Re-irradiation for recurrent cervical cancer: A single institutional experience

Junyun Li [a],[1], Lin Huang [a],[1], Haiying Wu [a],[1], Jia Li [a], Xinping Cao [a],[**], Zhimin Liu [b],[*]

[a] Department of Radiation Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center
[b] Department of Gynecologic Oncology, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Sun Yat-sen University Cancer Center

A B S T R A C T

Purpose: Salvage treatment of recurrent cervical cancer of patients with a history of radiotherapy is currently a major clinical challenge. The purpose of our study was to retrospectively analyze clinical outcomes of radiation in patients with recurrent cancer who have previously received radiotherapy at our hospital and further explore the efficacy and safety of this treatment modality.
Methods: All consecutive patients who underwent re-irradiation were included in our department between January 2015 and December 2017. All the patients received Volumetric Modulated Arc Therapy (VMAT) alone or VMAT followed by three dimensional–image-guided brachytherapy (3D-IGBT). The volume and dose for re-irradiation depended on previous radiation fields, dosimetry and recurrence sites. All patients received systemic chemotherapy before or after re-irradiation.
Results: Fifty patients were included in our study. The median time from primary radiotherapy to re-irradiation was 12 months. Local recurrence, which was the most common failure following primary treatment, was present in 25 patients (50.0 %) while regional recurrence, loco-regional recurrence and distant recurrence combined in-filed recurrence was present in 8 (16.0 %), 9 (18.0 %) and 8 patients (16.0 %). Re-irradiation dose to lymph nodes was 45 Gy with or without a boost up to 55–60 Gy, and to the gross mass was 36–45 Gy with or without a boost up to 45–61 Gy. The median follow-up period was 22 (range,4–59) months. The 3-year local control (LC), progression-free survival (PFS), and overall survival (OS) rates were 58.0, 38.7, and 44.4 %, respectively. The median time of PFS and OS was 14 and 26 months, respectively. The interval between two successive radiotherapies beyond 12 months was significantly associated with better LC and PFS ($p \leq 0.05$), but without the benefit of OS ($p > 0.05$). Serum SCC antigen level less than 1.5 ng/ml had a significantly better impact on PFS ($p \leq 0.05$). Overall, 14 patients (28 %) experienced $\geq$ grade 3 acute toxicities, while 9 (18 %) experienced $\geq$ grade 3 late toxicities.
Conclusions: Re-irradiation with VMAT is an effective and safe salvage treatment option with a reasonably good clinical outcome and toxicity profile in selected patients. In our experience, recurrent cancer patients with an interval between two successive radiotherapy courses beyond 12 months and with a serum SCC-Ag level less than 1.5 ng/ml, had improved outcomes.

Introduction

In women, cervical cancer is the fourth most frequently diagnosed cancer and the fourth leading cause of cancer death, estimated at 569,847 new cases and 311,365 deaths in the year 2018 worldwide [1].

Despite advances and improvements in treatment techniques, some patients experience treatment failures such as local, regional and distant recurrences, or a combination of these. In Embrace I prospective study, which included 1341 IB-IVA cervical cancer patients, 5-year local control, pelvic control and nodal control was 92 %, 87 % and 87 %,

respectively [2]. Once treatment failure occurred, the patients would have a poor prognosis, whose 5-year OS rate was 10–20 % [3,4]. Therefore, the management of recurrent cervical cancer is a therapeutic challenge, especially for those with a history of radiotherapy.

Various treatment options are available for different cases of recurrence, ranging from surgical exenteration to palliative measures. Radiotherapy is a feasible treatment option that allows for organ preservation in out-field recurrent cancer patients, whereas historically, re-irradiation has not been considered for the in-field recurrent cancer patients, owing to its risk of complications. Traditionally, re-irradiation is associated with considerable toxicities, which may cause severe organ injury due to high accumulative radiation dose. Early re-irradiation studies revealed that the incidence of severe complications was from 50 % to 56 %[5,6]. Recurrences in previously irradiated territory have poor prognosis [7], with very low response rate to systemic treatment in irradiated territory. Recurrence in irradiated territory is also a stratification element in some trials evaluating systemic therapy [8].These elements justify the evaluation of local treatments such as re-irradiation. With the recent improvements in high-precision radiotherapy, which include image-guided radiotherapy (IGRT), stereotactic body radiotherapy (SBRT), and intensity-modulated radiotherapy (IMRT), as well as image-guided stepping source brachytherapy, there has been renewed interest in re-irradiation for these groups [9–11]. Recently, a few retrospective studies reported that salvage re-irradiation with the high-precision radiotherapy techniques obtain encouraging local control and toxicity profiles[10,12]. With the use of advanced radiotherapy techniques, a local control of disease has been reported 45 %-49 % at 3 years in patients with high-dose-rate brachytherapy[13–15], and 53 %-82 % at 2 years in patients with SBRT[16–18]. However, there is to no consensus on these radiation modalities including patient selection, dose, and technique for those who previously underwent radiotherapy.

The purpose of our article is to retrospectively analyze the clinical outcomes of radiation in recurrent cancer patients who have previously received radiotherapy at our hospital and further explore the efficacy and safety of this treatment modality.

Methods

Patients

The study initially included 57 patients with recurrent cervical cancer who received re-irradiation through Volumetric Modulated Arc Therapy (VMAT) in our institution between January 2015 and December 2017. The inclusion criteria were: (1) histologically confirmed primary cervical cancer; (2) histology types of squamous cell carcinoma (SCC), adenocarcinoma (AC) or adenosquamous carcinoma; (3) complete response after initial treatment, which included definitive radiotherapy or surgery followed by radiotherapy; (4) treated with curative intent with re-irradiation (with or without chemotherapy); and (5) distant metastasis in two or fewer sites. Recurrent cancer patients who (1) received surgery after definitive radiotherapy as a salvage treatment (n = 2); (2) had no follow-up after re-irradiation (n = 1); and (3) did not finish re-irradiation (n = 4) were excluded. Finally, following the criteria, a total of 50 patients were included in our study. Patients' clinical information was obtained from our institution's digital medical records system. This study was approved by the Ethics Committee of the Sun Yat-sen University Cancer Center.

Treatment

Regarding treatment planning, imaging examinations (PET/CT, MRI or CT) were performed for extension assessment and target definition during pre-planning. As for suspicious lesions, which were assessed according to MRI (Fat-suppressed T2-weighted signal, contrast enhanced T1 signal, T1/T1-weighted signal, Diffusion Weighted Imaging), PET/CT (hypermetabolic sites) or CT (contrast enhanced).

Firstly, patients were immobilized within a thermoplastic shell. Secondly, Intravenous contrast-enhanced CT simulation was performed at 3-mm slice thickness on the whole abdomen plus pelvic or supraclavicular region by using a CT simulator. Reconstructed CT images were transmitted to a Monaco treatment planning system (TPS). Then gross target volume and OARs were contoured. The gross target volume included all grossly enlarged lymph node with a short diameter greater than 0.8 cm and the other recurred lesions. Organs at risk (OARs) to be contoured were the bladder, small intestine, rectum, kidney, spinal cord and femoral head etc.

After external beam radiation, a high-dose-rate 192Ir unit was used to conduct computed tomography (CT) image guided adaptive brachytherapy (IGABT). Parameters included high-risk clinical target volume (HRCTV) of the gross mass (D90%), the intermediate CTV (IRCTV) and the irradiation dose received by 2 cm3 (D 2 cm 3) of the high-dose area to the bladder, rectum, sigmoid. We used the quadratic linear model (a/$\beta = 10$ was adopted for gross tumor volume, and a/$\beta = 3$ was adopted for OARs). The physical dose of image guided adaptive brachytherapy (IGABT) was converted into the bioequivalent dose of 2 Gy. The dose received by 90 % of the clinical target volume (HRCTV) of the gross mass (D90%), the intermediate CTV (IRCTV) (D90%) and the irradiation dose received by 2 cm3 (D 2 cm 3) of the high-dose area to the OARs were calculated. Then, the doses of IGABT and VMAT were added to obtain the cumulative D90% to the HRCTV and the cumulative D 2 cm 3 to the OARs. Brachytherapy was performed 1–2 times a week and the prescription were 18–28 Gy (EQD2 24–40 Gy) in 6–7 Gy (EQD2 8–10 Gy) per fraction. In addition, the platinum-based chemotherapy was given according to patient status. Most patients completed 4–6 cycles of chemotherapy.

Follow-up and toxicity

The follow-up schedule included every 3 months for the first 2 years, twice yearly for the next 3 years, and then once yearly after 5 years. The final follow-up date for the patients was on January 2023. The routine follow-up items included gynecological pelvic examinations and imaging examinations, including computed tomography (CT), magnetic resonance imaging (MRI), or positron emission tomography(PET). Local recurrence was defined as any recurrence in the vaginal vault, cervix, or parametrial tissue. Regional recurrence was defined as lymph node failures within the pelvis and/or in the *para*-aortic area (patients with *para*-aortic lymph node metastases must have been treated with extended field radiation therapy during primary treatment). Recurrence beyond the pelvic region (excluding *para*-aortic lymph node involvement) was defined as distant metastasis. Acute hematologic and late toxicities were graded based on the criteria devised by the Radiation Therapy Oncology Group and the European Organization for Research and Treatment of Cancer [19]. Acute hematologic toxicities were evaluated weekly during the course of re-irradiation and 1 month after completion. Late toxicities were defined as adverse events that occur 90 days after treatment.

Statistics

Local control (LC), progression-free survival (PFS), and overall survival (OS) were estimated using the Kaplan–Meier method. LC was calculated from the date of beginning salvage treatment to the date of any subsequent recurrence inside the target sites. PFS was calculated from the date of beginning salvage treatment to the date of any subsequent recurrence or death. While OS was calculated from the date of recurrence to the date of all-cause death or last follow-up. All tests were two-sided and performed using the SPSS software (version 19.0 IBM Corporation, Armonk, NY, USA). $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

The median age of the patients was 50 years (range: 27——70 years) as shown in Table 1. There were 43 patients (86.0 %) with SCC, which was the most common histological type, while seven (14.0 %) of them had AC. Based on the International Federation of Gynecology and Obstetrics (FIGO) staging system of 2009, the initial diagnosis were as follows: 37 patients (74.0 %) had stage I to II diseases (I = 17, II = 20), while 13 (26.0 %) had stage III to IV diseases (III = 12, IV = 1). As for the cases of primary treatment, 27 patients (54.0 %) underwent surgery followed by radiotherapy while 23 (46.0 %) underwent definitive radiotherapy. The median time from primary radiotherapy to re-irradiation was 12 months (range: 3 to 114 months). All the patients received VMAT alone or VMAT followed by 3D-IGBT. VMAT alone was performed in 30 patients (60.0 %), while VMAT with 3D-IGBT was performed in 20 patients (40.0 %). A total of 43 patients with SCC had a record of SCC antigen presence at recurrence, with a median value of 2.6 ng/ml (range: 0.5——48.4 ng/ml). Local recurrence, which was the most common failure following primary treatment, was present in 25 patients (50.0 %) while regional recurrence was present in eight (16.0 %), and loco-regional recurrence was present in nine (18.0 %). Distant recurrence combined with local, regional, or loco-regional recurrence was present in eight patients (16.0 %).

Re-irradiation

In cases of in-field recurrence, radiation dose to lymph nodes was 45 Gy in 1.8 Gy per fraction with or without a boost up to 55–60 Gy. Dose profile to the other recurred lesions included VMAT alone and VMAT followed by BT. Firstly, 36–45 Gy/18–25 fractions were delivered to the gross mass. Secondly, the patients of VMAT alone group were conducted CT scans to re-evaluate the size of the residual gross mass, then a boost to the residual size up to 45–61 Gy were delivered. High-dose-rate intra-cavitary combined with interstitial brachytherapy were applied in these selected patients as a boost following VMAT. Brachytherapy was performed 1–2 times a week and the fraction dose were 6–7 Gy (EQD2 8–10 Gy).

In cases of oligo-metastases with in-field recurrence, for oligo-metastatic sites, which were radiation-naive, the radiation dose of 45–50 Gy/25 fractions were given to the lymph node basin with a boost up to 60–72 Gy to lymph nodes; for in-field recurrence sites, treatment regimens were as mentioned earlier (Table 2).

Survival outcomes

The median follow-up period was 22 (range: 4——59) months, while the overall 3-year LFFS LC, PFS and OS were 58.0, 38.7 and 44.4 %, respectively (Fig. 1). The median time of PFS and OS was 14 and 26 months, respectively. We collected and analyzed different factors to identify treatment outcomes; these factors included age, histology, initial FIGO stage, prior radiotherapy, salvage radiotherapy modality, the interval between two radiotherapies, SCC antigen level at recurrence, and the recurrence site (Fig. 2, Fig. 3, Fig. 4). The interval time between two radiotherapies beyond 12 months was significantly associated with better LC and PFS (Fig. 2. E; Fig. 3. E; $p \le 0.05$), but without a benefit of OS (Fig. 4. E; $p > 0.05$). The 3-year LC, PFS and OS rate was 60.6, 40.5 and 48.6 % in the SCC group, 42.9, 28.6 and 16.7 % in the AC group, respectively. The SCC group seemed to have a better LC, PFS, OS rate in our study, with no significant differences between that of SCC and AC groups (Fig. 2. B; Fig. 3. B; Fig. 4. B; $p > 0.05$). We compared the survival of different recurrence sites in total population, the regional recurrence group had a significantly better OS compared to the local recurrence group (Fig. 4. I; $p \le 0.05$). Moreover, there was no significant difference in LFFS LC, PFS and OS among patients with or without distant recurrence (Fig. 2. G; Fig. 3. G; Fig. 4. G; $p > 0.05$). We analyzed 43 SCC patients with the SCC antigen: 3-year PFS with the presence of SCC antigen < 1.5 ng/ml was 74.1 % compared to a 27.4 % in those with SCC antigen $\ge$ 1.5 ng/ml, therefore showing a significant impact of the antigen on PFS (Fig. 3. G; $p \le 0.05$). However, LC and OS did not have any significant impact with the presence of the antigen (Fig. 2. G; Fig. 4. G; $p > 0.05$).

Toxicity evaluation

We observed acute toxicities such as hematologic toxicities, digestive toxicities, dermatitis and cystitis in 50 patients (Table. 3). Overall, 14 patients (28 %) experienced $\ge$ grade 3 acute toxicities. The details were as follows: 10 patients (20 %) experienced $\ge$ grade 3 acute hematologic toxicities, of which nine (18 %) experienced $\ge$ grade 3 leukocytopenia, two patients (4 %) experienced $\ge$ grade 3 anemia, and two (4 %) experienced $\ge$ grade 3 thrombocytopenia. 9 patients (18 %)

Table 1
Patient characteristics.

	No. Patients (N = 50) (%)
Age, median (range), y	**50 (20-70)**
Age $\le$ 50	27 54 %
Age > 50	23 46 %
Histology	
SCC	43 86 %
AC	7 14 %
Initial Figo Stage	
I	17 (34 %)
II	20 (40 %)
III	12 (24 %)
IV	1 (2 %)
Prior radiotherapy	
Definitive	23 (46 %)
Postoperative	27 (54 %)
The interval between two radiotherapies (months)	
$\le$12	29 (58 %)
>12	21 (42 %)
Salvage radiotherapy treatment	
VAMT	30 (60 %)
VAMT + 3D-IGBT	20 (40 %)
SCC-Ag level at recurrence (ng/ml)	
<1.5	12 (24 %)
$\ge$1.5	31 (62 %)
unknown	7 (14 %)
Distribution of tumor recurrence	
Local only	25 (50 %)
Regional only	8 (16 %)
Local and regional	9 (18 %)
Distance	8 (16 %)

Abbreviations: SCC = squamous cell carcinoma; AC = adenocarcinoma; VAMT = volumetric modulated arc therapy; 3D-IGBT = 3 dimensional - image guided brachytherapy.

Table 2
Treatment regimen and radiation dose for Re-irradiation.

| Irradiation site	Case number	Treatment regimen	Delivered median dose (EQD2, Gy), median (range)
Local only	25	VMAT alone VMAT + BT	Lymph node:60(45–60) Other recurred lesion: 61 (30–75)
Regional only	8	VMAT	Lymph node:60(45–60) Other recurred lesion: 61 (45–61)
Local + regional	9	VMAT alone VMAT + BT	Lymph node:60(45–60) Other recurred lesion: 61 (45–68)
Oligo-metastases with in-field recurrence	8	VMAT	Lymph node: 60(54–72) Lymph node basin 45 (45–50)
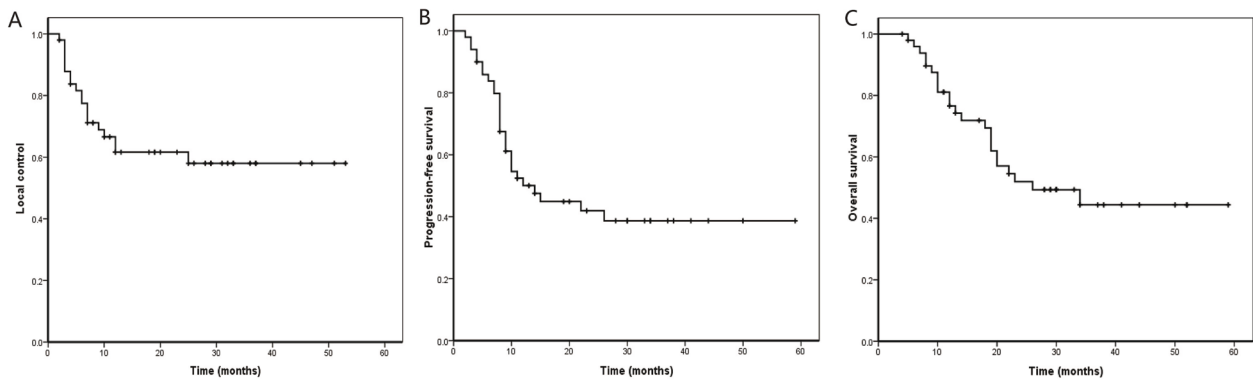
Fig. 1. Kaplan-Meier curves for local control (LC) (A), progression-free survival (PFS) (B), and overall survival (OS) (C) after re-irradiation.
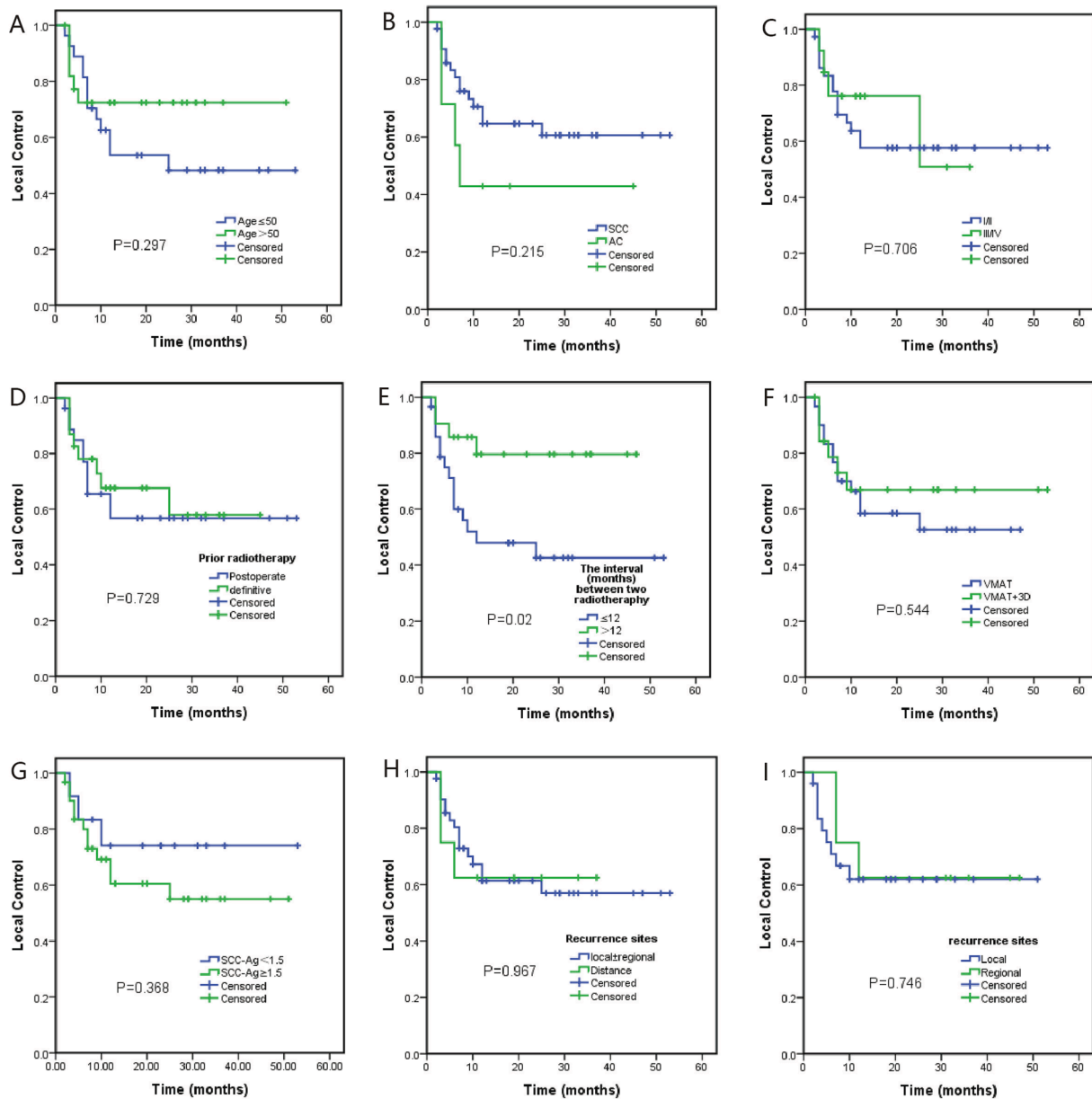

Fig. 2. Kaplan-Meier curves for LC with respect to different factors. A: Age; B: Histology; C: Initial Figo stage; D: Prior radiotherapy; E: Interval between two radiotherapies; F: Salvage radiotherapy; G: SCC-Ag; H and I: Recurrent sites.

Fig. 3. Kaplan-Meier curves for PFS with respect to different factors. A: Age; B: Histology; C: Initial Figo stage; D: Prior radiotherapy; E: Interval between two radiotherapies; F: Salvage radiotherapy; G: SCC-Ag; H and I: Recurrent sites.
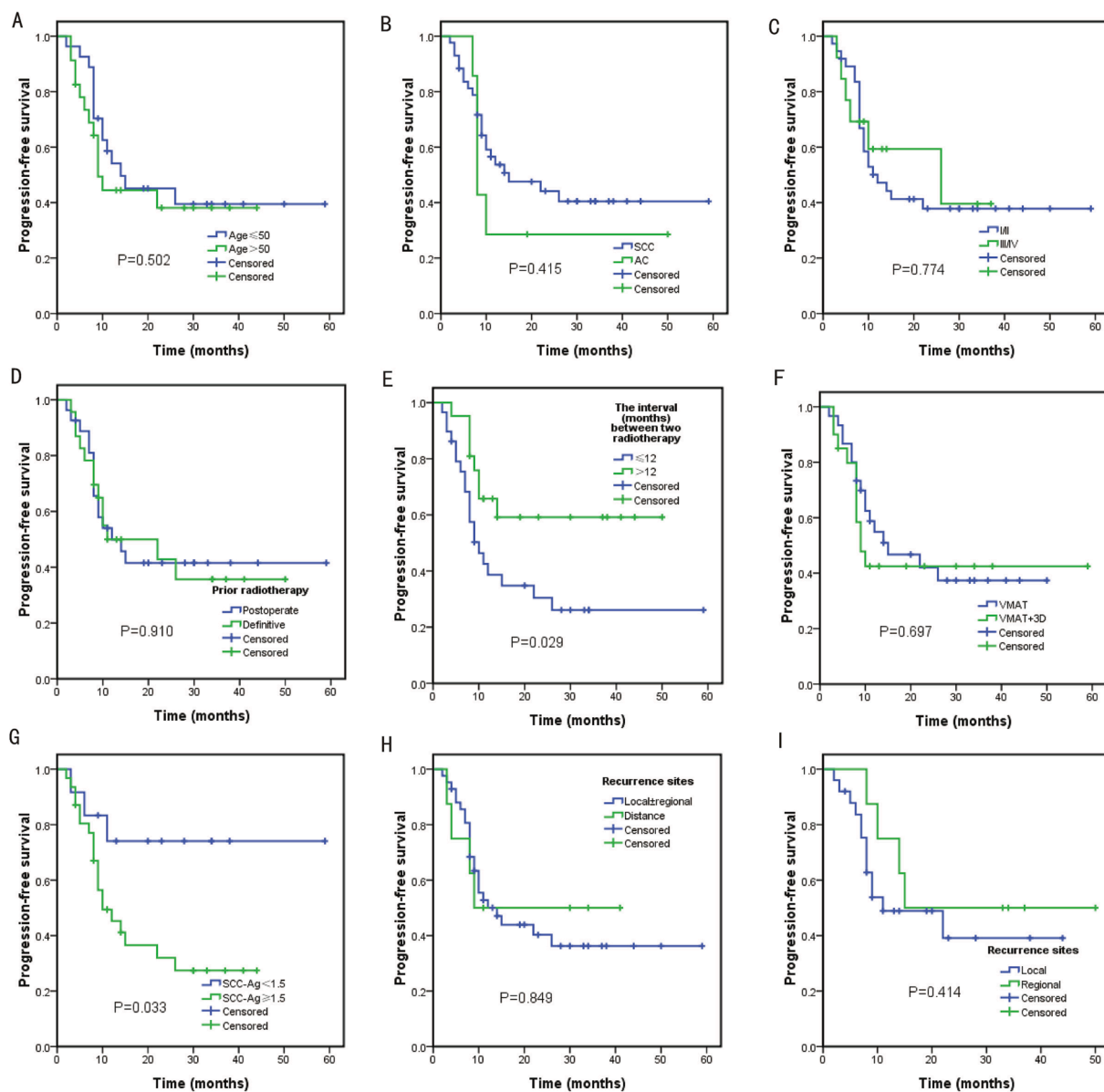
experienced ≥ grade 3 acute digestive toxicities, of which four patients (8 %) experienced ≥ grade 3 acute intestinal toxicities, and nine patients (18 %) experienced ≥ grade 3 nausea. 5 patients (10 %) experienced ≥ grade 3 Dermatitis. 3 patients (6 %) experienced ≥ grade 3 acute Cystitis. There was no toxic death in our study.

We also observed late toxicities in our study (Table 3), which included the intestine as well as the bladder. Overall, nine patients (18 %) experienced ≥ grade 3 late toxicities, of which five (10 %) experienced ≥ grade 3 intestinal toxicities, which included grade 3 in four patients (8 %), and grade 4 in one patient (2 %). Meanwhile five (10 %) of them experienced ≥ grade 3 bladder toxicities, which included grade 3 in four patients (8 %), and grade 4 in one patient (2 %).

Discussion

The salvage treatment of recurrent cervical cancer in patients with a history of radiotherapy is currently a major clinical challenge. Disease recurrence pattern and previous radiotherapy history are two important factors for selecting treatment modality. For out-field recurrent cancer

patients, radiotherapy is the most effective radical treatment modality, due to better response and less resistance to therapy. However, the management of in-field disease recurrence for cervical cancer patients is a dilemma, since a balance of the relationship between the radiation effects to the tumor region and the protection of normal tissues should be considered. Pelvic exenteration is frequently considered to be the only potentially curative option in strictly selected patients, but the presence of severe postoperative complications and low success rates are unacceptable in most patients. Traditionally, re-irradiation with conventional EBRT techniques in recurrent cervical cancer is not feasible due to high toxicity. Fortunately, with new developments in EBRT technology, re-irradiation with high precisive radiation therapy has become a good treatment option. In a study by Kim et al. [9], most of the re-irradiated patients received IMRT, which was shown to be the preferable salvage modality. However, compared to IMRT, VMAT is advanced, as it is more conformal and has a reduced treatment delivery time [20]. VMAT has been applied to treat patients with cervical cancer at our institution since 2012. In a previous study [21], VMAT showed feasible outcomes in definitive radiotherapy and had no significant
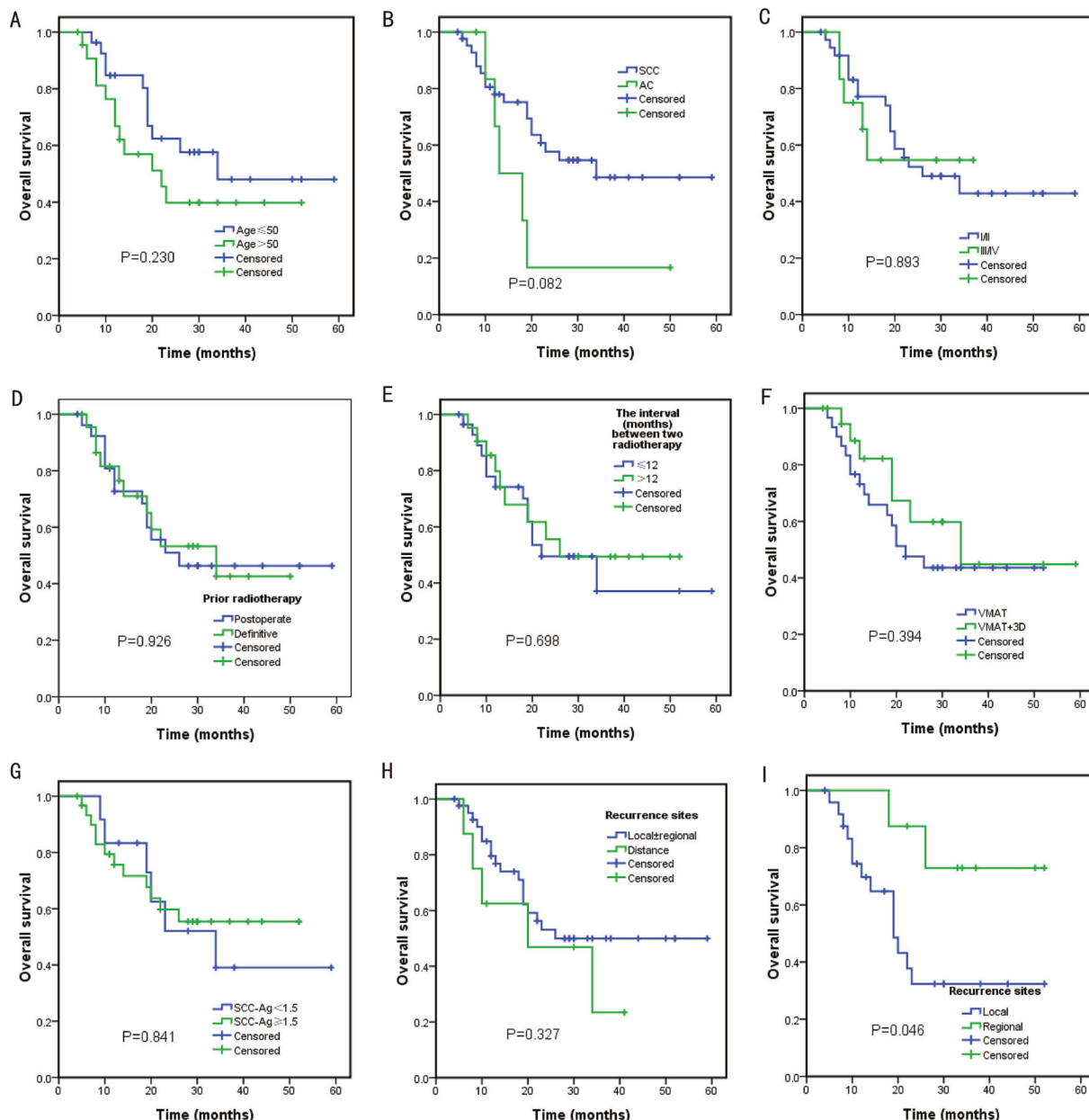
Fig. 4. Kaplan-Meier curves for OS with respect to different factors. A: Age; B: Histology; C: Initial Figo stage; D: Prior radiotherapy; E: Interval between two radiotherapies; F: Salvage radiotherapy; G: SCC-Ag; H and I: Recurrent sites.

difference in treatment outcomes (OS/PFS/LC) in correlation with IMRT, but it had a lower incidence of acute anemia and chronic enterocolitis. In our study, the modalities of salvage radiotherapy used were either VMAT with or without 3D-IGBT.

The available data, regarding patient selection and technology used for those with recurrent cervical cancer who received re-irradiation, was relatively sparse and limited mostly to retrospective single-institution series. Bockel et al reviewed recent literature concerning 3D-IGBT for reirradiation in the context of local recurrences from gynecological malignancies, they founded that 3D-IGBT appears to be a feasible alternative to salvage surgery in inoperable patients, with an acceptable outcome for patients who have no other curative therapeutic options [22]. A study by Mahantshetty et al. [23] included 30 patients with local disease recurrence who underwent re-irradiation with brachytherapy alone; the 2-year LFFS, PFS, and OS rate was 44, 42, and 52 %, respectively. Umezawa et al. [24] analyzed 18 patients with local recurrence who received image-guided interstitial high-dose-rate brachytherapy; the 2-year local control (LC), PFS and OS rate was 51.3, 20.0 and 60.8 %, respectively. In the current study, we included 50 patients who underwent re-irradiation performed with VMAT, where their 3-year LC, PFS, and OS rate was 58.0, 38.7, and 44.4 %, respectively. The clinical outcomes in our study were different, which may be largely attributable to patients' selection, such as recurrence volumes, current site, RT dose and etc.

We compared the local disease recurrence group with the regional group with respect to LC, PFS, and OS rates. The regional group had a significantly better OS ($p \leq 0.05$). Furthermore, previous studies focused more on the local recurrence of re-irradiation [25], whereas our finding suggests that the regional recurrence might be more beneficial from re-irradiation. In our study, there were no significant differences in the LC, PFS, OS rates among patients with or without distant disease recurrence ($p > 0.05$), which showed that re-irradiation is still worth considering for in-field recurrent cancer patients with distant oligometastases in selected patients.

Table 3
Acute toxicities and late toxicities in patients with cervical cancer.

	Toxicity	Grade	Patients(n = 50)	%
Acute Toxicity	**Leukocytopenia**	0–2	41	82 %
		3–4	9	18 %
	Anemia	0–2	48	96 %
		3–4	2	4 %
	Thrombocytopenia	0–2	48	96 %
		3–4	2	4 %
	Dermatitis	0–2	45	90 %
		3–4	5	10 %
	Nausea	0–2	41	82 %
		3–4	9	18 %
	Intestine	0–2	46	92 %
		3–4	4	8 %
	Cystitis	0–2	47	94 %
		3–4	3	6 %
Late Toxicity	**Intestine**	0–2	45	90 %
		3–4	5	10 %
	Bladder	0–2	45	90 %
		3–4	5	10 %

Few articles have reported that the best selection criteria, for patients with cervical cancer to receive re-irradiation, to be the time between the interval of two successive radiotherapies. In head-neck cancers, the longer the interval between two radiotherapy courses, the fewer the severe complications were and had a better prognosis with local control [26]. Though a few studies used an interval time $\geq$ 6 months to determine the eligibility for re-irradiation, Chen et al. [27] recommended an interval time of < 12 months to be a risk factor. Whereas, Mabuchi et al. [28] reported that in 52 patients who received re-irradiation with brachytherapy, an interval time beyond 6 months was an independent prognostic factor. In our study, the > 12 months interval between two radiotherapy courses was a significantly favorable factor (*p $\leq$ 0.05*). The results of our study suggested that the interval between the two radiotherapies was an important practical consideration that aided clinical decision.

Serum SCC-Ag level is a common marker for SCC of the cervix, which is often used to assess the therapeutic effect and prognosis of the disease [29]. However, the clinical relevance of the SCC-Ag level is still controversial especially in recurrent cancers, due to the lack of literature reports. Choi et al. [30] reported that the SCC-Ag level after treatment and at recurrence was useful in predicting tumor recurrence and patient survival. However, Kim et al. [9] analyzed 125 patients with recurrent cervical cancer treated with radiotherapy and found a level of > 1.55 ng/ml SCC-Ag to be an independent poor prognostic factor. In our study, we analyzed 43 patients with SCC of the cervix, with an SCC-Ag level > 1.5 ng/ml to be a significant poor prognostic variable for PFS (*p $\leq$ 0.05*). Our result corroborated previous studies. Serum SCC-Ag level may be a useful predictive factor for patients when determining the use of re-irradiation.

There was a lack of reports regarding acute hematologic toxicities following re-irradiation in previous studies. In a previous study of primary radiotherapy with VMAT, a grade 3 or higher acute hematologic toxicity was experienced by 13.6 % of the patients [21]. In the current study, 10 patients (20 %) experienced $\geq$ grade 3 acute hematologic toxicity while leukocytopenia was the most present with nine patients (18 %) experiencing $\geq$ grade 3 toxicity. Furthermore, re-irradiation with VMAT showed acceptable toxicity, but more studies are needed to confirm the effect of re-irradiation on acute hematologic toxicity. Regarding late toxicities, 18 % of the patients had $\geq$ grade 3 toxicities in our cohort. In a previous study, there was a report of 45 patients who underwent re-irradiation mostly with IMRT, where 15.6 % observed $\geq$ grade 2 toxicities [9]. Sturdza A et al. [12] conducted a literature review of re-irradiation in gynecologic cancers where the rate of $\geq$ grade 3 late toxicities was 14—33 % in those that used brachytherapy and 13—19 % in those that used stereotactic body radiation therapy. Our results suggested that VMAT was relatively a safe treatment modality in

selected patients with recurrent cervical cancer receiving re-irradiation.

Our study does have some limitations. First, main limitation is that there was possible selective bias associated with the retrospective study design. Secondly, Missing data are another bias for this retrospective study. Thirdly all the patients were treated in our institution only, and the resultant sample size was small. Therefore, a large, multi-center-based study is needed to confirm our results.

Conclusions

Our study suggests that re-irradiation with VMAT is an effective and safe salvage treatment option with a reasonably good clinical outcome and toxicity profile in selected patients. In summary, several prognostic factors, including the interval between two radiotherapy courses and the serum SCC-Ag level, should be considered when making decision on re-irradiation before treatment and combined with clinical factors such as general condition, topography and size of recurrence, therapeutic alternatives and sequelae of the first treatment. However, re-irradiations remained a complex situation, and such treatments should be concentrated in high-volume centers. In our experience, recurrent cancer patients with an interval between the two radiotherapy courses beyond 12 months and with a serum SCC-Ag level less than 1.5 ng/ml had improved outcomes.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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