

*Research Article*

## Feasibility of minimally invasive surgery with implementation of ERAS protocol versus traditional laparotomy in the management of early stage endometrial cancer

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### Abstract

**Background:** It has been suggested that the laparoscopic approach is associated with a reduction in operative morbidity. Over the last two decades there has been a steady increase in the use of laparoscopy for endometrial cancer. This review investigated the evidence of benefits and harms of laparoscopic surgery with implementation of ERAS program, versus traditional laparotomy for presumed early stage endometrial cancer. **Study objective:** To study the efficacy of laparoscopic radical hysterectomy with implementation of ERAS protocol for treatment of endometrial cancer on operative outcome and overall survival in comparison with traditional abdominal hysterectomy. **Selection criteria:** Non randomized controlled trial comparing laparoscopy with ERAS and laparotomy with mechanical bowel preparation for treatment of early stage endometrial cancer. **Data collection and analysis:** The study was done in El- Salam Oncology center, Cairo and Minia maternity university hospital (MMUH), Egypt. The study included two groups of patients diagnosed as endometrial carcinoma ( stage I) prepared for operations. First group (27 patients ) managed with laparoscopy with implementation of ERAS protocol while the other group (31 patients) managed with conventional laparotomy. **Results:** There was statistically significant reduction in action group than in conventional group as regarding : LOS ( $2.15 \pm 0.71$  Vs  $0.39 \pm 0.80$ ), reduction in post operative pain which assessed by VAS score (  $3.04 \pm 1.05$ ) vs (  $5.71 \pm 1.00$ ) and post operative fluid balance ( $916.67$  ml) vs (  $2345.16$  ml). There was statistically insignificant difference between both groups in postoperative pneumonia, urinary tract infection, surgical site infection. As a result readmission to hospital was less in active group than conventional (2 vs 8patients). **Conclusion:** Implementation of ERAS protocol in gynecologic surgery for endometrial carcinoma tailored according to the situation in each case, But in general; use of laparoscopy with ERAS was associated with controlled intravenous fluids utility, comparable pain, better operative outcome with less complication rates compared to conventional laparotomy.

**Keywords:** Enhanced recovery after surgery (ERAS) endometrial carcinoma(EC),length of hospital stay (LOS).

### Introduction

Endometrial carcinoma (EC) is the most commonly diagnosed gynecologic malignancy in the western countries with approximately 63,230 cases and 11350 estimated deaths recorded in 2018 in the United States alone. It is the fourth most common malignancy in women, and the eighth most common cause of cancer death (American Cancer Society, 2018).

Endometrial carcinoma occurs most often in the sixth and seventh decades of life, with an average age at onset of 60 years. It is estimated

that 75% to 85% of the cases occur in patients 50 years old and older and uncommon in women under the age of 45 (American Cancer Society, 2018).

Surgery is the main treatment for most women with endometrial cancer but in certain situation, a combination of these treatment depend on the type & the staging of the disease (Amant et al., 2005).

Laparoscopic technique has been used in the field of endometrial cancer (Reich et al.,1989).

Enhanced recovery programs include several evidence-based procedures targeting at reducing perioperative stress and organ dysfunction by modulating factors that improve postoperative recovery such as gut function, immobility and pain (Ljungqvist et al., 2012)

### **Aim of the work**

The aim of the present study is to prove the efficacy of laparoscopic hysterectomy versus traditional abdominal hysterectomy in treatment of endometrial cancer and to study the impact of implementing modified enhanced recovery after surgery (ERAS) program for endometrial carcinoma on length of hospital stay and operative outcome.

### **Patients and Methods**

#### **Setting:**

The current study was a prospective no randomized clinical study on women who underwent surgery for endometrial carcinoma in Minia maternity University Hospital (MMUH) and EL-Salam Oncology Center, Cairo. The study was conducted during the period between January 2015 and September 2018.

#### **Patients:**

##### **Inclusion criteria**

- 1- Women newly diagnosed with endometrial cancer either peri or post menopausal.
- 2- Patients who were classified as (FIGO) stage TAI to stage IIA.
- 3- Patients eligible for follow up.
- 4- Eligible subjects were American Society of Anesthesiologists (ASA) physical status I and II females undergoing exploration for endometrial carcinoma. Patients with a history of coagulopathy, recent infection (>1 month), current use of an opioid analgesic or corticosteroid, allergies to drugs included in the study protocol,

##### **Exclusion criteria:**

- 1- Presence of distant metastasis.
- 2- Major medical problems.
- 3- Patients who had treated with prior pelvic radiotherapy and/ or chemotherapy
- 4- Locally advanced disease with invasion into adjacent pelvic organs.

#### **Surgical techniques:**

##### **Group A:**

Four ports entry was initiated. A 10-mm trocar that incorporates the 30-degree laparoscope

(Karl Storz, Tuttlingen, Germany) was inserted through a supra umbilical vertical incision.

Three suprapubic ancillary trocars were used: One 5-mm trocar was inserted in the mid line 5 cm under the umbilicus just suprapubic and one in each iliac fossa (5 and 10 mm each) with transillumination to avoid vascular injury. A uterine manipulator was inserted through the cervix.

In this study, transperitoneal bilateral pelvic lymphadenectomy was done after total laparoscopic hysterectomy.

##### **a- Total laparoscopic hysterectomy**

The ureter along its whole pelvic course crossing over the bifurcation of common iliac artery till piercing the cardinal ligament and passing through the ureteric canal should be clearly identified. It lies on the medial peritoneal leaf of broad ligament.

The broad and round ligaments were already dissected, the infundibulopelvic ligaments were sealed and dissected bilaterally using the Ligasure® (Vallylab™, Tyco Healthcare UK Ltd). A uterine manipulator placed inside the uterus vaginally was helpful in retracting the uterus in the opposite direction, facilitating the stretch on the infundibulopelvic ligament.

The uterovesical peritoneum was identified, grasped, and elevated with forceps while scissors were used to dissect the bladder off the cervix. The bladder was dissected from the uterus by pushing downward - with the tip of a blunt probe or a piece of sponge on grasper - along the vesicocervical plane until the anterior cul-de-sac is exposed completely.

The uterine vessels were identified, desiccated. It was easily identifiable by following the obliterated umbilical artery till its origin from the hypogastric artery. It was sometimes sealed and cut flushing to the uterus and others at its origin from the anterior division of hypogastric artery. In some cases the anterior division of hypogastric artery was also sealed.

Using contralateral retraction of the uterus, the cardinal ligament was dissected to identify tissue planes, vessels, and the ureter. Once the ureter was displaced laterally, the cardinal

ligament tissue closest to the cervix was coagulated and transected using the LigaSure®.

Anterior and Posterior Culdotomy was done over (KOH Colpotomizer, Cooper Surgical) or over a piece of sponge in the fornices in some cases. Once completely freed, removal of the specimen was done through the vagina.

Pneumoperitoneum was retained by putting a glove filled with cotton inside the vagina.

The cuff was closed either by continuous suturing or two midline or lap intra corporeal interrupted sutures after completion of lymphadenectomy. The pelvic and abdominal cavities were evaluated laparoscopically, irrigated, and cleared of blood clots and debris. Intra abdominal pressure was reduced and the pedicles were reinspected to confirm hemostasis. Fascial repair was done to the other ports after removal of trocars with delayed absorbable sutures.

#### **B. Pelvic lymphadenectomy:**

This study adopted the technique described by Nezhat et al. Lymphadenectomy was initiated by identification of the lateral umbilical ligament. Incision of the lateral peritoneum was done by incising the round ligament, identification of the paravesical and pararectal fossae. The paravesical and pararectal spaces were important anatomic landmarks. When developed, they provide an opportunity for thorough exploration of the intervening base of the broad ligament. The broad ligament was then dissected in a cephalad fashion lateral and parallel to the infundibulopelvic ligament.

Lateral and intermediate external iliac lymph nodes were addressed by the dissection of the external iliac vessels. Dissection was initiated laterally over the psoas muscle and proceeded medially. It was done along the adventitia of the external iliac vessels, the external nodal chain above the external iliac artery was dissected then the internal surface, followed by the superior surface of the external iliac vein. Dissection was continued caudally from common iliac vessels to the level of the deep circumflex iliac vein seen crossing over the distal portion of the external iliac artery. Caution was taken to avoid injury of the genitofemoral nerve.

Medial external iliac lymph nodes were addressed. The internal and inferior surfaces of the external iliac vein were dissected. This dissection was pursued to the pelvic wall.

The obturator space was entered by reflecting the external iliac vessels medially away from the psoas muscle and freeing the areolar tissue which located directly between these vessels and the lateral pelvic wall with blunt dissection. Once the space has been entered, the artery and vein were released and gently retracted laterally, and the obturator space was clearly exposed. The lymphatic and areolar tissue were dissected from the obturator space to the region of the pelvic floor, with care to avoid trauma to the obturator nerve and vessels.

The dissection was continued by removing all of the nodes below the bifurcation of the iliac vessels, including the hypogastric nodes and the nodes in the obturator fossa. The hypogastric artery was dissected with identification of the visceral branches of the anterior trunk. The anterior division of the hypogastric artery continues along the paravesical fossa to become the obliterated lateral umbilical ligament beneath the anterior abdominal wall. The uterine artery was ligated at its origin from the hypogastric artery. Sometimes the anterior division of the hypogastric artery was ligated just distal to the point of origin of its posterior division rather than ligating the uterine artery individually.

The lymph node chain was retracted posteriorly, their anterior attachments were divided after the use of Ligasure® for lymphostasis and avoiding lymphocyst formation. Finally the tissues harboring the nodal chains were extracted vaginally before closure of vaginal stump.

#### **• For second group: (conventional surgery): group B**

Patients in control group were ordered to fast overnight. All patients received a mechanical bowel preparation. The patients were admitted to the hospital for 2–5 days before the procedures. All patients of control group received general anesthesia, where induction of anesthesia was performed using 2 to 3 mcg/kg of IV fentanyl, 1.5 to 2.0 mg/kg of propofol, and 0.5mg/kg of atracurium. Anesthetic maintenance was achieved with isoflurane at 1 minimum alveolar concentration (MAC),

fentanyl 1 mcg/kg titrated to avoid arterial blood pressure values above 20% of baseline, and additional doses of atracurium to keep 2 twitches using a train-of-4 monitor. At skin closure, neuromuscular blockade was antagonized with 0.01 mg/kg of atropine and 0.05 mg/kg of neostigmine. Intraoperative fluid administration was managed by anesthesiologist according to the situation of each case. Postoperative fluids were continued until the intestinal motility was regained. The patients were instructed to start with clear liquid diet on the morning of postoperative day and then continued as afford postoperative pain management depended mainly on the use of opioids and other pain killers.

#### **Surgical technique of Group B:**

Midline vertical incision was the routine approach. The abdomen was kept open by a self-retaining retractor, and the bowel was kept in place with warm, wet pads. The abdominal viscera were thoroughly examined, including the liver, gallbladder, stomach, kidneys, and aortic lymph nodes.

#### **a- Total hysterectomy**

The round ligament was cut between the clamps, then the vesico-peritoneal fold was elevated, and the bladder was gently separated from the corpus and cervix and mobilized inferiorly by sharp or blunt dissection. Securing the infundibulopelvic ligament by double ligation was done. Then the uterine arteries were skeletonized, triply clamped, cut and suture ligated. The upper portions of the cardinal ligaments were cut and the uterosacral ligaments were clamped close to the cervix. The

vagina was cut free from the cervix and the free edges of the vagina were grasped with long Allis clamps. The vaginal angles were secured with figure-of-eight suture ligatures, then closure of the vaginal vault was completed.

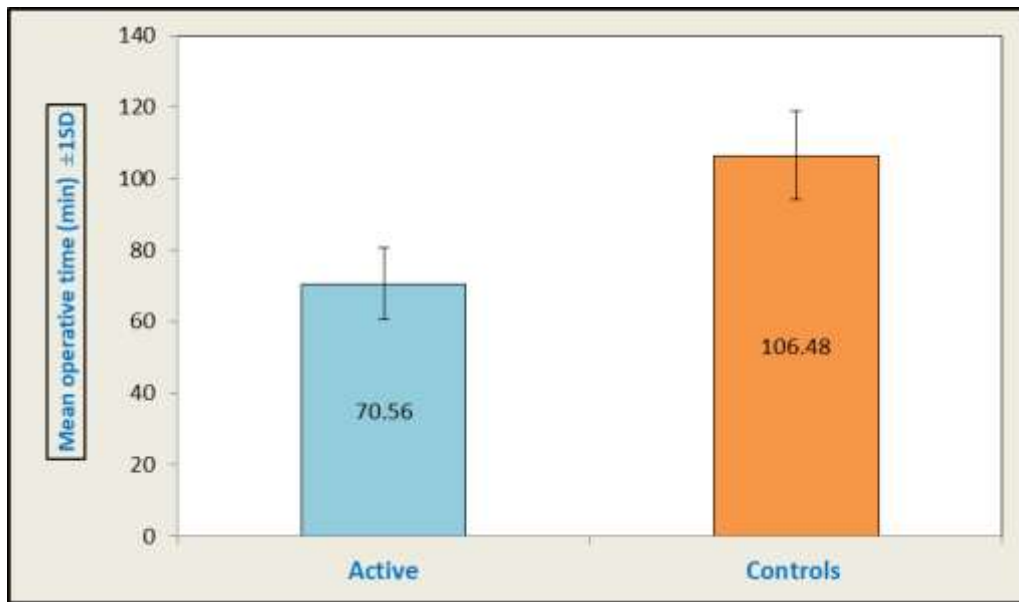
#### **b- Pelvic lymphadenectomy**

Transperitoneal pelvic lymphadenectomy was initiated. Node dissection was begun by separating the lymph nodes overlying the external iliac artery from the vessel by entering the plane of dissection between the adventitia of the artery and the areolar tissue. Dissection was carried out caudally down to the inguinal ligament and proximally up to the iliac bifurcation. The external iliac vessels were retracted medially and the dissection was carried between the vessels and the psoas staying on its fascia. Near the iliac bifurcation, the obturator nerve was easily identified emerging from under the psoas muscle. The specimen was detached from the medial aspect of the external iliac artery and vein along the adventitial plane. The artery and vein were separated to remove the lymph nodes located between them. The lymphatic tissue was detached from the inferior aspect of the external iliac vein. With blunt dissection, the entire obturator nerve was freed from the lymphatic pad. The specimen was isolated from the surrounding vessels and nerve, the caudal border was dissected at the femoral ring, and the cranial end was carefully detached from the anterior aspect of the hypogastric artery and vein. These nodes are called the superficial obturators and include nodes called obturator, interiliac, hypo gastric and medial external iliac nodes.

## **Results**

**Table (1): Intraoperative data among studied groups**

	Active N=27	Controls N=31	p-value
	Range Mean± SD	Range Mean± SD	
<b>Operative time (min)</b>	55-92 70.56±10.71	90-130 106.48±12.48	<0.0001
<b>Blood loss (ml)</b>	100-300 165.74±52.41	300-600 459.68±77.91	<0.0001
<b>Intraoperative fluid balance (ml)</b>	500-1200 779.63±207.67	1000-2000 1467.74±278.55	<0.0001



**Figure (1): Operative time among studied groups**

In this study, the mean operative time in group A (70.56± 10.71) was significantly lower than that of group B (106.48±12.48)..... operative time showed considerable improvement with

repetition of cases and progression in learning curve, use of LigaSure, good selection of cases with early stage endometrial cancer and restriction to only pelvic nodal dissection.

**Table (2): Intraoperative complications among studied groups**

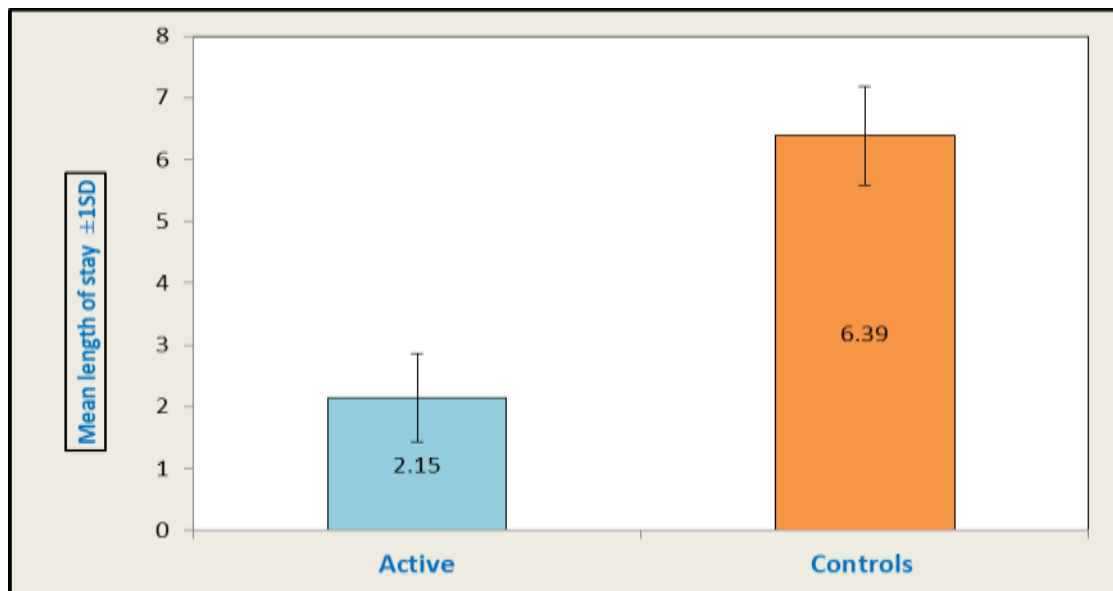
	Active N=27	Controls N=31	p-value
	N (%)	N (%)	
<b>Bowel injury</b>	0(0%)	0(0%)	-
<b>Bladder injury</b>	1(3.7%)	2(6.5%)	0.553
<b>Ureteric injury</b>	1(3.7%)	2(6.5%)	0.553
<b>Vascular injury</b>	0(0%)	0(0%)	-
<b>Blood transfusion</b>	3 (11.1%)	8 (25.8%)	0.157

Fortunately, the complications in this study were very limited in both groups. There was no cases of bowel, vascular injury nor cases of massive postoperative hemorrhage necessitating intervention. There were only one case of bladder and ureteric injury while 2 cases for

each among patients in group B.3 cases of group A received blood transfusion intra-operative representing (11.1%), however 8 cases in group B representing (25.8%).These differences were statistically insignificant.

**Table (3): Postoperative data among studied groups**

	Active N=27	Controls N=31	p-value
	Range Mean± SD	Range Mean± SD	
Length of hospital stay (days)	1-4 2.15±0.71	6-9 6.39±0.80	<0.0001
Visual Analogue Score	2-6 3.04±1.05	5-8 5.71±1.00	<0.0001
Postoperative fluid balance (ml)	500-2000 916.67±379.77	2000-3000 2345.16±295.34	<0.0001
Ambulation time (N of hours after)	2-5 2.61±0.76	5-10 6.25±1.39	<0.0001
Start oral fluids & soft food in 1st postoperative day: n (%)	23 (85.2%)	14 (45.2%)	0.002



**Figure (2): Length of stay among studied groups**

This figure proves the efficacy of minimally invasive surgery with implementation of ERAS protocol on shortening of the mean time of hospital stay in the group A (2.15± 0.71days) which was significantly lower than in group B (6.39±.80).

**Discussion**

The application of laparoscopy in the management of gynecologic malignancy has received much attention during the past few years (Mario Malzoni et al., 2009).

The laparoscopic approach is advantageous particularly in shortening hospital stay, decreasing total hospital charges and decreasing the overall postoperative morbidity and complications than traditional laparotomy. (Ghezzi et al., 2006).

In gynecology and gynecologic oncology early enteral intake was associated with a faster regain of bowel motility and a decreased length of stay without increase in postoperative complications. (Charoenkwan et al., 2014)

De Groot et al., [2015] formatted a design that directed to the nationwide implementation of the ERAS in gynecological surgery in the Netherland. The LAFA study (Vlug et al., 2011) proposed that the improvement of patient’s outcome is mainly linked to the

surgical techniques. Minimally invasive techniques were the only independent predictive factor to reduce LOS in that study. Apart from laparoscopic technique, the current study showed that ERAS has shared to some extent, but statistically significant, in decrease LOS.

The success in the current study is attributed mainly to the use of minimally invasive surgery and the strict implementation of ERAS protocol. These finding is in accordance with De Groot s hypothesis.(De Groot et al., 2015 )

Early mobilization is a lineament of ERAS. Traditional teaching and improvisation concluded that early mobilization decreases pulmonary complications, prevents loss of muscle mass, decreases insulin resistance, and improve bowel function. Also, late mobilization is associated with increased risk of thromboembolism and decreased oxygen delivery to tissues. However, there are no current RCTs that show that early mobilization results in improved postoperative outcomes, analysis of ERAS shows that a failure to mobilize is associated with increased length of stay suggesting that early mobilization is a key to achieve the advantageous results of ERAS protocols. (Vlug et al., 2012)

## References

1. Amant F, Moerman P, Neven P, et al., Endometrial cancer, *Lancet*.2005; 366:491-505
2. American Cancer Society: Cancer facts & figures 2018. Atlanta Ga; American cancer society (2018).
3. Charoenkwan K, Matovinovic E: Early versus delayed oral fluids and food for reducing complications after major abdominal gynaecologic surgery. *Cochrane Database Syst Rev* 2014(12):CD004508.
4. de Groot JJ MJ, Slangen BF, Winkens B, Dirksen CD, van der Weijden T.: A stepped strategy that aims at the nationwide implementation of the enhanced recovery after surgery programme in major gynaecological surgery: study protocol of a cluster randomised controlled trial. *Implement Sci* 2015, 10:106.
5. de Groot JJ, Ament SM, Maessen JM, Dejong CH, Kleijnen JM, Slangen BF: Enhanced recovery pathways in abdominal gynecologic surgery: a systematic review and meta-analysis. *Acta Obstet Gynecol Scand* 2016, 95(4):382-395.
6. Ghezzi F, Cromi A, Bergamini V, et al.: Laparoscopic management of endometrial cancer in nonobese and obese women: a consecutive series. *J Minim Invasive Gynecol* 13(2006) 269–75.
7. Ljungqvist O: Jonathan E. Rhoads lecture 2011: Insulin resistance and enhanced recovery after surgery. *JPEN J Parenter Enteral Nutr* 2012, 36(4):389-398.
8. Iug MS, Wind J, Hollmann MW, Ubbink DT, Cense HA, Engel AF, Gerhards MF, van Wagenveld BA, van der Zaag ES, van Geloven AA et al.: Laparoscopy in combination with fast track multimodal management is the best perioperative strategy in patients undergoing colonic surgery: a randomized clinical trial (LFAA-study). *Ann Surg* 2011, 254(6): 868-875.
9. Mario Malzoni, Raffaele Tinelli, Francesco Cosentino, et al.: Total laparoscopic hysterectomy versus abdominal hysterectomy with lymphadenectomy for early-stage endometrial cancer: A prospective randomized study, *Gynecologic Oncology* 112 (2009) 126 – 133.
10. Reich HJ, De Caprio J, McGlynn F.: Laparoscopic hysterectomy. *J Gynecol Surg* 5 (1989) 213.
11. Vlug MS BS, Wind J, et al.: Which fast track elements predict early recovery after colon cancer surgery? *Colorectal disease. the official journal of the Association of Coloproctology of Great Britain and Ireland* 2012, 14(8):1001–1008.