European Journal of Obstetrics & Gynecology and Reproductive Biology 207 (2016) 115–120

Contents lists available at ScienceDirect

European Journal of Obstetrics & Gynecology and Reproductive Biology

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

Survival endpoints for young women with early stage uterine endometrioid carcinoma: a matched analysis☆

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ARTICLE INFO

Article history:
Received 25 August 2016
Received in revised form 3 October 2016
Accepted 21 October 2016

Keywords:
Endometrial carcinoma
Young age
Recurrence
Matched analysis

ABSTRACT

Objectives: Younger age is thought to be a favorable prognostic factor in women with endometrial carcinoma (EC). Survival endpoints were compared between two matched groups of patients with early stage EC: women 45 years or younger and women older than 45 years.
Methods and materials: Two matched groups of patients were created based on stage, grade, lymph node dissection and adjuvant management. Recurrence-free (RFS), disease-specific (DSS) and overall survival (OS) were calculated.
Results: A total of 525 patients (88 younger patients and 437 older patients, matched 1:5) were included in this study. The two groups were well balanced except for less myometrial invasion in the younger patients. There were no significant differences between younger and older patients in regards to 5-year RFS (94% vs. 91%, $p = 0.6902$). Similarly, there was no significant difference in regards to DSS (96% vs. 97%, $p = 0.9000$). While 5-year OS was similar for both groups (89% vs. 89%, $p = 0.9942$), 10-year OS was longer in the younger group (83% vs. 68% with $p = 0.13$). On multivariate analysis for RFS, the presence of lymphovascular space invasion was the only predictor of shorter RFS ($p = 0.0007$). Tumor grade ($p = 0.0002$) and lower uterine segment involvement ($p = 0.0141$) were independent predictors of shorter DSS. Older age ($p < 0.001$) and stage II ($p = 0.01$) were the only predictors of shorter OS.
Conclusions: When matched based on tumor stage, grade and adjuvant management, our study suggests that there is no difference in survival endpoints between younger and older patients with early stage endometrial carcinoma.

Introduction

Approximately 320,000 women world-wide are diagnosed annually with endometrial cancer (EC), and 76,000 will ultimately perish from the disease [1]. Endometrial carcinoma is the most common gynecological malignancy in the US and is typically thought of as a disease in older women with median age at diagnosis of approximately 60 [2]. Pre-menopausal women younger than 45 account for less than 10% of reported cases of EC [3,4]. Many risk factors for development of endometrial cancer have been elucidated including: nulliparity, obesity, unopposed estrogen, early menarche, and late menopause [5,6]. Annovulatory, obese, and nulliparous women tend to develop EC at a younger age [5].

It is generally accepted that women older than 70 with endometrial cancer do worse overall than younger women. This is attributed to more adverse pathologic features including greater depth of myometrial invasion, higher grade, and more advanced stage [7–10]. Prospective randomized controlled trials from the Gynecologic Oncology Group (GOG-99) and Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC-1) showed that increasing age was a negative prognostic factor leading to increased recurrence and decreased survival [11,12]. Additionally, several studies reported the adverse prognostic impact of older age in women with endometrial carcinoma [13–15]. Conversely, there have been other studies that seem to suggest that EC in young women is frequently associated with earlier stage, lower tumor grade and improved prognosis/outcomes [13,14].

While useful, previous studies comparing survival outcomes of younger versus older women with EC were hampered by some study limitations such as low numbers of patients in the younger

☆ Presented as a featured poster at the 47th Annual meeting on Women's Cancer. Society of Gynecologic Oncology (SGO). San Diego, CA in March 2016.

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http://dx.doi.org/10.1016/j.ejogrb.2016.10.038
0301-2115/

age groups [13–18], and inclusion of patients of all stages [19] and histological subtypes [20]. Evans-Metcalf et al. compared the clinical characteristics and outcomes of EC patients younger and older than 45 years of age. This cross sectional study of 289 patients included only 40 patients younger than the age of 45. The authors reported that the overall distribution of tumor stage and survival endpoints were similar between the two age groups [16].

Other investigators were not able to show longer disease-free survival in younger patients. Gitsch et al. reported the outcomes of 17 women younger than 45 years of age. Their study was not limited to early stages and they included patient with endometrioid and non-endometrioid histological types. They reported that 35% of the young patients had lymph node involvement [17]. Tran et al. reviewed 41 women below the age of 45 compared to 416 patients older than 45. They reported that younger EC patients have a similar distribution of adverse pathological features as well as disease-free and cause-specific survivals compared to older patients [18].

Due to limited data in regards to prognostic impact of younger age in women with EC, the purpose of the present study was to investigate prognostic factors, recurrences, and survival endpoints in a larger cohort of women with early stage endometrial carcinoma solely of endometrioid histology. A matched analysis methodology was used to account for the impact of other prognostic factors.

Methods

After obtaining IRB approval, the medical records of women with early stage endometrial carcinoma (EC) were retrospectively reviewed. We identified 1254 consecutive patients with 2009 International Federation of Gynecology and Obstetrics (FIGO) stage I–II endometrial carcinoma who underwent surgical staging at our institution between the dates of 1/1990 and 12/2014.

All patients underwent hysterectomy, salpingo-oophorectomy (except five patients), pelvic and para-aortic lymph node evaluation with or without nodal dissection and peritoneal cytology examination. Only patients with endometroid histologies were included. Patients with non-endometroid and mixed histologies were excluded from this analysis. Patients who received preoperative radiation treatment or adjuvant systemic chemotherapy were also excluded. The ovaries were not removed in only five women in the younger age group.

In addition to patients' demographics, the following pathologic factors were assessed: tumor grade, depth of myometrial invasion, lymphovascular space invasion (LVSI), lower uterine segment involvement (LUSI), number of lymph nodes resected, and status of peritoneal cytology.

Women 45 years of age or younger at the time of hysterectomy were matched to older women based on 2009 FIGO stage, tumor grade, status of lymph node dissection (yes or no) and the type of adjuvant management received post hysterectomy (observation, pelvic radiation treatment or vaginal cuff brachytherapy). When more than 5 patients in the older age group matched a younger patient, 5 were selected at random. Once a patient in the older group was matched, she was removed from the potential match pool for consideration for future younger patients, thereby ensuring each patient is unique. All matching was blinded to patients' outcome.

The study cohort was then divided into two age groups; those 45 years or younger at time of hysterectomy and those older than 45 years of age. The age cut off of 45 years was selected similar to previously published studies [16,19].

The two groups were compared with regard to the patient's demographics, tumor characteristics, treatments received and survival endpoints. Survival endpoints included recurrence-free (RFS), disease-specific (DSS) and overall survival (OS). Kaplan–Meier plots were generated for each group for RFS, DSS and OS. Univariate comparisons were performed using Wilcoxon rank-sum and Fisher's exact tests. Cox regression model was used for multivariate analysis. Predictors with univariate p-values of 0.2 or less were included in a Cox proportional hazards model. A two-sided p-value < 0.05 was considered statistically significant. Statistical analysis was performed using SAS 9.4 (Cary NC, USA).

Results

Of the 1254 women with early stage uterine endometrioid carcinoma, 90 (7.2%) were 45 years of age or younger at the time of hysterectomy. Based on the matching variable, we were able to match each of the 86 younger with 5 older patients (1:5 match). Additionally, one younger patient matched with 4 older patients, and another one matched with 3. This created the final study cohort of 525 patients (88 younger patients and 437 older patients). The other two younger patients had zero matches and were excluded from the study cohort. Table 1 shows patient characteristics of the two groups included in this study. The two groups were well matched with regard to race, surgical staging, and the use of adjuvant radiation therapy. Younger patients were found to have significantly less myometrial invasion. Tumor recurrence rates and sites between the two groups were not statistically different.

Median follow-up time for the study cohort was 42.8 months (range, 6–334.1) calculated from the date of hysterectomy. The 5-year RFS for the younger age group was 94% (95% CI 0.84–0.98) compared to 91% in the older age group (95% CI 0.87–0.94) ($p = 0.69$) (Fig. 1). The 5-year DSS for the younger age group was 96% (95% CI 0.85–0.99) compared to 97% in the older age group (95% CI 0.94–0.98) ($p = 0.90$) (Fig. 2). While 5-year OS was similar for both groups (89%), 10-year OS was longer in the younger group (83% vs. 68% with $p = 0.13$). The 5-year OS for the younger age group was 89% (95% CI 0.77–0.95) compared to 89% for the older age group (95% CI 0.85–0.92) ($p = 0.99$) (Fig. 3). Of the five patients in the younger age group who had their ovaries preserved at the time of surgical staging, none developed any tumor recurrence at last follow-up visit.

Deep myometrial invasion, high tumor grade, positive peritoneal cytology, lower uterine segment involvement, the presence of LVSI, higher FIGO stage and lack of adjuvant radiation treatment were significant predictors of shorter RFS and DSS on univariate analysis of study cohort. The following variables were significant predictors of shorter OS on univariate analysis: older age, deep myometrial invasion, high tumor grade, lower uterine segment involvement, the presence of LVSI, higher FIGO stage and lack of adjuvant radiation treatment were significant predictors of shorter OS.

Multivariable analysis of RFS showed that the only two independent predictors of worse outcome are the presence of LVSI and higher FIGO stage. While LUS involvement and higher tumor grade were the only predictors for worse DSS, older age and higher FIGO stage were the only two independent predictors of shorter OS. The results of these multivariate analyses are summarized in Table 2.

Discussion

To our knowledge, this is the largest series of patients 45 years of age or younger with stages I–II endometrioid EC who underwent surgical staging with or without adjuvant therapies matched against older women by stage, grade, and adjuvant therapies. Endometrial carcinoma is typically thought of as a disease in older women with only approximately 10% of cases occurring in women younger than 45 years of age. Previous data suggests that older