BRACHYTHERAPY

Gynecologic Oncology

American Brachytherapy Society working group report on the patterns of care and a literature review of reirradiation for gynecologic cancers

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ABSTRACT

PURPOSE: Recurrences of previously irradiated gynecological malignancies are uncommon. Standardized management of these cases is not well established. We aim to provide an in-depth literature review and present current practice patterns among an international group of experienced practitioners in the reirradiation setting of gynecologic cancers.
METHODS AND MATERIALS: An extensive literature search was performed and 35 articles were selected based on preset criteria. A 20-question online survey of 10 experts regarding their retreatment practices was also conducted.
RESULTS: The reviewed publications include a diverse group of patients, multiple treatment techniques, a range of total doses, local control, overall survival, and toxicity outcomes. Overall, local control ranged from 44% to 88% over 1–5 years with OS in the range of 39.5–82% at 2–5 years. Late G3–4 toxicity varied very broadly from 0% to 42.9%, with most papers reporting serious toxicities greater than 15%. The most common reirradiation technique utilized was brachytherapy. Some low-dose-rate data suggest improved outcomes with doses >50 Gy. The high-dose-rate data are more varied with some studies suggesting improved local control with doses >40 Gy. In general, a longer time interval between the first and second course of radiation as well as recurrences < 2–4 cm tend to have improved outcomes.
CONCLUSIONS: Reirradiation with brachytherapy results in relatively reasonable local control and toxicities for women with recurrent gynecologic cancers. The appropriate dose for each case needs to be individualized given the heterogeneity of cases. Multidisciplinary management is critical to develop individualized plans and to clearly communicate potential side effects and expected treatment outcomes.
TAKE HOME MESSAGE: Reirradiation with brachytherapy is an acceptable effective organ preserving approach for recurrent gynecologic cancers with a reasonable local control and toxicity profile. Each case requires multidisciplinary management to develop an individualized approach. Monitoring for potential long-term toxicities is essential. © 2019 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords: Gynecologic; Brachytherapy; Reirradiation

Introduction

In the era of image-guided adaptive brachytherapy (IGABT), local control is excellent in most gynecological malignancies. However, local failures still occur in about 10% of cases after definitive chemoradiation in cervical cancer and in under 5% of endometrial cancer cases after surgery and adjuvant radiation (1−3). At the time of recurrence, 50−70% of patients are symptomatic with the most common presenting symptoms being vaginal bleeding and pelvic pain. In definitively treated cervical cancer, local recurrences tend to be central, in the distal vagina below the radiation field, and/or in the parametria/pelvic sidewall (4). In postoperative endometrial cancer treated with adjuvant radiation, about 75−80% of recurrences are at the apex of the vagina or periurethral regions (5−9).

There is no Level 1 evidence to guide patient care and so management of these cases is varied. Treatment options can range from palliative measures to surgical exenteration. Re-irradiation is also a reasonable treatment option that allows for organ preservation, but consensus regarding patient selection, dose, and technique are lacking.

The purpose of this article is to provide an in-depth literature review on reirradiation in the management of women with recurrent gynecologic cancers as well as to present current practice patterns among an international group of experienced practitioners.

Fig. 1. Flow diagram outlining the paper selection process.

Methods

In May 2018, a literature search using Pubmed (Medline) and Cochrane (Embase) for articles in English was performed on reirradiation for recurrent gynecologic malignancies using various combinations of the following terms: reirradiation, radiotherapy, recurrent, gynecology, cervix, cancer, oncology, and/or uterine. Four review articles on re-irradiation were identified and they were additionally screened for articles pertinent to this topic (10−13). After the initial search, 50 papers which addressed this topic and were available in English were found. Many articles combined patients with and without prior radiotherapy (RT) in the setting of recurrence. So papers were excluded if only a small number of patients were treated with irradiation (*n* = 5) and/or results for reirradiated patients were not separately available (*n* = 3). In addition, papers were excluded if they were published over 20 years ago (*n* = 7). This process resulted in a total of 35 articles (see Fig. 1).

Given the limited number of articles published on this topic and the limited number of cases included in individual publications (7−52 patients), an online survey of the 10 authors with clinical expertise included in this article was also completed. A link was provided to an online survey with 20 questions regarding their retreatment practices (see Supplement). All responses were anonymized. Responses were received from nine authors. The results were reviewed
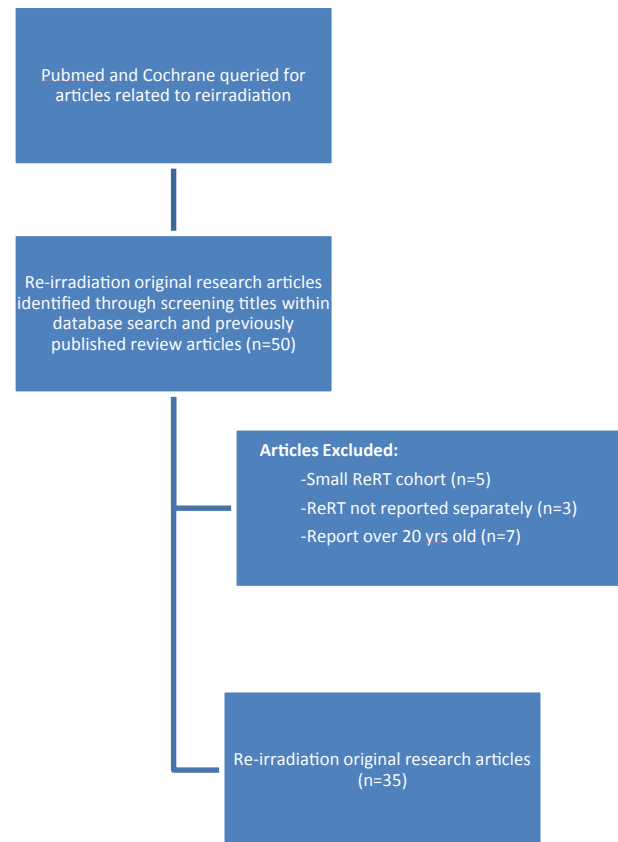
with the authors on a phone call to provide further insight into areas with variation in practice.

Even among the group of gynecologic specialists included on this article, the number of reirradiation cases that each person treats per year is low (five panelists treat 1−5, three treat 6−10, and one treats > 10 cases per year [Supplement Question # 20]). So the panelist's current practices are presented after each relevant literature review to provide some perspective on what people are doing in the reirradiation setting but not as a means of suggesting that this should be taken as the standard of care.

Results

Patient selection and evaluation

The same general principles of evaluation in the definitive setting apply in the recurrent setting. Patients are re-staged with clinical examination and imaging which should include evaluation of both local/regional as well as distant disease. At least a computed tomography (CT) of the chest, abdomen, and pelvis should be performed. Positron emission tomography can also be helpful in characterizing equivocal areas on CT, whereas magnetic resonance imaging (MRI) can be useful in better defining the

Table 1
Reirradiation studies that used brachytherapy

Series	Date	Study type	Patients (n)	Gyn ReRT (n)	Primary site	Treatment type	HDR/LDR	Median ReRT dose (dose range for each)	Median followup	Local control	Overall survival	Toxicity
Martinez-Monge, et al. (15)	2014	Prospective	50	25	Mixed	Interstitial	HDR	38 Gy in 8 BID (consecutive)	2.8 yrs	71.4% at 5 yrs	59.3% at 2 yr 39.5% at 5-yr	20% Grade 3+ 1 Grade 5
Badakh, et al. (16)	2009	Prospective	22	22	Cervix	Interstitial	HDR	25.8 Gy (12−45 Gy)	NR	NR	Median OS 9.2 mo	4 Grade 4
Ling, et al. (17)	2019	Retrospective	22	22	Uterine	IC/interstitial	HDR	Median HR-CTV D_{90} 64.5 Gy (IQR: 49.6−75.8)	27.6 mo	66% @ 3 yrs	68% OS at 3 yrs	No Grade ≥ 3 acute or late
Umezawa, et al. (18)	2018	Retrospective	18	18	Cervix	Interstitial	HDR	62.6 Gy (48.6−82.5)	18 mo	51.3% at 2 yrs	60.8% at 2 yrs	2 Grade 3, 1 Grade 4
Ling et al. (17)	2019	Retrospective	22	22	Uterine	IC/interstitial	HDR	Median HR-CTV D_{90} 64.5 Gy	27.6 mo	65.8% At 3 yrs	68.1% at 3 yrs	No Grade ≥3 acute or late
Kamran, et al. (19, 20)	2017	Retrospective	66	24	Uterine	Interstitial	HDR	45.2 Gy (27.2−67.9)	33 mo	71% at 3 yrs	54% at 3 yrs	33% Grade 3
Feddock, et al. (21)	2017	Retrospective	61	61	Mixed	Interstitial	LDR	45 (20−75)	16.3 mo	73% LC at death	52% OS at last f/u	Grade ≥ 3 16.7%
Huang, et al. (22)	2016	Retrospective	40	16	Uterine	Interstitial	HDR	74 Gy (cumulative)	18 mo	53% at 2 yrs	67% at 2 yrs	4 Grade 3
Liu, et al. (23)	2016	Cohort	16	16	Cervix	Interstitial	HDR	52.5 Gy	NR	NR	NR	NR
Murakami, et al. (24)	2016	Retrospective	26	10	Cervix	Interstitial	HDR	68.4 Gy (48.4−94.2)*	NR	45% at 3 yrs	51% at 3 yrs	1 Grade 4, 1 Grade 2
Amsbaugh, et al. (25)	2015	Retrospective	21	18	Mixed	Interstitial	both	LDR 41.5; HDR 22.5 Gy	16.5 mo	71.5% at 1 yr	82% at 1 yr	Grade 3: 28.5% vaginal, 9.5% urinary, 19% rectal
Zolciak-Siwinska, et al. (26)	2014	Retrospective	20	20	Mixed	Interstitial/ Intracavitary	HDR	48.8 Gy (19−91 Gy)	31 mo	45% at 3 yrs	68% at 3 yrs	3 Grade 3 (15%)
Mahantshetty, et al. (27)	2014	Retrospective	30	30	Cervix	Interstitial	HDR	42 Gy	25 mo	44% at 2 yrs	52% at 2 yrs	3 Grade 3 GU 3 Grade 3 GI (20%)
Mabuchi, et al. (28)	2013	Retrospective	52	52	Cervix	Interstitial	HDR	42 Gy/7 BID fractions	55.6 mo	77%	Median 32 mo	25% Grade 3 or 4
Wooten, et al. (29)	2013	Retrospective	14	7	Mixed	Interstitial	LDR (Cs 131)	78.25 Gy (Cs131 median 27.5 Gy)*	12 mo*	88% at 1 yr*	Median 12 mo*	1 Grade 3*
Yoshida, et al. (30)	2013	Retrospective	114	14	Cervix	Interstitial	HDR	42−51 Gy in 7−8 BID fx	41 mo	NR	NR	1 fistula; vaginal Grade 0/1/2: 29%/57%/14%
Weitmann, et al. (14)	2006	Retrospective	23	23	Mixed	Interstitial	HDR	64 Gy	64 mo	47% at 5 yrs	43% DSS at 5 yrs	5 Grade 3 (22%)
Gupta, et al. (31)	1999	Retrospective	69	15	Mixed	Interstitial	HDR	35 Gy (25−55)	4.7 yrs	49% at 3 yrs	NR	14% Grade 4*

HR-CTV = high-risk clinical target volume; HDR = High-dose-rate; LDR = low-dose-rate; NR = not reported; DSS = disease specific survival; GU = genitourinary; GI = gastrointestinal; LC = local control; OS = overall survival.

Only included studies published within the past 20 years. Some studies did not report results separately for patients receiving reirradiation (indicated with *).

local extent of disease. Some centers perform rectosigmoidoscopy and cystoscopy as part of their evaluation in previously irradiated patients (14). In the setting of pelvic MRI, the main purpose of rectosigmoidoscopy and cystoscopy is not to identify bladder and/or rectal invasion but to provide a visual assessment of the mucosa of these organs to rule out preexisting mucosal damage from the previous radiation (i.e., telangiectasia, ulcers). There is, however, no literature proving this approach should be routinely used. Finally, a biopsy should be performed to confirm recurrent disease. In general, metastatic disease precludes proceeding with curative intent reirradiation unless patients are symptomatic and treatment is considered with palliative intent.

Reirradiation of recurrences in gynecological malignancies

Tables 1 and 2 provide a summary of the selected reirradiation studies. They include a variety of reirradiation treatment modalities: interstitial brachytherapy (ISBT) either as an adjunct to external beam radiotherapy (EBRT) or as a stand-alone treatment option and EBRT, mainly in the form of stereotactic body radiation therapy (SBRT).

Brachytherapy

High-dose-rate (HDR) brachytherapy

Literature review. When just looking at recurrent endometrial cancer series (Table 1), three in particular are worth highlighting because of their size, use of IGABT, and differing approaches to dose selection. Kamran *et al.* (19) reported on a total of 24 patients with endometrial cancer who were reirradiated using IGABT. The authors delivered a dose of radiation which they felt was necessary to control the tumor even if this meant exceeding the standard organ at risk (OAR) tissue tolerances. The mean cumulative radiation dose to the high-risk clinical target volume (HR-CTV) (including prior treatment) was 89.2 Gy (range 52.5–106.6). Eight patients received previous treatment with a vaginal cylinder only (equivalent dose in 2 Gy [EQD2] ~30 Gy), had a mean time between first and second course of radiation of 34 months, and had a mean reirradiation EQD2 dose of ~51 Gy. Their 3-year local control was 80% and two patients developed G3 toxicity. Four patients received prior treatment with EBRT (EQD2 ~44 Gy), had a median time between first and second course of radiation of 42 months, and had a mean reirradiation EQD2 dose of ~42 Gy. Their 3-year local control was 100% and one patient developed G3 toxicity. Finally, 12 received prior EBRT and brachytherapy (EQD2 ~60 Gy), had a mean time of 39 months between first and second course of radiation, and had a mean reirradiation EQD2 dose of ~40 Gy. Their local control was 60% and five patients developed G3 toxicities.

Ling *et al.* (17) reported on 22 patients with recurrent endometrial cancer where the retreatment dose was

Table 2
Reirradiation studies that used stereotactic body radiation therapy

Series	Date	Study type	Patients (n)	Gyn ReRT (n)	Primary site	Treatment	Median ReRT dose (dose range)	Median followup	Local control	Overall survival	Toxicity
Hasan, *et al.* (32)	2016	Retrospective	30	15	Mixed	Cyberknife	27.5 Gy in 3–5 fx*	24 mo	73% at 2 yrs	42% at 5 years	1 Grade 3/4 RV/vesicovag fistula
Pontoriero, *et al.* (33)	2016	Retrospective	5	5	Cervix	Cyberknife	15–20 Gy in 3–4 fx	12 mo	NR	NR	No Grade 3–5 @ 1 yr
Seo, *et al.* (34)	2016	Retrospective	23	17	Cervix	Cyberknife	39 Gy in 3 fx	17 mo	65% LPFS at 2 yrs	43% at 2 yrs	13% Grade 4 (fistulas)
Park, *et al.* (35)	2015	Retrospective	85	68	Cervix	Cyberknife	39 Gy in 3 fx	20 mo	82.5% at 2 yrs	57.5% at 2 yrs	2 Grade 4, 3 Grade 3 (all prior RT)
Yazici, *et al.* (36)	2013	Retrospective	16	11	Mixed	Cyberknife	26.6 Gy (15–40 in 3–5 fx)	12 mo	NR	40% at 2 yrs	3 Grade 4 fistula (19%); 3 Grade 2–3 proctitis
Dewas, *et al.* (37)	2011	Retrospective	16	5	Mixed	Cyberknife	36 Gy in 6 fx	11 mo	51% at 1 yr	46% at 1 yr	No Grade 3–5 toxicity
Abusaris, *et al.* (38)	2012	Retrospective	27	8	Mixed	SBRT	34 Gy (1–10 fractions)	15 mo	53% at 2 yrs; (40% < 60 Gy, 100% > 60 Gy)	37% at 2 yrs	No Grade 3–5 toxicity
Deodato, *et al.* (39)	2009	Retrospective	11	6	Mixed	SBRT	30 Gy in 6 fx	19 mo	82% LPFS at 2 yrs	64% at 2 yrs	No Grade 3–5 toxicity

NR = not reported; SBRT = stereotactic body radiation therapy LPFS = local progress-free survival; RV = rectovaginal.
Studies including patients without prior RT did not report results separately for reirradiation patients.

determined based on treating until not exceeding a cumulative rectosigmoid and bladder D_{2cc} (EQD2) dose of 75 Gy and 90 Gy, respectively. Twelve patients received prior vaginal brachytherapy only with most receiving 21 Gy in three fractions, five patients received prior EBRT to a median dose of 45 Gy, and five received prior EBRT + vaginal brachytherapy. The median time interval between the first and second course of radiation was 26.6 months. The median D_{90} HR-CTV EQD2 (including prior dose) was 65 Gy. The 3-year local control was 66%, and one late G3 ureteral toxicity was noted.

Huang *et al.* (22) reported on 16 patients with recurrent endometrial cancer who were reirradiated. The retreatment dose was individualized based on incorporating the following factors: dose needed to achieve a reasonable chance of controlling the disease, time from prior radiation, prior radiation dose, and location of recurrence in the vagina. The median cumulative EQD2 was 71.1 Gy (63−105.8 Gy). Patients received brachytherapy alone if the pelvis had previously been treated or with 45 Gy EBRT followed by a brachytherapy boost in the setting of a previously untreated pelvis. Local control at 2 years was 53%. Four patients experienced any late G1−4 toxicity but the rate of Grade 3−4 toxicity was not specified.

When just looking at retreatment studies of patients with cervical cancer, there were three series that were noteworthy. Mahantshetty *et al.* (27) reported on 30 patients with cervical cancer who were retreated. Twenty had a recurrence at the vaginal cuff after prior surgery and radiation while four had a central recurrence after prior definitive treatment with radiation. The median time between courses of radiation was 25 months. All patients were retreated with brachytherapy alone (24 interstitial and 6 with a Vienna applicator). The median brachytherapy dose delivered was EQD2 42 Gy. Two-year local control was 44%. Local control seemed to be higher in patients receiving > EQD2 40 Gy (52% vs. 34%, $p = 0.05$). Two-year G3 toxicity (rectal, bladder, or vaginal) was seen in 23%. Umezawa *et al.* (18) retreated 18 patients with cervical cancer of which 14 had previously received surgery followed by radiation while four had received definitive radiation. The median interval between treatments was 14.9 months. The median CTV D_{90} was 62.6 Gy (range 48.6−82.5 Gy). Two-year local control was 51.3%. Late Grade 3 or higher toxicity was seen in three patients (16.6%). On univariate analysis, hemoglobin level and maximum tumor diameter were significantly associated with local control but dose was not. There was a correlation seen between a higher volume of the 100% and 200% isodose volumes outside the CTV with ≥ Grade 2 toxicities. Finally, Mabuchi *et al.* (28) retreated 52 patients with cervical cancer of which 17 had previously been treated with definitive intent and 35 in the postoperative setting. Patients were treated with 6 Gy × 7 BID (EQD2 56 Gy). Twelve patients underwent 3D planning, whereas the rest underwent 2D planning. Median time between first and

second radiation treatments was 13 months. Local control was reported based on a 2-month posttreatment assessment with a 77% response rate complete response and partial response. With a median followup of 55.6 months, 13 patients (25%) developed Grade 3/4 toxicities.

Low-dose-rate (LDR) brachytherapy

Literature review. Low-dose-rate (LDR) is also an effective technique to deliver permanent interstitial brachytherapy (PIB). PIB has the unique advantage over temporary implants in that dosing is calculated based on permanent decay and a curative dose can be delivered in a single procedure. Several published series now support the capability to yield long-term control rates of approximately 70−85% in well-selected patients (21, 29, 31, 40−43). In the series by Randall *et al.* (42), 13 patients with recurrent gynecologic disease were treated with either permanent or interstitial brachytherapy, mostly using ^{198}Au. A complete response was seen in 69% of patients and nearly half were still alive 4 years later with very few complications being identified. The average size of tumors in this series was 12 cm^2, and there appeared to be a relatively clear dose-response for improved outcomes when doses of 50 Gy or higher were delivered. The importance of small tumor size, prescription dose >50 Gy, and the use of PIB for reirradiation have also been identified as significant predictors for success in at least two other series by Brabham *et al.* and Wooten *et al.* (29, 43). In the largest series of PIB published to date, Feddock *et al.* (21) presented 42 patients being treated using ^{131}Cs as monotherapy for recurrent pelvic disease and identified a 2 year control rate of 81%, and a median time to failure was not met, identifying that PIB using LDR sources can be a potentially curative approach for reirradiation in well-selected patients.

Brachytherapy dose

Literature review. Dose is delivered most commonly using a high-dose-rate (HDR) or an LDR approach. Many centers use twice daily (BID) HDR fractionation with a median dose prescription per fraction of 4−6 Gy (range 2.3−8 Gy) and a median number of fractions between 5 and 10 (range 3−15). Only a few centers reported on once a day or weekly fractionation schemes: 3 Gy × 10−15 fractions daily or 5−7 Gy × 4−6 fractions weekly ± hyperthermia (26) and 7 Gy × 2−3 fractions weekly (14, 23). Dosing with LDR is dependent on the isotope being used and is not standardized. In the largest series from Feddock *et al.* (21) that used ^{131}Cs gave doses ranging from 22 to 75 Gy.

Brachytherapy insertion technique

ISBT is well suited for the management of central and paracentral lesions because (*1*) there is access through a transperineal approach, (*2*) it achieves better conformality

than EBRT techniques, and (*3*) its surface/depth dose profile is better than that of intracavitary brachytherapy. Intracavitary brachytherapy may be appropriate for reirradiation; however, in most cases, the extent of disease is > 0.5 cm in depth and so it is less commonly used.

Panelist's current practice

The panelists were presented with four different clinical scenarios and asked a series of questions regarding how they would manage them. The first three clinical scenarios all had the same clinical presentation of a patient with an endometrial cancer recurrence in the vaginal vault. The three different scenarios just changed the adjuvant treatment the patient received (external beam radiation therapy only, external beam radiation therapy and vaginal cuff brachytherapy boost, and vaginal cuff brachytherapy only). In the setting of prior EBRT only, 9/9 panelists would offer retreatment with brachytherapy alone with curative intent (Supplement Question # 1). In the setting of prior EBRT plus vaginal cuff brachytherapy boost, 7/9 panelists would offer retreatment with brachytherapy alone with curative intent, whereas one would consider retreatment with brachytherapy with palliative intent and another would consider EBRT with palliative intent (Supplement Question # 2). In the setting of prior vaginal cuff brachytherapy only, 9/9 panelists would consider retreatment with curative intent with 7/9 considering a combination of EBRT followed by a brachytherapy boost (Supplement Question # 3). No additional questions were asked about EBRT in the survey, but when discussed on the conference call, some physicians stated that for the EBRT, they would limit the EBRT dose to the vaginal area where there was prior brachytherapy to somewhere in the dose range of 30−36 Gy. The rationale for this was to limit the overlap of the prior radiation dose so that there would be more room for the brachytherapy boost. Other physicians just deliver 45 Gy to a standard pelvic field. The fourth clinical scenario presented a woman with cervical cancer treated with surgery followed by adjuvant EBRT who develops a sidewall recurrence. In this case, 8/9 panelists would treat this patient with curative intent but there was a range of techniques that people would use. Four would consider using brachytherapy alone, four would consider using non-SBRT EBRT, and one would consider using SBRT (Supplement Question # 4).

When using brachytherapy alone with curative intent in the retreatment setting for a patient with prior EBRT, 6/9 would treat with a dose >40 Gy (Supplement Question # 5). If the patient had received prior EBRT and vaginal cuff brachytherapy, 5/9 would treat with a brachytherapy dose >40 Gy when treating with curative intent (Supplement Question # 8). If the patient had received vaginal cuff brachytherapy, only then 8/9 would treat with a dose >40 Gy when treating with curative intent (Supplement Question # 10).

Perioperative brachytherapy

Literature review

One of the largest experiences using perioperative brachytherapy was published by Martinez-Monge *et al.* (15). It included 50 patients with locally advanced and recurrent gynecologic cancers of which 25 were previously irradiated. Reirradiation patients were treated with surgery followed by perioperative HDR (32 Gy in eight fractions for negative margins and 40 Gy in 10 fractions for close/positive margins). With a median followup of 10.1 years, 14-year local control was 60%, whereas 5-year disease-free survival and 15-year overall survival were 16% and 19%, respectively. 10 of 25 (40%) patients developed Grade ≥ 3 adverse events. This included four patients who died of pelvic bleeding between 7 and 12 months. After these events, the dose was changed to 24 Gy in six treatments and no Grade ≥3 adverse events have been observed since. Based on these observations, the group now recommends a maximal dose of 24 Gy, a time to loading not longer than 4 days, and an implant treated volume (TV) 100 not greater than 45 cm^3 (TV150 below 20 cm^3). The group also tries to use a transperineal approach rather than an abdominal route when possible and routinely interposes a layer of 2−3 mm of tissue (omentum flap) between the vascular structures and the catheters.

In a second large experience, 48 patients with gynecologic cancer with pelvic sidewall recurrences after prior primary or adjuvant pelvic radiation were treated with perioperative brachytherapy (44). Treatment was delivered with HDR and the dose was 24−36 Gy given twice a week (6 Gy per fraction) if prior radiation had been given less than 4 weeks prior and the dose was increased to 48−54 Gy if more than 6 months had passed since the previous RT. With a median followup of 33 months, the 5-year overall survival was 44%. Local control in the first 20 patients was 60% and in the latter 28 patients with a more aggressive surgical technique was 85%. On multivariate analysis, R1 vs. R2 resection and age over 40 years were significant for tumor progression. Overall local control was 68% and 85% in the last 25 patients in the series. Five-year overall severe complications were 33% (most were seen in the first 20 patients).

Panelist's current practice

No specific questions regarding perioperative brachytherapy were asked of the panelists.

External beam radiation therapy

Literature review. Reirradiation series with EBRT for pelvic recurrences of various malignancies have typically been performed with palliative intent (20, 41, 45). There are no clear selection criteria for EBRT candidates and target volumes, but in general, in the previously irradiated pelvis, if

EBRT is used, the target just encompasses the tumor with a variable margin (14, 18, 26).

When used with curative intent, it is most commonly in the setting of a patient with a prior history of vaginal cuff brachytherapy only. In these cases, most centers will deliver a microscopic dose to the pelvic lymph nodes to 45−52.2 Gy with dose fractionation between 1.6 and 2 Gy (14, 17, 20, 22, 25). In one center, the EBRT dose to the central structures, including the vaginal and paravaginal disease, was limited to 30.6 Gy to allow safe delivery of an additional dose of around 30 Gy in 2-Gy equivalents with brachytherapy (17). Involved nodes have been treated with either a sequential or an integrated boost to approximately 60 Gy.

Panelist's current practice

The panelists were given a clinical scenario of a patient with a history of endometrial cancer treated with surgery followed by adjuvant vaginal cuff brachytherapy alone (7 Gy × 3 to 0.5 mm depth, upper 4 cm of vagina) who develops an in-field recurrence and asked how they would manage this. In this case, all panelists would offer retreatment with curative intent and 7/9 would retreat with a course of EBRT followed by brachytherapy. As discussed previously, many retreat the pelvis to 45 Gy using a standard pelvic field, whereas others try to limit the retreatment dose to the area of prior brachytherapy to somewhere between 30 and 36 Gy while treating the rest of the pelvis to 45 Gy.

Panelists were also asked about a scenario of a patient with prior EBRT to the pelvis with 45 Gy with an in-field recurrence located in the pelvic sidewall who was going to be treated with curative intent with EBRT and what fractionation they would choose. Four of the nine would use SBRT, 1/9 hyperfractionation, 1 standard fractionation, and three would not treat with curative intent (Supplement Question # 6).

Stereotactic body radiation therapy

Literature review. At this time, there is some literature utilizing SBRT for reirradiation but it is limited (Table 2) (35−42). One of the larger studies is from Seo Y. *et al.* (34) who retrospectively looked at 17 patients with cervical cancer with isolated pelvic sidewall recurrences all with a prior history of pelvic radiation. The prior radiation dose received was not reported but the average GTV treated was 59 cc. Patients received an average dose of 12 Gy × 3 fractions and 16 patients received adjuvant chemotherapy. With a median followup of 15 months, there were six local failures and three patients developed rectovaginal fistulas. In another series, Yazici C *et al.* (36) treated 16 patients with recurrent gynecologic cancer with SBRT of which 11 received prior radiation (median dose of 50.4 Gy). Nine of the reirradiation patients had a central pelvic recurrence and two had pelvic sidewall recurrences. Before SBRT, four

patients received chemotherapy and four underwent salvage surgeries. The mean GTV at the time of recurrence was 111 cc. The mean prescribed dose was 26.6 Gy in 3−5 fractions. Median followup for the whole cohort of 16 patients was 12 months with 1-year overall survival of 60% and progression-free survival of 59%. Six of 16 patients showed a complete radiographic response. Three patients developed Grade 4 complications and three patients developed G2−3 proctitis. Pontoriero *et al.* (33) also retreated five patients with recurrent cervical cancer who had previously received 45 Gy external beam plus 15 Gy in three fractions of brachytherapy. Patients were retreated with 15−20 Gy in 3−4 fractions. The median cumulative EQD2 was 85 Gy and median tumor volume was 20 cc. Six months after treatment, a biopsy was performed showing three patients with a complete response (absence of neoplastic cells with the presence of inflammatory cells) and two patients with a partial response (persistence of neoplastic cells). At a median followup of 12 months, no Grade 3 or higher toxicities were noted. Other small series have included patients with gynecologic cancer treated with SBRT retreatment but unfortunately the results for the gynecologic patients is not reported out separately (37, 38).

The role of chemotherapy as additive to radiotherapy

Literature review

While concurrent chemotherapy can safely be delivered with brachytherapy in the definitive setting, its safety/effectiveness in the retreatment setting has not been formally evaluated (46). Data from Kamran *et al.* (19) suggest that the receipt of any chemotherapy was significant on multivariable analysis for improved local control. This study did not investigate whether there was a relationship between toxicity and chemotherapy. In another retrospective study of HDR interstitial reirradiation of cervical cancer pelvic recurrences, 5/7 patients treated with chemotherapy before HDR developed fistulas, whereas 2/6 treated with concurrent sensitizing chemotherapy developed fistulas (8). The role of chemotherapy in the retreatment setting is an area worthy of further investigation with insufficient data to make definitive conclusions.

Panelist's current practice

The survey did not ask any formal questions regarding the role of chemotherapy in the reirradiation setting. However, in the comments section of the survey, this question was raised. This topic was discussed among those able to make the conference call and there was no consensus among the participants regarding the role of chemotherapy. The most commonly cited consideration of using chemotherapy was in the setting of a large tumor where additional external beam could not be given but the physician wanted to see if the tumor could be reduced in size before proceeding with brachytherapy. There was no agreed-on

chemotherapy regimen or number of cycles when using chemotherapy in this clinical context.

Target delineation and organ-at-risk constraints

Literature review

In series that utilized image-guided brachytherapy, there is variation in their target contour delineation. Most have extrapolated the GEC ESTRO or ABS recommendations from definitive cervical cancer target delineation (47, 48). Most have defined their HR-CTV, whether using CT, MRI, ultrasound, or some combination, as the gross disease on imaging and clinical examination. Some also include gray zones if contouring on MRI. The utilization and definition of an IR-CTV is more variable. Some groups treat the HR-CTV without any additional margin (14), whereas others place variable margins around the HR-CTV (26, 28). In other papers, there is a somewhat "hybrid" definition of what was contoured that spans somewhere between an HR-CTV and IR-CTV. In the paper by Ling et al. (17), for example, the HR-CTV was defined by treating the pre-EBRT GTV superior and inferior extent but only the post-EBRT residual thickness. 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.

Panelist's current practice

9/9 panelists define the HR-CTV in the reirradiation setting as gross disease on MRI/CT and clinical examination only with one of the panelists also considering gray zones seen on MRI (Supplement Question # 12). Four of nine panelists use an IR-CTV in the reirradiation setting which includes a variable amount of vagina to a lower dose level than the HR-CTV (Supplement Question # 13). Additional planning considerations were not asked in the survey or discussed among the panelists but the ability to just treat a portion of the vagina will be dependent on the type of cylinder used (single vs. multichannel) and how heavily the central channel in the cylinder is weighted compared with the peripheral channels or interstitial needles.

Dose constraints for organs at risk

Literature review

In reviewing the available literature, there are two differing approaches to determining appropriate OAR dose constraints in the reirradiation setting. Some physicians choose to intentionally exceed normal tissue tolerance to achieve an intended dose to the tumor, whereas others utilize standard OAR dose constraints. In series when standard OAR dose constraints are exceeded, most studies report $\geq$ G3 toxicities over 15% (26). There is a wide range of toxicities reported but some of the more common ones

can include rectal bleeding, necrosis, fistula, cystitis, ureter stenosis, vaginal ulcers, and pain.

An alternative to exceeding OAR constraints is to keep them below standard OAR tolerances. This was the approach taken by Ling D. et al. (17), where the cumulative rectosigmoid and bladder D_{2cc} (EQD2) was limited to < 75 Gy and <90 Gy. Twenty-two patients were retreated and with a median followup of 27.6 months there were no $\geq$ G3 acute or late gastrointestinal or genitourinary complications.

Another paper suggested the urethra $D_{0.1cc}$ predicted for Grade 2 or higher urinary toxicity (25). Reports on vaginal toxicity have been limited and inconsistent and may depend on the location of the vagina that receives the reirradiation dose with the distal vagina more radiation sensitive than the proximal vagina. Murakami et al. (24) found D_{2cc} to be predictive of toxicity with a cut-point of 145 Gy EQD2. Patients over this cutoff had a 23.5% risk of vaginal ulcer. Yoshida et al. (30) reported G4 fistula at 127.6 Gy. Amsbaugh et al. (25) did a similar analysis but was not able to confirm a relationship between the vaginal D_{2cc} and toxicity. Volume-based dose constraints for the vagina are an area needing further investigation.

Panelist's current practice

There was no consensus regarding a minimum required time between a person's prior radiation and proceeding with retreatment (two panelists require at least 6−12 months, 3 > 1 year, and three do not consider time) (Supplement Question # 14). When asked whether panelists have a "rule of thumb" for how much dose they would forgive based on the duration of time that has passed from an initial course of radiation, there was also no consensus with a wide range of responses from not forgiving any dose to responses like 10% per year (Supplement Question # 15). In the reirradiation setting, 7/9 panelists said they would exceed the tolerance of the rectum, after appropriately informing and consenting the patient about appropriate risks, to achieve the dose that they want to the tumor (Supplement Question # 16). As a followup question, panelists were asked if they had a hard constraint for the rectum in the retreatment setting and 6/9 reported a D_{2cc} EQD2 range of 75−90 Gy (Supplement Question # 17). In the reirradiation setting, 8/9 panelists said they would exceed the tolerance of the bladder, after appropriately informing and consenting the patient about appropriate risks, to achieve the dose that they want to the tumor (Supplement Question # 18). As a followup question, panelist were asked if they had a hard constraint for the bladder in the retreatment setting and 6/9 reported a D_{2cc} EQD2 range of 90−100 Gy (Supplement Question # 19). No questions were asked about constraints to the vagina or other OARs.

Is there a role for hydrogels for OAR displacement in the retreatment setting?

One of the challenges of retreatment is trying to strike an appropriate balance between adequate dose to the tumor

while limiting the overlap of dose to surrounding OARs. In an effort to reduce the amount of normal tissue that is re-treated, it seems logical to find a means to displace some or all of the surrounding OAR (i.e., bladder, rectum, sigmoid). There are case series of hydrogels successfully being implanted to displace pertinent OARs in gynecologic cancers (49, 50). There is, however, no long-term data regarding whether the reduction in dose afforded by displacing OARs ultimately translates into reduction in toxicities. There is currently an ongoing prospective study formally investigating the role of hydrogels in gynecologic brachytherapy that will hopefully help answer some of these questions (Johns Hopkins University, PI: Viswanathan). Given the limited data available using hydrogels in gynecologic brachytherapy, it is best to enroll patients on prospective institutional registries if one is going to utilize this technique.

Followup

There are no specific evidence-based guidelines for ideal surveillance after reirradiation. We would recommend using a similar surveillance strategy as in other gynecologic cancers. This can include imaging at 3 months posttreatment to evaluate treatment response as well as clinical visits which include a pelvic examination every 3−4 months for the first 2 years, followed by every 6 months for years 2−5.

Discussion

Fortunately, the number of women who present with recurrent disease after a prior course of radiation is limited. However, for the small group of women who do, the ideal reirradiation treatment course is not known. We have reviewed the literature to see whether guidelines could be developed to help standardize practice in this setting but there is insufficient evidence to do this. Part of this is related to the fact that the clinical context of a recurrence is very heterogeneous and so it is unlikely that a simplified set of practice rules will emerge. Finally, given the preponderance of the literature, we reviewed pertained to central recurrences rather than pelvic sidewall recurrences we have limited our discussion to central recurrences.

Given the increased risks of complications in the reirradiation setting, a thoughtful discussion with the patient regarding the risks and benefits is necessary before proceeding. Some clinical factors that are important to consider in patient selection include time elapsed from the patient's prior radiation, prior radiation dose, and how it was given: EBRT alone vs. EBRT + brachytherapy, location of the recurrence relative to the prior radiation field, dose felt necessary to achieve the planned intent of treatment (curative vs. palliative), size of the tumor recurrence (14, 18, 26), histology and grade (19), patients performance

status, status of the rest of their disease, and the patient's prognosis (14, 16, 24, 25, 26, 28). Most of these clinical factors were gleaned from small retrospective studies that included heterogeneous groups of patients. In these studies, correlations were mostly based on univariate analysis, as typically there were not enough patients to perform multivariate analysis. In general, a longer time interval between the first and second course of radiation as well as recurrences <2−4 cm tend to do better. More specific guidance on the ideal time to wait between initial treatment and retreatment and prescription doses are not possible based on the currently published literature.

In addition to the clinical factors mentioned previously, it is also important to consider whether the patient can handle, both from a physical as well as emotional standpoint, a complication like a fistula that may require a permanent colostomy or urinary diversion. Related to this, one should consider what resources are available in their institution to assist with potential complications that can occur with retreatment (i.e., surgical expertise in managing reirradiation complications and hyperbaric oxygen treatment (51)). Finally, consideration for salvage treatment should also include an assessment of the likelihood of developing a fistula as a result of progressive disease left untreated.

If reirradiation is pursued, brachytherapy (ISBT) seems to be the therapy modality of choice either as an adjunct to EBRT or as a stand-alone treatment option. Clinical outcomes using HDR IGABT in recurrent endometrial cancer demonstrate local control rates between 53% and 66% and limited ≥ G3 toxicities (17, 20, 22). Clinical outcomes for cervical cancer central recurrences using HDR report local control rates between 44% and 51.3%, and ≥ G3 toxicities between 16.6% and 25% (51). Direct comparison between studies is challenging but local control rates appear lower and toxicities higher in recurrent cervical cancer likely related to a typically higher previous radiation dose. Reirradiation data with LDR is also very encouraging. In the largest study published to date, a 2-year local control rate of 81% was reported (21). PIB may offer certain radiobiological advantages for limiting normal tissue toxicity compared with HDR (52). The development of newer isotopes such as ^{131}Cs and ^{103}Pd that have shorter half-lives and lower energies also allows the volume of tissue being irradiated to be minimized which could improve the safety profile of reirradiation. However, one of the drawbacks to PIB techniques is that the dose delivered is dependent on appropriate source placement and spacing, therefore highlighting the importance of image guidance.

The relatively high G3 toxicities seen in reirradiation series reiterate the fine balance between achieving local control while trying to limit the risk of toxicities. Determining the "right" dose in the reirradiation setting is much more of an "art" rather than a science. Difficulties in striking the right balance are reflected in the wide range of doses reported in the literature (Table 1). An attempt was made to

find a correlation between dose and local control, based on the existing data, but we were unable to find one (Fig. 2). This is likely related to the heterogeneity of cases and re-treatment doses used in various studies. Some LDR data suggest improved outcomes with doses >50 Gy. The HDR data are more varied with some studies suggesting improved local control outcomes at doses >40 Gy.

EBRT alone for reirradiation rarely offers long-term control and carries a high risk of complications. It is mainly used in a palliative setting. Retreatment with a second course of EBRT has been more commonly carried out in rectal cancer but less so in patients with gynecologic can-cers. In a phase II multicenter study on 59 recurrent previ-ously irradiated rectal cancer patients, a hyperfractionated chemoradiation approach was used (53). RT was delivered to a planning target volume including the GTV plus a 4-cm margin to a dose of 30 Gy (1.2 Gy twice daily with a min-imum 6-h interval). A boost was delivered, with the same fractionation schedule, to the GTV plus a 2-cm margin (10.8 Gy). EBRT was concurrent with 5FU. The median in-terval between prior radiation therapy and the onset of reir-radiation was 27 months (range, 9−106 months). Half underwent surgery and some received additional chemo-therapy. This treatment was associated with a low rate of acute G3 toxicity (5%) and an acceptable incidence of late complications (≥G3 approximately 12%). The overall 5-year local control and overall survival was 38.8% and 39.3%, respectively. Whether a similar approach for reirra-diation of gynecologic cancers would be as effective is not known. Other emerging options include consideration of protons or carbon ions which may provide a more optimal dose fall off than photon-based external beam approaches.

Given the toxicities associated with larger field external beam, utilizing smaller fields with SBRT is appealing. Based on our literature review, there is limited data on re-treatment with SBRT in gynecologic cancers. So at this time, there is insufficient evidence to provide recommenda-tions regarding appropriate indications, dose/fractionation, or dose constraints for SBRT of pelvic recurrences in the previously irradiated pelvis. Prospective data are needed

to ensure a standardized treatment paradigm and followup so that we can better understand how best to implement this treatment modality.

Determining ideal dose constraints for OARs is also challenging. Again, there are limited published series with 3-dimensional planning and significant heterogeneity of cases/treatments. It is also difficult to figure out how to sum the previous dose of radiation with the planned retreat-ment dose. Many times the original treatment course is per-formed at another institution where the prior treatment records are unavailable or just a screenshot of a couple of slices are accessible. Even if the image data set is available, it is difficult to accurately fuse the prior dose given varia-tions in the position of the tumor and the OARs. It is also not established how to account for the heterogeneity of the brachytherapy dose. Therefore, when calculating the dose to OARs, a conservative approach is often taken where we assume the calculated dose to a specific OAR is always in the same position for each fraction of brachytherapy. There are also unanswered questions regarding how to ac-count for the time between the original course of radiation and the planned second course of treatment. It is not clear how much of the prior radiation dose may be able to be forgiven based on time. In general, it is felt that the longer the period between the two courses of treatment the better, but data are not available to provide more specific details.

The decision to exceed standard OAR tolerances requires a balanced discussion between the treating physician and the patient. Consideration of the potential morbidity of a pro-gressive tumor that is not adequately controlled vs. potential injury to OARs needs to be considered. There are challenges both in terms of not having clear data for the ideal dose to maximize local control in the reirradiation setting as well as limitations in our understanding of whether and how our standard OAR should be modified. If tolerances are going to be exceeded, then one should review the data from IGABT in definitive cervical cancer for the best available data on expected toxicities relative to doses for the rectum and the bladder. For example, the risk of a rectal fistula significantly increases at a D_{2cc} dose above 75 Gy and G2 or higher toxicities for the bladder occur above 80 Gy (54, 55). In addition, the dose to the bladder trigone needs to be considered as this appears to have a lower tolerance compared with the rest of the bladder. It is important to acknowledge that these constraints are derived from patients who received definitive chemotherapy and radiation as their primary treatment. Whether these constraints should be different in the reirradiation setting to potentially factor in repair to normal OARs that may occur with time, for example, is not well understood.

Fig. 2. Local control based on reirradiation dose, number of patients (in bullets), and follow-up in years.

Conclusions

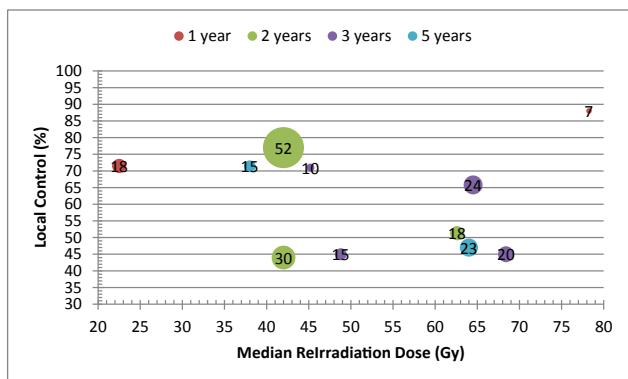We provide the current literature review and practice patterns of an international group of experienced

practitioners to offer a sense of what people are actually doing in their practices. This is by no means meant to serve as a surrogate for practice guidelines. Each clinician needs to evaluate their patient and to determine the best treatment course for the individual in front of them. Future areas of investigation need to include methods to improve local control while limiting the risk of acute/late toxicities as well as the biology of patients who develop local failures. Owing to the limited numbers of patients with recurrences in previously irradiated areas, centralization of such challenging cases may be warranted. International collaboration is needed to accomplish progress in managing this population of patients.

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Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.brachy.2019.11.008.

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