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Impact of Age-Adjusted Charlson Comorbidity score on outcomes for patients with early-stage endometrial cancer ☆

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HIGHLIGHTS

- Medical comorbidities can severely impact survival outcomes in endometrial cancer patients.
- Patients with high Age-Adjusted Charlson Comorbidity index scores have worse overall survival outcomes.
- Comorbidity score was as significant as pathological criteria for determining overall survival.

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ABSTRACT

Objectives. To determine the impact of Age-Adjusted Charlson Comorbidity (AAC) index score on survival outcomes for patients with early stage endometrial cancer.

Methods. After IRB-approval, AAC score at time of hysterectomy was retrospectively tabulated by physician chart review for 671 patients with 2009 FIGO stage I–II endometrioid adenocarcinoma. Patients were grouped based on their AAC scores as follows: 0–1 (n = 204), 2–3 (n = 293) and >3 (n = 174). Kaplan–Meier and log-rank test methods and univariate and multivariate modeling with Cox regression analysis was used to determine significant predictors of each survival endpoint.

Results. After a median follow-up of 85 months, 225 deaths were recorded (34 from EC and 191 from other causes) with a 7-year Overall (OS) and Disease-specific survival (DSS) of 77.6% and 94.0%, respectively. Based on AAC grouping, the 7-year OS, DSS, and Recurrence-free survival (RFS) were: 92.9%, 96.8%, and 94.9% for AAC 0–1; 81.7%, 95.3%, and 89.8% for AAC 2–3: and 56%, 88.2%, and 84.9% for AAC > 3 ($p < 0.0001$, $p = 0.005$ and $p = 0.013$, respectively). On multivariate analyses, higher AAC score, tumor grade, lower uterine segment involvement, and lymphovascular space invasion were significantly independent predictors for shorter OS, while for DSS and RFS, higher tumor grade and lymphovascular space invasion were significant predictors of worse outcome, but higher AAC score was not.

Conclusions. Comorbidity score is as important as pathological features for predicting overall survival outcomes in patients with early-stage endometrioid endometrial carcinoma. Higher AAC scores accurately predicted for worse OS. Comorbidity score should be considered in prospective clinical trials of endometrial carcinoma.

Introduction

Endometrial cancer is the most common gynecological malignancy in the United States with an estimated 49,560 diagnoses and 8190 deaths for 2013 [1]. Most of this cohort is elderly, have significant coexisting medical problems, relatively good cancer prognosis, and will most likely succumb to a non-endometrial cancer related cause [2,3]. A recent SEER study showed that the most common cause of death for this cohort was cardiovascular in nature [4]. Many studies have reported a significant association between endometrial cancer and other comorbid conditions like diabetes mellitus, hypertension, and obesity [2,3,5,6]. Several retrospective hospital and population-based studies have shown that other medical comorbidity significantly impact overall survival in patients with endometrial cancer [2,3,6,7], but none of the randomized studies of adjuvant radiation therapy for

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early-stage endometrial cancer fully consider the effects of medical comorbidity in their design or stratification [8–11].

There is also a paucity of data using a validated comorbidity score to account for the effect of medical comorbidity on survival outcome differences for patients with endometrial cancer.

The Charlson Comorbidity index is a prognostic taxonomy that was initially developed to account for the influence of patients' adverse medical conditions in longitudinal studies [12] and has been validated in many clinical settings [13–16]. The overall score was created by the summation of weight scores for 19 medical conditions found to be associated with poorer overall survival [12]. During the validation process, age was also determined to be a significant contributing factor for overall survival and was subsequently incorporated into to the Charlson comorbidity score to create a single index accounting for both age and medical comorbidity, the Age-Adjusted Charlson Comorbidity index (AAC) [17].

Due to the scarcity of data examining the prognostic impact of medical comorbidity on survival endpoints for endometrial cancer patients using a validated comorbidity score, the primary objective of this study is to determine the impact of the Age-Adjusted Charlson Comorbidity index score on survival endpoints in patients with early-stage uterine endometrioid carcinoma.

Methods

After IRB approval, we retrospectively reviewed our prospectively-maintained database of over 1450 endometrial cancer patients and identified 671 patients with 2009 International Federation of Gynecology and Obstetrics (FIGO) stages I–II endometrial carcinoma who underwent hysterectomy at our institution between January 1985 and December 2009. Data about pre-existing medical conditions present at time of hysterectomy were recorded retrospectively by physician medical records review. Based on the present comorbidities, all patients were assigned a comorbidity score based on the Age-Adjusted Charlson index score as described by Charlson et al. [17] with endometrial cancer being excluded from the scoring.

The overall score represents the weighted summation of their medical conditions with a high score representing a higher medical comorbidity. Table 1 illustrates the scored comorbidities and their relative weight in the scoring system. For conditions with more than one weighted score based on disease severity, points were only counted for the more severe condition. Non-melanomatous skin cancer was not scored as a solid tumor, and any new comorbid conditions that developed after hysterectomy were omitted from the AAC score calculations. Patients were then dichotomized into three groups by AAC score (AAC 0–1 (low, n = 204), AAC 2–3 (mild, n = 293) and AAC > 3 (severe, n = 174)). The three groups were compared with regard to patient demographics, tumor characteristics, treatment received and outcomes.

Table 1
Age-Adjusted Charlson Comorbidity index.

Score	Comorbid condition
1	Myocardial infarction (MI)
	Congestive heart failure (CHF)
	Cerebral vascular disease
	Peripheral vascular disease
	Dementia
	Chronic obstructive pulmonary disease (COPD)
	Connective tissue disease
	Peptic ulcer disease (PUD)
	Mild liver disease
	Age[a]
2	Diabetes
	Hemiplegia
	Moderate/severe renal disease
	Diabetes with end-organ damage
	Any solid tumor
	Leukemia
	Lymphoma
3	Moderate/severe liver disease
6	Metastatic solid tumor
	Acquired immunodeficiency syndrome (AIDS)

[a] For each decade after 40 years, a point is added (1 point for age group 41–50, 2 points for age group 51–60, 3 points for 61–70, 4 points for 71 or older).

All patients underwent surgical staging which included: total abdominal hysterectomy (TAH), bilateral salpingo-oophorectomy (BSO), pelvic and para-aortic lymph node evaluation with 84% underwent lymphadenectomy and 93% having peritoneal cytology. In order to ensure a homogeneous study cohort and remove some of the influence of some histological types with worse prognosis and different treatments on outcomes, only patients with endometrioid histology were included. Patients who received preoperative radiation treatment or systemic chemotherapy before relapse were excluded. Adjuvant radiation treatment was received by 36% of patients and consisted of the following: pelvic radiation therapy alone (7%), vaginal brachytherapy alone (12%), and both (18%). Peri-operative mortality was defined as death from any cause within 30 days of hysterectomy. The cause of death was defined as secondary to endometrial cancer or to other causes. In addition to medical records, Social Security Death Index was used to collect overall survival data.

Characteristic differences between AAC groups were evaluated with Fischer exact and χ^2 test for categorical variables and with analysis of variance or Kruskal–Wallis tests for continuous variables. Overall survival (OS), disease-specific survival (DSS), and recurrence-free survival (RFS) were estimated according to Kaplan–Meier product-limit method calculated from the date of hysterectomy to the time of death, or recurrence. Patients who did not experience any events during the follow-up period were censored at the time of last clinical follow-up. Overall survival was the primary outcome, while DSS and RFS were secondary. Cox regression analysis was used to explore relationships between various factors and outcomes using both univariate (UNA) and multivariate (MVA) models.

Results

The population consisted of 501 patients that were stage IA, 118 patients that were stage IB disease, and 52 patients that were stage II. All had endometrioid histology. All patients had post-operative clinical follow-up, with only 36 patients (5.4%) with less than one year follow-up after hysterectomy. After a median follow-up of 85 months, 225 deaths were observed with 34 attributed to endometrial cancer and 191 from all other causes. Five peri-operative deaths were observed. This resulted in a 7-year overall survival and disease-specific survival of 77.6% and 94.0%, respectively for the entire cohort.

The mostly commonly reported comorbid conditions were 22.2% with diabetes mellitus (DM), 10.0% with history of other solid tumors, 5.2% chronic obstruction pulmonary disease (COPD), 5.1% with history of myocardial infarction (MI), 3.6% with congestive heart failure (CHF), 2.8% with prior cerebrovascular accident (CVA), 2.1% with peptic ulcer disease, 1.6% with dementia, and 1.6% with peripheral vascular disease. Table 2 illustrates the influence of various comorbid conditions on overall survival in this population. For the combined cardiovascular disease group in the table, patients with history of myocardial infarction, congestive heart failure, cerebral vascular event, and peripheral vascular disease were combined together.

The median AAC score in the entire population was 2 and the mean score was 2.66 with a range of 0–14. Table 3 shows patient characteristics in each AAC group. The three groups were well balanced with regard to race, the type of surgery received, the number of lymph nodes examined, and death from endometrial cancer, but patients with higher AAC scores were obviously older, tended to have