Taiwanese Journal of Obstetrics & Gynecology 60 (2021) 111–118

Contents lists available at ScienceDirect

Taiwanese Journal of Obstetrics & Gynecology

journal homepage: www.tjog-online.com

Original Article

Stereotactic body radiotherapy for pelvic boost in gynecological cancer patients with local recurrence or unsuitable for intracavitary brachytherapy

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ARTICLE INFO

Article history:
Accepted 20 April 2020

Keywords:
Stereotactic body radiotherapy
Cervical cancer
Endometrium cancers
Recurrence

ABSTRACT

Objective: To evaluate efficacy of stereotactic body radiotherapy (SBRT) for pelvic boost irradiation in gynecological cancer patients with pelvic recurrence or with intact uterus unsuitable for brachytherapy.
Materials and methods: We retrospectively reviewed the medical records of 25 gynecological cancer patients who received SBRT boost for pelvic recurrence (salvage group, n = 14), or for local dose escalation instead of intracavitary brachytherapy due to unfavorable medical condition (definitive group, n = 11). The pelvis was irradiated with a median dose of 54 Gy in six weeks, and then SBRT was prescribed with a range of 10–25Gy in two to five fractions. The cumulative radiobiological equivalent dose in 2-Gy fractions (EQD2) to the tumors ranged from 62.5 to 89.5 Gy_{10} (median, 80.7). Overall survival (OS) and in-field relapse-free survival (IFRFS) were calculated using the Kaplan–Meier method.
Results: At the initial assessment, eighteen (72%) patients achieved complete or partial remission, and seven (28%) had stable or progressive disease. With a median follow duration of 12 months, the 1-year IFRFS for salvage and definitive group were 64.5% and 90.0%, whereas the 1-year OS for the two groups were 80.8% and 49.1%, respectively. One patient developed entero-vaginal fistula and one had sigmoid perforation. No patient experienced ≧ grade 3 genitourinary complications.
Conclusion: In gynecological cancer patients with recurrent pelvic tumors or intact uterus unsuitable for brachytherapy, local dose escalation with SBRT resulted in an initial response rate of 72% with acceptable early toxicities. A long-term follow-up is required to assess the impact on local control or survival.

Introduction

Almost 95,000 women are diagnosed with a gynecological malignancy each year [1,2]. Endometrial carcinoma represents the most common gynecological malignancy [2], whereas the incidence of cervical carcinoma has decreased in the Western countries over the last years but still remains a significant public health problem worldwide [2]. Moreover, around 30% of patients with gynecological malignancy will experience recurrence often with a dismal prognosis [3]. Thus, treatment of recurrent gynecological cancer is a challenging issue [1]. On the other hand, although intracavitary brachytherapy remains the most commonly practiced form of local boost in patients with cervical or endometrial cancers with an intact uterus, the possible disadvantages of brachytherapy include that it is invasive, resource-intensive, technically challenging or patients with high risk of sedation, presence of entero-vaginal fistula or vesico-vaginal fistula. As a result, it is not able to be ideally performed because of unfavorable anatomy or coexisting medical conditions [4].

Stereotactic body radiotherapy (SBRT) is a non-invasive, highly conformal treatment modality able to deliver a high radiation dose to neoplastic lesions largely sparing surrounding healthy tissues [5]. SBRT can escalate irradiated doses to tumors to achieve higher rates of local control. Currently, investigators have started to investigate early experiences of using SBRT, as a substitute for brachytherapy in

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https://doi.org/10.1016/j.tjog.2020.11.017

patients who are not deemed appropriate brachytherapy candidates [6–9], or patients with laterality of the recurrent tumors [10–13]. However, some unmet needs existed in these studies such as small sample size, wide range of fraction size, limited data of adequate normal tissue constraint, or whether adding conventional external beam radiotherapy (EBRT) before SBRT. To maximize the combination therapy; therefore, this prospective observation study was conducted to review the effectiveness of EBRT followed by SBRT for pelvic boost irradiation in gynecological cancers.

Materials and method

Patient population

Between January 2017 and May 2019, the effectiveness of SBRT boost in 25 gynecological cancer patients was prospectively recorded. All completed an allocated SBRT boost for pelvic recurrence (salvage group, n = 14), or for local dose escalation after EBRT to substitute for intracavitary brachytherapy (definitive group, n = 11).

Patient characteristics in the definitive RT group are listed in Table 1. Patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) [14]. The reasons of SBRT boost in patients with intact uterus included adverse medical condition (n = 3), technical difficulty due to unfavorable anatomy (n = 4), presence of entero-vaginal or vesico-vaginal fistula (n = 2), or patients' refusal (n = 2). All received pretreatment workup, including pelvic examination, computed tomography (CT), and/or positron emission tomography CT scan.

In the salvage group, Table 2 summarizes the initial tumor origin, histological types, response after primary treatment, time to tumor recurrence, and recurrent sites. Five patients had previous radiotherapy. Seven patients received concurrent chemotherapy consisting of weekly 40 mg/m^2 doses of cisplatin, administered intravenously to a total dose of 60 mg. This study was approved by the Institutional Review Board of China Medical University Hospital (CMUH106-REC3-119).

Radiotherapy

Patients were immobilized in the supine treatment position by a pelvic vacuum bag. The CT images were obtained and transferred to the treatment-planning system, an inverse planning system (Eclipse, Varian Medical Systems Inc, Palo Alto, California, USA). Except five patients with previous irradiation, most patients received EBRT with a prescribed dose of 45Gy to the tumors and pelvic lymphatics over a 5-week period. The treatment technique consisted of either intensity-modulated radiotherapy (IMRT) or arc therapy. The clinical target volume (CTV) of the initial EBRT included the gross disease, superior half of the vagina, presacral region, and regional lymph nodes (common, internal, and external iliac) as similar with consensus guidelines on CTV delineation [15]. We applied a 15-mm planning margin around the tumors, a 10-mm margin around the vagina, and an 8-mm margin around the remainder of the CTV [16].

In the definitive group, the uterus and whole pelvic lymphatics were irradiated with a median prescribed dose of 54 Gy. As listed in Table 3, SBRT boost was administered to the gross tumor volume (GTV) with a median prescribed dose of 25 Gy divided into five fractions. The median cumulative EQD2 to the GTV was 84.3 Gy_{10} (range, 65.6–89.5 Gy_{10}).

In the salvage group, the median volume of the recurrent tumors was 26.5 ml (range, 6.9–298.1). After a median prescribed dose of 63 Gy to the recurrent tumor, the residual GTV delineated by the simulation CT images for SBRT, defined as an adapted GTV, were irradiated with a dose of 5 Gy per fraction for two to six courses every other day. As shown in Table 3, the median size of the adapted GTV for SBRT was 18.5 ml (range, 8.7–200.1). Tumor regression ratio was defined as a value of the adapted GTV divided by the initial GTV. To compare the effectiveness of SBRT scheme, equivalent dose in 2Gy per fraction (EQD2) were calculated using the linear quadratic model with α/β ratios of 3 and 10 for late normal tissue effects and tumor, respectively. The median cumulative EQD2 to the residual GTV was 78.5 Gy_{10} (range, 62.5–82.8). Vaginal brachytherapy was adopted for six patients presenting gross visible tumors at vaginal stump.

In general, a margin of 3 mm was used for expanding the adapted GTV to generate planning target volume (PTV) for SBRT. Using a median of 6 (range, 5–8) coplanar beams, the 95% of the PTV was proposed to be covered by 80%–90% of the prescribed dose. The maximal dose of the PTV corresponded to the normalization point of the plan. The area where the irradiated dose more than the prescribed dose was restricted to the GTV. Image-guidance cone-beam CT was routinely

Table 1
Patient characteristics in definitive RT group.

Patient	Age (years)	Primary tumor	Histological type	FIGO stage	Reasons for substituting brachytherapy	Combination of chemotherapy	Tumor markers before RT (ng/ml)	Tumor markers after RT(ng/ml)
1	72	Endometrium	Endometrioid adenocarcinoma	IA	Comorbidity	No	CA-125: 6.0	CA-125: 5.4
2	94	Cervix	Squamous cell carcinoma	IIB	Comorbidity	No	SCC: 8.3	SCC: 1.7
3	59	Endometrium	Endometrioid adenocarcinoma	IA	Laterality of tumor location	No	not available	CA-125: 21.4
4	51	Vagina	Adenocarcinoma	II	Laterality of tumor location	Weekly cisplatin x 6	CA-125: 4.5; CEA: 1.8	CA-125: 4.1; CEA: 1.2
5	58	Cervix	Squamous cell carcinoma	IVA	Fistula	No	not available	SCC: 214.1
6	48	Cervix	Squamous cell carcinoma	IVB	Fistula	No	SCC: 98.5	SCC: 7.3
7	84	Cervix	Squamous cell carcinoma with focal neuroendocrine differentiation	IVB	Comorbidity	Weekly cisplatin x 5	SCC: 0.5; CA-125: 104.3	SCC: 0.9; CA-125: 23.5
8	85	Cervix	Squamous cell carcinoma	IIB	Patient's refusal	No	SCC: 33.0	not available
9	47	Cervix	Squamous cell carcinoma	IVA	Patient's refusal	Weekly cisplatin x 4	SCC: 47.7	SCC: 6.8
10	50	Cervix	Adenocarcinoma	IIB	Laterality of tumor location	Weekly cisplatin x 4	CA-125: 20.3; CEA: 2.9	CA-125: 19.3; CEA: 5.4
11	55	Endometrium	Endometrioid adenocarcinoma	IIIC2	Laterality of tumor location	Cisplatin + epirubicin x 6	CA-125: 909.9	CA-125: 12.5

Abbreviation: SCC = squamous cell carcinoma associated antigen; CEA = carcinoembryonic antigen; CA-125 = carbohydrate antigen 125.

Table 2
Patient characteristics in salvage RT group.

Patient	Age (years)	Primary tumor	Histological type	Initial FIGO stage	Initial treatment	Response after primary treatment	Time to recurrence (months)	Recurrent site	Combination of drug therapy	Tumor markers before salvage RT (ng/ml)	Tumor markers after salvage RT (ng/ml)
1	35	Cervix	Squamous cell carcinoma	IB2	Neoadjuvant chemotherapy + OP	CR	18	Pelvic side wall	Weekly cisplatin x 6	SCC: 5.3	SCC: 0.7
2	61	Cervix	Squamous cell carcinoma	IB2	OP	CR	220	Pelvic side wall	Weekly cisplatin x 7	SCC: 1.8	SCC: 1.0
3	43	Uterine sarcoma	Low-grade endometrial stromal sarcoma	IA	OP	CR	13	Central extending to pelvic side wall	No	CA-125: 6.3	CA-125: 5.2
4	44	Cervical	Squamous cell carcinoma	IIIB	RT	PR	4	Central extending to pelvic side wall	No	SCC: 4.9	SCC: 1.6
5	46	Uterine sarcoma	Uterine leiomyosarcoma	IIIA	OP + adjuvant chemotherapy	PR	2	Central	Paropanib x 6	CA-125: 182.8	CA-125: 14.5
6	73	Endometrium	Endometrioid adenocarcinoma	IIIC1	OP	CR	2	Central	No	CA-125: 165.8; CEA: 5.5	CA-125: 82.9; CEA: 4.1
7	55	Cervix	Squamous cell carcinoma	IIIB	RT	CR	20	Central extending to pelvic side wall	Weekly cisplatin x 6	SCC: 0.9	SCC: 0.9
8	36	Cervix	Squamous cell carcinoma	IA1	OP	CR	14	Central extending to pelvic side wall	Weekly cisplatin x 6	SCC: 1.6	SCC: 0.9
9	57	Endometrium	Clear cell carcinoma	IA	OP	CR	12	Central	No	CA-125: 141.1; CEA: 5.7	CA-125: 223.1; CEA: 13.8
10	39	Cervix	Adenocarcinoma mixed with neuroendocrine differentiation	1B1	OP	CR	13	Central extending to pelvic side wall	Weekly cisplatin x 7	CA-125: 6.7; CEA: 15.4	not available
11	95	Cervix	Squamous cell carcinoma	IIB	RT	CR	18	Pelvic side wall	No	SCC: 28.9	SCC: 3.1
12	53	Cervix	Squamous cell carcinoma	IIIB	RT	PR	5	Central extending to pelvic side wall	Weekly cisplatin x 4	SCC: 3.9	SCC: 0.9
13	62	Vulva	Squamous cell carcinoma	IIIA	RT	PR	8	Vulva	No	SCC: 33.8	SCC: 36.5
14	62	Endometrium	Endometrioid adenocarcinoma	IA	OP	CR	71	Central	No	CA-125: 173.3	CA-125: 7.4

Abbreviation: OP = operation; CR = complete remission; PR = partial response; SCC = squamous cell carcinoma associated antigen; CEA = carcinoembryonic antigen; CA-125 = carbohydrate antigen 125.

Table 3
Parameter of radiotherapy and cumulative dose of the tumor.

Parameter of radiotherapy and cumulative dose of the tumor	value (range)
Definitive group (n = 11)	
Dose of conventionally fractioned EBRT [median, Gy]	54 (45–65)
Dose of SBRT boost [median, Gy]	25 (8–30)
Fraction size of SBRT [median, Gy]	5 (4.0–6.5)
Cumulative EQD2 of the tumor [median, Gy]	84.3 (65.6–89.5)
Salvage group (n = 14)	
GTV of the recurrent tumor [median, ml]	26.5 (6.9–298.1)
Dose of conventionally fractioned EBRT [median, Gy]	63 (50–65)
Dose of SBRT boost [median, Gy]	14 (10–30)
Fraction size of SBRT [median, Gy]	5 (4–6)
Adapted GTV for SBRT [median, ml]	18.5 (8.7–200.1)
Tumor regression ratio after EBRT [%]	34.8 (0–72.9)
Cumulative EQD2 of the tumor [median, Gy]	78.5 (62.5–82.8)

Abbreviation: EBRT = external beam radiotherapy; EQD2 = equivalent dose in 2Gy per fraction; GTV = gross tumor volume.
Note: Tumor regression ratio was defined as a value of the adapted GTV divided by the initial GTV.

performed prior to all treatment and set-up errors were corrected online. Similar to guidelines of the Gynecological (GYN) GEC-ESTRO Working Group for image-guided brachytherapy [17], the dose constraint to adjacent organ at risk (OAR) was the cumulative EQD2 of the highest irradiated 2 cc volume (D2cc) for rectum, bladder, and sigmoid colon less than 70 Gy_3, 90 Gy_3, and 70 Gy_3, respectively.

Follow up

To assess initial treatment response, a follow-up CT scan was performed one to two months after the completion of SBRT. Thereafter, patients were regularly followed-up every three months. Besides a routine pelvic examination, the serum level of the tumor marker such as squamous cell carcinoma antigen, carbohydrate antigen 125, and carcinoembryonic antigen were examined during each follow-up. Additionally, CT scan of abdomen and chest X-ray were performed every six months. Patients experienced distant metastasis or local recurrence were treated with

Table 4
Treatment outcome and failure patterns according to treatment groups.

Study endpoints	Definitive group (n = 11)	Salvage group (n = 14)	Total population (n = 25)
Initial assessment of treatment response			
Complete remission	4	5	9
Partial remission	3	6	9
Stable disease	4	0	4
Progressive disease	0	3	3
Failure patterns			
In-field failure	1	4	5
Pelvic outfield failure	1	2	3
Para-aortic lymph node metastasis	2	1	3
Distant metastasis	3	4	7
Cause of death			
Death due to cancer progression	2	3	5
Death due to treatment-related complications	0	0	0
Death due to concurrent disease	2	0	2
Death due to unknown reason	1	1	2

Note: Of the two patients died of concurrent disease, one was dead due to congestive heart failure. The other had obstructive nephropathy before the treatment and experienced urinary tract infection without evidence of tumor recurrence.

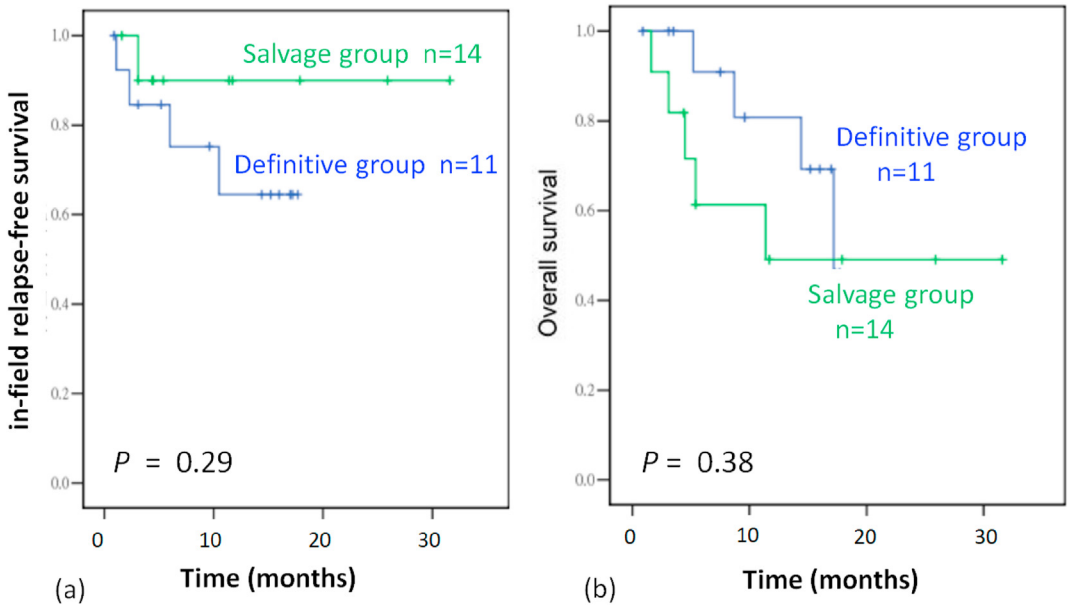

Fig. 1. In-field relapse-free survival (a) and overall survival (b) curves according to the treatment groups.

Table 5
Cumulative irradiated dose to organ at risk.

Cumulative doses in current treatment (n = 25)	value (range)
Gastrointestinal organ	
D2cc- EQD2 of rectum [median, Gy]	68.25 (44.31–95.69)
D2cc- EQD2 of sigmoid colon [median, Gy]	62.53 (44.94–89.88)
Bladder	
D2cc- EQD2 of bladder [median, Gy]	71.97 (44.60–94.85)
Cumulative doses by adding previous irradiated dose (n = 5)	
Gastrointestinal organ	
D2cc- EQD2 of rectum [median, Gy]	68.82 (44.31–141.59)
D2cc- EQD2 of sigmoid colon [median, Gy]	66.86 (44.94–138.71)
Bladder	
D2cc- EQD2 of bladder [median, Gy]	73.1 (44.60–166.41)

Abbreviation: D2cc = the highest irradiated 2 cc volume of normal organ; EQD2 = equivalent dose in 2Gy per fraction.

systemic chemotherapy. The Response Evaluation Criteria in Solid Tumors (version 1.1) was utilized to assess the initial treatment response [18]. Common Terminology Criteria for Adverse Events Version 4.0 [19] was used to score the maximum late toxicities, including gastrointestinal (GI) and genitourinary (GU) complications.

Statistical analysis

The outcome endpoints were overall survival (OS), and in-field relapse-free survival (IFRFS), all of which were calculated using the Kaplan–Meier method. The log-rank test was performed to examine the effects of clinical variables on these endpoints. Two sample t test was utilized to compare differences in continuous variables between groups. Correlation between toxicities and clinical or treatment parameters was performed by using the Chi-squared test. Patient survival was measured from the date of initiation of radiotherapy to the last follow-up. Two-tailed tests were used, and values $p < 0.05$ was considered statistically significant. All calculations were performed using SPSS, Version 13.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

Patient outcome

The initial assessment revealed that 18 patients (72%) achieved complete remission or partial remission (7 in the definitive group and 11 in the salvage group). Seven patients (28%) had stable or progressive diseases with 4 and 3 patients in the definitive and salvage group, respectively. The treatment outcome and failure patterns are listed in Table 4.

After a median follow-up of 12 months, 16 patients were alive and 9 patients had died. Five patients died of tumor progression, and 2 were dead due to concurrent diseases. None was dead due to the treatment-related complications. Eleven patients (44%) had disease progression (in-field recurrence, distant metastasis, and both in 5, 7, and 2, respectively). The median duration of cancer progression within the SBRT field was 2 months (range, 1–6). In addition, 6 patients experienced regional failures including 3 in pelvis outside the SBRT field, and 3 in para-aortic lymph nodes. As depicted in Fig. 1, the 1-year IFRFS for salvage and definitive groups were 64.5% and 90.0% ($p = 0.29$), whereas the 1-year OS for salvage and definitive groups were 80.8% and 49.1% ($p = 0.38$), respectively.

Table 6
Treatment-related early and late toxicities.

Category of side effect	Grade 1	Grade 2	Grade 3	Grade 4
Early toxicity				
Skin reaction	7	3	0	0
Gastrointestinal reaction				
Diarrhea	8	1	2	0
Nausea/vomiting	1	2	0	0
Hemorrhage	0	0	1	0
Genitourinary reaction				
Frequent urination	1	1	0	0
Dysuria	0	1	0	0
Late toxicity				
Gastrointestinal complication				
Radiation colitis	0	1	0	0
Sigmoid perforation	0	0	1	0
Entero-vaginal fistula	0	0	2	0
Genitourinary complication				
Frequent urination	1	0	0	0
Dysuria	1	1	0	0
Legs edema	0	1	0	0

Note: Common Terminology Criteria for Adverse Events Version 4.0 was used to score the maximum late toxicities.

Cumulative normal tissue dose

The cumulative doses to the OARs are tabulated in Table 5. In the current treatment, the median cumulative D2cc-EQD2 of rectum, sigmoid and bladder were 68.25 Gy_3, 62.53 Gy_3, and 71.97 Gy_3, respectively. In 5 patients who received previous radiotherapy, the cumulative doses to the OARs were calculated by adding two courses of irradiated dosage. The median D2cc-EQD2 of rectum, sigmoid colon and bladder were 66.82 Gy_3 (range, 44.83–141.59),

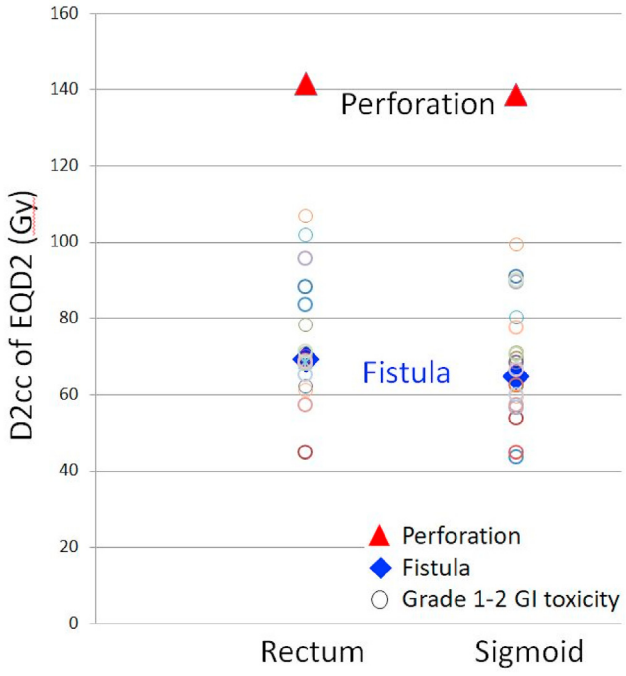

Fig. 2. The cumulative doses of rectum and sigmoid colon in two patients with grade 3 or above late gastrointestinal toxicities. One patient developed entero-vaginal fistula and the cumulative D2cc of EQD2 for the rectum was 69.3 Gy_3 (blue diamond). The other patient had perforation of sigmoid colon and the cumulative D2cc of EQD2 for the rectum and sigmoid colon were 141.6 Gy_3 and 138.7 Gy_3, respectively (red triangle). (For interpretation of the references to color in this figure legend, the reader is referred to the Web version of this article.)

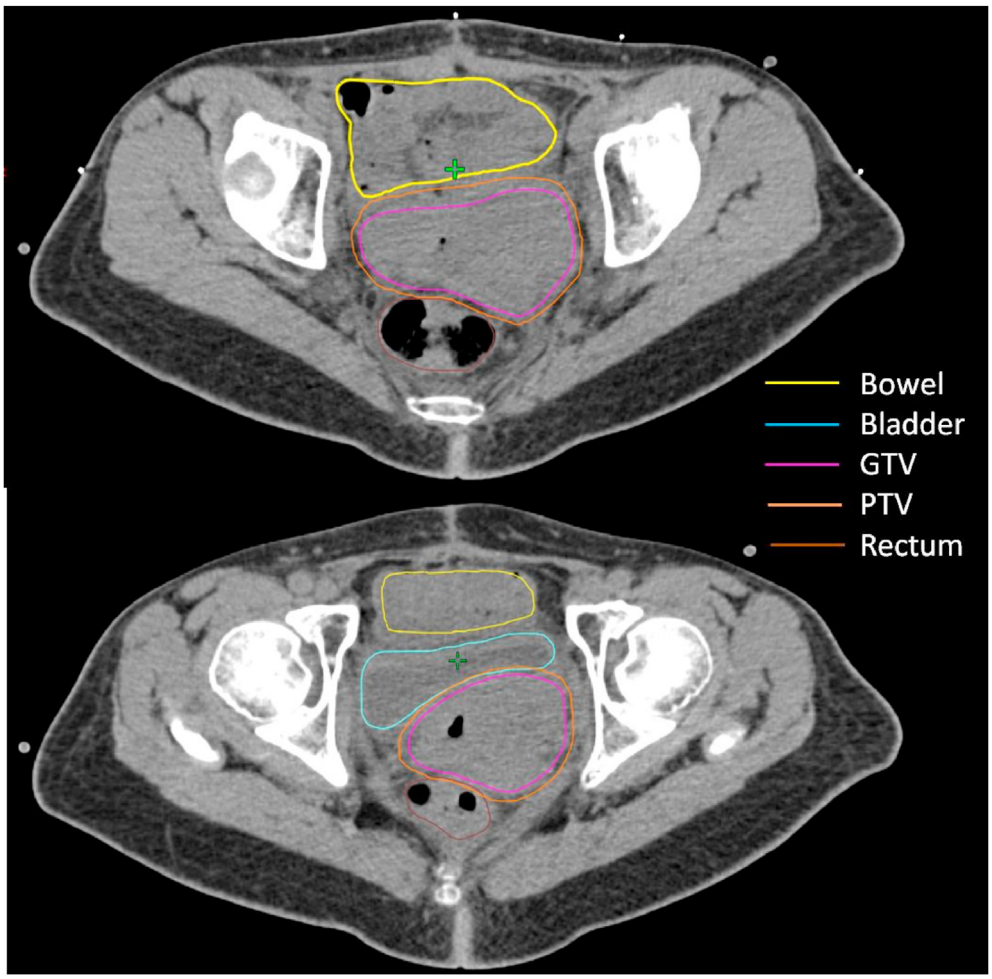

Fig. 3. The target volume and organs at risk of a patient who developed entero-vaginal fistula after SBRT. The cumulative D2cc of EQD2 of the rectum was 69.3 Gy_3. The images showed that the adapted gross tumor volume stayed close to the rectum. Abbreviation: GTV = gross tumor volume; PTV = planning target volume.

66.86 Gy_3 (range, 43.61–138.71), and 73.10 Gy_3 (range, 44.60–166.41), respectively.

Treatment-related toxicities

The early and late toxicities are summarized in Table 6. Three patients (12%) had grade 3 early toxicities, including two experienced grade 3 diarrhea during treatment and one suffered from bloody stool within six months after treatment. Two patients in salvage group developed grade 3 or above late GI complications. Fig. 2 shows the cumulative doses of rectum and sigmoid colon for the two patients with ≧grade 3 toxicities. One experienced entero-vaginal fistula and had diverting colostomy. Although the cumulative D2cc of EQD2 of the rectum for this patient was 69.3 Gy3 (Fig. 2, blue diamond), the adapted GTV stayed close to the rectum, as illustrated in Fig. 3. The other patient had previous radiotherapy to the pelvis and suffered from perforation of sigmoid colon at three months after SBRT. Hartmann's procedure was carried out to relieve the symptoms. The cumulative D2cc of EQD2 of the rectum and sigmoid colon in this patient were 141.6 Gy3 and 138.7 Gy3, respectively (Fig. 2, red triangle). None had grade 3 or above late GU toxicities in this cohort.

Prognostic factors for in-field failure

The impact of clinical variables, cumulative dose, or tumor volume on infield recurrence was further analyzed. The results showed that in-field relapse was not associated with cumulative EQD2 of the adaptive GTV ($p = 0.29$), histological type (squamous cell carcinoma type *vs.* non-squamous cell carcinoma, $p = 0.21$), or initial GTV values ($p = 0.14$). In salvage group, the volume of recurrent tumor ranges from 6.9 to 298.1 ml (median, 26.5). The median tumor regression ratio was 34.8% (range, 0–72.9%), and the values were not related to in-field recurrence (Area under the receiver operating characteristic curve: 0.5).

Discussion

This preliminary study indicated that pelvic SBRT boost after EBRT is an effective treatment modality with acceptable early toxicities for the management of patients with recurrent gynecological cancer, or a substitute when patients with intact uterus are unable to have brachytherapy. The SBRT boost resulted in an initial response rate of 72% with acceptable acute toxicities. With a median follow-up duration of 12 months, the 1-year IFRFS for salvage

and definitive group were 64.5% and 90.0%, respectively. Of the 20 patients without previous pelvic irradiation, only one (5%) developed grade 3 or above late toxicities. Additionally, this study highlighted that the cumulative doses of OARs should be reduced for patient who received re-irradiation. In patients with recurrent tumor, the benefit of upfront conventionally fractionated EBRT was verified because a median tumor regression ratio of 34.8% could be achieved. As a result, the SBRT boost could be focused on the adapted GTV and the irradiated volume to the OARs was able to be minimized.

The treatment of recurrent gynecological cancer is challenging. To choose the therapeutic options for recurrent tumors, the primary initial therapy and the site of recurrence must be taken into account. Pelvic exenteration is considered as an optimal form of surgery for central recurrence after primary or adjuvant RT, but for patients with recurrent tumors at periphery, radiotherapy-based treatment is always suggested. By using SBRT technique, previous studies showed that the IFRFS ranged from 65% to 82.5% [10–13]. However, the application of EBRT was heterogeneous in these studies. Guckenberger.et al. investigated a cohort of 19 locally recurrent gynecological cancer patients who were all treated with 50 Gy with local boost with SBRT for 15 Gy divided into three fractions with or without brachytherapy [10]. They reported that the 3-year local control reached 81%, whereas the 3-year OS was 34%. Notably, the rate of >grade 2 late toxicity was 25% at 3 years, and 3 (25%) developed grade 4 complications. Of them, two suffered from fistula and one from ileus. A Korean study reviewed 23 patients who had a range of SBRT dose ranging from 27 to 45 Gy for recurrent cervical cancer at the pelvic side [11]. They showed that 2-year OS and IFRFS were 43% and 65%, respectively. Severe toxicities were found in 13% of the patients. On the other hand, Park et al. reported that tumor $BED_{10} > 69$ Gy had marginal impact on local control [13]. Moreover, Seo et al. [11] disclosed that patients with initial tumor size less than 30 ml had superior 2-years survival. Because only four patients had in-field recurrence in our cohort, neither an optimal prescribed dose nor a highly curable tumor volume could be identified in this study. To maximize the role of SBRT boost, a large prospective trial is needed to identify the optimal scheme for achieving a satisfactory therapeutic window.

In cervical cancer patients who are ineligible for brachytherapy, SBRT plans achieved better target coverage and better dose distributions to critical organs except bone marrow compared with intracavitary brachytherapy plans [9]. According to our previous study for locally advanced cervical squamous cell carcinoma [16], the employment of image-guided brachytherapy showed the 2-year local relapse-free survival and OS were 89% and 85%, respectively. In this study, the 1-year IFRFS for the definitive group was 90%, which was comparable with the treatment outcome of the patients receiving image-guided brachytherapy, but the OS dropped to 49.1%. The main reason for the inferior OS was attributed to five out of the eleven patients died of either distant metastasis or concurrent non-cancer diseases. As a result, the survival benefit by superior local control was greatly diluted. By using SBRT boost for replacing brachytherapy in cervical cancer, previous studies showed that the IFRFS ranged from 85.7% to 100% [6,7]. In a propensity-matched analysis [8], those who received SBRT boost had equal survival when compared with brachytherapy, but those who received IMRT boost had worse survival. Accordingly, our study reconfirmed the role of SBRT boost in this patient setting.

The findings of this study should be interpreted cautiously because they represent a prospective observation study from a single institution. External validation studies using a large sample size are necessary to confirm these findings. Furthermore, the optimal cumulative dose that confers to superior local control could not be clarified because of the limited events of recurrences. Therefore, future trials are required to accrue more patients to maximize the therapeutic effect of SBRT and EBRT. Finally, the OAR constraints for treatment guideline of SBRT should be reviewed not only based on cumulative dose but also the geographical relation because one patient who had the rectum close to tumor developed fistula.

Conclusion

In gynecological cancer patients with recurrent pelvic tumors or intact uterus unsuitable for brachytherapy, local dose escalation with SBRT resulted in an initial response rate of 72% with acceptable acute toxicities. However, the cumulative doses of OARs should be minimized for patient who received re-irradiation. A long-term follow-up is required to assess the impact on local control or survival.

Declaration of competing interest

All authors declare no conflicts of interest.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

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