Ten-Year Results of Postoperative Adjuvant Treatment In Women With Stage I Endometrial Cancer

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Abstract

Background: It remains controversial whether postoperative adjuvant treatment is beneficial for the survival of patients after surgery for early-stage endometrial cancer. To evaluate whether postoperative adjuvant treatment is beneficial for the survival of patients after surgery for early-stage endometrial cancer. We analyzed the outcomes of patients treated with radiotherapy, chemotherapy, or progestagen combined with other adjuvant treatments.

Methods: We retrospectively examined disease-free survival (DFS), overall survival (OS) and high risk factors that affected the survival status of all patients who received different postoperative adjuvant therapies.

Results: The total relapse and mortality rates were 5.57% and 1.68%, respectively. During follow-up period, fourteen patients (7.29%) developed isolated local recurrence, and 2 patients died (1.04%) of recurrence. The 5-year DFS and OS rates in all patients were 95.83% and 93.75%, respectively. No significant differences were observed in the 5-year DFS, 5-year OS, OS, or DFS among the four groups of patients with FIGO stage I endometrial cancer. The differences in the log-rank test results of the estimates of the 5-year DFS, 5-year OS, DFS and OS of patients with different disease stages and different ages were all significant, but no differences were observed in these parameters between patients with varying degrees of differentiation. Histologic grade, CA125 level, ER and PR status and whether adjuvant therapies had no significant effect on the DFS and OS of all patients according to univariate and multivariate regression analyses, but age stratification did reveal significant differences in DFS and OS in the univariate and multivariate analyses.

Conclusion: This retrospective study showed that adjuvant treatments after surgery were not significantly associated with improved DFS or OS in patients with early-stage endometrial cancer. However, FIGO stage and age affected the survival of patients with stage I endometrial cancer.

Background

The worldwide incidence and mortality estimates for cancer of the corpus uteri were 382,069 and 89,929, respectively, in 2018, which suggests that the incidence of endometrial cancer has slightly increased since 1986 [1]. In China, 63,400 new cases of endometrial cancer and 21,800 deaths from this cancer type were reported in 2015 [2]. The standard therapy for early FIGO stage endometrial cancer with low-risk factors is operation, which has a five-year DFS rate of 95% [3]. Adjuvant therapy is regarded as the backbone of treatment for advanced endometrial cancer, but the optimal strategy to prevent recurrence and improve survival outcomes is still controversial, especially for early-stage endometrial cancer. Therefore, the selection of appropriate postoperative adjuvant therapy for patients with early-stage endometrial cancer is challenging.

Lympho-vascular space invasion (LVSI) was considered to be an independent prognostic factor for survival and recurrence, and it was shown to be related to lymphatic metastasis [4-6]. Patients with low

risk and low-intermediate risk factors do not need adjuvant treatment, as they would not derive a benefit. Moreover, the optimal adjuvant treatment is still controversial for patients with intermediate risk and high-intermediate risk factors. Although pelvic external-beam radiotherapy (EBRT) reduced the local recurrence rate after 15 years of follow-up, EBRT treatment of endometrial cancer is associated with lasting intestinal and urinary symptoms and role-physical functioning. Therefore, these data suggested that postoperative radiotherapy be avoided in patients with low- and intermediate-risk endometrial cancer [7]. Another randomized phase III trial randomly recruited 385 women to receive either pelvic radiation therapy or chemotherapy consisting of cisplatin/doxorubicin/cyclophosphamide. No significant differences were observed in the progression-free survival (PFS) or OS between two groups [8]. These findings supported the idea that the use of adjuvant radiotherapy does not improve disease-specific survival (DSS) or OS in women with stage I or IIA endometrial cancer.

In recent years, many doctors reconsider the use of chemotherapy in HIR stage I endometrial cancer patients despite the insufficiency of randomized data to support this. Chemotherapy may be an appropriate therapeutic option that can improve the outcomes of patients with risk factors (possibly improving PFS). Current NCCN guidelines recommend adjuvant chemotherapy for groups with a poor prognosis. The results of a Cochrane Collaboration meta-analysis suggested a small numerical benefit in PFS and OS after patients received platinum-based chemotherapy for endometrial cancer [9]. Of course, many scholars have expressed different viewpoints. According to a systematic review, adjuvant chemoradiotherapy had no advantage over radiotherapy alone for overall survival and failure-free survival in high-risk patients with FIGO stages I-II endometrial cancer [10]. Chemotherapy as an adjuvant treatment results in a benefit in terms of 5-year PFS, but not for OS, in early-stage EC with HIR factors [11]. Therefore, whether early-stage high-risk patients can benefit from adjuvant chemotherapy is worthy of further exploration.

The value of progestogenic agents in advanced endometrial carcinoma has been well demonstrated, while their role as adjuvant therapies in early-stage endometrial cancer is somewhat contentious. Some studies have shown that adjuvant progestagen therapy can reduce the recurrence and improve survival rate in patients with early endometrial cancer. In the 1970s and 1980s, several small studies suggested a survival benefit from progestagen in patients with endometrial cancer [12]. However, in observational studies, progestogens have been demonstrated to have a limited role in preventing recurrence compared with control treatments [13]. Four trials showed that the risk of death at five years between patients who received adjuvant progestagen therapy and those who received no further treatment was not significantly different. Importantly, in one study of patients with low-risk endometrial cancer, no difference was found in the risk of death in patients who did and did not receive progestogens, and an increased risk of death was observed in patients who were treated with progestogens compared with those who did not receive adjuvant progestagen treatment [14]. Since then, researchers have paid little attention to adjuvant endocrine therapy for early-stage endometrial cancer.

Therefore, the primary theme of this study was to retrospectively evaluate the oncologic outcomes and survival statuses associated with various postoperative adjuvant therapies and to assess the risk factors

that affect the status of women with stage I endometrial cancer.

Methods

Patients

We retrospectively patients treated for endometrial cancer at our hospital (one of the major tertiary referral hospitals in China) from 2006 to 2016, and 654 patients diagnosed with FIGO stage I-IV endometrial cancer were identified. The Ethics Committee of the Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, approved the study (TJ-IRB20210737). After diagnosis, all patients underwent either laparoscopic, open total hysterectomy or bilateral salpingo-oophorectomy with or without pelvic/para-aortic lymph node dissection and pelvic washing. Two gynecologic pathologists reviewed and confirmed the pathologic specimens. All patients were diagnosed as stage I endometrial cancer according to the revised FIGO staging criteria [15]. Surgical treatment was followed by adjuvant radiotherapy (RT) alone, chemotherapy (CT) alone, hormone therapy with other adjuvant treatments, or no further adjuvant treatment.

Adjuvant therapy after surgery

The selection of adjuvant therapy was at the discretion of the attending gynecological oncologist who managed the patient. Treatment of patients was performed according to international guidelines and included vaginal brachytherapy at a total dose of 45 Gray over 5 weeks. The chemotherapy regimen used at our institution during the study period was platinum-based chemotherapy, with paclitaxel (135-175 mg/m²) and carboplatin (AUC=5) given for two to four cycles every 3 weeks. Progestagen treatment was initiated 3 to 4 weeks after surgery or after other adjuvant treatments ended. The medroxyprogesterone acetate (MPA) dose was 250-500 mg administered once per day. This treatment was continued for 1 year.

Follow-up

Follow-up examinations were performed at either our institution or at hospitals local to the patients. All patients were followed-up after the completion of comprehensive treatment every 3 months for the first 2 years, every 6 months during the next 3 years, and then yearly thereafter during the study period. The oncological status of patients at the last medical visit was also assessed and determined to be either remission, recurrence or death.

Statistical analysis

SPSS 20.0 statistical software was used for the statistical analysis; the 'survival' package was utilized to apply complete survival analysis to the right-censored data, while the results were visualized with the 'survminer' package. The univariate comparison of the four groups was summarized by descriptive statistics and tested by Fisher's exact method. The count data were expressed as N (%), and the chi-square test was used to analyze differences between groups. The measurement data were expressed as x

± s, and variance analysis was used to test for differences between groups. The log-rank test was used for single-factor analysis of OS or DFS, and the Cox proportional risk model was used for multifactor analysis. The statistical significance threshold was $p < 0.05$.

Results

Patients and tumor characteristics

In all, 339 patients were successfully followed-up, whereas 315 patients were lost to follow-up after treatment. Overall, 147 patients with advanced-stage disease (II to IV) were excluded from this study. Finally, 192 patients were enrolled in the retrospective analysis. The women were then divided into five groups [A group (45.83%), non-adjuvant treatment; B group (5.73%), radiotherapy; C group (34.38%), chemotherapy; and D group (14.06%), MPA alone or combined with chemotherapy or radiotherapy]. Eleven patients and 66 patients received radiotherapy and chemotherapy, respectively. Twenty patients received adjuvant hormone therapy alone, and 7 patients received MPA combined with other adjuvant treatments (5 patients received chemotherapy and 2 patients received radiotherapy). The remaining 88 patients did not receive adjuvant treatment after surgery (Figure. 1).

The baseline characteristics of all patients are summarized in Table 1. The median follow-up for all patients was 51 months (range: 18-143). No significant difference was found among the four groups in terms of age, histologic subtype, ER expression or CA125 level in the serum. A few patients were diagnosed with rare pathological types, such as adenocarcinoma (endocervical type), adenocarcinoma/clear cell carcinoma, clear cell carcinoma, serous papillary carcinoma, mucinous papillary adenocarcinoma of the intestinal epithelium, and papillary adenocarcinoma (villous-tubular carcinoma subtype). The proportions of these rare subtypes did not differ among the groups. In addition, we found that histologic grade, FIGO stage and PR expression differed among the four groups ($p = 0.0005$, $p = 0.0112$ and $p = 0.0064$). Among 192 patients, 168 (87.5%) underwent pelvic lymphadenectomy, and 11.46% (22/192) underwent pelvic and para-aortic lymphadenectomy. No difference was found in the proportion of lymphadenectomy among the four groups ($p = 0.9688$ and $p = 0.4211$).

Table 1: Patient and tumor characteristics

Characteristic	A group	B group	C group	D group	<i>p</i> -value
N	88	11	66	27	
Age (%)					0.2823
<60 y	69 (78.41)	7 (63.64)	55 (83.33)	24 (88.89)	
≥60 y	19 (21.59)	4 (36.36)	11 (16.67)	3 (11.11)	
Histologic type (%)					0.7971
Adenocarcinoma	81 (92.04)	11 (100)	62 (93.93)	27 (100)	
Adenocarcinoma (endocervical type)	3 (3.41)	0 (0)	0 (0)	0 (0)	
Adenocarcinoma/Clear cell carcinoma	1 (1.14)	0 (0)	2 (3.03)	0 (0)	
Clear cell carcinoma	0 (0)	0 (0)	1 (1.52)	0 (0)	
Mucinous papillary adenocarcinoma of intestinal epithelium	1 (1.14)	0 (0)	0 (0)	0 (0)	
Papillary adenocarcinoma (villous-tubular carcinoma subtype)	0 (0)	0 (0)	1 (1.52)	0 (0)	
Serous papillary carcinoma	2 (2.27)	0 (0)	0 (0)	0 (0)	
Histologic grade (%)					0.0005*
G1	64 (72.73)	4 (36.36)	26 (39.40)	20 (74.07)	
G2	17 (19.32)	5 (45.45)	30 (45.45)	5 (18.52)	
G3	3 (3.41)	2 (18.18)	8 (12.12)	2 (7.41)	
Unknown	4 (4.54)	0 (0)	2 (3.03)	0 (0)	
FIGO stage (%)					0.0112*
IA	80 (90.91)	7 (63.64)	49 (74.24)	23 (85.19)	
IB	8 (9.09)	4 (36.36)	17 (25.76)	4 (14.81)	
Lymphadenectomy					
Pelvic lymph node	62 (70.45)	9 (81.82)	54 (81.82)	21 (77.78)	0.9688
Pelvic lymph + para-aortic node	12 (12.5)	1 (0.91)	8 (12.12)	1 (3.7)	0.4211
CA125					0.395

<35 U/ml	40 (45.45)	6 (54.55)	35 (53.03)	10 (37.04)
≥35 U/ml	11 (12.50)	2 (18.18)	6 (9.09)	1 (3.70)
Unknown	37 (42.05)	3 (27.27)	25 (37.88)	16 (59.26)
ER (%)	0.0743			
+	48 (54.55)	10 (90.91)	49 (74.24)	17 (62.97)
-	8 (9.09)	0 (0)	6 (9.09)	1 (3.70)
Unknown	32 (36.36)	1 (9.09)	11 (16.67)	9 (33.33)
PR (%)	0.0064*			
+	41 (46.59)	7 (63.64)	45 (68.18)	18 (66.67)
-	15 (17.05)	3 (27.27)	9 (13.64)	0 (0)
±	0 (0)	0 (0)	1 (1.52)	0 (0)
Unknown	32 (36.36)	1 (9.09)	11 (16.66)	9 (33.33)

A group, no adjuvant treatment; B group: radiotherapy; C group, chemotherapy; D group, MPA+ chemotherapy (or) radiotherapy. Abbreviations: FIGO, International Federation of Gynecology and Obstetrics; ER, estrogen receptor; PR, progesterone receptor.

Survival outcomes

The total relapse and mortality rates of all 192 patients were 5.57% and 1.68%, respectively. During the follow-up period, 14 patients (7.29%) developed isolated local recurrence, and 2 patients (1.04%) died of recurrence. The 5-year OS and DFS rates of all patients were 93.75% and 95.83%, respectively. In this study, the log-rank test was used to test the significance of different treatments. No statistically significant differences were observed in the 5-year DFS, 5-year OS, OS, or DFS among the four groups of patients with stage I endometrial cancer ($p=0.9849$, 0.7430 , 0.9754 and 0.4534) (Figure. 2). This result suggested that adjuvant chemotherapy, radiotherapy or hormone therapy + chemotherapy/radiotherapy after surgery did not improve the DFS and OS rates of patients with stage I endometrial cancer.

Not all types of postoperative adjuvant treatment are conducive to survival. Therefore, we analyzed the influence of stage, age and tumor differentiation on the 5-year DFS, 5-year OS, DFS and OS of early endometrial cancer patients. The differences in log-rank tests of the estimates of 5-year DFS, 5-year OS,

DFS and OS between stage IA and stage IB were all significant (hazard ratio, 0.1062, 95% CI, 0.0210–0.5366, $p = 0.0046$; hazard ratio, 0.0566, 95% CI, 0.078–0.4047, $p = 0.0043$; hazard ratio, 0.1062, 95% CI, 0.0273–0.6303, $p = 0.0112$; and hazard ratio, 0.0866, 95% CI, 0.0163–0.4584, $p = 0.0040$, respectively), which is similar to the pattern seen between different age groups in 5-year DFS, 5-year OS, DFS and OS (hazard ratio, 0.0838, 95% CI, 0.0181–0.3895, $p = 0.0039$; hazard ratio, 0.0372, 95% CI, 0.0058–0.2390, $p = 0.0011$; hazard ratio, 0.1203, 95% CI, 0.0279–0.5182, $p = 0.0040$; and hazard ratio, 0.0478, 95% CI, 0.0092–0.2478, $p = 0.0004$, respectively). It is worth mentioning that the 5-year DFS, 5-year OS, DFS and OS rates were not different between the different tumor differentiation groups ($p = 0.5952$, 0.6475, 0.5669 and 0.6200) (Figure. 3 and Figure. 4).

The clinical factors that affect survival status

To assess the risk factors that affect the survival status of women with stage I endometrial cancer, we performed a univariate analysis of different variables. The log-rank test (time series test) was used for the univariate analysis to analyze the impact of various factors on prognosis. Histologic grade, estrogen receptor status, progesterone receptor status and CA125 level were not associated with significant differences in DFS and OS (log-rank, $p = 0.6946$, 0.9199, 0.9347 and 0.3272), but patient age was associated with prognosis (log-rank, $p = 0.0045$ for DFS and 0.0003 for OS) (Table 2).

Table 2: Univariate analysis for risk factors affecting the survival status of women with stage I endometrial cancer

Parameter	Disease-Specific Survival		Overall survival	
	Chi-square	<i>p</i> -value	Chi-square	<i>p</i> -value
Age	8.0783	0.0045*	13.1273	0.0003*
Histologic grade	1.5171	0.6783	1.4468	0.6946
ER status	0.6729	0.7143	0.1670	0.9199
PR status	0.0054	0.9973	0.1350	0.9347
CA125	1.1792	0.2775	0.9601	0.3272
Adjuvant treatment	0.2145	0.9752	0.4775	0.9238

Furthermore, a Cox proportional hazard model was used for the multivariate regression analysis to determine the risk factors that affect the DFS or OS of stage I endometrial cancer patients. Six factors (age, histologic grade, ER status, PR status, CA125 level and adjuvant treatment) were introduced into the Cox model as independent variables. At a threshold of $p < 0.05$, no significant difference was found in prognosis among different histologic grades, ER and PR statuses, CA125 level and adjuvant treatment status (Table 3). However, age affected DFS and OS in early-stage endometrial cancer [HR (95% CI): 6.119 (1.502–24.924), $p = 0.0115$; and HR (95% CI): 9.088 (2.012–41.058), $p = 0.0041$].

Table 3: Multivariate analysis of risk factors affecting the DFS and OS status in women with stage I endometrial cancer

Parameter	Disease-specific survival		Overall survival	
	HR (95% CI)	<i>p</i> -value	HR (95% CI)	<i>p</i> -value
Age	6.119 (1.502-24.924)	0.0115*	9.088 (2.012-41.058)	0.0041*
Histologic grade	0.335 (0.079-1.412)	0.1361	0.49 (0.11-2.186)	0.3501
ER	0.133 (0.009-1.913)	0.138	0.227 (0.011-4.551)	0.3325
PR	0.974 (0.062-15.207)	0.9848	1.366 (0.063-29.5)	0.8424
CA125	-	0.9952	-	0.9961
Adjuvant treatment	1.513 (0.769-2.976)	0.2302	1.651 (0.828-3.294)	0.1547

Discussion

As China has become an aging society, the number of women who experience obesity and the incidence of EC have proportionally increased. Approximately 80% of endometrial cancers are hormone receptor-positive endometrioid adenocarcinomas. Most endometrioid carcinomas are well to moderately differentiate [16]. The percentages of patients with G1-G2 and G3 were 89% and 11%, respectively. The clinical data of this study are consistent with the literature and suggest that approximately 10% of endometrial cancers are type 2 (high-grade) lesions. Up to 40% of nonendometrioid endometrial cancers are mixed with an endometrioid component [17]. In our study, a few cases were diagnosed with rare pathological types, such as the endocervical type, clear cell carcinoma, mucinous papillary adenocarcinoma of the intestinal epithelium, the villous-tubular carcinoma subtype and serous papillary carcinoma. Since the number of cases was small, it was difficult to evaluate the prognosis of these subtypes and their impact on the results of this study.

Whether adjuvant therapy should be given after operation for early endometrial cancer is controversial. In one randomized trial, patients received postoperative radiotherapy and were given intravenous doxorubicin or no further treatment after surgery if the nodes were positive. NCCN guidelines recommend that complementary radiotherapy or systemic therapy be considered if patients have potential high risk factors including: age $\geq$ 60 years, deep myometrial invasion and / or LVSI [18]. Patients with focal or substantial LVSI received different adjuvant treatments according to a three-tiered system that quantitates LVSI. On the contrary, the presence of LVSI is associated with a high risk of mortality in patients with early-stage well-differentiated endometrial carcinoma [19]. No difference was found in the survival rates between groups after a 5-year follow-up [20]. The current retrospective study revealed no statistically significant differences in the 5-year DFS, 5-year OS, OS, or DFS across the four groups of

stage I endometrial cancer patients. Similar results were observed in two randomized trials (GOG-99 and PORTEC-1) and a retrospective study, which suggested no overall survival advantage of adjuvant radiation in patients with stage I, high-intermediate risk cancer [21-23]. In contrast, 50% of the 192 patients presented to our hospital for secondary surgery or further follow-up treatment after their first surgery, which was performed at other hospitals. As the LVSI status of these patients was unknown, we could not evaluate this factor.

A review from 2010 found no evidence that endocrine therapy improved survival in endometrial cancer [24]. In a few studies, researchers reported that adjuvant endocrine therapy may provide a benefit in terms of delaying recurrence or prolonging survival of patients with early endometrial cancer [25]. However, most randomized trials of adjuvant progestagen therapy have failed to show any advantage in endometrial cancer, and data have even revealed that death due to cardiovascular disease tended to be higher in the progestagen group than in the control group [26-28]. These findings are consistent with our results. Postoperative adjuvant chemotherapy is often recommended for high-risk stage I endometrial cancer. In our study, carboplatin plus paclitaxel was adopted as postoperative adjuvant chemotherapy in many patients with stage I disease. The data suggested that women gain little benefit from adjuvant chemotherapy, including women with high risk factors, such as deep myometrial invasion and the serous or clear cell histologic type. Indeed, many studies have demonstrated that adjuvant chemotherapy for high-risk endometrial cancer does not improve survival rates [29-30]. However, the results of randomized trials have varied, and some previous studies have suggested that adjuvant chemotherapy after surgery is beneficial for early-stage EC with HIR factors.³¹ Furthermore, two retrospective studies showed that adjuvant platinum-based chemotherapy plus vaginal brachytherapy (VBT) achieved excellent results in high-risk early-stage endometrial cancer [32-33]. However, we were unable to confirm this result because this retrospective study contained no such cases.

According to our retrospective observations, the differences in DFS and OS were significant between stage IA and stage IB. That is, even in early endometrial cancer, the FIGO stage still affects the DFS and OS of endometrial cancer patients. Moreover, it was found that age (< 60 years and ≥ 60 years) was another factor that influences the prognosis of patients with early-stage endometrial cancer. Notably, according to both the univariate and multivariate analyses, ER status, PR status, CA125 level, histologic grade and the type of adjuvant therapy did not affect PFS or OS in FIGO stage I endometrial cancer patients in our study, but age was associated with differences in OS and PFS. Many physicians have verified that the cancer antigen 125 (CA125) level, age older than 60 years, and depth of myometrial invasion $> 50\%$ were significant factors for overall survival in a retrospective study [34]. Age > 60 years (or > 50 years) and degree of differentiation may be high-intermediate risk factors according to a systematic review of guidelines in the US [35]. Among all the factors analyzed in our study, age was the only indicator that independently affected OS and DFS in stage I endometrial cancer. Due to incomplete data on lymph node metastasis in this study, it was not possible to analyze this factor and its impact on survival status.

The goal of adjuvant therapy in endometrial cancer is to reduce the risk of disease recurrence, and whether postoperative adjuvant therapy should be used for early endometrial cancer is controversial. Our results agree with the above findings and suggest that postoperative adjuvant treatments are not associated with better OS or DFS in patients with either FIGO stage IA or stage IB endometrial cancer. All the above evidence seems to support the conclusion that women do not gain a survival advantage from postoperative adjuvant therapy after operation for stage I endometrial cancer regardless of the disease stage (IA and IB). Nevertheless, our study still has some shortcomings. It is limited by its retrospective nature, the heterogeneity of the data and the reliance on clinical endometrial cancer data not originally collected for research purposes. Also, it was limited by single-center experience and the potential selection bias, which may limit its external validity. And our results may not represent the findings of other hospitals.

Therefore, it is necessary to further discuss the benefits and disadvantages of adjuvant endocrine therapy, chemotherapy and radiotherapy as well as major risk factors for early endometrial cancer. In the future, it will be possible to achieve the goal of personalized treatment for individual patients.

Abbreviations

FIGO: International Federation of Gynecology and Obstetrics; ER: estrogen receptor; PR: progesterone receptor; DFS: disease-free survival; OS: overall survival; LVSI: Lympho-vascular space invasion; EBRT: external-beam radiotherapy; disease-specific survival (DSS) ; MPA: medroxyprogesterone acetate

Declarations

Ethics approval and consent to participate

The Ethics Committee of the Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology approved the study (No: TJ-IRB20210737). The Ethics Committee does not require written or verbal informed consent for retrospective studies and was, thus, not sought after. The study was conducted ethically in accordance with the 2013 Helsinki World Medical Association Declaration.

Consent for publication

Not applicable.

Availability of data and materials

The data used and analysed during the study will be made available upon reasonable request made through the corresponding author.

Competing interests

All authors declare that there are no conflicts of interests.

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Authors' contributions

Conceived the experiment: RL. Analysed the data: RL and PF. Wrote the first draft of the manuscript: RL and PF. Assisted with the data analysis: SW and PF. Agree with the manuscript results and conclusions: PF, TZ, PC, SW and RL. All authors reviewed the manuscript.

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References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2018;68:394–24.
2. Chen W, Zheng R, Baade PD, Zhang S, Zeng H, Bray F, et al: Cancer statistics in China, 2015. *CA Cancer J Clin* 2016;66:115–32.
3. Tangjitgamol S, Manusirivithaya S, Lertbutsayanukul C: Adjuvant therapy for early-stage endometrial cancer: a review. *Int J Gynecol Cancer* 2007 17: 949–56.
4. Jorge S, Hou JY, Tergas AI, Burke WM, Huang Y, Hu JC, et al: Magnitude of Risk for Nodal Metastasis Associated with Lymphovascular Space Invasion for Endometrial Cancer. *Gynecol Oncol* 2016;140:387-93.
5. Ureyen I, Karalok A, Turkmen O, Kimyon G, Akdas YR, Akyol A, et al: Factors predicting recurrence in patients with stage IA endometrioid endometrial cancer: what is the importance of LVSI? Factors predicting recurrence in patients with stage IA endometrioid endometrial cancer: what is the importance of LVSI? *Arch Gynecol Obstet* 2020;301:737-44.
6. Harris KL, Maurer KA, Jarboe E, Werner TL, Gaffney D: LVSI positive and NX in early endometrial cancer: Surgical restaging (and no further treatment if N0), or adjuvant ERT? LVSI positive and NX in early endometrial cancer: Surgical restaging (and no further treatment if N0), or adjuvant ERT? *Gynecol Oncol* 2020;156:243-50.
7. Nout RA, van de Poll-Franse LV, Lybeert ML, Wárlám-Rodenhuis CC, Jobsen JJ, Mens JW, et al: Long-term outcome and quality of life of patients with endometrial carcinoma treated with or without pelvic radiotherapy in the post operative radiation therapy in endometrial carcinoma 1 (PORTEC-1) trial. *J Clin Oncol* 2011;29:1692-700.
8. Susumu N, Sagae S, Udagawa Y, Niwa K, Kuramoto H, Satoh S, et al: Randomized phase III trial of pelvic radiotherapy versus cisplatin-based combined chemotherapy in patients with intermediate-

- and high-risk endometrial cancer: a Japanese Gynecologic Oncology Group study. *Gynecol Oncol* 2008;108:226–33.
9. Galaal K, Al Moundhri M, Bryant A, Lopes AD, Lawrie TA: Adjuvant chemotherapy for advanced endometrial cancer. *Cochrane Database Syst Rev* 2014;5:CD010681.
 10. Jingjing H, Rui J, Hui P. Adjuvant chemoradiotherapy vs. radiotherapy alone in early-stage high-risk endometrial cancer: a systematic review and meta-analysis. *Eur Rev Med Pharmacol Sci* 2019;23:833-40.
 11. Helpman L, Perri T, Lavee N, Hag-Yahia N, Chariski HA, Kalfon S, et al: Impact of adjuvant treatment on outcome in high-risk early-stage endometrial cancer: a retrospective three-center study. *Int J Gynecol Cancer* 2019;29:133-39.
 12. Kauppila A. Progestin therapy of endometrial, breast and ovarian carcinoma. A review of clinical observations. *Acta Obstet Gynecol Scand* 1984;63:441-50.
 13. COSA-NZ-UK Endometrial Cancer Study Groups. Adjuvant medroxyprogesterone acetate in high-risk endometrial cancer. *Int J Gynecol Cancer* 1998;8:387–91.
 14. Vitale SG, Rossetti D, Tropea A, Biondi A, Laganà AS: Fertility sparing surgery for stage IA type I and G2 endometrial cancer in reproductive-aged patients: evidence-based approach and future perspectives. *Updates Surg* 2017;69:29–34.
 15. Amant F, Moerman P, Neven P, Timmerman D, Van Limbergen E, Vergote I: Endometrial cancer. *Lancet* 2005;366:491–505.
 16. Slomovitz BM, Burke TW, Eifel PJ, Ramondetta LM, Silva EG, Jhingran A, et al: Uterine papillary serous carcinoma (UPSC): a single institution review of 129 cases. *Gynecol Oncol* 2003;91:463–69.
 17. Morrow CP, Bundy BN, Homesley HD, Creasman WT, Hornback NB, Kurman R, et al: Doxorubicin as an adjuvant following surgery and radiation therapy in patients with high-risk endometrial carcinoma, stage I and occult stage II: a Gynecologic Oncology Group Study. *Gynecol Oncol* 1990;36:166–71.
 18. Keys HM, Roberts JA, Brunetto VL, Zaino RJ, Spirtos NM, Bloss JD, et al: A phase III trial of surgery with or without adjunctive external pelvic radiation therapy in intermediate risk endometrial adenocarcinoma: a Gynecologic Oncology Group study. *Gynecol Oncol* 2004;92:744–51.
 19. Creutzberg CL, van Putten WL, Koper PC, Lybeert ML, Jobsen JJ, Wárlám-Rodenhuis CC: Surgery and postoperative radiotherapy versus surgery alone for patients with stage-1 endometrial carcinoma: multicentre randomised trial. PORTEC Study Group. Post Operative Radiation Therapy in Endometrial Carcinoma. *Lancet* 2000;355:1404–11.
 20. Suidan RS, He W, Sun CC, Zhao H, Smith GL, Klopp AH, et al: National trends, outcomes, and costs of radiation therapy in the management of low- and high-intermediate risk endometrial cancer. *Gynecol Oncol* 2019;152:439–44.
 21. Kokka F, Brockbank E, Oram D, Gallagher C, Bryant A: Hormonal therapy in advanced or recurrent endometrial cancer. *Cochrane Database Syst. Rev* 2010;CD007926.
 22. Urbański K, Karolewski K, Kojs Z, Klimek M, Dyba T: Adjuvant progestagen therapy improves survival in patients with endometrial cancer after hysterectomy. Results of one-institutional prospective

- clinical trial. *Eur J Gynaecol Oncol* 1993;14:Suppl: 98–104.
23. DePalo G, Mangioni C, Periti P, Del Vecchio M, Marubini E: Treatment of FIGO (1971) stage I endometrial carcinoma with intensive surgery, radiotherapy and hormonotherapy according to pathological prognostic groups. Long-term results of a randomised multicentre study. *European Journal of Cancer* 1993;29A:1133–40.
 24. Lewis GC, Slack NH, Mortel R, Bross ID: Adjuvant progestogen therapy in the primary definitive treatment of endometrial cancer. *Gynecologic Oncology* 1974;2:368–76.
 25. Kneale BL, Quinn MA, Rennie GC: A randomised trial of progestagens in the primary treatment of endometrial carcinoma. *Br J Obstet Gynaecol* 1988;95:828.
 26. Malkasian G, Decker D. Aduvant progesterone therapy for stage 1 endometrial cancer. *Int J Gynaecol Obstet* 1978;16:48–9.
 27. de Boer SM, Powell ME, Mileschkin L, Katsaros D, Bessette P, Haie-Meder C, et al: Adjuvant chemoradiotherapy versus radiotherapy alone for women with high-risk endometrial cancer (PORTEC-3): final results of an international, open-label, multicentre, randomised, phase 3 trial. *Lancet Oncol* 2018;19:295–309.
 28. Maggi R, Lissoni A, Spina F, Melpignano M, Zola P, Favalli G, et al: Adjuvant chemotherapy vs radiotherapy in high-risk endometrial carcinoma: results of a randomised trial. *Br J Cancer* 2006;95:266–71.
 29. Gao M, Zhang N, Song N, Zheng H, Yan X, Gao Y: Chemotherapy as Adjuvant Treatment for Early Stage Endometrial Cancer With High Intermediate Risk Factors. *Int J Gynecol Cancer* 2018;28:1285-89.
 30. Yi L, Zhang H, Zou J, Luo P, Zhang J: Adjuvant chemoradiotherapy versus radiotherapy alone in high-risk endometrial cancer: A systematic review and meta-analysis. *Gynecol Oncol* 2018;149:612–19.
 31. Laliscia C, Cosio S, Morganti R, Mazzotti V, Fabrini MG, Paia F, et al: Patterns of Failures and Clinical Outcome of Patients with Early-Stage, High-Risk, Node-Negative Endometrial Cancer Treated with Surgery Followed by Adjuvant Platinum-Based Chemotherapy and Vaginal Brachytherapy. *Oncology* 2019;96:235-41.
 32. Lin YJ, Hu YW, Twu NF, Liu YM: The role of adjuvant radiotherapy in stage I endometrial cancer: A single-institution outcome. *Taiwan J Obstet Gynecol* 2019;58:604-09.
 33. Latif NA, Haggerty A, Jean S, Lin L, Ko E: Adjuvant therapy in early-stage endometrial cancer: a systematic review of the evidence, guidelines, and clinical practice in the U.S. *Oncologist* 2014;19:645-53.
 34. Abu-Rustum NM et al: National comprehensive cancer network guidelines. *Uterine neoplasms* (version 1.2020). 2020;Accessed March 06.
 35. O'Brien DJ, Flannelly G, Mooney EE, Foley M: Lymphovascular space involvement in early stage well-differentiated endometrial cancer is associated with increased mortality. *BJOG* 2009;116:991-94.

Figures

Figure 1

Retrospective study flow diagram

Figure 2

Kaplan-Meier estimates of the 5-year disease-specific survival, 5-year overall survival, overall survival and disease-specific survival among the four groups. Disease-free survival (A) and overall survival (B) after treatment with chemotherapy, radiotherapy or MPA+radiotherapy/chemotherapy. Patients who received no adjuvant treatment after surgery served as controls. The corresponding p-values in panels A-D are 0.9849, 0.7430, 0.9754 and 0.4534, respectively. Tick marks indicate censored data.

Figure 3

Estimates of the 5-year disease-free survival and 5-year overall survival in all patients by FIGO stage, age and degree of differentiation. Kaplan-Meier survival curves for the 5-year disease-free survival (A and C) and 5-year overall survival (B and D) by FIGO stage and age. [A, HR (95% CI): 0.1062 (0.0210- 0.5366), p=0.0046; B, HR (95% CI): 0.0566 (0.078-0.4047), p=0.0043; C, HR (95% CI): 0.0838 (0.0181- 0.3895), p=0.0039; and D, HR (95% CI): 0.0372 (0.0058-0.2390), p=0.0011]. Panels E and F show disease-free survival and overall survival according to different degrees of differentiation, respectively (E: p=0.5952; F: p=0.6475). Tick marks indicate censored data.

Figure 4

Disease-free survival and overall survival of all patients by FIGO stage, age and histologic grade. Kaplan-Meier survival curves for disease-free survival (A) and overall survival (B) by FIGO stage in all patients who received with different adjuvant treatments compared with patients who received no adjuvant treatment. Tick marks indicate censored data [A, HR (95% CI): 0.1314 (0.0273-0.6303), *p* = 0.0112; and B, HR (95% CI): 0.0866 (0.0163–0.4584), *p* = 0.0040]. DFS (C) and OS (D) by age [C, HR (95% CI): 0.1203 (0.0279–0.5182), *p* = 0.0040; and D, HR (95% CI): 0.0478 (0.0092–0.2478), *p* = 0.0004]. Panels E and F

show the DFS and OS, respectively, according to different degrees of differentiation (E: $p = 0.5669$; and F: $p = 0.6200$).