Gynecologic Oncology 154 (2019) 38–44

Contents lists available at ScienceDirect

Gynecologic Oncology

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

Recurrent early stage endometrial cancer: Patterns of recurrence and results of salvage therapy

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HIGHLIGHTS

- Women with vaginal recurrences had significantly longer survival than women with pelvic or distant recurrences.
- Salvage radiotherapy was the only factor we found associated with improved survival for vaginal recurrences.
- Salvage surgery, radiotherapy, and chemotherapy were associated with improved survival for pelvic recurrences.
- In the rare situation of a second locoregional recurrence, 50% of patients can be salvaged at 5 years.

ARTICLE INFO

Article history:
Received 26 October 2018
Received in revised form 11 April 2019
Accepted 14 April 2019
Available online 24 April 2019

Keywords:
Endometrial cancer
Recurrence
Radiotherapy
Salvage treatment

ABSTRACT

Objective. To analyze our institutional experience and oncologic outcomes for salvage treatment for the recurrence of early-stage endometrial cancer patients.

Methods. We included women of all ages diagnosed with FIGO stage I-II, any grade endometrial cancer from 2000 to 2016 at our institutions who were treated with at least a hysterectomy. Recurrences in the pelvis and/or vagina were considered locoregional recurrences (LRR). Overall survival (OS) was assessed using Kaplan-Meier survival analysis. Univariate (UV) and multivariate (MV) Cox proportional hazards modeling was also used.

Results. A total of 2691 women were analyzed. The majority had endometrioid histology (91%), stage IA disease (61%), and were grade 1 (57%). With a median follow-up of 6.1 years, the overall rate of recurrence was 7.2%, and the rate of LRR was 3.7%. Women with vaginal-only recurrences had a longer median OS after recurrence (14.0 years) compared to both pelvic (1.2 years) and distant (1.0 year) failures. For women with vaginal-only recurrences, salvage radiotherapy (RT) was the only factor associated with improved OS on MVA (HR 0.1, $p = .04$). For women with pelvic recurrences, salvage surgery (HR 0.3, $p = .01$), salvage RT (HR 0.3, $p < .01$), and salvage chemotherapy (HR 0.4, $p = .03$) were associated with improved OS.

Conclusions. Failure rates for women with early-stage endometrial cancer are low. Women with vaginal-only recurrences have improved OS compared to pelvic or distant recurrences. Salvage RT appears to be an important factor for treatment of women with vaginal-only recurrences. Aggressive multimodality treatment may be beneficial for women with pelvic recurrences.

1. Introduction

Endometrial cancer is the most common gynecologic malignancy in the United States, with an estimated 61,380 new cases diagnosed in 2017, and its incidence is increasing [1]. Initial treatment involves total hysterectomy with bilateral salpingo-oophorectomy and surgical staging [2]. Indications for adjuvant therapy for surgical stage I and II disease are based on pathologic stage, histologic grade, and other adverse risk factors, such as age, presence of lymphovascular space invasion (LVSI), tumor size, and lower uterine segment involvement or surface cervical glandular involvement [3,4].

In early-stage patients, adjuvant radiotherapy (RT) has been shown in multiple randomized trials to reduce the risk of local-regional

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https://doi.org/10.1016/j.ygyno.2019.04.676
0090-8258/

recurrence (LRR) but has not been shown to improve overall survival (OS) [5–8]. The role for adjuvant systemic treatment in early-stage patients is less clear [9,10].

Approximately 15% of patients with stage I and II endometrial cancer will recur [11–13]. There are currently no published prospective studies to guide treatment for these women. The ongoing GOG 238 protocol seeks to determine whether concurrent weekly cisplatin will improve results of salvage whole pelvis radiation plus boost in women with recurrent disease who have not previously received RT [14]. Until this trial is reported, current recommendations are based on consensus guidelines and retrospective data. For localized disease, consideration of RT and/or surgery or systemic therapy have been proposed [2]. In the setting of prior pelvic radiation, treatment recommendations are even less well defined. Overall, optimal treatment of localized recurrence remains unclear.

The purpose of our multi-institutional study was to analyze outcomes of women with recurrent endometrial cancer and seek to understand treatment factors associated with improved outcomes.

2. Methods

2.1. Patients

After approval by the both institutional review boards, we examined women with FIGO stage I and II endometrial treated at University of Utah Huntsman Cancer Institute or Intermountain Medical Center between 2000 and 2016. All women were treated surgically with simple hysterectomy, and the majority has lymph node evaluation. Patients with leiomyosarcoma or unknown histology, those who did not receive a hysterectomy, those who received neoadjuvant treatment, and those without follow-up records were excluded.

2.2. Statistical analysis

Baseline OS was analyzed using Kaplan-Meier survival analysis based on the initial date of diagnosis to the date of death or censoring. Survival analysis was stratified based on those who had recurrence of cancer as well as by the location of recurrence. Recurrence was defined as vaginal-only, pelvis, which could also have concurrent vaginal recurrence, and distant, which could have concurrent vaginal and/or pelvic recurrence. Local-regional recurrence was defined as patients with recurrence in the vagina and/or pelvis, but not distant.

Additional survival analyses were performed on patients with LRR (*Salvage Outcomes* section). Overall survival for this cohort was set from date of recurrence to date of death. Patients lost to follow-up were censored. Additionally, cancer-specific survival (CSS), set from date of recurrence to date of death from cancer, was analyzed. For this analysis, patients who were lost to follow-up or died of non-cancer causes were censored.

Follow-up time was calculated using Kaplan-Meier estimate of potential follow-up [15]. The Holm procedure was used to account for multiple comparisons when p-values of >2 groups were compared.

Univariate (UVA) and multivariate (MVA) Cox proportional hazards regression modeling were used to identify factors associated with OS after recurrence, reported as hazard ratios (HR). The MVA regression model was created by including all covariates initially, then using a stepwise backward elimination technique, removing covariates with $p < .2$. If elimination of a covariate resulted in a >10% change in the HR of the remaining covariates, then it was included in the final model [16,17].

All analyses were performed using Stata, version 14.2 (StataCorp, College Station, TX).

2.3. Subgroup analyses

Several subgroup analyses were performed based on specific clinical scenarios. Subgroup 1 consisted of women with vaginal-only recurrence who had not received prior RT but received salvage RT. This group was analyzed by receipt of salvage surgery or not. Subgroup 2 was the same subset of women as subgroup 1 but was analyzed comparing external beam radiotherapy (EBRT) with or without addition of vaginal brachytherapy (VB). Subgroup 3 included women with any LRR that either had no prior RT or had VB only. All of these women received salvage RT, consisting of EBRT ± VB. This group was analyzed by receipt of chemotherapy or not. Subgroup 4 included all women with recurrences and was analyzed by the receipt of salvage chemotherapy based on location of recurrence. Subgroup 5 included all women with recurrences and was analyzed based on time to recurrence from the date of initial diagnosis (≤1.5 years versus >1.5 years) and location of recurrence. Subgroup 6 included all women who received adjuvant radiotherapy and then developed locoregional recurrence and received salvage radiotherapy. See Supplemental Fig. 1 for schematic of subgroups. Subgroup analyses were done using Kaplan Meier survival curves and univariate Cox proportional hazards modeling.

3. Results

3.1. Patient characteristics

A total of 2691 women were included initially (Table 1). Most women were over 60 years of age at diagnosis (mean age 61 years, standard deviation (SD) 11.8 years). The overwhelming majority (91%) had endometrioid histology, 61% were stage IA, and 57% were grade 1. Thirty-nine percent of women were endometrioid histology, grade 1, and stage IA.

Adjuvant RT was received by 25% of women, and 9% received adjuvant chemotherapy. Vaginal brachytherapy was the most common adjuvant radiation modality (60%), followed by external beam radiotherapy (EBRT) (30%). A combination treatment of EBRT + VB was used in 10% of those who received adjuvant RT.

Table 1
Baseline patient characteristics.

	Total no.	Total %
Age group		
<60	1203	45
≥60	1488	55
Total	2691	100
KPS pre-treatment group		
≥80	2669	99
<80	22	1
Total	2691	100
Histology group		
Endometrioid	2440	91
Serous	79	3
Carcinosarcoma	83	3
Other	89	3
Total	2691	100
Grade		
1	1402	57
2	696	28
3	355	14
Total	2453	100
FIGO stage		
IA	1583	61
IB	843	32
II	168	6
Total	2594	100
Adjuvant radiation		
Yes	668	25
No	2023	75
Total	2691	100

Abbreviations: No., number; KPS, Karnofsky Performance Score; FIGO, International Federation of Gynecology and Obstetrics.

3.2. Recurrence

With a median follow-up of 6.1 years (95% confidence interval, 5.8–6.4), 194 (7.2%) women experienced a recurrence. Ninety-nine (3.7%) women had a LRR. Overall, 12.9% of women who received adjuvant RT recurred, and the majority of those were distant failures (57%). The failure rate was 5.3% for women who did not receive adjuvant RT. Baseline characteristics for women who recurred are found in Supplemental Table 1. Women who received adjuvant radiation were more likely to have more aggressive disease, including non-endometrioid histology (Odds Ratio [OR] 2.5), FIGO stage IB (OR 14.5) or II (OR 16.2), or higher grade (Grade 2 OR 2.6, Grade 3 OR 5.8) (see Supplemental Table 2). The overall rate of vaginal recurrence was 1.6%. The rate of vaginal recurrence was 1.7% for women who did not receive adjuvant RT, 1.3% after adjuvant VB, 1.5% after EBRT, and 1.5% after EBRT + VB (Supplemental Table 3). The rate of pelvic recurrence was 4.2% for those who received adjuvant RT and 1.4% for those who did not receive adjuvant RT, with an overall pelvic recurrence rate of 2.1%. The overall rate of distant recurrence was 3.5%. On univariate and multivariate analysis the only predictor of distant failure vs. locoregional recurrence was grade 3 disease (OR 5.0) (Supplemental Table 4).

The median OS for women who had a recurrence was 3.9 years, while the median OS for women without a recurrence was not met (Fig. 1), p < .001. The 1, 3, 5, and 10-year survival rates for women with recurrence were 93.3%, 58.3%, 43.4%, and 26.8%, respectively. The 1, 3, 5, and 10-year survival rates for women without recurrence were 97.9%, 93.7%, 89.5%, and 78.5%, respectively.

The median follow-up for women who experienced a recurrence was 8.5 years (95% CI 6.8–11.2). Women with vaginal-only recurrences had a longer median OS after recurrence of 14.0 years, compared to those with pelvic recurrences with a median OS of 1.2 years (adjusted, p = .001) and to those with distant recurrences with a median OS of 1.0 years (adjusted, p < .001) (Fig. 2). There was no statistical OS difference between pelvic and distant failures (adjusted, p = .569). The 3-year OS rates after recurrence for women with vaginal-only, pelvic, or distant recurrences were 64.2%, 25.9%, and 26.2%, respectively. The 5-year OS rates for women with vaginal-only, pelvic, or distant recurrences were 61.2%, 20.9%, and 20.0%, respectively.

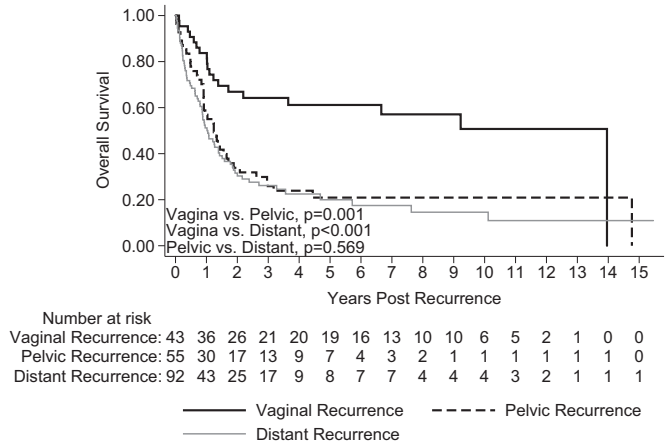

Fig. 2. Kaplan-Meier survival analysis based on site of cancer recurrence.

3.3. Salvage treatment

Among the 99 patients with LRR, the most common treatment given was RT (72%). Additionally, 35% of patients received surgery, 31% of patients received chemotherapy, 9% received endocrine therapy, and 6% did not receive any salvage treatments. A summary of salvage treatments is presented in Table 2.

Of the 72 women who received salvage radiation, 20 (28%) had previously received radiation (see Subgroup 6). Of the 35 women who received salvage surgery, 19 (54%) had already received upfront adjuvant radiation; 7 VB, 11 EBRT, 1 EBRT + VB. For women who received salvage EBRT, the median dose was 45 Gy (interquartile range [IQR], 45–55.9 Gy). The median VB dose was 19.5 Gy (IQR, 18–22 Gy). Most commonly 3 fractions for VB were utilized (IQR, 2–3.5 fractions), and 88% of VB was intracavitary.

Overall, 6 patients with LRR did not receive any salvage treatment. Three of these patients already received adjuvant radiation, and re-irradiation was not offered, and other treatments were not performed for unknown reasons; 1 declined any treatments, and 2 had very poor performance status secondary to other comorbidities.

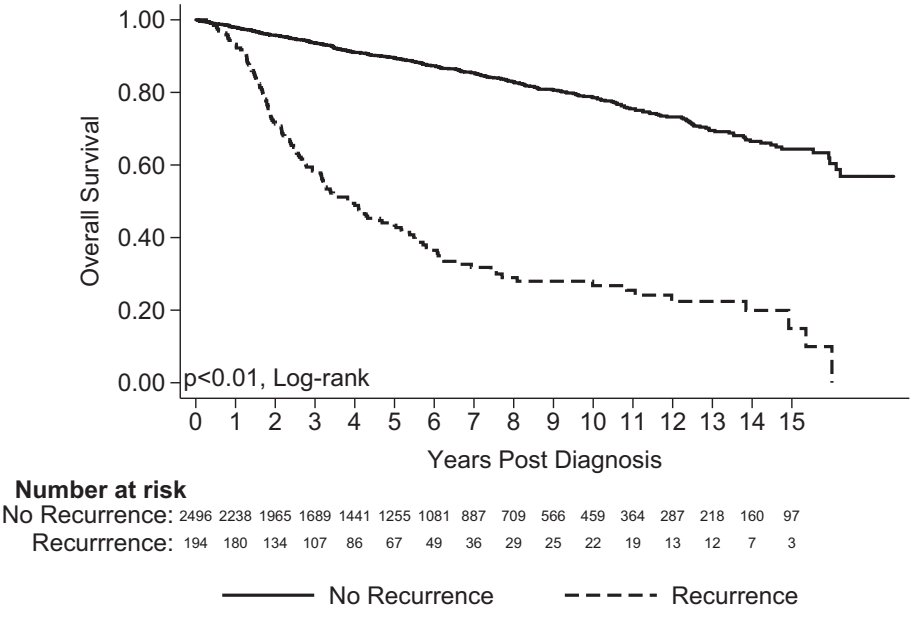

Fig. 1. Kaplan-Meier survival analysis for women with and without cancer recurrence.

Table 2
Summary of salvage treatments for locoregional recurrences.

Salvage treatment type	Site of locoregional recurrence					
	Vagina		Pelvis		Total	
	N = 43	(%)	N = 56	(%)	N = 99	(%)
Single modality						
RT alone	24	(56)	9	(16)	33	(33)
Surgery alone	3	(7)	6	(11)	9	(9)
Chemo alone	0	(0)	2	(4)	2	(2)
Endocrine alone	0	(0)	2	(4)	2	(2)
Dual modality						
RT + surgery	8	(19)	6	(11)	14	(14)
RT + chemo	4	(9)	12	(21)	16	(16)
RT + endocrine	0	(0)	2	(4)	2	(2)
Surgery + chemo	0	(0)	4	(7)	4	(4)
Surgery + endocrine	1	(2)	1	(2)	2	(2)
Chemo + hormone	0	(0)	2	(4)	2	(2)
Tri-modality						
RT + surgery + chemo	2	[24]	4	(7)	6	(6)
RT + chemo + endocrine	1	(2)	0	(0)	1	(1)
None	0	(0)	6	(11)	6	(6)

Abbreviations: N, number of patients; RT, radiothearpy; Chemo, chemothearpy.

3.4. Salvage outcomes

The median follow-up after time of recurrence was 5.9 years (95% CI 4.1–7.5). On Cox MVA for all patients with LRR, factors with a significant association with survival included: salvage RT (HR 0.3, p < .001), salvage surgery (HR 0.4, p = .04), salvage chemotherapy (HR 0.3, p = .01), advancing age (HR 1.0, p = .01),non-endometrioid histology (HR 3.3, p = .02)), grade 2 (HR 2.6, p = .04), and LVSI (HR 3.1, p = .02) (Table 3).

For women with vaginal-only recurrences, on Cox MVA, only salvage RT (HR 0.1, p = .03) had significant association with OS (Table 3). When analyzing women with pelvic recurrences, on MVA, salvage surgery (HR 0.3, p = .01), salvage RT (HR 0.3, p < .001), and salvage chemotherapy (HR 0.4, p = .03), and LVSI (HR 3.5, p = .01) had significant association with OS (Table 3).

After initial LRR, 40 patients (40.4%) were successfully salvaged and did not have a second failure, however, 49 women (49.5%) with an initial LRR went on to fail distantly and 10 women (10.1%) had a second LRR (Fig. 3). Those women without a second failure had a median OS that was not met compared to a median OS of 1.9 years for those with a second LRR and a median OS of 0.9 years for those with a distant second recurrence (p < .01). The 2-year OS rate for those without a second failure, those with a second LRR, and those who failed distantly was 94.1%, 50.0%, and 14.3%, respectively. The only factor predictive of subsequent failure after salvage treatment for LRR was initial pelvic site of failure compared to vaginal only failure (OR 3.6, p = .02, Supplemental Table 5).

3.5. Subgroup analyses

For women with vaginal-only recurrence with no prior RT that were treated with salvage RT, we did not find a statistical difference among those who received salvage surgery and those who did not (Subgroup 1, Supplemental Fig. 2) or for those treated with VB boost versus EBRT alone (Subgroup 2, Supplemental Fig. 3). In Subgroup 2, only 1 patient was treated with interstitial VB; all other received intracavitary treatment. Additionally, for women with any LRR who received salvage RT (Subgroup 3), we did not find a survival difference among women who received salvage chemotherapy and those who did not (Supplemental Fig. 4). However, on additional subgroup analysis (Subgroup 4), we found that salvage chemotherapy was associated with improved OS (HR 0.52, p = .045) for women with pelvic recurrences, but not vaginal or distant recurrences (Supplemental Fig. 5). The median and 1-year OS for women who received salvage chemotherapy was 1.7 years, and 71%, respectively. For women who did not receive salvage chemotherapy in this subgroup, the median and 1-year OS were 0.92 years, and 46%, respectively.

When analyzing women based on time to recurrence and OS after recurrence (Subgroup 5), we found that women who had distant recurrence >1.5 years after initial diagnosis had significantly improved OS compared to women with distant recurrences who recurred ≤1.5 years after initial diagnosis (HR 0.39, p < .001) (Supplemental Fig. 6). We did not find a difference in OS based on time to recurrence for vaginal or pelvic recurrences.

Of the 99 women with LRR, 37 received adjuvant radiation as part of their initial treatment. Eighteen had VB alone, 16 had EBRT alone, and 3 had EBRT + VB. Of these 37 previously irradiated women who recurred, 20 (54%) received salvage radiotherapy (Subgroup 6). Thirteen had prior VB alone and the other 7 had prior EBRT alone. Of those with prior VB alone, 12 received salvage EBRT alone, and 1 got EBRT + VB. Of those who had prior EBRT alone, 1 got salvage VB, 5 received EBRT alone, and 1 received EBRT + VB. Nine of these women who received reirradiation did not develop a subsequent recurrence and were successfully salvaged, 3 developed subsequent locoregional progression, and 8 developed distant disease. With a median follow-up of 7.2 years after recurrence (95% CI 5.1–9.2), the median OS after recurrence was 1.7 years for women who received salvage radiation compared to 0.9 years for women who did not (p = .13) (Supplemental Fig. 7).

4. Discussion

The overall rate of recurrence in our cohort of early-stage endometrial cancer patients was low at 7.2%. The recurrence rate was 12.9% for women who received adjuvant RT and 5.3% for those who did not. As expected, the rate of LRR was lower at 3.7%. Additionally, we found that women with vaginal-only recurrences had much longer median OS after recurrence compared to both pelvic and distant failures (Median OS 14.0, 1.2, and 1.0 years, respectively). For all women with LRR, we found that receipt of salvage RT, salvage surgery, and chemotherapy were associated with an improved OS on Cox MVA. For women with vaginal-only recurrences, salvage RT was the only factor associated with improved OS, while for women with pelvic recurrences, salvage surgery, salvage RT, and chemotherapy were associated with improved OS.

These rates of recurrence are in line with previously published reports. Most significantly, in the PORTEC-1 trial, out of 715 women there were a total of 59 LRR overall, or 8.3% [18]. The LRR rate was 4.0% in the radiotherapy arm and 14.9% in the observation arm. The 3-year OS rates for vaginal, pelvic, and distant relapse were 73%, 8%, and 14%, respectively. In the current study, we found a similar trend for decreasing OS based on site of recurrence, with 3-year OS rates for women with vaginal-only, pelvic, or distant recurrences of 71.7%, 55.4%, and 54.3%, respectively. None of the women treated with curative intent for recurrence from PORTEC-1 received salvage chemotherapy compared to 32% of women in our cohort. Additionally, we found that for women with pelvis recurrences, chemotherapy was associated with improved OS on MVA (HR 0.4, p = .03)). These higher 3-year OS rates for pelvic and distant recurrences, as well as our findings on MVA, demonstrate the importance of salvage chemotherapy for these women.

We found that surgery was also associated with improved OS for pelvic recurrences. Only 1 patient out of 10 treated with curative intent received salvage surgery in the PORTEC-1 salvage cohort, compared to 38% in our study. These differences could help further explain why our OS rates were higher for women with pelvic recurrence than reported on PORTEC-1.

It is important to note that we did not find a difference in OS for women with pelvic versus distant recurrences and both groups did much worse than women with vaginal-only recurrences. Interestingly, we found that for women who developed distant recurrence, those with prolonged time to recurrence (>1.5 years) had improved OS after

Table 3
Cox proportional hazards regression modeling for overall survival after recurrence.

		All LRR							
		Univariate Cox Regression				Multivariate Cox Regression			
		HR	95% CI		p-value	HR	95% CI		p-value
Age at Recurrence	per 1 year increase	**1.0**	**1.0**	**1.1**	**<0.01**	**1.0**	**1.0**	**1.1**	**0.01**
Histology	Endometrioid	Reference				Reference			
	Other	**3.2**	**1.7**	**5.9**	**<0.01**	**3.3**	**1.3**	**8.6**	**0.02**
Grade	1	Reference				Reference			
	2	**2.8**	**1.4**	**5.4**	**<0.01**	**2.6**	**1.1**	**6.4**	**0.04**
	3	**3.9**	**2.0**	**7.8**	**<0.01**	2.0	0.8	5.0	0.15
LVSI	No	Reference				Reference			
	Yes	1.9	0.9	3.9	0.10	**3.1**	**1.2**	**7.7**	**0.02**
Prior Radiation	No	Reference							
	Yes	1.6	1.0	2.8	0.06				
Recurrence Site	Vaginal-Only	Reference				Reference			
	Pelvis ± vagina	**2.5**	**1.5**	**4.4**	**<0.01**	1.9	0.9	4.1	0.10
Salvage Surgery	No	Reference				Reference			
	Yes	0.7	0.4	1.3	0.30	**0.4**	**0.2**	**1.0**	**0.04**
Salvage Radiation	No	Reference				Reference			
	Yes	**0.4**	**0.2**	**0.7**	**0.00**	**0.3**	**0.1**	**0.5**	**<0.01**
Salvage Chemo	No	Reference				Reference			
	Yes	0.8	0.5	1.4	0.47	**0.3**	**0.1**	**0.8**	**0.01**
Disease Free Interval	Per 1 year increase	1.0	0.9	1.2	0.99				
		Vaginal-Only Recurrence							
		Univariate Cox Regression				Multivariate Cox Regression			
		HR	95% CI		p-value	HR	95% CI		p-value
Age at Recurrence	per 1 year increase	**1.1**	**1.0**	**1.1**	**0.03**	1.1	1.0	1.3	0.06
Histology	Endometrioid	Reference				Reference			
	Other	**4.0**	**1.3**	**12.6**	**0.02**	2.9	0.6	13.5	0.18
Grade	1	Reference				Reference			
	2	2.7	0.8	9.1	0.10	3.3	0.9	11.5	0.07
	3	**4.5**	**1.4**	**14.2**	**0.01**	2.6	0.7	9.4	0.16
LVSI	No	Reference							
	Yes	2.6	0.6	11.8	0.21				
Prior Radiation	No	Reference							
	Yes	1.8	0.6	5.0	0.28				
Salvage Surgery	No	Reference				Reference			
	Yes	1.1	0.4	3.0	0.83	0.3	0.1	1.5	0.14
Salvage Radiation	No	Reference				Reference			
	Yes	0.3	0.1	1.1	0.07	**0.1**	**0.0**	**0.8**	**0.03**
Salvage Chemo	No	Reference							
	Yes	0.6	0.1	2.4	0.44				
Disease Free Interval	Per 1 year increase	0.9	0.6	1.2	0.41				
		Pelvic Recurrence							
		Univariate Cox Regression				Multivariate Cox Regression			
		HR	95% CI		p-value	HR	95% CI		p-value
Age at Recurrence	per 1 year increase	**1.0**	**1.0**	**1.1**	**0.04**				
Histology	Endometrioid	Reference				Reference			
	Other	**2.7**	**1.3**	**5.6**	**0.01**	2.5	1.0	6.5	0.06
Grade	1	Reference							
	2	2.0	0.9	4.5	0.10				
	3	**2.6**	**1.1**	**6.2**	**0.03**				
LVSI	No	Reference				Reference			
	Yes	1.4	0.6	3.3	0.45	**3.5**	**1.3**	**9.2**	**0.01**
Prior Radiation	No	Reference							
	Yes	1.2	0.7	2.2	0.57				
Salvage Surgery	No	Reference				Reference			
	Yes	0.6	0.3	1.1	.09	**0.3**	**0.1**	**0.8**	**0.01**
Salvage Radiation	No	Reference				Reference			
	Yes	0.6	0.3	1.1	0.07	**0.3**	**0.1**	**0.6**	**<0.01**
Salvage Chemo	No	Reference				Reference			
	Yes	**0.5**	**0.3**	**1.0**	**0.05**	**0.4**	**0.2**	**0.9**	**0.03**
Disease Free Interval	Per 1 year increase	**1.1**	**0.9**	**1.3**	**0.52**				

Abbreviations: LRR, locoregional recurrences; HR, hazard ratio; CI, confidence interval; LVSI, lymphovascular space invasion.
Bold indicates p-Value < .05, considered significant.

recurrence compared to those with short time to recurrence; however, for women with vaginal or pelvic recurrences, there was not a difference in OS based on time to recurrence.

There have been multiple reports of outcomes for treatment of women with vaginal-only recurrences treated with salvage RT with 3-year OS rates between 33 and 73% [18–20] and 5-year OS rates between

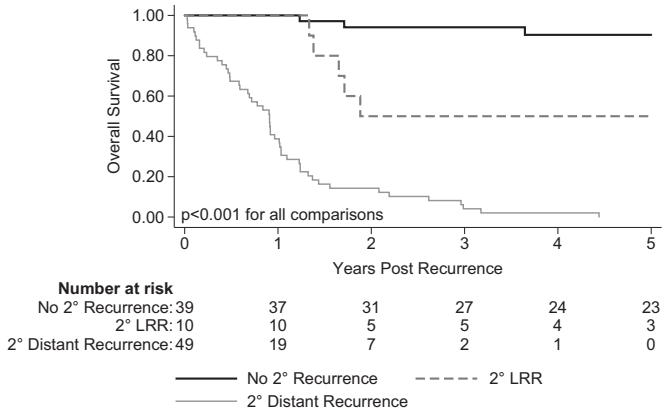

Fig. 3. Kaplan-Meier survival analysis based on second recurrence after salvage treatment. Abbreviations: LRR, locoregional recurrence.

25 and 53% [19,21,22]. Similarly, we found a 3-year OS rate of 64% and a 5-year OS rate of 61% for women with vaginal-only recurrences. We found that salvage RT was the only factor associated with improved OS for these women (HR 0.1, p = .01). While we did not find a difference in OS for EBRT compared to EBRT + VB for treatment of vaginal-only recurrences on subgroup analysis, we feel it is reasonable to consider VB boost, especially if salvage RT is the sole salvage treatment modality as indicated by the American Brachytherapy Society (ABS) guidelines [23]. For these women, we did not find a clear benefit to surgery on MVA or subgroup analysis, and therefore would not routinely recommend salvage surgery for vaginal-only recurrences.

Our study does have limitations. It is a retrospective analysis and therefore limited by incomplete medical records and lack of standardized follow-up procedures. Additionally, incorporation of selection and treatment biases are possible. We have utilized multivariable regression analyses to attempt to account for these imbalances. Given the low overall incidence of localized recurrent disease, our study does have a relatively small sample size; however, our overall cohort is large with 2691 cases of early-stage endometrial cancer and adds to the literature in recurrent endometrial cancer.

5. Conclusions

The rate of recurrence for women with early-stage endometrial cancer is low. However, women who develop recurrence have worse OS compared with those without recurrence. Women with vaginal-only recurrences have improved OS compared to pelvic or distant recurrences. We found that salvage RT was the most important factor for treatment of women with vaginal-only recurrences. In the rare situation of a second LRR, 50% of patients can be salvaged at 5 years. Chemotherapy was observed to increase OS in women with pelvic recurrences and aggressive multimodality treatment may be beneficial for women with pelvic recurrences.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ygyno.2019.04.676.

Conflict of interest and financial disclosure

None to disclose.

Author contribution

Samual Francis: Conceived and designed the analysis, collected the data, performed the analysis, wrote the paper.

Bryan Ager: Conceived and designed the analysis, collected the data, helped with analysis and preparation of the paper.

Olivia Do: Collected the majority of the data, organized the database for analysis.

Jessica Huang: Conceived and designed the analysis, feedback on manuscript preparation.

Andrew Soisson: Conceived and designed the analysis, feedback on manuscript preparation.

Mark Dodson: Conceived and designed the analysis, feedback on manuscript preparation.

Theresa L. Werner: Conceived and designed the analysis, helped write the paper.

William Sause: Conceived and designed the analysis, helped write the paper.

Jonathan Grant: Conceived and designed the analysis, supervisory role on project, key in editing and writing manuscript.

David Gaffney: Conceived and designed the analysis, supervised the project, edited and wrote the manuscript.

References

[1] R.L. Siegel, K.D. Miller, A. Jemal, Cancer statistics, 2017, CA Cancer J. Clin. 67 (1) (2017) 7–30.
[2] Network, N.C.C, *Uterine Neoplasms*. 2018 may 25, updated version 2.2018:[Available from: https://www.nccn.org/professionals/physician_gls/pdf/uterine.pdf 2018.
[3] C.L. Creutzberg, et al., Nomograms for prediction of outcome with or without adjuvant radiation therapy for patients with endometrial cancer: a pooled analysis of PORTEC-1 and PORTEC-2 trials, Int. J. Radiat. Oncol. Biol. Phys. 91 (3) (2015) 530–539.
[4] Group, S.G.O.C.P.E.C.W, et al., Endometrial cancer: a review and current management strategies: part II, Gynecol. Oncol. 134 (2) (2014) 393–402.
[5] C.L. Creutzberg, et al., 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 355 (9213) (2000) 1404–1411.
[6] H.M. Keys, 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. 92 (3) (2004) 744–751.
[7] J. Aalders, et al., Postoperative external irradiation and prognostic parameters in stage I endometrial carcinoma: clinical and histopathologic study of 540 patients, Obstet. Gynecol. 56 (4) (1980) 419–427.
[8] B. Sorbe, et al., External pelvic and vaginal irradiation versus vaginal irradiation alone as postoperative therapy in medium-risk endometrial carcinoma–a prospective randomized study, Int. J. Radiat. Oncol. Biol. Phys. 82 (3) (2012) 1249–1255.
[9] ASTRO, GOG-249 Confirms Adjuvant Pelvic Radiation as Standard of Care for High-Risk, Early-Stage Endometrial Cancer, 2017 June 18, 2018]; Available from: http://www.ascopost.com/News/58092 2017.
[10] S.M. de Boer, 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 19 (3) (2018) 295–309.
[11] H. Lajer, et al., Survival after stage IA endometrial cancer; can follow-up be altered? A prospective nationwide Danish survey, Acta Obstet. Gynecol. Scand. 91 (8) (2012) 976–982.
[12] M. Fung-Kee-Fung, et al., Follow-up after primary therapy for endometrial cancer: a systematic review, Gynecol. Oncol. 101 (3) (2006) 520–529.
[13] R.E. Bristow, et al., Cost-effectiveness of routine vaginal cytology for endometrial cancer surveillance, Gynecol. Oncol. 103 (2) (2006) 709–713.
[14] Radiation Therapy with or without Cisplatin in Treating Patients with Recurrent Endometrial Cancer, Available from https://clinicaltrials.gov/ct2/show/NCT00492778 June 18, 2018.
[15] M. Schemper, T.L. Smith, A note on quantifying follow-up in studies of failure time, Control. Clin. Trials 17 (4) (1996) 343–346.
[16] E. Budtz-Jorgensen, et al., Confounder selection in environmental epidemiology: assessment of health effects of prenatal mercury exposure, Ann. Epidemiol. 17 (1) (2007) 27–35.
[17] G. Maldonado, S. Greenland, Simulation study of confounder-selection strategies, Am. J. Epidemiol. 138 (11) (1993) 923–936.
[18] C.L. Creutzberg, et al., Survival after relapse in patients with endometrial cancer: results from a randomized trial, Gynecol. Oncol. 89 (2) (2003) 201–209.
[19] B. Jereczek-Fossa, A. Badzio, J. Jassem, Recurrent endometrial cancer after surgery alone: results of salvage radiotherapy, Int. J. Radiat. Oncol. Biol. Phys. 48 (2) (2000) 405–413.
[20] J.A. Vargo, et al., Definitive salvage for vaginal recurrence of endometrial cancer: the impact of modern intensity-modulated-radiotherapy with image-based HDR brachytherapy and the interplay of the PORTEC 1 risk stratification, Radiother. Oncol. 113 (1) (2014) 126–131.
[21] A. Jhingran, T.W. Burke, P.J. Eifel, Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy, Int. J. Radiat. Oncol. Biol. Phys. 56 (5) (2003) 1366–1372.
[22] L.L. Lin, et al., Definitive radiotherapy in the management of isolated vaginal recurrences of endometrial cancer, Int. J. Radiat. Oncol. Biol. Phys. 63 (2) (2005) 500–504.

[23] M. Kamrava, et al., American brachytherapy society recurrent carcinoma of the endometrium task force patterns of care and review of the literature, Brachytherapy 16 (6) (2017) 1129–1143.

[24] P. Blake, et al., Adjuvant external beam radiotherapy in the treatment of endometrial cancer (MRC ASTEC and NCIC CTG EN.5 randomised trials): pooled trial results, systematic review, and meta-analysis, Lancet 373 (9658) (2009) 137–146.