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Outcomes after definitive re-irradiation with 3D brachytherapy with or without external beam radiation therapy for vaginal recurrence of endometrial cancer

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HIGHLIGHTS

- 22 patients treated with definitive re-irradiation brachytherapy ± EBRT for vaginal recurrence of endometrial cancer.
- No ≥G3 rectosigmoid or bladder toxicities when cumulative rectosigmoid and bladder D2cc (EQD2) limited to <75 Gy and <90 Gy.
- 3-year local control, disease-free survival, and overall survival rates were 65.8%, 40.8%, and 68.1%, respectively.
- Re-irradiation with 3D conformal brachytherapy is feasible and safe when cumulative dose to organs-at-risk is limited.

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ABSTRACT

Background. Limited outcome data exists on salvage re-irradiation for vaginal relapse of previously-irradiated endometrial cancer. We report our 10-year experience with management of vaginal recurrence using definitive intent re-irradiation brachytherapy with or without EBRT.

Methods. A retrospective review was performed on 22 patients treated with definitive-intent re-irradiation brachytherapy ± EBRT for vaginal recurrence of endometrial cancer. The cumulative rectosigmoid and bladder D2cc (EQD2) were limited to <75 Gy and <90 Gy, respectively. Kaplan-Meier and Cox proportional hazards modeling were used to estimate survival. Severe (grade 3 or higher) radiation-related toxicities, defined according to CTCAE v4, were recorded.

Results. Prior radiation therapy consisted of vaginal brachytherapy (54.5%), pelvic EBRT (22.7%), or combination pelvic EBRT and brachytherapy (22.7%). Median re-irradiation interval was 26.6 months. Salvage re-irradiation consisted of EBRT with brachytherapy in 50.0% and brachytherapy alone in 50.0%. Median HR-CTV D90 (EQD2) was 64.5 Gy (IQR: 49.6–75.8). Median cumulative D2cc for bladder, rectum, and sigmoid were 72.1 Gy (range: 30.3–81.8), 70.6 Gy (range: 32.0–80.5), and 52.7 Gy (range: 29.6–75.3), respectively. At a median follow-up of 27.6 months, 3-year local control, regional control, disease-free survival, and overall survival rates were 65.8%, 76.6%, 40.8%, and 68.1%, respectively. There were no grade ≥ 3 acute or late rectosigmoid or bladder toxicities.

Conclusion. Re-irradiation with 3D conformal brachytherapy for vaginal recurrence is feasible and safe as long as cumulative dose to surrounding normal organs is limited, and offers a chance to potentially salvage 40% of patients presenting with vaginal recurrence in the setting of prior pelvic radiation.

1. Background

Women with early-stage endometrial cancer who have pathologic risk factors have a 10–15% risk of pelvic relapse after surgery alone, which is decreased to <5% with adjuvant radiation therapy [1–3]. About 75% of pelvic relapses occur in the vagina [2]. There is limited data on salvage re-irradiation therapy for patients with vaginal relapse of endometrial cancer treated with prior pelvic radiation therapy. In the PORTEC-1 trial, the reported salvage rate for vaginal cuff recurrence

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after prior external beam radiation therapy (EBRT) was 43%, with 3 out of 7 patients reported as having sustained complete remission after initial response assessment [4]. However, few details on the dose and technique of salvage therapy were given, and little guidance exists with respect to appropriate salvage treatment technique. According to the 2016 American College of Radiology Appropriateness Criteria, management options for recurrence of endometrial cancer within a previously irradiated area include surgery with or without re-irradiation, hormonal therapy, and/or chemotherapy [5]. Prior reports indicate that surgery consisting of pelvic exenteration may result in 5-year disease-free survival rates of 45%, but at the cost of significant morbidity and up to a 5% operative mortality rate [6,7]. While re-irradiation for vaginal recurrence may be an appropriate treatment option for some patients, outcome data is restricted to small retrospective series with limited sample sizes [8–10].

Given the scarcity of data on re-irradiation in this setting, the salvage rate, survival outcomes, and complications of such treatment are not well characterized. Modern 3D image-guidance techniques during brachytherapy are crucial to assuring proper applicator placement and allow precise delineation of target and organ-at-risk volumes. This results in improved ability to optimize dose to the target while minimizing dose to critical organs [11–14]. We thus aimed to report our institution's 10-year experience with management of vaginal recurrence by definitive intent re-irradiation using modern 3D image-guided brachytherapy technique, with or without EBRT.

2. Methods

2.1. Patient characteristics

A retrospective review was performed on 22 patients treated with definitive-intent re-irradiation brachytherapy ± EBRT for vaginal recurrence of endometrial cancer. Patients treated with palliative intent were excluded, as were those with distant metastases, with the exception of one patient with a concurrently diagnosed lung oligometastasis treated with definitive intent lung SBRT and one patient with concurrently diagnosed omental and vaginal recurrence who had complete resolution of omental disease after treatment with salvage chemotherapy; both of these two patients went on to have definitive intent pelvic EBRT with vaginal brachytherapy despite their limited distant disease and were included in this study.

Patients underwent vaginal biopsy for confirmation of disease recurrence, and patients underwent staging with either computed tomography (CT) or positron emission tomography (PET)/CT scan of the chest, abdomen, and pelvis to evaluate for pelvic nodal involvement and distant metastasis. Most patients (n = 19, 86.3%) also underwent a gadolinium contrast-enhanced pelvic magnetic resonance imaging (MRI) scan with water-based vaginal gel to better assess the extent of local disease and guide brachytherapy planning.

2.2. Re-irradiation treatment technique

Salvage re-irradiation therapy consisted of vaginal brachytherapy with or without pelvic EBRT. The choice of radiation technique was based on prior dose received by critical organs such as the rectum, bladder, and sigmoid colon, and whether patients had ever received prior pelvic EBRT. Patients who previously received pelvic EBRT were not considered candidates for re-irradiation with EBRT, and received vaginal brachytherapy alone.

EBRT was delivered using either CT- or PET/CT-based planning. Simulation scans were performed with an empty rectum and with both full and empty bladder, to generate an internal target volume to account for variation in bladder filling. The EBRT clinical target volume (CTV) included the entire vagina, paravaginal tissues, and distal common iliac, external and internal iliac, and obturator lymph nodes. Inguinal nodes were included if the distal one-half of vagina was involved. The CTV was expanded by 0.7 to 1 cm around the vagina and 7 mm around the lymph node volumes to create a planning target volume (PTV). EBRT was delivered to the entire vagina, paravagina, and pelvic lymph nodes to 30.6 Gy at 1.8 Gy per fraction, followed by a sequential boost to the pelvic nodes to a total dose of 45 to 50.4 Gy at 1.8 Gy per fraction. Involved nodes were treated with either a sequential boost to approximately 60 Gy, or a simultaneous integrated boost using 55 Gy in 25 fractions, a technique which we have previously described [15]. EBRT dose to the central structures, including the vaginal and paravaginal disease, was limited to 30.6 Gy in order to allow safe delivery of an additional dose of around 30 Gy in 2-Gy equivalents with subsequent brachytherapy. Daily image-guidance with either kV imaging or cone-beam CT was utilized.

All patients received 3D image-guided vaginal brachytherapy, delivered using a high-dose-rate (HDR) ^{192}Ir afterloader (Nucleotron, Elekta AB, Stockholm, Sweden). Depending on the extent and eccentricity of disease, either intracavitary or interstitial brachytherapy technique was utilized. For patients treated with an intracavitary applicator, early in our experience we used a non-MRI-compatible custom five-channel multi-channel vaginal cylinder (MCVC) applicator with 1 central and 4 peripheral channels. Subsequently, we used commercially available MRI-compatible applicators with 1 central and 6 or 8 peripheral channels (Nucletron, Elekta AB, Stockholm, Sweden). The MCVC applicator was placed prior to each fraction, and a planning CT and/or MRI scan was obtained with the applicator in place. CT-based planning was used prior to the availability of an MRI-compatible MCVC or in patients with contraindications to MRI. Most patients (77.3%) in this series underwent MRI-based brachytherapy planning, while the remainder underwent CT-based planning (22.7%). Further details of our treatment planning technique using MCVC have been previously described [11,12].

Patients with disease measuring >0.5 cm in thickness at the time of brachytherapy were treated with an interstitial approach. Patients underwent placement of the interstitial needles via a perineal template in the operating room, and typically received 5 fractions on a twice-daily schedule as an inpatient.

Brachytherapy was directed to the high-risk clinical target volume (HR-CTV), which was delineated based on both the pre-EBRT and post-EBRT gross tumor volume as defined by imaging and clinical examination. The length of vagina to which the mucosal surface was treated was determined by the extent of the pre-EBRT GTV, whereas the extent of post-EBRT GTV defined the area for which the entire thickness of the vagina plus residual disease was included. For disease limited to one wall, the circumferential wall of the vaginal surface at that level was included in the HR-CTV. Uninvolved vagina was not included in the brachytherapy treatment volume, and no intermediate-risk CTV was used.

Doses were converted to equivalent dose in 2-Gy fractions (EQD2) using the linear quadratic model, with alpha/beta ratios of 10 and 3 for target and organs-at-risk, respectively. Cumulative dose delivered to organs-at-risk was calculated by summating the doses from prior pelvic radiation treatments and re-irradiation EBRT and brachytherapy. The total dose delivered to the HR-CTV was governed by dose to critical organs, with a cumulative EQD2 of >60 Gy considered ideal. However, if it was not feasible to achieve this dose without compromising normal organ constraints, a lower HR-CTV dose was accepted. At our institution, our principle is to limit the cumulative rectosigmoid and bladder D2cc (EQD2) to <75 Gy and <90 Gy, respectively, and respecting these limits took precedence over target dose delivery. No dose reduction for potential repair was considered.

2.3. Statistical analyses

Kaplan-Meier modeling was used to estimate disease control and survival, which were calculated from the last day of re-irradiation treatment to the date of failure, death, or last follow-up. Local failure was

defined as vaginal recurrence, and regional recurrence was defined as recurrent disease within the pelvis or pelvic nodes. Cox logistic regression was used to assess for association between patient and treatment factors and clinical outcomes. A p-value of <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS Version 24 (IBM, Armonk, NY). Severe (grade 3 or higher) radiation-related toxicities, defined according to Common Terminology Criteria for Adverse Events v4, were recorded based on review of individual patient records.

3. Results

3.1. Patient and disease characteristics

Twenty-two patients were treated with definitive-intent re-irradiation for vaginal recurrence of endometrial cancer between August 2008 and July 2018, and were included for analysis. Baseline patient and treatment characteristics are shown in Table 1. Histology was endometrioid in 18 (81.8%) and papillary serous or clear cell in 4 (18.2%). All patients had undergone prior surgical staging of their primary tumor consisting of total abdominal hysterectomy, bilateral salpingoophorectomy, and pelvic lymphadenectomy with or without para-aortic lymphadenectomy, with the exception of 1 patient who was medically inoperable at diagnosis and treated with upfront radiation therapy alone. All patients had received prior radiation therapy, either as part of treatment for their uterine cancer (n = 21, 95.5%) or for a prior history of rectal cancer (n = 1, 4.5%). Prior radiation therapy consisted of vaginal brachytherapy in 12 (54.5%), pelvic EBRT in 5 (22.7%), and combination pelvic EBRT and vaginal brachytherapy in 5 (22.7%). Of the 10 patients who had received prior EBRT, 5 were treated with intensity-modulated radiation therapy, 4 were treated with 3D conformal radiation therapy, and for 1 patient the radiation treatment technique was unable to be determined based on chart review. The median prior EBRT dose was 45 Gy (range: 30.6–50.4) in 25 fractions, and the most common prior brachytherapy regimen was 21 Gy in 3 fractions delivered to the vaginal cuff using a vaginal cylinder. Median time from prior radiation therapy to re-irradiation was 26.6 months (interquartile range, IQR: 17.2–54.4).

Among patients with MRI done at the time of diagnosis of vaginal recurrence (n = 19), the median tumor size as measured on MRI scan was 2.3 cm (IQR: 0.3–3.3 cm). Tumor was located predominantly in the upper, middle, and lower third of vagina in 68.2% (n = 15), 18.2% (n = 4), and 13.6% (n = 3) of cases, respectively. Recurrent tumor involving the upper to middle third of vagina was in-field recurrence, while distal vaginal tumor was considered out-of-field recurrence. The exception was one patient who had initial distal vaginal involvement where the distal vagina was included in the prior radiation volume, so this patient was classified as having in-field recurrence. Thus, 20 (90.9%) of recurrences were in-field, and 2 (9.1%) were out-of-field. Two (9.1%) patients had a concurrent nodal recurrence; one was treated with a sequential boost to 59.4 Gy in 27 fractions to the involved nodal disease, and one was treated with a simultaneous integrated boost with EBRT to 55 Gy in 25 fractions. Two (9.1%) had a concurrent distant recurrence, but underwent definitive treatment as previously described above in the Methods section.

3.2. Salvage treatment characteristics

Table 2 displays details of the salvage treatments patients received as part of management of their vaginal recurrence. Eleven (50.0%) patients received re-irradiation EBRT in addition to vaginal brachytherapy, while the remaining 11 (50.0%) received brachytherapy without EBRT. Eight patients (36.4%) received salvage chemotherapy (5 sequentially prior to re-irradiation, 3 concurrently with radiation). Concurrent chemotherapy consisted of weekly cisplatin, while sequential

Table 1
Patient, disease, and prior treatment characteristics.

	N[a] (total = 22)	%
Histology		
Endometrioid	18	81.8%
Papillary serous or clear cell	4	18.2%
Median age at time of re-irradiation (range)	71 (49–90)	–
2009 FIGO stage at diagnosis		
IA	8	36.4%
IB	5	22.7%
II	3	13.6%
IIIA	3	13.6%
IIIC1 or IIIC2	3	13.6%
Grade at diagnosis		
Grade 1	6	27.3%
Grade 2	11	50.0%
Grade 3	5	22.7%
Presence of LVSI at diagnosis		
Yes	8	36.4%
No	9	40.9%
Unknown	5	22.7%
Prior pelvic radiation type		
Vaginal brachytherapy	12	54.5%
Pelvic EBRT	5	22.7%
Pelvic EBRT + vaginal brachytherapy	5	22.7%
Median prior EBRT dose (Gy) (range)	45 (30.6–50.4)	–
Prior brachytherapy dose regimen		
21 Gy in 3 fractions	9	40.9%
30 Gy in 6 fractions	2	9.1%
10 Gy in 2 fractions	2	9.1%
Other	4	18.2%
Prior chemotherapy		
Adjuvant	5	22.7%
Neoadjuvant	1	4.5%
Salvage	1	4.5%
Median re-irradiation interval (months) (IQR)	26.6 (17.2–54.4)	–

[a] Unless otherwise specified. LVSI = lymphovascular space invasion. EBRT = external beam radiation therapy. IQR = interquartile range.

Table 2
Salvage treatment characteristics.

	N[a] (total = 22)	%
Re-irradiation type		
Brachytherapy alone	11	50.0%
EBRT + brachytherapy	11	50.0%
Median re-irradiation pelvic EBRT dose (Gy) (range)	45 (24–45)	
Brachytherapy technique		
MCVC	11	50.0%
MCVC with free-hand needles	2	9.1%
Interstitial	8	36.4%
Single-channel vaginal cylinder	1	4.5%
Re-irradiation brachytherapy regimens (intracavitary)		
30 Gy in 6 fractions	6	27.3%
Other	8	36.4%
Re-irradiation brachytherapy regimens (interstitial)		
25 Gy in 5 fractions	4	18.2%
22.5 Gy in 5 fractions	2	9.1%
27.5 Gy in 5 fractions	1	4.5%
31.7 Gy in 7 fractions	1	4.5%
Median HRCTV (cc) (IQR)	23.2 (13.0–30.6)	–
Median HRCTV D90, EQD2 (Gy) (IQR)	64.5 (49.6–75.8)	–
Median cumulative D2cc, EQD2 (Gy) (IQR)		
Bladder	72.1 (30.3–81.8)	–
Rectum	70.6 (32.0–80.5)	–
Sigmoid colon	52.7 (29.6–75.3)	–
Salvage surgery		
Yes	5	22.7%
No	17	77.3%
Salvage chemotherapy		
Sequential	5	22.7%
Concurrent	3	13.6%
None	14	63.6%
Salvage hormonal therapy	3	13.6%

[a] Unless otherwise specified. EBRT = external beam radiation therapy. MCVC = multichannel vaginal cylinder. HRCTV = high-risk clinical target volume. EQD2 = equivalent dose in 2-Gy fractions. IQR interquartile range.

chemotherapy consisted of carboplatin and paclitaxel in 3 patients, ifosfamide and taxol in 1 patient, and unknown agent/s in 1 patients. Five patients underwent salvage surgery for their local recurrence prior to undergoing re-irradiation, consisting of partial vaginectomy in 3 patients, wide local excision of vaginal introitus recurrence in 1 patient, and cytoreductive surgery with tumor debulking of a concurrent cul de sac recurrence in 1 patient. Three patients (13.6%) received salvage hormonal therapy, consisting of megestrol acetate (n = 2) or both megestrol acetate and tamoxifen (n = 1). Median re-irradiation pelvic EBRT dose was 45.0 Gy (range: 24–45) in 25 fractions, and median EBRT dose to the central structures was 28.8 Gy (range: 23.4–30.6). Median re-irradiation brachytherapy dose was 28.75 Gy (IQR: 24.8–30) delivered over 4 to 7 fractions. The brachytherapy technique used was intracavitary multichannel vaginal cylinder (MCVC) in 11 (50.0%) patients, MCVC with free-hand needles in 2 (9.1%), interstitial needles with perineal template in 8 (36.4%), and single-channel vaginal cylinder in 1 (4.5%). Median HR-CTV at the time of brachytherapy was 23.2 cc (IQR: 13.0–30.6), and median HR-CTV D90 (EQD2) was 64.5 Gy (IQR: 49.6–75.8). Median cumulative D2cc (EQD2) to bladder, rectum, and sigmoid, including contribution from prior radiation courses, were 72.1 Gy (range: 30.3–81.8), 70.6 Gy (range: 32.0–80.5), and 52.7 Gy (range: 29.6–75.3), respectively.

3.3. Disease outcomes and toxicity

With a median follow-up of 27.6 months (IQR: 7.5–50.0), the 3-year local control, regional control, distant control, disease-free survival, and overall survival rates were 65.8%, 76.6%, 64.6%, 40.8%, and 68.1%, respectively (Fig. 1). On Cox regression analysis, histology (endometrioid vs. non-endometrioid) did not predict for local control (3-year local control 67.6% vs. 75.0%; $p = 0.668$, HR 1.66, 95% CI 0.17–16.64). HR-CTV D90 greater or equal to median of 65 Gy did not predict for local control (3-year local control 78.8% for D90 ≥ 65 Gy vs. 50.5% if D90 < 65 Gy; $p = 0.480$, HR 0.54, 95% CI 0.10–2.99). Use of re-irradiation EBRT plus

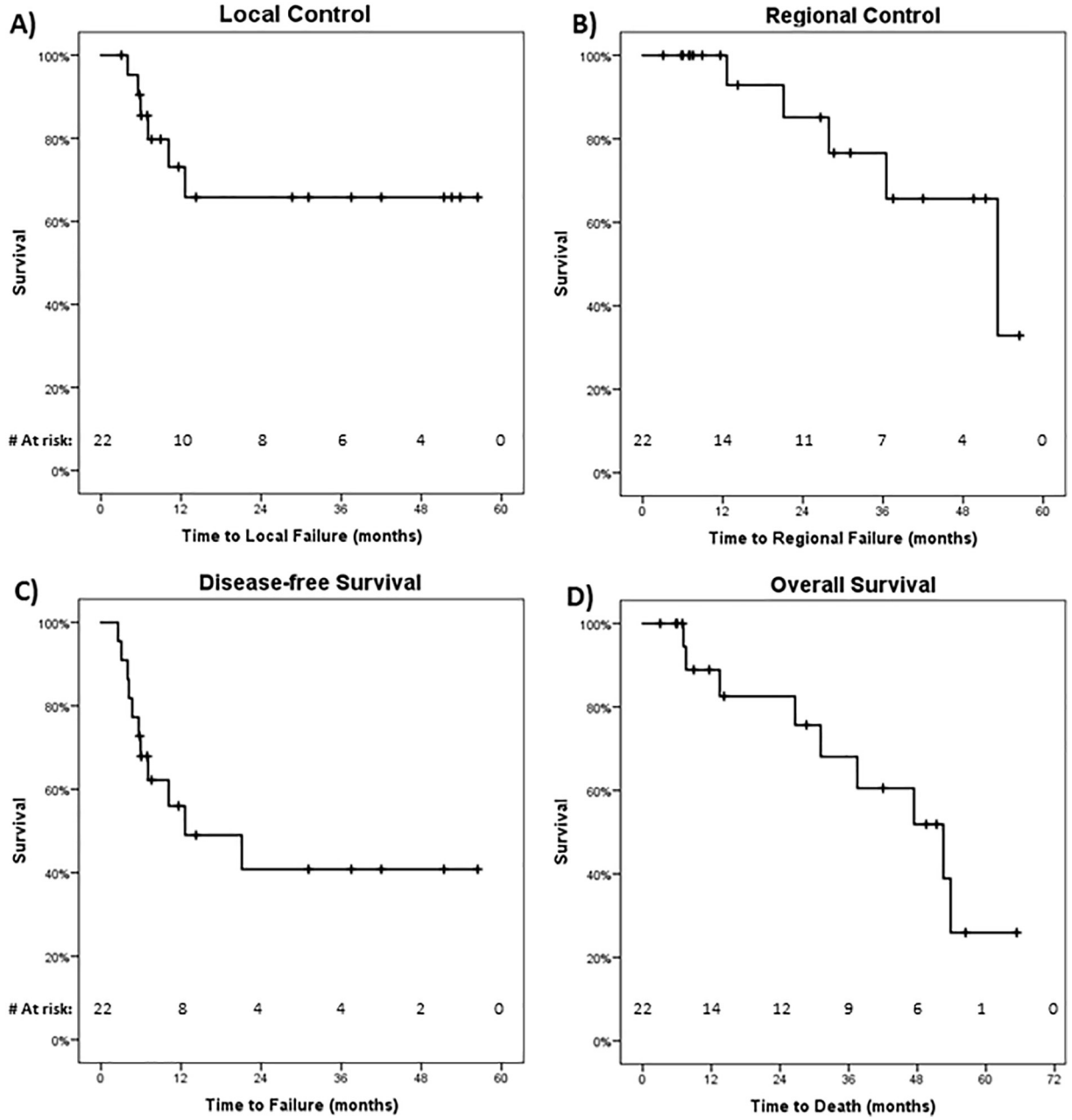

Fig. 1. Kaplan Meier survival curves displaying actuarial (A) local control, (B) regional control, (C) disease-free survival, and (D) overall survival.

brachytherapy vs. brachytherapy alone did not predict for local control (3-year local control 61.7% vs. 71.6%; $p = 0.981$, HR 1.02, 95% CI 0.21–5.09). Recurrence-free interval did not predict for local control ($p = 0.677$) or disease-free survival ($p = 0.227$). There were no grade ≥ 3 acute radiation-related toxicities, and no patients developed late severe rectosigmoid or bladder toxicity. One (3.8%) patient developed a late grade 3 left ureteral stricture requiring chronic stent placement.

4. Discussion

Re-irradiation for vaginal recurrence of endometrial cancer in the setting of prior pelvic radiation poses significant challenges due to difficulty delivering a therapeutic dose while respecting normal organ tolerances. Because of limited published data, the optimal tumor dose and true normal tissue tolerance, salvage rate, survival outcomes, and complication rates of re-irradiation in this setting are not known. Modern radiation techniques such as 3D image-guided brachytherapy and intensity-modulated radiation therapy have improved the ability to control dose delivered to the target and organs-at-risk [12–14]. We sought to evaluate the outcomes and toxicities of re-irradiation for vaginal recurrence of endometrial cancer when using our modern treatment approach incorporating 3D image-guided brachytherapy. To our knowledge, ours is one of the largest series on re-irradiation of vaginal recurrence of endometrial cancer. Our study is also one of the few which reports the cumulative dose received by organs-at-risk, including dose contribution from both the prior radiation and re-irradiation courses. We found that when the cumulative rectosigmoid and bladder D2cc (EQD2) were limited to <75 Gy and <90 Gy, respectively, no patients experienced severe acute or late rectosigmoid or bladder toxicity, while 3-year local control and disease-free survival rates of 65.8% and 40.8%, respectively, were achieved.

According to the American Brachytherapy Society (ABS) task force review on recurrent endometrial cancer, management options for patients who recur within a previously-irradiated area include pelvic exenteration, re-irradiation, or systemic therapy [16]. Considering the wide range of doses and volumes that patients who received prior radiation therapy may have been treated with, the ideal re-treatment dose and volume for optimizing local control while keeping treatment safe are unknown. Given the lack of evidence-based guidance on re-irradiation in this setting, the ABS task force describes two treatment approaches that have been utilized. The first approach is to limit cumulative normal organ doses just as in the upfront setting, and the second is to purposefully exceed the accepted tolerance of normal tissues in order to deliver a higher dose to the target. There was no consensus between the ABS panelists over which of these two approaches to follow, with 6 of 9 panelists stating that they would choose a re-treatment dose they believe would achieve local control even if it meant exceeding normal organ tissue tolerances.

Given the lack of evidence-based guidance, our institutional philosophy is to err on the side of caution in prioritizing normal organ cumulative dose limits over target dose delivery. This approach has been adopted by our treating physicians for re-irradiation cases of recurrent endometrial cancer. One explanation for the lack of severe complications in our series is that cumulative dose to rectosigmoid and bladder were kept below pre-specified dose limits. We aimed for D2cc (EQD2) to the rectosigmoid and bladder of <75 Gy and <90 Gy, respectively, which are extrapolated based on data from definitive treatment of cervical cancer patients and are the dose constraints set forth by the ABS for HDR cervix brachytherapy [17,18]. In addition, our reported complication rate does not take into account the factor of normal tissue recovery. The median re-irradiation interval in our study was over 2 years, but we did not account for normal tissue recovery when considering cumulative organ-at-risk dose limits.

Since the complication rate in our study was so low, there may be opportunity for further dose escalation to potentially improve the salvage rate, albeit with caution because the exact dose tolerance of the rectosigmoid and bladder are unknown, especially with varying re-irradiation intervals. Injection of a hydrogel spacer in between the bladder and rectum may be one method of decreasing dose to the rectum worth exploring to allow further dose-escalation safely [19]. There has been suggestion of a potential dose response with improved local control using doses > 40 Gy EQD2 [20]. We found that the 3-year local control rate was numerically higher for patients receiving HR-CTV D90 ≥ 65 Gy (78.8% vs. 50.5%), although this finding was non-significant, possibly due to the small sample size. At this time, the extent of possible dose escalation is not known. As there exists a fine balance between local control and complications, more data is needed in order to better define the optimal dose to meet this balance.

A retrospective study from Lee et al. reported on 44 women receiving salvage radiation therapy for vaginal recurrence of endometrial cancer with 3D image-guided brachytherapy, but only 13 patients in that series had received prior radiation therapy, which included vaginal brachytherapy (n = 6), pelvic EBRT (n = 4), and vaginal brachytherapy plus pelvic EBRT (n = 3) [9]. For these 13 patients undergoing re-irradiation, salvage radiation consisted of brachytherapy alone in 6 and EBRT plus brachytherapy in 7. The 2-year local failure, disease-free survival, and overall survival rates were 39%, 26%, and 55% for patients with prior radiation therapy, compared to 4%, 72%, and 80% for those without prior radiation therapy. In contrast to our study, grade 3 late toxicities were reported in 3/13 (23%) of patients, consisting of colovaginal fistula, vulvovaginal necrosis requiring operative debridement, and proctitis requiring colostomy or transfusion. The reason for this discrepancy is not clear and may have to do with small sample size, although at the author's institution the practice was to discount prior radiation dose to organs-at-risk by approximately 10% per year to maintain cumulative doses to an EQD2 of <70–75 Gy if feasible. This is in contrast to our practice, where we do not discount prior dose over time and prioritize organ-at-risk dose limits over target dose. While the median D2cc to the bladder, rectum, and sigmoid were lower than in our study, the full range of D2cc to these organs was not reported, so it is not clear what upper limit dose was received by the organs-at-risk in their series. In addition, the authors in that study covered perceived microscopic disease in the intervening vaginal lymphatics by including the entire length of vagina in an intermediate-risk clinical target volume (IR-CTV) for brachytherapy, which was specified to receive a minimum EQD2 of 60 Gy. By contrast, we directed brachytherapy to the HR-CTV, defined by the pre-EBRT length of vagina and post-EBRT width of involved vagina only, without routine inclusion of uninvolved vagina in an IR-CTV. Others have concluded that reducing the length of vagina included in the brachytherapy volume to the region of involvement may help reduce morbidity, and thus this variation in volume definition may also have accounted for some of the discrepancy in toxicity between Lee et al.'s series and ours [21].

A more recent study from Kamran et al. included 24 patients who had received prior radiation and were treated with high-dose-rate interstitial brachytherapy for vaginal recurrence of endometrial cancer [8]. Prior radiation consisted of brachytherapy only in 8 (33%), EBRT only in 4 (17%), and EBRT plus brachytherapy in 12 (50%). The median interval between primary hysterectomy and salvage radiation for recurrent disease was 20 (range: 7–210) months. In contrast to our study, 8 patients who had received EBRT in the past were treated with re-irradiation EBRT + interstitial brachytherapy at the time of relapse. The median D90 HR-CTV EQD2 (including prior dose) was 78.1 (range: 37.0–108.7) Gy, compared to a median of 65 Gy in our study. The authors reported 3-year local control, disease-free interval, and overall survival rates of 71%, 52%, and 54%, respectively. However, toxicities included 10 Grade 3 rectal and urinary events in eight patients (33.3%), possibly a function of one-third of patients in their series having received repeat pelvic EBRT, which we have avoided in our experience. In addition, the cumulative D2cc (EQD2) to the rectum, bladder, and sigmoid were not reported in that study. Although our 3-year disease-free survival rate was lower at 40.8%, this may be partially

explained by the fact that our study included patients with adverse non-endometrioid histologies, which made up 18% of our cohort, whereas all patients in Kamran et al.'s study had endometrioid histology. While it is possible that the higher DFS achieved in their study may be related to higher doses delivered especially if there was no institutional preference for prioritizing normal organ dose-constraints over target dose, this must be considered in light of the much higher toxicity rate seen in their study compared to ours.

In one of the few prospective series on re-irradiation of recurrent gynecologic cancer, Martinez-Monge et al. reported outcomes on 15 patients with previously irradiated cervical, endometrial, or vulvovaginal cancer who were treated with HDR interstitial brachytherapy alone to a median dose of 38 Gy in 8 twice-daily fractions over 4 consecutive days [22]. All patients had received prior EBRT, and 9 (60%) had received prior brachytherapy. The median re-irradiation interval was 3.9 years (range: 0.4–22.7). The 5-year local control, disease-free survival, and overall survival rates were 71%, 21%, and 40%, respectively. They reported a 20% grade ≥ 3 toxicity rate consisting of grade 3 intestinal obstruction ($n = 1$), grade 4 rectovesical fistula ($n = 1$), and grade 5 intestinal obstruction ($n = 1$). However, the cumulative D2cc (EQD2) for the rectum and bladder were 111 Gy and 121 Gy, respectively, which is much higher than the limits allowed at our institution.

Our study is limited by its retrospective design and small sample size, although other studies on previously-irradiated vaginal recurrence of endometrial cancer have been similarly plagued by these shortcomings. Because toxicities were recorded based on chart review, it is possible that toxicities were underreported in cases where the patient received follow-up care at a different institution. We only reported grade 3 toxicities, as the presence of grade 1 and 2 toxicities oftentimes could not be accurately determined based on retrospective review of the records. Our study is strengthened by our consistent reporting of cumulative EQD2 dose to organs-at-risk taking into account contribution from all prior courses of radiation therapy. Finally, our study population is more homogenous than other re-irradiation series in the literature, which contain patients with a mix of gynecologic primary sites, both patients who did and did not have prior pelvic radiation therapy, and patients treated with definitive and palliative intent [8,9,22–27].

5. Conclusion

Re-irradiation with 3D conformal brachytherapy for vaginal recurrence is feasible and safe as long as cumulative dose to surrounding normal organs is limited, and offers a chance to achieve local control and potentially salvage 40% of patients presenting with vaginal recurrence in the setting of prior pelvic radiation.

Conflicts of interest statement

No acute or potential conflicts of interest exist.

Author contributions

Study conception and design: Beriwal.
Acquisition of data: Ling.
Analysis and interpretation of data: Ling, Vargo, Glaser, Kim, Beriwal.
Drafting of manuscript: Ling.
Critical revision: Ling, Vargo, Glaser, Kim, Beriwal.

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