

Bevacizumab increases late toxicity in re-irradiation with image-guided high-dose-rate brachytherapy for gynecologic malignancies

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Abstract

Introduction: Patients with recurrent gynecologic malignancies having had pelvic irradiation, generally have limited salvage options. This study investigated patients with gynecologic malignancies, who had a history of pelvic irradiation and received salvage re-irradiation using image-guided high-dose-rate brachytherapy (IG-HDR-BT).

Material and methods: Patients with gynecologic malignancies, who had a history of previous irradiation and received re-irradiation using IG-HDR-BT for disease recurrences from June 2014 to March 2020 were included in this study.

Results: A total of 37 patients were included in this retrospective analysis. Primary tumor was uterine cervical cancer in 31 patients, endometrial cancer in 5 patients, and vaginal cancer in 1 patient. Median follow-up period of patients who were alive at the time of analysis was 15.4 months (range, 4.1-61.4 months). Two-year overall survival, progression-free survival, and local control were 68.9%, 49.3%, and 67.5%, respectively. Severe late toxicities \geq grade 3, which were related to re-irradiation, were observed in 9 patients (24.3%). Usage of bevacizumab in the entire course of treatment was associated with development of late \geq grade 3 fistula formation, bowel perforation, or vaginal ulcer (50% vs. 6.9%, $p = 0.013$). Tumor size ≥ 2.5 cm was associated with development of late \geq grade 3 of rectum, bladder, or vaginal toxicities (0% vs. 28%, $p = 0.047$).

Conclusions: If the recurrent disease was found in small size and there was no history of bevacizumab usage, re-irradiation with IG-HDR-BT could be considered, even in patients with a previous history of pelvic irradiation.

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Key words: re-irradiation, image-guided high-dose-rate brachytherapy, gynecologic malignancies, bevacizumab, late toxicities.

Purpose

Radiation therapy, including brachytherapy, can be used as a curative treatment for recurrent tumors without a history of pelvic irradiation or recurrence outside of the radiation field [1, 2]. According to the Japan Society of Gynecologic Oncology guidelines 2017 for the treatment of uterine cervical cancer, with a recurrence within the radiation field, re-irradiation is not recommended because the rate of radiation-related late toxicities could be unacceptably high after re-irradiation. Therefore, palliative treatment for symptom relief, such as palliative chemotherapy, should be offered. In a highly selected group

of patients with central recurrence in the vaginal stump or uterine cervix, total pelvic exenteration (TPE) or hysterectomy is recommended [3]. TPE could be a curative treatment option at the cost of complications related to challenging surgery and decreased quality of life removing the bladder, the rectum, or both, with reported 5-year overall survival of around 40% [4-6].

Our group previously reported clinical outcomes of 18 cervical cancer patients who were previously irradiated and salvaged by re-irradiation involving image-guided high-dose-rate interstitial brachytherapy, in which median clinical target volume (CTV)-D₉₀ (minimum dose covering 90% of clinical target volume) was 62.6 Gy, and

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2-year local control rate was 51.3% [7]. In this study, our group tried to increase the total dose in re-irradiation settings incorporating gel spacer or artificial ascites whenever feasible, to decrease doses to surrounding normal organs at risk (OARs), such as the rectum, bladder, or bowel [8-11].

The aim of this study was to report the outcomes of salvage re-irradiation using image-guided high-dose-rate brachytherapy (IG-HDR-BT) with adjusting to our previous report.

Material and methods

Patients with gynecologic malignancies, who had a history of previous pelvic irradiation and received re-irradiation using IG-HDR-BT for disease recurrences from June 2014 to March 2020 were included in the present study. In all cases, recurrent diseases were diagnosed by computed tomography (CT) and/or magnetic resonance imaging (MRI) and/or fluorodeoxyglucose-positron emission tomography (FDG-PET), and were confirmed histopathologically. Salvage IG-HDR-BT was offered if salvage TPE was not indicated, or patients refused TPE but still wanted to receive local curative treatment. Informed consent was obtained from each patient after explaining the results of the previously reported our re-irradiation results [7]. This retrospective study was approved by institutional review board of the National Cancer Center Hospital (the National Cancer Center Hospital Certified Review Board, approval number 2017-091) according to ethical standards of the Declaration of Helsinki.

Brachytherapy

One patient with a history of 30 Gy in 3 fractions of only intracavitary brachytherapy (ICBT), received a combination of 50.4 Gy in 28 fractions of whole pelvic external beam radiation therapy, followed by 36 Gy in 6 fractions of high-dose-rate interstitial brachytherapy (HDR-ISBT). The other patients received only IG-HDR-BT as a single modality to salvage their recurrent disease. Patients with recurrent disease thicker than 5 mm received image-guided HDR-ISBT. Not only central recurrences but also tumors infiltrating parametrium/paracolpium were candidates for salvage HDR-ISBT. Tumors thickness of less than 5 mm on the surface of vaginal received conventional ICBT. Our technique of IG-HDR-BT for patients with gynecologic malignancies has been previously described in detail [7]. In brief, intracavitary applicator and/or interstitial needle implantation was performed under general or sacral epidural anesthesia in the lithotomy position under real-time transrectal ultrasound (TRUS) guidance. Both template-based and free-hand needle implantation were performed; free-hand needle implantation was applied more recently due to its' flexibility and fewer restrictions. Since 2015, hyaluronic acid gel injection (HGI) in rectovaginal septum (RVS) or vesicovaginal septum (VVS) has been administered to protect organs at risks, such as the rectum or bladder [9-11]; therefore, if possible, spacer gel injection using Suvenyl (Chugai Pharmaceutical Co., Tokyo, Japan) was applied. Since 2018, artificial

ascites injection has been started to protect bowels, especially for post-hysterectomy patients [8]; therefore, if indicated, artificial ascites injection was also performed in addition to HGI. After applicator placement and spacer injection, a planning CT without contrast enhancement was obtained, with a slice thickness of 2 mm generated by a large-bore CT simulator (Aquilion, Canon, Tokyo, Japan). Dose calculation for brachytherapy was performed by planning software Oncentra (Elekta, Veenendaal, The Netherlands). Clinical target volume was defined based on physical examination, latest diagnostic CT/MRI with contrast enhancement, and real-time TRUS findings performed during brachytherapy applicators placement. Reference points were set on the surface of CTV and dose-point volume optimization was initially performed, followed by manual graphical modification slice-by-slice to cover CTV with prescription isodose line, and the goal of CTV- D_{90} being over the prescription dose while minimizing the dose to OARs as low as possible.

A single implant, with twice daily irradiation at 6-hour intervals, without needle removal was selected if there was enough room for remote after-loading system (RALS) irradiation, namely once in the morning and once in the evening for several days. The patients agreed or deemed tolerable with lying on the bed during needles were in place. When applicators stayed in place overnight, applicator displacement was monitored by extra CTs before every treatment session, and was corrected in case of displacement greater than 5 mm. Otherwise, applicators were removed after each brachytherapy irradiation, and once daily treatment was performed (multiple implants).

Prescription dose differed on the individual clinical case depending on patients' or attending physician's preference or availability of enough room for RALS in each clinical situation. Dose per fraction was equal to or lower than 6 Gy in all the patients included in this study. Some physicians believed that lowering the dose per fraction to lower than 4 Gy and increasing treatment sessions to minimize dose to the surrounding OARs while maintaining adequate dose for CTV, would be better in re-irradiation settings; therefore, 47.5 Gy in 19 fractions or 50 Gy in 20 fractions delivered in 2 weeks with HDR-ISBT were also performed. All brachytherapy treatment was performed with a 192-iridium RALS system (MicroSelectron HDR, Elekta, Veenendaal, The Netherlands).

The equivalent dose in 2 Gy fractions (EQD_2), which was based on linear-quadratic dose model was utilized for dose evaluation. For calculating doses for the tumor and OARs, α/β ratios of 10 Gy and 3 Gy were applied, respectively. Minimum dose covering 90% of CTV (CTV- D_{90}) in EQD_2 was used as representative doses for tumor dose. Doses delivered to the most exposed 2 cc of the rectum (rectum D_{2cc}) and the bladder (bladder D_{2cc}) were used as representative doses for OARs. Because most of the patients were previously irradiated in different hospitals, it was difficult to collect all dosimetric data of prior RT and calculate the total combination dose. Therefore, the only dose delivered by the re-irradiation was analyzed in this study.

Table 1. Patients' characteristics at time of re-irradiation (*n* = 37)

Factors	
Age at re-irradiation (years), median (range)	63 (31-85)
Diagnosis	
Cervical cancer	31
Endometrial cancer	5
Vaginal cancer	1
FIGO stage at initial diagnosis	
I-II	29
II-IV	8
Histopathology	
SCC	20
Adenocarcinoma	10
Adenosquamous carcinoma	2
Endometrioid carcinoma	5
Prior radiotherapy	
Definitive	19
Post-operative	18
Types of prior radiotherapy	
EBRT + BT	25
EBRT	9
BT	3
Interval to re-irradiation (months), median (range)	13 (range, 0.7-54.8)
Maximum tumor diameter at re-irradiation (mm), median (range)	31 (0.5-70)
Presence of regional lymph nodes at re-irradiation	
Yes	7
No	30
Usage of bevacizumab through entire course of disease	
No	29
Yes	8
Before re-RT	5
After re-RT	3

SCC – squamous cell carcinoma; RT – radiation therapy; EBRT – external beam radiation therapy; BT – brachytherapy

For patients with regional lymph node metastasis simultaneous to local recurrence, if pelvic external beam irradiation was already delivered before, no additional irradiation was attempted, and salvage IG-HDR-BT and systemic chemotherapy were performed.

Statistical analysis

Treatment-related adverse events were assessed according to common terminology criteria for adverse events version 5.0. Overall survival rate (OS) was calculated from the first date of re-irradiation until death from any cause, or was censored at the last date of confirmed survival. Progression-free survival rate (PFS) was calculated from the first date of re-irradiation until any disease recurrence or death from any causes, whichever was first,

or was censored at the last date of confirmed survival. Local control (LC) was calculated from the first date of re-irradiation until histological or apparent radiological evidence of disease recurrence in the local region or death from any causes, whichever was first, or was censored at the last date of confirmed survival. In-field recurrence was calculated from the first date of re-irradiation until histological or apparent radiological evidence of disease recurrence within the radiation field, or death from any causes, whichever was first, or was censored at the last date of confirmed survival. Cumulative survival was estimated using Kaplan-Meier method, and difference in the survival between groups was analyzed using log-rank test. Student's unpaired *t*-test was applied to compare continuous variables, and Person's χ^2 test to compare categorical variables. A *p*-value < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS Statistics (version 18.0; SPSS, Inc., Chicago, IL, USA).

Results

A total of 37 patients were included in this retrospective analysis. Patients and tumor characteristics are summarized in Table 1. The primary tumor was uterine cervical cancer in 31 patients, endometrial cancer in 5 patients, and vaginal cancer in 1 patient. The International Federation of Gynecology and Obstetrics stages at initial diagnosis in I, II, III, and IV were 13, 16, 6, and 2, respectively. There were 20 patients with squamous cell carcinoma, 10 patients with adenocarcinoma, 2 cases with adenosquamous carcinoma, and 5 patients with endometrioid carcinoma. There were 18 patients with local recurrence after hysterectomy with post-operative irradiation, and 19 patients with recurrence after definitive radiation therapy. Twenty-five patients (67.6%) received a combination of external beam radiation therapy (EBRT) and brachytherapy (BT) as prior radiotherapy, followed by 9 patients (24.3%) with EBRT alone and 3 patients (8.1%) with BT alone. The median interval between previous irradiation and salvage re-irradiation was 13 months (range, 0.7-54.8 months). One post-hysterectomy endometrioid cancer patient with vaginal recurrence had an interval of only 0.7 months between previous irradiation and salvage re-irradiation. Initially, the patient received 50 Gy in 25 fractions of whole pelvic radiation therapy, followed by 10 Gy in 5 fractions of shrunk field boost EBRT for vaginal recurrence in previous hospital. On CT simulation used for the boost EBRT, it was evident that the tumor shrinkage was not enough; therefore, she was referred to our hospital for further salvage HDR-ISBT. Other patients had an interval of more than three months between previous irradiation and salvage re-irradiation. Seven patients had regional lymph node metastasis simultaneous to pelvic recurrence before re-irradiation. Eight patients received bevacizumab in their entire course of treatment (5 before salvage IG-HDR-BT and 3 after salvage IG-HDR-BT, respectively), whose primary disease was all cervical cancer. Among 3 patients who received bevacizumab after salvage IG-HDR-BT, 2 patients received bevacizumab after the development of distant metastasis at 17.9 and 3.5 months after salvage IG-HDR-

BT, and one received bevacizumab following re-irradiation because this patient also had regional lymph node metastasis as well as local recurrence.

Table 2 summarizes treatment details. The majority of patients were treated with HDR-ISBT (34 out of 37 patients). The most frequently used dose schedule was 48 Gy in 8 fractions (21 out of 37 patients), and the most frequently used dose per fraction was 6 Gy (32 out of 37 patients). The median CTV-D₉₀ was 73.5 Gy (EQD₂) (range, 32.5-99.7 Gy). The median rectum and bladder D_{2cc} were 27.5 Gy (EQD₂) (range, 4.6-102 Gy) and 33.4 Gy (EQD₂) (range, 5.0-117.5 Gy), respectively. The most frequently used spacer was HGI in RVS (31 out of 37 patients), followed by HGI in VVS (15 out of 37 patients) and artificial ascites (3 out of 37 patients).

The median follow-up period of patients who were alive at the time of the analysis and overall cohort of patients was 15.4 months (range, 4.1-61.4 months) and 16.2 months (range, 4.0-61.4 months), respectively. The two-year OS, PFS, and LC were 68.9%, 49.3%, and 67.5%, respectively. While only two patients experienced disease progression in the re-irradiation field, 7 patients experienced local relapse outside of the re-irradiation field, which can be classified as marginal recurrence. Two patients with the re-irradiation in-field recurrence received 30 Gy in 10 fractions (CTV-D₉₀ = 33 Gy) and 36 Gy in 6 fractions (CTV-D₉₀ = 67.1 Gy), both of which were under median CTV-D₉₀ of 73 Gy.

Table 3 summarizes clinical factors associated with PFS and LC. The presence of regional lymph node metastasis before salvage brachytherapy was strongly associated with disease progression (*p* = 0.01, hazard ratio [HR] = 3.55, 95% CI: 1.22-10.42%). Single implant was associated with better LC (*p* = 0.04, HR = 0.38, 95% CI: 0.13-1.09%). CTV-D₉₀ ≥ 73 Gy was associated with trends towards better local control (*p* = 0.08).

Toxicities

Severe late toxicities ≥ grade 3, which were related to re-irradiation were observed in 9 patients (24.3%). Details of late severe toxicities ≥ grade 3 are summarized in Table 4. The most frequently observed toxicity was both recto-vaginal and vesico-vaginal fistula that happened simultaneously (*n* = 3). Tumor size ≥ 2.5 cm was associated with the development of late ≥ grade 3 rectum, bladder, or vaginal toxicities (*n* = 7) [0% (0 out of 12) for tumors < 2.5 cm vs. 28% (7 out of 25) for tumors ≥ 2.5 cm, *p* = 0.047]. Table 5 summarizes clinical factors associated with the development of fistula, bowel perforation, and vaginal ulcer greater than grade 3 (*n* = 6). The usage of bevacizumab in the entire course of treatment was associated with the development of late ≥ grade 3 fistula formation (*n* = 4), bowel perforation (*n* = 1), or vaginal ulcer (*n* = 1) [50% (4 out of 8) for patients with bevacizumab vs. 6.9% (2 out of 29) for patients without bevacizumab, *p* = 0.01].

Discussion

As mentioned in the section of the introduction, it is generally considered to be unacceptable to perform

re-irradiation for patients with recurrence within a previously irradiated field and salvage PE. Instead, palliative chemotherapy or palliative care are recommended in such a situation [3]. However, with the application of IG-HDR-BT, re-irradiation for gynecologic malignancies has been reported with severe late toxicities ranging from 20% to 30% [1, 7, 12-14]. Overall, the incidence of severe late toxicities ≥ grade 3 was 24.3%, while achieving 67.5% of 2-year LC in re-irradiation settings, and it was in line with a previously reported range and slightly better than our report [7], presumably because a higher dose was delivered and spacer was used in the majority of patients to protect OARs in the present cohort of patients. In subsequent sub-group analyses, it was suggested which groups of patients were better candidates for re-irradiation in terms of late severe toxicities, and this can have a significant impact on patients' quality of life. There were two factors found in this study that were associated with the development of late severe toxicities ≥ grade 3: 1. Tumor size ≥ 2.5 cm before salvage HDR-BT was associated with the development of the late rectum, bladder, or vaginal toxicities; 2. The usage of bevacizumab in the entire course of

Table 2. Treatment details

Type of brachytherapy	
HDR-ISBT	34
HDR-ICBT	3
Radiation schedule, dose per fraction	
54 Gy/9 fx., 6 Gy/fx.	2
48 Gy/8 fx., 6 Gy/fx.	21
42 Gy/7 fx., 6 Gy/fx.	2
36 Gy/6 fx., 6 Gy/fx.	6
24 Gy/4 fx., 6 Gy/fx.	1
52 Gy/16 fx., 3.5 Gy/fx.	1
57.8 Gy/17 fx., 3.4 Gy/fx.	1
30 Gy/10 fx., 3 Gy/fx.	1
47.5 Gy/19 fx., 2.5 Gy/fx.	1
60 Gy/20 fx., 2 Gy/fx.	1
Q.D. or B.I.D.	
Q.D. (once a day)	17
B.I.D. (twice a day)	20
CTV-D ₉₀ (Gy), median (range)	73.5 (32.5-99.7)
Rectum D _{2cc} (Gy), median (range)	27.5 (4.6-102)
Bladder D _{2cc} (Gy), median (range)	33.4 (5-117.5)
Usage of spacer	
HGI in RVS	31
HGI in VVS	15
Artificial ascites	3

HDR-ISBT – high-dose-rate interstitial brachytherapy; fx. – fraction (s); HDR-ICBT – high-dose-rate intracavitary brachytherapy; CTV-D₉₀ – the minimum dose covering 90% of the clinical target volume; rectum/bladder D_{2cc} – doses delivered to the most exposed 2 cc of the rectum/bladder; HGI – hyaluron-ic acid gel injection; RVS – recto-vaginal septum; VVS – vesico-vaginal septum

Table 3. Hazard ratios for progression-free survival and local control after salvage image-guided high-dose-rate brachytherapy

Variables	p-value	HR (95% CI)*
Progression-free survival		
Age (< 63 vs. ≥ 63)	0.55	
Histology (SCC vs. non-SCC)	0.79	
Prior radiotherapy (definitive vs. post-operative)	0.52	
Interval to re-irradiation (< 12 months vs. ≥ 12 months)	0.76	
Maximum tumor diameter (< 30 mm vs. ≥ 30 mm)	0.54	
Presence of regional lymph nodes at relapse (no vs. yes)	0.01*	3.55 (1.22-10.42)
Q.D. or B.I.D.	0.52	
Single implant vs. multiple implant	0.50	
Dose per fraction (< 6 Gy vs. 6 Gy)	0.38	
CTV-D ₉₀ (< 73.5 Gy vs. ≥ 73.5 Gy)	0.60	
Local control		
Age (< 63 vs. ≥ 63)	0.86	
Histology (SCC vs. non-SCC)	0.18	
Prior radiotherapy (definitive vs. post-operative)	0.17	
Interval to re-irradiation (< 12 months vs. ≥ 12 months)	0.10	
Maximum tumor diameter (< 30 mm vs. ≥ 30 mm)	0.80	
Presence of regional lymph nodes at relapse (no vs. yes)	0.19	
Q.D. or B.I.D.	0.56	
Single implant vs. multiple implant	0.04*	0.38 (0.13-1.09)
Dose per fraction (< 6 Gy vs. 6 Gy)	0.67	
CTV-D ₉₀ (< 73.5 Gy vs. ≥ 73.5 Gy) ss	0.08	

* Cox proportional hazard model; Q.D. – once per day; B.I.D. – twice per day

treatment was associated with the development of fistula formation, bowel perforation, or vaginal ulcer (Table 5). It should be emphasized that in patients without bevacizumab exposure, only 6.9% (2 out of 29) developed ≥ grade 3 hollow organ fistula, bowel perforation, or vaginal ulcer. Similarly, in patients with tumor size < 2.5 cm, no patient (0 out of 12) developed ≥ grade 3 of rectum, bladder, or vaginal toxicities.

It was demonstrated in a prospective phase III clinical trial of Gynecologic Oncology Group (GOG) protocol 240, that combination of chemotherapy and bevacizumab, a molecular-targeted agent against vascular endothelial growth factor (VEGF), improved survival in recurrent, persistent, or metastatic cervical cancer patients [15, 16]. After that, a combination of systemic chemotherapy and bevacizumab was also recommended for recurrent, persistent, or metastatic cervical cancer by the Japan Society of Gynecologic Oncology 2017 guidelines [3]. On the other hand, it has been reported that usage of bevacizumab was related to gastrointestinal perforation (GI) in colorectal cancer, with an incidence of around 1% [17]. Similarly, GI perforation was reported in a recurrent cervical cancer patient, who was previously treated by definitive chemoradiotherapy (CRT), and received bevacizumab combined with paclitaxel and carboplatin (TC) for persisting disease after CRT [18]. Sturdza *et al.* also

reported an increased GU fistula rate after administration of bevacizumab in recurrent cervical cancer patients initially treated by CRT, including image-guided adaptive brachytherapy [19]. Therefore, it is conceivable that the use of bevacizumab was associated with fistula of hollow organs, bowel perforation, and vaginal ulcer formation, which are related to poor blood supply caused by VEGF blockade in re-irradiation settings.

Our group previously reported that (although this study was a retrospective report on previously unirradiated patients) CTV > 100 cm³ was associated with the incidence of grade 2-4 complications [20]; therefore, it is also more likely that tumor size was found to be associated with late severe rectum, bladder, and vaginal toxicities in this study.

Compared to our previous study, in which the median CTV-D₉₀ was 62.6 Gy (range, 48.6-82.5 Gy) and the mean rectum D_{2cc} was 36.8 Gy (range, 12.0-62.0 Gy) [7], in the current study, the CTV-D₉₀ was 73.5 Gy (range, 32.5-99.7 Gy) and the median rectum D_{2cc} was 27.5 Gy (range, 4.6-102 Gy), and this widening of a therapeutic window could be attributed to the introduction of HGI in RVS. However, because only 6 patients did not use spacer in the current study, statistical analysis could not evaluate the superiority of spacer application with regard to late toxicities (Table 5).

Table 4. Detail of nine patients with late severe toxicities \geq grade 3 related to re-irradiation

Pt. No.	Late severe toxicities	Age	Prior RT	Interval (m)	Recurrent tumor size (cm)	Q.D. or B.I.D.	Dose/f (Gy)	Rectum D _{2cc} (Gy)	Bladder D _{2cc} (Gy)	Spacer	Bev
1.	Both recto-vaginal and vesico-vaginal fistula	45	BT	15.1	4.0	B.I.D.	6.0	72.2	87.5	Yes	no
2.	Both recto-vaginal and vesico-vaginal fistula	73	EBRT + BT	6.9	3.0	Q.D.	6.0	31.9	35.6	Yes	yes
3.	Both recto-vaginal and vesico-vaginal fistula	70	EBRT + BT	28.7	4.0	B.I.D.	6.0	31.7	17.1	No	yes
4.	Vesico-vaginal fistula	36	EBRT	44.0	4.8	B.I.D.	6.0	102.0	69.9	No	yes
5.	Hematuria requiring blood infusion	54	EBRT	9.6	3.0	Q.D.	6.0	24.0	41.9	Yes	no
6.	Rectal bleeding requiring blood infusion	85	EBRT + BT	11.4	3.8	B.I.D.	6.0	24.2	55.5	Yes	no
7.	Grade 3 vaginal ulcer	84	EBRT + BT	54.8	2.7	Q.D.	6.0	13.6	39.8	Yes	no
8.	Grade 4 bowel perforation requiring surgery	41	EBRT + BT	3.2	3.7	B.I.D.	3.4	18.0	33.4	Yes	yes
9.	Grade 3 ileus requiring hospitalization	74	EBRT + BT	13.4	1.0	Q.D.	6.0	39.0	27.5	Yes	no

Pt. – patient; RT – radiotherapy; EBRT – external beam radiation therapy; BT – brachytherapy; Interval – interval to re-irradiation; m – month; Dose/f – dose per fraction; Q.D. – once a day irradiation; B.I.D. – twice a day irradiation; Bev – bevacizumab

Therefore, taken all together, if a recurrent disease is found in small state and there is no history of bevacizumab usage, re-irradiation with image-guided brachytherapy incorporating gel spacer can be safely offered and should be considered.

It was shown that a single implant was better than multiple implants with regard to LC (Table 3). The possible reason for this result could be that after several fractions of irradiation, tumor shrinkage made it difficult to detect the tumor edge or margin by trans-rectal ultrasound or CT without contrast agent, which was used for our image-guided adaptive brachytherapy; thereby, some part of the tumor would have been missed in the latter of HDR-ISBT sessions.

Patients with regional lymph node metastasis were more likely to develop disease progression after re-irradiation. It was unsurprising because no attempt was made to deliver re-irradiation to the metastatic regional pelvic lymph nodes, and systemic chemotherapy was only given if the patient had been previously irradiated. In highly selected patients, it is possible to insert interstitial needles up to the obturator lymph node or external iliac lymph node level with CT guidance. Therefore, we would like to include regional lymph node metastasis in CTV if possible in future studies.

Local recurrence outside of the radiation field was frequently observed in the current study. It was supposed that due to the limitation of currently available diagnos-

tic modalities, such as CT, MRI, or FDG-PET, it was very difficult to determine the precise extent of local disease spread in the recurrence site. CTV-D₉₀ \geq 73 Gy was associated with trends towards better local control in the current study ($p = 0.08$). It is possible that when as high as 73 Gy is delivered to the 90% of volume covering CTV, microscopic disease spread, which cannot be visualized by conventional imaging modalities, can also be eradicated and resulted in better local control than those patients treated with CTV-D₉₀ < 73 Gy.

Because there were only 5 patients who were treated by dose per fraction under 6 Gy and only 2 of them achieved CTV-D₉₀ higher than 73 Gy, it was difficult to show the benefit of dose per fraction under 6 Gy. Such a low-dose per fraction was selected to keep doses to OARs at a low level, while delivering sufficient tumoricidal doses to the target volume. However, when low-dose per fraction is selected, multiple treatment session is inevitably needed to achieve adequate tumor dose; therefore, patients need to be implanted for a long period of time, which is challenging for both patients and healthcare providers. It should be noted that no patient developed severe late toxicities to the rectum or bladder, and only one patient who received bevacizumab experienced grade 4 bowel perforation requiring surgery. Therefore, dose per fraction lower than 6 Gy could be considered, especially in tumor size \geq 2.5 cm to minimize doses to the rectum or bladder while maximizing

Table 5. Hazard ratios for development of fistula, bowel perforation, and vaginal ulcer greater than grade 3 after salvage image-guided high dose-rate brachytherapy

	With events (n = 6)	Without events (n = 31)	p-value
Age (years)			0.59
< 63	3	14	
≥ 63	3	17	
Indication of prior radiotherapy			0.53
Definitive	3	18	
Post-operative	3	13	
Interval to re-irradiation			0.41
< 12 months	4	16	
≥ 12 months	2	15	
Maximum tumor diameter			0.08
< 25 mm	0	12	
≥ 25 mm	6	19	
Q.D. or B.I.D.			0.041
Q.D.	2	15	
B.I.D.	4	16	
Dose per fraction			0.61
< 6 Gy	1	4	
6 Gy	5	27	
Rectum D _{2cc}			0.25
< 30 Gy	2	18	
≥ 30 Gy	4	13	
Bladder D _{2cc}			0.25
< 35 Gy	2	18	
≥ 35 Gy	4	13	
Usage of spacer			0.25
Yes	4	27	
No	2	4	
Usage of bevacizumab			0.01*
Yes	4	4	
No	2	27	

Q.D. – once a day irradiation; B.I.D. – twice a day irradiation

the tumor dose. This topic should be solved in future studies.

There are several limitations to this study. This was a retrospective study based on only a limited number of patients, and the follow-up period was relatively short. Furthermore, the background and actual treatments delivered were heterogeneous in this study. However, still, re-irradiation is not a standard treatment, and so far, only limited number of patients have been treated by re-irra-

diation using IG-HDR-BT. Therefore, the authors believe that information obtained from this study should be shared in our community and used to improve the treatment quality for better future cancer treatment.

Conclusions

Pelvic recurrence without regional lymph node metastasis, with largest diameter of less than 2.5 cm can be considered for re-irradiation incorporating spacer gel injection, even in patients with a history of pelvic irradiation. For cervical cancer patients with pelvic recurrence, who are candidates for re-irradiation or who were heavily treated by radiation therapy, bevacizumab might better be avoided not to develop late severe radiation-related toxicities.

Disclosure

The authors report no conflict of interest.

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