

# Surgical Outcomes, Risk Factors, and Patterns of Recurrence in Endometrial Cancer

G Balamurugan<sup>1</sup>, A Suresh Venkatachalam<sup>2</sup>

<sup>1</sup>Associate Professor, Department of Surgical Oncology, Regional Cancer Centre, Government Coimbatore Medical College Hospital, Coimbatore, Tamil Nadu, India, <sup>2</sup>Professor, Department of Surgical Oncology, Regional Cancer Centre, Government Coimbatore Medical College Hospital, Coimbatore, Tamil Nadu, India

## Abstract

**Introduction:** Endometrial cancer (EC), being the third most common gynecologic cancer, is now increasing in prevalence among the developed countries. The morbidity and mortality rates are rising gradually in spite of available advancing treatment modalities. This study aims to brief on the patterns and risk factors of recurrence and surgical outcomes of EC.

**Aim:** This study aims to study the patterns of recurrence and surgical outcomes of EC based on surgical and adjuvant therapy.

**Materials and Methods:** The study was conducted among 60 women with EC in a tertiary care center. Disease staging was done by 2009 FIGO criteria. Post-operative adjuvant therapy in the form of pelvic radiation or vaginal radiation was offered along with chemotherapy to appropriate patients. The risk factors, surgical outcomes, and prognostic factors were studied by radiological imaging and blood parameters.

**Results:** The mean age of the occurrence of EC was 51.22 years and abnormal uterine bleeding was the common presenting symptom. About 86.6% of the patients underwent total abdominal hysterectomy and 52 of 60 patients required bilateral salpingo-oophorectomy (BSO). Pelvic lymph node dissection was done in 47 cases (61.6%) and 10 cases (16.6%) needed para-aortic node dissection. Laparoscopic vaginal hysterectomy with BSO was done in one patient due to associated comorbidity. One patient needed only vaginal hysterectomy due to early-stage disease. The complication rate in this series was found to be 15% (9/60 cases). Two recurrences and one reported death were noticed.

**Conclusion:** EC is common in postmenopausal women and comprehensive surgery, adjuvant radiotherapy and chemotherapy can help in reducing disease recurrence. Open surgery and minimally invasive surgery both have more or less equal outcomes.

**Key words:** Adjuvant therapy, Chemotherapy, Endometrial cancer, Hysterectomy, Perimenopausal, Radiation, Recurrence

## INTRODUCTION

Endometrial cancer (EC), also called uterine cancer, begins in the layer of cells that form the lining (endometrium) of the uterus. Other types of uterine cancer include uterine sarcoma, but they are much less common than EC.<sup>[1]</sup> The first sign of the disease is vaginal bleeding which is not associated with menstruation which prompts the women to meet the doctor. EC occurs most commonly in women who have crossed menopausal age.<sup>[2]</sup>

EC is the most frequent gynecologic cancer in developed countries that killed around 34,700 women in 2012 (Bogani *et al.*, 2016).<sup>[3]</sup> Although it primarily affects postmenopausal women, 25% are premenopausal and 3–5% are under 40 years.<sup>[4]</sup> A history of ovarian dysfunction, anovulation, infertility, and obesity is often found in this younger group with EC. In young women who have never been pregnant and have a strong desire to preserve fertility, endometrial carcinoma is an estrogen-dependent well-differentiated endometrioid carcinoma and does not tend to invade the myometrium and also exhibits good prognosis (Benshushan, 2004; Zivanovic *et al.*, 2009).<sup>[5]</sup> Therefore, these patients could be candidates to a conservative approach in preserving a potential fertility.<sup>[6]</sup>

EC has a favorable prognosis and women are often diagnosed at an early stage; therefore, they are managed by

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**Corresponding Author:** Dr. A Suresh Venkatachalam, Department of Surgical Oncology, Regional Cancer Centre, Government Coimbatore Medical College Hospital, Coimbatore, Tamil Nadu, India.

surgery alone and carry a low risk of recurrence. The 5-year overall survival rate is 80%.<sup>[7]</sup> For women with increased risk of recurrence, adjuvant radiotherapy and systemic treatment are other options. Women's age, histological type and grade, depth of myometrial invasion, cervical involvement, and lymphovascular space involvement (LVSI) status are predicting factors of recurrence and survival.<sup>[8]</sup> Although the prognosis of EC is good, about 13% can still recur and most EC-related deaths are due to recurrence.<sup>[9]</sup> The types of recurrence in EC have not been clearly defined till date although authors agree that the development of distant metastases to brain, lung, liver, bone metastases, and supradiaphragmatic nodal metastases can result in a significant reduction in overall survival rates.<sup>[10]</sup>

It is important to identify the prognostic factors that predict the development of recurrence and also improve the choice of adjuvant therapy subsequently. The risk groups for recurrence have been discussed in this study based on the clinicopathological prognostic factors to identify women with poor prognosis and high recurrence rates so that they may benefit from adjuvant therapy.

### Aims

The aims of this study are as follows:

1. Patterns of risk factors for recurrence in EC
2. Outcomes of EC based on surgical and adjuvant treatment.

## MATERIALS AND METHODS

This retrospective study was conducted in the Department of Surgical Oncology at a tertiary care center in EC patients. Data were collected from medical records such as baseline characteristics, disease profiles, surgical outcomes, complications, biopsy details, and adjuvant treatment. Patients were staged according to the 2009 FIGO criteria. Outcome measures included the use of blood and blood products and complications of the surgery such as infections, hemorrhage, wound breakdown, and lymphocysts. Recurrence was diagnosed based on clinical and radiological imaging. A local recurrence was defined as any disease confirmed by histopathologic examination at the vault region. Distant recurrence was defined as disease out of the pelvis as shown clinically or on imaging.

Pelvic lymph node dissection (PLND) involved the opening of the retroperitoneum and removing all fibrofatty tissues along the major pelvic vessels. The distal limit of the node dissection was up to the circumflex iliac vessels over the external iliac and the obturator nerve, leaving the pelvis at the obturator fossa. The upper limit was the common

iliac nodes at the bifurcation of the common iliac arteries. Para-aortic node dissection was performed up to the level of the inferior mesenteric artery. Completion surgery (post-hysterectomy) for patients operated elsewhere was offered if there was a deep myometrial invasion, or a Grade 3 tumor, or if high-risk histology and ovaries had been retained. Baseline imaging was performed, followed by a restaging laparotomy that included peritoneal washings, and pelvic and para-aortic node dissection as indicated. Patients were followed for 3 months.

## RESULTS

During the study period, a total of 60 women were operated on for EC. The mean age of the patients was 51.22 (standard deviation of 7.48). Most of the patients presented with postmenopausal bleeding (41 cases). Perimenopausal abnormal uterine bleeding was observed in 10 cases. The mean CA-125 (cancer antigen) levels were  $41.28 \pm 122.2$  IU/ml and the mean endometrial thickness measured by vaginal ultrasonography (TVS) was  $22.48 \pm 8.12$ . Of the 60 patients, 52 patients underwent total abdominal hysterectomy (TAH) (86.6%) and all 52 patients required bilateral salpingo-oophorectomy (BSO). PLND was done in 47 cases (61.6%) and 10 cases (16.6%) needed para-aortic node dissection. Laparoscopic vaginal hysterectomy (LAVH) with BSO was done in one patient due to associated comorbidity. One patient needed only vaginal hysterectomy due to early-stage disease. The complication rate in this series was found to be 15% (9/60 cases) [Table 1 and Figure 1].

Urinary tract infection, vessel injury, and post-operative ileus/intestinal obstruction were the most frequently encountered complications (two cases each). Post-operative fever and sepsis, deep venous

**Table 1: Operative Details**

Operative details	Frequency
Total abdominal hysterectomy+bilateral salpingo-oophorectomy	6
Total abdominal hysterectomy+bilateral salpingo-oophorectomy+pelvic lymph node dissection	37
Total abdominal hysterectomy+bilateral salpingo-oophorectomy+pelvic lymph node dissection+para-aortic node dissection	10
Laparoscopic vaginal hysterectomy+bilateral salpingo-oophorectomy	1
Vaginal hysterectomy	1
Others	5

thrombosis (DVT), and wound breakdown were the other complications observed [Figure 2]. Post-operative biopsy revealed that approximately two-thirds of the tumor were >2 cm (67%) and the rest were <2 cm. About 88.3% of the tumors were endometrioid and 11.6% was non-endometrioid. Most of the patients had Grade 1 disease (58.3%), 17 patients had Grade 2 disease (28.3%), and 8 patients had Grade 3 disease (13.3%). LVSI was positive in 16 cases (26.6%) and negative in 39 cases (65%). Twenty-two patients had >50% gross myometrial invasion which can be associated with a high prevalence of pelvic lymph node metastasis. Myometrial invasion of <50% was noticed in 36 cases. The mean PLND is 6 and the mean PAND is 4. Positive peritoneal cytology was seen in four patients and a positive parametrium was seen in two cases.

About 50% of the women (30 cases) had the early-stage disease (IA) and 13 cases were Staged I-B. Highly advanced and metastatic Stage IV disease was seen in 3 patients (5%)

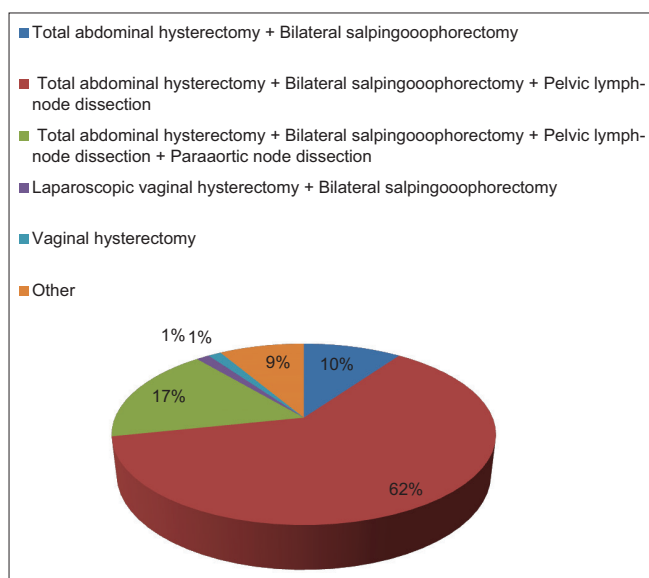


Figure 1: Distribution of procedures performed

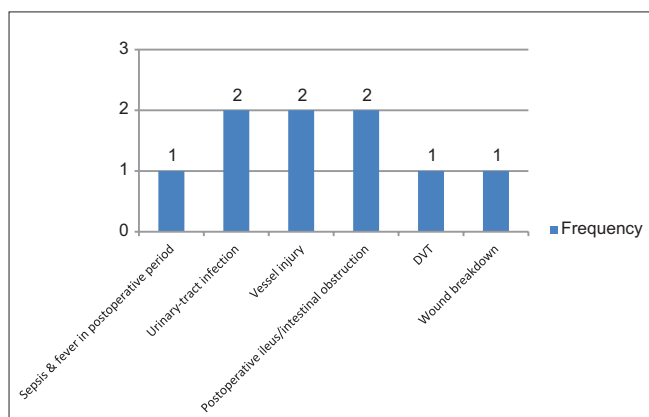


Figure 2: Complications

[Figure 3]. As most of the patients had Grade 1 early disease, they did not receive adjuvant therapy. Adjuvant therapy was given to 27 patients who were in the progressive phase and advanced stage of the disease. Twenty-three patients received radiation, 13 patients received chemotherapy, and 9 patients had a combination of both. Of the 23 patients who received radiation therapy, vaginal brachytherapy alone was administered to eight patients and abdominal radiation was given to three patients. Twelve patients received both vaginal and abdominal radiation. Chemotherapy was offered with a combination of paclitaxel+carboplatin to nine patients and carboplatin alone to one patient. For patients who were sensitive to these drugs, other platinum drugs were used. Combination of radiotherapy and chemotherapy was given to patients who had positive peritoneal cytology and other high-risk factors like pelvic node involvement [Figure 4].

In this case series, only two patients had a recurrence and one death was reported. An attempt was made to examine various factors that could have possibly affected survival. Logistic regression was computed for all these factors. Risk factors such as a deep myometrial invasion, higher grade of the tumor (G3), parametrium being positive, and adjuvant treatment were significant for disease-free survival (DFS) on univariate analysis.

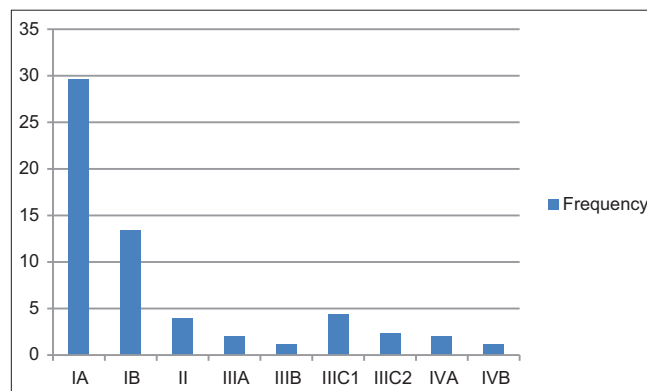


Figure 3: Stage of the disease

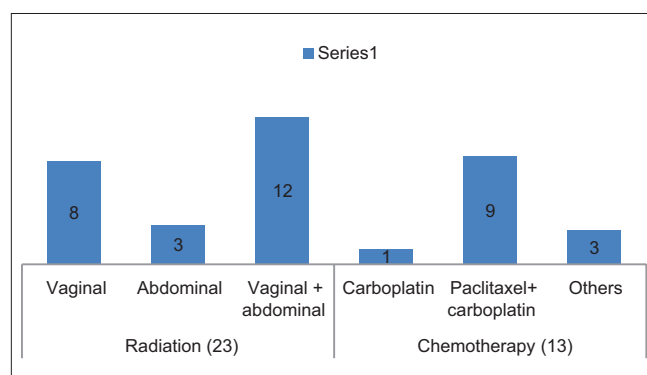


Figure 4: Adjuvant therapy

## DISCUSSION

EC is the third most commonly occurring gynecologic malignancies. The first sign of the disease is vaginal bleeding that is not associated with a menstrual period.<sup>[11,12]</sup> Other symptoms may include painful urination, pain during sexual intercourse, or pelvic pain.<sup>[13]</sup> EC occurs most commonly after menopause and over 40% of the cases are related to obesity.<sup>[14]</sup> The other risk factors include diabetes mellitus, high estrogen levels, use of tamoxifen, absence of pregnancy, and advancing age.<sup>[15,16]</sup> Genetics and environmental factors also contribute to 2–10% of EC.<sup>[17]</sup> The initial treatment for EC is some form of surgery which typically consists of hysterectomy and BSO.<sup>[18]</sup> For tumors above Grade II, PLND or PAND is performed.<sup>[16]</sup>

This retrospective analysis of surgical outcomes in EC emphasizes the importance of comprehensive surgical staging and the need to adhere to protocols based on which treatments are implemented for a better outcome. Our study results show that EC is more common in postmenopausal women, the mean age of occurrence being 51 years. Abnormal uterine bleeding was the most common presenting symptom. A study by Gao *et al.* among Chinese women in 2016 also states that the prevalence of both type I and type II EC is more likely to occur in postmenopausal women than before.<sup>[19]</sup> Around 86.6% of the patients in our study underwent TAH with BSO and the mean uterine thickness as measured by ultrasonography was 22.48 mm. Estrogen plays an important role in the development of EC and the risk increases with increased exposure to unopposed estrogen.<sup>[20]</sup> Here, the increased endometrial thickness can be attributed to increased estrogen levels. In obesity, the excess adipose tissue increases the conversion of androstenedione into estrone, an estrogen. This causes less or no ovulation and, in turn, exposes the endometrium to continuously high levels of estrogen.<sup>[21]</sup> Hence, obesity is one of the main risk factors for EC.

USG examination was routinely performed for all patients based on institutional protocols as pre-operative evaluation may assist the surgeon in deciding the extent of surgery and also to assess the grade, tumor size, and tumor extension. More than 90% of the patients underwent TAH in our study and the complication rate associated was 15% which is comparable to the quoted complication rate of open surgery by other researchers.<sup>[22]</sup> Urinary tract infection, vessel injury, and post-operative ileus/intestinal obstruction were the most frequently encountered complications. Post-operative fever and sepsis, DVT, and wound breakdown were the other complications observed. The recent advancement is laparoscopic hysterectomy which is associated with less hospital stay and less morbidity. Two

patients in this study series underwent an LAVH as they had the early-stage disease and to avoid a complicated open surgery. However, in general, removal of the uterus through the abdomen is recommended over the removal of the uterus through the vagina as it allows to examine and obtain washings of the abdominal cavity to detect any further evidence of cancer. Staging of the cancer is done during the surgery.<sup>[23]</sup>

Para-aortic and pelvic lymphadenectomy was required in many patients in our study (table) based on the operative character of the tumor. Post-operative biopsy was done and most of the tumors were >2 cm. Endometrioid tumors constituted 88.3% of the tumors in our study. Endometrioid adenocarcinoma is the most commonly occurring EC according to literature.<sup>[24]</sup> Most of the patients had Grade 1 disease (58.3%) and LVSI was positive in 16 cases (26.6%). Twenty-two patients had >50% gross myometrial invasion which can be associated with a high prevalence of pelvic lymph node metastasis. Positive peritoneal cytology was seen in four patients and a positive parametrium was seen in two cases. All these can be high-risk factors for disease recurrence even after extensive surgery.

About 50% of the women in our study had early-stage disease (IA) and 13 cases were Staged I-B. Highly advanced and metastatic Stage IV disease was seen in 3 patients (5%). As most of the patients had Grade 1 early disease, they did not receive adjuvant therapy. Adjuvant therapy was given to 27 patients who were in the progressive phase and advanced stage of the disease. Following risk stratification protocols, adjuvant radiation therapy, vaginal brachytherapy, or abdominal radiation were offered appropriately to high-risk patients. Chemotherapy was offered with a combination of paclitaxel + carboplatin to nine patients and carboplatin alone to one patient. For patients who were sensitive to these drugs, other platinum drugs were used. Combination of radiotherapy and chemotherapy was given to patients who had positive peritoneal cytology and other high-risk factors like pelvic node involvement.

Despite receiving pelvic radiation and vaginal brachytherapy, two patients had a recurrence in our study and one death was reported. CA-125 levels act as an important prognostic factor in determining disease progression and recurrence. Tumor recurrence is preceded by an increase in serum CA-125 levels.

The limitations of this study are its retrospective nature, small sample size, and the failure to obtain certain follow-up details. The compliance of advanced stage disease patients with further treatments was not satisfactory. If the follow-up period had been extended, the results would have been different.

## CONCLUSION

This study concludes that EC is common among postmenopausal women and the risk increases with advancing age. Combination of comprehensive surgery involving pelvic and para-aortic lymph node dissection followed by appropriate adjuvant radiation therapy or chemotherapy or a combination of both could result in better DFS rates. Endometrioid cancer is the most commonly occurring histologic type and most patients are diagnosed early. High-grade tumors, positive parametrium, deep myometrial invasion, and adjuvant treatments are risk factors of this disease. The outcomes of open surgery and minimally invasive surgery were more or less equal and more focus should be on developing adequate training skills to gynecologic surgeons and the need for referral of suspected cases to the oncologic set-up so as to make an early diagnosis.

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