minimally invasive lymph node dissection may have reduced the complication rate of lymphadenectomy (46-48).

The impact of lymphadenectomy on long-term QOL in EC patients is not clear. Recently, a Dutch population-based analysis (49) evaluated the health-related QOL and symptoms following pelvic lymphadenectomy and radiation therapy (alone or in combination) vs no adjuvant therapy in patients with FIGO stage I and II EC. Lymphedema, gastrointestinal tract symptoms, diarrhea, back and pelvic pain, and muscular joint pain were the most commonly reported symptoms. The authors showed that, despite different symptom patterns, in patients who had pelvic lymphadenectomy (eg, lymphedema), radiotherapy (eg, diarrhea), or both, no clinical differences in overall

QOL were observed compared with women not receiving adjuvant therapy, lymphadenectomy, or both (49).

At Mayo Clinic, we analyzed the related surgical costs of lymphadenectomy in our low-risk EC population and reported that lymphadenectomy increased the median 30-day cost of care by about $4,500 per patient (10).

In conclusion, patients undergoing lymphadenectomy experience longer operative times and higher complication rates than patients who have hysterectomy plus adnexectomy alone. Also, the overall cost of surgical care is higher. The influence of lymphadenectomy on long-term QOL is less clear. For the above reasons, it is important to limit the performance and the extent of lymphadenectomy to patients who may potentially benefit from it.

6. When Lymph Node Metastases Are Identified, Is Adequate Treatment Available?

Although lymphadenectomy is aimed at documenting the presence of lymphatic metastases, there is still no consensus about the best adjuvant approach in EC patients with positive lymph nodes. The Gynecologic Oncology Group 122 trial (50) suggested that chemotherapy (doxorubicin and cisplatin) provides better survival than radiotherapy (whole abdominal irradiation) in stage III or IV and with 2 cm or less of residual disease. However, chemotherapy decreased the distant recurrence rate (from 19% to 10%) at the cost of a higher pelvic recurrence rate (from 13% to 18%). Interestingly, the authors reported that chemotherapy was not significantly better than abdominal radiation in patients with nonendometrioid tumors (50). Similarly, the results of 2 randomized studies (NGSO/ERTC and MaNGO ILIADE–III), including high-risk EC patients (stage I to III), indicated that the addition of adjuvant chemotherapy to radiation improved disease-free survival overall, especially in the subgroup with grade 1 and 2 endometrioid EC. Chemotherapy was less likely to be beneficial in patients with

endometrioid grade 3 and type 2 EC (51). In agreement with the above results, we recently demonstrated that chemotherapy did not significantly impact prognosis in stage III patients with high-risk histology (endometrioid grade 3 and type 2 EC) (17). Although in our study radiotherapy (with or without chemotherapy) independently influenced survival in patients with stage III poorly differentiated cancer, the treatment failure rates remained extremely high, with a 67% recurrence rate at 3 years in patients with stage III and lymphovascular invasion (17).

Similarly, Sutton et al (52), in another Gynecologic Oncology Group study, reported that patients with stage III and IV high-risk histology (serous and clear cell) experienced 3-year recurrence-free and overall survival of 27% and 35%, respectively, when treated with whole abdominal radiotherapy.

Owing to the fact that radiotherapy seems to provide adequate locoregional protection of the targeted tissues but not systemic control, several authors suggested that combining radiotherapy and chemotherapy may guarantee better locoregional and systemic protection (53,54). Alvarez Secord et al (55), in a multi-institutional series of 265 stage IIIC ECs (type 1 and type 2), reported that patients undergoing chemotherapy alone had a 2.2- and 4.0-fold increased risk of recurrence and death than patients who had chemotherapy plus radiotherapy. In contrast, there was no difference in survival between patients undergoing radiotherapy alone vs chemotherapy plus radiotherapy. Interestingly, the authors showed that among patients undergoing the combined regimen, overall survival for a “sandwich” regimen of chemotherapy plus radiotherapy plus chemotherapy was 98% vs 90% for radiotherapy plus chemotherapy and 82% for chemotherapy plus radiotherapy. However, no difference in disease-free survival was recorded among these 3 combination regimens (55).

In conclusion, in stage IIIC EC, the therapeutic role of chemotherapy remains unproven, especially in type II and more aggressive endometrioid tumor (grade 3) (56).

Lymphadenectomy, like radiotherapy, is a locoregional treatment and likely has limited ability to prevent distant recurrences outside the surgical field, which in turn can be prevented only by an effective systemic treatment. It has been suggested that systemic cytotoxic chemotherapy may be more effective in advanced endometrioid grade 1 and 2 EC and less effective in advanced poorly differentiated EC (17,46,51). For this reason, aggressive locoregional treatment (systematic lymphadenectomy and external radiotherapy) is more likely to improve the overall patient prognosis in tumors that are responsive to systemic adjuvant therapy.

7. How Can We Design a Study to Test the Diagnostic and Therapeutic Role of Lymphadenectomy?

While the role of lymphadenectomy in the identification of patients with lymphatic dissemination is well established, its role in patient selection for targeting postoperative treatment, and therefore decreasing postoperative morbidity and improving QOL, is less clear. Similarly, the available data do not allow us to draw definitive conclusions on the therapeutic value of lymphadenectomy in EC patients. We believe that a trial aimed at demonstrating a therapeutic benefit of lymphadenectomy should focus on patients at significant risk (>15%) of lymph node dissemination (57). Two main questions should be addressed in the trial: 1) Is lymphadenectomy therapeutic or mainly diagnostic for directing postoperative adjuvant treatment? 2) Is lymphadenectomy increasing or decreasing the cumulative treatment-related (surgery with or without adjuvant therapy) morbidity, costs, and QOL? Although it is intuitive that a prospective, randomized controlled trial will best answer these questions, a well-designed prospective cohort study is potentially more feasible and more likely to provide a definitive answer (58).

The diagnostic role of lymphadenectomy in documenting areas of lymphatic dissemination is well recognized in EC. The identification of sites of tumor dissemination allows patient selection and targeting of postoperative treatment.

Based on our data on patterns of lymphatic dissemination in EC, we recently reported that isolated para-aortic dissemination (with negative pelvic nodes) is rare (usually <5%), with the exception of patients with deeply invasive endometrioid grade 2 and 3 cancer, in whom this percentage is higher than 10% (15). For this reason, from a purely diagnostic perspective (ie, if lymphadenectomy is aimed only at identifying those patients with extrauterine disease), pelvic lymphadenectomy is usually sufficient (with the above exceptions, which include only 6% of the overall EC population [14]). However, if lymphadenectomy is therapeutic, as suggested by the SEPAL trial, the para-aortic area needs to be targeted by surgery, radiation, or both in most (if not all) patients with documented lymphatic dissemination in the pelvis (9,32). In these cases, we need also to be aware that para-aortic disease is usually present in the anatomic area above the IMA (15).

After many decades of debate, there are still not convincing data demonstrating a therapeutic role of lymphadenectomy in EC. Why is that? First, lymphadenectomy, like radiotherapy, is a locoregional treatment. For this reason, if lymphadenectomy is therapeutic, it is more likely to improve locoregional control and less likely to affect systemic disease. However, as overall patient survival is mainly driven by the presence of occult systemic disease, in the absence of an efficacious adjuvant systemic treatment, it is unlikely that lymphadenectomy will demonstrate any survival benefits (17). We are therefore in a difficult situation. Patients with poorly differentiated EC (grade 3 or type II) are more likely to present with occult lymphatic dissemination (15), but are also more likely to die of systemic disease (17). But patients with endometrioid grade 1 and 2 cancer are less likely to die of systemic disease and more likely to respond to systemic treatment (51) and to be cured at the time of lymphatic recurrence (14). However, in

these patients, lymphatic dissemination is rare (14,15) (Figure 4), making it very difficult to demonstrate a therapeutic role of lymphadenectomy. Perhaps use of SLN mapping will be helpful for adequate patient selection in patients with low-risk tumor (38-41). The continuing debate about the role of lymphadenectomy will probably end only when molecularly guided imaging or new biologic therapy becomes available to identify and treat systemic metastatic disease.

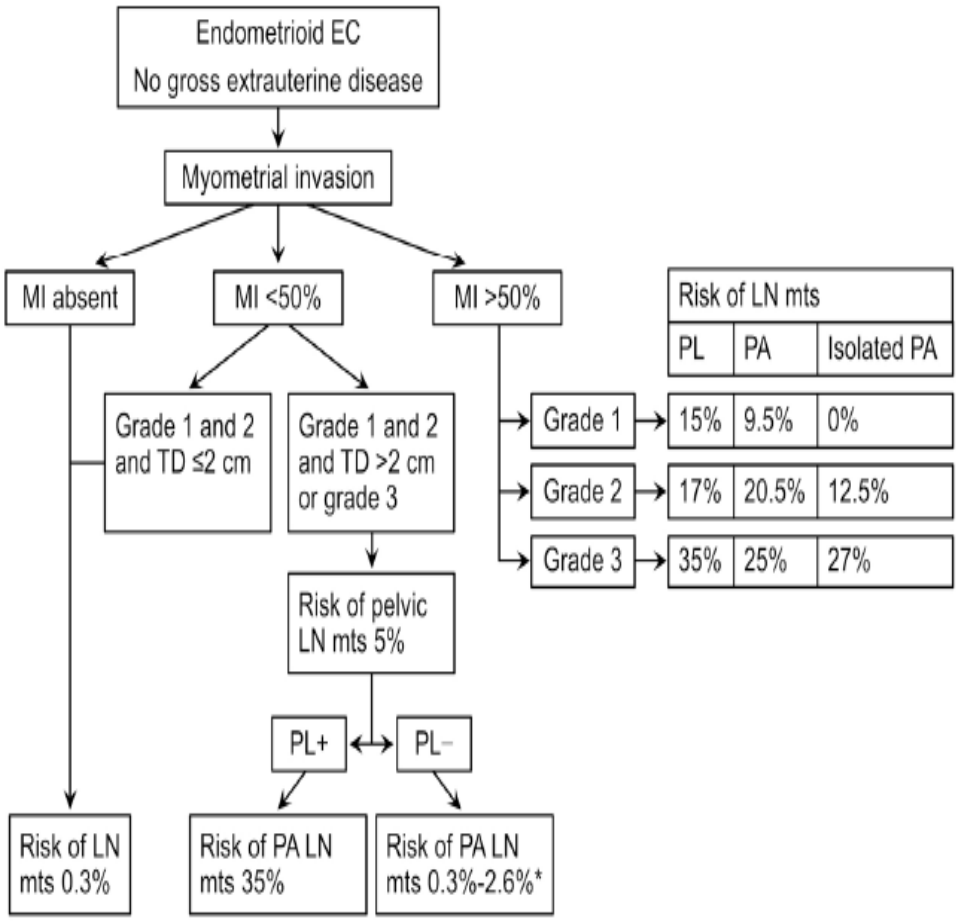


Figure 4: Risk of lymph node metastasis. Para-aortic lymph node metastases may be associated with lymphovascular space invasion. EC indicates endometrial cancer; LN, lymph node; MI, myometrial invasion; mts, metastases; PA, para-aortic; PL, pelvic. (Adapted from Kumar et al [14,15]. Used with permission.)

Table 1. Endometrial Cancer Risk Stratification

Low risk
Endometrioid, grade 1 and 2, MI < 50%, PTD ≤ 2 cm
Endometrioid, MI 0%, any grade or PTD
Low-intermediate risk
Endometrioid, grade 1 and 2, MI < 50%, PTD > 2 cm (or unknown)
High-intermediate risk
Endometrioid, grade 1 and 2, 50% < MI ≤ 66%
Endometrioid, grade 3, MI < 50%
High risk
Nonendometrioid
Endometrioid, grade 1 and 2, MI > 66%
Endometrioid, grade 3, MI > 50%
Adnexal metastasis
Ultra-high risk (IP and EA spread)
Grade 3 EC, USC, and CCC subcohorts

Abbreviations: CCC, clear cell carcinoma; EA, extra-abdominal; EC, endometrial cancer; IP, intra-peritoneal; MI, myometrial invasion; PTD, primary tumor diameter; USC, uterine serous cell carcinoma.

Table 2. Prevalence of Node Metastases in EC "At Risk" for Lymphatic Spread

Type of EC	+PL Nodes, %	+PA Nodes, %	−PL Nodes With +PA Nodes, %
Endometrioid			
G1, MI =<50%[a]	3.8	0.8	0
G1, MI >50%	15.2	9.4	0
G2, MI ≤50%[a]	7.3	5.3	1.4
G2, MI >50%	17.1	20.5	12.5
G3, MI =<50%	6.9	0	0
G3, MI >50%	35.3	25.0	27.3
Nonendometrioid	19.5	13.1	3.4

Abbreviations: –, negative; +, positive; EC, endometrial cancer; G, grade; MI, myometrial invasion; PA, para-aortic; PL, pelvic.

Only patients with tumor diameter >2 cm. Data from Kumar et al (14).

Robotic Surgery

The *da Vinci* Surgical System is a sophisticated robotic platform designed to expand the surgeon's capabilities and offer a state-of-the-art minimally invasive option for major surgery. The *da Vinci* Surgical System is a sophisticated robotic platform designed to expand the surgeon's capabilities and offer a state-of-the-art minimally invasive option for major surgery. With the *da Vinci* Surgical System, surgeons operate through just a few small incisions. The *da Vinci* System features a magnified 3D high-definition vision system and tiny wristed instruments that bend and rotate far greater than the human wrist. As a result, *da Vinci* enables your surgeon to operate with enhanced vision, precision, dexterity and control.

Minimally invasive *da Vinci* uses the latest in surgical and robotics technologies. *da Vinci* is beneficial for performing routine and complex surgery. Your surgeon is 100% in control of the *da Vinci* System, which translates his or her hand movements into smaller, more precise movements of tiny instruments inside your body. *da Vinci* – taking surgery beyond the limits of the human hand. Surgery is the mainstay of treatment for EC patients. Interestingly, in the last decade the EC surgical approach has been dramatically modified (59). Accumulating evidence supports that minimally invasive surgery upholds oncologic effectiveness of open surgery, minimizing peri-operative morbidity (60-66). However, the diffusion of minimally invasive surgery evolved slower than expected (66). In fact, complex laparoscopic procedures require specialized technical skills (59-60). More recently, robotic-assisted technology has been developed in order to overcome limitations of conventional laparoscopic surgery. Robotic-assisted surgery provides better control of instrumentations, precision "scaling" of movements and three-dimensional vision, thus offering technical advantages to the

surgeons and increasing the rate of procedures performed via minimally invasive surgery (64-66).

However, costs related to robotic-assisted surgery are a source of ongoing concerns (67,68). In fact, the main barrier to the diffusion of robotic-assisted technology is represented by its acquisition and instrumentation cost. Recently, several publications assessed the cost-effectiveness of robotic-assisted surgery in comparison to other surgical approaches for EC treatment (67-70). However, these studies did not adjust results based on confounding factors (related to patient-, disease- and surgical-characteristics), thus limiting the interpretation of retrospective data comparisons. Additionally, investigations did not always take into account the increased costs of robotic-assisted surgery during its implementation phase and compared the new and still evolving robotic approach with other consolidated techniques.

Aim of the Study:

In the present invesigation, we sought to evaluate the impact of the introduction of robotic-assisted surgery for EC on treatment-related morbidity and costs of surgical staging. We compared robotic-assisted to standard (open abdominal) staging surgery, thus auditing the experience of a high-volume institution. In addition, we evaluated how outcomes in robotic-assisted surgery improved with time and increasing expertise.

Methods of the study:

The Mayo Clinic Institutional Review Board (IRB) approved the present study. All consecutive patients undergoing surgery for newly diagnosed EC at Mayo Clinic (Rochester MN, USA) during 01/02/2007 to 11/30/2012 were considered. In compliance with the Minnesota Statute for Use of Medical Information in Research, only the medical records for patients who consented to the use of their medical records were retrospectively reviewed.

Inclusion criteria were: (a) primary treatment for epithelial EC; (b) the execution of surgical staging (including hysterectomy plus lymphadenectomy); (c) staging performed via robotic-assisted or open surgery; (d) non-stage IV disease. A small percentage of patients underwent vaginal and laparoscopic hysterectomy and surgical staging (Figure 5). They were excluded from the main analyses in the present study, and they will be analyzed separately in a different study (manuscript in preparation).

Surgical procedures were performed according to Mayo Clinic's surgical guidelines during the time period of the study. Details of the algorithm in use at Mayo Clinic are reported elsewhere (2). The open abdominal approach was the standard of care until 2006, with few exceptions (59,60). In 2007, we started a gradual implementation of the use of robotic-assisted surgery (59,60). Detailed descriptions of our surgical techniques and clinical protocols regarding perioperative patients' management are reported elsewhere (2,71-73). During the study period there were no significant differences in the clinical pathway for women undergoing surgery for EC.

Figure 5.

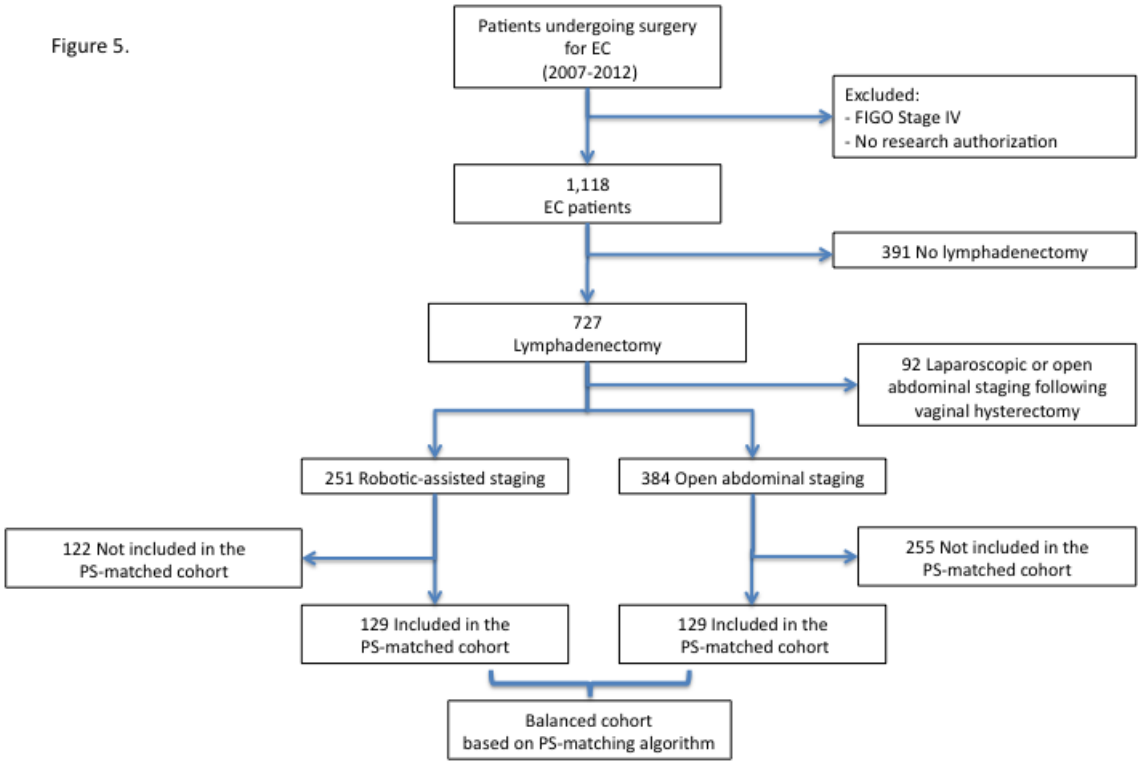


Figure 5: Study design

Demographic-, disease- and treatment-specific characteristics of patients were abstracted from the medical records. Data included general demographic characteristics, obstetrical, past medical (comorbidity conditions were classified by the Charlson comorbidity index (74)) and surgical histories, surgical results (operative time, blood loss, blood transfusion, uterine weight, as well as intraoperative and postoperative complications), length of stay, date of last-follow-up, and vital status (74,75). Operative times were recorded from the first skin incision to the last suture (skin to skin); for robotic-assisted procedures, operative times also included robot-docking time. Data on blood loss were extracted from surgical records, as estimated by the surgeon during the procedure. Hospital stay was calculated from the admittance date. Intraoperative

complications included any unintentional opening or damage to any organs or structures. We classified conversions as either conversions needed for completing staging procedures (mostly due to the inability to perform a high para-aortic lymphadenectomy via a robotic-assisted trans-peritoneal approach in obese patients) or conversions needed to manage intra-operative surgical complications or technical difficulties. The patient's surgical modality was considered based on the intent to treat principle; hence, patients who had a conversion from a robotic-assisted to open approach were included in the robotic-assisted group. Postoperative complications were included if they occurred within 30 days after surgery. Only data about grade 2 or higher postoperative complications (according to the Accordion Severity Classification (76) were collected.

Cost data for patients included in the study were captured from the Mayo Clinic Cost Data Warehouse (MCCDW), formerly known as the Olmsted County Healthcare Utilization and Cost Database (OCHEUD) (60)]. MCCDW provides inflation-adjusted standardized costs as per Medicare reimbursement rates for every service and procedure received by patients at Mayo Clinic, including inpatient and outpatient and emergency room visits. While the details of the costing method is provided elsewhere (60), briefly, MCCDW uses a Medicare cost-to-charge ratio that is established for each calendar year to value Medicare Part A items (e.g., room and board), while Medicare Part B reimbursement rates are applied for costing items in the Part B list (e.g., physician consultation, diagnostic and therapeutic procedures). For each patient in this study, standardized costs were extracted from the date of surgery through 30 days post-surgery and inflated to 2012 values.

Since the type of procedure (robotic-assisted versus open) was not randomly assigned in this retrospective cohort, we used propensity score (PS) matching to obtain matched cohorts with potentially balanced differences in measured baseline patient characteristics . A PS was defined as the estimated probability of a patient having a robotic-assisted procedure given a set of measured baseline patient covariates, and was derived from a multivariable logistic regression model that included the following 9 covariates: age (and age^2), BMI, Charlson index, ASA, prior abdominal surgery (yes vs. no), parity, prior cesarean section (yes vs. no), preoperative histology (endometrioid vs. non-endometrioid vs. complex hyperplasia), and preoperative FIGO grade. Prior to fitting the logistic model, missing values were imputed for patients with missing BMI or Charlson index using the overall median for each covariate. Patients who underwent a robotic-assisted procedure were matched 1:1 to patients who underwent an open procedure using a greedy matching algorithm that matched on a) the logit of the PS within 0.2 of the standard deviation of the logit, b) surgery date within 180 days in the same calendar year, and c) histology. For each robotic-assisted case, a patient with an open procedure was randomly selected from the potential pool of patients with an open procedure defined by the matching calipers. Standardized differences for each covariate were calculated to assess the balance between the matched groups. Comparisons were made between the two procedures groups (full cohort of open vs. robotic-assisted; matched cohort of open vs. robotic-assisted) using the chi-square test or Fisher's exact test for categorical variables and the Wilcoxon rank sum test for all other variables. All calculated p-values were two-sided and p-values less than 0.05 were considered statistically significant. Statistical analysis was performed using the SAS software package, version 9.3 (SAS Institute, Inc.; Cary, NC).

Results:

During the study period, 1,118 consecutive EC patients (with non-stage IV disease) had primary surgical treatment at our institution. Among these, 727 patients had surgical staging: 92 (13%) had a combination of vaginal and laparoscopic surgery, 251 (35%) had robotic-assisted surgery, and 384 (53%) had open staging (Figure 5 and 6). The proportion of robotic-assisted procedures per calendar year increased over the study period, while the proportion of open surgeries declined dramatically ($p<0.001$). Specifically, the proportion of robotic-assisted procedures increased from 4% in 2007 to 56% in 2012, whereas the proportion of open procedures decreased from 79% in 2007 to 34% in 2012 (Figure 6).

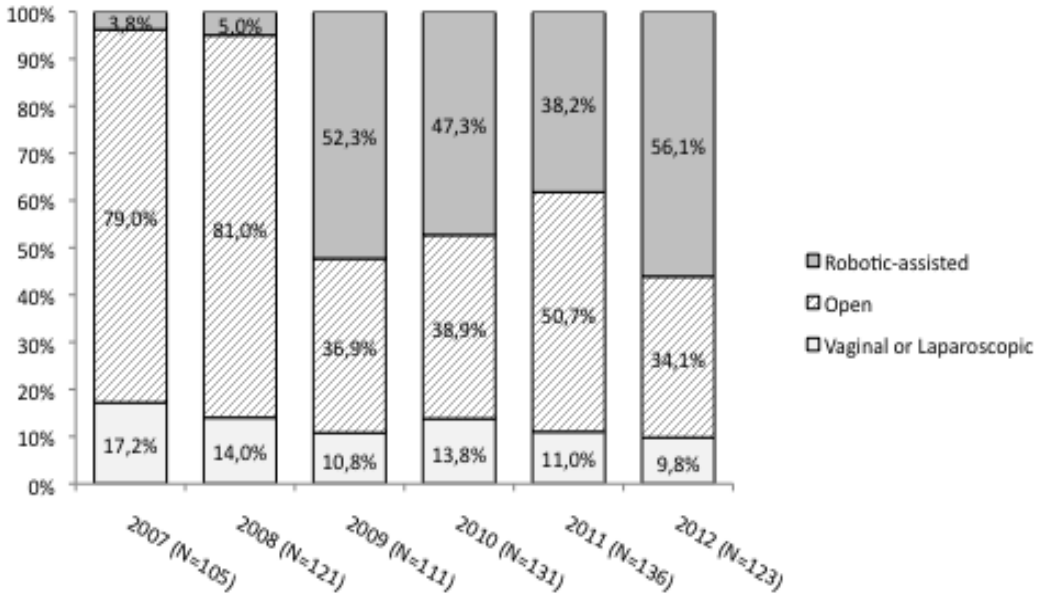


Figure 6 : Changes in surgical approaches over the time

The results hereafter focus on the patients with either surgical staging via robotic-assisted or open surgery (251 robotic and 384 open). The left-hand side of Table 3 reports the general demographic and preoperative characteristics of patients.

In comparison to open abdominal procedures, robotic-assisted surgery correlated with lower postoperative complications rate within 30 days, lower peri-operative transfusion rate, lower readmission rate within 30 days of the surgery, shorter median length of hospital stay, but longer operating time. . Patients in the robotic-assisted surgery cohort had significantly lower median costs from surgery to discharge ($18,517 vs. 19,737; p=0.024), than patients treated with open surgery. Consistent with the shorter operating time for the open cohort, costs of the operative room and anesthesia were significantly lower in the open cohort. Likewise, consistent with the shorter length of hospital stay in the robotic-assisted cohort, the total "room and board" costs for the initial hospitalization were significantly lower in the robotic-assisted cohort. Surgery-related outcomes and costs are summarized in Table 4.

Of note, we observed that one of the factors impacting costs in the robotic group was conversion from robotic-assisted to open surgery. Overall 26 (10%) conversions occurred. The reasons for conversion included need to complete comprehensive surgical staging for the presence of high-risk disease and/or positive lymph nodes at frozen section analysis (n=22), bleeding (n=2), adhesions (n=1) and technical issues (n=1). The median cost of the initial hospitalization was $5,951 higher for robotic assisted patients who had a conversion compared to robotic-assisted patients who did not have a conversion; the median total cost from surgery to 30 days post-surgery was $7,579 higher between these two groups. Table 5 reports outcomes based on all 251 robotic-assisted cases, separately for the converted and not converted.

PS-Matched analysis comparing robotic-assisted and open staging surgery

The unadjusted results described above are based on two cohorts that differ in terms of clinical variables. In fact, cases treated with open surgery had significantly higher risk features (like grade 3, non-endometrioid histology – Table 3) in comparison to patients included in the robotic-assisted cohort. For this reason, in order to perform a more appropriate comparison of similar patients, we used PS methodology to obtain matched cohorts with potentially balanced differences in measured baseline patient characteristics. A total of 129 propensity-matched pairs (258 patients) undergoing staging were identified. By doing this, we excluded mainly patients in the open group who had high-risk characteristics (grade 3, non-endometrioid histology), with associated higher morbidity and costs, and patients in the robotic-assisted group with low risk characteristics and associated lower morbidity and costs (data not shown). The right-hand side of Table 3 summarizes baseline characteristics within the PS-matched cohort and presents the standardized difference for each covariate within the full cohort and the PS-matched cohort. The decrease in the total standardized difference for the full cohort of patients with open and robotic-assisted procedures compared with the matched cohort (2.791 to 0.582, respectively) demonstrates a substantial reduction (79%) in bias due to measured covariates with PS-matching methodology. The similar distribution of PS values between the two matched groups is displayed in Figure 7.

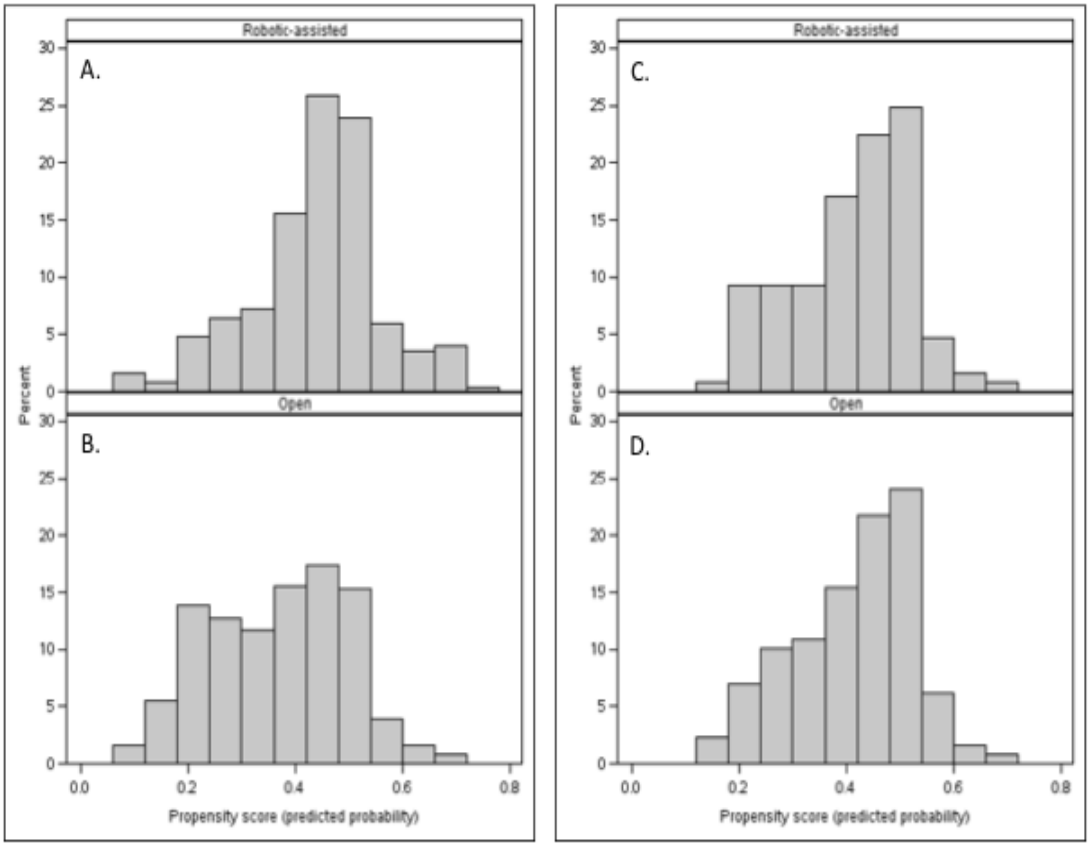


Figure 7: Distribution of propensity-score values

Surgery-related outcomes and costs compared between the PS-matched groups are summarized in Table 6 The proportion of patients with an intraoperative complication was statistically similar in the two groups, as was the proportion with a postoperative grade 3 or higher complication within 30 days. However, patients with a robotic-assisted surgery had a significantly lower postoperative grade 2 or higher complication rate (7.0% vs. 20.2%; p=0.007), lower blood transfusion rate (3.1% vs. 24.0%; p<0.001), longer operating time (median, 4.6 vs. 2.5 hours; p<0.001), and shorter length of stay (median, 1 vs. 3 days; p<0.001). Readmission rate was lower after robotic than open surgery (5.4% vs. 9.3%); however this difference was not statistically

significant (p=0.23) Overall, the median total cost from surgery to 30 days post-surgery was similar in the PS-matched groups, (open approach was $58 (difference in medians) more costly than robotic staging; p=0.66). Similarly, no significant difference between open and robotic-assisted was observed in total costs from admit to discharge (difference in medians, $96; p=0.30). Robotic-assisted surgery had significantly higher median operating room costs (difference in medians, $2,530; p<0.001), but lower median "room and board" costs (difference in medians $2,407); p<0.001) in comparison to open surgery.

Comparison of Early and Late Phases of Robotic-Assisted Surgery

Robotic-assisted surgery was introduced in 2007 at our institution. Due to the initial "implementation phase", through the study period [2007-2008 (n=10) vs. 2009-2010 (n=120) vs. 2011-2012 (n=121)] the increasing experience with robotic-assisted staging correlated with a decrease of operative time, length of stay, conversions as well as readmissions rates among our robotic-assisted population (p<0.05; Table 7).

Table 3: Summary of the baseline characteristics and the standardized differences within the full cohort and the PS-matched pairs cohort.

Characteristic	Full cohort			PS-matched pairs		
	Robotic (N=251)	Open (N=384)	Standardized differences	Robotic (N=129)	Open (N=129)	Standardized differences†
Age (years), mean (SD)	62.9 (10.0)	64.1 (10.7)	0.114	63.2 (9.9)	62.1 (10.7)	0.105
BMI (kg/m2), mean (SD)	35.0 (9.2)	34.2 (8.9)	0.094	34.7 (9.5)	35.3 (8.4)	0.067
Charlson index, mean (SD)	3.0 (1.8)	3.4 (2.2)	0.197	3.0 (1.8)	3.2 (2.2)	0.067
ASA ≥2, N (%)	94 (37.5%)	167 (43.5%)	0.123	52 (40.3%)	54 (41.9%)	0.032
Parity, mean (SD)	2.2 (1.9)	2.4 (1.8)	0.136	2.1 (1.6)	2.1 (1.6)	0.048
Prior cesarean section, N (%)	35 (13.9%)	30 (7.8%)	0.198	8 (6.2%)	12 (9.3%)	0.116
Prior abdominal surgery, N (%)	100/244 (41.0%)	150/375 (40.0%)	0.016	52/129 (40.3%)	55/128 (43.0%)	0.047
Preoperative histology, N (%)						
Non-endometrioid	37 (14.7%)	107 (27.9%)	0.325	25 (19.4%)	25 (19.4%)	0
Endometrioid	200 (79.7%)	238 (62.0%)	0.397	100 (77.5%)	100 (77.5%)	0
Complex hyperplasia	8 (3.2%)	10 (2.6%)	0.035	2 (1.6%)	2 (1.6%)	0
No endometrial sampling	6 (2.4%)	29 (7.6%)	0.239	2 (1.6%)	2 (1.6%)	0
Preoperative grade, N (%)						
1	129 (51.4%)	133 (34.6%)	0.343	56 (43.4%)	59 (45.7%)	0.047
2	61 (24.3%)	87 (22.7%)	0.039	34 (26.4%)	32 (24.8%)	0.036
3	55 (21.9%)	135 (35.2%)	0.296	37 (28.7%)	36 (27.9%)	0.017
No endometrial sampling	6 (2.4%)	29 (7.6%)	0.239	2 (1.6%)	2 (1.6%)	0

† The standardized differences based on the comparisons using the PS-matched pairs are all below the recommended threshold of 0.10, except for two at 0.105 and 0.116. The percent reduction in the overall standardized differences was 79.1%.

Table 4: Surgery-related outcomes and costs of open and robotic-assisted surgical staging

Outcome	Open (N=384)	Robotic-Assisted (N=251)	p value‡
Intraoperative complication, N (%)	5 (1.3%)	1 (0.4%)	0.41
Postoperative complication grade 2+, N (%) †	92 (24.0%)	16 (6.4%)	<0.001
Postoperative complication grade 3+, N (%) †	37 (9.6%)	8 (3.2%)	0.002
Blood transfusion, N (%)	87 (22.7%)	11 (4.4%)	<0.001
Operating time (hours), Median (IQR)	2.8 (2.3, 3.6)	4.5 (3.6, 5.4)	<0.001
Length of stay (days), Median (IQR)	4 (3, 5)	1 (1,2)	<0.001
Readmitted within 30 days, N (%)	49 (12.8%)	9 (3.6%)	<0.001
Costs *			
Overall, surgery to 30 days post-surgery			0.024
Mean (SD)	23075 (12353)	20393 (6638)	
Median (IQR)	19737 (16568, 25275)	18517 (16572, 22575)	
Initial hospitalization, surgery to discharge			0.21
Total			
Mean (SD)	20217 (6003)	19333 (4752)	
Median (IQR)	18949 (16196, 22263)	18203 (16330, 21248)	
Index procedure			0.19
Mean (SD)	2248 (567)	2122 (325)	
Median (IQR)	2127 (2061, 2269)	2128 (2075, 2176)	
Anesthesia (index procedure)			<0.001
Mean (SD)	679 (161)	860 (165)	

Outcome	Open (N=384)	Robotic-Assisted (N=251)	p value‡
Median (IQR)	686 (585, 765)	854 (757, 960)	
Operating room (index procedure)			<0.001
Mean (SD)	4461 (763)	7296 (1195)	
Median (IQR)	4393 (3929, 4807)	7014 (6391, 8137)	
Room and board			<0.001
Mean (SD)	4968 (2845)	1942 (1891)	
Median (IQR)	4180 (3284, 5654)	1191 (1045, 2334)	
Discharge to 30 days post-surgery			0.68
Mean (SD)	2859 (10018)	1060 (3922)	
Median (IQR)	0 (0, 358)	0 (0, 318)	

Abbreviation: ICU, intensive care unit; IQR, interquartile range; Room and board costs included costs of regular room as well as any ICU stay.

† Postoperative complications were within 30 days of the surgery and were graded per the Accordion classification as part of the data collection. [76]

‡ Comparisons based on the chi-square test or Fisher's exact test for categorical variables and the Wilcoxon rank sum test for all other variables.

* Costs were set based on the Medicare cost-to-charge ratio for each calendar year and inflated to 2012 US dollars.

Table 5: Surgery-related outcomes and costs of patients experiencing conversion from robotic-assisted to open surgery

Outcome	Robotic-Assisted, Not converted (N=225)	Robotic-Assisted, Converted (N=26)	p value‡
Intraoperative complication, N (%)	1 (0.4%)	0	1.00
Postoperative complication grade 2+, N (%) †	11 (4.9%)	5 (19.2%)	0.016
Postoperative complication grade 3+, N (%) †	6 (2.7%)	2 (7.7%)	0.20
Blood transfusion, N (%)	7 (3.1%)	4 (15.4%)	0.018
Operating time (hours), Median (IQR)	4.4 (3.5, 5.2)	5.6 (4.6, 6.6)	<0.001
Length of stay (days), Median (IQR)	1 (1, 2)	3 (3, 4)	<0.001
Readmitted within 30 days, N (%)	7 (3.1%)	2 (7.7%)	0.24
Cost *			
Overall, surgery to 30 days post-surgery			<0.001
Mean (SD)	19468 (5700)	28398 (8671)	
Median (IQR)	18126 (16330, 21060)	25705 (23233, 29297)	
Initial hospitalization, surgery to discharge			<0.001
Total			
Mean (SD)	18620 (3978)	25499 (6317)	
Median (IQR)	17718 (16036, 20232)	23669 (22159, 27434)	
Index procedure			0.045
Mean (SD)	2103 (298)	2290 (477)	
Median (IQR)	2124 (2088, 2176)	2201 (2074, 2502)	

Outcome	Robotic-Assisted, Not converted (N=225)	Robotic-Assisted, Converted (N=26)	p value‡
Anesthesia (index procedure)			<0.001
Mean (SD)	849 (164)	955 (143)	
Median (IQR)	845 (751, 942)	976 (875, 1027)	
Operating room (index procedure)			0.21
Mean (SD)	7270 (1179)	7526 (1332)	
Median (IQR)	6949 (6391, 8115)	7380 (6813, 8189)	
Room and board			<0.001
Mean (SD)	1643 (1473)	4525 (2928)	
Median (IQR)	1167 (1008, 2244)	3567 (3236, 4765)	
Discharge to 30 days post-surgery			0.002
Mean (SD)	848 (3274)	2900 (7338)	
Median (IQR)	0 (0, 235)	348 (0, 2187)	

Abbreviation: ICU, intensive care unit; IQR, interquartile range; Room and board costs included costs of regular room as well as any ICU stay.

† Postoperative complications were within 30 days of the surgery and were graded per the Accordion classification as part of the data collection. [76]

‡ Comparisons based on the Fisher's exact test for categorical variables and the Wilcoxon rank sum test for all other variables.

* Costs were set based on the Medicare cost-to-charge ratio for each calendar year and inflated to 2012 US dollars.

Table 6: Comparison of surgery-related outcomes and costs based on the 129 propensity score-matched pairs of open and robotic-assisted cases.

Outcome	Open (N=129)	Robotic-Assisted (N=129)	p value‡
Intraoperative complication, N (%)	1 (0.8%)	1 (0.8%)	1.00
Postoperative complication grade 2+, N (%) †	26 (20.2%)	9 (7.0%)	0.002
Postoperative complication grade 3+, N (%) †	9 (7.0%)	5 (3.9%)	0.27
Blood transfusion, N (%)	31 (24.0%)	4 (3.1%)	<0.001
Operating time (hours), Median IQR)	2.5 (1.9, 3.2)	4.6 (3.9, 5.3)	<0.001
Length of stay (days), Median (IQR)	3 (2, 4)	1 (1, 2)	<0.001
Readmitted within 30 days, N (%)	12 (9.3%)	7 (5.4%)	0.23
Costs *			
Overall, surgery to 30 days post-surgery			0.66
Mean (SD)	21856 (11463)	20892 (7472)	
Median (IQR)	18811 (16248, 23039)	18753 (16909, 22575)	
Initial hospitalization, surgery to discharge			0.30
Total			
Mean (SD)	19430 (5648)	19509 (4967)	
Median (IQR)	18317 (15500, 21345)	18413 (16786, 20917)	
Index procedure			0.99
Mean (SD)	2228 (327)	2116 (335)	
Median (IQR)	2126 (2075, 2224)	2128 (2097, 2180)	
Anesthesia (index procedure)			<0.001
Mean (SD)	722 (127)	849 (171)	

Outcome	Open (N=129)	Robotic-Assisted (N=129)	p value‡
Median (IQR)	710 (650, 772)	859 (751, 960)	
Operating room (index procedure)			<0.001
Mean (SD)	4615 (842)	7271 (1070)	
Median (IQR)	4419 (3982, 5059)	6949 (6508, 8115)	
Room and board			<0.001
Mean (SD)	4390 (2569)	1983 (2015)	
Median (IQR)	3574 (2422, 4843)	1167 (1008, 2334)	
Discharge to 30 days post-surgery			0.79
Mean (SD)	2426 (8768)	1383 (4953)	
Median (IQR)	0 (0, 269)	0 (0, 318)	

Abbreviation: ICU, intensive care unit; IQR, interquartile range; Room and board costs included costs of regular room as well as any ICU stay.

† Postoperative complications were within 30 days of the surgery and were graded per the Accordion classification as part of the data collection. [76]

‡ Comparisons based on the chi-square test or Fisher's exact test for categorical variables and the Wilcoxon rank sum test for all other variables.

* Costs were set based on the Medicare cost-to-charge ratio for each calendar year and inflated to 2012 US dollars.

Table 7: Comparison across time periods of baseline characteristics and surgery-related outcomes among patients with a robotic-assisted surgery.

Characteristic	2007-2008 (N=10)	2009-2010 (N=120)	2011-2012 (N=121)	p value‡
Age (years), mean (SD)	63.2 (8.3)	62.1 (10.5)	63.6 (9.5)	0.48
BMI (kg/m^2), mean (SD)	32.8 (6.2)	35.6 (10.2)	34.6 (8.3)	0.54
Charlson index, mean (SD)	3.0 (1.3)	3.0 (1.7)	3.0 (1.9)	0.99
ASA ≥2, n (%)	5 (50.0%)	42 (35.0%)	47 (38.8%)	0.58
Parity, mean (SD)	1.7 (1.3)	2.2 (2.2)	2.2 (1.7)	0.71
Prior cesarean section, n (%)	0 (0.0%)	17 (14.2%)	18 (14.9%)	0.42
Prior abdominal surgery, n (%)	4 (40.0%)	54 (45.0%)	42 (34.7%)	0.26
Preoperative histology, n (%)				0.74
Non-endometrioid	3 (30.0%)	15 (12.5%)	19 (15.7%)	
Endometrioid	7 (70.0%)	99 (82.5%)	94 (77.7%)	
Complex hyperplasia	0 (0.0%)	3 (2.5%)	5 (4.1%)	
No endometrial sampling	0 (0.0%)	3 (2.5%)	3 (2.5%)	
Preoperative grade, n (%)				0.83
1	4 (40.0%)	60 (50.0%)	65 (53.7%)	

Characteristic	2007-2008 (N=10)	2009-2010 (N=120)	2011-2012 (N=121)	p value‡
2	2 (20.0%)	32 (26.7%)	27 (22.3%)	
3	4 (40.0%)	25 (20.8%)	26 (21.5%)	
No endometrial sampling	0 (0.0%)	3 (2.5%)	3 (2.5%)	
Intraoperative complication, N (%)	0 (0.0%)	1 (0.8%)	0 (0.0%)	0.52
Postoperative complication grade 2+, N (%) †	2 (20.0%)	9 (7.5%)	5 (4.1%)	0.11
Postoperative complication grade 3+, N (%) †	1 (10.0%)	3 (2.5%)	4 (3.3%)	0.33
Blood transfusion, N (%)	1 (10.0%)	7 (5.8%)	3 (2.5%)	0.30
Operating time (hours), Median IQR)	6.1 (5.4, 7.0)	4.4 (3.6, 5.4)	4.3 (3.5, 5.1)	0.002
Conversion, N (%)	3 (30.0%)	10 (8.3%)	13 (10.7%)	0.11
Length of stay (days), Median (IQR)	2 (2, 3)	1 (1, 2)	1 (1, 2)	0.002
Readmitted within 30 days, N (%)	2 (20.0%)	4 (3.3%)	3 (2.5%)	0.06

Abbreviation: ICU, intensive care unit; IQR, interquartile range; Room and board costs included costs of regular room as well as any ICU stay.

† Postoperative complications were within 30 days of the surgery and were graded per the Accordion classification as part of the data collection. [18]

‡ Comparisons based on the chi-square test or Fisher's exact test for categorical variables, the F-test from a one-way ANOVA model for age, BMI, Charlson index, and parity, and the Kruskal-Wallis test for operating time and length of stay.

Conclusions:

The present study evaluated how the introduction of robotic-assisted surgery influenced morbidity and costs related to EC staging, thus demonstrating a number of noteworthy findings. First, our results demonstrated that the implementation of robotic-assisted technology has reduced the rate of open abdominal staging for EC patients. Second, we observed that patients with EC who are surgically staged using robotic-assisted surgery have significantly better perioperative outcomes (postoperative complications, transfusions, length of stay, readmissions) and lower overall costs when compared to patients staged with open surgery. When taking into account the differences between the two cohorts (patients who had open surgery had more aggressive cancers), and considering only a PS-matched population, perioperative clinical outcomes were still significantly better in the robotic-assisted population, but with similar total costs. Third, we observed that conversion from robotic-assisted to open surgery increases morbidity and costs, thus suggesting the need (when possible) to maximize our attempts to complete surgery with a minimally invasive approach. Fourth, our data suggested that increased experience in robotic-assisted surgery correlates with improved surgical outcomes, with potential improved patients' turnover and costs' saving.

Although robotic-assisted surgery has been harshly criticized to be costly and unnecessary, robotic-assisted surgery is increasingly being used in the setting of both benign and malignant diseases (77,78). Interestingly, as of December 31, 2014, 2,233 da Vinci robotic systems have been installed in the US, with more than 1,200 gynecologic surgeons who have been trained to use this device (77,78). Owing these features, thorough investigation of the economic impact of robotic-assisted surgery on healthcare

system is paramount. In fact, costs of acquisition of the surgical system ($0.6M-$2.5M), maintenance fees ($100,000-$170,000, annually) and instruments and accessories represent the main barrier against its universal adoption (77,78).

As demonstrated by the present paper and others, the implementation of robotic-assisted surgery is associated with a reduction of open abdominal procedure rates (63,69,77). Lau et al. reported that the introduction of robotic-assisted surgery increases the number of patients undergoing staging surgery via a minimally invasive approach, thus improving patients outcomes and reducing the overall hospital costs (63). Similarly, Leitao et al., in a cost modeling based on a theoretical scenario characterized by the implementation of robotic-assisted surgery into a clinical setting (in which the rate of laparoscopic procedures is stable over the years), observed that the introduction of robotic-assisted surgery decreases costs, reducing open abdominal procedure rates (69). However, two criticisms of this model are: (a) these results arise from a hypothetical model; (b) the model is based on the results of a comparison in which patients had planned robotic-assisted and open abdominal procedures on the basis of constitutional and disease variables; hence, we can expect (like in our first unmatched comparison in Table 1) that the two groups are not fully comparable. Our investigation overcomes these two concerns. In fact, our study is the first demonstrating the beneficial effect of the introduction of robotic-assisted surgery into a preexisting clinical setting, utilizing the PS analysis. This analysis enabled us to balance observed covariates between patients in the two surgical groups, and thereby obtain potentially less biased comparisons of outcome measures between the two approaches. As supported by the findings of other authors, we observed that robotic-assisted surgery increases costs related to the surgical procedure itself, especially due to the longer operative time

needed to perform staging when compared to open surgery; but, costs related to the postoperative period are decreased due to a shorter length of hospital stay and a lower rate of complications. Moreover, the introduction of robotic-assisted surgery may improve patients' turnover. At academic medical centers such as ours, limited bed capacity is an ongoing concern. There are concerted efforts to reduce length of hospital stay based on clinical guidelines and benchmarked comparative length of stay data, and bed control staff monitor bed availability and facilitate patient flow. Our unmatched data demonstrated that robotic-assisted surgery has a lower length of stay compared to open surgery (1 vs. 4 days), and this reduction has helped facilitate hospital patient flow and increased patient access to our hospital gynecologic surgery unit. Based on the data of our institution, over the study period, robotic-assisted surgery may potentially have saved 750 bed days, thus allowing for care of additional patients without increase in facility or staff. In fact, considering patients undergoing endometrial cancer surgical staging via robotic-assisted approach versus an open approach, over the six-year study period, 250 to 500 additional patients could have been served within the surgical hospital unit by utilizing robotic-assisted surgery.

While some previous health economic publications have focused on the cost of care from admission to discharge, we expanded this time horizon to include the 30-day readmission period in addition to the initial admit to discharge period. We included the readmission time period as hospitals are increasing focusing on readmission rates and their associated cost and especially given the focus within the Affordable Care Act (79). The Hospital Readmissions Reductions Program, which started on October 1, 2012 (FY '13), cut up to 1% of Medicare inpatient payments for hospitals with excess readmissions for patients with pneumonia, heart failure, and acute myocardial

infarctions. This penalty increased to 2% in FY ’14, and starting on October 1, 2015 (FY ’15), the maximum penalty for excess readmissions is 3%, which is the highest allowable based on ACA regulations. Added to the list of clinical indications included in the Hospital Readmissions Reductions Program in FY ’15 are chronic obstructive pulmonary disease and knee and hip arthroplasty. Although surgical interventions are not on the list of indications included in the Hospital Readmissions Reductions Programs, readmissions for any cause impact hospital throughput, capacity, and financials, and this is true even at our institution. Data from our unmatched group indicates that robotic-assisted surgery had a lower readmission rate (3.6% vs. 12.8%) compared to open surgery. On average, readmissions cost to our institution for endometrial cancer patients is $ 13,263. To calculate a cost savings due to the reduction in readmission attributable to robotic-assisted surgery, we utilized the unmatched data as it demonstrates the true change in practice patterns. Over the time period of our analysis, robotic-assisted surgery saved the institution more than $ 3,000,000.00 (0.92 X 251 robotic patients X $13,263 (average cost of readmission)) due to lower readmission rates. Similarly other authors have shown that, compared to open surgery, robotic-assisted surgery has the ability to significantly lower readmission rates and in turn, save costs (63,67,69,70), which are crucial elements in today’s healthcare environment.

Another interesting point of the present investigation, which was not analyzed by previously published studies on this issue, is represented by the evaluation of the impact of the initial “implementation phase” on the cost-effectiveness of robotic-assisted surgery. Interestingly, we observed that increasing expertise in robotic-assisted surgery improves surgery-related outcomes, including a significant decrease of readmissions. Although it is not possible provide a fair comparison on costs between

different time periods (since costs are established each year based on the Medicare cost-to-charge ratio for that calendar year), we can speculate that the reduction of operative time, length of hospital stay and complication rates potentially play a role in minimizing the burden of the healthcare

Another point deserving attention is the exclusion of patients undergoing laparoscopic staging. However, as it is evident from figures 1 and 2, historically, laparoscopy had a limited role in our department. Only the advent of robotic surgery allowed having a clear shift from open to minimally invasive surgery in endometrial cancer at our Institution, like in the rest of the US and Canada (63, 69). Also, it is generally suggested that robotic-assisted surgery increased costs in comparison to conventional laparoscopic surgery (67-69). However, these costs only reflect the hospital standpoint; while previously published investigations suggested that the main advantages of the robotic-assisted surgery are based on the reduction of costs from a societal prospective (i.e. the possibility for more women to have access to minimally invasive surgery), thus suggesting the need of further studies comparing robotic and laparoscopic staging procedures.

The main weaknesses of the present study include the inherent biases of a single institution, non-randomized study design. Additionally, we did not consider amortization costs, which obviously may influence our results, in institutions lacking robotic system. However, as aforementioned many institutions already have robotic systems in the US. Therefore our results clearly reflect a commonly observed scenario.

Strengths of the present study include the large sample size, and the use of a PS analysis, which reduces the potential bias of measured covariates driving the choice of

surgical approach. Moreover, other novelties of the present investigation include the evaluation of the impact of the initial "implementation phase" and conversions on costs of EC patients surgically staged via the robotic-assisted approach.

In conclusion, the present study evaluated the impact of the implementation of robotic-assisted technology on morbidity and costs of surgically staged EC. Our findings demonstrated that the implementation of robotic-assisted surgery, in a setting of surgically staged EC, allows more patients to be treated with minimally invasive surgery, thus decreasing morbidity and overall costs. The observed decrease in length of hospital stay and readmission introduced with robotic-assisted surgery promotes a more rapid turnover of patients, thus improving patient access, in comparison with open surgery. Increasing experience with robotic-assisted platform and attempts to decrease conversions significantly improve patient outcomes and potentially decrease costs.

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Confict of Interest:

In 2013, Dr Bogani worked as a research fellow supported by the University of Insubria, Varese, Italy, and Fondo Miglierina, Provincia di Varese, Italy. The present thesis reported the cumulative results of two investigation (one published (reference: 80) and the another one still under consideration for publication)

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