



Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

The role of adjuvant radiotherapy in stage I endometrial cancer: A single-institution outcome

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ARTICLE INFO

Article history:
Accepted 11 April 2019

Keywords:
Endometrial neoplasms
Radiotherapy
Adjuvant

ABSTRACT

Objective: Postoperative radiotherapy for early endometrial cancer has been investigated in several randomized trials. These trials demonstrate that it reduces loco-regional recurrence, but has no impact on overall survival. The aims of this study were to better understand the role of adjuvant radiotherapy and determine predictors for loco-regional recurrence or development of distant metastasis.

Materials and methods: A retrospective medical records review was performed on patients with surgical stage I endometrial cancer treated at Taipei Veterans General Hospital between 2006 and 2013. Multi-variable analysis was conducted using Cox regression for prognostic predictors.

Results: A total of 337 patients were identified. The estimated five-year overall survival and loco-regional recurrence-free survival were 96.3% and 97.9% in the non-radiotherapy group, and 91.6% and 97.1% in the radiotherapy group ($p = 0.06$ overall survival, $p = 0.956$ loco-regional recurrence-free survival). Multi-variable analysis revealed that elevated preoperative serum Cancer Antigen 125 (CA-125) level (hazard ratio (HR) = 2.54), age older than 60 years old (HR = 3.34), and depth of myometrial invasion > 50% (HR = 3.37) were significant factors in overall survival. Elevated preoperative CA-125 level (HR = 5.37), age older than 60 years (HR = 6.57), positive lymphovascular space invasion (HR = 50.20), and adjuvant radiotherapy (HR = 0.05) were independent predictors of loco-regional recurrence-free survival. For distant metastasis, deep myometrial invasion was a significant risk factor.

Conclusions: Postoperative radiotherapy delivery is an independent predictor for loco-regional recurrence-free survival but has no impact on overall survival in this population. Preoperative CA-125 level is a risk factor for loco-regional recurrence, and deep myometrial invasion was correlated with distant metastasis.

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Introduction

Endometrial cancer is a common gynecologic malignancy. According to the Taiwan Cancer Registry annual report in 2015, endometrial cancer was the sixth most common malignancy of female cancer, and the thirteenth leading cause of cancer death. The age-adjusted annual incidence was 14.14 per million women, and the median age of diagnosis was 55 years old [1].

Most endometrial cancers are diagnosed at stage I disease [2]. Ninety percent of the tumors are endometrioid adenocarcinoma

[3]. The prognosis is favorable, with a five-year recurrence-free survival of approximately 90% [4]. The primary treatment for stage I disease is surgery including a hysterectomy, bilateral salpingo-oophorectomy and lymph nodes assessment.

The role of adjuvant postoperative radiation has been investigated in two randomized trials. In the first Post Operative Radiation Therapy in Endometrial Carcinoma (PORTEC-1) trial, 714 patients with the International Federation of Gynecology and Obstetrics (FIGO 1988) stage I, grade 1 with deep ($\geq 50\%$) myometrial invasion, grade 2 with any invasion, or grade 3 with superficial ($< 50\%$) invasion were randomized to receive either pelvic external beam radiotherapy (EBRT) or observation. All histological types of endometrial tumors were included in the study. The authors concluded that EBRT reduced the risk of loco-regional recurrence from 14% to 4% but had no impact on overall survival [5]. In addition, the result

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was not implied for superficially invasive grade 2 diseases and for patients younger than 60 years. The Gynecological Oncology Group (GOG) 99 trial followed a similar study design (6). Three hundred and ninety-two women with surgically staged FIGO IB, IC, and II (occult) endometrial adenocarcinoma were analyzed. The study showed that whole pelvic radiation lowered the risk of recurrence by 58%, while overall survival was not significantly improved (92% in radiotherapy (RT) group and 86% in control group). Because the largest reduction of recurrence was the in high-intermediate-risk group (as defined by the study), the trial suggested that adjuvant EBRT should be limited to those patients who fit the criteria risk factors.

The PORTEC-2 trial investigated the outcomes of vaginal brachytherapy (VBT) and EBRT in high-intermediate risk patients. The study demonstrated that the five-year vaginal recurrence rate was less than 2%, and there was no significant difference in five-year loco-regional recurrence [7]. The survival benefits of using VBT in intermediate-risk or high-risk stage I patients remains controversial [3].

A retrospective study reported that surgical-pathological prognostic factors of progression-free survival were tumor grade, peritoneal cytology, and patient age. For local control, the prognostic factors are grade, peritoneal cytology, and uterine serosal involvement [4]. PORTEC-1 showed that major risks factors for recurrence were deep myometrial invasion, grade 3 histology, and age greater than 60 years.

The value of preoperative Cancer Antigen 125 (CA-125) level has been investigated in several studies. Elevated preoperative CA-125 is associated with reduced survival of endometrial cancer [8] and extensive surgery should be considered in patients with increased CA-125 [9]. A retrospective multi-center study found that using serum CA-125 to counsel patients receiving adjuvant radiotherapy had relatively low accuracy (58.5–65.8%) [10]. The predictive significance of preoperative CA-125 for survival is unclear.

Our study aims to report the value of adjuvant radiation therapy in surgical stage I endometrial cancer and to identify the prognostic factors for loco-regional recurrence-free survival, overall survival, and distant metastasis-free survival.

Methods

Study population

The medical records of patients with pathologically-confirmed stage I endometrial carcinoma who were treated in our institute from January 2006 to December 2013 were retrospectively reviewed. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (No. 2018-07-024CC).

Treatment and adjuvant radiotherapy

All patients received hysterectomy with or without bilateral salpingo-oophorectomy and bilateral pelvic/para-aortic lymphadenectomy. Postoperative cancer stage was assigned according to the International Federation of Gynecology and Obstetrics (FIGO) 2009 staging system.

Patients received adjuvant radiotherapy according to our institute's practice guideline for gynecological cancer and also followed the multidisciplinary tumor board's decisions. The general principles are giving adjuvant RT to positive cut end margin and to two or more risk factors as below: bulky tumor (≥ 4 cm), positive LVSI, and deep myometrial invasion. EBRT was administered with four-field box technique, three-dimensional conformal radiotherapy (3D-CRT), or volumetric modulated arc therapy (VMAT). The treatment field was the whole pelvis region along with the

upper vagina. The dose delivered to this field was 50.4 Gy, with daily fraction of 1.8 Gy, five days a week. High-dose-rate vaginal brachytherapy (HDR VBT) was given with a cylinder of 3 cm diameter, and the dose was prescribed at a depth of 5 mm from the vaginal surface. Treatment doses ranged from 8 to 20 Gy in two to six fractions.

Statistical analysis

Differences in the categorical variables were compared with Fisher's exact test. The Kaplan–Meier method was used to construct overall and loco-regional recurrence-free survival curves, which were compared with log-rank test. Univariable and multivariable analysis for overall survival, loco-regional recurrence-free survival, and metastasis-free survival were performed using Cox proportional hazard regression. Loco-regional recurrence-free survival and metastasis-free survival were defined as the time from the date of pathological diagnosis to the date of clinically proven recurrence by physical examination or imaging, or to the date of last follow-up on clinical records. Subjects were censored at date of last follow-up or date of death. Overall survival was defined as the time from the date of pathological diagnosis to the date of death or December 31, 2016. Patients who only developed vaginal recurrence or pelvic recurrence as the first failure pattern were considered as loco-regional failure.

Patients whose first failure was distant recurrence only were considered as distant failure.

The first failure type was defined as loco-regional failure if vaginal/pelvic recurrence and distant metastasis were noticed simultaneously. Several studies in the literature demonstrated that age, grade, deep myometrial invasion, and positive lymphovascular space invasion (LVSI) were prognostic factors of survival [4,11–13]. Therefore, multivariable analysis was conducted including the factors below: preoperative CA-125 level, age, histology grade, depth of invasion, presence of LVSI, and with or without receiving adjuvant RT. Statistical analyses used SPSS software (version 22.0; SPSS, Chicago, IL, USA). A p value ≤ 0.05 was considered statistically significant.

Results

Four hundred and forty women were eligible. We excluded 79 patients who had more than one cancer diagnosis or had a follow-up time less than three months. Twenty-four women with a tumor histology other than Bokhman type I endometrial carcinoma were also excluded. A total of 337 women were included in the final analysis. Fig. 1 shows the study profile.

The median age was 54 years (interquartile range, (IQR), 47–61 years) and the median follow-up time was 73.4 months (IQR, 53.2–100 months). A total of 84 patients received adjuvant radiotherapy. Among these, 21 (25%) were treated with EBRT alone, 46 (55%) were treated with VBT alone, and 13 (15%) received both. Table 1 shows the baseline characteristics separated by adjuvant RT. Women older than 60 years, with depth of myometrial invasion $>50\%$, high histological grade, and positive LVSI were observed more frequently in adjuvant RT group (all, $p < 0.001$).

Twenty-two patients died during follow-up, of whom nine received adjuvant radiotherapy and 13 did not. The estimated five-year overall survival rate was 96.3% in the non-RT group, and 91.6% in RT group (log-rank test, $p = 0.06$). There were nine and 15 women who developed loco-regional recurrence and distant metastasis, respectively. The five-year loco-regional recurrence rate was 2.0%. The estimated 5-year loco-regional recurrence-free survival rate was 97.9% in the non-RT group, and 97.1% in with RT group (log-rank test, $p = 0.956$). The five-year distant metastasis rate was

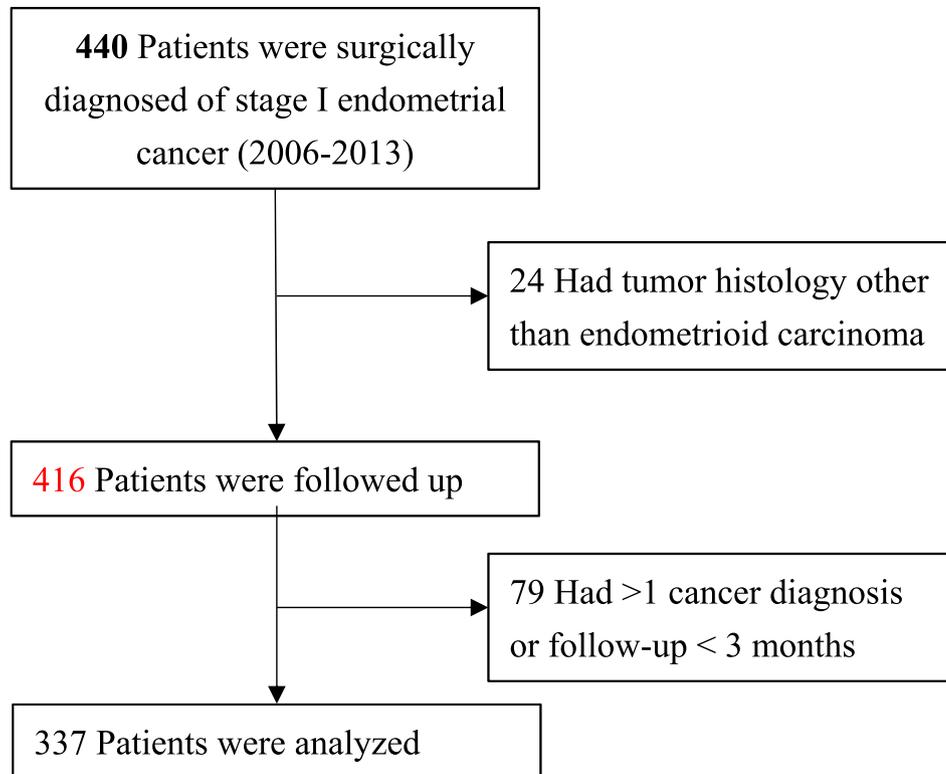


Fig. 1. Study profile.

Table 1
Patients, tumor, and treatment characteristics.

	No RT	With RT	p-value
Age			
≤60	200 (79.1%)	47 (56.0%)	<0.001
>60	53 (20.9%)	37 (44.0%)	
Preoperative CA-125 level			
≤35 (normal)	187 (77.2%)	54 (67.5%)	0.076
>35	66 (22.7%)	27 (32.5%)	
Depth of myometrial invasion			
<50%	245 (98.0%)	47 (56.0%)	<0.001
≥50%	5 (2.0%)	37 (44.0%)	
Grade			
1	71 (29.5%)	5 (6.0%)	<0.001
2 and 3	170 (70.5%)	79 (94.0%)	
Histology type			
Endometrioid	242 (95.7%)	76 (90.5%)	0.162
Endometrioid/mucinous	10 (4.0%)	7 (8.3%)	
Adenosquamous	1 (0.4%)	1 (1.2%)	
LVSI			
No	242 (97.6%)	57 (70.4%)	<0.001
Yes	6 (2.4%)	24 (29.6%)	
GOG-99			
High intermediate risk	26 (10.2%)	44 (52.4%)	<0.001
Low intermediate risk	229 (89.8%)	40 (47.6%)	

Abbreviations: LVSI, Lymphovascular space invasion; RT, Radiotherapy.

3.86%. The estimated 5-year metastasis-free survival rate was 96.7% in the non-RT group, and 92.0% in RT group (log-rank test, $p = 0.012$). Fig. 2 shows the Kaplan-Meier survival curves of patients with or without adjuvant RT. Among the 84 patients who received adjuvant RT, two developed pelvic lymph nodes recurrence and eight developed distant metastases. There was no vaginal recurrence noted. Among the remaining women who did not receive RT, there were four vaginal failures, one pelvic failure, two simultaneous vaginal/pelvic failures, and seven distant failures.

Among 7 patients had only loco-regional recurrence but no distant metastases at initial failure, four patients received salvage chemotherapy, one patient received EBRT to pelvic lymphadenopathy, one patient received VBRT for vaginal recurrence, and one patient did not have any salvage treatment.

Among 337 patients in this study, only 7 patient received CCRT as the initial treatment after operation.

In univariable analysis, preoperative CA-125 level > 35 U/ml, age > 60 years, depth of myometrial invasion > 50%, and positive LVSI were significantly associated with overall survival (all, $p < 0.05$). In multivariable analysis, preoperative CA-125 level > 35 (hazard ratio (HR), 2.54; 95% confidence interval (CI), 1.04–6.19, $p = 0.040$), age > 60 years (HR, 3.44; 95% CI, 1.27–9.28, $p = 0.015$) and depth of myometrial invasion > 50% (HR, 3.37; 95% CI, 1.01–11.34, $p = 0.049$) remained significantly associated with overall survival (Table 2). Variables associated with loco-regional recurrence free survival in the univariable analysis were preoperative CA-125 level > 35 U/ml and positive LVSI. In multivariable analysis, preoperative CA-125 level > 35 U/ml (HR, 5.37; 95% CI, 1.22–23.76, $p = 0.027$), age > 60 years (HR, 6.57; 95% CI, 1.10–39.27, $p = 0.039$), positive LVSI (HR, 50.20; 95% CI, 7.02–359.10, $p < 0.001$), and adjuvant RT (HR, 0.05; 95% CI, 0.03–0.63, $p = 0.023$) were significant associated with loco-regional recurrence-free survival (Table 3). For distant metastasis-free survival, the significant associated variables were depth of myometrial invasion > 50% and adjuvant RT in univariable analysis. In multivariable analysis, only depth of myometrial invasion > 50% was associated with distant metastasis-free survival (HR, 5.70; 95% CI, 1.27–25.69, $p = 0.023$, Table 4).

Further analysis was performed a further analysis to interpret whether different RT modalities affected loco-regional recurrence free survival. The result showed no statistically significant differences between EBRT, VBT, or combined therapy.

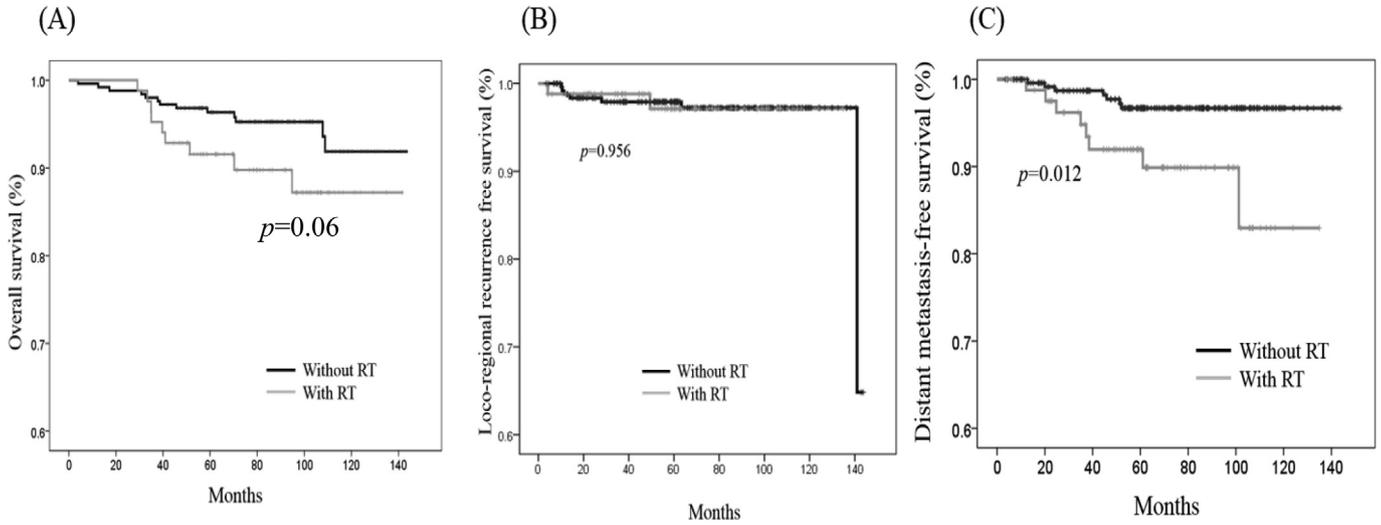


Fig. 2. Kaplan-Meier survival curves of patients with or without adjuvant RT for (A) overall survival (B) locoregional recurrence-free survival (C) Distant metastasis-free survival. Abbreviations: RT, Radiotherapy.

Table 2
Univariable and multivariable analysis of prognostic factors for overall survival.

	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Pre-operative CA-125 level > 35 (U/ml)	3.19 (1.36–7.53)	0.008	2.54 (1.04–6.19)	0.040
Age > 60 years	5.37 (2.25–12.81)	<0.001	3.44 (1.27–9.28)	0.015
Grade 2 and 3	2.27 (0.67–7.70)	0.188	1.81 (0.38–8.63)	0.457
Depth of myometrial invasion ≥ 50%	5.11 (2.19–11.97)	<0.001	3.37 (1.01–11.34)	0.049
Positive LVSI	3.30 (1.21–8.96)	0.019	2.09 (0.62–7.07)	0.236
Adjuvant RT	2.22 (0.95–5.12)	0.067	0.46 (0.13–1.34)	0.229

Abbreviations: CI, Confidence interval; HR, Hazard ratio; LVSI, Lymphovascular space invasion; RT, Radiotherapy.

Table 3
Univariable and multivariable analysis of prognostic factors for locoregional recurrence-free survival.

	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Pre-operative CA-125 level > 35 (U/ml)	5.91 (1.41–24.76)	0.015	5.37 (1.22–23.76)	0.027
Age > 60 years	6.07 (0.77–12.28)	0.114	6.57 (1.10–39.27)	0.039
Grade 2 and 3	2.83 (0.35–22.69)	0.328	1.82 (0.20–16.76)	0.598
Depth of myometrial invasion ≥ 50%	1.75 (0.35–8.73)	0.489	0.57 (0.05–7.34)	0.668
Positive LVSI	10.57 (2.64–42.27)	<0.001	50.20 (7.02–359.10)	<0.001
Adjuvant RT	1.05 (0.21–5.19)	0.956	0.05 (0.03–0.63)	0.023

Abbreviations: CI, Confidence interval; HR, Hazard ratio; LVSI, Lymphovascular space invasion; RT, Radiotherapy.

Table 4
Univariable and multivariable analysis of prognostic factors for distant metastasis free survival.

	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Pre-operative CA-125 level > 35 (U/ml)	0.82 (0.23–2.90)	0.755	0.74 (0.20–2.70)	0.647
Age > 60 years	1.64 (0.56–4.81)	0.367	0.76 (0.22–2.55)	0.653
Grade 2 and 3	5.00 (0.66–38.05)	0.120	NA	NA
Depth of myometrial invasion ≥ 50%	7.77 (2.72–33.16)	<0.001	5.70 (1.27–25.69)	0.023
Positive LVSI	2.85 (0.80–10.11)	0.105	1.10 (0.262–4.62)	0.897
Adjuvant RT	3.67 (1.33–10.13)	0.012	1.16 (0.25–5.45)	0.848

Abbreviations: CI, Confidence interval; HR, Hazard ratio; LVSI, Lymphovascular space invasion; RT, Radiotherapy.

Discussion

Studies from Taiwan that have investigated the role of postoperative radiotherapy and the predictive factors for endometrial cancer are scarce. Two retrospective, single-institution studies investigated the topic; however, the sample populations were relatively small (69 and 55 patients) [14,15]. In the present study, the sample size is 337 women, and the median follow-up time is longer compared with previous studies. We believe these factors contribute to the compelling nature of our results. The findings of our study may contribute to changes to the decision-making for adjuvant treatment in patients with stage I endometrial cancer in Taiwan.

The PORTEC-1 trial and GOG 99 trial compared adjuvant pelvic EBRT versus no further treatment for patients with stage I endometrial carcinoma. Both studies found that EBRT reduced the risk of loco-regional recurrence from 14–18% to 3–4% but had no impact on overall survival [5,6]. Our study aimed to identify the role of adjuvant RT in early stage endometrial cancer. In contrast to the previous mentioned trials, our study includes only women with stage I and Bokhman type I endometrial cancer. Our study shows a five-year loco-regional recurrence rate of 2.38% in the RT group, which is compatible with that reported in PORTEC-1 (4% in the RT group). Creutzberg and colleagues analyzed 15-year outcomes of PORTEC-1 and showed the 15-year actuarial locoregional recurrence rates were 6% for EBRT vs. 15.5% for no adjuvant therapy ($p < 0.0001$) [16]. In the present study, we also demonstrate that receiving adjuvant RT is a protective factor for loco-regional free survival when other variables are adjusted.

Several studies have reported various clinical and histopathologic factors with prognostic significance in early stage endometrial carcinoma. Grigsby and colleagues analyzed 858 patients at clinical stage I who received irradiation and surgery. They found that grade, positive peritoneal cytology, and uterine serosal involvement were significant prognostic factors for local control [4]. Two retrospective studies showed that LVSI was relevant to vaginal relapse and poor overall survival in patients at stage I [11,17]. Zusterzeel et al. reported that in women with stage I and II disease, only age was an independent factor for all recurrence ($p = 0.02$) [18]. In our retrospective study, we identify age and positive LVSI as having a prognostic significance for loco-regional recurrence-free survival. For overall survival, age and the depth of myometrial invasion are independent prognostic factors. The reason that our results varied from the previous studies may be due to the small number of patients with recurrence. Morrow et al. evaluated surgical-pathological parameters and postoperative treatment in the recurrence-free interval of patients at stage I and II. The results showed that adjuvant irradiation did not influence survival ($p = 0.06$) in a proportional hazard model [19]. Two other studies also found adjuvant RT was not a prognostic factor of recurrence-free survival in patients in early-stage disease [11,18]. All these studies define recurrence as both local and distant, which differs from our design. As radiotherapy is a local or loco-regional treatment, the endpoint for its effects should be loco-regional control. The present study demonstrates that adjuvant radiotherapy is a significant protective factor (HR, 0.05; 95% CI, 0.03–0.63) for loco-regional recurrence-free survival. The result is consistent with PORTEC-1 which revealed the HR for loco-regional recurrence was 3.46 for no-adjuvant-treatment compared to EBRT ($p < 0.0001$) after adjusted for prognostic factors [16].

CA-125 is a valuable tumor marker for the diagnosis of epithelial ovarian cancer [20]; however, its role in endometrial carcinoma remains controversial. Histological grade, stage, depth of myometrial invasion, peritoneal cytology, and lymph nodes metastasis have been correlated with preoperative CA-125 level [8,21]. In

addition, there has been evidence that elevated pretreatment serum CA-125 was associated with vessel invasion and extrauterine disease in stage I and II patients [22]. However, the appropriate cut-off and clinical usefulness have not been established [23]. We use 35 U/ml as the cut off, because it is the upper normal limit tested in our institute. Preoperative CA-125 level does not tailor the indication of adjuvant RT in our practice. However, we do find that abnormal CA-125 level is a significant independent factor for loco-regional recurrence-free survival and overall survival. Sood and colleague reported that a preoperative CA-125 level greater than 35 U/ml ($p < 0.001$, HR: 3.1) was the most powerful predictor of overall survival compared with other histopathological variables [8]. The study included all stages and all histological types of endometrial tumors. In current literature, the patient population is limited to pathological T1 and node negative disease and found elevated preoperative serum CA-125 still has a prognostic significance for survival.

Deep myometrial invasion has been demonstrated as an independent predictor of lymph node metastases or extrauterine disease [24,25]. Its predictive value for distant metastasis is debatable. Another retrospective study found that grade, positive peritoneal cytology, and presence of extrauterine disease were associated with the development of distant metastasis but not deep myometrial invasion [4]. However, some studies showed deep myometrial infiltration was significant for distant failure by multivariable analysis [26,27]. Bahng et al. analyzed patients with stage I–II (occult) disease with high-intermediate-risk (HIR) disease defined by GOG 99 [27]. They found deep one-third myometrial invasion was a risk factor of distant metastasis. In our study, myometrial invasion equal to or larger than 50% is the only risk factor of distant metastasis. A recent randomized trial compared adjuvant chemoradiotherapy with radiotherapy alone for high-risk endometrial cancer [28], including stage I disease, endometrioid-type grade 3 with deep myometrial invasion. The study concluded that adjuvant chemoradiotherapy increased failure-free survival but not overall survival. Although systemic therapy is not provided to HIR patients in current management, a subgroup of patients with multiple risk factors for distant failure may be candidates for adjuvant chemotherapy.

Our study has some limitations. First, its retrospective nature produces selection bias. Patients with risks factors predictive of poor outcome frequently receive adjuvant radiotherapy, which modifies the overall recurrence risk. Second, the population in our study is relatively small and only few patients developed recurrence. The small number of patients with disease recurrence limits the statistical power. Third, due to variant forms of pathological reports, there are several missing variables. Prospective studies are necessary to confirm our results.

In conclusion, we show that postoperative radiotherapy in surgical stage I endometrial cancer is an independent predictor for loco-regional recurrence free survival but has no impact on overall survival. Worse overall survival is predicted by elevated preoperative CA-125 level, age older than 60 years, and depth of myometrial invasion $\geq 50\%$. CA-125 determination in pretreatment workup may be considered for tailoring adjuvant therapy. Additionally, deep myometrial invasion is a significant risk factor for the development of distant metastasis.

Conflict of interest

The authors have no conflicts of interest relevant to this article.

Acknowledgments

None.

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