

Gynecologic Oncology

High-dose-rate interstitial brachytherapy for vaginal endometrial cancer recurrence after prior surgery and radiotherapy

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ABSTRACT

PURPOSE: Characterize the clinical outcomes of endometrial cancer vaginal recurrences after previous surgery and radiation therapy treated with reirradiation including image-guided interstitial high-dose-rate (HDR) brachytherapy.

METHODS AND MATERIALS: A single-institution retrospective study identifying women receiving reirradiation for vaginal recurrence of endometrial cancer between 2004 and 2017.

RESULTS: Twenty-three women had vaginal recurrences of endometrial cancer, median 13.7 months (range 3.5–104.9) from initial radiation. All received reirradiation with interstitial HDR brachytherapy, and seven also received external beam radiation. Median reirradiation EQD2_10 was 48 Gy (range 24.0–68.81), and median cumulative EQD2_10 was 106.25 Gy (range 62.26–122.0). Median follow-up after reirradiation was 40.2 months (range 4.5–112.7). At 3 years, overall survival was 56%, cancer-specific survival was 61%, and disease-free survival was 46%. 14 patients experienced disease recurrence; 10 including distant sites, one at a regional node only. Three patients experienced local recurrences, two of whom did not complete the prescribed course of reirradiation. The overall crude local control rate was 87%. Three patients experienced Grade 3 vaginal toxicity. There was no bladder or rectal toxicity with Grade >2.

CONCLUSIONS: Reirradiation including interstitial HDR brachytherapy is a promising option for vaginal recurrences of endometrial cancer after prior radiation, with high rate of local control and acceptable toxicity. However, distant failure is common. Further studies are needed to determine cumulative radiation dose limits and the role of systemic therapy in this scenario. © 2020 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords:

Brachytherapy; Endometrial cancer; Local recurrence; Reirradiation; Salvage therapy; Retrospective

Introduction

After hysterectomy for endometrial cancer, adjuvant vaginal brachytherapy and/or pelvic external beam radiation therapy can reduce the risk of isolated locoregional recurrence to approximately <5% (1–3). Yet for patients who do have locoregional recurrences after initial adjuvant radiation therapy, there is little guidance on appropriate

treatment and expected outcomes. An analysis of prospectively collected data from the PORTEC1 randomized trial reported a 5-year survival of 43% after reirradiation with or without surgery in women who previously had adjuvant radiation (4). However, this only represented seven patients, and there was no information provided about the radiation therapy technique. The remaining data regarding reirradiation for locoregional relapse of endometrial cancer comes from smaller studies using a variety of doses and techniques (5), making comparisons across studies challenging. An American Brachytherapy Society task force concluded in 2017 that ideal volumes and dose for endometrial reirradiation are unknown and must be determined on a case-by-case basis (6).

HDR image-guided interstitial brachytherapy has been described in several studies as a useful technique for reirradiation due to precise targeting and steep dose gradients.

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Prospective studies including multiple gynecologic tumor types have provided details on techniques, dose limits, and potential toxicity (7–8). Retrospective series limited to recurrent endometrial cancer have provided additional data regarding expected outcomes (9–12). However, because these studies altogether still represent less than 200 patients receiving brachytherapy reirradiation for recurrent endometrial cancer, we have chosen to contribute our institutional experience and help further characterize the expected outcomes in this setting.

Material and methods

Patients

A single-institution prospective clinical database was reviewed to identify women who received radiation therapy between 2004 and 2017 for endometrial cancer recurrent after prior hysterectomy and radiation therapy (vaginal brachytherapy and/or external beam radiation therapy [EBRT]). Prior radiation therapy could be either adjuvant after initial surgery or for recurrence after initial surgery without adjuvant radiation. Inclusion criteria were histopathologically confirmed vaginal recurrence (with or without regional node recurrence) and no evidence of distant metastases at time of recurrence by imaging (CT or fluorodeoxyglucose (FDG)-positron emission tomography (PET)/CT. Stage of disease at initial surgery was recorded to match the International Federation of Gynecology and Obstetrics 2018 revised staging (13). This retrospective chart review was conducted under an institutional review board approved study.

Reirradiation

Reirradiation consisted of brachytherapy alone (typically in patients with prior EBRT) or brachytherapy with EBRT (typically in patients with prior brachytherapy only). All brachytherapy was performed using a vaginal cylinder with one central and six peripheral channels combined with transvaginal and transperineal interstitial catheters as needed. All brachytherapy implants included at least three transvaginal interstitial catheters, providing complete coverage of the vaginal cuff scar. Additional interstitial catheters were added based on extent of disease determined by imaging (e.g., nodules beyond the vaginal cuff apex, periurethral disease, or disease >5 mm deep from vaginal cuff mucosa). Catheters were placed freehand without template under transrectal ultrasonography guidance following a standard pattern (Fig. 1). Radiopaque gold fiducial markers were also placed in the vaginal cuff apex and any additional regions of interest. After implantation, a treatment planning CT scan was obtained. The CT scan as well as available PET and/or MRI imaging were used to delineate the clinical target volume (CTV), defined as gross disease, vaginal cuff scar line, and the upper vaginal

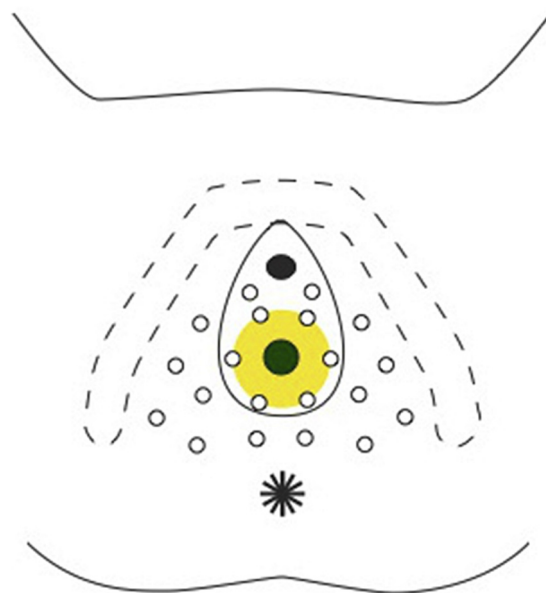


Fig. 1. Interstitial brachytherapy needle implant pattern. All plans included vaginal cylinder with central and six peripheral channels. Periurethral, perirectal, and perineal needles placed as needed based on tumor extent.

cuff mucosa to the level of the midpubic symphysis (Fig. 2). Organs at risk (OAR) including bladder, rectum, and small bowel were also contoured. Treatment planning was performed using 3-dimensional inverse planning—simulated annealing (Oncentra Brachy, Elekta) as detailed previously (14). Treatment planning goals were prescription dose to $\geq 90\%$ of the CTV and 75% of prescription dose (V75%) to less than 1 cc of rectum, bladder, or bowel. Patients received up to three fractions per implant, ≥ 6 h between fractions. Brachytherapy was delivered using an ^{192}Ir source via remote afterloading device (microSelectron, Elekta). In selected patients with larger tumors, radiosensitizing hyperthermia was also delivered via microwave antennae (BSD-500, Pyrexar Medical), and thermometers placed within the interstitial catheters, with the goal of maintaining a tissue temperature of 43°C for 60 min immediately after brachytherapy. EBRT was targeted to the vaginal cuff, pelvic lymph nodes (internal, external, and common iliac plus obturator chains), and additional lymph node regions as needed (inguinal for lower third vaginal involvement, para-aortic for common iliac, or para-aortic nodal involvement).

Outcome measures and statistics

Disease outcome measures were overall survival (OS), cause-specific survival (CSS), and disease-free survival (DFS). Actuarial estimates of OS, CSS, and DFS were determined by the Kaplan-Meier method. Recurrence locations after reirradiation were coded as “local” (vaginal cuff/periurethral), “regional” (pelvic or para-aortic lymph nodes), or “distant” (other lymph nodes, peritoneal, or hematogenous spread). Disease status was established by

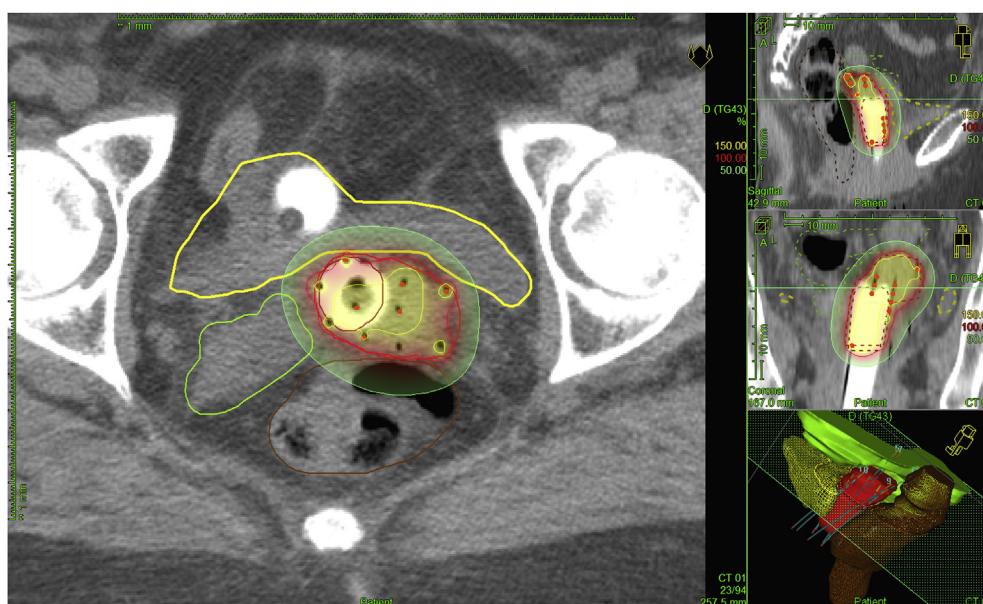


Fig. 2. Example interstitial brachytherapy treatment plan. Contoured structures include CTV, bladder, rectum, and small bowel. Dose color-wash indicates 150%, 100%, and 50% of prescription. (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

documented clinical examination and imaging. Patient records were cross referenced to a prospective multi-institutional cancer registry to obtain information about second recurrences or changes to vital status recorded by other institutions. For comparing radiation doses with varying fractionation, EBRT, and brachytherapy doses were converted to their equivalents in 2 Gy fractions using $\alpha/\beta = 10$ (EQD2_10) for tumor effects and $\alpha/\beta = 3$ (EQD2_3) for normal tissue effects (15). Treatment-related complications were evaluated using the Common Toxicity Criteria (CTCAE v4). Statistical computing was performed using R v.3.4.3 (R Statistical Foundation for Computing). Log-rank tests were used for univariate comparisons of DFS estimates by disease features. Fisher's exact tests were used to compare rates of toxicity grade 2–3 by reirradiation volume and doses dichotomized around the median. Statistical significance was determined at $p \leq 0.05$.

Results

Patients and initial treatment characteristics

Twenty-three women were identified who met the inclusion criteria. For 18 patients, reirradiation was performed at the first recurrence after initial surgery and adjuvant radiation. For five patients, reirradiation was performed at the second recurrence, with first radiation previously performed at recurrence after initial surgery alone. Initial disease characteristics are presented in Table 1. All patients underwent total abdominal hysterectomy and bilateral salpingo-oophorectomy and pelvic node sampling. Detailed

pathology reports were available for 15 patients; among those, the median number of nodes removed was 18 (range 4–54).

First course radiation details are included in Table 1. Three patients had received vaginal brachytherapy alone, all as 21 Gy in three fractions. Eight patients had received pelvic EBRT alone; the most common prescription was 45 Gy in 25 fractions ± 9 Gy sequential boost to the vaginal cuff (6/8 patients). 12 patients had received combined EBRT and vaginal brachytherapy. The most common reason combination radiation was recommended was for cervical stromal invasion (6/12 patients), and next most common was for local recurrence after surgery alone (3/12 patients). The most common prescription combination was 45 Gy in 25 fractions EBRT with 18 Gy in three fractions brachytherapy (6/12 patients).

Nine patients had chemotherapy as part of their initial adjuvant treatment, most commonly carboplatin/paclitaxel preceding radiation (6/9 patients). Two patients did not complete initial adjuvant EBRT and received only 14.4 Gy and 23.4 Gy; both patients had local recurrences within 6 months. The median prescription EQD2_10 for the initial course of radiation was 58.25 Gy (range 23.01–73.56 Gy), median EQD2_3 59.2 Gy (range 22.46–80.78 Gy).

Initial recurrence details

Tumor recurrence and reirradiation treatment details are listed in Table 2. The median time from completion of first course of radiation therapy to local recurrence was 13.7 months (range 3.5–104.9 months). The median age

Table 1
Initial tumor and therapy details

Characteristic	Patients	Percent
Initial tumor histology		
Endometrioid adenocarcinoma	12	52%
Papillary serous carcinoma	7	30%
Adenosquamous carcinoma	2	9%
Clear cell carcinoma	2	9%
Initial tumor grade		
1 (well differentiated)	4	17%
2 (moderately differentiated)	3	13%
3 (poorly differentiated)	16	70%
Initial tumor stage (FIGO 2018)		
IA	6	26%
IB	5	22%
II	4	17%
IIIA	1	4%
IIIB	1	4%
IIIC1	4	17%
IIIC2	2	9%
Initial tumor myometrial invasion		
Greater/equal to 50%	11	48%
Less than 50%	6	26%
Unknown	6	26%
Initial tumor lymphovascular invasion		
Present	12	52%
Absent	5	22%
Unknown	6	26%
Initial radiation type		
Combined EBRT and vaginal brachytherapy	12	52%
EBRT alone	8	35%
Vaginal brachytherapy alone	3	13%
Chemotherapy with initial radiation		
None	14	61%
Sequential to radiation	8	35%
Concurrent to radiation	1	4%

at reirradiation was 75 years (range 50–91). The median size of local recurrence nodule by pelvic examination was 2.0 cm (range 0.5–6.0 cm). Restaging imaging at the time

Table 2
Initial tumor recurrence and reirradiation details

Characteristic	Patients	Percent
Local recurrence location		
Vagina, NOS	6	26%
Vagina, upper third	5	22%
Vagina, middle third	5	22%
Vagina, lower third	3	13%
Periurethral	4	17%
Lymph node recurrence		
None	22	96%
Para-aortic	1	4%
Reirradiation type		
Vaginal/interstitial brachytherapy alone	16	70%
Combined EBRT and brachytherapy	7	30%
Interstitial hyperthermia with reirradiation		
No	21	91%
Yes	2	9%
Chemotherapy with reirradiation		
None	22	96%
Gemcitabine/carboplatin/paclitaxel after reirradiation	1	4%

of recurrence was performed by FDG-PET/CT in 14 patients. Nine patients were restaged using CT chest/abdomen/pelvis alone, although two had subsequent negative FDG-PET/CT after reirradiation. All patients except one had recurrent disease limited to the vaginal and periurethral area; one patient had an enlarged para-aortic lymph node in addition to a periurethral recurrence. The upper and middle third of the vagina were the most common recurrence locations. Three patients had vaginal recurrences tethered to the pelvic sidewall on pelvic examination.

Reirradiation

The most common reirradiation technique was interstitial brachytherapy alone (16 patients), performed in patients who had previously received pelvic EBRT with or without brachytherapy. 13 patients received 36 Gy in six fractions, one patient received 32 Gy in four fractions, one patient received 18 Gy in three fractions due to refusal of second implant, and one patient received 6 Gy \times 1 then 15 Gy \times 1 due to inability to tolerate bedrest for multiple fractions per implant. Seven patients underwent reirradiation by combined EBRT and interstitial brachytherapy. Two patients without prior pelvic EBRT and one patient who only received 14.4 Gy pelvic EBRT were treated with pelvic EBRT to 45 Gy followed by interstitial brachytherapy, 18 Gy in three fractions, or 16 Gy in two fractions. Two patients with recurrences in the lower vagina and prior pelvic EBRT received 45 Gy EBRT to the bilateral inguinal nodal regions, 30–45 Gy EBRT to the vagina, and interstitial brachytherapy 18 Gy in three fractions. One patient with recurrence in the lower vagina and initial vaginal brachytherapy only received 36 Gy EBRT to the pelvis, 50 Gy EBRT to the inguinal nodes, and interstitial brachytherapy 22.5 Gy in three fractions. Finally, one patient with prior pelvic EBRT and vaginal brachytherapy with a periurethral and para-aortic nodal recurrence received 54 Gy EBRT to the para-aortic region and 34 Gy EBRT to the periurethral area plus 15 Gy in three fractions interstitial brachytherapy. Two patients undergoing reirradiation with interstitial brachytherapy alone also received hyperthermia. One patient received chemotherapy with gemcitabine, carboplatin, and paclitaxel for nine cycles after combined EBRT/brachytherapy.

Reirradiation doses are reported in Table 3, including EBRT and/or brachytherapy; the median prescription EQD2_10 was 48.0 Gy for brachytherapy alone and 68.25 Gy for combined EBRT/brachytherapy. Reirradiation OAR doses were available for 18 patients. There were insufficient details from initial radiation plans to estimate cumulative OAR doses; however, the median cumulative prescription EQD2_10 was 106.25 Gy (range 62.26–122.0 Gy), and cumulative prescription EQD2_3 was 124.0 Gy (range 87.26–145.58 Gy). Brachytherapy treatment plan details were available for 24 implants/plans from

Table 3
Reirradiation dose volumes

Volume (number of patients)	Median (range)
CTV prescription EQD2_10	
All patients (23)	48.0 Gy (24.0–68.81 Gy)
Brachytherapy alone (16)	48.0 Gy (24.0–48.0 Gy)
EBRT and brachytherapy (7)	68.25 Gy (52.75–68.81 Gy)
CTV D90% EQD2_10	
All patients (17)	54.01 Gy (43.7–71.33 Gy)
Brachytherapy alone (10)	52.48 Gy (43.7–66.15 Gy)
EBRT and brachytherapy (7)	68.35 Gy (53.72–71.33 Gy)
Bladder D2cc EQD2_3	
All patients (17)	39.13 Gy (19.26–60.82 Gy)
Brachytherapy alone (10)	37.05 Gy (19.26–41.38 Gy)
EBRT and brachytherapy (7)	48.62 Gy (36.84–60.82 Gy)
Rectum D2cc EQD2_3	
All patients (17)	38.04 Gy (9.03–60.82 Gy)
Brachytherapy alone (10)	36.53 Gy (9.03–44.79 Gy)
EBRT and brachytherapy (7)	53.97 Gy (37.32–60.82 Gy)
Urethra D0.1 cc EQD2_3	
All patients (5)	87.77 Gy (39.13–102.64 Gy)
Brachytherapy alone (4)	70.61 Gy (39.13–91.3 Gy)
EBRT and brachytherapy (1)	102.64 Gy (NA)

17 patients (two implants/plans for seven patients); they are listed in [Supplemental Table S1](#).

Disease outcomes and recurrence after reirradiation

After a median follow-up of 40.2 months (range 4.5–112.7 months) after reirradiation, seven patients remained alive without recurrence, 13 patients were deceased from endometrial cancer after recurrent disease, two were deceased from other causes without recurrent disease, and one was deceased from other cause after recurrent disease. By Kaplan–Meier estimates, 3-year OS was 56% (median 55.8 months); 3-year CSS was 61% (median 63.1 months); and 3-year DFS was 46% (median 24.8 months ([Figs. 3–5](#))). Of the 14 patients with recurrences after reirradiation, the most advanced site at recurrence was distant for 10 patients (median 13 months from reirradiation), regional for two patients (16 and 19 months from reirradiation), and local only for two patients (25 and 36 months from reirradiation). 80%

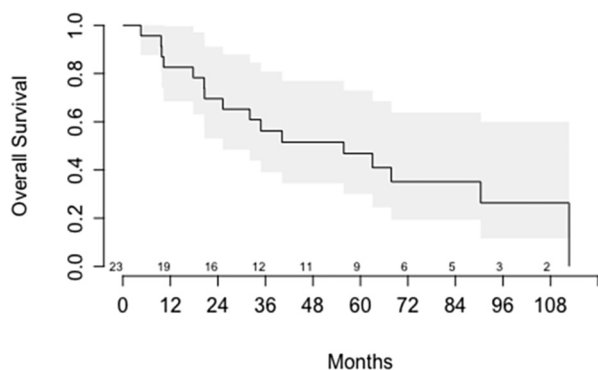


Fig. 3. Kaplan–Meier estimates of OS (3), CSS (4), and DFS (5) after reirradiation. Shaded area is 95% confidence interval.

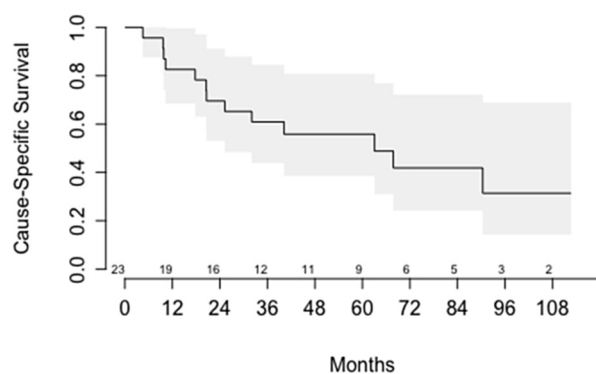


Fig. 4. Kaplan–Meier estimates of OS (3), CSS (4), and DFS (5) after reirradiation. Shaded area is 95% confidence interval.

of recurrences occurred within 24 months of reirradiation and 93% by 36 months.

Of the two patients who recurred with regional disease as the most advanced site, one was the patient with an involved para-aortic node at reirradiation, who recurred in another para-aortic node as well as in the vagina. The other was a patient who previously received pelvic EBRT after surgery, had a vaginal recurrence treated with interstitial brachytherapy alone, and then developed an obturator node recurrence without vaginal recurrence.

The two patients who recurred locally only after reirradiation had both chosen not to complete interstitial brachytherapy and received the lowest CTV doses (EQD2_10 equaled 24 Gy and 39.25 Gy). Only three patients had any recorded local recurrence after reirradiation, for a total crude local control rate of 87%. Other than one of the patients who received a low CTV dose, none of the patients with Grade 1 disease at initial presentation had recurrence after reirradiation. However, this association was not statistically significant ($p = 0.298$, log-rank comparison for DFS).

Initial tumor depth of myometrial invasion $\geq 50\%$ was a statistically significant univariate predictor of DFS after reirradiation ($p = 0.022$, recurrence in 2/6 vs. 9/11 patients), although this information was missing for six patients.

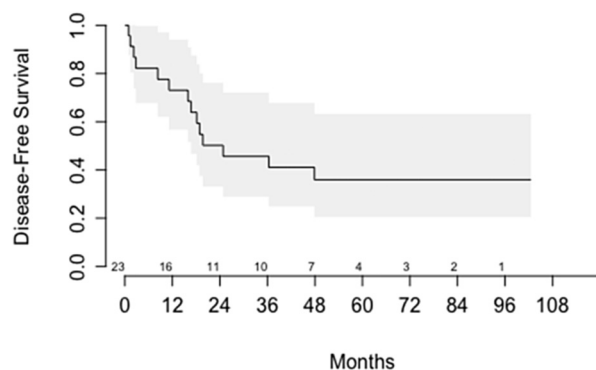


Fig. 5. Kaplan–Meier estimates of OS (3), CSS (4), and DFS (5) after reirradiation. Shaded area is 95% confidence interval.

Otherwise, there were no associations seen between initial disease characteristics and recurrence after reirradiation, including grade, endometrioid histology, lymphovascular invasion, or pelvic node involvement. There were no differences seen in recurrence after reirradiation between patients who received their first course of radiation as adjuvant or recurrence treatment. There were also no associations seen between recurrent tumor size and subsite (upper/middle/distal vagina or periurethral) with recurrence after reirradiation. There was no significant difference in rates of recurrence between patients restaged with PET/CT versus CT alone (Supplemental Table S2).

Treatment-related toxicity

17 patients had treatment-related toxicity reported after reirradiation. Three patients had Grade 1 toxicity and nine patients had Grade 2 toxicity, with vaginal strictures (5 patients), dysuria (3 patients), urinary frequency/urgency (2 patients), urinary incontinence (1 patient), and hematuria (1 patient). Four patients had Grade 3 vaginal mucositis/necrosis and were treated with hyperbaric oxygen. Grade 3 toxicity occurred a median of 5.5 months from completion of reirradiation (range 1.8–22.8 months). There was no association seen between occurrence of Grade 2–3 toxicity (13 patients) and CTV volume, reirradiation prescription dose or cumulative prescription dose (EQD2_3), or reirradiation OAR dose (bladder D2cc, rectum D2cc, or urethra D0.1 cc as EQD2_3; Supplemental Table S3).

Discussion

Our series describes reirradiation for endometrial cancer using primarily interstitial brachytherapy alone for patients with prior pelvic EBRT and interstitial brachytherapy plus pelvic EBRT for patients with prior vaginal intracavitary brachytherapy only. However, because of the retrospective design, there are significant areas of heterogeneity between patients, including use of chemotherapy, use of hyperthermia, and use of EBRT on additional nodal sites (inguinal or para-aortic). Strengths of the data include the consistent use of transrectal ultrasonography /CT image guidance and interstitial catheters for brachytherapy. Although the retrospective design is the primary limitation of our study, we collected long-term median follow-up of 40 months, with nearly all recurrences occurring before then.

The median CTV prescription dose as EQD2_10 was 48 Gy for patients treated with interstitial brachytherapy alone (median D90% 68.35 Gy) and 68.25 Gy for those treated with a combination of interstitial brachytherapy and pelvic EBRT (median D90% 68.35 Gy). These doses are similar to those recommended for newly diagnosed inoperable endometrial cancer (16). This provided a high rate of local control, with 87% of patients remaining free from local failure at last follow-up. The only isolated local

failures occurred in patients who did not complete reirradiation as prescribed and received less than 48 Gy EQD2_10. Although some isolated vaginal recurrences of endometrial cancer are <5 mm thick and conceivably amenable intracavitary brachytherapy only, in our experience interstitial catheters provide the best coverage of the gross disease and the CTV of the remaining vaginal cuff scar and upper vagina. In comparable studies such as Ling *et al.*, the median CTV D90% was 64.5 Gy EQD2_10 (12). They reported a 3-year local control of 65.8%. In that study, 55% of patients received intracavitary brachytherapy without interstitial needles. There were no identified predictors of local control, although local control rates for intracavitary versus interstitial implants were not examined. Huang *et al.* reported the use of intracavitary brachytherapy for 16 patients with previous radiation and 24 patients without prior radiation; local control was 60% at 24 months (10). By contrast, Kamran *et al.* reported 3-year local control of 78% with CT planning and 100% with MRI planning using interstitial brachytherapy and median EQD2_10 of 73.8–75.5 Gy (9). Baek *et al.* reported a 5-year local control of 85% using interstitial brachytherapy versus 56% with intracavitary brachytherapy, with a median EQD2_10 of 69 Gy (11). In our previous publication of interstitial brachytherapy for vaginally recurrent endometrial cancer without prior radiation, 5-year local control was 87% with median prescription dose 68.25 Gy EQD2_10. These retrospective series together suggest improved local control with interstitial brachytherapy and advanced image-based planning, although high-quality evidence is lacking.

The high rate of local control in our study was disappointingly coupled with a high rate of distant failure (43%). A similar rate of distant failure was seen in other reirradiation experiences, with Ling *et al.* reporting a 3-year distant control rate of 65%, and Huang *et al.* reporting a 2-year OS of 72% (10,12). The high rate of distant metastases in our series was also reflected in the low OS, 56% at 3 years. As only one of our patients received chemotherapy along with reirradiation, this raises the question of whether chemotherapy should be used more frequently, particularly in patients with initial risk factors. The ongoing Phase III trial GOG 238 is randomizing women with pelvic recurrence of endometrial cancer to radiation with or without concurrent cisplatin, although this has not yet reported results. Whether higher dose sequential chemotherapy would provide greater benefit is unknown.

In our series, the rate of Grade 3 toxicity was 17%. All toxicities occurred in the vagina with no high-grade rectal or bladder toxicity. However, due to the retrospective nature of our study, it is possible that high-grade toxicity is underreported. Detailed treatment plans for all patients were also unavailable, so we were also unable to conduct a more detailed analysis of toxicity and cumulative OAR doses. Other series with detailed toxicity data report rates of Grade 3 toxicity between 3.8% and 20% (7,8,10,12), with the

lowest rate reported by Ling *et al.* In that series, previous treatment plans were summed to ensure a cumulative rectal D2cc < 75 Gy and bladder D2cc < 90 Gy as EQD2_3. In the series reporting 20% Grade 3 toxicity, the median cumulative rectal D2cc was 111 Gy and bladder D2cc was 121 Gy, and toxicity was correlated with CTV volume (8). Because patients with pelvic recurrence of endometrial cancer may have limited options after repeated local recurrence, our practice has been to focus on target coverage and not expressly account cumulative radiation dose during radiation treatment planning. From the 2017 American Brachytherapy Society task force publication on recurrent endometrial cancer (6), “six of nine panelists agreed with the statement that in the retreatment setting, when choosing a retreatment dose, they choose a dose to the tumor that they believe will achieve local control even if this means exceeding normal organ at risk tissue tolerances.”

Conclusions

Reirradiation of locally recurrent endometrial cancer using interstitial brachytherapy with or without external beam radiation is an effective technique. Doses similar to those used in the setting of initially inoperable endometrial cancer provide a high rate of local control. Retrospective series suggest improved local control with interstitial technique and image-based planning. Distant relapse is common, and the role of chemotherapy in this setting needs to be further explored. Significant late toxicities may occur at a rate of 15–20%. This may potentially be reduced by controlling cumulative OAR doses, although current expert opinion advises not compromising target dose to meet normal tissue tolerance.

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Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.brachy.2020.12.011>.

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