Advances in Radiation Oncology (2020) **5**, 1240-1247

advances
in radiation oncology

www.advancesradonc.org

Scientific Article

Outcomes After Salvage Radiation Therapy for Recurrent Endometrial Cancer in Patients With No Prior Adjuvant Therapy: An Institutional Review

Jessica D. Arden, MD, PhD,[a] Morgan F. Gruner, MD,[a,b] Charles C. Vu, MD,[a,c] Kimberly Marvin, BS,[a] Hong Ye, PhD,[a] Sirisha R. Nandalur, MD,[a] Zaid Al-Wahab, MD,[d] Jill Gadzinski, MD,[d] Joseph Anthony Rakowski, DO,[d] Jayson Field, MD,[d] Barry Rosen, MD,[d] and Maha Saada Jawad, MD[a,*]

[a]Department of Radiation Oncology, Beaumont Health System, Royal Oak, Michigan; [b]Ob/Gyn and Women's Health Institute, Cleveland Clinic, Cleveland, Ohio; [c]Department of Radiation Oncology, Parkview Cancer Institute, Fort Wayne, Indiana; and [d]Department of Gynecologic Oncology, Beaumont Health System, Royal Oak, Michigan

Received 28 April 2020; revised 25 August 2020; accepted 28 August 2020

Abstract

Purpose: After definitive surgery, women with early-stage, low-risk endometrial cancer are observed. However, some will require salvage radiation therapy for recurrence. The purpose of this study was to evaluate our experience using salvage radiation for recurrent endometrial cancer in patients who did not receive upfront adjuvant therapy.

Methods and Materials: Twenty-eight women with endometrial cancer who had undergone initial definitive hysterectomy without adjuvant therapy developed isolated local or regional recurrence and were treated with salvage radiation in our department from 2004 to 2018. Salvage radiation included whole pelvic radiation, vaginal brachytherapy, or both. Patient and tumor characteristics, treatment details, and toxicities were recorded and analyzed.

Results: The median time to first recurrence was 1.7 years. First recurrences consisted of local recurrence in 23 patients, regional recurrence in 4, and both in 1. The median times from hysterectomy to first recurrence, local and regional, were 1.2 and 4.0 years, respectively. All patients underwent salvage radiation for management of their first recurrence. The median total equivalent dose in 2 Gy fractions for this treatment was 67.6 Gy (37.5−81.8 Gy). Two second recurrences occurred following salvage treatment, both local recurrence, at 6.5 and 13.5 months after radiation. The 2-year rates of local control, disease-free survival, and overall survival were 93%, 80%, and 88%, respectively. Treatment was well-tolerated, with low rates of gastrointestinal and genitourinary toxicity.

Conclusions: In this group of patients, salvage radiation therapy for local or regional recurrence of endometrial cancer resulted in excellent control with low rates of acute and chronic toxicities.

Sources of support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.
Disclosures: The authors have no conflicts to declare.
Research data are not available at this time.

* Corresponding author: Maha Saada Jawad, MD; E-mail: maha.jawad@beaumont.org

https://doi.org/10.1016/j.adro.2020.08.012

Introduction

Endometrial cancer is the most common cancer of the female reproductive organs in the United States.[1] More than 70% of endometrial cancers are stage I at the time of diagnosis, and the 5-year overall survival (OS) rate for such patients is 90%.[2] Patients with low-risk stage I endometrial cancer are managed with definitive surgery alone, as the randomized clinical trial by Sorbe et al[3] reported a 3.1% rate of local recurrence in these patients after hysterectomy with no adjuvant radiation (radiation therapy [RT]).

Additionally, some early-stage, intermediate-risk patients may not receive adjuvant RT treatment. This is based on data from the Post OPerative Radiation Therapy in Endometrial Carcinoma (PORTEC)-1 and Gynecologic Oncology Group (GOG)-99 clinical trials, which showed that patients with intermediate-risk endometrial cancer do not derive an OS benefit from adjuvant RT.[4,5] However, data from these studies did show that high-intermediate risk patients receive a substantial locoregional control benefit from adjuvant treatment (specifically, locoregional recurrences were reduced from 10%-14% to 2%-4%, with an absolute benefit of 8%-10%). For patients who elect to forgo adjuvant RT, the majority of recurrences occur within 3 years of initial treatment.[6,7] Therefore, close follow-up is indicated to identify local recurrences early on, when salvage therapy may be successfully implemented.[8,9]

There are limited data on the outcomes of patients who initially receive no adjuvant therapy after hysterectomy and who subsequently require salvage treatment for recurrent disease. Retrospective data support the use of RT for salvage of isolated vaginal recurrences; however, RT approaches and doses vary widely in the literature. Currently, there is no set standard in place.

The purpose of this study is to report our institutional experience with salvage radiation therapy (SRT) for patients with recurrent early stage endometrial cancer.

Methods and Materials

Patient population

In this retrospective study, we evaluated patients with endometrial cancer who received SRT therapy for recurrence after initial definitive surgery and no adjuvant treatment. This study was approved by our hospital's institutional review board, which waived the requirement for written informed consent.

Treatment technique

At the time of initial diagnosis of uterine cancer, patients underwent staging surgery with total hysterectomy, bilateral salpingo-oophorectomy, and lymph node evaluation. They then continued with routine surveillance in the gynecologic oncology office. Upon diagnosis of recurrence, patients were presented and discussed at a multidisciplinary tumor board before initiating treatment. Salvage treatment for the recurrence included RT with whole pelvic external beam radiation (EBRT), vaginal brachytherapy alone, or a combination of both, with or without chemotherapy.

Although no standardized fractionation scheme for SRT was adopted at our institution, in general, SRT consisted of combination EBRT and vaginal brachytherapy for vaginal recurrences and EBRT alone with an external beam boost to the site of gross disease for pelvic recurrences. A few exceptions to these practices were made on an individual basis. Brachytherapy, when used, was delivered using high-dose-rate brachytherapy with either a vaginal cylinder or by interstitial implant, depending on the size and location of the tumor. For patients treated with a vaginal cylinder, radiation was prescribed to a depth of 5 mm. A total of 6 patients (21%) received chemotherapy, most commonly with carboplatin and paclitaxel, given sequentially. No patients in this study received concurrent chemotherapy.

For patients who received intracavitary (IC) brachytherapy, the median cylinder size used was 3.0 cm (range, 2.0-3.5 cm) and the median dose was 3000 cGy (1200-3000 cGy) delivered in a median of 6 fractions (3-8 fractions). Dose was prescribed to a depth of 5 mm in all cases. Most patients received initial treatment to a longer vaginal length (median length of 8 cm; range, 5-12 cm) followed by a boost to the proximal vagina (median length of 4 cm; range, 3-6 cm), whereas 3 patients received treatment to a single length (2 received 2000 cGy in 4 fractions to a length of 5 cm, and 1 received 3000 cGy in 6 fractions to a length of 7 cm).

Follow-up

Surveillance after treatment was performed in accordance with published national guidelines.[10] Typical follow-up included a history and physical examination every 3 months for the first 2 years after treatment, then every 6 months for the next 3 years, then annually. Imaging was ordered only for clinical suspicion of recurrent disease; no routine surveillance imaging was performed.

Statistical analysis

Clinical outcomes were analyzed using t tests for continuous variables and χ^2-tests for categorical variables. Kaplan-Meier estimates of OS, disease-free survival (DFS), and distant metastasis-free survival were calculated. Patients lost to follow-up were censored at the time of the last available observation. Acute (up to 6

Table 1 Demographics and tumor characteristics of patients who underwent salvage radiation for recurrence of endometrial cancer after initial surgical management with no adjuvant therapy

Age (years)	
Median (range)	66 (48-85)
Follow-up (years, from initial surgery)	
Median (range)	3.0 (0-13.7)
Tumor size (cm)	
Median (range)	3.8 (1-8.2)
Histology	
Endometroid	20 (71%)
Papillary	1 (4%)
Mixed mullerian	1 (4%)
Mucinous	1 (4%)
Mixed	1 (4%)
Unknown	4 (14%)
Grade	
I	17 (61%)
II	5 (18%)
III	5 (18%)
Unknown	1 (4%)
FIGO T stage	
1a	19 (68%)
1b	7 (25%)
2	2 (7%)
FIGO stage	
IA	19 (68%)
IB	7 (25%)
II	2 (7%)
LVSI	
Yes	3 (11%)
No	23 (82%)
Unknown	2 (7%)
Chemotherapy	
Yes	6 (21%)
No	19 (68%)
Unknown	3 (11%)
Time from surgery to first recurrence (years)	1.7 (0.3-7.8)

Abbreviations: FIGO = The International Federation of Gynecology and Obstetrics; LVSI = lymphovascular space invasion.

months post-RT) and chronic (beyond 6 months post-RT) gastrointestinal (GI), genitourinary (GU), and gynecologic toxicities were graded according to the Common Terminology Criteria for Adverse Events v3.0.[11] *P* values of $< .05$ were considered significant.

Results

Baseline characteristics

The patient cohort consisted of 28 patients treated with SRT at our institution from 2004 to 2018. The median follow-up time after SRT treatment was 3.2 years. Although follow-up duration ranged from 0.16 to 13.7 years, the majority of patients were treated more recently (13 out of 28, 46%, received SRT between 2015 and 2018). Six patients were lost to follow-up 0.16, 2.1, 2.7, 4.3, 9.0, and 9.7 years, respectively, after salvage. Of note, the patient who was lost to follow-up after only 0.16 years had no evidence of disease at the time of last follow-up.

The median age at recurrence was 66 years (48–85 years), and the median time to recurrence after surgery was 1.7 years (0.3-7.8 years). The initial median tumor size at the time of initial surgery was 3.8 cm (1.0-8.2 cm; Table 1). Most patients had endometrioid histology (71%); the remainder included papillary serous, mixed mullerian, mucinous adenocarcinoma, or mixed histologies. Sixty-one percent, 18%, and 18% of patients had The International Federation of Gynecology and Obstetrics (FIGO) grade 1, 2, and 3 disease, respectively.

Most patients (68%) were initially staged as FIGO stage IA, but 25% of patients were FIGO stage IB and 7% were FIGO stage II. Lymphovascular space invasion was present in 11% of patients (Table 1). Overall, 12 (43%) of the patients included in our study had either stage II disease or high-intermediate risk disease based on age, tumor grade, depth of myometrial invasion, or lymph vascular invasion (Table E1).

First recurrences

Twenty-three of the 28 patients included in this study (82%) were treated for a first recurrence limited to the vagina (isolated local recurrence), 4 patients (14%) experienced regional recurrence only (1 pelvic lymph node, 1 perirectal mass, 1 intraluminal rectal mass, and 1 abdominal wall mass), and 1 (4%) experienced both local and regional recurrence (involving the vaginal apex and a pelvic/perirectal mass). The median time from surgery to first recurrence was 1.7 years (range, 0.3-7.8 years), and 61% of patients experienced recurrence during the first 2 years after surgery (Table 1). Once recurrence was diagnosed, patients began salvage after completion of appropriate workup (a median of 38 days after recurrence was first documented).

Salvage treatment

The details of SRT treatment, including doses, are shown in Table 2. Patients were treated with various RT techniques, including EBRT to the pelvis followed by an EBRT boost (6 patients), EBRT followed by either an IC brachytherapy boost (20) or an interstitial (IS) brachytherapy boost (1), or IC brachytherapy alone (1). Although there was no standardized SRT dose or fractionation scheme adopted at our institution, all but 1 patient received pelvic EBRT. One patient with a 1-cm nodule at the vaginal apex refused pelvic RT and was therefore treated with brachytherapy alone to a dose of 40

Table 2 Details of salvage radiation treatments at time of recurrence

Salvage therapy details	Number (%)
Treatment modality	
IC alone	1 (4%)
EBRT alone	6 (21%)
Pelvis and IC	20 (71%)
Pelvis and IS	1 (4%)
RT modality for patients treated with EBRT	
3D CRT	19 (68%)
IMRT	8 (29%)
Midline block used	
Yes	10 (36%)
No	18 (64%)
Para-aortic lymph nodes treated	
Yes	3 (11%)
No	25 (89%)
Abdomen treated	
Yes	1 (4%)
No	27 (96%)
Nodal boost delivered	
Yes	1 (4%)
No	27 (96%)
RT doses by treatment type	**Median (range)**
Total radiation dose (Gy)	
For all patients	60.6 (30.0-75.0)
For patients treated with EBRT alone	50.4 (45.0-66.0)
For patients treated with EBRT + IC/IS boost	60.6 (50.6-75.0)
IC only	40.0
Dose to pelvis (Gy)	45.0 (45.0-50.4)
Dose to abdomen (Gy)	54.0
Boost dose (Gy)	
All boosts	20.0 (5.40-30.0)
EBRT boost	12.6 (5.40-21.6)
IC/IS boost	20.0 (12.0-30.0)
IC boost details	
Cylinder size (cm)	3.0 (2.0-3.5)
Initial treatment length (cm)	8 (5-12)
Boost treatment length (cm)	4 (3-6)
Total dose in $EQD2_{10}$ (Gy)	
For all patients	67.6 (37.5-81.8)
For patients treated with EBRT alone	57.2 (49.6-65.5)
For patients treated with EBRT + IC boost*	69.3 (55.1-81.8)
For patients treated with EBRT + IS boost	89
For patients treated with IC only*	50
Total dose in BED (Gy)	
For all patients	81.1 (45.0-98.1)
For patients treated with EBRT alone	68.7 (59.5-78.6)
For patients treated with EBRT + IC boost*	83.1 (66.1-98.1)
For patients treated with EBRT + IS boost	107
For patients treated with IC only*	60

Abbreviations: 3D CRT = 3-dimensional conformal radiation therapy; BED = biologically effective dose; EBRT = external beam radiation; EQD2 = equivalent dose in 2 Gy fractions; IC = intracavitary; IMRT = intensity modulated radiation therapy; IS = interstitial; RT = radiation therapy.

* EQD2 and BED calculated at a depth of 0.5 cm for patients who received IC brachytherapy.

Gy delivered in 8 fractions. She was alive and free from evidence of recurrent disease at the time of last follow-up. Also, 6 patients received EBRT alone, and 5 of these had pelvic recurrences. The sixth patient received an EBRT boost to a bulky vaginal cuff mass because she was unable to undergo brachytherapy due to severe medical comorbidities. She received a 21.6 Gy boost to gross disease (her cumulative dose was 66.6 Gy, which was the highest dose that could safely be delivered while respecting normal tissue tolerances). She was also alive and free from evidence of recurrent disease at the time of last follow-up. The remaining 5 EBRT boost patients received 45 Gy to the pelvis and the following boost doses: 5.4 Gy to a perirectal mass, 9 Gy to an abdominal wall mass (located along the inferior aspect of the abdominal wall), 9 Gy to an intraluminal rectal mass, 16.2 Gy to a pelvic lymph node recurrence, and 18 Gy to a peri-rectal mass. Of note, the patient who received a boost to an abdominal wall mass was classified as having received a cumulative dose of 54 Gy to the abdomen because her pelvic field was extended to include the lower abdominal wall mass. EBRT boost doses were determined by individual patient factors, such as size of gross disease, and by the maximum dose that could be safely delivered while meeting dose constraints.

Nineteen patients in this study (68%) were treated with 3-dimensional conformal radiation therapy (3D CRT), whereas 8 were treated with intensity modulated radiation therapy (IMRT). All EBRT boosts except 1 were delivered using IMRT (3D CRT was used for 1 patient who received her boost in 2007, before the routine adoption of IMRT at our institution). In general, IMRT was used if dose constraints could not be met using 3D CRT. Normal tissue dose constraints were determined on an individual basis by the treating physician, and no standard constrains were applied.

Twenty-one (75%) of the patients included in this study received pelvic RT followed by a brachytherapy boost. Only 1 patient underwent an IS boost (to dose of 20 Gy in 4 fractions), while 20 received an IC boost. IC boost doses included the following: 12 Gy in 3 fractions (2 patients), 20 Gy in 4 fractions (9), and 30 Gy in 6 fractions (9).

Clinical outcomes

Second recurrence rates and survival outcomes after salvage treatment are shown in Table 3. The 2-year rate of

Table 3 Clinical outcomes after salvage therapy, calculated from time of salvage treatment

	1 year	2 year	3 year	4 year
Overall survival	92.6%	88.4%	82.9%	77.3%
Disease-free survival	88.9%	80.4%	80.4%	74.7%
Local recurrence	3.6%	7.1%	7.1%	7.1%
Regional recurrence	0%	0%	0%	0%
Distant metastases	10.7%	14.3%	14.3%	14.3%
Distant metastasis-free survival	88.9%	84.7%	84.7%	84.7%

DFS was 80.4%, whereas the 2-year rates of local recurrence and distant metastasis were 7.1% and 14.3%, respectively (Table 3). The 1-, 2-, 3-, and 4-year OS rates from the time of salvage were 92.6%, 88.4%, 82.9%, and 77.3%, respectively. Kaplan-Meier estimates of OS and DFS are shown in Figure 1. There were 6 deaths, 5 of which were due to endometrial cancer. Specifically, 4 patients developed distant metastasis and subsequently expired, and 1 had locally recurrent disease when she enrolled in hospice. The sixth patient had no evidence of disease at the time of her death.

Two patients experienced a second vaginal recurrence after salvage treatment. One patient developed an isolated second recurrence at the vaginal apex, within the field of prior salvage radiation, 1.1 years after SRT. Her first recurrence consisted of a less than 1-cm area of friable tissue at the vaginal cuff, which was superficial (no palpable thickness on examination). Her SRT consisted of 45 Gy to the pelvis followed by an IC boost to 12 Gy in 3 fractions (prescribed to a depth of 5 mm to a length of 12 cm for 2 fractions and 6 cm for 1 fraction). Her second recurrence was successfully treated with pelvic exenteration. The second patient also developed a second recurrence at the vaginal apex within the field of prior salvage radiation 0.6 years after SRT. This patient also developed metastatic disease at the time of her second recurrence. Her first recurrence consisted of a vaginal cuff lesion, which measured approximately 2 cm in diameter and 0.5 cm in depth. Her SRT consisted of 45 Gy to the pelvis with a midline block after 30.6 Gy, followed by an IC brachytherapy boost to 30 Gy in 6 fractions (prescribed to a depth of 5 mm and to a length of 8 cm for 4 fractions and 4 cm for 2 fractions). She ultimately succumbed to metastatic disease.

There was 1 isolated regional recurrence (involving the anterior rectal wall), which occurred 6.4 years after salvage, and there were 4 distant metastases (1 to bone, 1 to the omentum, and 2 to the lungs). Again, 1 patient who developed distant metastases also had concurrent local failure (0.6 years after salvage). The 2-year rate of DFS after salvage treatment was 80%.

Toxicity

Toxicity data were available for 21 of the 28 patients included in this study. There were very few acute GI and GU toxicities, all but 1 of which were grade 1. One patient experienced grade 2 diarrhea in the acute period. Three patients developed acute grade 1 or 2 vaginal stenosis, and 3 developed acute grade 1 vaginal discharge. No grade 3 or higher acute toxicities were seen (Table E2). Few patients developed chronic grade 1 GI or GU toxicities: 1 patient developed grade 2 diarrhea and 1 developed grade 2 urinary incontinence. Six patients developed chronic vaginal stenosis (1 grade 2, 1 grade 3). There were no grade 4 or 5 chronic toxicities.

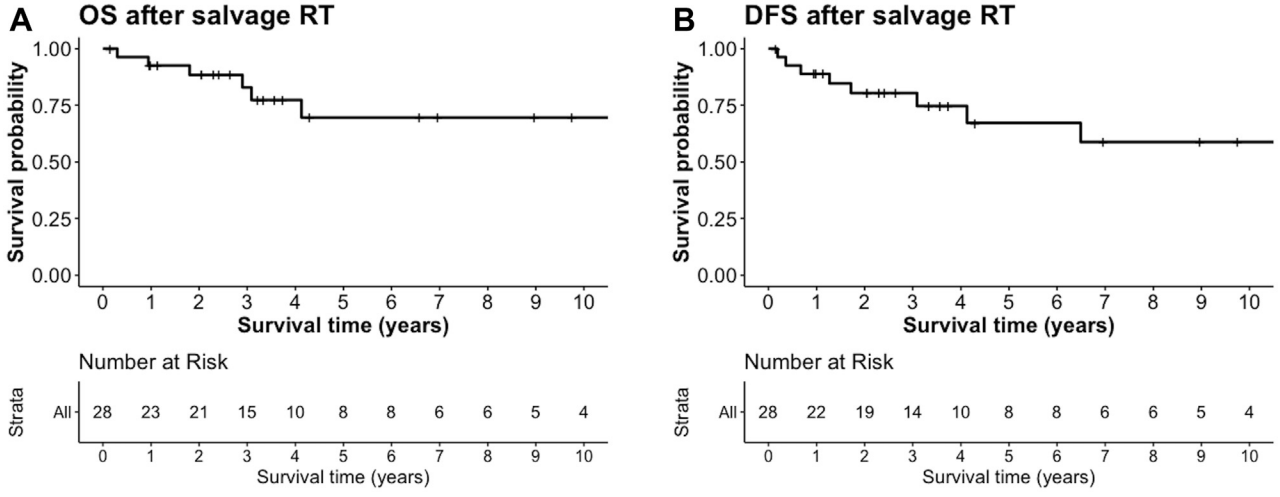

Figure 1 Kaplan-Meier estimates of overall survival (OS) (a) and disease-free survival (DFS) (b) after salvage radiation therapy (SRT).

Table 4 Summary of the literature on salvage therapy for patients with endometrial cancer who experience local and/or regional recurrence after surgical management alone[16-26]

	Yrs	Pts	Med fu	Pelv fail	Prior RT	Grade 3	Salvage radiation	Med dose (Gy)	Outcomes	Grade 3-5 toxicities
Arden (this work)	2004- 2018	28	21	Yes, 18%	No	18%	EBRT: 21% Brachy: 4% Both: 75%	Total: 60.6 EQD2: 67.6	4y LC 93% 4y DFS 75% 4y OS 77%	G3: 1 (6%)
Sekii et al.[26] (2017)	1992- 2014	37	48	No	Yes, 3%	16%	Brachy: 30% Both: 70%	EQD2: 62	4y LC 78% 4y PFS 57% 4y OS 81%	G3-5: 0
Baek et al.[25] (2016)	1997- 2012	43	58	No	Yes, 9%	12%	Brachy: 60% Both: 40%	EQD2: 69	5y LC 78% 5y PFS 52% 5y OS 84%	G3: 6 (14%) G5: 1 (2%)
Vargo et al.[24] (2014)	2004- 2013	41	18	No	No	22%	Both: 100%	Total: 76.0	3y LC 95% 3y RFS 68% 3y OS 67%	G3: 1 (2%) G4: 1 (2%)
Huh et al.[23] (2007)	1975- 2002	69	63	No	No	25%	EBRT: 90% Brachy: 3%	Not reported	5y OS 75%	Not reported
Petignat et al.[22] (2006)	1997- 2003	22	32	No	Yes, 9%	14%	Brachy: 18% Both: 82%	Not reported	5y LC 100% 5y DFS 96%	G3: 13 (59%) G4: 2 (9%)
Lin et al.[21] (2005)	1967- 2003	50	53	No	Yes, 22%	12%	EBRT: 6% Brachy: 16% Both: 78%	Total: 60	5y DFS 68% 5y OS 53%	G3-4: 5 (10%)
Jhingran et al.[20] (2003)	1960- 1997	91	58	No	Yes, 37%	31%	EBRT: 31% Brachy: 12% Both: 57%	Total: 75	5y LC 75% 5y DFS 45% 5y OS 43%	G3: 3 (3%) G4: 8 (9%)
Hasbini et al.[19] (2002)	1986- 1999	25	28	Yes, 28%	Yes, 28%	24%	Brachy: 12% Both: 54%	Not reported	3y OS 48%	G4: 1 (4%)
Jereczek-Fossa et al.[18] (2000)	1975- 1995	73	Not reported	Yes	No	27%	EBRT: 17% Brachy: 23% Both: 60%	Total: 75.9 Normalized Total: 86.6	5y OS 25%	G3: 1 (1%)
Nag et al.[17] (1997)	1989- 2000	15	47	No	Yes, 53%	Not reported	Brachy: 67% Both: 33%	Not reported	5y LC 67% 5y DFS 68% 5y OS 42%	G3: 1 (7%)
Sears et al.[16] (1994)	1973- 1991	45	89	Yes, 13%	No	13%	EBRT: 40% Brachy: 2% Both: 58%	Not reported	5y LC 54% 5y DFS 51% 5y OS 44%	G3: 1 (2%)

The following are outlined for each study: first author and year of publication; the years during which patients were treated (yrs); number of patients included (pts); length of median follow-up in months (med fu); whether patients with pelvic/regional failures were included (pelv fail); whether patients with prior adjuvant radiation therapy were included (prior RT); the percent with grade 3 disease (grade 3); the percent receiving external beam RT alone (EBRT), brachytherapy alone (brachy), or both EBRT and brachy (both); median total radiation dose reported as either total prescribed dose (total) or EQD2 (equivalent dose in 2 Gy fractions) (med dose, Gy); clinical outcomes after salvage radiation including local control (LC), disease-free survival (DFS), and overall survival (OS); and the number of patients who experienced chronic grade 3 to 5 toxicities (G3-5).

Discussion

Many patients with low- and intermediate-risk stage I endometrial cancer receive no adjuvant treatment after hysterectomy and experience low rates of recurrence. In this study, we found that the majority of patients treated with SRT for locoregional recurrence after hysterectomy and initial observation were successfully salvaged.

Our results are consistent with salvage rates from randomized trials. PORTEC-1, which randomized intermediate-risk patients to observation or pelvic RT, reported a 15% rate of locoregional recurrence 8 years after observation (10% vaginal, 5% pelvic).[12] Of those who then received SRT, 79% had a complete response, and updated results confirmed that most recurrences were local and were successfully treated with SRT.[13-15]

The existing data on SRT mostly consist of small retrospective series similar to our own, and these data and our findings are summarized in Table 4.[16-26] Although inclusion criteria, RT strategies, and reported outcomes vary considerably, most series show excellent local control after SRT, and our study compares favorably to these outcomes. This is particularly impressive given that our analysis included patients with both local and regional recurrences, while all but 3 others limited their analysis to patients with isolated vaginal recurrences.[16,18,19] Our findings importantly show that patients with regional recurrences can also be successfully salvaged, which is consistent with data supporting the ability of RT to control para-aortic lymph node disease.[27]

Although only 18% of the patients included in our study had grade 3 disease, this is consistent with similar series, where the percent of patients with grade 3 disease ranged from 12% to 31% (Table 3). Because these studies predominantly included patients with low-grade disease (grade 1-2), one must be cautious about generalizing these results to patients with grade 3 disease. Several studies have shown that tumor grade is predictive of OS.[20,25,26] However, the study by Jhingran et al[20] showed that tumor grade was not predictive of LC after recurrence, suggesting that SRT may be able to control local recurrence of grade 3 disease as well.

The small size of most studies of SRT makes correlating RT dose and outcomes challenging. However, 2 of the larger studies included in our review, those by Jhingran et al[20] and Jereczek-Fossa et al,[18] showed a higher RT dose, and the use of combined EBRT and brachytherapy were associated with improved local control and survival, respectively. However, higher doses might also lead to greater toxicity: although no studies have directly studied this, several studies included in Table 4 reported both high total doses and grade 4 to 5 toxicity events.[20,24,25] In contrast, our total dose was slightly lower, but we saw only 1 grade 3 and zero grade 4 or 5 toxicities. Additionally, Petignat et al[22] reported a 5-year local control of 100% but higher toxicities (rates of grade 3 and 4 events were 59% and 9%, respectively). However, the median total dose was not reported in the study by Petignat et al, making it difficult to interpret these findings. It is important that future studies of SRT for recurrent endometrial cancer include detailed reporting of RT doses as done here, so that a better understanding of the relationship between dose, local control, and toxicity can be gained. For now, any attempt to compare doses between studies must be done with great caution, because only a few studies have used equivalent dose in 2 Gy fractions (EQD2) to report doses. Also, brachytherapy doses can be prescribed in a variety of ways (to surface, depth, volume, etc), making comparison between studies difficult.

There is no standardized fractionation scheme for SRT for recurrent endometrial cancer; however, we noticed that the most common fractionations shifted over time. Twenty-one (75%) of the patients included in this study received pelvic RT followed by a high-dose radiation brachytherapy boost. Among these, 8 received either pelvic RT with a midline block (added after delivery of 30.6 Gy to the whole pelvis) and a brachytherapy boost of 30 Gy delivered in 6 fractions ($EQD2_{10}$, 67.6 Gy; biologically effective dose, 81.1 Gy), and 9 received pelvic RT without a block (to 45 Gy) and a boost of 20 Gy in 4 fractions ($EQD2_{10}$, 69.3 Gy; biologically effective dose, 83.1 Gy). Treatment with a block was the older preferred regimen (6 of the 8 patients treated this way were treated before 2013), while pelvic RT to 45 Gy followed by a 20 Gy boost was favored more recently (7 of the 9 patients treated this way were treated after 2013). Of note, no patient experienced a local recurrence after either of these SRT schemes. The use of combined EBRT and brachytherapy ranged from 40% to 82% in other studies (Table 4), and the total doses of our 2 most common fractionations (EQD2s 67.6 Gy and 69.3 Gy) are comparable to other studies that reported this metric (62-69 Gy).[25,26]

Although 21% of patients included in this study received chemotherapy, the role of chemotherapy in patients with locally recurrent endometrial cancer is unclear. Our rate of chemotherapy use is similar to other retrospective studies, which report rates of chemotherapy utilization for patients with recurrent disease ranging from 7% to 34%.[18,24] This question will be further addressed in the ongoing GOG 238 trial, which is randomizing patients with endometrial cancer and locoregional recurrence to whole pelvic RT therapy with or without concurrent cisplatin chemotherapy. All patients will receive a boost (IC, IS, or external beam) after whole pelvic RT.

Limitations to our study include our small patient cohort size and the retrospective design of the work. Also, because there were few recurrences after salvage therapy in our patient population, no univariate or multivariate analysis of predictors of outcome could be performed.

Conclusions

In summary, our study demonstrates that localized recurrence of endometrial cancer after surgery with initial observation can be successfully salvaged with good control and low toxicity.

Acknowledgments

We thank the Beaumont Health System Departments of Radiation Oncology and Gynecologic Oncology for their support.

Supplementary Materials

Supplementary material for this article can be found at https://doi.org/10.1016/j.adro.2020.08.012.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin*. 2017;67:7.
2. Creasman WT, Odicino F, Maisonneuve P, et al. Carcinoma of the corpus uteri. FIGO 26th Annual Report on the Results of Treatment in Gynecological Cancer. *Int J Gynaecol Obstet*. 2006; 95:S105.
3. Sorbe B, Nordstrom B, Maenpaa J, et al. Intravaginal brachytherapy in FIGO stage I low-risk endometrial cancer: A controlled randomized study. *Int J Gynecol Cancer*. 2009;19:873.
4. Keys HM, Roberts JA, Brunetto VL, 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.
5. Creutzberg CL, Nout RA, Lybeert ML, et al. Fifteen-year radiotherapy outcomes of the randomized PORTEC-1 trial for endometrial carcinoma. *Int J Radiat Oncol Biol Phys*. 2011;81:e631.
6. Fung-Kee-Fung M, Dodge J, Elit L, et al. Follow-up after primary therapy for endometrial cancer: A systematic review. *Gynecol Oncol*. 2006;101:520.
7. Sohaib SA, Houghton SL, Meroni R, et al. Recurrent endometrial cancer: Patterns of recurrent disease and assessment of prognosis. *Clin Radiol*. 2007;62:28.
8. Wui-Jin K, Abu-Rustum NR, Bean S, et al. *NCCN Guidelines Index Uterine Neoplasms Version 1*. 2018:1-109. Available at: https://www.nccn.org. Accessed September 28, 2020.
9. Salani R, Backes FJ, Fung MF, et al. Posttreatment surveillance and diagnosis of recurrence in women with gynecologic malignancies: Society of Gynecologic Oncologists recommendations. *Am J Obstet Gynecol*. 2011;204:466.
10. Nadeem R, Abu-Rustum M, Bean S, et al. *Uterine Neoplasms, Version 1.2020, NCCN Clinical Practice Guidelines in Oncology*. 2020:1-105. Available at: https://www.nccn.org. Accessed September 28, 2020.
11. Cancer Therapy Evaluation Program Common Terminology for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS. Available at: http://ctep.cancer.gov. Accessed August 9, 2006.
12. Creutzberg CL, van Putten WL, Koper PC, et al. Survival after relapse in patients with endometrial cancer: Results from a randomized trial. *Gynecol Oncol*. 2003;89:201.
13. Creutzberg CL, van Putten WL, Koper PC, 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*. 2000;355:1404.
14. Hemminki K, Aaltonen L, Li X. Subsequent primary malignancies after endometrial carcinoma and ovarian carcinoma. *Cancer*. 2003; 97:2432.
15. Nout RA, Putter H, Jurgenliemk-Schulz IM, et al. Quality of life after pelvic radiotherapy or vaginal brachytherapy for endometrial cancer: First results of the randomized PORTEC-2 trial. *J Clin Oncol*. 2009;27:3547.
16. Sears JD, Greven KM, Hoen HM, et al. Prognostic factors and treatment outcome for patients with locally recurrent endometrial cancer. *Cancer*. 1994;74:1303.
17. Nag S, Martinez-Monge R, Copeland LJ, et al. Perineal template interstitial brachytherapy salvage for recurrent endometrial adenocarcinoma metastatic to the vagina. *Gynecol Oncol*. 1997;66:16.
18. Jereczek-Fossa B, Badzio A, Jassem J. Recurrent endometrial cancer after surgery alone: Results of salvage radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000;48:405.
19. Hasbini A, Haie-Meder C, Morice P, et al. Outcome after salvage radiotherapy (brachytherapy +/- external) in patients with a vaginal recurrence from endometrial carcinomas. *Radiother Oncol*. 2002;65:23.
20. Jhingran A, Burke TW, Eifel PJ. Definitive radiotherapy for patients with isolated vaginal recurrence of endometrial carcinoma after hysterectomy. *Int J Radiat Oncol Biol Phys*. 2003;56:1366.
21. Lin LL, Grigsby PW, Powell MA, et al. Definitive radiotherapy in the management of isolated vaginal recurrences of endometrial cancer. *Int J Radiat Oncol Biol Phys*. 2005;63:500.
22. Petignat P, Jolicoeur M, Alobaid A, et al. Salvage treatment with high-dose-rate brachytherapy for isolated vaginal endometrial cancer recurrence. *Gynecol Oncol*. 2006;101:445.
23. Huh WK, Straughn JM Jr, Mariani A, et al. Salvage of isolated vaginal recurrences in women with surgical stage I endometrial cancer: A multiinstitutional experience. *Int J Gynecol Cancer*. 2007; 17:886.
24. Vargo JA, Kim H, Houser CJ, 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*. 2014;113:126.
25. Baek S, Isohashi F, Yamaguchi H, et al. Salvage high-dose-rate brachytherapy for isolated vaginal recurrence of endometrial cancer. *Brachytherapy*. 2016;15:812.
26. Sekii S, Murakami N, Kato T, et al. Outcomes of salvage high-dose-rate brachytherapy with or without external beam radiotherapy for isolated vaginal recurrence of endometrial cancer. *J Contemp Brachytherapy*. 2017;9:209.
27. Shirvani SM, Klopp AH, Likhacheva A, et al. Intensity modulated radiation therapy for definitive treatment of paraortic relapse in patients with endometrial cancer. *Pract Radiat Oncol*. 2013;3:e21.