Gynecologic Oncology 138 (2015) 133–140

Contents lists available at ScienceDirect

Gynecologic Oncology

journal homepage: www.elsevier.com/locate/ygyno

Risk-adjusted outcomes in elderly endometrial cancer patients: Implications of the contrasting impact of age on progression-free and cause-specific survival

Mariam M. AlHilli [a], Jamie N. Bakkum-Gamez [a], Andrea Mariani [a], Amy L. Weaver [b], Michaela E. McGree [b], Gary L. Keeney [c], Aminah Jatoi [d], Sean C. Dowdy [a], Karl C. Podratz [a,*]

[a] Division of Gynecologic Surgery, Mayo Clinic, Rochester, MN, USA
[b] Division of Biomedical Statistics and Informatics, Mayo Clinic, Rochester, MN, USA
[c] Department of Laboratory Medicine and Pathology, Mayo Clinic, Rochester, MN, USA
[d] Department of Oncology, Mayo Clinic, Rochester, MN, USA

HIGHLIGHTS

- Elderly patients with endometrial cancer are likely to have multiple adverse prognostic factors.
- Age is not an independent risk factor for progression free survival after risk adjustment for multiple adverse risk factors.
- Patients >70 years of age have a worse cause-specific survival after risk adjustment.

ARTICLE INFO

Article history:
Received 4 February 2015
Accepted 10 April 2015
Available online 17 April 2015

Keywords:
Endometrial cancer
Elderly

ABSTRACT

Objective. To reexamine the tenet that advanced age independently impacts progression-free and cause-specific survival in patients with endometrial cancer (EC).

Methods. Patients undergoing surgery for stages I–IIIC EC between 1999 and 2008 were stratified by age (<70 vs ≥70 years). Three propensity score (PS) methods were utilized to adjust for confounding risk factors. The PS, or conditional probability of being ≥70 years old, given a patient's baseline covariates, was derived using logistic regression. The Cox proportional hazards models were fit to estimate the effect of age ≥ 70 years on outcomes.

Results. Of 1182 eligible patients, 822 (69.5%) were <70 and 360 (30.5%) were ≥70. Patients ≥70 were more likely to have multiple adverse risk factors. The total standardized difference of these factors was reduced by 74% and 81%, respectively, using PS-stratification and PS-matching analyses. The nonsignificant trend toward an association between progression-free survival and age ≥ 70 in an unadjusted analysis (hazard ratio [HR], 1.40; 95% CI, 0.95–2.04) was further attenuated in the 3 PS analyses. The unadjusted HR for the association between age ≥ 70 and cause-specific survival was 2.03 (95% CI, 1.32–3.13). HRs were attenuated in PS analyses but retained significance (except for PS matching), potentially reflecting differences in salvage therapies ($P < .001$), including a 3-fold greater use of chemotherapy in those <70.

Conclusion. When risk-adjusted for the higher prevalence of adverse prognostic factors in elderly EC patients, progression-free survival after primary therapy is *not* age dependent but the less favorable cause-specific survival in this cohort may reflect age-related postrecurrence treatment differences.

1. Introduction

The integration of age in risk stratification for endometrial cancer (EC) has been deemed meritorious by several cooperative groups, including PORTEC (Postoperative Radiation Therapy in Endometrial Carcinoma), GOG (Gynecologic Oncology Group), and JGOG (Japanese Gynecologic Oncology Group) [1–3]. To date, the ethos that age at diagnosis adversely impacts disease-related outcomes has been minimally challenged [4–6]. Since the greater majority of patients with EC present

Abbreviations: ASA, American Society of Anesthesiologists; CSS, cause-specific survival; EC, endometrial cancer; FIGO, International Federation of Gynecology and Obstetrics; GOG, Gynecologic Oncology Group; HR, hazard ratio; JGOG, Japanese Gynecologic Oncology Group; PFS, progression-free survival; PORTEC, Postoperative Radiation Therapy in Endometrial Carcinoma; PS, propensity score.

* Corresponding author at: Department of Obstetrics and Gynecology, Mayo Clinic, 200 First St SW, Rochester, MN 55905, USA. Tel.: +1 507 538 5867; fax: +1 507 266 9300.
E-mail address: podratz.karl@mayo.edu (K.C. Podratz).

http://dx.doi.org/10.1016/j.ygyno.2015.04.010
0090-8258/

during the seventh decade of life or older and frequently have acquired comorbidities (eg, obesity, diabetes mellitus, metabolic syndrome, cardiovascular disease, pulmonary dysfunction), it is intuitive that overall survival will be age dependent [5,7–10]. Conversely, the rationale is not readily apparent for accepting age as a risk factor for progression-free survival (PFS) and cause-specific survival (CSS). After removal of the primary tumor, extrauterine disease is presumably the etiology of subsequent recurrence and compromised disease-related longevity. However, the medical literature is essentially devoid of information demonstrating that the pathophysiology, natural history, and/or efficacy of contemporary therapeutic modalities for EC are modified by age at diagnosis. Hence, the impact of age on PFS and CSS remains uncertain.

Numerous therapeutic indices applicable to oncologic care are adversely affected by age, particularly if treatment includes surgical intervention. Surgical morbidity, mortality, and length of hospitalization are increased in the elderly, resulting in surgical complexity being tailored accordingly [11–16]. Likewise, the indications, selection, and doses of adjuvant therapy are more frequently personalized in frail elderly patients [16–19]. These potential therapeutic modifications are further compounded in EC by the fact that the elderly generally harbor more adverse cancer-related risk factors [4,6,8,16]. Consequently, determining the direct impact of age on PFS and CSS requires analyses to be appropriately risk-adjusted for pertinent patient-, disease-, and treatment-specific risk factors.

Propensity score (PS) methods have been utilized to reduce bias in nonrandomized prospective and retrospective observational analyses [20–22]. This methodology estimates the conditional probability of group assignment on the basis of the assimilation of the patient's covariate values. The PSs can then be used via matching, stratification, and regression techniques to balance measured covariates in comparison groups and to potentially obtain less biased comparisons of outcome measures between groups [20]. We present what we believe to be the first application of PS methodology in critically assessing the impact of age, comparing patients <70 and ≥ 70, on PFS and CSS in EC.

2. Methods

2.1. Study patients

The medical records of all patients who elected primary surgical intervention for EC at the Mayo Clinic, Rochester, Minnesota, from January 1, 1999, to December 31, 2008, were retrospectively evaluated. Patients were excluded if they had stage IV disease or synchronous invasive cancers, if they received neoadjuvant chemotherapy, or if they declined the use of their medical information for research purposes. This study was approved by the Mayo Clinic Institutional Review Board.

2.2. Data collection

Patient-, disease-, and treatment-specific variables were abstracted from medical records by a dedicated registered nurse using a modified American College of Surgeons National Surgical Quality Improvement Program platform [23,24]. To ensure that information was current regarding complications, we assessed disease progression from the date of surgery and periodically reviewed vital status, medical records, and tumor registry records. Additionally, death certificates were reviewed and surveys sent to patients and their personal physicians to gather additional details when information about disease status was insufficient.

Demographic and clinical data were recorded, including body mass index, medical comorbidities (eg, pulmonary dysfunction, prior cardiac event, vascular disease, diabetes mellitus, smoking status), and the American Society of Anesthesiologists (ASA) score. Pulmonary dysfunction included at least one of the following: dyspnea, history of chronic obstructive pulmonary disease, current pneumonia, history of sleep apnea, and use of continuous positive airway pressure. Prior cardiac event was defined as congestive heart failure within 30 days, myocardial infarction within 6 months, previous cardiac stenting or previous cardiac surgery, and/or history of angina within 30 days. Vascular disease included history of revascularization/amputation for peripheral vascular disease and/or resting pain/gangrene.

Disease-specific variables included the International Federation of Gynecology and Obstetrics (FIGO) grade and stage (by the 2009 FIGO classification system [25]), presence of residual disease, histologic subtypes as designated by the taxonomy principles of the World Health Organization [26], and multiple applicable pathologic parameters. The primary tumor diameter was defined as the largest of the 3 tumor dimensions. All pathology slides were reviewed by the same gynecologic oncology pathologist (G.L.K.).

Treatment-specific factors included operative complexity, surgical approach, type and extent of lymphadenectomy, and adjuvant therapy. An adequate systematic lymphadenectomy was defined as removal of at least 10 pelvic and 5 para-aortic lymph nodes. In January 2004, a standardized surgical algorithm for EC was formally implemented. Patients were assessed by intraoperative frozen section, as previously described [27]. Hysterectomy alone was deemed sufficient in the absence of extrauterine disease and Mayo defined low-risk histology, as previously reported [28]. Definitive surgical staging with lymphadenectomy to the level of the renal vessels was recommended for specimens that failed to meet these criteria [29].

2.3. Statistical analysis

Statistical analyses were performed using the SAS version 9.2 software package (SAS Institute, Inc). All calculated *P* values were 2-sided, and *P* values less than .05 were considered statistically significant. The annotated demographic, clinical, and pathologic characteristics of patients aged <70 vs ≥ 70 at the time of surgery were compared using the 2-sample *t* test for body mass index and the χ^2 test or the Fisher exact test for all other variables. The primary outcomes evaluated were PFS and CSS (death due to disease). Duration of follow-up was calculated from the date of surgery to the date of the outcome of interest; otherwise, patients were censored at the date of last follow-up.

The goal of PS methodology is to balance observed covariates between patients in study groups, such as those aged <70 vs those ≥ 70 years, to obtain potentially less biased comparisons of outcome measures between groups. A PS value was calculated for each patient from a multivariable logistic regression model that was fit to estimate the conditional probability of being age ≥ 70, given a patient's baseline covariates. The model included all the demographic and clinical covariates listed in Table 1, with missing values imputed for peritoneal cytology and primary tumor diameter. To achieve better balance in baseline covariates, we investigated and added to the model higher-order terms for continuous variables and 2-way interactions. Before the impact of age ≥ 70 was evaluated by outcome, the balance produced by the PS values was assessed by examining the distribution of the values and the standardized difference of each covariate, defined as the difference in means or proportions of that covariate between the 2 age groups divided by a measure of the pooled SD of the covariate. An advantage of the standardized difference is that it does not depend on the unit of measurement or the sample size. A standardized difference of <0.10 likely denotes negligible imbalance between groups [30]; therefore, that criterion was used to assess the balance in this study. With adequate balance, 3 PS approaches were utilized to estimate the impact of age ≥ 70 on each outcome: stratification, inverse probability weighting, and matching.

2.4. Stratification approach

The patients were placed into 1 of 5 strata by their PS values. The stratum boundaries were defined by quintiles for the distribution of PS values in common to both age groups; patients with a PS value