

## Original Article



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# Safety and efficacy of 3D-printed templates assisted CT-guided radioactive iodine-125 seed implantation for the treatment of recurrent cervical carcinoma after external beam radiotherapy

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## ABSTRACT

**Objective:** To investigate the safety and efficacy of 3-dimensional (3D) printing non-coplanar templates (PNCT) assisted computer tomography (CT) guided radioactive <sup>125</sup>I seed implantation (RISI) for the treatment of recurrent cervical carcinoma (RCC) after external beam radiotherapy (EBRT).

**Methods:** A total of 103 patients with inoperable post-EBRT RCC were included in this retrospective study. A total of 111 lesions received RISI. Eight lesions were at the pelvic center, 75 lesions were at the pelvic lateral, and 28 lesions were extra-pelvic metastasis. The median prescription dose was 120 Gy. The primary end points were adverse events and local control (LC), and the secondary end points were overall survival (OS) and progression-free survival.

**Results:** Grade 2 adverse events of acute nausea, diarrhea, and pollakiuria occurred in 1, 2, and 1 patient, respectively. One patient suffered from grade 3 acute proctitis. Late toxicity was observed in 2 patients with rectovaginal fistula. No grade 5 toxicity occurred. The 3-year LC and OS rates were 75.1% and 20.8%, respectively. The median OS was 17 months. The multivariate analysis showed that the minimum dose received by the “hottest” 90% of the gross tumor volume ( $D_{90}$ )  $\geq 130$  Gy, squamous cell carcinoma, hemoglobin  $\geq 80$  g/L and good short-term efficacy (complete response or partial response) were independent predictors of LC and OS (all  $p < 0.05$ ).

**Conclusions:** 3D-PNCT assisted CT-guided RISI is a safe, effective, and minimally invasive modality for RCC. The hemoglobin level, pathological type, dose distribution and short-term efficacy are considered as independent factors for clinical outcomes.

**Keywords:** Interstitial Radiotherapy; Image-Guided Radiation Therapy; Radiation Dosimetry; Brachytherapy; Uterine Cervical Neoplasms; Neoplasm Recurrence, Locoregional

### Conflict of Interest

No potential conflict of interest relevant to this article was reported.

### Author Contributions

Conceptualization: J.P., W.J.; Data curation: L.Y., J.P., Z.H.; Formal analysis: L.Y.; Funding acquisition: W.J.; Methodology: L.Y., W.J.; Project administration: W.J.; Resources: J.P., Z.H., W.J.; Software: L.Y.; Supervision: W.J.; Validation: W.J.; Visualization: L.Y.; Writing - original draft: L.Y.; Writing - review & editing: J.P., W.J.

## INTRODUCTION

Surgery and radiotherapy are currently the main approaches for the treatment of cervical carcinoma. The recurrence rates of patients of International Federation of Gynecology and Obstetrics (FIGO) stages Ib, IIa, IIb, III and IVa are 10%, 17%, 23%, 42% and 74%, respectively, and 80% of cervical cancer recurrences occur within 2 years after initial treatment [1,2]. The treatment options for recurrent cervical carcinoma (RCC) have always been challenging due to the fact that nearly 70% RCC patients have received previous pelvic external beam radiotherapy (EBRT) and re-irradiation will increase the risk of damage to normal tissues [3]. As a standard treatment for early low-risk prostate cancer, radioactive <sup>125</sup>I seed implantation (RISI) could overcome this problem. RISI can deliver extremely high dose to tumor while sparing normal tissue. RISI has showed its good efficacy and been recognized as a salvage or palliative (pain-relief) therapy for various recurrent cancers after multiple therapies, including rectal cancer, cervical cancer, head and neck cancer, pancreatic cancer and so on [4-9]. Moreover, RISI has been referenced in the National Comprehensive Cancer Network guidelines for the management of locally recurrent rectal cancer [10]. With computer tomography (CT)-guidance and 3-dimensional (3D)-printing non-coplanar templates (PNCT) assistance, the accuracy and efficacy of RISI have been greatly increased [8,11]. The purpose of this non-randomized multicenter retrospective study was to further clarify the safety and efficacy of 3D-PNCT assisted CT-guided RISI as a salvage treatment for patients with post-EBRT RCC. Moreover, we wished to explore the relationship between dose and outcome, and to help determine the appropriate prescription dose.

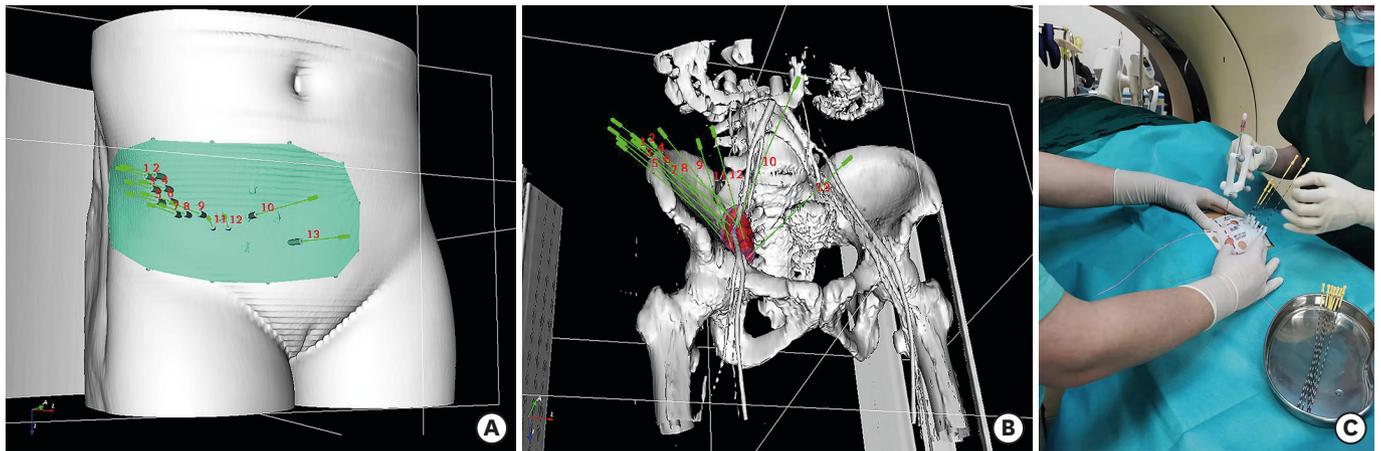
## MATERIALS AND METHODS

### 1. Patient eligibility

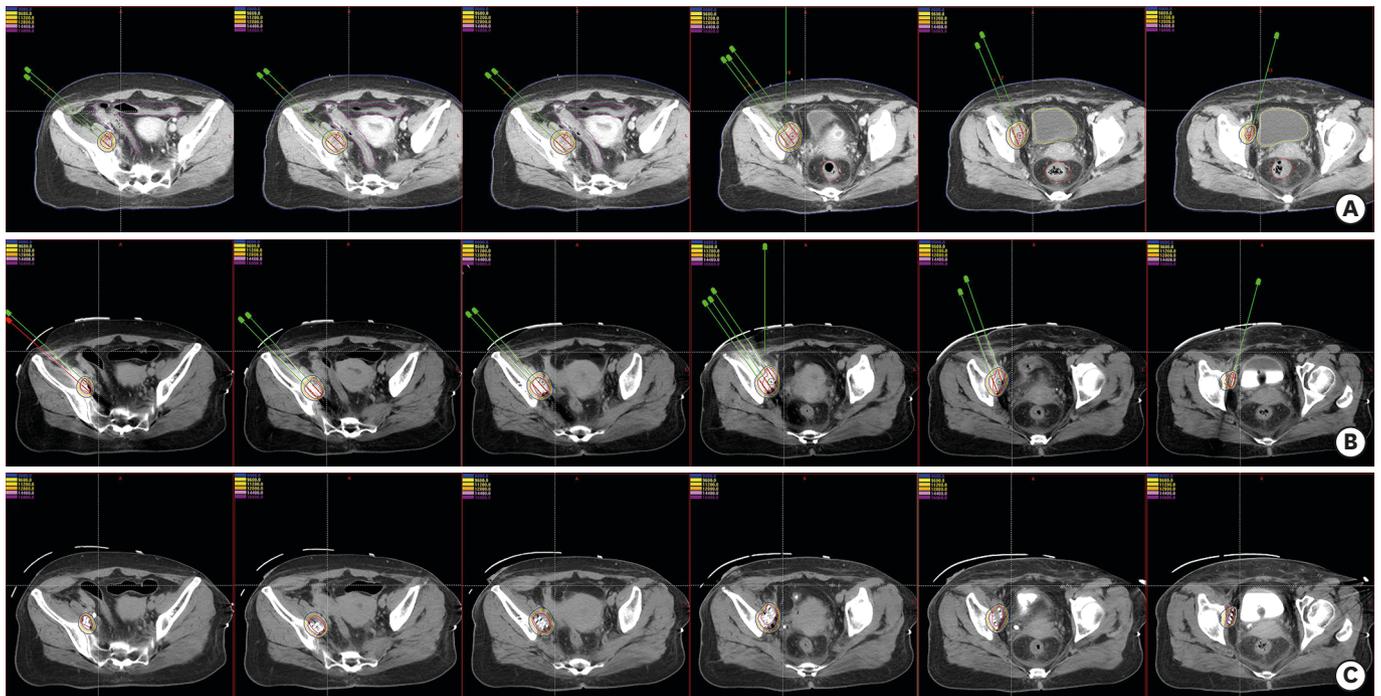
This retrospective study enrolled totally 103 patients with post-EBRT RCC from December 2015 to September 2019 in 2 hospitals with approval by the Institutional Review Boards (IRB00006761-M2019118). The written informed consent was signed by all patients. The inclusion criteria of RISI: ① a Karnofsky performance status (KPS) of  $\geq 70$ ; ② an expected survival of  $\geq 3$  months; ③ pathologically or radiologically confirmed RCC; ④ a tumor diameter of less than 7 cm, with no metastasis or no more than 2 unstable metastatic lesions; and ⑤ patients who refused surgery and/or EBRT or were unfit for surgery and/or EBRT. The exclusion criteria: ① severe disturbance to coagulation functions; ② tumor bleeding, necrosis and fistula formation; ③ unable to design a suitable needle path. All the patients received 3D-PNCT assisted CT-guided RISI.

### 2. Procedure

All patients selected for RISI received CT simulation (Brilliance, Philips Inc., Netherlands) with contrast and 5-mm slice thickness 2 days prior to RISI (**Supplementary Data 1** and **Supplementary Fig. 1**). The CT simulation image dataset was imported into a brachytherapy treatment planning system (BT-TPS, KLSIRPS-3D; Beijing Tianhang Kelin Technology Development Inc., Beijing, China) for pre-plan (**Figs. 1A, 1B, and 2A**), target volume and organ at risk (OAR) delineation. We set the prescribed dose to the gross tumor volume (GTV) and the activity of <sup>125</sup>I seeds. The median prescription dose was 120 Gy (range, 100–180 Gy). The BT-TPS simulated the distribution of needles and seeds, and calculated the dose distribution. The pre-plan dataset was used for digital modeling and printing of individualized 3D-PNCTs, which included the biologic surface characteristics of the seed



**Fig. 1.** (A, B) 3D-PNCT assisted RISI reconstruction visualization for RCC. (C) Implementation of RISI (another patient). 3D, 3-dimensional; PNCT, printing non-coplanar templates; RCC, recurrent cervical carcinoma; RISI, radioactive <sup>125</sup>I seed implantation.



**Fig. 2.** The pre-plan (A), real-time dose optimization (B) and post-plan (C). The prescription dose was 120 Gy, the GTV was 21.2 cm<sup>3</sup>, the number of seeds was 45, and the D<sub>90</sub> in pre-plan, real-time and post-plan was 160, 158, and 155 Gy, respectively. D<sub>90</sub>, the minimum dose received by the “hottest” 90% of the GTV; GTV, gross tumor volume.

implantation area, the X-axis and Y-axis laser lines, a registration mark, and information of the simulated needle path. RISI was carried out under local infiltration anesthesia or spinal anesthesia. After patient and 3D-PNCT re-set up, single-use needles were inserted into the target lesion under CT guidance (Figs. 1C, 2C, and Supplementary Data 2). A Mick applicator was used to implant seeds. After seed implantation, CT scan was performed again to check the distribution of actual <sup>125</sup>I seeds in the targets, and additional seeds would be implanted if the distribution of the <sup>125</sup>I seeds in the target volume was not satisfactory. The CT image dataset was transferred to the BT-TPS for post-planning dose evaluation (Fig. 2C). The patients were discharged 1–2 days after RISI. All procedures were performed by qualified

and well-trained personnel, and the safety measures by the International Commission on Radiological Protection were strictly followed.

### 3. The end-points and follow-up

The following dosimetry parameters were defined and recorded: the minimum dose received by the “hottest” 90% of the GTV ( $D_{90}$ ); the minimum dose received by the GTV ( $D_{100}$ ); percentage of the GTV receiving 100% ( $V_{100}$ ), 150% ( $V_{150}$ ), and 200% ( $V_{200}$ ) of prescription dose; and the external index, conformal index, and homogeneity index of the target area. External index described the volume exceeding the prescription dose outside GTV, and the greater the value of external index was, the greater the prescription dose received outside GTV. Conformal index described the conformity of dose distribution; the ideal conformal index was 1, which indicated that GTV was properly covered by the prescription dose, and the dose outside GTV was lower than prescription dose. Homogeneity index described the uniformity of dose distribution; the closer the homogeneity index was to 100%, the more uniform the dose distribution of GTV.

Follow-up assessments were performed at 3, 6, 9, and 12 months after RISI and every 6 months after one year. The assessments involved regular outpatient visits and telephone interviews. Diagnostic imaging with CT scans or magnetic resonance imaging (MRI) examinations was used to evaluate the tumor response for each post-operative visit.

The primary endpoints were adverse events and local control (LC), and the secondary endpoints were overall survival (OS) and progression-free survival (PFS). Local tumor response was evaluated by Response Evaluation Criteria in Solid Tumors (RECIST) after RISI. Pain intensity was assessed using a numerical rating scale categorized into 5 grades: 0, no pain; 1–3, mild pain; 4–6, moderate pain; 7–9, severe pain; and 10, unbearable pain. The pre-RISI and post-RISI pain scores were compared. Adverse events were graded according to the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) criteria.

### 4. Statistical analysis

Statistical analysis was performed using SPSS version 25.0 (SPSS, Chicago, IL, USA). If a patient underwent RISI for 2 different sites, each site was considered separately when the LC was analyzed. Receiver operating characteristic (ROC) analysis was used to identify the optimal cutoff values to divide patients into high-risk and low-risk groups. Kaplan-Meier survival analysis was used to estimate LC, OS and PFS; log-rank test was used for inter-group comparisons. Cox proportional hazards regression analysis was used to identify the factors independently influencing LC, OS and PFS. The factors identified in the multivariate analysis were used to plot nomograms by R-3.6.2 (Lucent Technologies Inc., New Providence, NJ, USA) for result visualization. The nomogram showed the importance of risk factors and could be used to predict LC. For a risk factor, the greater its point, the greater the impact on LC. Total point obtained by adding the points of all risk factors of a patient could be used to predict 1-year or 3-year LC. The results were expressed as a concordance index (C-index). The principle of C-index was to randomly pair all research samples in the study and evaluate the difference between the model predicted value and the true value. The range of C-index was 0.5–1, and the closer the value to 1, the higher the accuracy. The p-value  $\leq 0.05$  was considered statistically significant.

## RESULTS

During the last follow-up carried out in February 2020, the median follow-up time was 12 months (range, 2–43 months), while 48 patients were alive.

The median age was 52 years (range, 29–72 years) (**Table 1**). Ten patients with early cervical cancer (stages IA1 to IB1) at first visit received radical surgery with/without EBRT, brachytherapy (BT) or paclitaxel plus platinum chemotherapy (**Supplementary Fig. 2**). Ninety-one patients had locally advanced cervical cancer (stages IB2 to IVA) and 63 patients of them received an initial standard treatment of EBRT with concurrent paclitaxel plus platinum chemotherapy followed by intracavitary BT. Fourteen out of the 63 patients received salvage surgery after recurrence. The other 28 out of the 91 patients with locally advanced cervical cancer received surgery and EBRT, with/without paclitaxel plus platinum chemotherapy and BT. Two patients had late cervical cancer (stage IVB) received EBRT with concurrent paclitaxel plus platinum chemotherapy followed by BT. The median interval from the initial treatment to the recurrence was 11 months (range, 2–70 months). After initial treatment, 42 patients had multiple cervical cancer recurrences and had undergone surgery, radiation, or platinum-based chemotherapy. Before RISI, all patients had undergone pelvic EBRT, 9 patients had undergone re-EBRT, 52 patients had undergone surgery, and 95 patients had been given chemotherapy. Even if the total dose is the same during radiotherapy, different dose segmentation will lead to different biological effects. Therefore, we converted

**Table 1.** Clinical characteristics

Parameter	Value
Age (yr)	52 (29–72)
Histologic type	
Adenocarcinoma	16 (15.5)
SCC	87 (84.5)
FIGO stage at the first visit	
I	18 (17.5)
II	35 (34.0)
III	39 (37.8)
IV	11 (10.7)
Previous therapy	
Surgery	52 (50.5)
Chemotherapy	95 (92.2)
Radiation therapy	103 (100)
Cumulative dose at the implantation site EQD2 (Gy)	64 (36–138)
Interval from initial treatment to recurrence (mo)	11 (2–70)
Symptoms	
Pain	77 (74.8)
Limb/nerve compression	46 (44.7)
Hydronephrosis	45 (43.7)
KPS at diagnosis	80 (70–100)
Hemoglobin (g/L)	101 (64–146)
Site of seeds implantation	
Central pelvic	8 (7.2)
Lateral pelvic	75 (67.6)
Extra-pelvic	28 (25.2)
GTV (cm <sup>3</sup> )	37.7 (2.6–237.8)
Prescription dose (Gy)	120 (100–180)
GTV D <sub>90</sub> (Gy)	138.3 (33.4–290.7)

Values are expressed as median (range) or number (%).

D<sub>90</sub>, the minimum dose received by the “hottest” 90% of the GTV; EQD2, equivalent dose in 2 Gy/f; FIGO, International Federation of Gynecology and Obstetrics; GTV, gross tumor volume; KPS, Karnofsky performance status; PFS, progression-free survival; SCC, squamous cell carcinoma.

the doses that received by targets into equivalent dose (EQD). The median cumulative equivalent dose in 2 Gy/f (EQD2) at the implantation sites before RISI was 64 Gy (range, 36–138 Gy). The median KPS was 80 (range, 70–100). In 103 patients, a total of 111 lesions were successfully treated by RISI. The lesions were at the pelvic center in 8 patients, and at the pelvic lateral region in 75 patients, and 28 patients had pelvic lesions with extra-pelvic metastasis. The median lesion volume was 37.7 cm<sup>3</sup> (range, 2.6–237.8 cm<sup>3</sup>). The median activity of <sup>125</sup>I seeds was 0.6 mCi (range, 0.4–0.8 mCi), and the median number of <sup>125</sup>I seeds was 63 (range, 8–186).

### 1. Adverse events

Two of the 103 patients (1.9%) suffered from intensified pain and recovered 1 week later. Seed migration occurred in one patient. Four patients suffered from grade 2 adverse events: 1 of acute nausea, 2 of diarrhea, and 1 of pollakiuria. One patient suffered from grade 3 acute proctitis. Late toxicity in this study was rare and only two patients suffered from rectovaginal fistula, and no grade 5 late toxicity occurred (**Table 2**). The toxicity prevalence was low in this study, so the factors that might be related to toxicity could not be evaluated.

### 2. Outcomes

A total of 111 lesions in 103 patients were treated by RISI. Complete response (CR) was achieved in 15/111 (13.5%) lesions and partial response (PR) was achieved in 65/111 (58.6%) lesions. Stable disease (SD) was seen in 30/111 (27.0%) lesions and progressive disease (PD) was found in 1/111 (0.9%) lesion. The overall local control rate was 99.1% (110/111 lesions of CR, PR, or SD). The 1- and 3-year LC was 87.4% (95% confidence interval [CI]=80.9%–93.4%) and 75.1% (95% CI=65.1%–85.1%), respectively. The median OS was 17 months (95% CI=14.5–19.5 months); the 1- and 3-year OS was 68.1% (95% CI=58.5%–77.7%) and 20.8% (95% CI=9.4%–32.6%), respectively. The median PFS was 14 months (95% CI=12.2–15.8 months); the 1- and 3-year PFS was 56.1% (95% CI=46.1%–66.1%) and 17.2% (95% CI, 5.8%–28.9%), respectively (**Fig. 3A**).

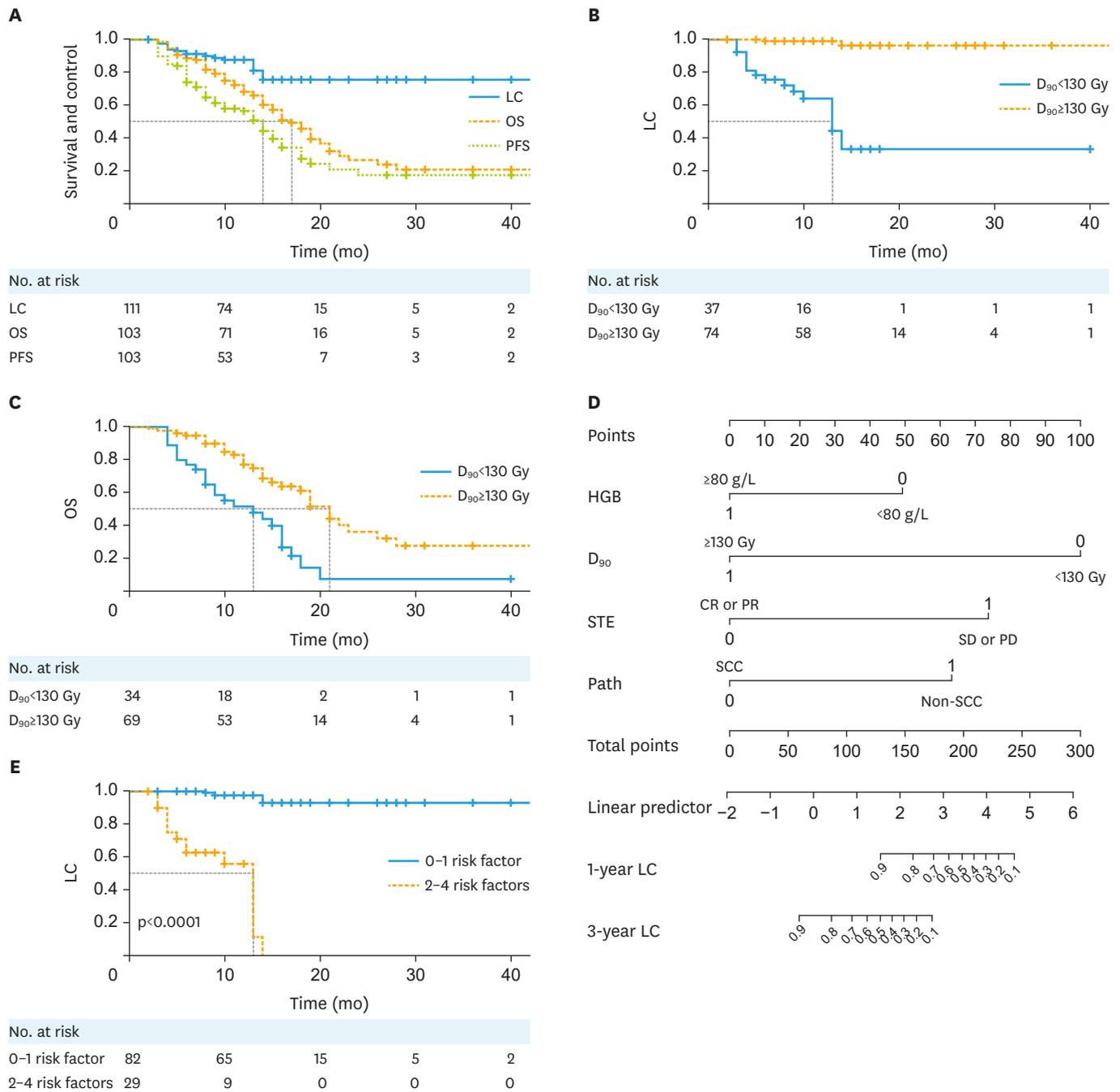
**Table 2.** Side effects possibly, probably, or definitely related to radioactive <sup>125</sup>I seeds implantation\*

Adverse effects	Grade		
	1	2	3
<b>Early radiation-related side effects</b>			
Dermatitis	4 (3.8)	0	0
Nausea	9 (8.6)	1 (1.0)	0
Diarrhea <sup>†</sup>	7 (6.7)	2 (1.9)	1 (1.0)
Pollakiuria	8 (7.6)	1 (1.0)	0
<b>Late radiation-related side effects</b>			
Dermatitis	0	0	0
Nausea	0	0	0
Diarrhea	1 (1.0)	0	0
Pollakiuria	1 (1.0)	0	0
<b>Puncture-related side effects</b>			
Bleeding		0	
Increased pain		2 (1.9)	
Implantation metastasis		0	
<b>Other</b>			
Radiation-related nerve injury		0	
Migration of radioactive seeds		1 (1.0)	

Values are expressed as number (%).

\*No patient had grade 4 or 5 side effects, except as noted; <sup>†</sup>Two patients (1.9%) had rectovaginal fistula, which is a grade 4 side effects.

**I-125 seed for recurrent cervical cancer**



**Fig. 3.** (A) LC, OS, and PFS. (B) LC in patients with different  $D_{90}$ . (C) OS in patients with different  $D_{90}$ . (D) Nomogram for predicting the chance of local control after RISI. (E) LC in patients with different stratifications of risk factors. CR, complete response;  $D_{90}$ , the minimum dose received by the “hottest” 90% of the GTV; GTV, gross tumor volume; HGB, hemoglobin; LC, local control; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RISI, radioactive  $^{125}\text{I}$  seed implantation; SCC, squamous cell carcinoma; SD, stable disease; STE, short-term efficacy.

Prior to RISI, 77/103 (74.8%) patients suffered from pain caused by the tumors, with 19/77 (24.7%) patients of severe pain, 44/77 (57.1%) of moderate pain, and 14/77 (18.2%) of mild pain. After RISI, 64/77 (79.2%) patients experienced partial or complete pain relief.

**Table 3.** Univariate and multivariate analysis of factors associated with local control

Factor	Group	No.	1 yr (%)	3 yr (%)	Univariate analysis			Multivariate analysis		
					$\chi^2$	HR	p	HR	95% CI	p
Age (yr)	<60	92	89.3	76.1	0.95	1.70	0.306	-	-	-
	≥60	19	76.7	68.2						
KPS	<90	56	78.6	65.3	6.18	0.30	0.021	0.59	0.16–2.19	0.429
	≥90	55	96.4	85.2						
Pathologic type	SCC	95	92.9	83.1	19.68	9.68	<0.001	5.00	1.68–14.93	0.004
	Other	16	52.5	17.5						
Prescription dose (Gy)	<60	55	86.5	74.2	0.12	0.86	0.735	-	-	-
	≥60	56	88.0	75.4						
PFS after previous therapy (mo)	<12	60	88.0	80.0	0.82	1.51	0.370	-	-	-
	≥12	51	86.2	70.8						
Hemoglobin (g/L)	<80	20	65.4	65.4	7.70	0.20	0.002	0.26	0.07–0.91	0.035
	≥80	91	91.7	78.7						
Implantation site	Pelvic	83	86.2	71.4	1.77	0.41	0.237	-	-	-
	Other	28	92.4	92.4						
GTV (mL)	<55	76	94.1	86.7	12.99	5.25	<0.001	0.64	0.14–2.81	0.551
	≥55	35	73.1	46.5						
D <sub>90</sub> (Gy)	<130	37	63.8	33.1	36.10	0.04	<0.001	0.06	0.01–0.30	0.001
	≥130	74	98.6	95.8						
STE	CR + PR	80	97.0	92.2	34.50	17.92	<0.001	5.97	1.48–24.12	0.012
	SD + PD	31	61.8	23.2						

CI, confidence interval; CR, complete response; D<sub>90</sub>, the minimum dose received by the “hottest” 90% of the GTV; GTV, gross tumor volume; HR, hazard ratio; KPS, Karnofsky performance status; PD, progressive disease; PR, partial response; SCC, squamous cell carcinoma; SD, stable disease; STE, short-term efficacy.

### 3. Prognostic factors

In the univariate analysis, the factors of KPS ≥90, squamous cell carcinoma, hemoglobin ≥80 g/L, GTV <55 cm<sup>3</sup>, D<sub>90</sub> ≥130 Gy and good short-term efficacy (STE; CR or PR was defined as good STE, SD or PD was defined as bad STE) were significantly associated with higher LC (Table 3) and OS (Supplementary Table 1) (all p<0.05). Compared to extra-pelvic recurrence, pelvic recurrence was associated with a better OS. In the multivariate analysis, the factors independently associated with the LC were pathologic type, hemoglobin levels, D<sub>90</sub>, and STE (all p<0.05). The factors independently associated with the OS were pathologic type, hemoglobin levels, implantation sites, D<sub>90</sub>, and STE (all p<0.05). For both LC and OS rates, the ROC analysis showed that D<sub>90</sub> of 130 Gy was the optimum cutoff value for identifying patients with a high risk of local failure and short survival. The Kaplan-Meier analysis showed that the patients with D<sub>90</sub> ≥130 Gy had better LC and OS than others (Fig. 3B and C).

A nomogram was created using the above 4 factors independently associated with LC (Fig. 3D) for visualization. The C-index (per internal validation) was 0.945 (95% CI=0.912–0.978), indicating that the predicted value was consistent with the actual value. Significant differences in the prognosis were observed between patients with risk factors of 0 or 1 and patients with risk factors of 2 to 4 (p<0.001). The 3-year LC and OS rates of the patients with risk factors of 0 or 1 were 92.7% and 28.1%, respectively, whereas both the 3-year LC and OS rates of patients with risk factors of 2 to 4 were zero (Fig. 3E).

## DISCUSSION

The standard management for patients with early-stage cervical cancer is surgery and/or EBRT with or without chemotherapy [12]. EBRT alone and/or combined with concurrent cisplatin-based chemotherapy with BT is the first line option for patients with locally advanced cervical cancer [13]. Locoregional recurrence or local control failure occurs in

15%–61% of cervical cancer patients after radical surgery or EBRT plus chemotherapy [1,2]. Surgery or EBRT may be curative for some patients with locally recurrence or limited metastatic diseases, whereas most patients cannot be cured by surgery or EBRT [2]. The 5-year OS rate of patients with recurrent cervical carcinoma is only 3.2%–16.5% [14-16].

For patients with post-EBRT RCC, re-EBRT is associated with a high risk of toxicity to the intestine, rectum and bladder, and the morbidity of grade 3 or 4 side effects is up to 15.6%–56% [13,17]. Other possible salvage treatment modalities are surgery, High-dose rate (HDR)-BT, stereotactic body radiotherapy (SBRT), low-dose rate (LDR)-BT and chemotherapy. The management of RCC depends mainly on previous therapeutic approaches as well as the site and extent of recurrence [18]. RCC is classified into pelvic central, pelvic lateral or/and extra-pelvic RCC [19,20].

Patients with pelvic central recurrence without pelvic wall invasion or distant metastasis after EBRT were suitable candidates for pelvic exenteration. The 5-year OS rate and operative mortality were 20%–60% and 0%–12%, respectively [21,22]. Meanwhile, positive margin was indicated in half of the patients after surgery. The recurrence rate of these patients is up to 13%–64% [23,24]. Therefore, the use of pelvic exenteration has been declining due to its limited indications.

The HDR-BT technique was introduced to treat pelvic central RCC due to its advantages of good conformity and short treatment. All published reports used small sample sizes, while the rate of >grade 2 adverse events was 25%–55% [25-28]. Therefore, the efficacy and safety of HDR-BT need further investigations to evaluate and clarify the indications and dose restriction for OARs.

The prognosis of patients with pelvic lateral recurrence after EBRT was poor due to lack of standard treatments [20]. Laterally extended endopelvic resection (LEER) with or without intraoperative RT was reported to treat post-EBRT RCC. The 5-year OS rate was 42%–58%, and the morbidity of severe intestinal or neurological side effects was up to 25%–50%. The life quality of patients after LEER was very unfavorable [22,29,30].

As an emerging technique, SBRT had the advantages of good conformity and short treatment, which is suitable to treat tumors with a diameter of less than 3 cm. SBRT was reported to treat pelvic lateral RCC with the 2-year LC rate of 43-57.5%. The morbidity of severe effects was 8.5%–17.6% [31,32]. All published reports were retrospective studies of small sample sizes. Therefore, to clarify the efficacy and safety of SBRT, it remains to further improve the patient selection and dose restriction in OARs.

Chemotherapy of cis-platinum combined with other drugs was an option for RCC, the response rate was 36%–59.9%, with a median OS of 9.6–12.9 months [2,16,33]. Some reports suggested that platinum-based chemotherapy combined with bevacizumab significantly extended the median OS to 17 months [4].

RISI is a kind of LDR-BT using a sealed radiation source directly placed into the tumor or around the tumor. The implantation of radioactive seeds is permanent, and only one operation is needed. The advantages of RISI: ① it is a minimally invasive procedure and can continuously deliver ablation doses to tumor targets at a LDR; ② the implantation is precise and efficient under image-guidance as well as template assistance; and ③ the operation

often lasts one hour and the patients can return to their normal life within one day. RISI has been used for the treatment of various solid tumors, especially as a salvage treatment for recurrent cancers after EBRT [6,8,34,35]. Compared with surgery, RISI has more indications with the advantages of protecting normal tissues and less side effects. Compared with other RT techniques, RISI is able to deliver a higher dose to the tumor site while sparing normal tissues. Therefore, RISI is suitable for treating post-EBRT RCC.

The CT guidance for RISI has been put into clinical practice in 2002 in China. The indications of RISI have been expanded from prostate carcinoma to head and neck, thoracic, abdomen, retroperitoneal, and spinal cord carcinomas [4,36]. The effect of CT-guided RISI depends on the experience and expertise of physicians performing the procedure. Therefore, it is hard to repeat and evaluate the efficacy and safety of CT-guided RISI. Qu et al. [4] used CT-guided RISI to treat 36 patients with post-EBRT RCC, the 1-year OS rate was 52% and the median OS was 11.5 months. The optimal  $D_{90}$  should be more than 105 Gy. The disadvantages of CT-guided RISI are that the distribution quality of seed implantation doses cannot be assured as a pre-plan design parameter under the free-hand CT-guided procedure due to the interferences to the OARs, such as blood vessels, bones, and nerves.

3D-PNCT assisted CT-guided technique has been integrated into RISI in 2015. The accuracy and efficacy of seed implantation have been greatly increased [13,37,38]. This not only significantly improved the safety and effect of RISI, but also made the treatment less dependent on the skills and experience of individual operators. Therefore, the combination of CT-guided and 3D-PNCT made RISI more evaluable and repeatable. 3D-PNCT assisted CT-guided RISI was easy to operate and popularize, and its cost was lower than that of EBRT. With the assistance of 3D-PNCT, physicians can accomplish RISI treatment independently after a 3- to 6-month standardized training. Previously, Ji et al. [37] reported that 3D-PNCT assisted CT-guided RISI could enable the post-plan dose to meet the requirements of the pre-plan. Based on such quality assurance, we could give a specific dose to tumors to analyze the safety and efficacy of RISI in the treatment of cervical cancer.

The patients included in this study mainly had pelvic lateral RCC. The preliminary results indicated that RISI was more suitable for treating pelvic lateral recurrence, while surgery or HDR-BT was the first choice for pelvic central recurrence [4]. Therefore, in this study, the patients with pelvic central recurrence were all deemed unsuitable for further surgery and HDR-BT.

There was no dose escalation clinical trial which had been conducted in RISI for pelvic RCC. Thus, we determined the prescription dose by referring to the dose selection of RISI for prostate cancer. The acceptable dose range for postimplant  $D_{90}$  for RISI for prostate cancer may be 130–180 Gy [39]. Since prostate cancer grew slowly and was less sensitive to radiotherapy than cervical cancer, we set the prescribed dose of 120 Gy for most patients. There existed two special circumstances: 1) the lesions of some patients invaded the OARs, making it difficult to limit the dose received by the OARs, thus, we would reduce the prescribed dose to 100 or 110 Gy to protect the OARs; 2) the lesions of some patients were small and far away from the OARs, making it possible to deliver relatively high doses to targets, thus, we would increase the prescribed dose to 140–180 Gy in order to achieve better tumor control efficacy.

We limited the doses received by OARs by referring to the OARs dose limitation of RISI for prostate cancer. The OARs in RISI for prostate cancer mainly included the rectum

and urethra. American Brachytherapy Society suggested a peripheral distribution of sources, frequently referred to as a “modified peripheral or modified uniform loading” is recommended so that the portion of the urethra receiving 150% dose or greater can be limited [39]. The volume of the rectum receiving the prescription dose ideally should be <1 mL [39]. Wallner et al. [40] suggested the volume of the rectum receiving 100 Gy ideally should be <1 mL. The OARs in RISI for pelvic RCC mainly included the small intestine, rectum, and bladder. All the patients in this study had undergone pelvic EBRT before RISI, and most of them had undergone intracavitary brachytherapy. Therefore, the OARs dose limitation in this study was stricter than the limitation in RISI for prostate cancer. In this study, the OARs dose limitation was the maximum dose received by the small intestine, rectum, and bladder, which should be <50, 70, and 80 Gy, respectively. In this study, most of the lesions were lateral pelvic recurrence and far away from the OARs. Thus, in most cases, it was easy to deliver high dose to targets while meeting the OARs dose limitation. For some lesions which were close to the OARs, we referred to the urethral protection method in RISI for prostate cancer. The distances between the seeds and the OARs should be >1 cm, and the targets were covered by the edges of the seeds' influence areas. This method might result in high  $V_{150}$  and  $V_{200}$ , but it could effectively reduce the doses received by the OARs. If the doses received by the OARs still exceeded the limitation, the treatment plans would be fully discussed and evaluated according to the patients' specific situations on case-by-case basis. In general, OARs dose limitation might be appropriately loosed if a radical cure is possible; however, if palliative care could be achieved only, the dose delivered to the target might be reduced to protect the OARs.

In this study, the LC rates were 87.4% at 1 year and 75.1% at 3 years, which were higher than those reported in previous studies. However, the OS and PFS rates in this study were lower because the failure pattern in most patients was distant metastasis. Twenty-eight patients with extra-pelvic recurrence had a worse median OS than others (10 vs. 18 months). Isolated lesions were identified and targeted in these patients, but undetected potential distant metastases might still exist. The indication selections, the optimal prescription dose, and the target regions of CTV for 3D-PNCT assisted CT-guided RISI remain ambiguous. Based on the safety and efficacy consideration, some patients with advanced or late stage RCC were included in this study and influenced the outcomes.

3D-PNCT assisted CT-guided RISI is safe to treat patients with post-EBRT RCC. Two patients suffered from intensified pain, one patient had seed immigration, and four patients suffered from grade 2 acute toxicity. One patient whose  $D_{90}$  was 133.8 Gy suffered from grade 3 acute proctitis and soon recovered with no treatment. Only two patients, whose  $D_{90}$  was 146.2 and 175.9 Gy, respectively, suffered from late toxicities of rectovaginal fistula and received salvage surgery. One died 14 months after RISI due to disease progression and the other one is still alive. No grade 5 late toxicities occurred.

In this study, the LC rate was higher in patients of squamous cell cancer than that in patients of non-squamous cell carcinoma, although further investigations are needed to clarify the mechanisms. High doses of RISI were associated with a better LC and favorable outcomes. The LC rate was higher in patients with a  $D_{90}$  of  $\geq 130$  Gy than that in patients with a  $D_{90}$  of <130 Gy, and the result was consistent with the cutoff value identified by the ROC analysis, providing an important reference for selecting the prescription dose and designing future dose escalation regimens. Squamous cell pathology,  $D_{90}$  values of  $\geq 130$  Gy, and CR/PR were all associated with a better OS because a good LC was more likely to translate into a survival benefit. Patients

with pelvic recurrence had a longer OS than those with extra-pelvic recurrence, which was consistent with previous clinical reports. A hemoglobin level of <80 g/L was associated with unfavorable prognosis, which might be due to the poor general conditions of these patients. Age was not associated with the prognosis in this study, which might be attributed to the fact that most of the patients had experienced multiple recurrences and their life expectancy was short. GTV was significantly associated with LC in the univariate analysis but was not significantly associated with LC in the multivariate analysis, which was different from the results of other reports and might be due to the fact that 3D-PNCT assisted CT-guided RISI is more accurate than other RT techniques and is able to deliver a higher dose to the tumor, thereby improving the outcomes of patients with a large tumor. There was no significant difference in the prognosis between patients with central and lateral pelvic recurrence, which was different from the results of previous studies. This might be attributed to the small sample size of patients with central pelvic recurrence in this study and the selection bias, because only patients who were unsuitable for surgery and HDR-BT were treated by RISI.

In conclusion, 3D-PNCT assisted CT-guided RISI is a safe, effective, and minimally invasive option for RCC. The hemoglobin level, pathological type and dose distribution are considered as independent factors for clinical outcomes. Large cohort prospective studies are needed to further clarify the efficacy, safety, and technical standards.

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## SUPPLEMENTARY MATERIALS

### Supplementary Data 1

Preparation before radioactive <sup>125</sup>I seed implantation (RISI)

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### Supplementary Data 2

The work-follow of radioactive <sup>125</sup>I seed implantation (RISI)

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### Supplementary Table 1

Univariate and multivariate analysis of factors associated with overall survival

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### Supplementary Fig. 1

Work-flow of 3D-PNCT assisted CT-guided RISI.

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## Supplementary Fig. 2

(A) FIGO stages at first visit of the patients. (B) Initial treatment of patients with early cervical cancer. (C) Initial treatment of patients with locally advanced cervical cancer.

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