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Is older age a poor prognostic factor in stage I and II endometrioid endometrial adenocarcinoma?☆

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ABSTRACT

Objective. Prior studies have shown that age ≥70 years is associated with more aggressive non-endometrioid histology and worse survival in endometrial cancer. The purpose of this study is to assess if age is an independent poor prognostic factor in endometrioid histologies.

Methods. Under an IRB-approved protocol, we identified patients with surgical stage I to II endometrioid endometrial adenocarcinoma from 1995 to 2008 at two institutions. Patients were divided into two groups based on age at diagnosis: Group A (age 50–69 years) and Group B (age ≥70 years). All patients underwent hysterectomy, bilateral salpingoophorectomy, +/−pelvic/aortic lymphadenectomy and adjuvant therapy. Prognostic factors were evaluated by univariate and multivariate analyses.

Results. We identified 338 patients with stage IA to IIB endometrioid endometrial adenocarcinoma. The median age in Group A was 59 years (range 50–69) and Group B was 75 years (range 70–92). Patients in Group B were more likely to have hypertension (51% vs. 68%, $p=0.006$) and coronary artery disease (9% vs. 18%, $p=0.03$). There were no differences in progression-free or disease-specific survival, however, Group B had a worse overall survival (OS) (50.1 vs. 62.6 months, $p=0.03$). On univariate analysis, age ($p=0.04$), grade ($p=0.006$), and coronary artery disease ($p=0.01$) were associated with worse OS. After adjusting for grade and coronary artery disease, age was no longer a significant variable for OS ($p=0.17$).

Conclusions. After adjusting for other poor prognostic factors, age ≥70 years alone may not be a significant variable affecting overall survival in patients with early stage endometrioid endometrial adenocarcinoma.

Introduction

By the year 2030, the number of Americans greater than the age of 65 years will double and become 20% of the U.S. population [1]. Endometrial cancer is the most common gynecologic malignancy in the United States with an estimated 43,470 new cases projected in 2010, resulting in 7950 deaths [2]. Approximately half of all endometrial cancers are diagnosed in the patients older than 65 years [3]. Prior studies have shown advanced age to be a poor prognostic factor in endometrial cancer, which is thought to be related to more aggressive histologies and less aggressive use of postoperative therapy [4–9]. A study by Ahmed et al. utilizing the SEER database, looked at over 27,000 women with endometrial cancer age 50 to 95, including all stages and histologies. Fifty-five percent of the patients were greater than the age of 65. They showed a significant trend ($p<0.001$) suggesting that elderly women received less surgical treatment than patients age 50–64. They also found that endometrial cancer specific survival decreased with increasing age [9].

Age has become a central part of debate and prognostic indicator determining adjuvant therapy for early stage, high-risk subgroups of endometrial cancer. The Postoperative Radiotherapy in Endometrial Cancer (PORTEC) trial compared patients with high-risk, stage I endometrial cancer receiving surgery and postoperative radiotherapy vs. surgery alone. All histologic subtypes were included, and they found that locoregional relapse rate was threefold higher for patients age 60 and over ($p=0.003$) [10]. Similarly, the Gynecologic Oncology Group study (GOG-99) looked at historical data from GOG-33 and identified factors associated with an increased recurrence rate of 25% at 5 years. They found increasing age, including age ≥70 years, in addition to other high-risk uterine features as poor prognostic factors. It is because of this that the need for postoperative adjuvant therapy is stratified based on age [11]. Another study by Alektiar et al., looked at the influence of age greater than 70 in patients with stage IB to II endometrial cancers treated with postoperative radiotherapy. With all histologic subtypes included, they found that age greater than 70 was a poor prognostic factor for locoregional recurrence ($p=0.02$), disease-free survival ($p=0.03$), overall survival ($p=0.001$), and disease-specific survival ($p=0.02$) [7].

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The studies mentioned earlier evaluated age as a prognostic factor in early stage endometrial cancers, however in all histologies. We know that histologies such as clear cell and papillary serous predispose patients to a worse prognosis, and their incidence increase in frequency with age [4]. The objective of our study is to determine if age is a poor prognostic factor in early stage endometrial adenocarcinomas solely of endometrioid histology.

Materials and methods

A retrospective analysis of patients with stages I and II endometrioid endometrial cancer from 1995 to 2008 was conducted following the Institutional Review Board approval from two institutions, Cedars-Sinai Medical Center and Kaiser Permanente Los Angeles Medical Center. Patients were identified from institutional Tumor Registry data in addition to operating room case logs. Data was abstracted using electronic and manual chart reviews. Using GOG-99 criteria, the patients were divided into two groups based on age at diagnosis: Group A (age 50–69) and Group B (age 70 or older). Those patients 49 years or younger, with non-endometrioid histologic subtypes, and those who underwent primary medical management were excluded. All patients underwent hysterectomy and bilateral salpingoophorectomy. Pelvic and periaortic lymphadenectomy was performed at the discretion of the treating surgeon. Adjuvant therapy was given at the discretion of the treating physician. The International Federation of Gynecology and Obstetrics (FIGO) 1988 staging system was used to determine stage. Pathology was determined by reports created by gynecologic pathologists at each respective institution.

Statistical analysis was performed using STATA Software. Pearson's chi-square test was used to compare histopathologic and demographic data, medical comorbidities, lymphadenectomy, and adjuvant therapy. Plots for progression-free survival (PFS), overall survival (OS), and disease-specific survival (DSS) were created using Kaplan–Meier analysis. Univariate Cox proportional hazards models were used to assess the effects of the aforementioned variables on survival. Multivariate analysis was performed using the Cox proportional hazard model to assess the impact of age on survival while controlling for other known high-risk prognostic factors.

Results

Between January 1995 and December 2008, we identified 338 patients who underwent a surgical staging procedure with stage IA to IIB endometrioid endometrial cancer and met the inclusion criteria. The median age in Group A ($n=232$) was 59 years (range 50–69) and Group B ($n=106$) 75 years (range 70–92; Table 1). The patients in Group A had a higher median body-mass index (BMI) of 31 (range 13–82) compared to a median BMI of 28 (range 17–45) in Group B ($p=.004$). There was no difference between the two groups with regards to race or presence of diabetes mellitus. However, significantly more patients in group B had hypertension (52% vs. 68%, $p=0.006$) and coronary artery disease (9% vs. 18%, $p=0.03$).

There were no differences between the two groups regarding stage or FIGO grade. Most patients in our study were stages IA and IB, representing 78% of patients in group A and 74% of patients in group B. 89% of patients in group A and 84% of patients in group B had FIGO grades 1 and 2 endometrioid histologies. There was no difference between the two groups regarding rates of pelvic (65% vs. 63%) and periaortic (39% vs. 33%) lymphadenectomy as part of their surgical staging or mean numbers of pelvic (8 vs. 5.2 nodes) and periaortic (7.8 vs. 4.8 nodes) nodes removed. There was no difference in the rates of adjuvant postoperative radiation therapy in all stages between the two groups: external beam radiation therapy (10% vs. 8%), vaginal brachytherapy (5% vs. 8%), and combination external beam radiation therapy and vaginal brachytherapy (7% vs. 4%). Altogether, 22% of patients in group A and 20% of patients in group B had some type of adjuvant postoperative radiation therapy. A small proportion of patients in each group also received postoperative chemotherapy (3% vs. 4%). However, when looking specifically at the high-risk subgroups, treatment differences between the two groups were seen with patients in Group A receiving more adjuvant radiation therapy in stage IC (78% vs. 46%, $p<.0001$) and stage II (59% vs. 33%, $p<.0001$) disease (Table 2).

There were 16 recurrences (6.9%) in Group A and 7 recurrences (6.7%) in Group B. There was no difference in progression-free survival (Fig. 1) or disease-specific survival (Fig. 2) between the two groups. However, patients in Group B had a shorter overall survival of 62.6 months vs. 50.1 months ($p=0.03$, Fig. 3). On univariate Cox proportional hazard model, hypertension, stage, pelvic and periaortic lymphadenectomy, and adjuvant therapy did not affect overall survival (Table 3). However, age 70 or older [HR 2.24 (95% CI, 1.03

Table 1
Patient characteristics and adjuvant therapy.

	Group A ($n=232$)	Group B ($n=106$)	*P*-value
Median age (range)	59 (50–69)	75 (70–92)	
Median BMI (range)	31 (13–82)	28 (17–45)	0.004
Race			NS
White	136 (62%)	73 (71%)	
Black	20 (9%)	13 (13%)	
Other	63 (29%)	16 (16%)	
Comorbidities			
Diabetes mellitus	62 (29%)	19 (20%)	NS
Hypertension	110 (52%)	65 (68%)	0.006
Coronary artery disease	20 (9%)	17 (18%)	0.03
Stage			NS
IA	75 (32%)	21 (20%)	
IB	106 (46%)	58 (54%)	
IC	19 (8%)	15 (14%)	
IIA	13 (6%)	5 (5%)	
IIB	19 (8%)	7 (7%)	
Grade			NS
1	120 (52%)	47 (44%)	
2	87 (37%)	42 (40%)	
3	25 (11%)	17 (16%)	
Nodes			NS
Pelvic	150 (65%)	67 (63%)	
Periaortic	91 (39%)	35 (33%)	
Adjuvant therapy			NS
EBRT	22 (10%)	8 (8%)	
VB	12 (5%)	8 (8%)	
ERBT + VB	17 (7%)	4 (4%)	
Chemotherapy	7 (3%)	4 (4%)	
Recurrence rate	16 (6.9%)	7 (6.7%)	NS

BMI = Body-mass index, EBRT = External beam radiation therapy, and VB = Vaginal brachytherapy.

Table 2
Adjuvant therapy in Stage IB–II subgroups.

	Group A (age 50–69)	Group B (age ≥70)	*P*-value
Stage IB (# patients)	106	58	
VB only	7 (7%)	5 (9%)	NS
EBRT only	6 (6%)	3 (5%)	NS
VB + EBRT	0	1 (2%)	NS
Chemo	0	1 (2%)	NS
Stage IC (# patients)	19	15	
VB only	2 (10%)	2 (13%)	NS
EBRT only	9 (47%)	5 (33%)	.04
VB + EBRT	4 (21%)	0	<.0001
Chemo	0	0	NS
Stage II (# patients)	32	12	
VB only	0	1 (8%)	.004
EBRT only	7 (22%)	0	<.0001
VB + EBRT	12 (37%)	3 (25%)	NS
Chemo	0	1 (8%)	.004

VB = vaginal brachytherapy, EBRT = external beam radiation therapy, and chemo = chemotherapy.