# Clinico-Pathologic Factors of Endometrial Cancer in Young Filipino Women and Its Effect on Overall Survival Rate in a Tertiary Government Hospital*

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## ABSTRACT

**Introduction:** Endometrial cancer is one of the leading cancers affecting Filipino women, mostly affecting the older women; however, 5% of those with endometrial cancer are diagnosed before the age of 40. Only a few studies in the Philippines have been published regarding the clinico-pathologic factors and its association with overall survival rate of young women.

**Objective:** This study identified the prevalence and the different clinico-pathologic factors present in young patients diagnosed with endometrial cancer and its association with overall survival rate of these patients seen at a tertiary hospital in Baguio City, from January 2016 to December 2020.

**Methodology:** A retrospective cross-sectional study was done, with use patients' medical records. Frequencies and percentages of the different clinico-pathologic factors identified were done. Kaplan-Meier method was used for the overall survival rate, and association of the different clinico-pathologic factors with overall survival rates was identified using Multivariate Cox proportional hazard regression calculated at 95% confidence interval and significance level of 5%.

**Results:** The prevalence of young patients with endometrial cancer is 6.52%, with majority of patients being obese (56%), nulligravid (68%) and regularly menstruating (68%). Hypertension (28%) diabetes (16%) and PCOS (8%) were also noted as comorbidities but most of them had none. Mostly had endometrioid type (96%), <50% myometrial invasion (92%), Stage I (76%), with no involvement of LVSI, Lymph nodes and ovaries. There was a 100% survival rate on the 1st year, 90% on the 3rd year and 60% on the 5$^{th}$ year, with a mean survival time of 68 months. All of the patients underwent primary surgical treatment.

**Conclusion:** The overall survival rate of patients in this institution on the 1$^{st}$ year is good at 100%. In the study, there is no one significant clinic-pathologic factor that is associated with increased overall survival rate in young patients with endometrial cancer.


Keywords: Young patients, Endometrial Cancer, Clinico-pathologic Factors, Overall Survival Rate

## INTRODUCTION

Endometrial cancer is the 3$^{rd}$ most common genital tract malignancy and ranks 8$^{th}$ among all cancers affecting Filipino women[1] which affects mainly those at the age of 60, 90% of cases are found in women over 50 years of age and 20% will be diagnosed before menopause. Interestingly, even with these statistics, there is still 5% of the population who will develop **endometrial cancer before the age of 40**.[2] Even with the said percentage of young patients with endometrial cancer, a number is also being seen and treated in Baguio City. For the treatment of these young patients, there is a dilemma especially for those who are desirous of pregnancy, and the risk of having early menopause since current local guidelines recommend surgical management in the initial management of patients with endometrial carcinoma.[3] This radical surgery is a concern for young patients with the disease who still are desirous of pregnancy and ovarian preservation is now an interest as part of the conservative management for younger patients. A lot of factors should be considered when counselling patients regarding treatment options, which would include the type, grade, and extent of their disease[3].

Since these patients are young, the survival of this patients is of interest since they are still at their prime, yet acquiring cancer is a concern and knowing such might decrease their quality of life. Many studies have been published regarding factors that contribute to the overall survival rate of young patients with endometrial cancer but only a few studies were done in the Philippines. Some of the factors identified that were associated with improved overall survival rate include younger age, a

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well-differentiated endometrioid type, lower stage and no involvement of the lymph nodes.[2,4,5,6,7]

This study aimed to determine the clinical and pathologic factors associated with endometrial cancer among patients <=40 years old from January 2016-December 2020 seen at a tertiary hospital in Baguio City and their impact on the overall survival rate.

## METHODOLOGY

This is a retrospective cross-sectional study conducted at the Department of Obstetrics and Gynecology, Baguio General Hospital and Medical Center which identified the clinico-pathologic factors present in patients <=40 years of age diagnosed through histopathologic means with endometrial cancer from January 2016-December 2020 who was managed and followed up in the said institution.

This study underwent technical review by the Department of Obstetrics and Gynecology, and the Technical Review Board of the Baguio General Hospital and Medical Center, and was approved by the Ethics Review Committee of the same institution.

Records of patients <= 40 years of age at the time of diagnosis of Endometrial Cancer from January 2016- December 2020 were obtained from the medical records and the histopathologic results were obtained from the Department of Pathology of Baguio General Hospital and Medical Center. The tool used in data collection is a Data Abstraction Form and a code number was assigned per patient.

Age, BMI, Gravidity/ Parity, Age of Menarche, Interval of Menstruation, Use of OCP, Conorbidities, Family history of cancer, Primary management (medical vs surgical) and initiation of chemotherapy were the factors determined in this study. Histopathologic data for those who underwent surgical intervention included the Histologic Type, Myometrial invasion, Stage, Lymphovascular space invasion, presence of Lymph node metastasis and Ovarian metastasis. Data were presented as frequencies and percentages.

Records of their follow ups in this institution were done to identify the overall survival rate of these patients. Those that were lost to follow-up were noted and included in the statistical analysis as dropouts. The number of months each patient has lived from the time of diagnosis were determined and collated. The 1-year, 3-year and 5-year survival rates were determined using Kaplan-Meier method. The association of the different clinico-pathologic factors with overall survival rates were determined using Multivariate Cox proportional hazard regression was used, and was calculated at 95% confidence interval[12]. A $P < 0.05$ was considered statistically significant.

## RESULTS

Based on the review of records, a total of 25 patients were included in the study who were <= 40 years old diagnosed with endometrial cancer from January 2016 December 2020, with a prevalence rate of 6.52%. There is increase in the number of patients with increase in age, with almost half of the subjects (48%) are aged 36-40 years old, with the youngest being 25 years old. More than half of them was classified as Obese (56%) based on the Asia Pacific classification of BMI, 68% were nulligravid and have regular interval of menses, and only one had a history of OCP use. Hypertension was prevalent at 28%, followed by diabetes at 16%, and PCOS (8%) as concomitant comorbidity among patients. Three patients had family history of cancer in the family, which were ovarian and breast cancers. All of the patients underwent surgery, and no patient underwent primary medical treatment. 84% of the patients did not undergo adjuvant chemotherapy (Table 1). The 4 patients that underwent chemotherapy were at an advanced stages or had recurrence.

With regards to histologic types, majority are of Endometrioid type at 96%, with only 1 patient having a mucinous type. 84% of patients had <50% myometrial invasion. 76% were at Stage I, 16% were at Stage III, and 4% were at Stage II and IV. 24%, 20% and 8% of patients have lymphovascular invasion, lymph node metastasis and ovarian metastasis, respectively. Most of them had absence of the said parameters. (Table 1).

Table 1. Clinico-pathologic profile of patients <= 40 years of age with endometrial cancer

| CLINICO-PATHOLOGIC FACTORS | | FREQUENCY n=25 | PERCENTAGE % |
|---|---|---|---|
| **Age** | <= 25 y/o | 1 | 4 |
| | 26-30 y/o | 3 | 12 |
| | 31-35 y/o | 9 | 36 |
| | 36-40 y/o | 12 | 48 |
| **BMI (kg/m2)** | <18 | 0 | 0 |
| | 18-22 | 3 | 12 |
| | 23-25 | 0 | 0 |
| | 25-30 | 8 | 32 |
| | >30 | 14 | 56 |
| **Gravidity** | 0 | 17 | 68 |
| | 1 | 4 | 16 |
| | 2 | 2 | 8 |
| | 3 | 0 | 0 |
| | >3 | 2 | 8 |

| | | | |
|---|---|---|---|
| **Parity** | 0 | 17 | 68 |
| | 1 | 5 | 20 |
| | 2 | 1 | 4 |
| | 3 | 0 | 0 |
| | >3 | 2 | 8 |
| **Interval of Menses** | Regular | 17 | 68 |
| | Irregular | 8 | 32 |
| **Use of OCP** | yes | 1 | 4 |
| | no | 24 | 96 |
| **Comorbidities** | DM | 4 | 16 |
| | PCOS | 2 | 8 |
| | Metabolic Syndrome | 0 | 0 |
| | hypertension | 7 | 28 |
| | others | 0 | 0 |
| **Family history** | Endometrial | 0 | 0 |
| | Ovarian | 2 | 8 |
| | Colon | 0 | 0 |
| | Breast | 1 | 4 |
| | Others | 0 | 0 |
| **Primary management** | Surgical | 25 | 100 |
| | Medical | 0 | 0 |
| **Use of Systemic Chemotherapy** | Yes | 6 | 24 |
| | No | 19 | 76 |

| | | | |
|---|---|---|---|
| **Histologic Type** | Endometrioid | 24 | 96 |
| | Mucinous Carcinoma | 1 | 4 |
| | Serous Carcinoma | 0 | 0 |
| | Clear Cell Carcinoma | 0 | 0 |
| | Neuroendocrine Carcinoma | 0 | 0 |
| | Mixed Cell Adenocarcinoma | 0 | 0 |
| | Carcinosarcoma / Malignant Mixed Mullerian Tumor | 0 | 0 |
| | Others | 0 | 0 |
| **Myometrial invasion** | < 50% | 23 | 92 |
| | >50% | 2 | 8 |
| **Intraoperative Stage** | I | 19 | 76 |
| | II | 1 | 4 |
| | III | 4 | 16 |
| | IV | 1 | 4 |
| **LVSI** | PRESENT | 6 | 24 |
| | ABSENT | 19 | 76 |
| **Lymph Node Metastasis** | PRESENT | 5 | 20 |
| | ABSENT | 20 | 80 |
| **Ovarian Metastasis** | PRESENT | 3 | 12 |
| | ABSENT | 22 | 88 |

The overall survival rate of the sample patients in this institution, based on the Kaplan-Meier method (Figure 1) showed 100% survival on the 1st year, 90% on the 3rd year and 60% on the 5$^{th}$ year, with a mean survival time of 68 months. Comparison of survival rates of those who underwent primary medical versus surgical treatment was not possible because all of the samples underwent primary surgical treatment.

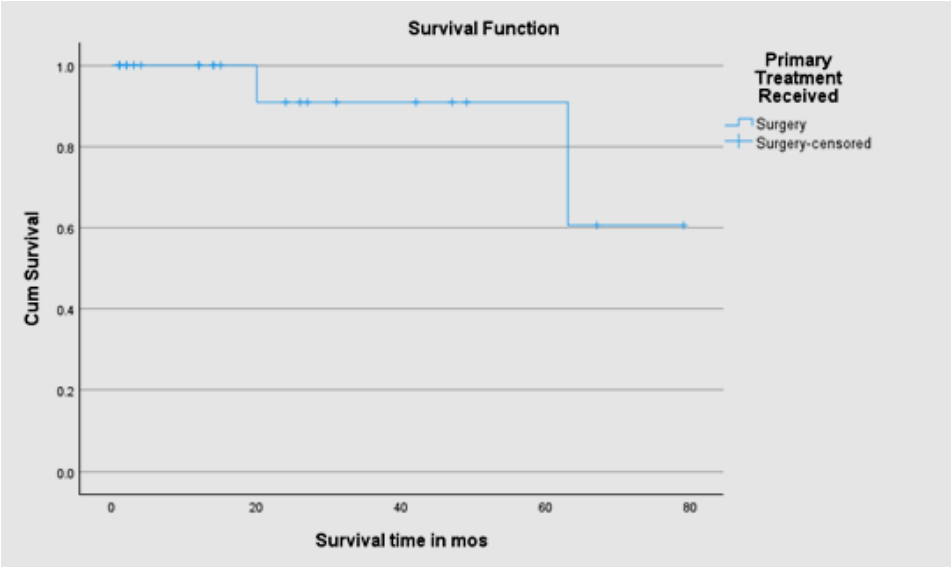


FIGURE 1. Survival rates of individual patients <=40 years of age with endometrial cancer

Table 2. Multivariate Cox proportional hazard regression table

**Variables in the Equation**

| | B | SE | Wald | df | Sig. | Exp(B) | 95.0% CI for Exp(B) Lower | Upper |
|---|---|---|---|---|---|---|---|---|
| Age | .000 | 1.343 | .000 | 1 | 1.000 | 1.000 | .072 | 13.911 |
| BMI | .000 | 4.690 | .000 | 1 | 1.000 | 1.000 | .000 | 9828.543 |
| OBscore | .000 | 3.071 | .000 | 1 | 1.000 | 1.000 | .002 | 410.864 |
| IntOfMenses | .000 | 3.071 | .000 | 1 | 1.000 | 1.000 | .002 | 410.864 |
| OCPuse | | | . | 0[a] | . | | | |
| Comorb | .000 | 2.803 | .000 | 1 | 1.000 | 1.000 | .004 | 243.203 |
| FamHxofCancer | .000 | 6.226 | .000 | 1 | 1.000 | 1.000 | .000 | 199296.992 |
| Surgery | | | . | 0[a] | . | | | |
| ChemoUse | .000 | 5.606 | .000 | 1 | 1.000 | 1.000 | .000 | 59147.615 |
| HistologicType | | | . | 0[a] | . | | | |
| MyometrialInvasion | .000 | 7.100 | .000 | 1 | 1.000 | 1.000 | .000 | 1106446.881 |
| IntraoperativeStage | .000 | 2.732 | .000 | 1 | 1.000 | 1.000 | .005 | 211.619 |
| Lymphovascularspaceinvasion | .000 | 4.690 | .000 | 1 | 1.000 | 1.000 | .000 | 9828.543 |
| Lymphnodemetastasis | | | . | 0[a] | . | | | |
| Ovarianmetastasis | | | . | 0[a] | . | | | |

a. Degree of freedom reduced because of constant or linearly dependent covariates

Due to constant or linearly dependent covariates, some of the covariates were dropped from the computation. Accounting all the different risk factors, it is shown in Table 2 that there is no one significant factor that is associated with increased overall survival rate since the value of Sig is >0.05.

## DISCUSSION

Risk factors in acquiring endometrial carcinoma are the states where unopposed estrogen is noted, which would include nulliparity, obesity[2,8,9], presence of polycystic ovarian syndrome (PCOS)[4] and family history of cancer in the family[8,9]. In the study, most of them were nulligravid and obese. Only 2 had a history of PCOS, and 3 having family history of cancer. Given any age, one of the strong risk factors for developing endometrial carcinoma is obesity, noted to increase the probability by two to five-fold, which is explained by the increased estrogen levels because of the peripheral conversion of androstenedione to estrone in adipose tissues.[4] Comorbidities identified to be associated with endometrial cancer were Diabetes and Metabolic syndrome, however in our study, hypertension was prevalent, followed by Diabetes and PCOS. Diabetes was already established to exhibit hyperinsulinemia and insulin resistance, which would decrease the production of sex hormone biding globulin (SHBG), leading to increased estrogen levels, increasing exposure to this hormone, thus promoting proliferation of the endometrium which could lead to cancer[11]. Having PCOS also increases the exposure to estrogen with prolonged anovulation[12]. Hypertension was noted to be a strong risk factor at 61% based on a meta-analysis, but was also noted that the result could not exclude the possibility of confounding variables such as obesity and diabetes, which is related to hypertension[13].

Majority of patients in the study had a stage 1 disease at the time of diagnosis, <50% myometrial invasion, endometrioid type of endometrial cancer, and without involvement of LVSI, lymph nodes and ovaries. It was noted that patients who are older have tendencies to have a higher stage and grade as compared to the younger patients[4] and that that there is generally better prognosis for those diagnosed with stage I disease and endometrioid histologic type of endometrial carcinoma.[5] Statistically, there was no identified independent risk factors associated with increased survival rates in our study. This could probably be explained by the small number of patients included in the study, with most of the data also being censored due to the most of the samples being lost to follow up. A study by Biler et al, also investigated clinicopathological characteristics, treatment, survival and prognosis of endometrial cancer in women ≤ 40 years of age who underwent surgical treatment, and only noted CA125 as a prognostic factor for increased survival.[14] The use of CA 125 in our setting, however, is still not recommended for routine clinical use, but may be requested for the management planning of certain patients who are unable to undergo comprehensive surgical staging and those with high-risk endometrial cancer histology.[3] Another study noted that there was no

significant correlation was found when age, reproductive history, smoking history, race, past medical history, or family history, was compared with histologic grade or surgical stage of the tumor.[2] Association between cancer cell type and stage of the disease was noted to be statistically significant.[2] Both factors were also noted to have a positive association with recurrence and survival.[2]

The recommended management for endometrial cancer is generally complete surgical staging, that is, extrafascial hysterectomy, bilateral salpingo-oophorectomy, and pelvic and para-aortic lymphadenectomy[3]; however, options for a more conservative approach in their treatment have become an interest, since hysterectomy would result to infertility, and oophorectomy would lead to these patients experiencing the effects of early menopause in young patients.[15] Medical management with progesterone is the main treatment used. Shah and Wright have compiled several studies which reported use of progesterone therapy in management of endometrial carcinoma. Two of these studies had 60% and 67% complete response rate with progesterone therapy for 24 and 26 weeks, respectively. Recurrence was also noted in those who initially responded to the therapy for both studies, 19% and 47%, respectively.[15] These could all explain why patients underwent and consented to undergo primary surgical management for endometrial cancer.

Another point of interest which is being studied recently is ovarian preservation as conservative management for young patients with endometrial cancer, since premature menopause is prevented, decreasing the risk for osteoporosis and cardiovascular disorders, and it was noted that women less than 50 years of age who undergo menopause have 12a higher overall mortality rate.[15] In the study, all underwent bilateral salpingo-oophorectomy, and most of the patients had no metastasis to the ovaries, making it a good opportunity for discussion regarding ovarian preservation for young patients; however, some studies have shown that young women are at risk of developing synchronous ovarian malignancies in up to 29%.[14] It is also important to note that there is approximately 5% incidence of ovarian metastasis in women with clinical stage I endometrial cancer.[16] Counselling patients regarding their treatment options, weighing the risks and benefits is very important in these subset of patients

## CONCLUSION

The prevalence of young patients with endometrial cancer in among <=40 y/o women in a Tertiary Hospital in Baguio City from January 2016-December 2020 is 6.52%, majority are obese, nulligravid, regularly menstruating and no history of OCP use. Mostly had no known comorbidities, but those that do had Hypertension, Diabetes and history of PCOS. On histopathologic results, most of the patients had Endometrioid type of Endometrial cancer, with <50% myometrial invasion, Intraoperatively Staged as I, without involvement lymphovascular space, lymph nodes and ovaries. The survival rate of young Filipino women in our institution showed 100% survival on the 1st year, 90% on the 3rd year and 60% on the 5th year, with a mean progression fee survival time of 68 months. Since there were no patients who underwent primary medical management, the comparison of survivals with those who underwent primary surgical management was not possible. For this study, there is no one significant factor among those identified that is associated with increase survival.

## RECOMMENDATIONS

Data registry for patients with endometrial cancer should be established to be able to easily retrieve records of patients. A multicenter, prospective cross-sectional study is also an option to better follow up patients and to increase the sample population. A longer duration for collection of data is recommended to be able to include as much patient as possible for the data to be more robust and for statistical analysis to be more valid.

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