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Date: November 7, 2017

Comparing Surgical Route for Type II Endometrial Cancer: Perioperative and Long Term Clinical Outcomes

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Comparing Surgical Route for Type II Endometrial Cancer: Perioperative and Long Term Clinical Outcomes

By

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ABSTRACT

Comparing Surgical Route for Type II Endometrial Cancer: Perioperative and Long Term Clinical Outcomes

By Leda Portia A. Gattoc, MD

Objectives: Type II endometrial cancers (serous, clear cell and carcinosarcoma) only account for approximately 10% of cancers, but they are responsible for a significant proportion of the morbidity and mortality. The goal of this study was to compare survival and perioperative outcomes in women with type II endometrial cancers who underwent staging via laparotomy (XL) vs. minimally invasive approach (MIS).

Methods: All patients who underwent surgery for Type II endometrial cancer at two academic cancer centers in Detroit, Michigan between January 2005 and December 2015 were retrospectively reviewed. Patients who received neoadjuvant chemotherapy or radiation, and those with endometrioid histology were excluded. Clinical, demographic characteristics, surgical outcomes were examined using univariate and multivariable analysis. Survival analysis was calculated using Kaplan-Meier estimates and Cox proportional hazards regression.

Results: A total of 249 patients were included, 193 underwent laparotomy, and 58 MIS, including conventional laparoscopic or robotic surgery. The majority had stage I disease (IA, 104 [41.3%] and IB, 20[7.9%]). Stages II, III, and IV were identified in 18 (7.1%), 79 (31.6%), and 31 (12.4%) respectively. Multivariate analysis demonstrated being African American (OR 0.29; 95%CI 0.14 - 0.61), having mixed histology(OR 0.29; 95% CI 0.16 - 0.98), and stage III-IV disease (OR 0.46; 95%CI 0.21-0.97) were inversely associated with undergoing MIS. MIS was associated with ability to complete staging. Higher perioperative transfusions, EBL >250 cc and longer hospital stay were also associated with laparotomy. Higher lymph node yield was associated with MIS compared to laparotomy. Recurrence rate was 38 % for the laparotomy group and 19% for MIS. There was no difference in 3 year-PFS after controlling for age, race, procedure, histology, stage and adjuvant therapy. There was no difference in overall survival between laparotomy and MIS for type II endometrial cancers in this series.

Conclusions: Certain clinical and demographic factors such as African American race, mixed histology and stage were associated with undergoing laparotomy for type II endometrial cancers. MIS approaches offered less morbidity and ability to complete staging.

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INTRODUCTION

Endometrial cancer is the most common gynecologic malignancy with an estimated 61,380 new cases in the United States in 2017 and 10,920 deaths [1]. In 1983, endometrial cancer was subdivided into two subtypes with different clinical behavior and prognosis [2]. Type I endometrial cancers are characterized by early stage and low grade presentation with a good clinical prognosis. Pathologically, these are endometriod type. Type II endometrial cancers are characterized by poor differentiation, increased incidence of metastatic spread and poor prognosis [3]. These are non-endometrioid histologies: uterine serous, mucinous, clear cell, mixed cell, carcinosarcoma and undifferentiated [4-8]. Uterine serous carcinoma is characterized by its aggressive clinical behavior resembling that of serous ovarian carcinoma. It represents only 10% of all endometrial cancers but accounts for >50 % of deaths and relapses [9, 10]. Clear cell endometrial cancer is rare and accounts for <5% of cases [11]. It is also clinically aggressive, usually presents at a high grade and advanced stage. Mixed tumors usually comprise of both an endometrioid histology and a high-grade non-endometrioid pattern. A minimum 5% component of the second component is the defining criteria for a mixed histology which also portends a poor prognosis despite the minimal secondary high grade component [12]. Carcinosarcomas are rare gynecological neoplasms that contains both epithelial and mesenchymal malignant components [13]. thus they are also called malignant mixed mullerian tumors. They only account for less than 5% of uterine malignancies, but present with advanced stage disease extending outside of the uterus and involving the peritoneum [13].

The standard of care for treatment of endometrial cancer is surgical staging which involves hysterectomy with removal of tubes and ovaries and evaluation of the pelvic and para-aortic lymph nodes, obtaining pelvic washings and removal of any other gross disease encountered during surgery. These procedures haven been traditionally performed via laparotomy. Laparoscopic hysterectomy for endometrial cancer was introduced in the 1990's and later adopted widely due to the reduction in peri-operative complications, quicker recovery, decreased morbidity, and improved quality of life when compared to laparotomy [14-17]. Robotic assisted surgery has recently emerged as another alternative minimally invasive approach for multiple surgical procedures including hysterectomies [14]. The Davinci robotic platform has been widely adopted due to its new technological advantages such as three dimensional visualization, improved instrument mobility, ergonomics and comfort for the surgeon [18, 19].

The overall prognosis for patients with Type II endometrial cancer is dismal with an average 5 year overall survival rate of 18-27% [9]. Type II endometrial cancers usually present at an advanced stage, with ≥ 38% of patients presenting with International Federation of Gynecology and Obstetrics (FIGO) stage III or IV disease [20-22]. Even in cases with disease limited to the uterus, the risk of recurrence is estimated to be as high as 31-80% [23]. Treatment of Type II endometrial cancer usually includes surgical staging as with Type I tumors. With a majority of these women presenting with extra uterine disease, optimal cytoreduction is an important component in surgical staging of these patients.

Different institutions have varied in their approach in treating Type II endometrial cancers. To date, there is no standard stage-based therapy in place and few prospective

studies have investigated the optimal surgical approach [22]. Several large prospective studies have been published demonstrating the superiority of minimally invasive surgery (MIS) approaches for managing early stage Type I endometrial cancer when compared to laparotomy. These studies have reported fewer postoperative adverse events, shorter hospital stay, improved pain control and quality of life as well as comparable 5 year overall survival rates [24, 25]. However, type II endometrial cancers are usually excluded or rarely represented in sufficient numbers in these studies. Therefore, there is a paucity of data supporting the use of an MIS approach for the treatment of Type II endometrial cancers. The goal of this study was to compare the surgical routes used in staging patients with type II endometrial cancers and evaluate the effect, if any, on overall and progression free survival. We also aim to compare operative data, clinical–pathologic factors, and post-operative morbidity for patients with type II endometrial cancer undergoing surgical staging via exploratory laparotomy (XL) and hysterectomy vs. a minimally invasive approach, laparoscopic hysterectomy (LAH) or robotic assisted hysterectomy (RAH).

BACKGROUND

Endometrial cancer is one of the most common female cancers in the United States, ranking fourth after breast, lung, and colorectal cancers. It is the most common cancer of the female reproductive organs with an estimated 61,380 new cases and 10,920 deaths in the United States for 2017 [26]. Endometrial cancer is a disease of postmenopausal women with the average age of diagnosis at age 60 and uncommon in women under age 45 [26].

In February 1983, Dr. Bokhman published an article defining two pathogenetic types of endometrial cancer [2, 3]. Type I cancers arise in the setting of hyper estrogenic state, and they are strongly associated with obesity, anovulation, infertility and other components of metabolic syndrome [2, 3]. Almost 80% of the patients described by Bokhman had low grade tumors, FIGO G1 and G2 while only 20% were high grade G3 [3]. Type I endometrial cancers consists of endometrioid adenocarcinoma and its variants [27]. In contrast, Type II cancers are high grade non-endometrioid tumors that include serous carcinoma, clear cell carcinoma, mixed histology and carcinosarcoma [27]. They typically present with deep myometrial invasion, extra uterine involvement and have a high propensity for lymph node metastasis [3]. Unlike type I tumors, these tumors develop through a separate pathway not associated with excess estrogen [28]. Uterine papillary serous is the most common of Type II endometrial cancers and make up approximately 10% of all endometrial cancer cases. It was first described in 1982 by Hendrickson and Lauchlan as an aggressive form of endometrial cancer with a 5-fold increased risk of recurrence and increased likelihood of abdominal metastasis [4, 5, 28]. Clear cell endometrial cancer is also a rare but aggressive tumor accounting for only 1 to

6% of all endometrial cancer cases [29]. Similar to uterine serous cancers, extra-uterine involvement upon clinical presentation is also common.

Carcinosarcomas are also highly aggressive tumors that contain both malignant sarcomatous and carcinomatous elements that can arise from the uterus as well as the ovary. Uterine carcinosarcoma is characterized as a polypoid, bulky mass filling the entire uterine cavity, and with a hemorrhagic and necrotic component. Similar to other type II endometrial cancers, myometrial invasion is frequently encountered along with disease involvement beyond the uterus [13]. Uterine carcinosarcoma accounts for less than 5% of uterine malignancies and typically affect postmenopausal women. It shares similar risk factors as endometrial cancer such as obesity, nulliparity, exogenous estrogen use, or tamoxifen therapy. Prior pelvic irradiation has also been implicated as a risk factor in 5% to 30% of patients [30]. Overall, carcinosarcoma of the uterus has a worse prognosis when compared to high grade endometrial cancers with an overall 5 year survival of less than 30%.

Comprehensive surgical staging of endometrial cancer includes total hysterectomy, bilateral salpingooopherectomy, pelvic and para-aortic lymphadenectomy, and peritoneal cytology. The dawn of minimally invasive surgical techniques have brought about questions as to which approach to choose, laparotomy versus traditional laparoscopy versus robotic-assisted laparoscopy. The Gynecology Oncology Group LAP2 study investigated the differences between laparotomy and laparoscopy when surgically staging endometrial cancer and compared recurrence-free survival as well as immediate morbidity and mortality, length of hospital stay, conversion to laparotomy, recurrence site, and patient-reported quality-of-life outcomes. The study found that

although laparoscopy was associated with a significantly longer intraoperative time, laparoscopy was associated with a shorter hospital length of stay and less postoperative complications and was not linked to increased intraoperative complications [24]. In addition, laparoscopy and laparotomy had similar recurrence rates and no significant difference in overall survival. These results concluded that laparoscopy is indeed a less morbid and reasonable approach toward comprehensive staging of endometrial cancer [25].

The LAP2 study reported a high occurrence of conversion from laparoscopy to laparotomy, with increasing BMI being the most significant factor. However, the LAP2 study did not report on any robotic-assisted approaches, which would most likely decrease the rate of conversion in the morbidly obese population [24]. Another systematic review article showed that robotic-assisted hysterectomy was associated with significantly less blood loss and lower conversion rate despite a population with higher BMI's when compared to traditional laparoscopy. This is coupled with a significantly longer operative time [31].

Recent studies have been conducted to further compare these two minimally invasive surgical approaches for the treatment of endometrial cancer. Kilgore specifically looked at robotic-assisted procedures to treat endometrial cancer and the impact on overall survival and recurrence [32]. The study comparable results with previous studies demonstrating the advantages of robotic-assisted surgery when compared to traditional laparoscopy [33]. Several studies have concluded that robotic-assisted surgical staging is a reasonable surgical modality given its effect on decreased perioperative morbidity and improved quality of life for patients. Robotic surgery has

demonstrated comparable short and long term survival and recurrence to laparotomy and traditional laparoscopic surgery [32, 34]. Although a handful of studies have demonstrated the efficacy of minimally invasive surgical procedures for the treatment of endometrial cancer, these studies did not specifically address type II endometrial cancer.

Although type II endometrial cancer accounts for only about 10% endometrial cancer cases, they make up a significant proportion of the morbidity and mortality related to endometrial cancer due to how aggressive the cancer presents and without having any precursor lesions [35]. Feuer *et al.* investigated robotic-assisted surgery on serous papillary and clear cell endometrial carcinoma and demonstrated that even histologically and clinically aggressive cancer types can be appropriately staged using the robotic platform [34].

Maximal cytoreductive effort to remove all gross disease is the cornerstone of surgical management in endometrial cancer and this especially applies to type II endometrial cancers. Given their identical clinical behavior to serous ovarian cancer with increased tendency to present with extra uterine disease, the traditional approach in surgical staging for type II endometrial cancers have been via laparotomy. With several landmark trials establishing the efficacy and safety of minimally invasive surgery for type I cancers, it has become standardized to use this approach when surgically staging those patients. However, the management for type II endometrial cancers continues to vary by institution and their clinical experience. It is our goal, in this study to demonstrate that MIS can be a safe and feasible option for type II cancers without compromising quality of surgery and negatively impacting survival.

The purpose of this study was to compare operative data, clinical–pathologic

factors, and post-operative morbidity for patients with type II endometrial cancer undergoing surgical staging via laparotomy and abdominal hysterectomy vs. a minimally invasive approach, laparoscopic hysterectomy (LAH) or robotic assisted hysterectomy (RAH) with pelvic ± aortic lymphadenectomy and other necessary staging procedures. The primary objective of the study was to compare progression free survival and overall survival in patients undergoing laparotomy vs. minimally invasive surgery for staging of Type II endometrial cancer. The secondary objective was to compare surgical and perioperative outcomes in women undergoing laparotomy vs. minimally invasive surgery for Type II endometrial cancer.

METHODS

This retrospective multicenter analysis was carried out between January 2005 and December 2015 at the Department of Obstetrics and Gynecology, Division of Gynecologic Oncology, Karmanos Cancer Center/Wayne State University and St. John Hospital and Medical Center in Detroit, Michigan. All pathology had been previously reviewed and confirmed by a Gynecologic Pathologist. Inclusion criteria was the presence of histologically confirmed type II endometrial cancer on final surgical pathology; specifically patients with uterine serous, clear cell, carcinosarcoma and mixed histology tumors were included. Primary surgical staging was also required for inclusion. Exclusion criteria were any patient that did not undergo primary surgical staging (i.e. received neoadjuvant chemotherapy or radiation therapy), the surgery was not performed at our institutions and any patient with endometrioid adenocarcinoma on final histology review. Each institution's respective Institutional Review Boards approved the study. 259 patients were confirmed to have type II endometrial cancer histology during this timeframe and therefore included in the study.

Demographic and oncologic characteristics, treatment, and recurrence data were abstracted from patient records. Baseline characteristics included age at diagnosis, race, body mass index (BMI), and comorbidities. Medical comorbidities included were hypertension, chronic obstructive pulmonary disease, coronary artery disease, stroke, diabetes, deep vein thrombosis, pulmonary embolus, and other malignancies. Each patient was assigned a score of 1, 2, 3+ based on the number of comorbidities present. Treatment data included procedures performed: exploratory laparotomy hysterectomy

with bilateral salpingo-oophorectomy, exploratory laparotomy hysterectomy with bilateral salpingo-oophorectomy with biopsies only, exploratory laparotomy hysterectomy with bilateral salpingo-oophorectomy with biopsies + pelvic/para-aortic lymph node dissection alone, exploratory laparotomy hysterectomy with bilateral salpingo-oophorectomy + pelvic/para-aortic lymph node dissection with omentectomy, laparoscopic hysterectomy with bilateral salpingo-oophorectomy with biopsies only, laparoscopic hysterectomy with bilateral salpingo-oophorectomy with biopsies + pelvic/para-aortic lymph node dissection, laparoscopic hysterectomy with bilateral salpingo-oophorectomy + pelvic/para-aortic lymph node dissection with omentectomy, robotic hysterectomy with bilateral salpingo-oophorectomy with biopsies only, robotic hysterectomy with bilateral salpingo-oophorectomy with biopsies + pelvic/para-aortic lymph node dissection alone, robotic hysterectomy with bilateral salpingo-oophorectomy + pelvic/para-aortic lymph node dissection with omentectomy, date of surgery, recurrence data and date of death or last contact. Adjuvant therapy, including chemotherapy, radiation or a combination of both modalities as well as hormonal therapy received by the patients was also obtained. Extracted pathologic data included number and location of lymph nodes obtained, uterine size (in grams), tumor size, final histology, and final FIGO stage. Lymph node counts were categorized as <10 or ≥ 10 for pelvic lymph nodes and <5 or ≥ 5 for para-aortic lymph nodes. Tumor size was similarly categorized into <5 and ≥ 5 centimeters. Peri-operative data was also obtained including estimated blood loss (EBL), length of hospital stay, and intraoperative complications, perioperative and post-operative blood transfusion and postoperative complications.

Progression free survival (PFS) was defined as time from surgery until first reported date of disease recurrence. Overall survival (OS) was defined as time from surgery until death from disease or any other reason.

Statistical Analysis

Univariate analysis using a student's t-test for continuous variables and chi-square test for categorical variables was performed to compare the patients that underwent minimally invasive surgery (MIS) group versus laparotomy (XL). Overall survival and 3 year PFS were estimated using Kaplan-Meier method. The primary analysis comparing hazard rates for recurrence with MIS relative to laparotomy was performed using a Cox proportional hazards model. Associations between factors known or suspected of influencing the risk of recurrence were also assessed using Cox proportional hazards models. Cox regression proportional hazards model with stepwise variable selection was used to analyze the role of clinicopathological parameters and treatment details as prognostic factors for progression free survival. Criterion for entry into the model was a significance 0.05 and 0.10 for exit. A p value of .05 was considered significant. To account for possible confounding factors, a multivariable logistic regression analysis was performed on the probability of receiving MIS vs. XL. A final model was developed and included variables noted to influence PFS as well as variables deemed to affect rate of recurrence based on clinical data. To compare the perioperative outcomes between the two surgical approaches, multivariable logistic regression analysis was performed. Statistical analysis was performed using SAS 9.3 Statistical Software. (SAS Institute, Cary, NC)

RESULTS

A total of 249 patients were included in the study, 193 underwent laparotomy (XL), and 58 minimally invasive surgery (MIS), including conventional laparoscopic or robotic surgery. The mean age was 65 for both laparotomy and MIS group. There were a higher percentage of African American patients in the XL group 58.5% (n=113) when compared to those that received MIS 32.8% (n=19). Patients in the XL group also had a higher mean BMI 36.3 (range 19.4-67 kg/m^3) vs. 31.4 (range 19-47.7 kg/m^3). Full demographics are depicted in **Table 1**. There was no difference in comorbidity scores between the two groups. A list of comorbidities documented is provided in the supplemental data (**Table S1**).

Surgical and clinical pathologic characteristics are summarized in **Table 2**. A majority of women in both groups (76.2% XL and 93.1% MIS) underwent surgical staging with pelvic +/- para-aortic lymph nodes and omentectomy. However, more women in the MIS group received a comprehensive surgical staging with hysterectomy bilateral salpingo-oophorectomy and pelvic/para-aortic lymphadenectomy (51.7% vs. 25.4%, p <.001). There was higher pelvic and para-aortic lymph node yield in patients who underwent MIS for surgical staging, and the tumor size and uterine weight were generally smaller in the MIS group when compared to the XL group. Tumor histology in the XL versus MIS was serous/clear cell 47.2% vs. 56.9%; carcinosarcoma 22.8% vs. 22.4%; mixed 27.5% vs. 19.0% (all non-significant). In the laparotomy group 43.0% had FIGO stage I disease, 8.3% were stage II, 33.7% stage III and 14.0 % were stage IV. A higher percentage of the MIS group were stage I 65.5%, 6.9 % were stage II, 25.9% were stage III and only 1.7% were stage IV, $p=.009$.

The duration of follow-up for the patient population was 35.3 months and the mean time to recurrence was 20 months. There were 72 (38%) recurrences in the laparotomy group and 9 (4.7%) deaths while the MIS group had 11 (19%) recurrences and 4 (6.9%) deaths. Three year PFS for the MIS group was 71% and 50% for the XL group, (*p =0.0189*) (**Figure 1**). OS was not statistically significant between the two groups (**Figure 2**).

The crude hazard ratio for 3 year PFS is 0.5 for MIS relative to the XL group, *p=.02.* Univariate cox regression analysis of individual variables known or suspected to influence the risk of recurrence was performed and demonstrated having a carcinosarcoma histology and stage (stage II-IV) as having significant association with 3 year PFS (**Table 3**). In order to determine the effect of these variables on mode of surgery (MIS vs. XL) and the association with PFS, additional cox regression analysis was performed with mode of surgery and each individual variable. Variables considered for this analysis included: age at diagnosis, race, procedure, histology, FIGO stage, and adjuvant therapy (**Table 4**). In evaluating the individual models, only stage strongly influenced the association between mode of surgery and PFS as evidenced by loss of significance and change in hazard ratio >10% (actual change of 37.5%).

In order to identify other variables that could affect the association between mode of surgery and PFS, a cox regression analysis with stepwise variable selection was performed. Mode of surgery was forced in the model as it is our primary variable of interest. Stage, histology and adjuvant therapy were the variables in the final model. After adjusting for these 3 variables, there was no association between mode of surgery 3 year PFS (**Table 5**).

To assess other possible confounders that influenced the mode of surgery, a logistic regression analysis was performed. African American race (OR 0.29; 95%CI .014-0.61, *p=.02*), FIGO stage 3-4 (OR 0.46; 95%CI 0.21-0.97, *p=.04*) were inversely associated with MIS. Staging procedure with hysterectomy bilateral salpingo-oophorectomy with pelvic and para-aortic lymph node sampling (TAHBSO+ PPALN) (OR 6.13; 95% CI 1.86-20.25, *p=.001*) was associated with MIS (**Table 6**). Therefore, a final cox regression analysis utilizing these factors as well as those identified in previous models was then performed. After holding all variables constant, there was still no association between the mode of surgery and PFS (**Table 7**).

Intraoperative and perioperative data is summarized in **Table 8**. The mean length of surgery was 186.8 minutes (range 56-461 minutes) in the laparotomy group versus 238.4 minutes (range 125-365 minutes) in the MIS group, p =.001. The laparotomy group also had a higher mean EBL 547.4 (range 50-2400ml) when compared to the MIS group 169.8 (range 50-600 ml), p<.001. Higher perioperative complications, EBL >250cc and need for transfusion were also observed in the laparotomy group. A list of intraoperative and post-operative complications included in this study are described in the supplemental data, **Table S2**.

A multivariable logistic regression analysis was utilized to compare the perioperative outcomes between the two surgical approaches. We adjusted for demographic and clinical variables including age, race, comorbidity score, histology, tumor size, and the extent of surgical staging. Results showed that undergoing a laparotomy was associated with higher perioperative complications, specifically a higher

EBL and need for perioperative blood transfusion. A longer postoperative hospital stay was also associated with exploratory laparotomy.

DISCUSSION

The management for endometrial cancer has evolved from clinical staging to surgical staging in the last 30 years [36]. The need for postoperative adjuvant treatment is further dictated by the histo–pathologic factors and the final stage which is determined via surgical staging[37]. Most women diagnosed with endometrial cancer will undergo surgical removal of their uterus, tubes and ovaries in addition to assessment of pelvic and para-aortic lymph nodes in order to assign a final stage. This has been traditionally performed via an abdominal incision until the advent of minimally invasive procedures such as laparoscopy and more recently robotic surgery. Several studies have demonstrated that laparoscopic surgery is associated with decreased peri-operative morbidity and allows for earlier return to baseline function when compared to laparotomy[38]. Robotic surgery has demonstrated similar benefits to laparoscopy in the treatment of endometrial cancer which has led to its widespread adoption. Survival and recurrence rates in patients undergoing minimally invasive surgery was also noted to be non-inferior to laparotomy as demonstrated in the follow up assessment of the LAP2 study[25]. Despite the established benefits of these procedures, very few studies have investigated if similar recurrence free and survival outcomes would apply to patients with type II endometrial cancers. In addition perioperative assessment for these patients comparing these modalities is lacking. These patients warrant special attention given the aggressive nature of their disease and the propensity to have extra-uterine metastatic disease at the time of surgical staging. The current study is a retrospective analysis focusing on the surgical management of type II endometrial cancers.

Primary survival analysis using Kaplan Meier estimates and crude hazard ratio for

the cox regression analysis showed that MIS has better 3 year PFS when compared to the laparotomy group. However, with further analysis and adjusting for variables that were suspected to influence risk of recurrence, such as age, race, procedure, stage, histology and adjuvant therapy, the association between mode of surgery and 3 year PFS was lost. The initial association noted in our initial survival analysis may be due to confounding by indication which occurs when patients who had factors that were associated with the outcome were preferentially assigned to one surgery mode versus the other. This is supported by the multivariate logistic model performed for MIS where African Americans, patients with advanced stage (FIGO stage 3&4) and those with mixed histologies were associated with undergoing laparotomy instead of minimally invasive surgery for their type II endometrial cancers. OS was not significantly different between the two groups. The overall length of follow up for our cohort was 35.3 months, and the mean time to recurrence was 20.6 months for both groups. We hope to re-evaluate OS with a follow up study at a later date when there is longer follow-up.

In this series, women in the MIS group were able to undergo a more comprehensive surgical staging with hysterectomy bilateral salpingo-oophorectomy and pelvic/para-aortic lymphadenectomy when compared to those that had laparotomy. Pelvic lymph node yield in the MIS was not inferior to the laparotomy group. Our data is in agreement with the literature regarding the benefits of laparoscopy. Our analysis also demonstrated that patients receiving minimally invasive surgery had less perioperative complications, lower estimated blood loss (EBL), perioperative transfusions and shorter hospital stays when compared to those undergoing laparotomy. We could not perform an analysis comparing the different minimally invasive surgical modalities due to the small

numbers in laparoscopy group. At our institution, staging for type II endometrial cancers is usually performed using robotic surgery. However, unlike prior studies that evaluated the benefits of MIS surgery in endometrial cancer, our data is comprised purely of patients with a type II endometrial cancer whose diagnoses were also confirmed by a gynecologic pathologist. Our cohort is not sizeable in number when compared to prior studies using public databases. However, our study does not suffer from the limitations that occur when analyzing data from large patient databases. We were able to accurately document intra-operative and post-operative complications including the use of blood products. Our follow-up data was accurate and truly reflects the time when patient recurrence occurred and obtain actual treatment records.

Limitations of our present study include its retrospective nature and inherent biases. There was also an imbalance in the number of patients in each group with a larger number of patients in the laparotomy group versus the MIS group likely a result of confounding by indication as previously discussed. The mode of surgery may have been dictated by pre-surgical evaluation of the patients- those with expected large burden of metastatic disease could have been selected to undergo laparotomy while those with no evidence of metastatic disease were chosen to undergo MIS. Mode of surgery can also be selected by the provider based on their comfort level of performing complex minimally invasive surgical procedures although in our series, we had the same set of surgeons performing the surgeries at both institutions in our study. The availability of the laparoscopic equipment as well as DaVinci robotic system could also influence the small number of patients in the MIS group. However, both systems were already available at both institutions during the time period for this study. Performing a sub-analysis on

patients with only stage I and II patients could have nullified the selection bias brought about by any pre-operative evaluation of the patient's disease leading increased tendency for laparotomy. However limiting our analysis to only early stage patients would have yielded an even smaller number in the MIS group. We performed a crude sub-analysis and performed Kaplan Meier estimates stratified by stage, stage I-II and stage III-IV, but this did not yield any significant difference in PFS between modes of surgery. **(Supplemental Data, Figures S1 and S2).** It is our plan to further pursue this analysis once we accrue more numbers by including a third cohort of patients from a third affiliate institution. We also did not assess the rate of conversion from MIS to laparotomy which could have contributed to the laparotomy numbers. The short follow up for the MIS group only allowed for 3 year progression free analysis. This may be due to the slow adoption of using minimally invasive surgery for the management of type II endometrial cancers despite its established application for surgery in type I tumors. Surgical management for type II endometrial cancers can vary depending on different institutional experience. Some practitioners still approach the management of type II endometrial cancer similar to the surgical management of ovarian cancer, as the two disease entities have similar clinical course and can present with disseminated disease on presentation. Nevertheless, our data demonstrated that patients with advanced stage disease can be surgically staged using minimally invasive surgical approaches without sacrificing the comprehensive quality of the staging procedure and impacting risk of recurrence. Both laparoscopic and robotic surgery should therefore be considered as viable options for treatment of women with type II endometrial cancers, even those with advanced stage disease.

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TABLES AND FIGURES

Table 1. Patient demographic characteristics

	Overall		XL		MIS		
	N	%	N	%	N	%	p-value
Age at diagnosis							
Mean, SD	65.0	9.7	65.1	10.0	64.6	9.2	0.745
Median, range	64	(34-92)	(34-92)		(39-85)		
Race							
Caucasian	87	34.9	56	29.0	31	53.4	**0.001**
African American	133	53.4	113	58.5	19	32.8	
Other (Asian, Latino, Other)	19	7.6	14	7.3	5	8.6	
Unknown/Missing	13	5.2	10	5.2	3	5.2	
BMI (kg/m2)							
Mean, SD	34.4	8.2	36.3	8.3	31.4	7.1	**0.001**
Median, range	33.4	(19.0-67.0)	(19.4-67.0)		(19.0-47.7)		
Comorbidity score							0.281
0	20	8.0	13	6.7	7	12.1	
1	60	24.1	46	23.8	14	24.1	
2	75	30.1	55	28.5	20	34.5	
3+	92	36.9	76	39.4	16	27.6	
Unknown/Missing	2	0.8	1	0.5	1	1.7	

BMI= body mass index; Open = laparotomy group; MIS = minimally invasive group (laparoscopy and robotic surgery)

Table 2. Surgical and pathologic outcomes for patients undergoing laparotomy versus minimally invasive surgery for type II endometrial cancer

	Overall		XL		MIS		
	N	%	N	%	N	%	p-value
Staging							**<.001**
Total hysterectomy + BSO +/- bx	48	19.3	44	22.8	4	6.9	
Total hysterectomy + BSO + pelvic LN +	51	20.5	43	22.3	8	13.8	
Total hysterectomy + BSO + PPALND	79	31.7	49	25.4	30	51.7	
Total hysterectomy + BSO + PPALND +	71	28.5	55	28.5	16	27.6	
Unknown/Missing	0	0.0	0	0.0	0	0.0	
Pelvic LN yield							**<.001**
No LND	53	21.3	48	24.9	5	8.6	
<10	74	29.7	64	33.2	10	17.2	
>=10	121	48.6	78	40.4	43	74.1	
PA LN yield							**<.001**
No LND	98	39.4	86	44.6	12	20.7	
<5	59	23.7	49	25.4	10	17.2	
>=5	92	36.9	56	29.0	36	62.1	
Uterine Wt (g)							**<.001**
<250g	186	74.7	129	66.8	57	98.3	
250-499g	36	14.5	35	18.1	1	1.7	
>=500g	27	10.8	27	14.0	0	0.0	
Tumor Size (cm)							**0.030**
<5	159	63.9	115	59.6	44	75.9	
>=5	90	36.1	76	39.4	14	24.1	
Histology							0.348
Serous/Clear cell	124	49.8	91	47.2	33	56.9	
Carcinosarcoma	57	22.9	44	22.8	13	22.4	
Mixed	64	25.7	53	27.5	11	19.0	
Unknown/Missing	4	1.6	3	1.6	1	1.7	
FIGO 2009 stage							**0.009**
I	121	48.6	83	43.0	38	65.5	
II	20	8.0	16	8.3	4	6.9	
III	80	32.1	65	33.7	15	25.9	
IV	28	11.2	27	14.0	1	1.7	

Open = laparotomy group; MIS = minimally invasive group (laparoscopy and robotic surgery); BSO=bilateral salpingo-oophorectomy; bx= biopsies; LN = lymph nodes; PPALND= pelvic and para-aortic lymph node dissection; OMX= Omentectomy

*non-parametric

Table 3. Univariate Cox proportional hazard regression to determine the predictive value of different variables in relation to 3 year progression free survival

Variable	Crude HR	95% CI	p-value
Surgery route			
XL	1.00	referent	
MIS	0.50	0.27-0.90	**0.02**
Age at diagnosis*			
	1.00	0.97-1.02	0.82
Race			
Caucasian	1.00	referent	
African American	1.39	0.85-2.28	0.19
Other (Asian, Latino, Other)	1.91	0.66-5.51	0.23
Procedure			
Total hysterectomy + BSO +/- b	1.00	referent	
Total hysterectomy + BSO + pel	1.30	0.65-2.61	0.46
Total hysterectomy + BSO + PP/	0.76	0.41-1.42	0.39
Histology			
Serous/Clear cell	1.00	referent	
Carcinosarcoma	3.01	1.81-5.02	**<.001**
Mixed	1.10	0.61-2.00	0.76
FIGO 2009 stage			
I	1.00	referent	
II	3.33	1.55-7.18	**0.002**
III	2.48	1.44-4.26	**0.001**
IV	4.68	2.45-8.93	**<.001**
Adjuvant therapy			
None	1.00	referent	
Radiation only	0.97	0.28-3.41	0.96
Chemo only	1.10	0.59-2.03	0.77
Chemoradiation	0.48	0.22-1.06	0.07
Other (Hormone, other)	0.17	0.02-1.28	0.08

PFS=progression free survival; XL = laparotomy group; MIS = minimally invasive group (laparoscopy and robotic surgery); BSO=bilateral salpingo-oophorectomy; bx= biopsies; LN = lymph nodes; PPALND= pelvic and para-aortic lymph node dissection; OMX= Omentectomy

*continuous variable (no significance reached when run in age categories of <60, 60-69, 70-79, 80+)

Table 4. 3 year PFS Cox proportional hazard for MIS vs. XL adjusted for potential prognostic co-variates.

Variable	adjusted HR	95% CI	p-value	% HR change
Surgery route				
XL	1	referent		
MIS	0.49	0.27-0.90	**0.02**	0.81
Age at diagnosis*	1	0.97-1.02	0.67	
Surgery route				
XL	1	referent		
MIS	0.45	0.23-0.87	**0.02**	9.48
Race				
Caucasian	1	referent		
African American	1.17	0.70-1.93	0.56	
Other (Asian, Latino, Other)	1.9	0.66-5.50	0.24	
Surgery route				
XL	1	referent		
MIS	0.53	0.29-0.96	**0.04**	-6.05
Comorbidity score				
0	1	referent		
1	1.09	0.40-2.95	0.87	
2	1.25	0.48-3.26	0.65	
3+	1.28	0.49-3.35	0.62	
Surgery route				
XL	1	referent		
MIS	0.52	0.29-0.96	**0.04**	-5.44
Procedure				
Total hysterectomy + BSO +/- bx	1	referent		
Total hysterectomy + BSO + pelvic LN +/- bx	1.37	0.68-2.77	0.37	
Total hysterectomy + BSO + PPALND +/- bx	0.88	0.47-1.64	0.68	
Surgery route				
XL	1	referent		
MIS	0.47	0.25-0.86	**0.02**	6.25
Histology				
Serous/Clear cell	1	referent		
Carcinosarcoma	2.93	1.76-4.88	<.001	
Mixed	1.02	0.56-1.86	0.95	
Surgery route				
XL	1	referent		
MIS	0.68	0.37-1.27	0.23	-37.5
FIGO 2009 stage				
I	1	referent		
II	3.06	1.41-6.67	0.005	
III	2.37	1.38-4.10	0.002	
IV	4.13	2.11-8.08	<.001	
Surgery route				
XL	1	referent		
MIS	0.54	0.29-1.00	**0.05**	-9.07
Adjuvant therapy				
None	1	referent		
Radiation only	0.93	0.26-3.26	0.9	
Chemo only	1.19	0.64-2.21	0.57	
Chemoradiation	0.58	0.26-1.29	0.18	
Other (Hormone, other)	0.19	0.03-1.44	0.11	

% HR change = (Crude HR for surgery route / adjusted HR for surgery route) x 100

XL = laparotomy group; MIS = minimally invasive group (laparoscopy and robotic surgery); BSO=bilateral salpingo-oophorectomy; bx= biopsies; LN = lymph nodes; PPALND= pelvic and para-aortic lymph node dissection; OMX= Omentectomy

*continuous variable (no significance reached when run in age categories of <60, 60-69, 70-79, 80+)

Table 5. 3 year PFS Cox proportional hazard for MIS vs. XL: Adjusting for variables in stepwise model- stage, histology and adjuvant therapy

Variables	HR	95% CI	p-value
Surgery route			
XL	1	referent	
MIS	0.83	0.42-1.65	0.6
Histology			
Serous/Clear cell	1	referent	
Carcinosarcoma	3.33	1.94-5.71	**<.001**
Mixed	1.16	0.63-2.14	0.63
FIGO 2009 stage			
I			
II	4.85	2.09-11.26	**<.001**
III	2.76	1.51-5.05	**<.001**
IV	4.55		**<.001**
Adjuvant therapy			
None	1	referent	
Radiation only	0.78	0.22-2.82	0.78
Chemo only	0.73	0.38-1.41	0.73
Chemoradiation	0.31	0.13-0.75	**0.01**
Other (Hormone, other)	0.19	0.03-1.50	0.19

XL = laparotomy group; MIS = minimally invasive group (laparoscopy and robotic surgery)

Table 6. Multivariate logistic regression assessing for potential confounders influencing route of surgery

Demographic/Clinical variables	adjusted OR*	95% CI		p-value
Age at diagnosis	1.00	0.96	1.04	1.00
Race				
Caucasian	1.00	Referent		
African American	0.29	0.14	0.61	**0.02**
Other (Asian, Latino, Other)	0.64	0.18	2.36	0.79
Comorbidity score				
0	1.00	Referent		
1	0.59	0.16	2.14	0.61
2	0.77	0.22	2.68	0.70
3+	0.50	0.13	1.83	0.30
FIGO 2009 Stage				
I/II	1.00	Referent		
III/IV	0.46	0.21	0.97	**0.04**
Histology				
Serous/Clear cell	1.00	Referent		
Carcinosarcoma	0.97	0.39	2.40	0.34
Mixed	0.39	0.16	0.98	**0.04**
Staging				
Total hysterectomy + BSO +/- bx	1.00	Referent		
Total hysterectomy + BSO + pelvic LN +/- b	1.71	0.43	6.88	0.34
Total hysterectomy + BSO + PPALND	6.13	1.86	20.25	**0.001**
Total hysterectomy + BSO + PPALND + OM	3.51	0.99	12.43	0.25

MIS vs. XL as referent

XL = laparotomy group; MIS = minimally invasive group (laparoscopy and robotic surgery); BSO=bilateral salpingo-oophorectomy; bx= biopsies; LN = lymph nodes; PPALND= pelvic and para-aortic lymph node dissection; OMX= Omentectomy

Table 7. Cox Regression Model Adjusting for variables deemed to influence 3 year progression free survival .

Variables	HR	95% CI	p-value
Surgery route			
XL	1	referent	
MIS	0.85	0.40-1.80	0.67
Age at diagnosis*			
	1	0.98-1.02	0.87
Race			
Caucasian	1	referent	
African American	1.2	0.69-2.08	0.52
Other (Asian, Latino, Other)	1	0.31-3.23	1
Procedure			
Total hysterectomy + BSO +/-	1	referent	
Total hysterectomy + BSO + p	1.56	0.72-3.37	0.26
Total hysterectomy + BSO + P	0.88	0.43-1.79	0.72
Histology			
Serous/Clear cell	1	referent	
Carcinosarcoma	4.06	2.27-7.28	**<.001**
Mixed	1.42	0.75-2.71	0.28
FIGO 2009 stage			
I	1	referent	
II	5.55	2.26-13.60	<.0**01**
III	3.13	1.67-5.87	**<.001**
IV	5.34	2.47-11.52	**<.001**
Adjuvant therapy			
None	1	referent	
Radiation only	0.83	0.23-3.03	0.78
Chemo only	0.63	0.32-1.27	0.2
Chemoradiation	0.29	0.12-0.73	**0.01**
Other (Hormone, other)	0.23	0.03-1.81	0.16

XL = laparotomy group; MIS = minimally invasive group (laparoscopy and robotic surgery); BSO=bilateral salpingo-oophorectomy; bx= biopsies; LN = lymph nodes; PPALND= pelvic and para-aortic lymph node dissection

Table 8. Univariate analysis of perioperative outcomes comparing laparotomy versus minimally invasive surgery for type II endometrial cancers

	Overall		XL		MIS		
	N	%	N	%	N	%	p-value
EBL (mL)							**<.001**
<250	101	40.6	52	27	49	84.5	
250-499	59	23.7	54	28	5	8.6	
>=500	87	34.9	84	44	3	5.2	
Length of Stay (days)							**<.001**
<3	62	24.9	18	9	44	75.9	
3-6	150	60.2	138	72	12	20.7	
>=7	37	14.9	35	18	2	3.4	
Intraop complication							0.779
Unknown/Missing	3	1.2	3	1.6	0	0	
Yes	19	7.6	13	6.7	6	3.1	
Intraop transfusion							**0.021**
Unknown/Missing	4	1.6	3	1.6	1	0.5	
Yes	24	9.6	22	11.4	0	0	
postop complication							**<.001**
Unknown/Missing	7	2.8	5	2.6	2	1.0	
Yes	92	36.9	81	42.0	9	4.7	
Postop complication score							**0.001**
0	152	61.0	105	54.4	47	81.0	
1	41	16.5	37	19.2	4	6.9	
2	49	19.7	44	22.8	5	8.6	
Unknown/Missing	8	3.2	5	2.6	2	3.4	
Postop transfusion							**0.049**
Unknown/Missing	7	2.8	5	2.6	2	1.0	
Yes	26	10.4	24	12.4	2	1.0	

EBL = estimated blood loss

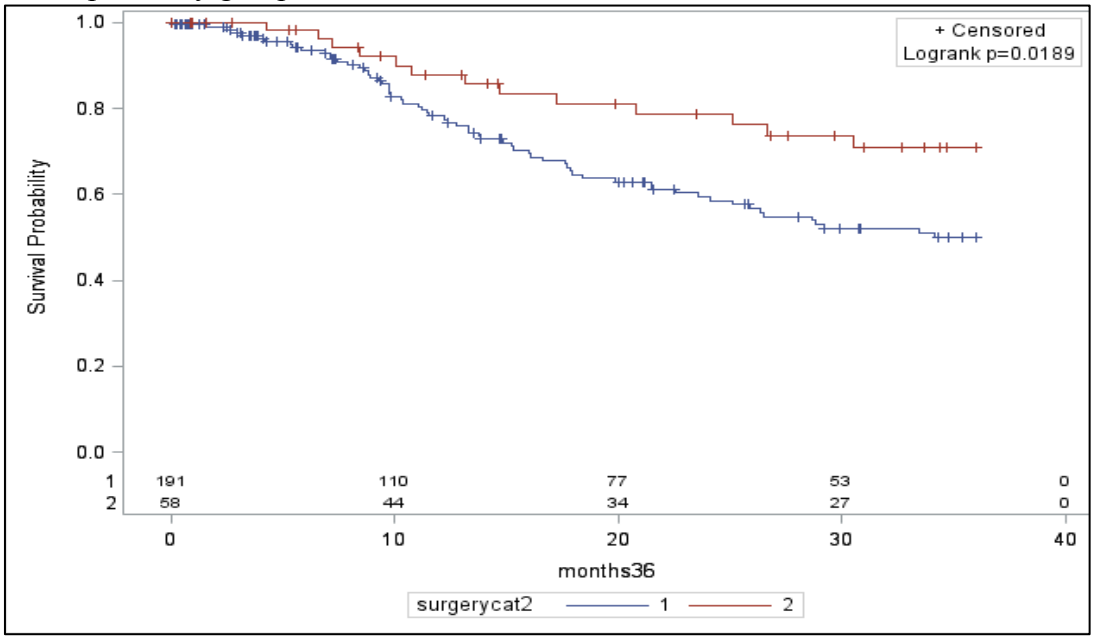
Table 9. Multivariable analysis comparing perioperative outcomes between laparotomy vs. MIS for type II endometrial cancer

Surgical outcome variable	adjusted OR*	95% CI	p-value
Periop complications* **			
0	1	Referent	
1	1.82	0.62-5.36	0.929
2+	3	1.03-8.78	0.164
EBL (mL)* **			
<250	1	Referent	
250-499	23.37	6.56-83.24	**0.011**
>=500	18.93	5.46-65.63	**0.035**
Periop transfusion* **			
No	1	Referent	
Yes	4.73	0.99-22.51	0.051
Hospital days* **			
	2.58	1.86-3.59	**<.0001**
Adjuvant therapy* **			
No	1	Referent	
Yes	0.24	0.08--0.75	**0.014**

EBL = estimated blood loss; **XL vs MIS (as referent)**

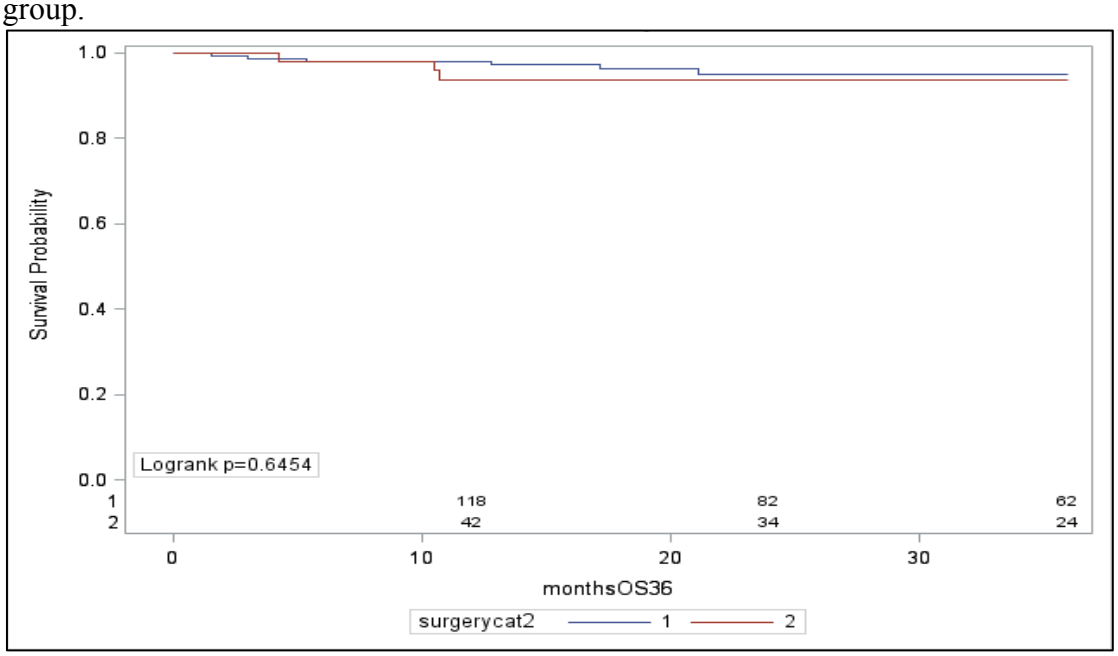
*** Each are separate models looking at association between each variable and surgical route adjusted for demographic and clinical variables: Age, Race, comorbidity score, and histology, tumor size, and the extent of surgical staging

Figure 1. Kaplan Meier curve estimating 3 year progression free survival between MIS and Laparotomy group



(1= xlap; 2= MIS)

Figure 2. Kaplan Meier Curve- Overall Survival 36 months between laparotomy and MIS group.



(1= xlap; 2= MIS)

SUPPLEMENTAL DATA

Table S1. List of recorded comorbidities.

Comorbidities	Overall		Open		MIS	
	N	%	N	%	N	%
Total	231	89.2	179	92.7	51	87.9
HTN	182	70.3	146	75.6	35	60.3
COPD	10	3.9	7	3.6	3	5.2
CAD	33	12.7	25	13.0	8	13.8
CVA/stroke	17	6.6	17	8.8	0	0.0
DVT/PE	9	3.5	5	2.6	3	5.2
DM	85	32.8	66	34.2	18	31.0
Other malignancy	38	14.7	29	15.0	9	15.5
Other	157	60.6	125	64.8	31	53.4
Unknown/Missing	2	0.8	1	0.5	1	1.7

HTN=hypertension; COPD=Chronic obstructive pulmonary disease; CAD=coronary artery disease; CVA= cerebrovascular accident; DVT= deep vein thrombosis; PE= pulmonary embolus; DM= diabetes mellitus;

Table S2. Recorded intra-operative and post-operative complications

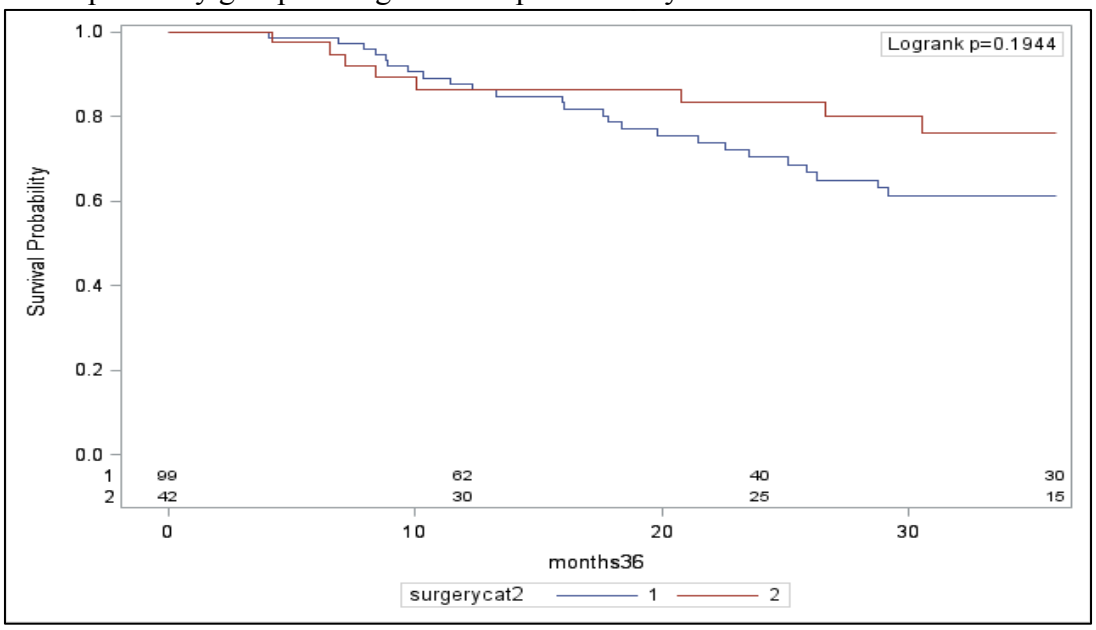
	Overall		Open		MIS	
	N	%	N	%	N	%
Intraop complication						
1. Urinary	3	1.2	1	0.5	2	1.0
2. Vascular	3	1.2	1	0.5	2	1.0
3. Bowel injury	1	0.4	1	0.5	0	0
4. Neurologic	0	0	0	0	0	0
5.EBL > 1L	8	3.2	7	3.6	1	0.5
6. Other	4	1.6	3	1.6	1	0.5
Postop complication						
1. UTI	11	4.2	11	5.7	0	0.0
2. Pulmonary	8	3.1	6	3.1	1	0.5
3. Wound infxn	16	6.2	14	7.3	2	1.0
4. Wound dehiscence	13	5.0	12	6.2	1	0.5
5. DVT/PE	8	3.1	8	4.1	0	0.0
6. Ileus	17	6.6	17	8.8	0	0.0
7. SBO	3	1.2	3	1.6	0	0.0
8. Re-operation	9	3.5	6	3.1	3	1.6
9. LOS >5 days	15	5.8	13	6.7	2	1.0
10. ICU admit (unexpected)	16	6.2	14	7.3	2	1.0
11. Readmit w/in 30 d	19	7.3	15	7.8	4	2.1
12. Other	50	19.3	46	23.8	4	2.1

EBL = estimated blood loss; UTI= urinary tract infection; DVT= deep vein thrombosis; PE= pulmonary embolus; SBO= small bowel obstruction; LOS= length of stay

Table S3: Recurrence, Death Rate and Duration of Follow-up

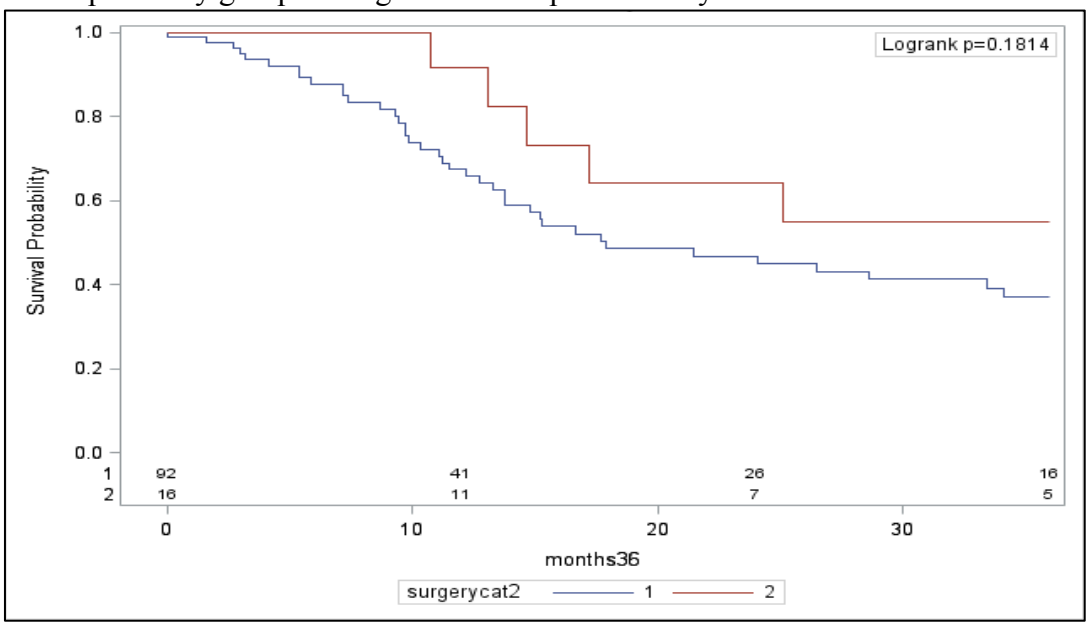
	Overall		XL		MIS	
Recurrence	83	33.2%	72	37.70%	11	18.97%
Death	13	5.2%	9	4.71%	4	6.90%
Time to recurrence (months)						
Mean, SD	20.6	18.1	21.5	19.1	16.4	8.4
Median, range	14.8	(0.03-92.7)	(0.03-92.7)		(6.6-30.5)	
Follow-up time (months)						
Mean, SD	35.3	75.10	36.4	84.9	32.1	23.9
Median, range	20.5	(0.03-1102.7)	(0.1-1102.7)		(0.03-103.3)	

Figure S1. Kaplan Meier curve estimating 3 year progression free survival between MIS and Laparotomy group in Stage I and II patients only.



(1= xlap; 2= MIS)

Figure S2. Kaplan Meier curve estimating 3 year progression free survival between MIS and Laparotomy group in Stage III and IV patients only.



(1= xlap; 2= MIS)