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American Brachytherapy Society recurrent carcinoma of the endometrium task force patterns of care and review of the literature

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ABSTRACT

PURPOSE: The purpose of this American Brachytherapy Society task force is to present a literature review and patterns of care by a panel of experts for the management of vaginal recurrence of endometrial cancer.

METHODS AND MATERIALS: In 2016, the American Brachytherapy Society Board selected a panel of experts in gynecologic brachytherapy to update our current state of knowledge for managing vaginal recurrence of endometrial cancer. Practice patterns were evaluated via an online survey and clinical updates occurred through a combination of literature review and clinical experience and/or expertise.

RESULTS: There are various retrospective series of patients treated with radiation for vaginal recurrence of endometrial cancer, which include a varied group of patients, multiple treatment techniques, and a range of total doses and demonstrate a wide scope of local control and overall survival outcomes. In the era of image-guided brachytherapy, high local control rates with low significant late-term morbidities can be achieved. Lower rates of local control and higher late-term toxicity are reported in the retreatment setting. In patients with no previous history of radiation treatment, external beam radiation therapy followed by brachytherapy boost should be used. There are varying practices with regard to the definition and appropriate doses of both the high-risk clinical target volume and the intermediate-risk clinical target volume in the setting of vaginal recurrence of endometrial cancer. There are limited data to provide appropriate dose constraints for some organs at risk with the majority of guidance taken from the definitive cervical cancer literature.

CONCLUSIONS: A summary of literature and expert practice patterns for patient selection, dose recommendations, and constraints are provided as guidance for practitioners.

Keywords: Endometrial cancer; Brachytherapy; Vaginal recurrence

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Introduction

Endometrial cancer is the most commonly diagnosed gynecologic cancer in the United States with an estimated 60,000 new cases per year (1). Most women are diagnosed with early-stage disease and are managed with definitive surgery followed by consideration of adjuvant radiation therapy, for selected patients. After definitive treatment, it is vital that women, even those with Stage I-II disease, undergo close surveillance. This is especially important for women with early-stage disease who do not receive radiation therapy, because they have an approximately 10–15% risk of recurrence after surgery alone as compared to <5% in those who receive adjuvant radiation (2, 3). Recommendations as per the National Comprehensive Cancer Network guidelines suggest women have a physical examination every 3–6 months for 2–3 years and then every 6 months or annually (4). Imaging should be performed as clinically indicated.

Close surveillance is recommended in the first 2–3 years because most recurrences will occur within 3 years of a patient's initial treatment. The vagina is one of the most common sites of recurrence (particularly in women without a previous history of radiation after surgery) with most recurrences occurring in the upper part of the vagina (5).

At the time of recurrence, 50–70% of patients are symptomatic with the most common presenting symptom being vaginal bleeding. Patients who present with more advanced recurrences may also report hematuria, hematochezia, decreased appetite, weight loss, pain (in the pelvis, abdomen, hip, or back), cough, shortness of breath, or swelling (in the abdomen or legs) (6–8).

The American Brachytherapy Society published consensus guidelines for interstitial brachytherapy for vaginal cancer that included comments on vaginal recurrence of endometrial cancer but this was not its primary focus (9). The purpose of this manuscript is to provide a more in depth literature review of the management of women with vaginal recurrence of endometrial cancer and current patterns of care among a group of experienced practitioners.

Methods and materials

A literature search of patients with vaginal recurrence of endometrial cancer was performed of published English medical literature in MEDLINE and PubMed from 1988 to 2016 using the terms "endometrial cancer," "radiation," and "recurrent." References in identified manuscripts were also reviewed. Series were selected for review if radiation was the primary treatment modality. Emphasis of manuscripts selected for review were those that predominantly included recurrent endometrial cancer patients, more than 10 patients, and use of 3D imaging for treatment planning. The data were summarized by one of the authors (MK) for the rest of the panel to review. After the panelists reviewed the data, it was apparent that there is insufficient evidence to provide consensus recommendations in many areas.

Given that an evidence-based consensus is not possible at this time, the panelist's current practice patterns were gauged through a 21 question survey developed by two co-authors (MK, LL). The purpose of the survey was to document the range of current practices of the panelists on questions where uncertainty arose during discussion of the literature review (Supplement). Each of the nine physicians was sent the questions via an online survey. All nine physicians responded to the survey and all responses were anonymized.

The results of the literature review and panelist's current practice is presented in five different sections: (*1*) patient selection and/or evaluation, (*2*) role of external beam radiation, brachytherapy, and chemotherapy, (*3*) clinical outcomes, (*4*) target delineation and organs at risk, and (*5*) followup. Each section has questions which are addressed with either a literature review followed by a panelist's current practice section or just a panelist's current practice section.

Given that there is insufficient evidence to provide evidence-based consensus treatment recommendation for many areas, the panelist's current practices are presented to provide the reader with the range of treatments currently being offered by an experienced group of practitioners.

Results

Patient selection and/or evaluation

How should women with endometrial cancer vaginal recurrence be evaluated and selected for treatment with radiation?

Panelist's current practice. When a woman presents with a suspicious area of recurrence in the vagina, a thorough evaluation is mandatory. Evaluation should include a pelvic examination to fully characterize the extent of disease. Ideally, a diagram will be drawn to depict the extent of disease to include information regarding the maximum diameter of the tumor, the location of the tumor including upper, mid, and/or lower vagina as well as left and/or right, anterior and/or posterior vaginal wall involvement, paravaginal involvement, and extension to the pelvic sidewall. Before initiating any treatment, the patient should undergo biopsy confirmation of the recurrence. If a patient has received previous radiation it is important to limit the extent of the biopsy as increased complications can occur with more aggressive approaches in the setting of previous radiation (10). Imaging is also an important component of patient evaluation and should include at least a CT scan of the chest and/or abdomen and/or pelvis to define pelvic and extrapelvic disease. If a positron emission tomography scan can be authorized, it can also be useful in characterizing the extent of disease and assessing any concomitant nodal

recurrences (pelvic and/or paraaortic). An MRI of the pelvis is also helpful as it provides better soft tissue resolution than CT and can provide improved details regarding the local extent of disease (11). It can also assist in future brachytherapy planning. Instillation of vaginal gel during the pelvic MRI promotes vaginal distension and may allow for improved evaluation of the extent of disease.

In patients with a previous course of radiation, it is imperative to obtain their previous radiation treatment fields and/or brachytherapy records to determine whether the recurrence is within the previously treated regions. It is possible with a distal vaginal recurrence that the disease may be inferior to the most distal extent of the prior radiation fields. Appropriate laboratory work-up including an evaluation of kidney function is also important for patients who will be considered for chemotherapy.

When considering the ideal treatment option, it is important that the patient be evaluated by a multidisciplinary team of physicians including a gynecologic oncologist and a medical oncologist if the gynecologic oncologist does not administer chemotherapy. There are multiple treatment options that may be appropriate including radiation, surgery ± intraoperative radiation therapy, and/or chemotherapy (4).

Role of external beam radiation, brachytherapy, and chemotherapy

What is the role of external beam radiation therapy in women with vaginal recurrence of endometrial cancer?

Literature review. In patients who have not previously received external beam radiation therapy (EBRT), doses of 45–50 Gy to the pelvis should be given before brachytherapy. This serves two purposes; the first is to treat the lymph nodes and paravaginal tissues because they are at risk for harboring microscopic disease. Curran et al. reported the risk of pelvic failure after salvage treatment using a modified vaginal staging system (Stage I—confined to mucosa, Stage IIA—subvaginal extension, Stage IIB—extravaginal extension without pelvic sidewall involvement, and Stage III— pelvic wall involvement). They reported 0 of 15 recurrences in patients with modified International Federation of Gynecology and Obstetrics vaginal Stage I disease, 9 of 15 in patients with Stage IIA disease, 12 of 17 in patients with Stage IIB disease, and 8 of 8 in patients with Stage III disease. Overall, the pelvis was a component of failure in 29 of 55 (57%) patients. Extrapelvic failures were reported in 23% of all cases in this study (12). Twenty-six of 55 patients in this series received a combination of external beam and brachytherapy, 17 of 55 received external beam alone, four received brachytherapy only, and eight received no radiotherapy (RT). Patterns of failure were not reported according to the type of radiation received. Jereczek-Fossa et al. noted similar findings with a pelvic progression rate (with or without extrapelvic metastasis) of 76%. In the 50 patients in whom progression was seen, including patients who initially responded and then progressed as well as initial nonresponders, local progression was seen in 30 patients (8). Out of the 73 patients in this series, 44 patients were treated with external beam and brachytherapy, 17 with brachytherapy only, and 12 with external beam only. Using the modified vaginal staging, 7% were Stage I, 59% were Stage II, and 34% were Stage III. Only 56% of the patient cohort had adenocarcinoma, and Stage III patients received a lower total dose compared with Stage IIA patients. This higher risk group of patients with lower total doses in the higher Stage patients may account for the relatively high pelvic progression rates reported in this study. In a third study by Baek et al., 0 of 17 patients treated with external beam and brachytherapy developed a nodal failure whereas 6 of 26 (23%) developed a nodal recurrence when treated with brachytherapy alone ($p = 0.047$) (13).

The second reason to use EBRT is to shrink the gross disease in the vaginal cuff so that brachytherapy can be performed on a smaller volume of disease, thereby limiting higher doses of radiation to the surrounding organs at risk.

The literature documents superior outcomes with a combined approach of EBRT and brachytherapy. In one of the largest studies on recurrent endometrial cancer, Jhingran et al. reported on univariate analysis that the use of EBRT and brachytherapy compared with single-modality therapy was a significant predictor of overall survival (OS) (5-year OS: EBRT only 28%, brachytherapy only 36%, EBRT and brachytherapy 52%) (14). Other studies show an improvement in local control with combination therapy. Sears et al. reported an improvement in local control on multivariate analysis with the use of brachytherapy as a boost technique compared with EBRT as a boost or no boost (5-year local control with brachytherapy 64%, EBRT 44%, and none 28%) (15). Lastly, in a small study of 15 patients by Nag et al. those treated with brachytherapy only had a local control rate of 64% compared with 100% for those treated with EBRT + brachytherapy (16). Until subsets of patients are identified where brachytherapy alone will suffice or where the EBRT field can be limited to only the site of recurrent disease, it is recommended to treat with pelvic radiation therapy followed by brachytherapy as the treatment of choice.

With respect to the treatment technique for EBRT, either 3-D conformal or intensity modulated radiotherapy (IMRT) is appropriate. The standard vs. intensity-modulated pelvic radiation therapy in treating patients with endometrial or cervical cancer (TIME-C) trial has been presented in abstract form and does provide level 1 evidence showing reduced patient reported acute gastrointestinal toxicity with IMRT (17). Long-term followup of these patients will demonstrate whether the improvement in acute toxicities translates into reduced late-term morbidity.

It is important, when simulation is performed, to place a marker at the most distal and lateral extent of disease either

before or at the time of simulation to ensure adequate margin on the most distal and/or lateral extents of disease. When treating with IMRT, it is also necessary to consider bladder filling and/or emptying and issues with rectal distention when evaluating appropriate planning target volume (PTV) margins. Physicians are encouraged to use an internal target volume for the bladder by performing both a bladder full and bladder empty scan at the time of simulation. Also, if the rectum is significantly distended at the time of simulation, consideration should be made either to increase the posterior PTV margin or to resimulate the patient with an empty rectum. It is more important to ensure that the recurrent disease is adequately encompassed by the PTV than be overly concerned over tight dose constraints or margins for the rectum and the bladder. Some form of daily image guidance should also be used, particularly with IMRT, to ensure that the vaginal cuff is adequately encompassed in the PTV volume on a daily basis. Inguinal nodes should be included for patients with recurrences extending into the distal third of the vagina.

In patients who have previously received EBRT, additional full pelvic EBRT is generally not recommended. An exception to utilizing repeat EBRT may be in those patients who have a distal vaginal recurrence at the edge of the previously treated external beam fields. These patients should also be considered for elective inguinal irradiation.

Panelist's current practice. Panelists routinely incorporate EBRT in patients with a vaginal recurrence of endometrial cancer before brachytherapy in the setting of no prior history of pelvic radiation. With respect to the amount of vagina to include during the external beam portion of treatment, for a recurrence located in the upper half of the vagina, four of nine panelists would treat a 3–4 cm margin on the most distal extent of disease, four of nine would treat the entire vagina, and one of nine would treat the upper 3/4th of the vagina (Supplement—Survey Question 2). For a recurrence located in the lower half of the vagina, eight of nine panelists would treat the entire vagina (Supplement—Survey Question 3). Some of the variation in practice is related to the uncertainty of the true risk of submucosal disease spread and whether the entire vagina is at risk for harboring microscopic disease. Most panelists would include the whole vagina if the recurrence was located in the mid-vagina.

For patients who have previously received vaginal cuff brachytherapy, additional EBRT should be strongly considered. All panelists agreed that in a patient who received prior adjuvant vaginal cuff brachytherapy, the EBRT would routinely be offered (Supplement—Survey Question 1). The appropriate dose and treatment field will depend on the location and extent of recurrent disease as well as the dose and area of the vaginal cuff previously treated with brachytherapy. Careful consideration of the previous doses to the bladder and the rectosigmoid should be a part of this planning. The specifics of EBRT in these cases must be determined on a case-by-case basis.

What is the role of brachytherapy in the management of a vaginal recurrence of endometrial cancer?

Brachytherapy is an essential component in the management of all localized recurrent cases. For some rare cases, it may not be possible to implant the full extent of disease. For these cases, it may be preferable to use a highly conformal image-guided external beam boost. Brachytherapy can be performed using either an intracavitary or an interstitial technique. In general, an interstitial approach should be used when the extent of disease remaining at the time of brachytherapy is >0.5 cm in thickness. Making this determination involves a combination of a detailed pelvic examination at the end of external beam as well as MRI. Some locations in the vagina are difficult to discern the thickness (e.g., anterior vaginal wall), and in these patients, MR can be especially pivotal.

What total dose of external beam radiation and brachytherapy should be prescribed in patients without a previous history of radiation therapy?

Literature review. There are no prospective trials that provide evidence regarding the optimal dose for treating endometrial cancer vaginal recurrence. Despite this, multiple studies do suggest improved local control outcomes with higher doses of radiation (Table 1). The study by Jhingran et al. is noteworthy in that it is the largest reported study in the literature with 91 patients with a median followup of 70 months. Patients who received at least 80 Gy had improved local control compared to patients who received less than 80 Gy ($p = 0.04$) (14). Other studies listed in Table 2 also suggest improvements in local control outcomes with increased dose: >60–65 Gy (12, 18, 19), >70 Gy (20), and >80 Gy (21).

Other important studies include three recent image guided brachytherapy series that used D90 doses in the range of: 74.8 Gy (in patients without previous RT) (20), 76 Gy (22), and 83 Gy (23). Local control rates in these series are excellent: 2 years 96% (Lee et al., in patients without previous RT), 3 years 95% (Vargo et al.), and 2 years 92% (Fokdal et al.). The doses used in these three image guided series are higher than those used in previous studies. It is not clear whether the use of image guidance, the higher total dose, or that the dose is being prescribed to an individualized volume are responsible for these encouraging outcomes.

Panelist's current practice. When panelists were asked what their typical dose of EBRT and brachytherapy to the high-risk clinical target volume (HR-CTV) would be in the setting of no previous history of radiation therapy, seven of nine panelists responded that they treat to a dose of between 75 and 79 Gy (Supplement—Survey Question 4). No

Table 1
Treatment outcomes by dose

Author, publication date	Outcomes by dose	*p*-value
Kuten, 1989	≤65 Gy: local failure 21% (4/21 pts) >65 Gy: local failure 10% (2/20 pts)	Not sig
Curran, 1998	<60 Gy: pelvic control/overall survival—10%/12% ≥60 Gy: pelvic control/overall survival—68%/47%	0.004 (PC) 0.002 (OS)
Morgan, 1993	<60 Gy: local failure 44% (4/9 pts) ≥60 Gy: local failure 5% (1/21 pts)	0.03
Sears, 1994	No boost: 5-year local failure 72% EBRT boost: 5-year local failure 56% Brachy boost: 5-year local failure 36%	Boost tech sig on UVA and MVA for local control
Wylie, 2000	<80 Gy: 5-year local failure 46% ≥80 Gy: 5-year local failure 28%	Not sig ($p = 0.07$)
Jhingran, 2003	<80 Gy: 5-year local failure 34% ≥80 Gy: 5-year local failure 17%	EBRT + Brachy sig on MVA ($p = 0.03$)
Sorbe, 2013	EQD2 brachy dose (OR = 1.054, $p = 0.0018$) and total EBRT dose (OR = 1.038, $p = 0.0010$) associated with complete response No difference in outcome when comparing ≥80 Gy vs. <80 Gy	Sig on univariate analysis
Lee, 2013	Median cumulative dose for patients with local failure 66.2 Gy vs. no local failure 73.9 Gy	0.02
Jereczek-Fossa, 2000	Increased total RT dose associated with improved OS; higher response rate seen in Stage IIB-III disease with increased dose but not in lower staged disease	0.047 (on MVA)

PC = pelvic control; OS = overall survival; MVA = multivariate analysis; EBRT = external beam radiation therapy; RT = radiotherapy; pts = patients; OR = odds ratio; sig = significant; EQD2 = Equivalent dose in 2 Gy fractions; UVA = univariate analysis.

consensus was reached for evaluation of D90 of the HR-CTV as only five panelists use this parameter (Supplement—Survey Question 5). The most common high-dose-rate per fraction used by the panelists is between 5 and 5.9 Gy (six of nine panelists) (Supplement—Survey Question 6).

What total dose of external beam radiation and brachytherapy should be prescribed in patients with a previous history of radiation therapy?

Literature review. Patients who recur within their prior treatment field are at high risk for both recurrence- and retreatment-related complications. Options for therapy include pelvic exenteration, reirradiation or treatment with systemic therapy.

Patients with a previous history of radiation will have received a wide range of doses and volumes of tissues irradiated. This can range from vaginal cuff brachytherapy alone to whole pelvis radiation therapy with a vaginal cuff boost (Equivalent dose in 2 Gy fractions [EQD2] ~30–60 Gy). The ideal volume that can safely be retreated and the dose that should be used to optimize local control in this setting are not known. Given the uncertainties that exist in the retreatment setting as well as the high risk of toxicities and overall worse outcomes in this patient population, patients should only undergo retreatment after a detailed evaluation with multidisciplinary input. The decision to pursue retreatment with radiation must be determined on a case-by-case basis, and the patient should receive a thorough informed consent regarding expected outcomes and potential toxicities. General factors to consider in the retreatment setting should include disease-free interval from previous radiation, previous radiation dose, location of recurrence in relation to previous radiation, local only vs. local and regional and/or distant recurrence, grade and/or histology of the recurrence, size of the recurrence, the patient's performance status, and baseline gastrointestinal and/or genitourinary and/or vaginal morbidity.

A summary of selected retreatment literature for gynecologic malignancies is presented in Table 2. Prospective data come from Viswanathan et al. and Martinez-Monge et al. In Viswanathan et al., in a combined series of prospective (MRI) and retrospective (CT) guided interstitial brachytherapy for 44 patients with recurrent endometrial cancer, 13 received reirradiation (24). For patients who were reirradiated, the retreatment cumulative dose (EQD2) was 66.5 Gy (range 25–76.9 Gy), with D_{2cc} bladder was 56.9 Gy, rectum was 53.5 Gy, and sigmoid was 45.1 Gy. Their 2-year local failure was 39%, disease-free survival (DFS) was 26%, and OS was 55%. Two patients had Grade 3 proctitis requiring transfusion or a colostomy. This group recently updated their retreatment experience of vaginal recurrences of endometrial cancer which now includes 24 patients (25). Patients received a median cumulative (i.e., prior and retreatment dose) HR-CTV EQD2 of 89.2 Gy (range 52.2–106.6) and retreatment D90 of 41.8 Gy. Three-year local control and/or disease-free interval and/or OS were 71%, 52%, and 54%, respectively. Toxicities

Table 2
Summary of literature for patients previously treated with radiation therapy

Author	No of pts	Pt mix	Median followup (year)	Retreatment and/or cumulative EQD2 dose	Clinical outcomes	Toxicity	Comments
Martínez-Monge R et al., 2014	15	Cervical (6) Endometrial (6) Vulvovaginal (3)	2.8	Retreatment dose: 46 Gy 4.75 Gy × 8[a]	5-year LC 71% 5-year DFS 21% 5-year OS 40%	20% Grade ≥3	Lifetime D2cc rectum/bladder EQD2: 111 Gy/121 Gy
Kamran et al., 2017	24	Endometrial only	2	Retreatment D90 dose: 42 Gy Cumulative dose: 89.2 Gy (52−107)	3-year LC 71% 3-year DFI 52% 3-year OS 54%	10 G3 toxicities in 8 pts (6 rectal and 4 urinary)	Lifetime D2cc rectum/bladder EQD2: not reported
Huang et al., 2016	16	Endometrial only	1.5	Cumulative dose: 74 Gy (63−105.8 Gy)	2-year LC 60% 2-year PFS 51% 2-year OS 72%	4/40 pts with G3-4 toxicities[c]	2.5% soft tissue 5% GI 2.5% GU 2.5% MSK For whole cohort of 40 pts
Zolciak-Siwinska A et al., 2014	20	Cervical (19) Vaginal (1)	2.6	Retreatment dose: 48.8 Gy Cumulative dose: 133.5 Gy	3-year LC 45% 3-year DFS 42% 3-year OS 68%	2 pts G3 rectal 1 pt G3 bladder 8 pts G3-4 vaginal	[b]Lifetime EQD2 D2cc rectum/bladder: 94.4 Gy/99.3 Gy An interval of ≤12 months and tumor diameter >3 cm were significant predictors of worse treatment outcomes
Baek S et al., 2016	4	Endometrial only	4.8	Retreatment dose: 56 Gy 6 Gy × 7	5-year LC 75% 5-year PFS 67%	6 pts G3 complications[d]	2/3 pts with vaginal fistula had previous RT
Brabham J et al., 2009	19	Cervical (6) Endometrial (5) Vaginal (4) Vulva (3) Urethra (1)	1.8	Retreatment dose: 50 Gy 198Au	LC 63%	5% G3 (acute vaginal mucositis) 0% late G3/4	

LC = local control; PFS = progression-free survival; DFS = disease-free survival; OS = overall survival; G = grade; MSK = musculoskeletal; GU = genitourinary; GI = gastrointestinal; RT = radiotherapy; pt = patient; EQD2 = Equivalent dose in 2 Gy fractions; DFI = disease free interval.

[a] This dose was given to 12/15 patients.

[b] 3D data available for 9 patients.

[c] Overall series included 40 total patients but 16 patients had previous radiation.

[d] Overall series included 43 total patients but only four had previous radiation.

included 10 Grade 3 rectal and urinary toxicities in 8 patients (six rectal and four urinary).

In Martinez-Monge et al., the outcomes of 15 patients with previously radiated gynecologic cancers (six cervical, six endometrial, and three vulvovaginal tumors) were reported (26). The retreatment dose with interstitial brachytherapy was 38 Gy in eight fractions (EQD2 46.7 Gy) in 12 of 15 cases. With a median followup of 2.8 years, 5-year local control and/or DFS and/or OS were 71%, 21%, and 40%, respectively. Three patients (20%) developed Grade ≥3 complications. The lifetime EQD2 of the rectum D_{2cc} was 111 Gy and the bladder was 121 Gy. There was a trend for an increased risk of complications with an increased volume treated ($p = 0.08$).

When compared to patients treated in the upfront setting, those who undergo reirradiation have a >10% risk of developing a Grade 3 toxicity and local control rates are poorer (50–60%). When approaching EQD2 D_{2cc} doses of about 100 Gy there seems to be a 15–20% risk of combined Grade three bladder and/or rectal complications.

Panelist's current practice. For patients who undergo retreatment, evidence-based guidance is limited, as many series do not report the outcomes of patients with previous treatment separately from those without previous treatment and the series that do exist are small. One of two treatment approaches have been typically adopted: (*1*) limit the total normal tissue doses as one would in the upfront setting or (*2*) purposefully exceed the accepted tolerance of the normal tissues in an effort to increase the dose to the tumor. 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 (Supplement—Survey Question 7).

When panelists were asked what their typical retreatment dose would be in the case of a patient having received either prior vaginal cuff brachytherapy alone or pelvic radiotherapy (± vaginal cuff brachytherapy), five of nine and seven of nine panelists, respectively, stated that they individualize the dose for each case (Supplement—Survey Questions 8 and 9). Eight of nine panelists also do not use an intermediate-risk clinical treatment volume (IR-CTV) in the retreatment setting (Supplement–Survey Question 10).

What is the role of chemotherapy?

Literature review. The utility of concurrent chemotherapy with radiation has been demonstrated in the definitive and postoperative setting in cervical cancer, but whether this can be extrapolated to the recurrent endometrial cancer setting is currently not known. Gynecologic Oncology Group (GOG) 0238 is a randomized trial of pelvic radiation with or without concurrent weekly cisplatin in women with pelvic-only recurrences of endometrial carcinoma and will ultimately answer this question.

There is only a single study to date that has combined radiation with a targeted agent. In this study of 15 patients with recurrent endometrial cancer it seems safe to combine radiation with bevacizumab (27). With a median followup time of 5.5 years, 10 patients that had large tumors with multiple sites of involvement had no evidence of disease, while 5 patients developed distant metastases. The 5-year DFS was 58% and OS was 73%.

Finally, there are no data to provide guidance on the role of outback chemotherapy.

Panelist's current practice. Five of nine panelists routinely recommend current chemotherapy with external beam radiotherapy and three of nine recommend its use based on factors such as tumor size and grade (Supplement—Survey Question 11). When these responses were discussed, an example of a small low-grade superficial lesion was brought up as a case where concurrent chemotherapy would likely not be recommended.

Clinical outcomes

What are the expected treatment outcomes after radiation therapy for endometrial cancer vaginal recurrence?

Literature review. Diverse outcomes with regard to local control, relapse-free survival, and OS after definitive radiation therapy have been reported (Table 3 and Fig 1). Drawing definitive conclusions based on these studies is challenging, as almost all studies are retrospective and heterogeneous in the types of patients included and radiation doses and/or techniques used.

One factor often correlated with outcomes is the size and/or extent of the recurrence. Some groups have classified the size and/or extent of recurrence by applying a modified International Federation of Gynecology and Obstetrics vaginal cancer staging system as discussed earlier in this manuscript. In a study by Curran et al., for example, this modified vaginal staging system predicted OS on multivariate analysis. Three-year actuarial survival and pelvic control rates according to this staging system were Stage I 85%/100%, Stage II 41%/43%, and Stage III 13%/0% (12). A correlation between treatment outcomes and vaginal staging has also been reported by other groups (8, 15, 21). This staging system is related to tumor size which also makes these findings consistent with other studies that have noted larger tumor size to be associated with poorer treatment outcomes (15, 21, 22, 28–30). Another factor associated with outcomes is tumor grade with multiple studies demonstrating strong correlations with higher grade disease and worse treatment outcomes (14, 20, 23, 31, 32).

In terms of treatment outcomes, one of the most often cited studies is the experience from the Postoperative

Table 3
Summary of selected treatment outcomes

Author, year of publication	Years of treatment	No of patients	Median F/U (m)	Included patients with previous RT	Concurrent chemo/hormonal treatment	Local control (LC)	Disease-free survival (DFS)/progression-free survival (PFS)/relapse-free survival (RFS)	Overall survival	Complications
Greven K, 1987	1971–1982	18	NR	No	No	3 years 44% (crude)			
Curran W, 1988	1965–1985	55	NR	Yes	Yes	5-year pelvic control: 48%		5 years 36%[a]	2 with sig late complications
Kuten A, 1989	1959–1986	51	57.6	Yes	No	82% vaginal control 35% locoregional control		10 years 13%	10% severe
Lybeert M, 1989	1974–1984	36	NR	No	No		5-year RFS 28%		0% G3/4
Hoekstra C, 1993	1965–1985	26	NR	No	Yes	5-year local regional control 83%		5 years 44%	2 severe GI
Morgan J, 1993	1964–1987	34	48	Yes	No		5-year DFS 60%	5 years 68%	
Sears J, 1994	1973–1991	45	89	No	Yes	5 years 54%	5-year DSS 51%	5 years 44%	
Ackerman I, 1996	1983–1989	21	NR	No	No	Pelvic control in 79% with disease confined to mucosa vs. 43% with disease extending beyond mucosa			
Nag S, 1997	1989–1995	15	47	Yes	No		5-year DSS 68%	5 years 42%	1 pt RTOG G3 vaginitis
Pai H, 1997	1984–1992	20	47.5	No	No	10 years 74%	10-year DSS 71% 10-year DFS 46%	10 years 48%	
Hart K, 1998	1980–1994	26	15 (mean)	No	Yes	LC 46%		5 years 35%	
Tewari K, 1999	1979–1991	30	NR	Yes	No	5 years 77%	5-year DFS 65%		17% sig long term
Jereczek-Foassa B, 2000	1975–1995	73	42	No	Yes			5 years 33%	1% severe GU
Wylie J, 2000	1984–1988	58	105.6	No	No	10 years 62%		10 years 41%	
Hasbini A, 2002	1986–1999	25	28	Yes	No	3 years 92%		3 years 48%	4% severe late
Nag S, 2002	1989–2000	13	60	None	No		8-year DSS 77%		15% G3-4
Creutzberg C, 2003	1990–1997	39	44	No	No		77% disease free at median 44 m followup	5-year OS with no previous RT 65% and with previous RT 43%	
Jhingran A, 2003	1960–1997	91	70	Yes	No	5 years 75%		5 years 43%	9% G4
Lin L, 2005	1967–2003	50	58.8	Yes	No		10-year DFS 53%	10 years 40%	5 pts G3-4 GI
Petignat P, 2006	1997–2003	22	32	Yes	No	5 years 100%	5-year DFS 96% 5-year DSS 96%		18% G3-4 GI, 50% G3 vaginal RTOG
Huh W, 2007	1975–2002	69	63	No	No			5 years 75%	<5% G4
Lee L, 2013	2003–2011	44	24	Yes	Yes	2-year no prior RT: 96% 2-year LC with prior RT 61%	2-year DFS no prior RT 72% 2-year DFS with prior RT 26%	2-year OS no prior RT 80% 2-year OS prior RT 55%	9% G3
Sorbe B, 2013	1990–2005	40	66[a]	Yes	No	5 years 75%		5-year CSS 65% 5-year OS 50%	11% G3-4 GI
Fokdal L, 2014	2006–2013	43	30	None	No	2 years 92%	2-year DFS 59%	2-year OS 78%	12% G3
Vargo J, 2014	2004–2013	41	18	None	Yes	3 years 95% LC	3-year DFS 68%	3-year OS 67%	8% G3

(*Continued*)

Table 3 (*continued*)

Author, year of publication	Years of treatment	No of patients	Median F/U (m)	Included patients with previous RT	Concurrent chemo/hormonal treatment	Local control (LC)	Disease-free survival (DFS)/progression-free survival (PFS)/relapse-free survival (RFS)	Overall survival	Complications
Viswanathan A, 2014	2008–2010	15	45.7	None	Yes		3-year PFS 67%	3 years 80%	1 pt G3 blood/BM toxicity
Hardarson H, 2015	2003–2012	33	53.0[b]	None	No		2-year free of recurrence: 60%	2 years 83%	
Vance S, 2016	1989–2013	40	40.9	None	Yes		5-year DSS 7%	5 years 72%	
Huang K, 2016	2004–2012	40	18	Yes	No	2 year 60%	2-year PFS 51%	2 years 72%	Late G3-4 2.5% soft tissue 5% GI 2.5% GU 2.5% MSK
Baek S, 2016	1997–2012	43	58	Yes	No	5 years 78%	5-year PFS 52%	5 years 84%	14% G3

LC = local control; PFS = progression-free survival; DSS = disease-specific survival; DFS = disease-free survival; OS = overall survival; DC = distant control; G = grade; MSK = musculoskeletal; GU = genitourinary; GI = gastrointestinal; BM = bone marrow; RT = radiotherapy; pt = patient; RTOG = radiation therapy oncology group; CSS = cause specific survival.

[a] For patients still alive.

[b] For the 26 patients treated with RT only.

Radiation Therapy after Endometrial Cancer (PORTEC) randomized trial of observation vs. radiation therapy after surgery for Stage I patients (5). In this study 39 women presented with an isolated vaginal relapse. Thirty-five of these women were subsequently treated with curative intent most commonly with a combination of EBRT and brachytherapy. While a complete response was obtained in 31 of 35 patients (89%), five women subsequently developed distant metastasis and two developed a second vaginal recurrence. This resulted in a 5-year OS of 65% in patients who had not previously received radiation and 43% in those previously treated with pelvic radiation. It is important to appreciate that these numbers are based on the 35 women treated with curative intent and most of these patients had early stage low risk disease at presentation.

Salvage outcomes have also been reported for patients treated as part of GOG 99 which randomized early stage endometrial cancer patients to observation vs. whole pelvis radiation. 12 out of 13 patients in the observation arm developed a vaginal only recurrence and were treated with salvage radiation. Five of the 13 patients (38.5%) died as a result of endometrial cancer (3). While the results from PORTEC and GOG are insightful, they represent outcomes from prospective studies with regularly scheduled followup and in women with predominantly endometrioid histologies which may limit its generalizability.

When reviewing the additional available literature, it is challenging to formulate definitive conclusions. This includes, for example, how local control might impact OS. When considering studies, for instance, that report 2- to 5-year local control rates in the 83–100% range, their reported 2- to 5-year disease free or relapse-free survival rates are 59–96%, and 2- to 5-year OS rates are between 44% and 80% (Table 1). This demonstrates that even in the setting of high local control, this population of women still has a relatively high rate of developing regional and/or distant metastasis. It is notable that in series with lower local control outcomes (3–5 years 44–75%), OS outcomes are worse than when local control is higher (3–5 years 35–53%) (Table 1). Conclusions are limited, however, given differences between studies, types of imaging used to restage patients, and the risk of distant metastasis also being correlated with the initial stage and the grade of disease (22). Even if local control does not impact OS, achieving local control of a vaginal recurrence is an important singular endpoint as many women will present with vaginal bleeding and or pain that can be effectively managed with radiation.

It is also apparent that certain factors portend worse treatment outcomes. A previous course of radiation therapy seems to consistently portend worse outcomes when compared with women with radiation-naïve recurrence. Creutzberg et al., for example, reported 5-year OS in patients with a previous history of RT compared with those without to be 43% vs. 65% (5). Similar data from Curran et al. reported 5-year pelvic control and/or OS of 56%/48% in

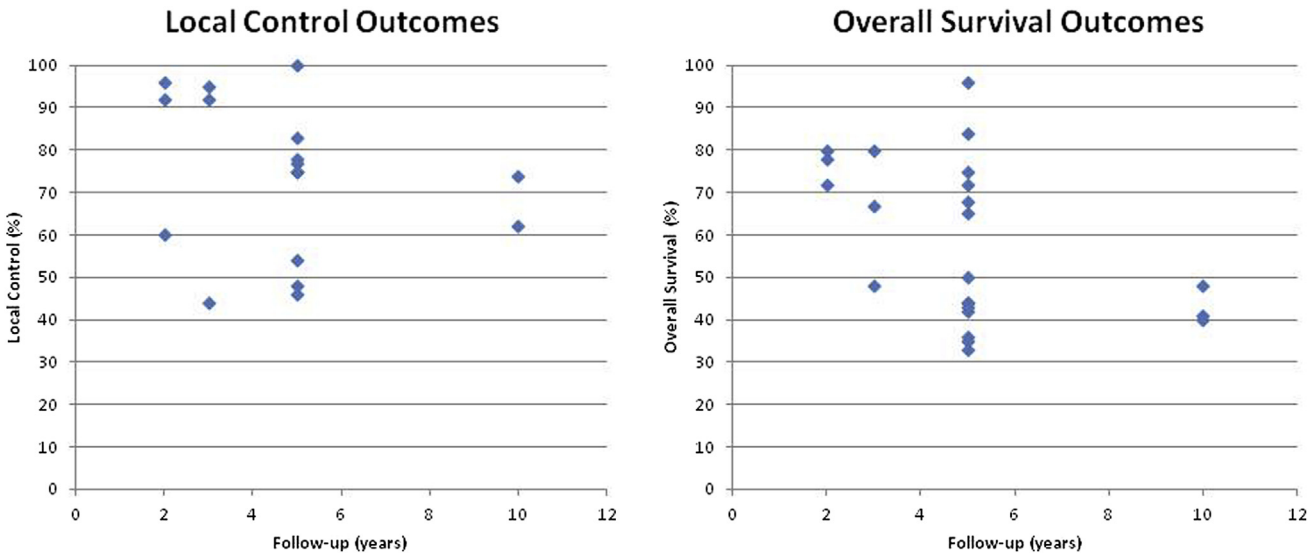

Fig. 1. Treatment outcomes for local control and overall survival. A summary of local control reported in various studies showing a wide range of reported outcomes. The following studies are included in the above graph: Greven et al, Curran et al, Hoekstra et al, Sears et al, Pai et al, Hart et al, Tewari et al, Wylie et al, Hasbini et al, Jhingran et al, Petignant et al, Lee et al, Sorbe et al, Fokdal et al, Vargo et al, Huang et al, Baek et al. A summary of overall survival reported in various studies showing a wide range of reported outcomes. The following studies are included in the above graph: Curran et al, Hoekstra et al, Morgan et al, Sears et al, Nag et al, Pai et al, Hart et al, Jereczek-Foassa et al, Wylie et al, Hasbini et al, Creutzberg et al, Jhingran et al, Lin et al, Petignant et al, Huh et al, Lee et al, Sorbe et al, Fokdal et al, Vargo et al, Viswanathan et al, Vance et al, Huang et al, Baek et al.

patients with no previous history of radiation whereas it was 33%/16% in those with a previous history (12).

Even in the era of image guided brachytherapy, local control and OS rates are reported to be inferior in patients with prior radiation therapy with one study reporting 2-year local failure and OS rates of 4%/80% in patients with no previous history of radiation vs. 29%/55% in patients with a previous history of radiation therapy (20). It is likely that these inferior outcomes are related to the challenge of delivering tumoricidal radiation dose in the retreatment setting and a worse natural history for these types of tumors.

Target delineation and organ at risk constraints

How should the high-risk clinical target volume and the intermediate-risk clinical target volume be defined?

Literature review. GEC-ESTRO has published definitions for an HR-CTV as well as IR-CTV for definitive cervical cancer treatment. These target definitions have not been formally adapted for recurrent endometrial cancer lesions in the vagina. One of the challenges in modifying the HR-CTV concept from cervical cancer to lesions involving the vagina is that for cervical cancer the HR-CTV includes the entire cervix as high risk for residual disease. The morbidity associated with treating the entire vagina to doses in the range of 70–85 Gy is too high and so the whole vagina should not be taken to the full prescription dose.

There is variation in how the HR-CTV has been defined in recent image guided brachytherapy series (20, 22, 23). Vargo et al. describe their HR-CTV as including the original (before starting EBRT) superior and inferior extent of disease but only the residual thickness of gross disease present at the time of brachytherapy. For disease limited to one wall, the circumferential wall at that level was included. An IR-CTV was not used. Lee et al. describe their HR-CTV as clinically evident disease identified by examination, CT and/or T2 weighted MR images at the time of brachytherapy. They also treated the uninvolved vagina to a minimum of 60 Gy with the exception of patients who received prior RT. Finally, Fokdal et al. described their HR-CTV as the residual tumor noted at the time of brachytherapy. An IR-CTV was defined as the initial tumor volume including an individualized margin. The whole circumferential vaginal wall was included in the target.

Given the variations in defining the HR-CTV in the literature, a recommendation for the optimal definition is not possible and is beyond the scope of this review. Some of the variability is related to a lack of evidence-based guidance for the true risk of recurrence for the following three volumes: the original extent of disease at the start of external beam radiation, the extent of disease remaining at the time of brachytherapy, and the entire vagina.

Panelist's current practice. In an effort to understand panelist's current practice patterns, they were given two clinical cases to describe what they would draw as their target volumes. The first case was a patient with a right vaginal wall lesion with persistent disease after the completion of her EBRT. Panelists were asked how they would define the superior and/or inferior extent of their HR-CTV in this case if

they were planning on MRI. Five of nine panelists contour the superior and/or inferior extent of disease that remains at the time of brachytherapy while three of nine contour the original (i.e., before starting EBRT) superior and/or inferior extent of disease (Supplement—Survey Question 12). There were differences of opinion regarding how much of the circumference of the vagina (i.e., just the right lateral wall or the whole vaginal circumference) should be included and whether an IR-CTV should be used (Supplement—Survey Question 13, Survey Question 14). When used, six of nine panelists use an IR-CTV dose of between 55 and 60 Gy (Supplement—Survey Question 15).

When panelists were asked whether they would modify their HR-CTV contour if they had to contour on CT rather than MRI, no majority consensus was achieved (Supplement—Survey Question 16). The panel agreed that MRI allows clearer delineation of the HR-CTV and typically results in smaller treatment volumes. Proponents of limiting the HR-CTV to just the visible disease on each slice of the vagina felt that on MRI imaging this could be clearly defined and potentially limit morbidity compared with treating the whole circumference of the vagina. Opponents of this approach felt that there are limited data to support treating less than the whole circumference of the vagina. In addition, more clinicians are likely to have access to only CT-based planning and accurately defining the extent of vaginal disease was not felt to be reliable on CT alone. In addition, when using CT only for treatment planning, the panel felt strongly that fiducial marker seeds should be placed before starting EBRT to help delineate the original extent of disease.

The panelists were also asked about a second clinical scenario where a patient has a right lateral vaginal wall recurrence and has a complete response at the time of brachytherapy. All panelists agreed that the original superior and inferior extent of disease should be treated but there were differences of opinion regarding how much of the circumference of the vagina (i.e., just the right lateral wall or the whole vaginal circumference) should be included and whether an IR-CTV should be used (Supplement—Survey Question 17). The panelists were also asked that when there has been a complete response at the time of brachytherapy what thickness of the vagina they contour as their HR-CTV. Four of nine panelists contour the surface of the vaginal cylinder while four of nine contour a thickness (1 person, a 5 mm margin from the surface of the cylinder and three MRI or CT determined thickness) (Supplement—Survey Question 18). The panel recommends that physicians use image-based brachytherapy to ensure adequate coverage of the intended targets as recent data using MRI simulation for postoperative vaginal cylinder planning demonstrated potential underdosing of the target that may only be visible on MRI (33).

At this time, the panelists use a range of doses to the following at risk volumes: whole vagina (45–60 Gy), original superior and/or inferior extent of disease (60–80 Gy), and residual disease at the time of brachytherapy (70–80 Gy). There is clearly a range of contouring practices among the panelists with a strong need to develop a set of agreed upon guidelines. It was beyond the scope of this group to develop consensus contouring guidelines.

What are the recommended organs at risk dose constraints?

Our understanding of optimal constraints to organs at risk is evolving in the era of image-guided brachytherapy. Most data regarding what we know are derived from the management of locally advanced cervical cancer (34). While these are the best data available, it is important to appreciate that most cervical cancers do not involve more than the upper vagina. With recurrent endometrial cancer, a much longer length of the vagina may need to be treated which puts the rectum, bladder, and urethra at risk. Also, in the posthysterectomy setting, the bowel is often located just superior to the vaginal cuff, thereby creating a different relationship between the target and the normal organs at risk compared to an intact cervical cancer case. There are insufficient data to suggest that constraints should be different for intracavitary vs. interstitial cases. However, in general, women treated with interstitial implants tend to have larger volumes of disease that can expose more normal tissues to radiation (i.e., the rectum) and so caution should be exercised. All panelists routinely contour the rectum, sigmoid, and bladder in the setting of a vaginal recurrence of endometrial cancer (Supplement—Survey Question 19). Contouring of other organs at risk such as the small bowel, vagina, urethra, and ureter were more variable. It was discussed that contouring the small bowel is challenging without contrast which makes utilizing dose constraints for it difficult.

Rectum and/or sigmoid dose constraints

Literature review

The largest analysis of correlation between dose and rectal toxicities comes from the prospective EMBRACE study of 960 patients with a median followup of 25.4 months (35). An equieffective D_{2cc} dose for a 10% probability for overall rectal grade ≥2 morbidity was found to be 70 Gy. A D_{2cc} dose ≥75 Gy was associated with a 12.5% risk of a fistula at 3 years vs. 0–2.7% for doses lower than 75 Gy. Also, a D_{2cc} dose ≤65 Gy was associated with a two times lower risk of proctitis than for doses ≥65 Gy. The EMBRACE trial treated definitive cervical cancer patients with either an intracavitary alone or a hybrid-based technique.

There are data using interstitial brachytherapy for women with primary and recurrent gynecologic cancers showing the estimated dose that resulted in a 10% risk of grade 2–4 rectal CTCAE, version 4, toxicity was a D_{2cc} dose greater than 62 Gy (36). In another interstitial study

of residual and/or recurrent cervical cancer treated with interstitial brachytherapy the estimated dose for a 10% risk of CTCAE, version 3, grade ≥2 rectal toxicity was a D_{2cc} dose greater than 55 Gy (37). While these two studies suggest lower dose constraints for the rectum compared with the EMBRACE study, these are small retrospective series while the EMBRACE study is a large prospective study. So, there is currently insufficient evidence to support utilizing different dose constraints for intracavitary and/or hybrid vs. interstitial cases. Practitioners should however be cautious when utilizing interstitial brachytherapy as these cases include larger tumors with more potential exposure of dose to organs at risk.

There are no specific constraints for the sigmoid but similar constraints are assumed for the rectum and the sigmoid until there are additional data to guide us.

Panelist's current practice

Seven of nine panelists use a D_{2cc} dose constraint for the sigmoid and/or rectum of <70 Gy (Supplement—Survey Question 20).

Bladder dose constraints

Literature review

There is more limited literature demonstrating correlations between bladder doses and toxicities with the majority of data coming from treating definitive cervical cancer patients. The largest study to date comes from EMBRACE on 680 cervical cancer patients where a significant dose relationship was shown with increased ≥Grade 2 morbidity at D_{2cc} doses >80 Gy (34).

Panelist's current practice

Five of nine panelists use a D_{2cc} bladder constraint of < 80 Gy while three of nine use a constraint of <90 Gy (Supplement–Survey Question 20).

Urethra dose constraints

Literature review

These are limited data regarding appropriate dose constraints for the urethra. In one series of 73 patients treated with interstitial brachytherapy (21 recurrent disease and 52 initial presentation), a 10% probability of a Grade 3 toxicity was observed with a dose of 23.1 EQD2 to a 0.1 cc volume of the urethra from brachytherapy after a median dose of 45 Gy of EBRT (38). In another study of 16 patients, increased urethral toxicities were seen in patients who received higher than 5 Gy per fraction as well as a 0.1 cc EQD2 dose of 85 Gy (39). It is important to consider that these findings are hypothesis generating as in another study of 10 women treated with periurethral cancer where the median D0.1 cc urethra EQD2 was 86 Gy, no patients developed a urethral stricture (40).

Panelist's current practice

Four of nine panelists provided dose constraints that they use for the urethra but no evidence-based conclusion or recommendation is possible based on the currently available literature (Supplement—Survey Question 20).

Ureter dose constraints

Literature review

There is also limited literature regarding dose constraints for the ureters. They are difficult to contour without either contrast administered at the time of simulation or the placement of temporary stents. It is also difficult to accurately assess ureteral toxicity in followup. Data from the EMBRACE study estimate a 3-year actuarial rate of Grade 3–4 ureter stenosis of 2.6% after the image guided brachytherapy for definitive cervical cancer (41). In another series of definitively treated cervical cancer patients treated with interstitial brachytherapy, the crude rate of ureteral strictures was 4.5% in patients who did not have temporary ureteral stents placed (42). In 34 patients who had bilateral ureteral stents placed at the time of their brachytherapy catheter insertion no ureteral strictures were observed in the followup. In this series the ureters were constrained to a D0.1 cc of <120%. This constraint can be considered during planning; however, this recommendation is based on a small retrospective series, and additional data are really needed to make more definitive recommendations.

Panelist's current practice

Two of nine panelists provided dose constraints that they use for the ureter but no evidence-based conclusion or recommendation is possible based on the currently available literature (Supplement—Survey Question 20).

Small bowel dose constraints

Literature review

The small bowel is not routinely contoured by the panelists, and three of nine panelists provided various constraints that they use (Supplement–Survey Question 20). Evidence-based constraints are limited. Data from 115 definitive cervical cancer patients treated with pulsed dose rate therapy with a median of 35.5 months of followup were not able to establish a correlation between the D_{2cc} or D0.1 cc small bowel dose and late-term small bowel morbidity (43). A bowel planning goal of D_{2cc} <70–75 Gy has been reported in a joint series of patients treated at Aarhus University Hospital, Vienna Medical Center, and Utrecht Medical Center (44). Brigham and Women's hospital has also used a bowel dose constraint of a D_{2cc} <65 Gy (45). Ultimately, there is insufficient evidence at this time to provide any conclusive guidance on a small bowel constraint.

Vagina dose constraints

Literature review

Most data available providing guidance on vaginal dose tolerance are from the primary cervix literature. Even this literature is limited and predominantly based on low dose rate, nonimage guided experiences. Hintz et al. reported on 16 primary vaginal cancer patients treated with either external beam or a combination of external beam and low-dose-rate brachytherapy (46). In this study, they made the following observations: the distal vagina should be limited to <98 Gy, there were no cases of vaginal necrosis up to doses of 140 Gy to the upper vaginal mucosa, the posterior vaginal wall was more prone to radiation injury than the lateral and/or anterior walls, the dose of radiation to limit the risk of fistula should be limited to less than 80 Gy, and the threshold dose for a vesicovaginal fistula was higher than 150 Gy. This relatively high proximal vaginal tolerance was also confirmed in a retrospective review of cervical cancer patients treated with low-dose-rate brachytherapy by Au et al. (47).

As we move toward 3-dimensional imaging there is increasing interest in moving away from point-based organ at risk evaluation and more toward volume-based assessments. This is a challenging task as reaching consensus on how to define the vagina on 3-dimensional imaging (CT or MRI) so that it is easily reproducible between physicians has not proven straightforward (48). This likely explains why there is currently mixed evidence regarding correlations between the vaginal D_{2cc} dose and toxicities. Two groups have shown a correlation between D_{2cc} doses to the vagina when contoured as a 4 mm thick structure. One study showed a correlation between a 2-year incidence of a vaginal ulcer with a D_{2cc} EQD2 dose ≤145 Gy vs. >145 Gy of 3.7% and 23.5% (49). In a second study, Susko et al. found a CTCAE Grade 2 or greater toxicity of 36% below a D_{2cc} dose of 108 Gy and 71% when greater than 108 Gy (50). A correlation between vaginal D_{2cc} dose and toxicities was not seen in another series of cervical cancer patients (51).

An alternative to contouring the vagina in 3-dimensions is to consider using multiple points as defined by Westerveld et al. (52). Based on a subset of 153 patients from the EMBRACE study, dose at the applicator surface left and/or right and anterior and/or posterior, at 5 mm depth, and at the posterior–inferior border of the symphysis, and 2 cm above and below this point were measured as surrogates for vaginal doses. The posterior–inferior border of the symphysis ±2 cm points were proposed to standardize dose points that should be recorded and felt to represent dose to the upper, mid, and lower portions of the vagina. It remains to be seen whether these proposed points correlate with acute and/or late-term vaginal morbidity.

Others have suggested using the international commission on radiation units (ICRU) rectal point as a surrogate for dose to the upper vagina. The rationale for this is based on data from EMBRACE showing that dose to the ICRU rectal point is correlated with an increased risk of vaginal stenosis: 20% at 65 Gy, 27% at 75 Gy, and 34% at 85 Gy (53). Updates from the ICRU report that 89 have actually relabeled the ICRU rectum point to the rectovaginal point based on this observation.

Panelist's current practice

When the panelists were asked how they contour the vagina, three of nine provided responses as most panelists do not regularly contour the vagina at this time (Supplement—Survey Question 21). Panelists were also asked for dose constraints for the proximal and distal vagina and panelists provided significant variation in their dose constraints (Supplement—Survey Question 20). At this time, it is not possible to provide guidance regarding a recommended method to contour the vagina or dose constraints.

As consensus emerges regarding how to contour the vagina and what points and/or volumes to record, we will be able to develop a more sophisticated understanding of correlations between dose and vaginal morbidities. It is important for clinicians to be aware of the dose being delivered to the vaginal mucosa and to limit hot spots. There is a greater morbidity when treating the entire length of the vagina and the distal vagina is less tolerant than the proximal vagina.

Followup

What kind of followup should be performed after treatment?

Literature review. All patients should have regular followup to evaluate for local recurrence and any treatment-related adverse events. Even patients who have an initial complete response to treatment may subsequently develop a local recurrence (8). It is suggested that patients be followed every 3–4 months for the first 2 years, every 6 months from years 3–5, and then annually thereafter (54). The first followup imaging, whether a PET or MRI, can be considered at 3 months after completion of treatment (panelist's current practice). A vaginal dilator is recommended to help reduce the risk of stenosis (panelist's current practice).

Continuing controversies and future directions. There are multiple unanswered questions in the setting of a vaginal recurrence of endometrial cancer. GOG 238 will answer the role of chemotherapy in combination with radiation. However, this study does not address the role of targeted agents as it is only using cisplatin chemotherapy nor does it address the potential benefit of adjuvant chemotherapy. There are other unanswered questions regarding the optimal dose and treatment volumes in both the setting of no previous radiation and in cases of previous radiation. There is also limited guidance on whether some women may be adequately treated with brachytherapy alone. In order for answers to be reached, collaboration among

multiple institutions is necessary to reach consensus on contouring and/or doses and/or constraints.

Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.brachy.2017.07.012.

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