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The effect of age on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer

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Abstract

Objective. To evaluate the effect of age on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer.

Methods. All women with surgically treated endometrial cancer at the University of Washington in Seattle, Washington between January 1990 and January 2000 were eligible; 396 patients underwent retrospective chart review. Statistical analysis was performed by SPSS. Median follow-up time was 33 months (range, 1 to 120 months).

Results. Age was <45 years in 15% of patients, between 46 and 64 years in 47% of patients, and >65 years in 38% of patients. Younger patients were statistically more obese than older patients (Body Mass Index of 40.3 kg/m^2 vs. 35.3 kg/m^2 vs. 31.0 kg/m^2, $P < 0.001$). Intraoperatively, there were no differences between the three groups in the percentage of patients with lymph node sampling, operative time, blood loss, or complications. Postoperatively, older patients had more wound infections ($P = 0.002$), more cardiac events ($P = 0.001$), and more episodes of ileus ($P = 0.025$). Evaluation of pathology revealed that patients <45 years old were statistically more likely to have endometrioid histology, grade I tumors, and stage IA disease. Women over age 65 were significantly more likely to have papillary serous histology, grade 3 tumors, and stage IC as compared to the younger patients. A subset analysis of patients >75 years of age showed an increase in the percentage of patients with papillary serous histology (22% vs. 3%, $P = 0.055$), grade 3 disease (42% vs. 16%, $P < 0.001$), and stage IC disease (21% vs. 3%, $P = 0.001$) when compared to patients <45 years old. Evaluation of endometrioid tumors only revealed a similar pattern of deeper myometrial invasion and higher tumor grade as age increased.

Conclusions. Younger patients with endometrial cancer are generally more obese, with lower grade, lower stage disease, and with more favorable histologic cell types. Despite this, approximately a quarter have stage II–IV disease and 9% have positive lymph nodes. The older patients represent a dramatically different subset of patients. They are more likely to have aggressive papillary serous histology, higher grade tumors, and advanced stage disease. Age should be a consideration in appropriate referrals to gynecologic oncologists.

Keywords: Endometrial cancer; Age; Surgical morbidity; Histology

Introduction

Endometrial cancer is the most common gynecologic cancer in the United States, and the fourth most common malignancy among women. In 2005, there projects to be approximately 40,880 new cases and 7310 deaths from endometrial cancer in the U.S., and over 95% of these will be of epithelial origins [1]. The median age at diagnosis is 63 years [2] with 75% of women diagnosed in the postmenopausal period. The remaining 25% are diagnosed in the premenopausal period and of those, 5–10% are under the age of 40 years [3]. Recently, there has been a rise in the incidence of endometrial cancer in older women. While the exact reason is unknown, one possibility may be the increasing life expectancy of the elderly population. Previously, it has been reported that the histopathology of endometrial cancer in the elderly differs from the general population [4,5].

Bokhman proposed two different pathways of endometrial carcinogenesis. The "classic" pathway describes endometrial cancer that arises from a hyperplastic precursor or area of atypical endometrial hyperplasia, which with estrogen stimulation undergoes malignant change to the more common endometrioid adenocarcinomas. These tumors occur more

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frequently in younger, more obese women, and are associated with lower stage and lower grade disease, also referred to as Type I tumors [6–8]. In contrast, the "alternative" pathway, describes a tumor (Type II disease) that arises from an atrophic endometrium in the absence of excess estrogen. This lesion is associated with mutations in the p53 tumor suppressor gene and with the development of serous endometrial cancers. These cancers occur more frequently in older women and are associated with non-endometrioid histologies, higher grade, and poorer prognosis [6,9,10].

Age is a prognostic factor for endometrial cancer. However, it is unclear if this is due to more aggressive histology or due to differences in the treatment received. The elderly have often been undertreated due to a lack of inclusion in clinical trials, and an assumption of increased surgical risk, secondary to concurrent comorbid conditions. They have also been less likely to receive additional adjuvant therapy in the form of radiation or chemotherapy [11]. With the increasing life expectancy of women and the increasing incidence of malignancy in the elderly, further evaluation of this group is warranted. Our study sought to determine the effects of age on clinical/pathologic features, surgical morbidity, and outcome in patients with endometrial cancer.

Material and methods

International Classification of Diseases codes were used to create a list of patients surgically treated at the University of Washington for endometrial cancer from 1 January 1990 to 1 January 2000. Four hundred thirty-nine patients were identified. Forty-three were excluded for incomplete medical records. Three hundred ninety-six patient charts were retrospectively reviewed. Women were stratified into three age groups: 45 and under, those aged 46–64, and those 65 and over. These cutoffs are somewhat arbitrary but were chosen based on previous studies which used similar age cutoffs. Clinical data collected included age at diagnosis, height, weight, calculated body mass index (BMI), race, and comorbid conditions. Comorbid conditions specifically screened for included diabetes, hypertension, pulmonary disease, coronary artery disease, thyroid disease, and arrhythmias. Pulmonary disease was defined as any patient with a diagnosis of asthma, chronic bronchitis, chronic obstructive pulmonary disease (COPD), emphysema, restrictive lung disease, or sleep apnea. Coronary artery disease was defined as any patient with a positive coronary catheterization, history of myocardial infarction, or history of coronary bypass surgery. All surgical specimens were reviewed as part of routine clinical care by a board-certified pathologist with interest and expertise in gynecology. Pathologic data collected included cell type, FIGO staging, including depth of myometrial invasion, grade, node status, and peritoneal cytologic results.

Six gynecologic oncologists at the University of Washington performed all surgical staging procedures. Every patient underwent total abdominal hysterectomy, with or without removal of adnexal structures. Lymphadenectomy was performed in 85% of all patients, including para-aortic sampling in 81%. In the remaining 15% of patients, lymphadenectomy was omitted either due to morbid obesity or gross intra-abdominal disease. All patients received peri-operative antibiotic prophylaxis in the form of cefazolin or cefotetan, except where penicillin-allergic, in which cases, clindamycin was substituted. All patients had teds hose and sequential compression devices placed preoperatively and these were maintained until time of discharge.

Surgical data collection included operative time, estimated blood loss, transfusions, number of hospital days, number of intensive care unit (ICU) days, intraoperative complications, postoperative complications, and adjuvant treatment. Intraoperative complications specifically screened for included hemorrhage (defined as more than one l of blood loss), bowel injury, bladder injury, ureteral injury, and vessel injury. We also included any other complication listed in the operative report under complications. Postoperative complications specifically screened for included wound separation, wound infection, sepsis, pneumonia, small bowel obstruction, ileus (failure of return to normal bowel function within 5 days), urinary retention (failed voiding trial), cardiac events (myocardial infarction or arrhythmias), deep venous thrombosis, urinary tract infections, and postoperative death.

Outcome data collected included time from diagnosis to recurrence, site of recurrence, salvage therapy, time from recurrence to death, time from diagnosis to last follow-up or death, and status at last follow-up visit. Follow-up data were obtained from hospital tumor registries as well as state data banks. Median follow-up was 33 months (range 1–120).

Frequency distributions were calculated for each of the variables. Pearson's χ^2 test was used to assess the association between categorical variables, and one-way analysis of variance was used to compare the distributions of continuous variables. Post hoc analysis was performed by using the Duncan multiple range test. All statistical analysis was performed using the SPSS system (SPSS 10.1.3 for Windows 2000, Chicago, IL) and conducted by Dr. Mandel, statistician for the Department of Obstetrics and Gynecology.

Results

Mean age for the entire population was 60 years (range, 23–95 years). Fifty-eight patients (15%) were less than 45 years of age, 187 patients (47%) were between the ages of 46 and 64, and 151 patients (38%) were over the age of 65. Racial distribution appeared similar to that of our hospital population, and the Pacific Northwest in general, with 371 white (93.7%), 12 Asian or Pacific Islander (3.0%), 7 Native American (1.8%), 4 Hispanic (1.0%), and 2 black (0.5%) patients. The mean BMI was 34 (range, 15–69).

Comorbid conditions are shown in Table 1. BMI decreased with age ($P < 0.001$). Twenty-two percent of all patients had diabetes with no difference in incidence between the three groups. Nearly 43% of all patients had hypertension and the incidence statistically increased with age ($P < 0.001$). Ten percent of patients had coronary artery disease and 7% had cardiac arrhythmias, and the incidence of both comorbidities increased with age ($P < 0.001$). The incidence of pulmonary disease was similar among the three groups.

Surgical characteristics are shown in Table 2. The percentage of patients receiving complete surgical staging with lymphadenectomy among the three age groups was 74%, 86%, and 87%, respectively ($P = 0.052$). Overall, 85% of patients had lymph

Table 1
Comorbid conditions by age[a]

	Age <45	Age 46–64	Age >65	Totals	*P* value
Number of patients	58 (15%)	187 (47%)	151 (38%)	396	
Comorbid conditions					
Mean BMI[b] (kg/m^2)	40.3	35.3	31	34	**<0.001**
Diabetes	10 (17%)	39 (21%)	38 (25%)	87 (22%)	0.408
Hypertension	12 (21%)	73 (39%)	85 (56%)	169 (43%)	**<0.001**
Coronary artery disease	0 (0%)	15 (8%)	26 (17%)	41 (10%)	**<0.001**
Arrhythmias	0 (0%)	5 (3%)	24 (16%)	29 (7%)	**<0.001**
Pulmonary disease	4 (7%)	17 (9%)	17 (11%)	38 (10%)	0.6

Note. Boldface indicates $P < 0.05$ and statistically significant.
[a] Age calculated in years.
[b] BMI, body mass index.