Uterine Endometrial Carcinoma: 10 Years' Experience with Long-Term Follow-Up at a Single Korean Institution

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Key Words

Endometrial cancer • Korean • Prognostic factor

Abstract

Aim: To evaluate prognostic factors in Korean patients with endometrial cancer. **Methods:** A retrospective analysis was conducted on 248 patients who were staged surgically at the Samsung Medical Center between 1995 and 2004. Survival data were analyzed using Kaplan-Meier estimates, and multivariate analysis was performed using the Cox regression method. **Results:** The median age was 51 years (range 21–75), which was younger than in previous studies in Western patients, and the age of 50 years was the cutoff to predict survival. More than half (55.6%) were normal weight or underweight (BMI <25). Multivariate analysis revealed that age, Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage, and histopathology were independent predictors of disease-free survival, and FIGO stage and p53 mutation were independent prognostic factors for disease-specific survival (DSS). The 5-year DSS for patients with stage I, II, III and IV disease was 95.6, 93.8, 69.8 and 50%, respectively. The 5-year DSS rate for patients with a p53 mutation was 84.4%, compared with 97.1% for patients without. **Conclusions:** Korean patients with endometrial cancer were young-

er and had a lower BMI than previously reported. Furthermore, age greater than 50 years was predictive of a poor outcome. Age, FIGO stage, histopathology and a p53 mutation were independent prognostic factors for survival.

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Introduction

Endometrial carcinoma is the seventh most common cancer in women worldwide [1]. Between 1987 and 2006, the number of women in the United States who were newly diagnosed annually with endometrial cancer increased from 35,000 to 41,200 [2]. In contrast to this gradual increase in the USA, the incidence of endometrial cancer has increased dramatically in Asia. The total number of cases in Japan was 976 in 1983, 2,115 in 1994 and 4,267 in 2005 [3]. In Korea, the registered number of endometrial cancer cases was 132 in 1991, 239 in 1994, 425 in 2000 and 862 in 2004 [4]. The increased incidence of endometrial cancer in the USA reflects in part the increase in obesity, a growing problem worldwide, and aging of the popula-

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tion, but no information is available on the increase in Asian women. There is little doubt that endometrial cancer will continue to be of major concern for all health care professionals.

Various clinical and pathological prognostic factors for endometrial cancer have been reported. Patient age, histopathology type, Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage, tumor grade, myometrial invasion, steroid hormone receptor status, DNA index and p53 mutation status have been correlated with patient survival [5–10]. However, previous studies included inconsistencies with regard to the significance of these various factors. In the present study, the clinical and pathological features associated with endometrial cancer were evaluated in a large series of Korean patients from a single institution with long-term follow-up. Additionally, independent factors associated with the prognosis of endometrial carcinoma in Korean women were determined using a multivariate analysis.

Materials and Methods

Patients

In total, 248 patients with histopathologically proven endometrial carcinoma were included. Patients with uterine sarcomas, malignant mixed Müllerian tumors of the uterus, or a secondary malignancy were excluded. Patients who died from unrelated diseases were not included. Patients enrolled in this study underwent staging surgery as primary treatment between 1995 and 2004 at the Department of Gynecological Oncology, Samsung Medical Center, Seoul, Korea. Surgical staging procedures were defined as a total hysterectomy, bilateral salpingo-oophorectomy, pelvic cytological evaluation and pelvic lymphadenectomy. Twenty-three (9.2%) of the patients underwent laparoscopy. Forty-two (16.9%) of the patients had incomplete staging (without oophorectomy and/or pelvic lymph node dissection) for grade 1 disease, and were diagnosed as having superficial invasion on frozen sections taken from young women. Eight patients had a para-aortic lymphadenectomy with pelvic lymphadenectomy and these nodes were negative on histopathology.

A database was generated based on information from the hospital records, including surgical notes and pathological reports. Information collected included: age, weight and height of the patients; additional systemic diseases, such as diabetes mellitus, hypertension and malignancy; type of surgery; tumor stage; histopathological tumor type; tumor grade and recurrence. Body mass index (BMI) was calculated as weight/height squared in kilograms/square meter. None of the patients had received preoperative pelvic radiation. Disease stage was assigned based on surgical and pathological findings according to the FIGO staging system [11]. Experienced pathologists reviewed all histological specimens. All tumors were classified according to the WHO/ISGPy classification [12]. Mixed carcinoma was defined as a combination of two or more pure types, in which the component account-

ed for at least 10% of the tumor. The tumor grade was evaluated for both architectural and nuclear grades [13]. The depth of myometrial invasion was described as none, inner half, or outer half.

Statistical Analysis

The primary outcomes evaluated were disease-free survival (DFS) and disease-specific survival (DSS). DFS was defined as the time in months from the time of the last therapy to any recurrence. DSS was defined as the time from surgery to the time of a known cancer-related death. DFS and DSS were evaluated using Kaplan-Meier estimates and compared using the log-rank test. Median values were analyzed using the nonparametric Mann-Whitney U test. Dichotomous groupings were analyzed using the χ^2 and Fisher's exact tests, as appropriate. Multivariate analysis was performed using the Cox regression method. All p values were two-sided, and statistical significance was defined as $p < 0.05$. Statistical analysis was performed using SPSS version 15.0 (SPSS Inc., Chicago, Ill., USA).

Results

The study population consisted of 248 patients diagnosed with primary endometrial adenocarcinoma. Their demographic characteristics are presented in tables 1 and 2. The median age of the patients was 51 years (range 21–75). In total, 105 (42.3%) patients were less than 50 years old. According to the World Health Organization's definitions, 138 (55.6%) were normal weight or underweight (BMI < 25); 82 (33.1%) were overweight ($25 \leq \text{BMI} < 30$) and 28 (11.3%) were obese (BMI ≥ 30). One hundred thirty-three (53.6%) patients were premenopausal. The most common presenting symptom for patients with any disease stage was abnormal spotting/bleeding (75.8%). Nine patients (3.6%) had a history of malignancy and 44 (17.7%) had a history of diabetes or hypertension. Thirty-six (14.5%) patients had a family history of malignancy. Patients with a family history of gynecologic cancers included 4 uterine endometrial cancers and 1 cervical cancer.

Table 3 summarizes the histopathology of the tumor types. The most common type was endometrioid adenocarcinoma. Pure endometrioid type and mixed carcinoma with a dominant endometrioid component accounted for 85.9 and 4.8% of cases, respectively. Two mixed serous and endometrioid carcinomas included 10 and 15% serous components, respectively. These were classified as endometrioid type in the survival analysis because mixed carcinomas containing 25% or greater serous component behave as pure serous carcinomas [14]. Each mixed clear-cell and endometrioid carcinoma contained a 10% clear-cell component. Twenty-three cases (9.3%) were classified as nonendometrioid tumor types.

Table 1. Demographic characteristics of the 248 patients with endometrial cancer

Characteristics	
Median age (range), years	51 (21–75)
Median BMI (range)	24.6 (16.6–38.3)
Menopause	
Premenopausal	133 (53.6)
Postmenopausal	113 (45.6)
Unknown	2 (0.8)
Presenting symptoms	
Abnormal spotting/bleeding	188 (75.8)
Incidental (routine checking)	24 (9.7)
Menorrhagia	16 (6.5)
Abdominal symptoms	9 (3.6)
Postoperative (myoma)	4
Palpable mass	3
Others	4
Personal history of malignancy	9 (3.6)
Diabetes mellitus/hypertension	44 (17.7)
Diabetes mellitus only	10
Hypertension only	24
Diabetes mellitus and hypertension	10
Family history of malignancy	36 (14.5)
Nulliparous	41 (16.5)

Unless otherwise specified, the data represent numbers and percentages (shown in parentheses) of patients.

Table 2 summarizes the clinical/pathological characteristics of the cases. The majority of cases were grade I tumors (69.4%) and were diagnosed as FIGO stage I (79.8%). Approximately 24% of the total study population (60/248) had deep myometrial invasion ($\geq 1/2$). Sixteen patients (6.4%) had pelvic lymph node involvement and 40 (16.1%) had abnormal serum CA125 levels. The status of p53 mutation, estrogen receptor (ER) status and progesterone receptor (PR) status were positive in 27 (10.9%), 100 (40.3%) and 102 (41.1%) patients, respectively.

Because the median age of the patients was 51 years, which is much younger than that in prior studies, the patients were stratified by age (47–65 years), and survival was compared between women below and above the threshold age. A univariate analysis revealed that DSS was always significantly better in younger patients. However, this was not the case in the multivariate analysis (fig. 1a). When the patients were stratified by age, DFS was significantly better in the 47–55-year-old group, but not in the 56–65-year-old group. Moreover, when the women were stratified as 49, 50 and 51 years old, DFS was significantly different in multivariate analysis adjusted

Table 2. Patient characteristics and univariate and multivariate analysis of 5-year DFS and DSS rates

	Patients n	Univariate p value		Multivariate p value	
		DFS	DSS	DFS	DSS
Age		0.001	0.01	0.027	NS
<50 years	105 (42.3)				
≥ 50 years	143 (57.7)				
BMI		NS	NS	–	–
<25	138 (55.6)				
≥ 25 , <30	82 (33.1)				
≥ 30	28 (11.3)				
Histopathology		<0.001	<0.001	0.015	NS
Endometrioid					
and mixed	225 (90.7)				
Other type	23 (9.3)				
Grade		<0.001	<0.001	NS	NS
1	172 (69.4)				
2	38 (15.3)				
3	32 (12.9)				
Unknown	6 (2.4)				
Myometrial invasion		<0.001	0.033	NS	NS
None	95 (38.3)				
<1/2	93 (37.5)				
$\geq 1/2$	60 (24.2)				
FIGO stage		<0.001	<0.001	0.009	0.019
I	198 (79.8)				
II	24 (9.7)				
III	22 (8.9)				
IV	4 (1.6)				
Pelvic LN metastasis		<0.001	<0.001	NS	NS
Negative	178 (71.8)				
Positive	16 (6.4)				
Unknown	54 (21.8)				
CA125		ND	<0.001	–	–
Normal	165 (66.5)				
Abnormal	40 (16.1)				
Unknown	43 (17.3)				
p53 mutation		NS	0.014	–	0.023
Negative	79 (31.9)				
Positive	27 (10.9)				
Unknown	142 (57.2)				
Estrogen receptor		0.009	NS	NS	–
Negative	35 (14.1)				
Positive	100 (40.3)				
Unknown	113 (45.6)				
Progesterone receptor		0.001	0.001	NS	NS
Negative	31 (12.5)				
Positive	102 (41.1)				
Unknown	115 (46.4)				

Figures in parentheses are percentages. LN = Lymph node; NS = $p > 0.05$; ND = not determined.

Fig. 1. p values for univariate and multivariate analyses of DSS (**a**), and DFS (**b**) in patients stratified by age.

Table 3. Histopathological data

Diagnosis	Patients, n (%)
Endometrioid adenocarcinoma	213 (85.9)
Other types	23 (9.3)
Papillary, serous	11
Mucinous	4
Undifferentiated	2
Clear cell	1
Adenosquamous	1
Serous and clear	2
Small round cell tumor	1
Squamous cell	1
Mixed carcinoma	12 (4.8)
Mucinous	7
Serous	2
Clear cell	2
Undifferentiated	1

for stage, histology, tumor grade, myometrial invasion, lymph node metastasis, ER status and PR status (fig. 1b). This finding suggested that the age of 50 years could be the threshold to predict clinical survival in Korean patients with endometrial cancer.

The mean follow-up interval was 56 months (range 1–151) and complete follow-up was available in 241 patients (97.2%). Sixteen (6.5%) patients died, 26 patients

(10.5%) experienced recurrence and 2 patients (0.8%) showed disease progression without a disease-free interval (persistent disease). Univariate survival analysis showed that age, histopathology type, tumor grade, myometrial invasion, FIGO stage, pelvic lymph node metastasis, ER status and PR expression are associated with DFS. Moreover, age, histopathology type, tumor grade, myometrial invasion, FIGO stage, pelvic lymph node metastasis, serum CA125, p53 mutation and PR status were associated with DSS (table 2). Cox multivariate analysis for an association between prognostic factors (age, stage, histopathology, tumor grade, myometrial invasion, lymph node metastasis, and ER and PR status) and DFS showed that older age, advanced tumor stage and other histopathology type are associated with a worse prognosis ($p = 0.027$, $p = 0.009$ and $p = 0.015$, respectively). Multivariate analysis adjusted for age, tumor stage, histopathology, tumor grade, myometrial invasion, lymph node metastasis, p53 mutation and PR status showed that an advanced FIGO stage and the presence of a p53 mutation are strongly associated with a poor DSS rate ($p = 0.019$ and $p = 0.023$, respectively).

The estimated overall cumulative 5-year and 10-year survival rates for all patients were 92.1 and 86%, respectively. A significant correlation was observed between DFS or DSS and disease stage ($p < 0.001$; fig. 2a). When the patients were stratified by the presence of p53 mutation, the 5-year DSS was significantly shorter in the group

Fig. 2. Kaplan-Meier actuarial survival curves for patients with endometrial carcinoma. Significant differences were observed in the overall cumulative DSS according to stage (**a**; log-rank test, $p < 0.001$). Women with tumors carrying a p53 mutation had a lower cumulative survival rate than women with no mutation (**b**; log-rank test, $p = 0.014$).

with the mutation (84.4%) than in the group without it (97.1%); this difference is statistically significant (log-rank, $p = 0.014$; fig. 2b).

Discussion

In this study, two distinctive features of Korean patients with endometrial cancer were identified compared with Western women. One was age at diagnosis, which has long been recognized as a clinical predictor of survival. Based on previous studies, endometrial cancer is more likely to develop in elderly women with an average age in the early 60s [15, 16], and advanced age is associated with a poorer prognosis. In the present study, the median age of the patients was 51 years, suggesting that endometrial cancer is developing at a younger age in the Korean population than in Western women. Since the PORTEC study, which showed that the risk of local/regional relapse and death is significantly higher for patients aged 60 years and over compared with those below 60 [17], 60 years has been used as an arbitrary age to predict prognosis and to indicate the need for adjuvant radiotherapy. However, our multivariate analysis failed to

show a statistically significant difference between patients aged 60 years and over and those below this age. The level of significance was highest in the multivariate analysis when the patients were stratified according to ages 49, 50 and 51 years (fig. 1). Thus, the age of 50 years might be a more meaningful threshold to predict disease survival for patients with endometrial cancer in the Korean population. Further studies are necessary to confirm this finding.

The other distinctive feature of this study population was the BMI. Epidemiological studies have reported that a BMI of 25 or greater is an important risk factor for endometrial cancer [18, 19]. Obesity is a common factor associated with excess estrogen exposure, which increases the mitotic activity of endometrial cells and promotes cellular replication, leading to hyperplasia and eventually to carcinoma. In this Korean population, patients with endometrial cancer and a BMI of 25 or greater accounted for 44.4% of the cases, which is lower than the range of 66.9–83.9% reported previously [20]. More than half of our patients (55.6%) were of normal weight or underweight, and no relationship was found between BMI and histopathology (data not shown). Results from a multiethnic cohort study, showing a positive dose-response

relationship between BMI gain and the risk of endometrial cancer might partially explain our finding [21]. In particular, Asian women showed an increase in risk after a BMI gain of $\geq 5\%$ whereas Africans and Caucasians showed an increase in risk with a much larger gain ($\geq 35\%$). Since a smaller BMI gain increased the risk of endometrial cancer in Asian women, an increase in adiposity may contribute to the development of endometrial cancer in normal-weight or underweight women. Another possible explanation might be the effects of nonestrogenic factors, such as race differences in epigenetic factors [22], polymorphism in hormonal receptors [23], or alternative oncological mediators, including aneuploidy and mutations in PTEN, K-ras and p53 [24].

According to Creasman et al. [25], the 5-year survival rate is 91% for patients with stage Ia cancers, 91% for stage Ib, 85% for stage Ic, 83% for stage IIa, 66% for stage IIb, 50% for stage IIIa, 50% for stage IIb, 57% for stage IIc and 25% for stage IV. In the present single-institution study, the patients' survival characteristics were better than these values for all tumor stages. This finding is partially explained by the fact that the patients were younger than those included in previous studies. Women aged less than 50 years had a significantly better survival rate than those aged 50 years or older, and 42.3% of patients in this study were younger than 50.

The therapeutic effects of para-aortic lymphadenectomy in patients with endometrial cancer remain unproven. Studies that have compared the prognosis of a para-aortic lymphadenectomy group with a non-para-aortic lymphadenectomy group [26–28] have reported conflicting results. Additionally, two prospective randomized studies failed to show any therapeutic benefit of this procedure [29, 30]. In the present study, although only 8 of the 248 patients received para-aortic lymphad-

enectomy, and these nodes were negative on pathology, no abatement was observed in the survival rate for these patients. Therefore, we did not obtain any scientific evidence supporting the role of para-aortic lymphadenectomy.

Many clinical and histopathological variables, such as age, BMI, histopathology, tumor grade, depth of myometrial invasion, FIGO stage, lymph node involvement, abnormal CA125 serum level, presence of a p53 mutation, and ER and PR status affect the clinical outcome of patients treated for endometrial cancer. With the exception of BMI, the correlation of these factors with the DFS and DSS prognosis was confirmed by univariate analysis in the present study. Multivariate analysis showed that age, FIGO stage and histopathology were independent prognostic factors associated with DFS whereas FIGO stage and the presence of a p53 mutation were the only variables that correlated significantly with DSS.

In conclusion, this study revealed the independent prognostic factors associated with survival in Korean patients with endometrial cancer. Our patients were younger and had a lower BMI compared with those in previous studies on Western patients with endometrial cancer. Our data indicated that 50 years might be a more appropriate threshold age to predict patient survival in Korean women. However, these results must be confirmed by studies including a larger number of patients.

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