RESEARCH COMMUNICATION

Endometrial Adenocarcinoma in Young Thai Women

Tarinee Manchana*, Nipon Khemapech

Abstract

Objective: To evaluate the clinicopathological characteristics and survival analysis in endometrial adenocarcinoma women younger than the age of 40 years compare to older women. Methods: Medical records of 423 endometrial adenocarcinoma patients who received primary surgical treatment at King Chulalongkorn Memorial Hospital during 1996-2005 were reviewed. The patients were divided into two groups; 40 years of age or younger (group A, 42 patients) and older than 40 years (group B, 381 patients). Results: Up to 10% (42/423) of endometrial adenocarcinoma patients were younger than the age of 40 years. The higher incidence of nulliparous and obesity (BMI > 30 kg/m2) was significantly demonstrated in group A (81%/34.1% and 52.4%/ 25.2%, respectively). However, obesity was an only independent factor in multivariate analysis. No significant difference in surgical stage distribution and the other pathologic characteristics was demonstrated between both groups. However, poor histologic grade (grade 3) and deep myometrial invasion (myometrial invasion more than 50%) tended to be found more frequent in the patients older than the age of 40 years, although there was no statistical significance (16% versus 4.7% and 31% versus 14.3%, respectively). Moreover, synchronous ovarian cancer seemed to be higher in young patients (7.1% and 2.9%, p > .05). Median time to follow was 63 months (range 0 – 145 months). Five years disease free survival and 5 years overall survival were 87.3% and 92.4% in group A versus 83.8% and 88.0% in group B without statistical significance between both groups. Conclusions: Obesity was the only independent factor associated with endometrial adenocarcinoma in young patients. Distribution of the surgical stage and the other pathologic characteristics were similar between both groups without survival benefit in young patients.

Key Words: Endometrial adenocarcinoma - risk factor - survival - young age

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Introduction

Endometrial adenocarcinoma is the third most common gynecologic malignancy in Thailand; however, it's the most common gynecologic malignancy in the developed countries. It is common in postmenopausal women and usually occurs in the sixth and seventh decades of life. Generally, 25-30% of the patients are premenopause and only 3-5% are younger than 40 years of age (Crissman et al., 1981; Benshushan et al., 2004). Recently, the incidence in young patients seems to be increasing. However, the definition of young patient is still controversial. Some studies included the patients younger than the age of 40 years but the others included patients younger than the age of 45 years. This study focused on the patients younger than the age of 40 years at the time of diagnosis because endometrial adenocarcinoma in this aged group is uncommon. In addition, median age of menopause in Thai women was 49 years and median age of endometrial adenocarcinoma patient was 55 years which seemed to be younger than the patients from the developed countries (Chompootweep et al., 1993; Worasethsin et al., 2004).

The risk factors associated with endometrial adenocarcinoma include obesity, nulliparity, unopposed estrogen, chronic anovulation, early menarche, late menopause, diabetes mellitus, and hypertension. However, few studies focused on the risk factors associated with endometrial adenocarcinoma in young patients. This study aimed to review the clinicopathological characteristics in endometrial adenocarcinoma patients who were younger than the age of 40 years compared to older than the age of 40 years. Survival comparison between both groups was also evaluated.

Materials and Methods

During 10-years period (1996 to 2005), 434 medical records of patients with endometrial adenocarcinoma who received the treatment at King Chulalongkorn Memorial Hospital were reviewed. Of the 434 patients, 10 patients who received primary radiation and 1 inoperable patient were excluded. The remaining 423 patients who underwent primary surgery were enrolled into this study. The patients were divided into 2 groups, 40 years of age or younger (group A) and older than 40 years (group B). Clinical characteristics such as age at diagnosis, parity,

*Gynecologic Oncology Unit, Department of Obstetrics and Gynecology, Faculty of Medicine, Chulalongkorn University, Bangkok 10330, Thailand *For Coreespondence: Tel: 66-2-2564241 Fax: 66-2-2549292 Email : T_manchana@hotmail.com*

duration of presenting symptom, body mass index (BMI), history of diabetes mellitus (DM) and hypertension (HT) were recorded. Pathological characteristics such as histology, grade, depth of myometrial invasion, lower uterine segment involvement, cervical involvement, adnexal involvement, lymphovascular space invasion, omental metastasis and lymph node involvement were obtained from pathologic reports. Surgical stage was generated from these pathological characteristics and assigned according to the International Federation of Gynecology and Obstetrics (FIGO 1998) (International Federation of Gynecology and Obstetrics, 1989).

The Chi-square test or Fisher exact test was used to analyze the categorical variables and continuous variables were analyzed by Student t test. Multivariate analysis was used to analyze the independent factors. Survival analysis was generated by Kaplan-Meier method and log rank test was used to compare between both groups. P value of less than 0.05 was determined to be statistical significance.

Table 1. Clinical Characteristics of Endometrial Adenocarcinoma Patients Younger (Group A) and Older (Group B) than the Age of 40 Years

Characteristics		Group A (N = 42)	Group B (N = 381)	P value
Parity (%)	Nulliparous	34 (81.0)	130 (34.1)	
	Multiparous	8 (19.0)	251 (65.9)	0.00
Median BMI (kg/m^2)		30.3 (17.7-46.7)	25.7 (16.0-53.7)	0.01
BMI (%)	<25	14 (33.3)	167 (43.8)	
	25.1-30	6 (14.3)	118 (31.0)	
	>30	22 (52.4)	96 (25.2)	0.00
DM and/	No	32 (76.2)	214 (56.2)	
or HT (%)	Yes	10 (23.8)	167 (43.8)	0.36

Table 2. Pathological Characteristics of Endometrial Adenocarcinoma Patients Younger (Group A) and Older (Group B) than the Age of 40 Years

Characteristics		Group A (N = 42)	Group B (N = 381)	P value
Surgical stage (%)	1	33 (78.6)	292 (76.6)	
	2	4 (9.5)	27 (7.1)	
	3	5 (11.9)	51 (13.4)	
	4	0 (0.0)	11 (2.9)	0.67
Histology (%)				
Endometrioid		42 (100)	367 (96.3)	
Non-endometrioid		0 (0.0)	14 (3.7)	0.28
Grade (%)	1	33 (78.6)	257 (67.5)	
	2	7 (16.7)	63 (16.5)	
	3	2 (4.7)	61 (16.0)	0.14
Myometrial	No	10 (23.8)	82 (21.5)	
invasion (%)	<50%	26 (61.9)	181 (47.5)	
	>50%	6 (14.3)	118 (31.0)	0.07
Lower segment	No	24 (57.1)	225(59.1)	
involvement (%)	Yes	18 (42.9)	156 (40.9)	0.87
Cervical	No	36 (85.7)	327 (85.8)	
involvement (%)	Yes	6 (14.3)	54 (14.2)	1.00
Adnexal	No	38 (90.5)	338 (88.7)	
involvement (%)	Yes	4 (9.5)	43 (11.3)	1.00
LVSI (%)	No	36 (85.7)	320 (84.0)	
	Yes	6 (14.3)	61 (16.0)	1.00
Omental	No	42 (100)	371 (97.4)	
metastasis (%)	Yes	0 (0.0)	10 (2.6)	0.45
Pelvic node	No	33 (78.6)	285 (74.8)	
metastasis (%)	Yes	1 (2.4)	22 (5.8)	
	Not available	8 (19.0)	74 (19.4)	0.65
Paraaortic node	No	16 (38.1)	196 (51.5)	
metastasis (%)	Yes	0 (0.0)	7 (1.8)	
	Not available	26 (61.9)	178 (46.7)	0.14
Complete surgical	No	26 (61.9)	178 (46.7)	
staging (%)	Yes	16 (38.1)	203 (53.3)	0.07
Synchronous	No	39 (92.9)	370 (97.1)	
ovarian cancer (%)	Yes	3 (7.1)	11 (2.9)	0.15

Results

The clinicopathological characteristics are shown in Table 1 and 2. Of the 423 patients, 42 patients (9.9%) were younger than the age of 40 years. The median age at the time of diagnosis in group A was 37 years (range 27-40 years) and group B was 56 years (range 41-93 years). Thirty four patients in group A (81.0%) were nulliparous and the median BMI was 30.3 kg/m2 (range 17.7-46.7 kg/m2). Six patients (14.3%) were overweight (BMI = 25-30 kg/m2), and 22 patients (52.4%) met the criteria of obesity (BMI > 30 kg/m2). The incidence of nulliparous and obesity was significantly higher in group A than group B. However, obesity was an only independent factor in multivariate analysis (Table 3). Three patients (7.1%) had diabetes mellitus, 4 patients (9.5%) had hypertension and 3 patients (7.1%) had both. Mean duration of vaginal bleeding in group A was 7.9 months which was longer than group B (5.8 months), although there was no statistical significance (p =0.12). Polycystic ovarian syndrome (PCOS) or polycystic ovary was found in 5 patients (11.9%) and synchronous ovarian cancer was found in 3 patients (7.1%).

Fewer patients in group A received complete surgical staging included pelvic and paraaortic lymphadenectomy (38.1% and 53.3%, P = 0.07). Although the incidence of pelvic lymphadenectomy was similar between both groups (80.5% and 80.6%, p=0.57) but the incidence of paraaortic lymphadenectomy was significant lower in group A (38.1% and 53.0%, p=0.04). Most patients were presented in surgical stage I in both groups (78.6% and 76.6%, respectively). No significant difference in stage distribution and the other pathological characteristics was demonstrated between both groups. However, poor histologic grade (grade 3) and deep myometrial invasion (myometrial invasion more than 50%) tended to be more frequently found in the patients older than the age of 40 years although there was no statistical significance. (Table 2)

Median time to follow in this study was 63 months (range 0-145 months). At the time of analysis, 5 patients (11.9%) in group A and 58 patients (15.2%) in group B developed recurrent disease. Three patients (7.1%) in group A and 44 patients (11.5%) in group B died from

Table 3. Multivariate Analysis to Determine Independent Factors Associated with Endometrial Adenocarcinoma in Young Patients

Factors	OR (95%CI)	P value
Parity	0.33 (-0.06 - 0.73)	0.09
BMI	3.05 (2.76 - 3.34)	0.00

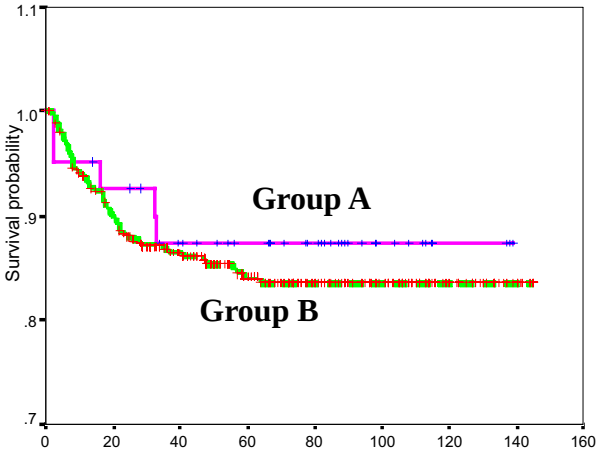

Figure 1. Comparison of Disease Free Survival (months) in Endometrial Adenocarcinoma Patients Younger (Group A) and Older (Group B) than the Age of 40 Years

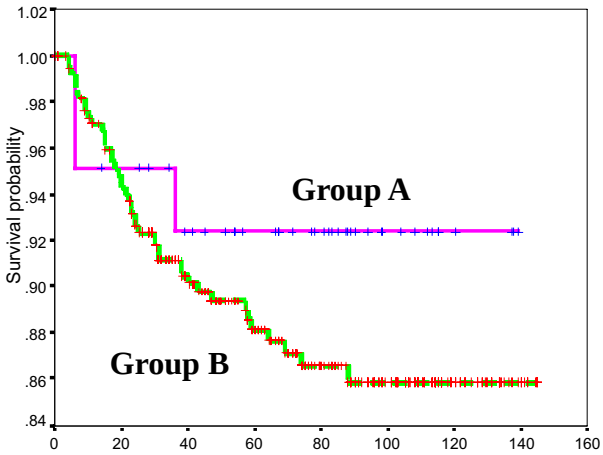

Figure 2. Comparison of Overall Survival (months) in Endometrial Adenocarcinoma Patients Younger (Group A) and Older (Group B) than the Age of 40 Years

recurrent disease, while 1 patient (2.4%) in group A and 17 patients in group B (4.5%) died from the other causes. Five years disease free survival (DFS) and 5 years overall survival (OS) were 87.3% and 92.4% in group A versus 83.8% and 88.0% in group B. However, there was no statistically significant difference between the two groups (Figures 1 and 2).

Discussion

This study confirmed the incremental incidence of young endometrial adenocarcinoma patients (40 years of age or younger). The incidence was about 10 percent in this study which was higher than the previous studies (3-5%) (Crissman et al., 1981; Benshushan et al., 2004). Abnormal vaginal bleeding is the most common presenting symptom in endometrial adenocarcinoma. However, this symptom in young women especially younger than the age of 40 years was usually diagnosed as a benign condition and received medical treatment without or delayed to perform endometrial biopsy or dilatation and curettage. Mean duration of vaginal bleeding in young patients was longer than older patients in this study (8 months and 6 months, respectively). Criteria for selection of high risk young patients who require pathological diagnosis should be determined. Obesity and nulliparous were significantly more common in young patients than older patients although obesity was an only independent factor in multivariate analysis in this study. Obesity (BMI > 30 kg/m2) increases the risk of endometrial adenocarcinoma with relative risk of 2-10 and nulliparous increases the risk about three times (MacMahon, 1974; Folsom et al., 1989; Brinton et al., 1992). The incidence of obesity in young endometrial adenocarcinoma patients was reported up to 40-60% (Gallup et al., 1984; Soliman et al., 2005). Half of patients in this study met criteria of obesity which was similar to the previous studies. However, the incidence of nulliparous in this study (79%) was higher than the previous studies (20-45%) (Crissman et al., 1981; Gallup et al., 1984; Parslov et al., 2000). Recently, Soliman et al. was reported 71% incidence of nulliparous in women aged 40 years or younger which was similar to this study (Soliman et al., 2005). Higher incidence of nulliparous might be explained by increased marital age and age at first birth.

Chronic anovulation is the other factor which increases the risk of endometrial adenocarcinoma. Polycystic ovarian syndrome (PCOS) is a common reproductive abnormality which associates with chronic anovulation, obesity and hyperinsulinemia. Many studies demonstrated that PCOS in young endometrial adenocarcinoma patients was significantly higher than older patients (Niwa et al., 2000; Navaratnarajah et al., 2008). Although, it might be a possible risk factor for endometrial cancer, this evidence was inconclusive (Navaratnarajah et al., 2008). However, this study could not demonstrate that PCOS was the risk factor of endometrial adenocarcinoma because there was limited number of young patients with PCOS.

Synchronous ovarian cancer was also associated with endometrial adenocarcinoma in young patients with the incidence ranged from 10-30% (Soliman et al., 2005; Gitsch et al., 1995; Evans-Metcalf et al., 1998). Lower incidence of synchronous ovarian cancer in young patient was reported in this study (7.9%). This finding might be explained from different definition of young patient and different race. However, we found higher incidence of synchronous ovarian cancer in young patients compare to older patients (7.1% and 2.9% respectively, $p > 0.05$).

Previously, endometrial cancer in young patients was believed to have better prognosis than older patients (Zaino et al., 1996). However, many studies included this study reported the similar disease free survival and overall survival (Evans-Metcalf et al., 1998; Tran et al., 2000). Generally, surgical stage was accepted as the most significant prognostic factor in endometrial cancer patients (Wolfson et al., 1992). No difference of overall stage distribution and the other pathological characteristics between both groups might be a possible explanation. Moreover, lower incidence of complete surgical staging especially paraaortic lymphadenectomy was reported in young patients. As this result, true stage I patients in the

older aged group might be compared to higher stage in the young aged group. These might be the reasons of negative survival benefit in young patients.

In conclusion, this study reported about 10% of endometrial adenocarcinoma in the patients aged younger than 40 years. Nulliparous and obesity were significantly demonstrated in young patient although obesity was an only independent factor in multivariate analysis. The young patients with this high risk factor who presented with abnormal uterine bleeding should not hesitate to perform endometrial biopsy or dilatation and curettage especially after failed medical treatment. If the patients had early detection, this might improve the prognosis.

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