Radical Hysterectomy Versus Simple Hysterectomy and Brachytherapy for Patients with Stage II Endometrial Cancer

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Research article

Keywords: Endometrial cancer, Postoperative radiation, Propensity score matching, Survival

Posted Date: August 26th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-60842/v1

Abstract

BACKGROUND: To compare the survival outcome between radical hysterectomy and simple hysterectomy with implants radiation in patients with stage II endometrial cancer.

METHODS: This is a retrospective cohort study. We identified 1349 patients diagnosed with stage II endometrial cancer from Jan 1, 1988 to Dec 31 2015 in the Surveillance, Epidemiology, and End Results. Patients were divided into two groups based on the primary treatment (simple hysterectomy combined with brachytherapy or radical hysterectomy). The primary outcome was the rate of overall survival and cause-specific survival of two groups.

RESULTS: A total of 1349 patients were enrolled in the study, 117(7.35%) patients received radical hysterectomy and 460 patients who received simple hysterectomy and vaginal brachytherapy were selected as control. All patients received external beam radiation therapy after the surgery. Overall, the median follow-up duration was 82.77±1.44months (95%CI: 79.94-85.61months). There was no difference in the baseline information between two groups, including ages, ethnicity, and rates of histologic subtypes. The 5-year mortality was 62.31% among women who underwent radical hysterectomy which was lower than 78.48% among those who underwent simple hysterectomy and vaginal brachytherapy (HR, 2.22; 95% CI, 1.52 to 3.24; P <0.001 by the log-rank test). Women who underwent radical hysterectomy also had shorter 5-year cause-specific survival (74.60 vs.85.38%; HR, 1.91; 95% CI, 1.13 to 3.23; P =0.01 by the log-rank test) than those who underwent simple hysterectomy and vaginal brachytherapy. However, the negative outcomes were further validated in patients with high-risk endometrial cancer, not in patients with grade 1-2 low-risk EC both on cause-specific survival and overall survival. Grade 3 low-risk endometrial cancer was only found with lower overall survival not cause-specific survival.

CONCLUSIONS: This study revealed that in patients' stage II high-risk endometrial cancer, radical hysterectomy radiation was associated with shorter overall survival and cause-specific survival than simple hysterectomy and vaginal brachytherapy.

Background

The incidence and mortality rates of endometrial cancer (EC) remain high in developed countries and are increasing among women in developing countries [1],[2]. An estimated 382069 new cases of EC were diagnosed around the world in 2018, and 89929 people died of the disease. As a general principle, EC should be removed en bloc to optimize outcomes and intraperitoneal morcellation should be avoided [3], [4]. For patients with suspected or gross cervical involvement (endometrioid histology), Simple hysterectomy (SH) or radical hysterectomy is recommended along with bilateral salpingo-oophorectomy, cytology (peritoneal lavage), and dissection of lymph nodes if indicated [5]. In these patients, radical or modified radical hysterectomy may improve local control and survival when compared with SH [6],[7]. Alternatively, the patient may undergo external beam radiation therapy (EBRT) and vaginal brachytherapy

(BT) (category 2B) followed by SH, bilateral salpingo-oophorectomy and surgical staging. For patients with stage II disease who have had a radical hysterectomy with negative surgical margins and no evidence of extrauterine disease, observation, or vaginal BT are options. However, there is no better choice due to limited comparative studies between the outcomes of two modalities.

This study has aimed to evaluate the survival of different treatment models in patients with EC involved cervix. We conducted a retrospective cohort study of 577 patients to give a more complete picture of the real-world clinical outcomes to enhance the body of different treatment modalities.

Methods

Study design and patient selection

This study was a retrospective study involving data from patients' stage II EC, registered in the Surveillance, Epidemiology, and End Results (SEER) registry (Third Edition, SEER 18 registry database November 2019 submission) [8] from 1988 to 2015. This database covers approximately 27.8% of the U.S. population and is publicly available and de-identified. The data reported in this study represent the most recent follow-up (April 30, 2019) available in the SEER database.

Patients diagnosed between Jan 1, 1988, and Dec 31, 2015, with primary EC involving cervix treated with radical hysterectomy or SH and vaginal BT were eligible for participation. All patients received EBRT after the surgery. Patients who didn't undergo radiation for any reasons were excluded, and we also excluded patients if we could not determine whether they matched the inclusion criteria because of missing data (e.g., surgery information or postoperative radiotherapy).

Study Procedures and Data Collections

SEER*Stat 8.2.3 was used to extract the data and women fulfilling the aforementioned enrollment criteria were offered participation in the study. Detailed demographic, oncological, and survival data were collected. We divided our cohort into two groups according to treatment modalities: SH (group A) and radical hysterectomy (group B). Group A was considered having postoperative with vaginal BT after SH with Federation International of Gynecology and Obstetrics (FIGO) stage II EC, Group B contained patients with FIGO stage II EC and didn't receive vaginal BT. The cancer stage was reclassified into FIGO 2019, based on tumor size, tumor extension, and lymph node status recorded in the database.

Propensity score matching for each group was computed for each case determined by multivariable logistic regression analysis. Patient demographics, tumor characteristics, and treatment patterns were entered in the propensity score model. Four-to-one propensity score matching between Group A and Group B was performed through an automated algorithm with the propensity score difference cut off being 1%.

Outcome Measurements

Survival data, including 5-year-cause-specific survival (CSS) and 5-year-overall survival (OS) (all-cause mortality), are collected through linkages with state mortality records and the National Death Index. CSS was defined as the time interval between the initial diagnosis of uterine EC and the date of death resulting from this specific disease. OS was defined as the time interval between the initial uterine EC diagnosis and the date of death for any reason. Among women who died, causes of death were examined (uterine EC and other diseases) and grouped as previously described.

The primary outcome was to examine the 5-year-OS among women in the two groups, respectively. The secondary outcome was to examine the 5-year-CSS in the two groups, respectively.

Statistical analysis

Rank sum test or $\chi 2$ test was used to exam base-line characteristics: age at diagnosis, ethnicity, year at diagnosis, grade, surgery modality, postoperative radiation, chemotherapy. Cox regression was used to evaluate proportional hazard regression models, and the magnitude of statistical significance was expressed with a hazard ratio (HR) and 95% CI.

We employed Kaplan-Meier analysis to construct survival and cumulative risk curves, and statistical significance between the curves was compared with log-rank tests. Survival was also examined using Cox Covariates, entered in the final model were patient demographics, tumor factors, and treatment patterns.

Statistical analyses were conducted using SPSS23. All P-values reflected 2-sided tests, and significance was set at <0.05.

Results

Study Population

A total of 1718 patients were screened and 1349 patients were enrolled in the study from 1988 to 2015 (Fig. 1). All patients were found with cervical stromal invasion and received cancer-directed hysterectomy and postoperative EBRT. 117(7.35%) patients received radical hysterectomy and 460 patients who received SH and vaginal BT were selected as control. The baseline characteristics of the patients are summarized in Table 1. The mean age of the patients in group A was comparable to the patients in group B (61.27 ± 12.34 vs.61.39 ± 11.80 years, p = 0.92). There were no significant differences between the two groups with respect to age(p = 0.96), ethnicity(P = 0.06), year at diagnosis(P = 0.06), grade(P = 0.63), chemotherapy(p = 0.51).

Table 1
Clinicopathologic and Treatment Characteristics of Study Patients

Values	Group A (n = 117)	GroupB (n = 460)	P-value
Age	61.27 ± 12.34	61.39 ± 11.80	P = 0.92
< 45	10(8.5)	36(7.8)	P = 0.96
45–55	28(23.9)	113(24.6)	
55–65	35(29.9)	140(30.4)	
65–75	27(23.1)	115(25.0)	
>=75	17(14.5)	56(12.2)	
Ethnicity			
White	84(71.8)	359(78.0)	P = 0.06
Black	16(13.7)	32(7.0)	
Other	17(14.5)	69(15.0)	
Year at diagnosis			
1998–2000	14(12.0)	70(15.2)	P = 0.06
2001–2005	25(21.4)	147(32.0)	
2006–2010	38(32.5)	118(25.7)	
2011–2015	40(34.2)	125(27.2)	
Grade			
Grade 1–2 low-risk endometrial cancer	48(41.0)	211(45.9)	P = 0.63
Grade 3 low-risk endometrial cancer	46(39.3)	163(35.4)	
High-risk endometrial cancer	23(19.7)	86(18.7)	
Chemotherapy			
No	83(70.9)	324(70.4)	P = 0.51
Yes	34(29.1)	136(29.6)	

Impact of different treatment modalities on survival

The median follow-up time was 82.77 ± 1.44 months (95%CI: 79.94–85.61 months). Figure 2 shows the results of Kaplan-Meier analyses of 5-year OS (Fig. 2A) and 5-year-CSS (Fig. 2B) associated with different treatment modalities. Women who underwent radical hysterectomy had shorter 5-year OS (62.31%

vs.78.48%; HR, 2.22; 95% CI, 1.52 to 3.24; P < 0.001 by the log-rank test) and 5-year-CSS (74.60 vs.85.38%; HR, 1.91; 95% CI, 1.13 to 3.23; P = 0.014 by the log-rank test).) than those who underwent hysterectomy and implants radiation. To better know the effect of pathological type on survival, we further compared the survival outcomes in patients with grade 1–2 low-risk EC, grade 3 low-risk EC, and high-risk EC, independently. Women who underwent radical hysterectomy had shorter OS (53.39% vs. 70.99%; HR, 2.12; 95% CI, 1.19 to 3.77; P = 0.0018 by the log-rank test) and CSS (62.53% vs.78.79%; HR, 1.90; 95% CI, 0.90 to 3.38; P = 0.044 by the log-rank test) in patients with high-risk EC. However, the same results were not found in patients with grade 1–2 low risk EC both on CSS (75.29% vs. 69.44%; HR, 1.06; 95% CI, 0.42 to 2.66; P = 0.90 by the log-rank test) and OS (75.38% vs. 90.05%; HR, 1.15; 95% CI, 0.52 to 1.98; P = 0.96 by the log-rank test). Grade 3 low risk EC were only found with lower OS (75.38% vs. 90.05%; HR, 2.34; 95% CI, 1.16 to 4.70; P = 0.0012 by the log-rank test) not CSS (88.84% vs. 94.09%; HR, 2.04; 95% CI, 0.64 to 6.45; P = 0.12 by the log-rank test).(Fig. 3)

Discussion

The present study compared two different treatment modalities of stage II EC and found that radical hysterectomy without vaginal BT was associated with a higher risk of death than women who underwent SH with vaginal BT for stage II EC.

Previous studies have shown that stage II EC constitutes approximately 5.1–10% of all ECs [9]. Reported recurrence rates for stage II EC vary from 10–28% [10]. The optimal treatment for patients with FIGO 2009 Stage II disease (those harboring cervical stromal invasion) is uncertain and is debated [11]. Some studies have found that radical hysterectomy was associated with an increased OS. Sartori et al evaluated 203 patients with stage II EC and compared patients who underwent a SH and radical hysterectomy. They found a significant improvement in 5-year OS that was 94% in the radical hysterectomy group versus 79% in the SH group [7]. On the other hand, similar results could not be obtained by other investigators [12],[13], [14]. A recent study published by Takano et al evaluated 300 patients with stage II EC. They compared 186 patients treated with radical hysterectomy, and 114 had a SH; they found that the type of hysterectomy was not an independent prognostic factor for Disease-free survival and OS. Besides, they reported that perioperative and late adverse events were more common in patients treated with radical Hysterectomy.

Although surgical resection is the mainstay of treatment for patients with EC, randomized studies have shown that adjuvant radiation treatment for patients with early-stage disease and high-risk features such as high-grade histology and one-half or greater myometrial invasion decreased rates of local recurrence [15],[16]. Although EBRT is a reasonable treatment option for many patients, the use of vaginal BT allows for the delivery of localized radiation to the vaginal cuff, the area of highest risk of recurrence. FIGO Stage II patients have been included in randomized studies with both low-risk patient populations as well as included with patients with positive lymph nodes, serosal involvement, or vaginal involvement, which are at a significantly higher risk for both locoregional as well as distant recurrence. These studies failed to answer the question of optimum radiation therapy (RT) treatment regimens or treatment type for Stage II disease.

In contrast, wright et al [12] evaluated 1577 patients with stage II EC and found that adjuvant RT was associated with an improvement in survival in patients with high-risk pathologic features who underwent a radical hysterectomy. Conversely, they found that adjuvant RT only improved local control in patients received SH and no recurrence was observed in patients received radical hysterectomy, regardless of the administration of adjuvant RT [17]. A study related with stage II EC was published by Cornelison et al, who reported that there was no significant survival difference in radiation versus no radiation in total or radical hysterectomy groups [18]. In a retrospective study, Eltabbakh[19] reported on 48 patients with surgical stage II EC treated either by total abdominal hysterectomy followed by both whole pelvic and vaginal cuff RT or by radical hysterectomy alone; estimated 5-year overall and disease-free survival rates were 92.1% and 89.9%, respectively. There was no difference in survival among the two groups. The study published by Ayhan et al evaluated 48 stage II EC patients and compared patients treated with SH plus RT with patients who had radical hysterectomy without adjuvant therapy [20]. They reported that OS and disease-free survival were not significantly different between the 2 groups. However, these results are biased by heterogeneity and small sample sizes. And the staging system from FIGO 2009 had a different definition of Stage II EC. In our study, we found that in the case of external irradiation in both groups, the survival period of SH plus vaginal BT was higher than that of radical operation group. However, the negative outcomes were further validated in patients with high-risk EC, not in patients with grade 1–2 low-risk EC both on cause specific survival and OS. Grade 3 low-risk EC were only found with lower OS not CSS. The different results in low-risk grade I patients indicated that other reasons undying the death of this population. Then prospective studies are needed for further validation.

Our study did not acquire any information on tumor recurrence or exact details, which could have helped to investigate differences in the progression-free survival. Data from large-scale trials and prospective multi-centered studies are needed because of the rarity of Stage II EC in a single center.

Conclusions

This study revealed that in patients stage II EC, radical hysterectomy radiation was associated with shorter OS and CSS than SH and vaginal BT in patients with high-isk EC.

Abbreviations

EC, Endometrial cancer; **SH,** Simple hysterectomy; **BT,** Brachytherapy; **EBRT,** External beam radiation therapy; **SEER,** Surveillance, Epidemiology, and End Results; **OS,** Overall survival; **CSS, C**ause specific survival; **FIGO,** Federation International of Gynecology and Obstetrics; **HR,** Hazard ratio; **RT,** Radiation therapy.

Declarations

Ethics approval and consent to participate: This article does not contain any studies with human participants or animals performed by any of the authors. All data involving in this study come from SEER

registry.

Consent for publication: Not applicable.

Availability of data and material: The datasets generated during and/or analyzed during the current study are available in the SEER database.

Competing Interest: The authors declare that they have no conflict of interest.

Funding: There is no funding support for this study.

Acknowledgement: All authors have no conflict of interest to be disclosed.

Author Contributions:

Dr. Yumei Wu proposed the concept and designed the study, Drs. Ming Wang and Ran Ran contributed to the acquisition of data. Drs. Wang and Ran performed the statistics and interpreted the data and wrote the manuscript with assistance from Dr. Yumei Wu. All authors provided inputs for the manuscript. All authors read and approved the final manuscript. Ran Ran and Ming Wang are equal first author contribution status.

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Figures

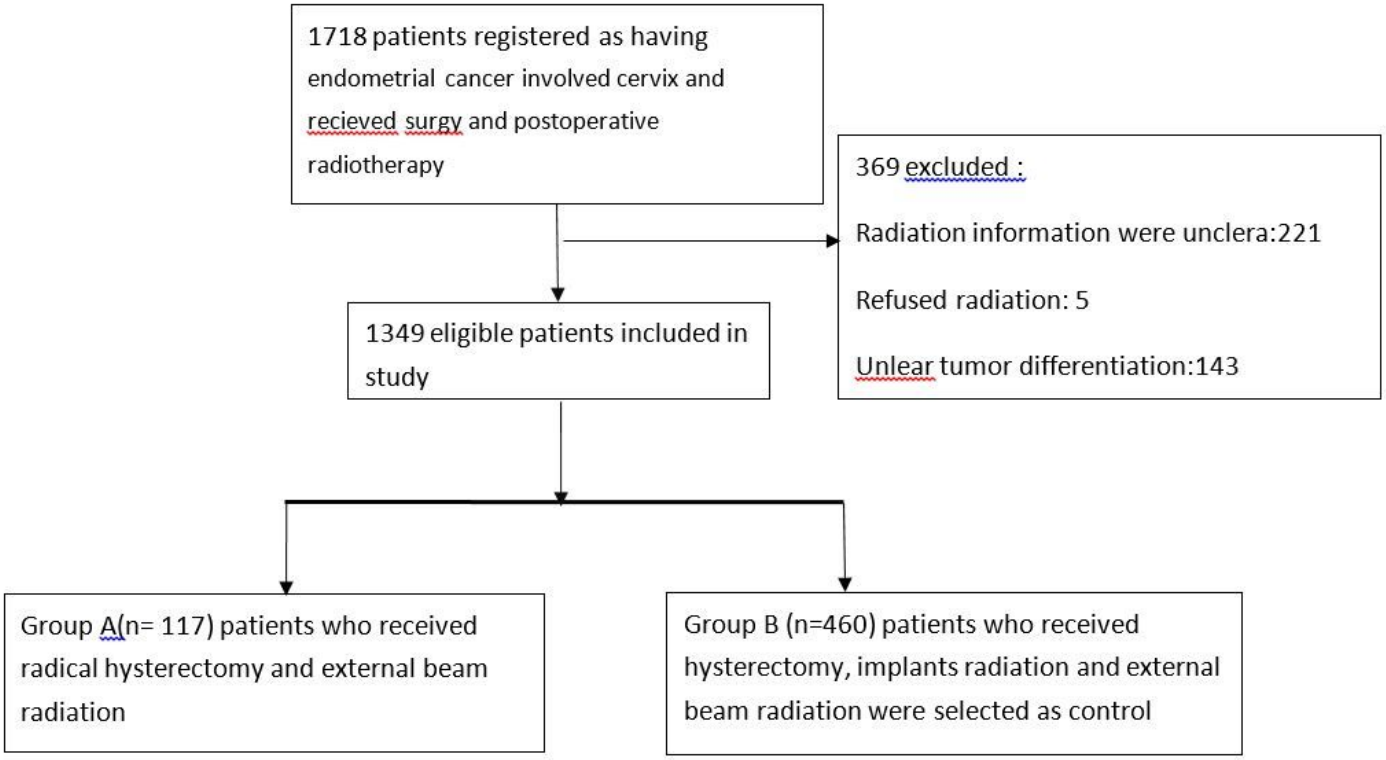

Figure 1

Patients selections and study design

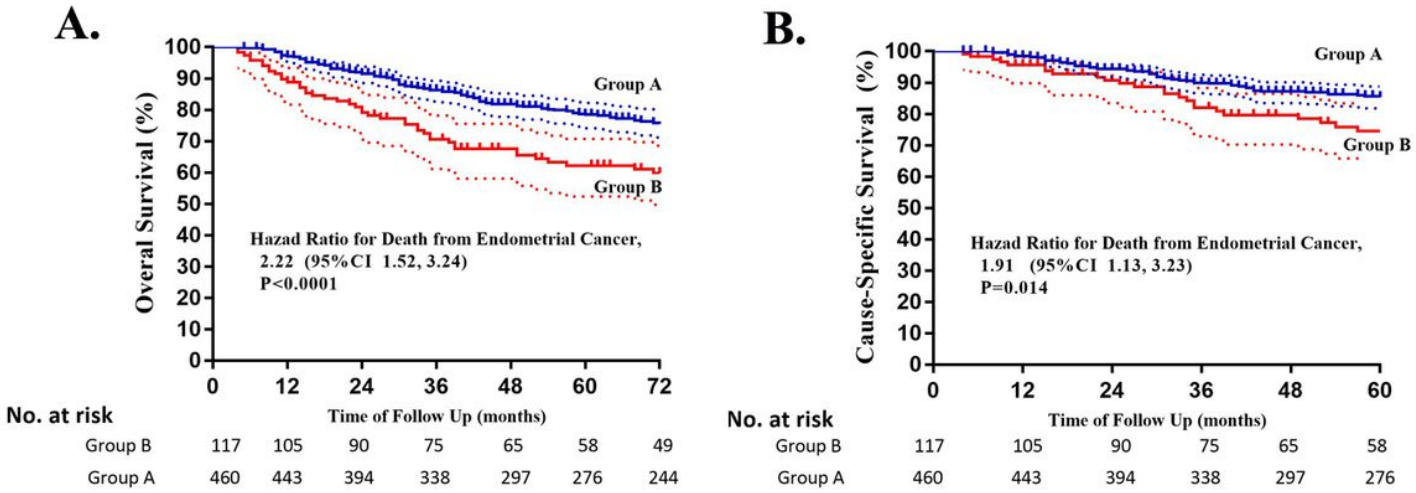

Figure 2

Kaplan–Meier Estimates of Overall Survival and Cause-specific Survival. Figure 2A shows the Kaplan–Meier plot for overall survival in Patients with Stage II Endometrial Cancer who received Radical Hysterectomy or Simple Hysterectomy and Brachytherapy. Figure 2B shows the cause-specific survival in Patients with Stage II Endometrial Cancer who received Radical Hysterectomy or Simple Hysterectomy

and Brachytherapy. A Cox proportional hazards model was used to determine the hazard ratio and 95% confidence interval. Tick marks indicate censored data.

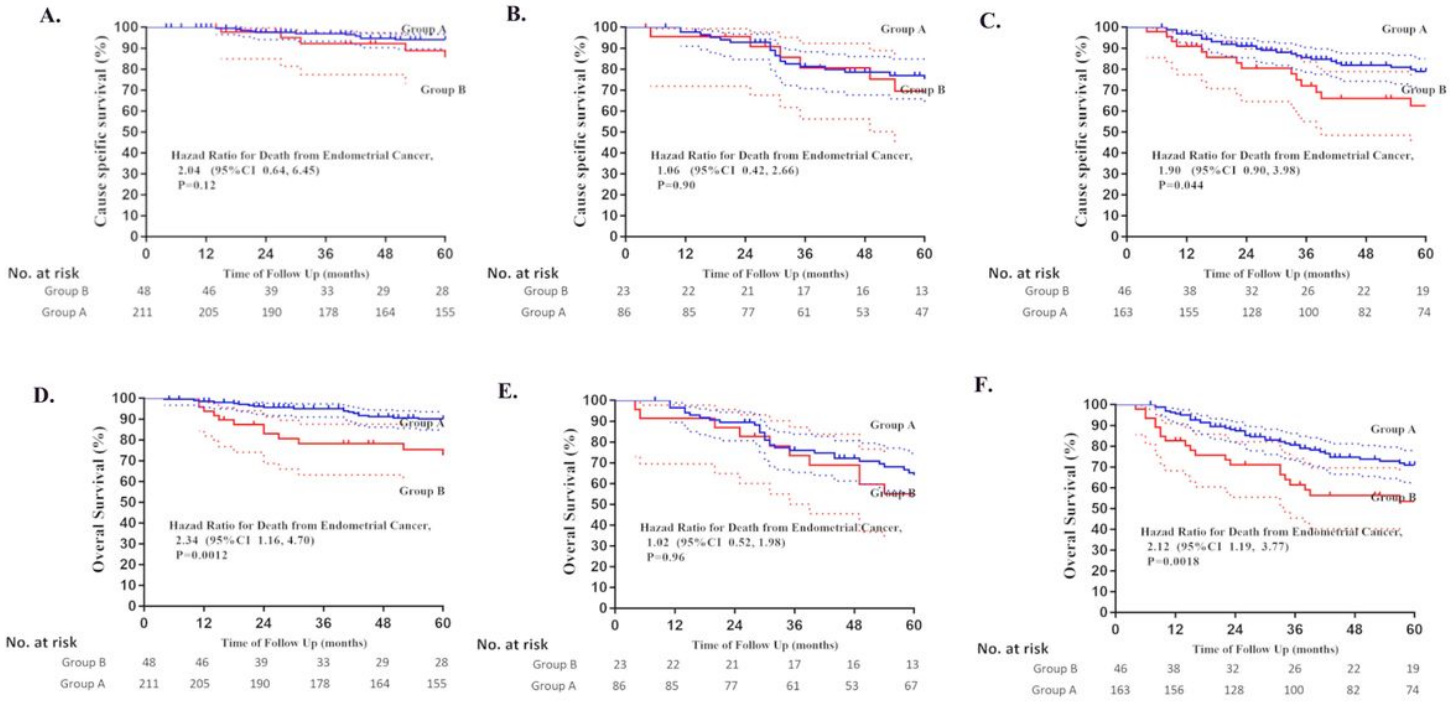

Figure 3

Kaplan–Meier Estimates of Overall Survival and Cause-specific Survival in Patients with different disease differentiation. Figure 3A shows the Kaplan–Meier plot for cause-specific survival in patients with grade 1-2 low risk EC; Figure 3B shows the Kaplan–Meier plot for cause-specific survival in patients with grade 3 low risk EC; Figure 3C shows the Kaplan–Meier plot for cause-specific survival in patients with high-risk EC; Figure 3D shows the Kaplan–Meier plot for overall survival in patients with grade 1-2 low risk EC; Figure 3E shows the Kaplan–Meier plot for overall survival in patients with grade 3 low risk EC; Figure 3F shows the Kaplan–Meier plot for overall survival in patients with high-risk EC.