

Accuracy and dosimetric parameters comparison of 3D-printed non-coplanar template-assisted computed tomography-guided iodine-125 seed ablative brachytherapy in pelvic lateral recurrence of gynecological carcinomas

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Abstract

Purpose: To investigate the accuracy of needle distribution and dosimetric parameter differences of 3D-printing non-coplanar template (3D-PNCT)-assisted computed tomography (CT)-guided iodine-125 seed ablative brachytherapy (¹²⁵I-SAB) in gynecological cancer patients with non-central pelvic recurrence between pre-operative plan and post-operative plan.

Material and methods: Thirty-eight patients with forty-one non-central pelvic recurrent gynecological carcinomas after radiotherapy were enrolled in this study. All patients received 3D-PNCT-assisted CT-guided ¹²⁵I-SAB from January 2016 to January 2019. The position, angle, and depth of seed needles were measured in both pre-operative plan and intra-operative real-time plan in brachytherapy treatment planning system (B-TPS). Dosimetric parameters of D₉₀, D₁₀₀, V₁₀₀, V₁₅₀, and V₂₀₀ as well as quality parameters of conformal index (CI), external index (EI), and homogeneity index (HI) were compared between pre-operative plan and post-operative plan. Peri-operation complications and radiation-related toxicity were assessed.

Results: Median follow-up time was 12 months (range, 5-34 months). Prescribed dose was 100-170 Gy (median, 120 Gy). Radioactivity of ¹²⁵I seed was 0.4-0.7 mCi (median, 0.55 mCi). Mean depth deviation for 499 needles was 0.8 ± 1.0 cm. Mean angular deviation was 2.2 ± 2.1 degrees. Mean tip distance deviation of needles was 0.4 ± 0.3 cm. There were significant differences between pre-operative and post-operative plans in CI ($p = 0.001$) and EI ($p = 0.005$). No significant differences were shown in D₉₀, D₁₀₀, V₁₀₀, V₁₅₀, V₂₀₀, and HI between pre-operative and post-operative plans. Only few patients suffered from ≤ grade 2 toxicities.

Conclusions: 3D-PNCT-assisted CT-guided ¹²⁵I-SAB is safe and feasible for non-central pelvic recurrence of gynecological cancer. All complications are tolerable and mild.

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Key words: interstitial permanent brachytherapy, gynecological carcinoma, 3D printing template, iodine-125.

Purpose

High rates of morbidity and mortality associated with gynecological cancer concern all females in the world [1], with cervical cancer as the most common genital carcinoma in women. Concurrent chemoradiotherapy is the standard treatment for patients with locally advanced cervical carcinomas. According to the International Federation of Gynecology and Obstetrics (FIGO), the relapse rate of cervical cancer ranges from 11% to 22% stage IB-IIA

and 28% to 64% in FIGO stage IIB-IVA [2]. Pelvic recurrences of gynecological cancer are classified into central and non-central types. The prognosis in non-central pelvic recurrent gynecological cancer patients is very poor, with a 5-year overall survival below 10%. Also, no acceptable curative optional modality is presently available [3,4,5,6]. Pelvic exenteration is considered for selected patients with central recurrence, but high-risk complications are unavoidable [7,8]. Although re-irradiation is an alternative option, it is hard to deliver enough doses

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to lesions previously treated with radiotherapy [9,10]. In addition, chemotherapy is mostly applied as palliative treatment [11,12].

Iodine-125 seed ablative brachytherapy (^{125}I -SAB) is a minimally invasive modality, which allows high-dose delivery to the target and low-dose distribution to surrounding normal tissues [13,14]. Computed tomography (CT)-guided ^{125}I -SAB is successfully applied as re-irradiation in tumors located at different sites, such as head and neck, thorax, abdomen, retroperitoneum, and vertebra [15,16,17,18]. Indications for ^{125}I -SAB are being rapidly expanded, especially for recurrent solid carcinomas after external beam radiotherapy (EBRT). However, the deviation of needles puncture under CT-guidance is inevitable, and it is very difficult to keep the conformity of target doses as pre-operative plan designed pattern, since it involves the experience of operator, interference of organs at risk, and organ movements.

3D-printing non-co-planar template (3D-PNCT) was invented and integrated into CT guidance for ^{125}I -SAB in our institution. The safety, accuracy, and feasibility of 3D-PNCT application in various tumors and locations has been explored [19,20,21,22]. In this retrospective study, we analyzed the accuracy of needle position between pre-operative plan and intra-operative plan as well as the dosimetric parameters of 3D-PNCT-assisted CT-guidance ^{125}I -SAB between pre-operative plan, intra-operative plan, and post-operative plan in gynecological cancer patients with a non-central pelvic recurrence.

Material and methods

Indications for selection and ^{125}I -SAB preparation

Thirty-eight patients with non-central pelvic recurrent cervical carcinomas treated with ^{125}I -SAB between January 2016 and January 2019 were enrolled into the study (Table 1). Inclusion criteria were as follows: 1. Karnofsky performance status (KPS) score ≥ 70 and expected survival ≥ 3 months; 2. Pathologically or radiologically confirmed diagnosis; 3. Diameter of the tumor ≤ 5 cm, recurrent location in lateral region of the pelvic;

4. The number of metastasis \leq three; 5. Non-candidate for surgery or unresectable tumor, or refused to EBRT. Exclusion criteria involved: 1. Severe organ dysfunction; 2. Coagulation dysfunctions; 3. Recent use of anticoagulant and infection; 4. Mental illness; 5. Tumor-invaded vagina, rectum, or bladder. The study protocol was approved by the Ethics Committee of Peking University Third Hospital (BMU2017JC001-3). All participated patients provided a written informed consent.

The selected patients were immobilized with vacuum pad in supine position or prone position, and underwent CT simulation. Both native and contrast CT scan was performed with 5 mm slice thickness. Co-ordinate positioning lines were marked on the skin of patient. CT images were transferred into a brachytherapy treatment planning system (B-TPS, brachytherapy treatment planning system provided by the Beijing University of Aeronautics and Astronautics, and Beijing Astro Technology Co., Ltd., China). Both target and OARs were defined and delineated. The prescribed dose and activity of ^{125}I seeds were determined. The implantation needle path and distribution of ^{125}I seeds were set and calculated. Doses received by 90% of gross tumor volume (GTV) (GTV D_{90}) were supposed to be as close to the prescription doses (PD) as possible, whereas doses received by organs at risk (OARs) were kept as low as possible. The median PD was 120 Gy (range, 110-170 Gy), the activity of ^{125}I seeds (^{125}I seed model 6711-99; length 4.5 mm, diameter 0.8 mm, half-life 59.4 days; Beijing Atom High Tech Pharmaceutical Company Inc., China) were 0.4-0.7 mCi, with median 0.55 mCi (1 Ci = 3.7×10^{10} Bq).

3D-PNCT design and production

The seed needle distribution in the target was designed in B-TPS pre-operative plan, and kept in parallel way if possible. In the meanwhile, OARs, such as blood vessels, bone, and nerves, were avoided or kept away from needles pathways, with a safety distance of 0.5-1.0 cm.

The B-TPS datasets were transferred into Magics 19.01 (Materialise, Belgium) for digital modeling of 3D individualized template. Information about the needle pathway was added to the model. The individual template was printed on a 3D light-cured rapid forming printer (RS6000, Shanghai Liantaiv 3D Technology Company Inc., China). The individual template included body surface morphology of treated area, X-axis, and Y-axis coordinate registered marks and the simulated needle path information. Two or three fixation needles were used to make sure that the 3D-PNCT was aligned with patient body (Figure 1).

Workflow of ^{125}I -SAB

The ^{125}I -SAB procedure was as follows: 1. Spinal anesthesia was carried out. Patients were immobilized with vacuum pad on a setup position. The 3D-PNCT was aligned to the patient body by X-axis and Y-axis positioning reference lines. Two or three fixation needles were inserted into the patient's body, 2-3 cm in depth; 2. CT scan was performed to determine the accurate position of

Table 1. General information ($n = 38$)

	Numbers	Percentage (%)
Age (years), range (median)	33-72 (49)	
Primary tumor		
Cervical cancer	34	89.5
Endometrial cancer	4	10.5
Pathology		
Squamous cell carcinoma	31	81.5
Adenocarcinoma	7	18.4
Previous therapy		
Surgery	24	63.2
Chemotherapy	35	92.1
Radiotherapy	38	100.0
Median dose (Gy)	50 (42-90)	

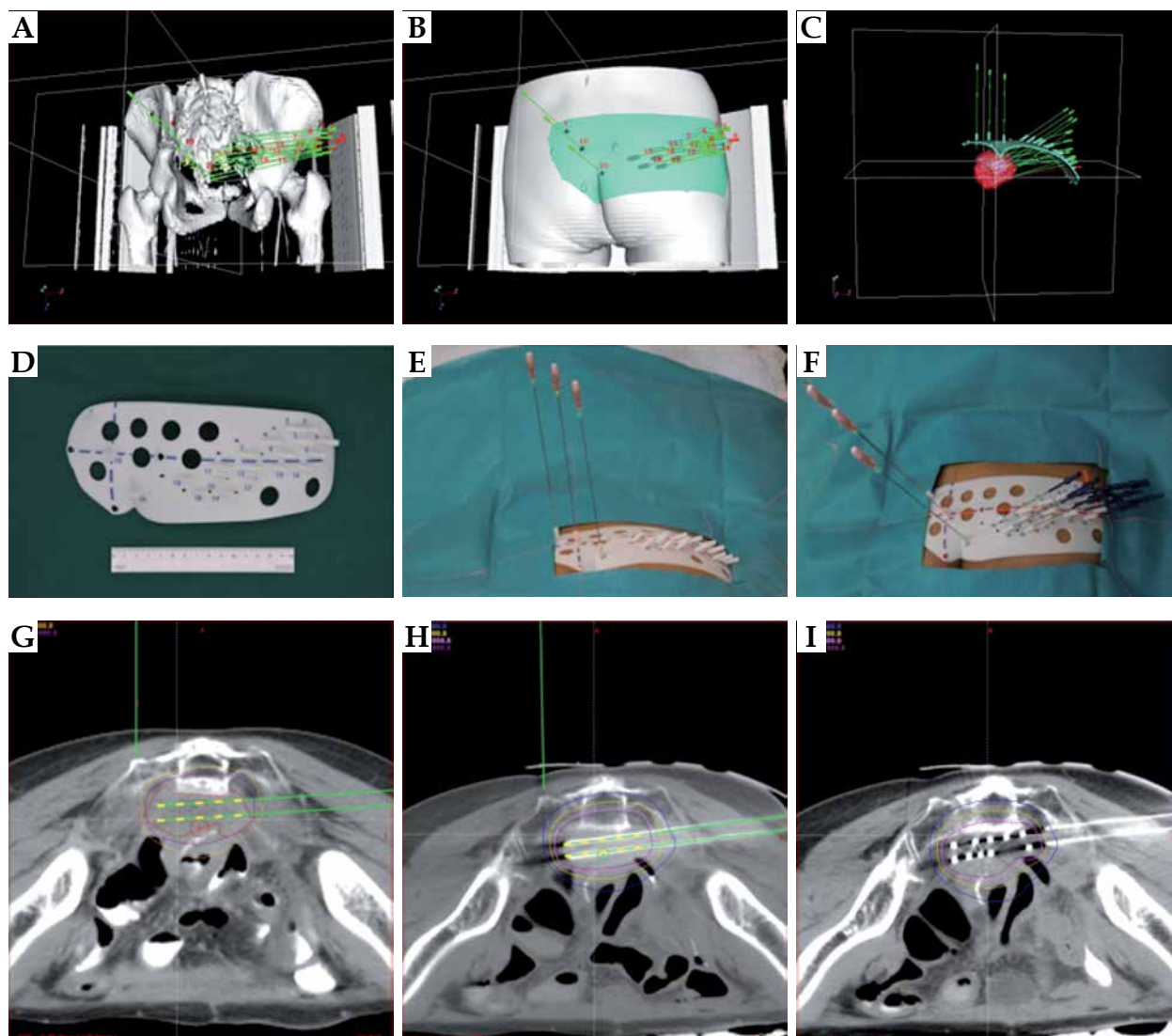


Fig. 1. Procedure of the 3D-PNCT-assisted CT guidance ¹²⁵I SAB. **A)** Simulation of needles and template distribution based on pre-operative CT images, **B)** 3D reconstruction of needles and 3D-PNCT, **C)** 3D reconstruction of needles, **D)** 3D-PNCT, **E)** stable needles insertion, **F)** seed needles insertion, **G)** CT image of pre-operative planning, **H)** intra-operative needles distribution, **I)** seed distribution into the target

fixation needles according to the designed pre-operative plan; 3. If the fixation needles position was mismatched between real-time images and pre-operative plan images with a deviation of more than 2 mm, it was finely adjusted; 4. The needles were all inserted into the targets; 5. CT scan was performed again to confirm the position of needle tips, if the deviation was more than 2 mm, a fine adjustment was made; 6. Another CT scan was performed to verify the position of the implantation needle compared with pre-operative plan, and intra-operation real-time doses optimization was performed; 7. ¹²⁵I seed implantation was delivered with an applicator (Mick 200-TPV, Mick Radio-Nuclear Inc., USA); 8. CT scan was performed again to confirm the actual distribution of ¹²⁵I seeds within the targets. All CT images were transferred into the B-TPS for doses evaluation of post-operative plan. Patients would be discharged 1-2 days after ¹²⁵I-SAB procedures.

Post-operative plan doses evaluation

The dose parameters comparison included the dose delivered to 90% (D_{90}) and 100% (D_{100}) of GTV, and volume percentage of GTV receiving 100% (V_{100}), 150% (V_{150}), and 200% (V_{200}) of PD between pre-operative and post-operative plans. The quality of targets doses distribution was represented by external index (EI), conformal index (CI), and homogeneity index (HI) of targeted volumes between pre-operative plan and post-operative plan. The CI of doses distribution in targets was evaluated by CI [23]. $CI = (VT_{ref}/VT) \times (VT_{ref}/V_{ref})$, where VT is the volume of GTV in ml, VT_{ref} is the volume of GTV receiving the PD, and V_{ref} is the total volume receiving the PD. The best CI was 1, which indicated that GTV was just covered by the PD and the dose outside GTV was lower than the PD. The volume exceeding the PD outside GTV was described by EI [24]. $EI = (V_{ref} - VT_{ref})/VT$.

The greater the value of the EI, the greater the recommended dosage received outside GTV. The uniformity of dose distribution was evaluated by HI [24]. $HI = (VT_{ref} - VT_{1.5ref}) / VT_{ref}$, where $VT_{1.5ref}$ was the volume of GTV, in which the dose exceeded 1.5 times of the PD. The closer to 100% of HI, the more uniform dose distribution of GTV.

Follow-up and examinations

Follow-up assessments were performed every 3 months for the first 2 years, and every 6 months from 3rd to 5th year. The assessments involved routine outpatient examination and telephone interviews. The imaging examination of CT or magnetic resonance imaging (MRI) scans, even positron emission tomography (PET)-CT scans, were used to evaluate the tumor response for each follow-up visit.

The primary end-points of the study were as follows: 1. The accurate assess of needles distribution between pre-operative plan and intra-operative plan, the dosimetric parameters, such as D_{90} , D_{100} , V_{100} , V_{150} , and V_{200} between pre-operative and post-operative plans. The quality parameters, such as CI, HI, and EI between pre-operative and post-operative plans; 2. The puncture-related peri-operation complications, such as bleeding, infection, fever, and pain was assessed using CTCAE 5.0 [25].

Statistical analysis

Statistical analysis was performed by SPSS version 25.0 (IBM Corp., Armonk, NY, USA). Paired sample *t*-test

was applied to compare the mean of pre-operative and post-operative dosimetric parameters. $P < 0.05$ was considered statistically significant.

Results

The median follow-up was 12 months (range, 5-35 months). The number of needles for pre-operative plan was 501 in 41 lesions, the actuarial number of needles for post-operative plan was 507. The number of seeds in pre-operative plan was 16-164 (median, 57), and the number of seeds in post-operative plan was 16-183 (median, 63).

The mean angular deviation was 2.20 ± 2.10 degrees ($p < 0.001$). The mean depth deviation for all 499 needles was 0.8 ± 1.0 cm ($p < 0.001$). The needle tip deviation was 0.4 ± 0.3 cm (Table 2). The differences of D_{90} , D_{100} , V_{100} , V_{150} , V_{200} , and HI between pre- and post-operative plans were not statistically significant ($p > 0.05$). There was a significantly difference between pre-operative and intra-operative plans in CI ($p = 0.005$) and between intra-operative and post-operative plans in EI, while the differences of pre- and post-operative plans of CI ($p = 0.001$) and EI were statistically significant ($p = 0.005$) (Table 3).

There was no more than grade 2 peri-operative complications, such as bleeding, infection, fever, and pain. Five patients experienced grade 1 pain after ¹²⁵I-SAB. One patient suffered from grade 1 fever, and two patients experienced grade 1 hematuria (Table 4).

Table 2. Deviation of needles during seeds implantation ($n = 499$, $\bar{x} \pm s$)

	Pre-operative plan	Intra-operative plan	Deviation*	P-value
Angle (°)	90.1 ± 33.5	90.6 ± 33.1	2.2 ± 2.1	< 0.001
Depth (cm)	12.2 ± 2.5	12.0 ± 2.6	0.8 ± 1.0	< 0.001
Needle tip distance* (cm)	–	–	0.4 ± 0.3	–

Data are expressed as $\bar{x} \pm s$.

Table 3. Physical characteristics of ¹²⁵I seeds implantation ($\bar{x} \pm s$)

Parameter	Pre-operative plan	Intra-operative plan	Post-operative plan	P-value ¹	P-value ²	P-value ³
Number of needles	13 ± 7	13 ± 7	13 ± 7	0.268	0.822	0.279
Number of seeds	64 ± 33	67 ± 32	67 ± 35	< 0.001	0.963	0.005
GTV volume (cm ³)	47.4 ± 59.2	47.2 ± 59.0	47.2 ± 59.2	0.776	0.510	0.951
D_{90} (Gy)	142.4 ± 21.1	142.1 ± 23.2	141.5 ± 23.6	0.843	0.777	0.656
D_{100} (Gy)	69.9 ± 23.4	71.0 ± 25.3	74.9 ± 24.7	0.798	0.109	0.147
V_{100} (%)	93.8 ± 3.9	93.0 ± 6.0	92.8 ± 6.7	0.187	0.836	0.185
V_{150} (%)	75.1 ± 17.5	71.7 ± 13.0	71.1 ± 14.8	0.241	0.670	0.167
V_{200} (%)	45.4 ± 16.2	46.6 ± 16.7	46.7 ± 17.2	0.606	0.960	0.572
CI	0.54 ± 0.17	0.51 ± 0.18	0.49 ± 0.19	0.005	0.126	0.001
EI	0.84 ± 0.80	1.03 ± 1.04	1.13 ± 1.02	0.065	0.014	0.005
HI	0.23 ± 0.09	0.23 ± 0.10	0.29 ± 0.29	0.631	0.220	0.172

D_{90} , D_{100} – dose delivered to 90% or 100% of the gross tumor volume, V_{100} , V_{150} , V_{200} – percentage of the volume receiving 100%, 150%, 200% of the prescription dose, CI – conformal index, HI – homogeneity index, EI – external index, ¹pre-operative plan vs. intra-operative plan, ²intra-operative plan vs. post-operative plan, ³pre-operative plan vs. post-operative plan

Discussion

Radiotherapy combined with chemotherapy is the main treatment for patients with unresectable gynecological cancer, most of them resulting with excellent optimal outcomes. However, there are still some patients who experience recurrences in pelvic or pelvic combined with extra-pelvic recurrence [26,27]. The salvage treatment for recurrent patients after EBRT is still sub-optimal. Laterally extended endopelvic resection with or without intra-operative radiotherapy may be a choice, but severe intestinal and neurological toxicities might occur in 25-30% of patients [28]. Also, there is no significant progression for system therapy. The re-irradiation may cause severe toxicities, including intestine fistula, subcutaneous tissue fibrosis, bone necrosis, and lower limb lymphedema [4]. There is no optimum modality for patients with recurrence in non-central pelvic after EBRT [8].

With the development of ¹²⁵I-SAB, its advantage of delivering high-dose to the target while sparing the surrounding normal tissues with rapidly dose drop-off, proved ¹²⁵I-SAB to be a unique option as a monotherapy or combined with EBRT for cancer treatment [29,30,31]. In 2015, CT guidance was integrated into ¹²⁵I-SAB, which provided a new salvage solution for recurrent carcinomas after EBRT [29,30,31,32]. However, the dosimetric patterns in post-operative plan cannot be accurately implemented compared to pre-operative plan requirements under free-hand CT guidance [33]. The multiple needles puncture accuracy was still uncertain, and procedures were unrepeatable, even for experienced personnel.

Qu *et al.* reported their results about ultrasound/CT guidance of ¹²⁵I SAB for recurrent cervical cancer after previous EBRT [34], and observed no lethal toxicities. One patient had a vaginal fistula, which was considered as radiation-related injury. ¹²⁵I SAB could markedly release the pain. The 1- and 2-year local progression-free survival (LPFS) rates were 34.9% and 20%, respectively. The 1- and 2-year overall survival (OS) rates were 52.0% and 19.6%, respectively. Recurrence site, tumor volume, and dose were the main factors affecting efficacy. The preliminary results showed that D₉₀ ranges were wide, and that a favorable prognosis had an association with D₉₀ ≥ 105 Gy. Compared to central recurrence, image-guided ¹²⁵I-SAB was safe, effective, and more suitable for patients with pelvic wall recurrent cervical cancer after EBRT.

The advantages of CT-guided ¹²⁵I-SAB include high-resolution, real-time image reconstruction, and contrast scans, which make the targets' demonstration more clearly compared with ultrasound guidance. However, there are some drawbacks of CT guidance: 1. It takes a long time to train a skilled puncture personnel; 2. The quality assurance of ¹²⁵I-SAB is difficult to be kept in agreement with pre-operative plan due to OARs interferences; 3. The procedure takes time, with an average of 2-3 hours; 4. It poses an excessive radiation exposure to the patients. All these factors limit the use of ¹²⁵I-SAB.

3D printing technique was suggested as an additive manufacturing or rapid prototyping [35]. The process first uses computer-aided design software to create a virtual 3D object, which is then computationally sliced into thin

Table 4. Peri-operative complication of seeds implantation (CTCAE 5.0)

Complication	Grade 1	Grade 2	Grade 3	Grade 4
Pain	5	0	0	0
Fever	1	0	0	0
Hematuria	2	0	0	0
Infection	0	0	0	0

layers. The recently developed 3D printing technique has been widely applied in medical care [36,37]. Brachytherapy (BT) plays a very important role in the treatment of breast, prostate, and skin cancers as a monotherapy or combined with EBRT. Quality assurance in BT is basically dependent on template assistance. Image guidance combined with template assistance, made BT a unique modality for cancer treatment. However, the indications of BT were still limited due to template techniques and image guidance immaturity, until 3D printing template methods development. The 3D-PNCT was invented, and the software program was integrated with B-TIPS. The needles position, angles, and direction can be reverse-designed to meet the target volume of doses requirements and to avoid OARs. In the meantime, 3D-PNCT obtained a co-ordinate, which was the reference for immobilization with patient's body. The precision and accuracy of ¹²⁵I-SAB has been significantly improved [38,39,40,41].

The results of the present study showed that 3D-PNCT combined with CT guidance could greatly reduce the misalignment error and improve the accuracy of needles puncture for non-central pelvic lesions. Under the 3D-PNCT-assisted CT guidance, each needle could be accurately placed in the target. Therefore, the exact doses delivered to the targets could meet the requirements of pre-operative plan. 3D-PNCT-assisted CT guidance not only facilitated the puncture procedure, but also significantly improved the efficacy. All 38 patients with 38 templates were accurately aligned, closely fitted to the skin marked lines with stable needles. Although the needles angles and depth in pre-operative plan were all deviated compared with intra-operative, the D₉₀, D₁₀₀, V₁₀₀, V₁₅₀, and V₂₀₀ showed no differences between pre-operative plan and post-operative plan. The reason for needles direction and depth deviation could be due to muscles relaxation after spinal anesthesia and OARs, such as blood, nerve, or colorectum motion during intra-operation as well as the needles pathway was very long for the pelvic recurrent location and the bony structure interference. The CI and HI did not show significant difference under intra-operative plan optimization, and both reached the pre-operative plan requirements.

3D-PNCT-assisted CT guidance ¹²⁵I-SAB is an alternative option for cervical cancer patients with non-central pelvic recurrences. The care for cervical cancer patients with non-central pelvic recurrences is surgery or EBRT. To the best of our knowledge, there are few evidences to support the safety and effectiveness of ¹²⁵I-SAB as an alternative to surgery or EBRT. Our study showed that,

compared with surgery or EBRT for non-central pelvic recurrences in cervical cancer patients, ¹²⁵I-SAB proved to be minimally invasive, effective, and with lower toxicity. It is an optimal salvage treatment for patients with non-central pelvic recurrent cervical cancer after EBRT.

In conclusion, 3D-PNCT-assisted CT guidance ¹²⁵I-SAB demonstrated to be a feasible, safe, and accurate modality as a salvage therapy. It is also suitable for the aged patients or as a palliative therapy.

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Ethics approval and consent to participate

All patients provided a written informed consent to participate in this study.

Disclosure

The authors report no conflict of interest.

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