

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

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Research

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Abstract

Purpose

To compare the survival outcome between radical hysterectomy and total hysterectomy with radiation therapy 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 (total hysterectomy combined with brachytherapy or radical hysterectomy). All patients received external beam radiation therapy after the surgery. The primary outcome was the rate of 5-year-cause-specific survival and 5-year-overall survival.

Results

A total of 1349 patients were enrolled in the study, 117(7.35%) patients received radical hysterectomy and 460 patients who received total hysterectomy combined with 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 ± 1.44 months (95%CI: 79.94-85.61 months). There was no difference in the baseline information between two groups, including ages, ethnicity, and rates of histologic subtypes. The 5-year overall survival was 62.31% among women who underwent radical hysterectomy which was lower than 78.48% among those who underwent total hysterectomy combined with 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 total hysterectomy combined with 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 endometrial cancer both on cause-specific survival and overall survival. In patients with grade 3 low-risk endometrial cancer, the tendency was only found with lower overall survival not cause-specific survival.

Conclusions

This study revealed that in patients' stage II endometrial cancer, radical hysterectomy was associated with shorter overall survival and cause-specific survival than total hysterectomy combined with vaginal brachytherapy. The choice of different treatment modalities should base on the histology subtype of patients and further study based on molecular classification is needed.

Introduction

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]. For patients with suspected or gross cervical involvement (endometrioid histology), total hysterectomy (TH) or radical hysterectomy is recommended along with bilateral salpingo-oophorectomy (BSO), cytology (peritoneal lavage), and dissection of lymph nodes if indicated [4]. In these patients, radical or modified radical hysterectomy may improve local control and survival when compared with TH [5, 6]. Alternatively, the patient may undergo external beam radiation therapy (EBRT) and vaginal brachytherapy (BT) (category 2B) followed by TH/ BSO 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 EBRTs are options.

To date, there is no better choice due to limited comparative studies between the outcomes of two modalities. In developing countries, especially the radiation equipment not widely used, the radical hysterectomy may be a better choice. For stage II EC patients who received radical hysterectomy with a negative surgical margin and no evidence of extrauterine disease, radiotherapy could be avoided in low and intermediate-risk patients [7]. A systematic review included 10 retrospective cohort studies enrolling 2866 patients. Patients who received radical hysterectomy did not show a significant survival benefit for either overall survival(OS) or progress free survival. Radical hysterectomy showed a 27% survival benefit (pooled Hazard ratio(HR) 0.73; 95% CI 0.53–1.00; P = 0.050) in earlier studies based on Federation International of Gynecology and Obstetrics(FIGO) 1988 staging, whereas showed increased risk of death (pooled HR 1.24; 95% CI 0.86–1.77; P = 0.245) in newly published studies based on FIGO 2009 staging [8]. However, all have no statistical significance. The reasons underlying this are still unclear. Surgeons may tend to perform radical hysterectomy in more severe cases with poorer prognostic factors. The advances in radiotherapy may lower the risk of pelvic or vaginal recurrence resulting from insufficient parametrial margins in TH.

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.

Materials And 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) [9] 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 TH combined with vaginal BT were eligible for participation. All patients received EBRT after the surgery. Patients who didn't undergo radiation therapy (RT) for any reason 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: TH (group A) combined with vaginal BT and radical hysterectomy (group B). Group A was considered having postoperative with vaginal BT after TH 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, all patients received EBRT after the surgery. 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-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 χ^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 TH combined with 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 TH combined with vaginal BT. 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 TH combined with vaginal BT for stage II EC.

The optimal treatment for patients with FIGO 2009 Stage II disease (those harboring cervical stromal invasion) is uncertain and is debated [10]. Sartori et al evaluated 203 patients with stage II EC and compared patients who underwent a TH and radical hysterectomy. They found a significant improvement in 5-year OS that was 94% in the radical hysterectomy group versus 79% in the TH group⁷. However, a recent study published by Takano et al evaluated 300 patients with stage II EC, 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. Similar results were observed by other investigators [11–13]. Although surgical resection is the mainstay of treatment for patients with early-stage EC, randomized studies have shown that adjuvant radiation treatment for patients with early-stage disease and high-risk factors reduced rates of local recurrence [14, 15], such as age ≥ 60 yrs., deep myoinvasion ($> 50\%$), lymph vascular invasion (LVSI) positive, and high-grade histology decreased rates of local recurrence. The use of vaginal BT allows for the delivery of localized radiation to the vaginal cuff which reduces the localized recurrence of TH. In previous studies in patients with stage II EC [16, 17], no difference was found between TH followed by both whole pelvic and vaginal BT or by radical hysterectomy alone. 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 TH plus vaginal BT was higher than that of the 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 was only found with lower OS, not CSS. The different results

in low-risk grade 1–2 patients indicated that other reasons underlying the death of this population. Now endometrial cancers were classified into four categories: POLE-mutated (POLE-mt), mismatch-repair-deficient (MMR-d), p53-abnormal (p53abn), p53-wild-type (p53wt) [18]. The p53-abn group showed the worst prognosis of four molecular types. Prevalence of high-risk factors (such as grade 3, deep myometrial invasion, LVSI, and lymph node involvement) is highest in the p53-abn group. Type II endometrial cancer (uterine carcinosarcoma, uterine serous carcinoma, and clear cell carcinomas) patients have a higher P53-abn than endometrioid carcinoma, even grade 3 endometrioid endometrial cancer patients. The prognosis for these patients was generally poor [19]. MMR-d group and POLE-mt group showed a similar prevalence of grade 3 and endometrioid histotype. The prevalence of parameters of aggressiveness (LVSI-positive and deep myometrial invasion) was lower in the POLE-mt group than the MMR-d group. In particular, the POLE-mt group was the only group that showed a null prevalence of lymph node involvement (0%). No endometrioid subtypes of these two groups have been described such as clear cell and mixed endometrioid/clear cell carcinomas [20–22]. These findings support the exceptionally favorable prognosis of the POLE-mt group. The second analysis of the PORTEC-1 and PORTEC-2 cohort found that fewer recurrences and a lower risk for cancer-specific death in patients with grade 3 POLE-mt tumors, compared with 30.9% of other grade 3 tumors within that cohort [23]. The majority of grade 1–2 endometrial cancers were classified into the p53-wt group and parameters of aggressiveness of this type is low. Therefore, since the prognosis of the p53-wt group varies from good to moderate [24]. The Disease spread beyond the uterus is seldom seen in high-grade endometrial cancer harboring POLE-mt. Thus, simple hysterectomy and bilateral salpingo-oophorectomy maybe an appropriate selection. POLE-mt did not increase sensitivity to radiotherapy nor chemotherapeutics in mouse-derived embryonic stem cells. These results support studies exploring the minimization of adjuvant therapy for early-stage POLE-mt endometrial cancers [25]. In contrast, more aggressive surgery seems appropriate for women with p53abn endometrial cancers. Molecular classification of grade 3 endometrial cancer reveals that these tumors are a mixture of molecular subtypes of endometrial carcinoma, rather than a homogeneous group [26]. Our study was in concordance with the above results which underlying the great need for molecular-driven clinical trials to stratify the patients into a better therapy modality on type of hysterectomy and adjuvant RT.

Our study did not acquire any information on tumor recurrence or exact details, which could have helped to investigate differences in 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 was associated with shorter OS and CSS than TH combined with vaginal BT in patients with high-risk EC.

Declarations

Authors Contribution

Dr. Wu proposed the concept and designed the study. Drs Wang and Ran contributed to the acquisition of data. Dr Wang performed the statistics. Dr Wang interpreted the data and wrote the manuscript at the help of Ran. Dr. Wu performed critical revision of the manuscript and addressed the comments from the journal.

Compliance with ethical standards

Conflict of interest: All authors declare that they have no conflict of interest.

Ethics approval and consent to participate: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This study was approved by the Ethic Committee (EC) from the Beijing Gynecology and Obstetrics Hospital. All data involving in this study come from the SEER registry.

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

Funding: There is no funding support for this study.

Informed consent: Informed consent was obtained from all individual participants included in the study

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Figures

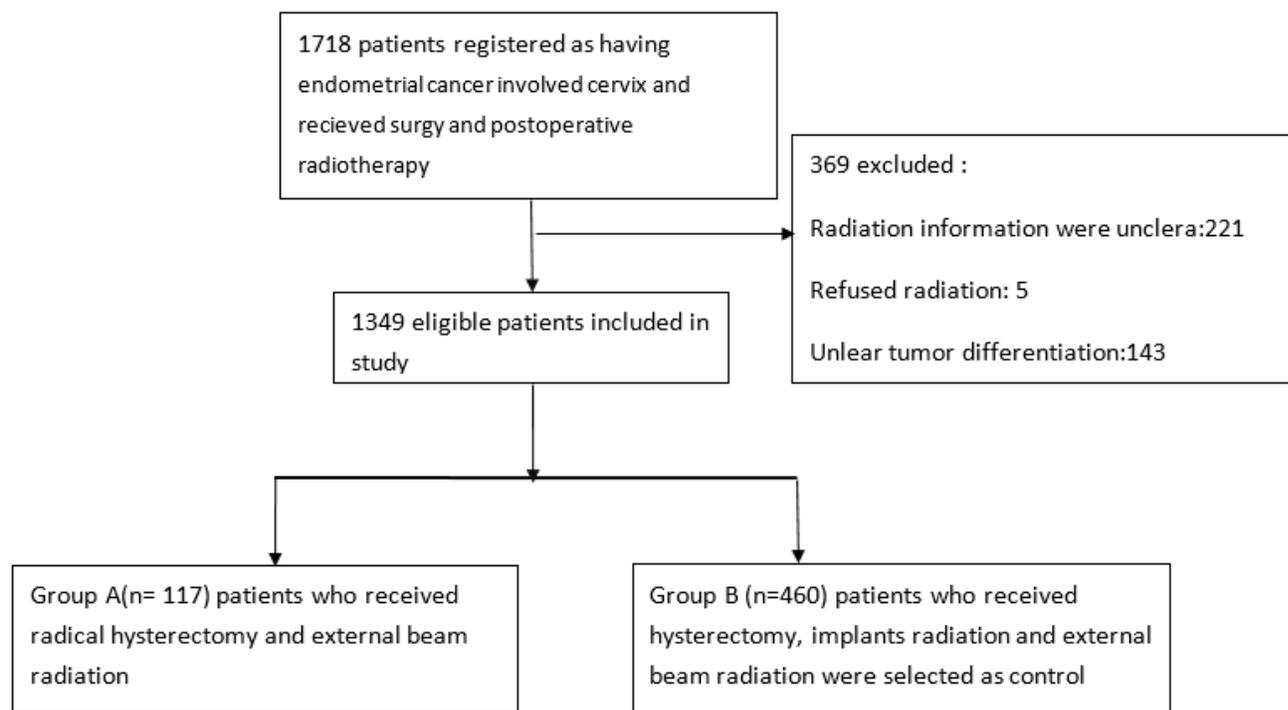


Figure 1

Patients selections and study design

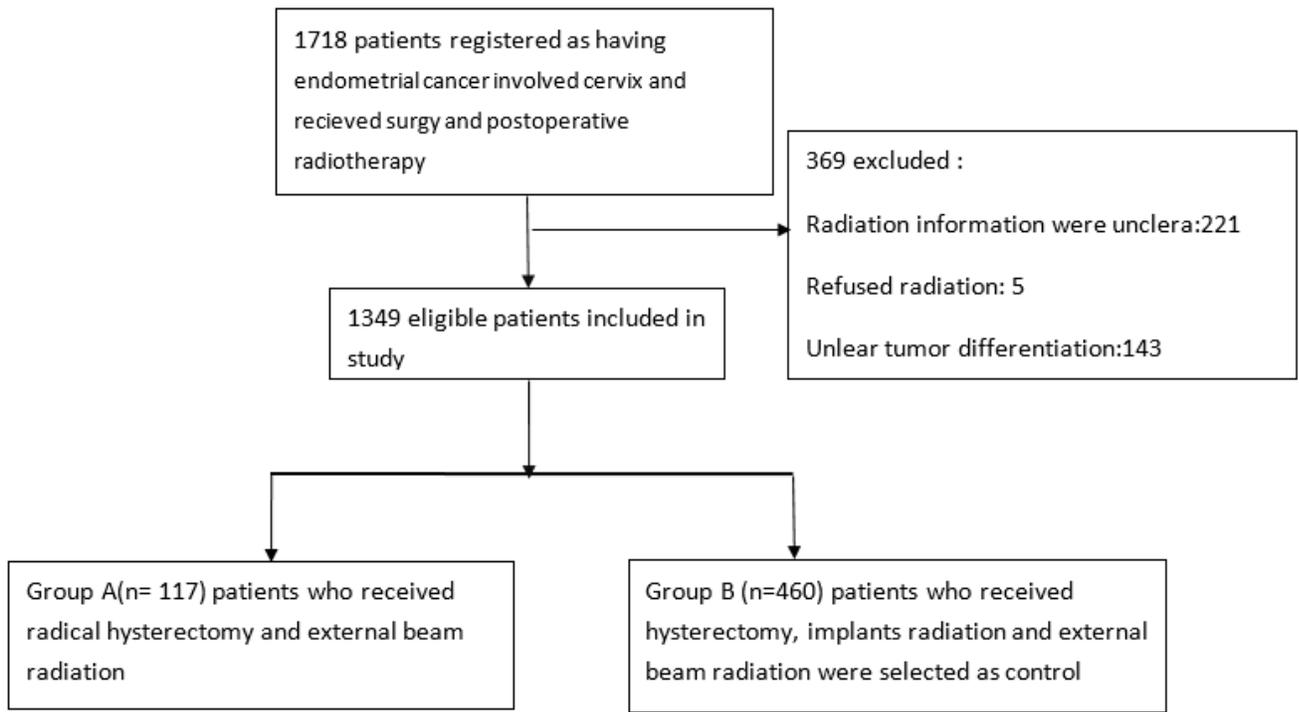


Figure 1

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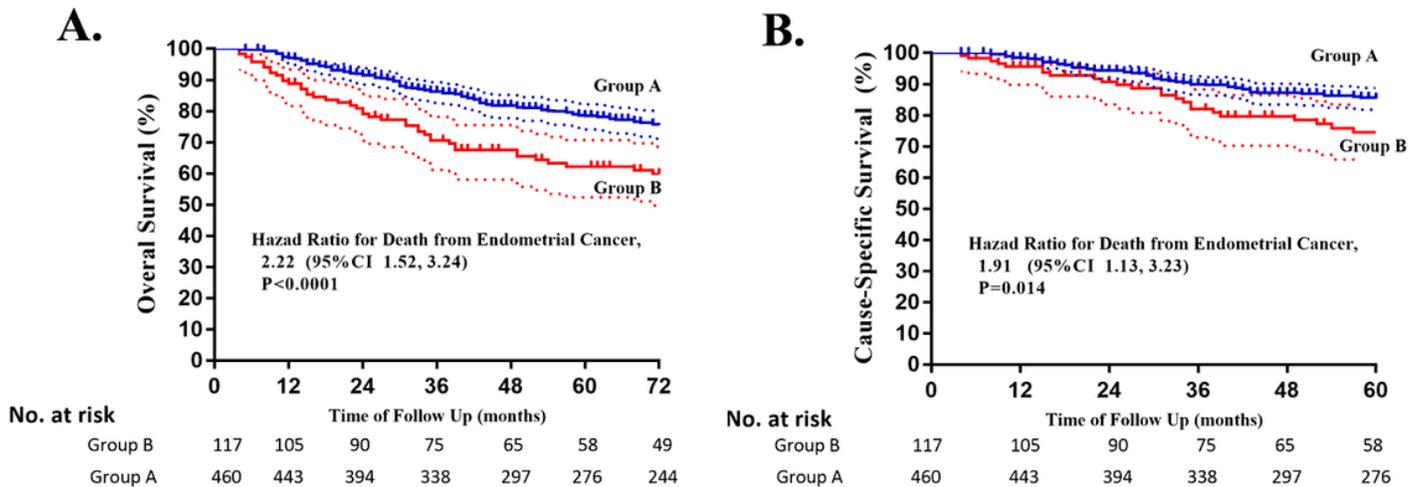


Figure 2

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

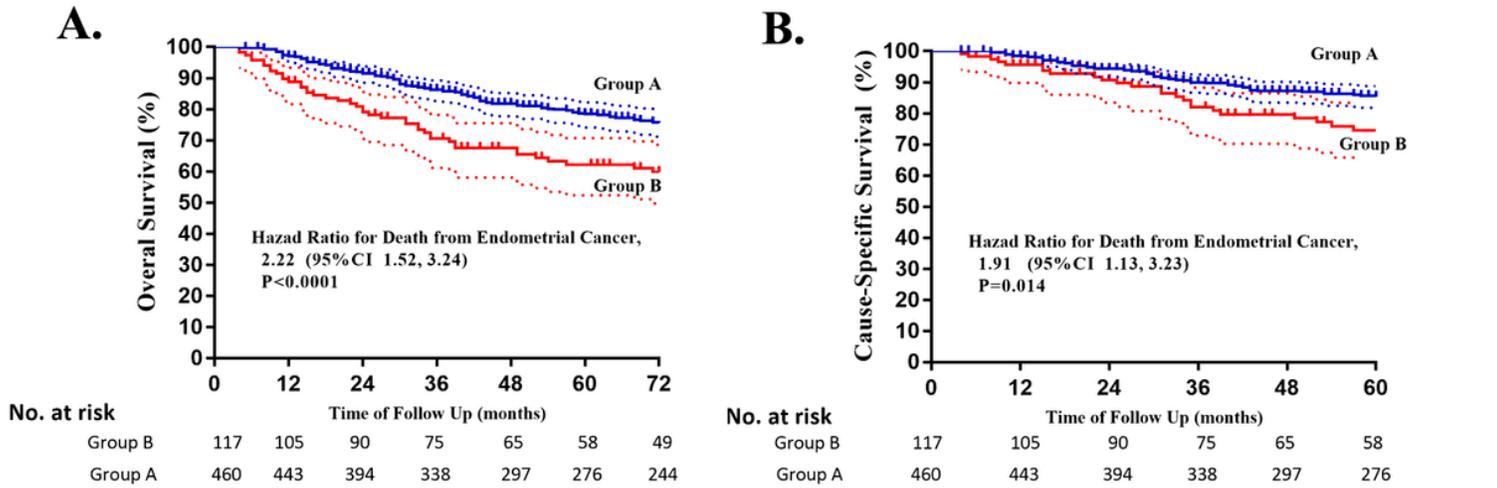


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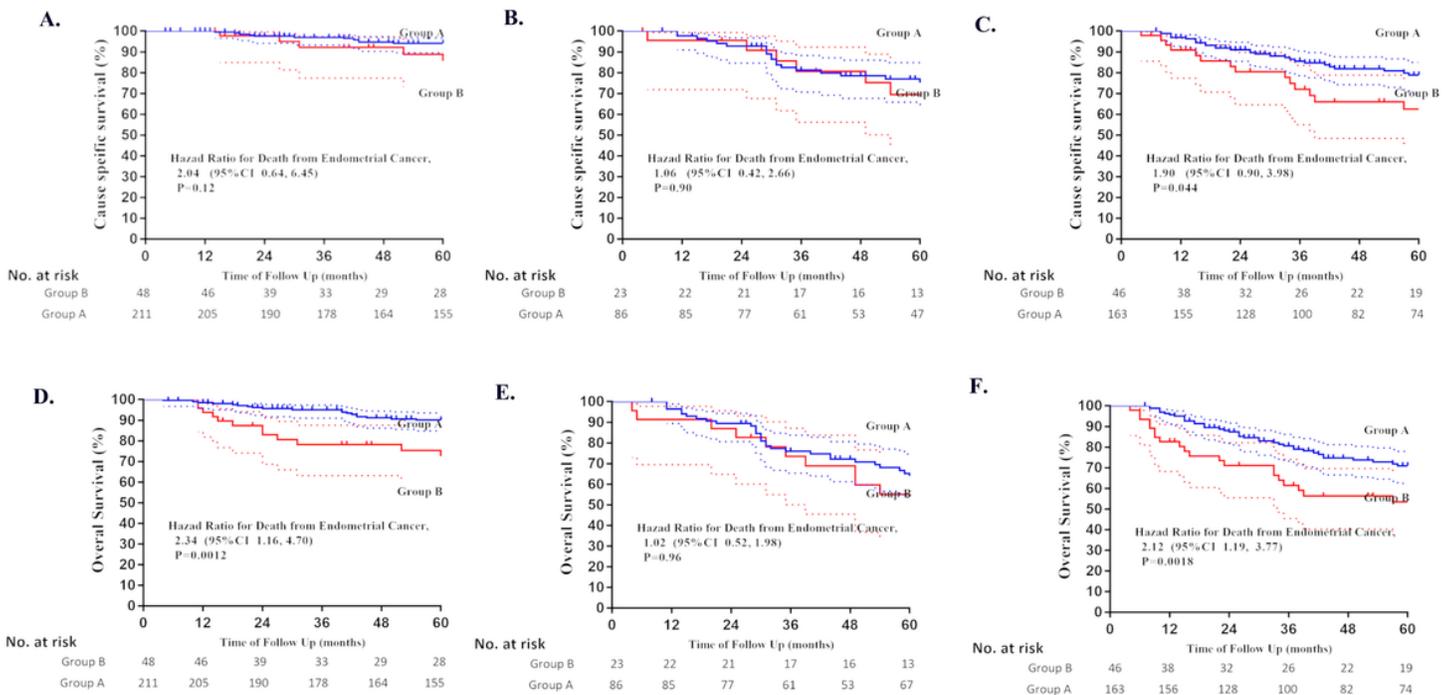


Figure 3

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

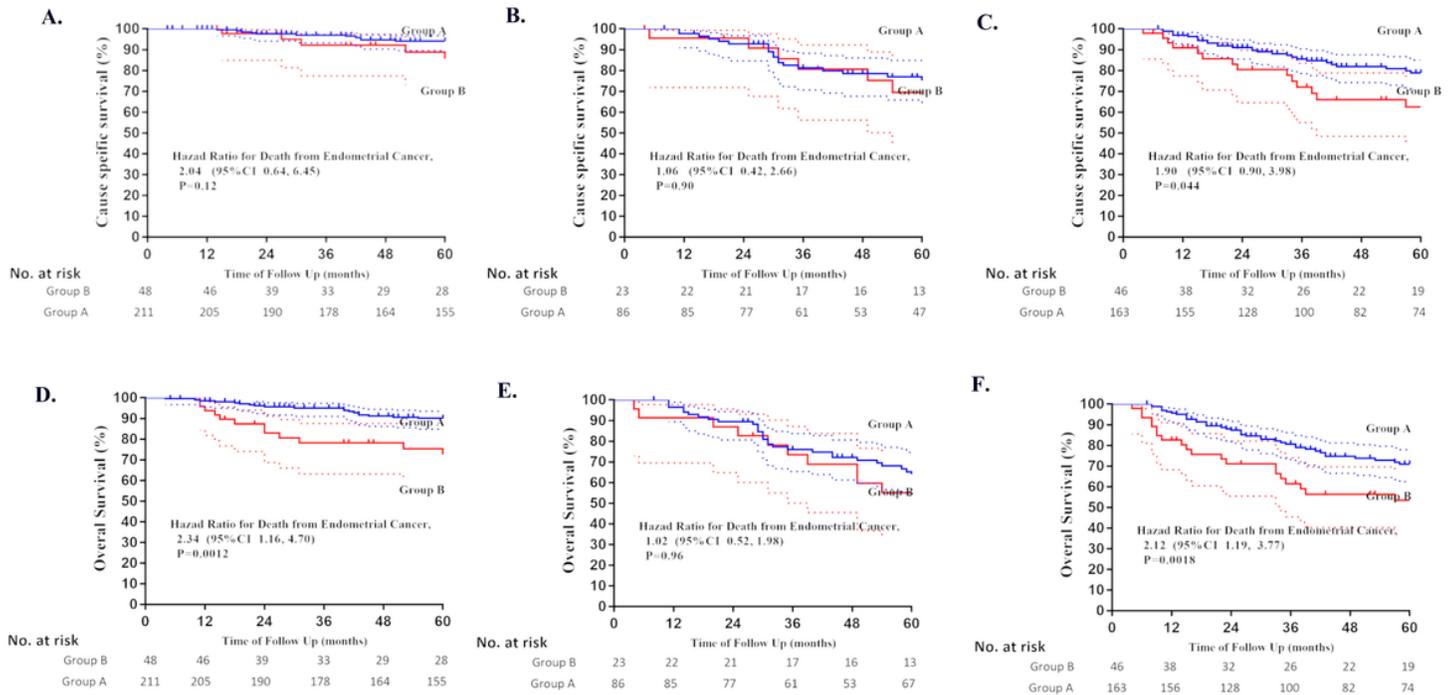


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