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Original Research Article

A phase I clinical trial evaluating the application of hydrogel in reducing rectal dose during cervical cancer brachytherapy

Yuxuan Wang [a,1], Hongnan Zhen [a,1], Ke Hu [a], Lang Yu [a], Jie Zhang [a], Chunli Luo [a], Lihua Yu [a], Junfang Yan [a,*], Fuquan Zhang [a,b,**]

[a] Department of Radiation Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Beijing, China
[b] Department of Radiation Oncology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science and Peking Union Medical College, Beijing, China

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ABSTRACT

Purpose: This study represents a prospective phase I clinical research to verify the effectiveness and reliability of hydrogel application in Chinese cervical cancer patients.
Materials and Methods: Eight patients were enrolled in the study. After completing intensity-modulated radiotherapy at 50.4 Gy/28 fractions, a 10 mL injection of hydrogel was administered to each patient through the posterior vaginal fornix under CT-guidance. Image-guided brachytherapy under CT or MRI guidance was given with a target dose of 6 Gy in 5 fractions to the high-risk clinical target volume. Rectal, sigmoid colon, and bladder D2cm3 were recorded for each brachytherapy. MRI scans were performed to measure the distance between the rectum and the cervix or tumor, as well as the spacer gel volume. Patients' QLQ-C30 and QLQ-CX24 scores were recorded to assess treatment outcomes, and all adverse events were documented.
Results: Among the eight patients, the average D2cc was 60.9 ± 3.4 Gy for the rectum, 64.7 ± 6.8 Gy for sigmoid colon and 77.1 ± 7.4 Gy for bladder, respectively. The distance between the cervix and rectum significantly increased after gel injection. None of the eight patients experienced grade 3 or higher acute toxic reactions during brachytherapy. None patient experienced late rectal toxicity. No adverse events definitively associated with the hydrogel were observed. Patients' subjective quality of life scores did not significantly change before and after gel injection. The reduction ro the volume of the hydrogel were observed during the 24 to 36 weeks after injection.
Conclusion: The application of the hydrogel effectively increased the distance between the cervix and rectum in brachytherapy for cervical cancer, limiting the rectal dose without increasing doses to other critical organs. In the short term, no severe adverse events were observed, indicating the safety and reliability of this approach. Further research is warranted to confirm its long-term safety and effectiveness.

1. Introduction

Brachytherapy to the cervical cancer is long known to pose a substantial risk to the rectum, which is an important organ at risk. In recent years, the application of image-guided brachytherapy (IGBT) using magnetic resonance imaging (MRI) or computed tomography (CT) has partially reduced the incidence of rectal toxicity reactions during the course of brachytherapy [1]. However, a considerable proportion of patients still experience acute or chronic radiation proctitis.

To further minimize the rectal dose and associated toxicity, a viable

Abbreviations: IGBT, image-guided brachytherapy; MRI, magnetic resonance imaging; CT, computed tomography; IMRT, intensity-modulated radiotherapy; HRCTV, high risk clinical target volume; OARs, organs at risk; CTCAE, Common Terminology Criteria for Adverse Events; EBRT, external beam radiotherapy; HDR, high dose rate; LDR, low dose rate; PEG, polyethylene glycol; QOL, quality of life; FIGO, International Federation of Gynecology and Obstetrics.

* Corresponding authors at: Department of Radiation Oncology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, NO.1 Shuaifuyuan Wangfujing, Dongcheng District, Beijing 100730, China.
** Corresponding author at: Department of Radiation Oncology, State Key Laboratory of Complex Severe and Rare Diseases, Peking Union Medical College Hospital, Chinese Academy of Medical Science & Peking Union Medical College, NO.1 Shuaifuyuan Wangfujing, Dongcheng District, Beijing, 100730, China.
E-mail addresses: wyx_xh@qq.com (Y. Wang), yanjfang@yeah.net (J. Yan), zhangfq@pumch.cn (F. Zhang).
[1] Yuxuan Wang and Hongnan Zhen contributed equally to this work.

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approach is to inject medical hydrogel to create a physical barrier between the cervix and rectum, thereby increasing the distance between them and reducing the radiation dose received by the rectum. Previous studies exploring the application of medical hydrogel in patients with prostate cancer have demonstrated the feasibility of this approach, which could effectively reduce rectal dose, decreased acute and late rectal toxicity, and improved quality of life in external beam radiotherapy (EBRT), high dose rate (HDR) brachytherapy and low dose rate (LDR) brachytherapy [2–10].

For cervical cancer, study on cadavers [11] and some small-scale studies conducted in regions such as Japan have shown its effectiveness in reducing rectal dose or guaranteeing clinical target volume dose during brachytherapy [12–15]. However, these studies primarily relied on retrospective research and did not explore whether the use of rectal spacers could truly provide benefits in terms of reducing rectal toxicity and improving patients' quality of life. The potential side effects of hydrogel spacers were also not given much attention.

In this study, a prospective phase I clinical trial was conducted to verify the feasibility of applying hydrogel in the Chinese population with cervical cancer. The objectives of this study were to assess the safety and tolerability of CT-guided injection of hydrogel and to evaluate its impact on reducing rectal dose in cervical cancer patients, at the same time, evaluate the effect of hydrogel on rectal toxicity and patients' quality of life.

2. Materials and methods

2.1. Eligibility

This single-institution phase I clinical trial (registration: NCT05369221) was approved by the Ethics Committee for Drug Clinical Trials of Peking Union Medical College Hospital (No. HS2021169). Written consent was obtained from all participants. The inclusion criteria including 1) Patients with pathologically confirmed cervical cancer who must be scheduled to undergo radical radiotherapy by means of Intensity-Modulated Radiation Therapy (IMRT) combined with 3D brachytherapy; 2) Karnofsky score $\geq$ 70; 3) Subjects aged $\geq$ 18 years and $\leq$ 75 years; 4) Subjects must be able to cooperate in completing the entire study; 5) The subjects' pelvic and abdominal cavity and joints are free of metal implants and can tolerate MRI; 6) No contraindications to CT scanning; 7) Subjects must be able to understand the purpose of the trial, voluntarily participate and sign an informed consent form. Subjects who meet any of the following exclusion criteria should not be included in this trial: 1) Patients whose target tumors have been previously treated; 2) Patients whose tumors invade the injection site; 3) Patients with a history of other malignancies within the past 5 years; 4) Subjects with an infection at the injection site; 5) Subjects with severe mental illness, cognitive impairment, or thought disorders and other conditions make the subject cannot adhere to follow-up instructions; 6) Subjects allergic to the components of the investigational product.

2.2. Radiotherapy

Patients were staged according to the FIGO 2018 staging system. EBRT were delivered through Varian Trilogy linear accelerator. The clinical target volume (CTV) included the tumor, cervical, partial vaginal, and and the pelvic $\pm$ retroperitoneal lymphatic drainage area. IMRT was delivered to patients with 50.4 Gy in total, 1.8 Gy per fraction, 5 times per week. Concurrent chemotherapy is administered during IMRT, with a recommended regimen of weekly cisplatin at a dose of 40 mg/m^2, for a total of 3–6 cycles.

Hydrogel injection was conducted the day after the finish of EBRT. In a previously published case study, we detailed the injection process [16]. During the procedure, a special mold with multiple needle channels is inserted into the patient's vagina. By selecting different channels, the angle and position of the needle can be adjusted. Under CT guidance with 1–2.5 mm slice thickness, a 18G x 150 mm puncture needle was passed through the vaginal posterior wall and 1 mL of saline mixed with lidocaine hydrochloride was pre-administered to confirm the needle was positioned between the cervix and the rectum. Then hydrogel (Respacio®, Shanghai Reunion Biotech Co, Ltd, China), which was composited of polyethylene glycol (PEG) and cross-linking chemistries, was injected between the cervix of the experimental group subjects and the adjacent rectal wall, forming a gel in situ to create a temporary isolation space. The initial injection dosage for the first patient is 10 mL, and it would be adjusted according to the isolation effect and patients' reaction to the current dosage. Following the injection, the patients were provided with dexamethasone for a duration of three days to alleviate potential vaginal posterior discomfort. The reaction of subjects was documented, along with recording any instrument defects in the experimental apparatus.

3D-IGBT twice a week was given to each subject 3 days after the hydrogel injection. All patients received intracavitary brachytherapy with Tandem and Ovoid applicator. The brachytherapy plan was generated using the a high-dose-rate ^{192}Ir source Oncentra brachytherapy treatment planning system (Elekta, Stockholm, Sweden). The clinical target volume and organs at risk were contoured based on MRI images, followed the ICRU 89 report. The prescribed dose for each session of brachytherapy for the high-risk clinical target volume (HRCTV) was 6 Gy, with 5 sessions in total. The rectal $D^3_{0.1cm}$, D^3_{2cm}, and rectosigmoid/bladder D^3_{2cm} are recorded for each treatment plan. An MRI examination was conducted prior to the first brachytherapy session and after the completion of the final brachytherapy session. Based on the MRI images, the rectal periphery spaces and tumor volume were recorded for all subjects, along with the volume of the hydrogel. The European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and Cervical Cancer Module (QLQ-CX24) scores of the subjects were documented before the first brachytherapy and after the completion of the final brachytherapy session. The total course of treatment was approximately 8 weeks.

2.3. Measurement and follow-up

The primary endpoint was the cumulative dose of D^3_{2cm} in the rectum for brachytherapy. The doses from brachytherapy and EBRT were added together after being converted to Equivalent Dose in 2-Gy fractions (EQD2), with α/β ratio = 10 for tumors and α/β ratio = 3 for OARs, resulting in the final total dose. Historical control was conducted in this study, the results obtained were compared with the data from the EMBRACE-I study in order to observe initially if the hydrogel could provide a dosimetry benefit. Secondary endpoints included the acute rectal toxicity, the stability of the medical isolation gel and the assessment of QLQ-C30 and QLQ-CX24 scores. Changes were compared through a before-and-after comparison at each time point.

The rectal periphery space assessment was conducted based on the MRI images collected before and after the hydrogel injection. The minimum distance between the cervix to the rectum, and the average distance between the upper edge and the lower edge of cervix to the rectum was measured to evaluate whether there is a significant increase in the distance between the cervix and the rectum after the injection. Subjects were followed up on the 4 weeks, 12 weeks, 24 weeks and 36 weeks after the treatment. MRI examination was given on each time point to record the change of the distance between the rectum and cervix, and the volume of the hydrogel, thus assessed the stability of the hydrogel. The occurrence of toxicity scored using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE v5.0) grading criteria, and any hydrogel-related adverse effect was recorded. At the end of EBRT and before the start of IGBT, the patients' lower gastrointestinal, urinary, and other adverse effects were recorded as a baseline. Adverse effects would be recorded continuously during brachytherapy and for 24 weeks after the end of radiotherapy. If the grade of adverse effects increased relative to the baseline level, or if new

symptoms appeared, they were considered to be toxic reactions related to brachytherapy. QLQ-C30 and QLQ-CX24 scores of the subjects were documented 12 weeks after the treatment, and was compared with scores before brachytherapy.

The changes in the distance between the cervix and rectum before and after radiotherapy were compared using paired-sample t-tests at a significance level of 0.05. The dosage to each organ at risk was compared to previous literature data using one-sample t-tests at a significance level of 0.05. All data analyses were performed using SPSS (version 22.0; SPSS Inc., Chicago, IL).

3. Result

From April 2022 to July 2022, 10 patients were enrolled into the trial, while 8 of them completed the study. One patient was excluded from the trial because she was afraid of the injection procedure and another because she could not tolerate prolonged lying down due to pulmonary fibrosis. The clinical characteristics of 8 patients were shown in Table 1. The median age was 49.5 (35 ~ 71) years, and all eight individuals had squamous cell carcinoma. Among the eight individuals, two were in stage IIB, three were in stage IIIC1, and one was in stage IIIC2 according to the FIGO 2018 classification. Patient 001 experienced partial leakage of the hydrogel during the injection, resulting in some of the isolation gel not being administered into the rectovaginal septum, leading to a smaller volume of isolation gel in their body. The remaining 7 patients successfully completed the hydrogel injection.

This is the first time that Respacio® hydrogel has been studied in humans, in 8 subjects, the gel did not cause any systemic adverse effects. One patient reported experiencing vaginal posterior wall pain and two patients reported a sensation of heaviness between the vagina and the rectum after receiving the hydrogel injection, although the patient described these sensations as tolerable, and the occurrence of this adverse reaction may be related to the implantation of the hydrogel. No other local adverse effect was reported. The short-term safety of the hydrogel seems to be reliable in this trial.

Fig. 1 gives an example of MRI images taken before and after hydrogel injection. The distance change before and after the hydrogel injection between the cervical to the rectum was shown in Table 2. Before hydrogel injection, the average distance between the upper margin of the cervical tumor and the rectum was 8.1 ± 4.5 mm. After gel injection, this average distance increased to 15.8 ± 9.2 mm. The average distance increase after hydrogel injection compared to before was 7.9 ± 8.7 mm (P=0.036). Prior to hydrogel injection, the average distance between the lower margin of the cervical tumor and the rectum was 7.8 ± 2.9 mm. Following hydrogel injection, this average distance increased to 13.7 ± 3.9 mm. The relative increase in average distance after gel injection compared to before was 5.0 ± 5.0 mm (P=0.027). Similarly, the minimum distance between the tumor and the rectum before hydrogel injection was 0.65 ± 1.0 mm, and after gel injection, it measured 4.5 ± 2.2 mm, resulting in an increase of 3.8 ± 3.0 mm (P=0.008).

The dose distribution was shown as Fig. 2 and Table 3. In the case where the HRCTV D_{90} reached 90.7 ± 2.6 Gy, the average HRCTV volume was 31.8 ± 13.0 cm^3, the mean value of the rectum D^3_{2cm} for eight patients was 60.9 ± 3.4 Gy, and the average value of the rectum $D^3_{0.1cm}$ was 69.1 ± 6.7 Gy, D^3_{1cm} was 60.4 ± 3.8 Gy, D^3_{5cm} was 57.6 ± 2.4 Gy. Among the eight patients, seven of them met the recommended limit of 65 Gy for the rectum. Only patient 001 had a rectum D^3_{2cm} of 66.9 Gy, but it still fell within the hard constraint. Meanwhile, the D^3_{2cm} for the sigmoid colon and bladder were 64.7 ± 6.8 Gy and 77.1 ± 7.4 Gy, respectively, both within the recommended dose constraints of the EMBRACE-II study.

The scores of QLQ-C30 Diarrhea scale and QLQ-CX24 Symptom Experience scale were presented in Fig. 3. A lower score reflects a higher quality of life. The independent samples *t*-test results showed no significant changes in the QLQ-C30 scores and QLQ-CX24 scores before and after gel injection.

Among the 8 subjects, 1 showed Grade 1 acute radiation proctitis symptoms during brachytherapy, 3 exhibited Grade 2 acute radiation proctitis during EBRT, and 4 did not show any acute radiation proctitis symptoms. All these subjects presented with diarrhea as a clinical manifestation. Regarding acute urinary toxicity, one patient experienced grade 2 acute urinary toxicity during the brachytherapy phase, manifesting as difficulty in urination. Another two patients developed urinary tract infection during the course of EBRT, which persisted until the completion of radiotherapy. All eight patients experienced grade 1–2 leukopenia throughout the entire radiotherapy period, which quickly resolved after the end of radiotherapy. No cases of vaginal stenosis occurred during the follow-up period.

The volume changes of the hydrogel are presented in Table 4. The table records the volume of the hydrogel inside the patients' bodies on the day of injection, 4 weeks after, 12 weeks after, 24 weeks after, and 36 weeks after the end of radiotherapy. The volume of the hydrogel at the most recent follow-up for each patient was also measured and recorded. Gel volume was estimated by measuring the maximum transverse diameter in the axial section and the maximum thickness along with the maximum longitudinal diameter in the sagittal section. Some data were missing due to patients being unable to attend follow-up appointments on time because of COVID-19 infections. The data in the table indicated that within 24 weeks after the completion of radiotherapy, there was no significant change in the volume of the hydrogel. However, a noticeable reduction in hydrogel volume could be observed at around 36 weeks.

4. Discussion

According to the EMBRACE-I study, it is recommended to keep the rectal D^3_{2cm} dose below 65 Gy, with a hard constraint of < 75 Gy, to significantly reduce late complications in the rectum. The introduction of 3D-IGBT has reduced the dose to organs at risk such as the rectum, small intestine, and bladder. However, for certain anatomical positions, such as posterior uterus or tumors located too close to the rectum, it is difficult to control the rectal dose while meeting the requirements for the clinical target volume (CTV) dose. According to the inverse square law, increasing the distance between the clinical target area and the rectum can effectively reduce the rectal dose. Therefore, injecting

Table 1
Clinical characteristics.

Patient	001	002	003	004	005	006	007	008
Age	68	71	35	40	37	57	66	64
Height/cm	160	167	168	160	160	161	160	155
Weight/kg	71	67.5	53	71	68	65	60	58
Histology	SCC	SCC	SCC	SCC	SCC	SCC	SCC	SCC
T stage	T2b	T2b	T1b2	T1b1	T2b	T2b	T2b	T2a1
FIGO stage	IIB	IIIC1	IIIC1	IIIC2	IIB	IIIC1r	IIB	IIIC1
Karnofsky score	90	90	90	100	90	90	90	100
Maximum tumor diameter (cm)	3.9	3.7	4.5	3.1	5.3	7.7	2.8	2.8

Abbreviations: SCC: squamous cell carcinoma; FIGO: International Federation of Gynecology and Obstetrics.

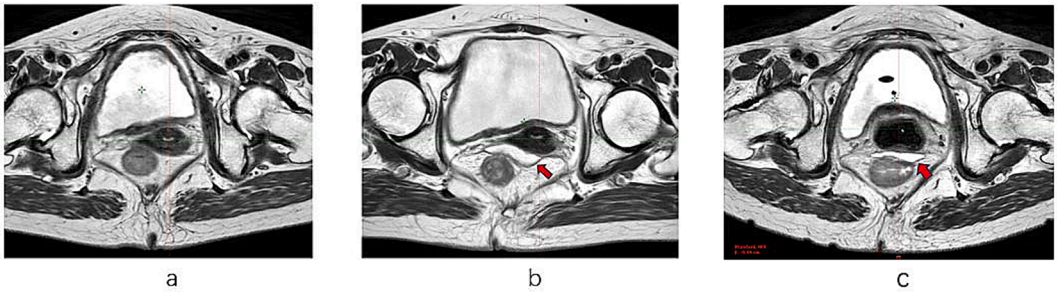

Fig. 1. MRI taken before and after hydrogel injection. MRI taken before (a) and after (b) hydrogel injection, with applicator in place (c). The arrow indicates the hydrogel.

Table 2
The distance (mm) between the tumor and rectum before and after hydrogel injection.

		1	2	3	4	5	6	7	8	average
Without hydrogel	Average distance at upper edge	0	11.1	14.3	6.0	4.5	13.4	9.0	6. 7	8.1 ± 4.8
	Average distance at lower edge	4.6	6.6	7.4	5.9	10.0	10.5	5.1	13.4	7.9 ± 3.1
	Minimum distance	0.9	0	0	0	2.6	1.7	0	0	0.6 ± 1.0
With hydrogel	Average distance at upper edge	3.1	12.7	19.0	32.2	2.7	21.6	21.0	15.9	16.0 ± 9.9
	Average distance at lower edge	10.7	18.2	14.4	10.5	13	16.1	7.9	12.6	12.9 ± 3.3
	Minimum distance	4.4	3.4	5.2	3.2	2.2	8.6	2.4	6.9	4.5 ± 2.2
Change	Average distance at upper edge	3.1	1.6	4.7	26.2	−1.8	8.3	12.1	9.2	7.9 ± 8.6
	Average distance at lower edge	6.1	11.6	7	4.6	3.0	5.6	2.8	−0.8	5.0 ± 3.6
	Minimum distance	3.5	3.4	5.2	3.2	−0.4	6.9	2.4	6.9	3.9 ± 2.4

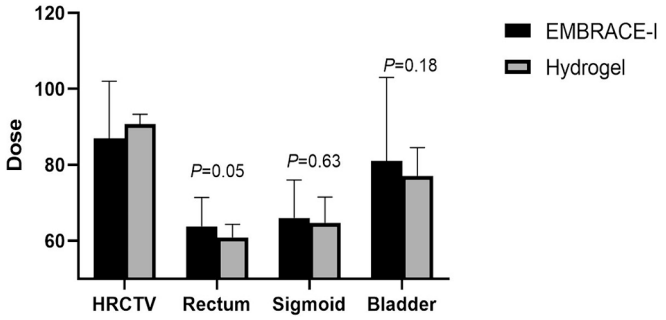

Fig. 2. Comparison of this study and the EMBRACE-I study on OARs D2cc doses. The rectum D2cc was significantly lower in this trial while the doses to other organs at risk showed no significant difference compared to the EMBRACE-I study data.

isolation gel to reduce the rectal dose is another viable option, as it has been confirmed to be effective in prostate cancer research.

The median increase in distance between the injection and the upper margin of the cervix to the rectum was 7.9 mm, and the median increase in distance between the injection and the lower margin of the cervix to the rectum was 5.0 mm. Based on the experience of studies in prostate cancer, we set 10 ml as the initial hydrogel dosage [17]. We did not attempt a higher injection dosage due to the fact that the first three patients experienced rectal discomfort after receiving a 10 mL gel injection. Therefore, we decided to refrain from dose escalation in this study in order to minimize patient discomfort.

Compared with EMBRACE-I study, in which average value of rectum D^3_{2cm} was 63.8 ± 7.6 Gy, [1], the D^3_{2cm} showed a significant decrease of 2.9 Gy (P=0.050). The average value of rectum $D^3_{0.1cm}$ was 72.9 ± 11.9 Gy while the decrease of 3.8 Gy in $D^3_{0.1cm}$ was not statistically significant. The average HRCTV volume was 31.8 ± 13.0 cm^3, which showed no significant difference with the results from EMBRACE-I study (P=0.44) [18]. This preliminary result suggests that by increasing the distance between the target volume and the rectum, the spacer gel can effectively limit the dosage received by the rectum. However, another point of concern is that while the spacer gel separates the rectum from the cervix, it also alters the pelvic anatomy, potentially bringing the clinical target area closer to other organs at risk (such as the bladder and sigmoid colon), leading to increased doses to these organs, which is unacceptable; therefore, measurements of the doses to these organs were included in our study. Historical literature on IGBT research has indicated that an average D^3_{2cm} dose for the bladder was 81 ± 22 Gy, while 66 ± 10 Gy for the sigmoid colon [19]. Our results showed that the doses to the remaining organs at risk were within the recommended dose constraints of the EMBRACE-II study, and there was no significant

Table 3
Cumulative dose to the clinical target volume and organs at risk in all patients.

	1	2	3	4	5	6	7	8	average
HRCTV									
D_{90}	89.89	86.82	91.39	90.28	89.88	93.94	94.81	88.45	90.7 ± 2.6
Rectum									
$D^3_{0.1cm}$	82.08	65.91	61.69	66.65	63.37	71.70	74.80	66.59	69.1 ± 6.7
D^3_{2cm}	66.94	59.23	57.57	58.08	58.09	64.44	62.86	60.09	60.9 ± 3.4
D^3_{5cm}	61.57	56.26	55.67	55.32	55.97	60.96	58.22	56.84	57.6 ± 2.4
Sigmoid									
D^3_{2cm}	68.43	60.97	65.62	74.49	71.35	65.72	54.74	57.08	64.7 ± 6.8
Bladder									
D^3_{2cm}	85.39	78.06	75.43	66.74	82.91	82.24	80.67	65.88	77.1 ± 7.4

All values are in Gy. Dose values are all converted to the equivalent dose in 2 Gy (EQD2; $\alpha/\beta = 10$ Gy for tumor, $\alpha/\beta = 3$ Gy for OARs).

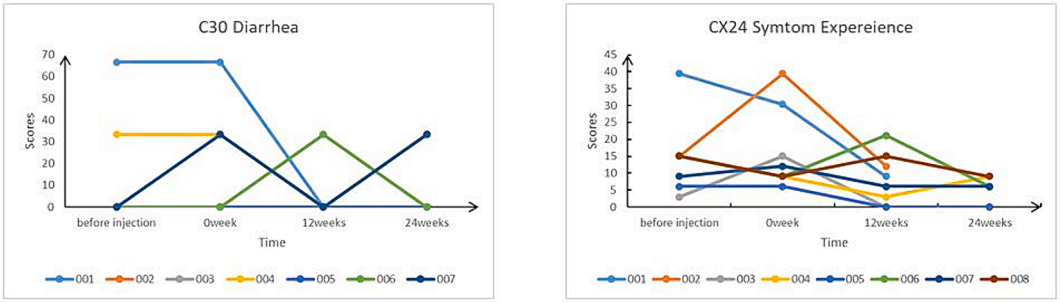

Fig. 3. QLQ-C30 and QLQ-CX24 score during follow-up. Lower scores represent a higher quality of life. The scores shoed no significant difference before and after hydrogel injection.

Table 4
The changes in the volume of the hydrogel. The gel volume is calculated as the product of the maximum longitudinal diameter in the sagittal section, the maximum transverse diameter in the axial section, and the maximum thickness along the sagittal section, with units in millimeters (mm).

	1	2	3	4	5	6	7	8
after injection	17.9*27.5*2.5	43.4*35.9*15.2	37.1*43.6*15.6	33.5*39.1*19.7	26.4*40.9*16.7	29.2*36.3*14.9	48,9*41.9*13.9	26.2*45.5*8.6
4 weeks	26.1*25.9*2.7	42.3*36.2*13	35.1*47.7*12.9	miss	23.5*42.6*25.5	28.1*36.8*14.1	42.3*42.3*16	31.7*47.3*10.4
12 weeks	42.6*48.6*6.9	miss	37.1*49.6*16.7	36*39.7*22.1	25.6*42.3*25.9	25.4*37.6*15.3	44*44*14.6	35.1*48.7*14.1
24 weeks	23.1*16.9*3.4	47.6*34.9*17.4	28.6*46.3*15.1	28.5*37.3*20.1	28.1*38.9*19.7	26.4*33.5*13	41*43.6*14.6	30.9*46*10.3
36 weeks	miss	0	21.7*30.4*10.4	22.0*30.5*11.9	0	11.9*4.4*4.5	0	0
last follow-up	0	0	0	17.6*27.3*6.7	0	11.9*4.4*4.5	0	0

difference compared to the literature data. This suggested that the application of the spacer gel did not have a significant impact on the doses to other organs at risk.

In our observation of adverse effects, none of the eight patients experienced grade 3 or higher acute toxic reactions. Gastrointestinal toxicity was minimal, with only one patient experiencing grade 1 mild diarrhea during the brachytherapy. Regarding the safety of the spacer gel, one patient reported mild vaginal posterior pain and two patients reported a sensation of heaviness behind the vagina after the gel injection. However, these symptoms were alleviated after administering dexamethasone. The remaining patients did not exhibit significant adverse reactions related to the spacer gel. These preliminary findings suggest that the use of the spacer gel could be safe and reliable. It effectively controls gastrointestinal adverse reactions during the acute phase while not significantly increasing urinary tract side effects.

The QLQ-C30 scores and QLQ-CX24 scores of the 8 patients did not show significant changes before and after gel injection, demonstrating good tolerability of the hydrogel injection. During the six-month follow-up period, there were no significant changes observed in the Quality of Life (QOL) scores. The evaluation of QOL scores may still require a larger sample size and a longer follow-up period to be more comprehensive.

Compared to the hyaluronic acid gel used in some of the previous trials, the polyethylene glycol gel used in this trial was absorbed in vivo for a longer period of time, and therefore did not need to be injected repeatedly before each brachytherapy session [14,15]. From the available data, there was no significant change in the volume of the spacer gel during the 6-month follow-up period. We extended the follow-up duration for the initial cases and identified a substantial reduction in the hydrogel volume approximately 6 to 9 months post-treatment. In previous studies concerning the application in prostate cancer, it has been observed that the volume of the PEG hydrogel within patients tends to exhibit noticeable reduction around the 3-month mark following the conclusion of radiotherapy, with minimal changes occurring prior to that time frame [5]. In another study on gynecological tumors, the volume of hydrogel on 3 and 6 months post-injection changed to 69.3 ± 53.4 % and 43.7 ± 34.2 % respectively, relative to day of injection [20]. This difference in absorption time might be attributed to different cross-linking chemistries of hydrogel used in our study compared to that used in prostate cancer research, as well as differences in injection sites and patient gender. The time required for complete absorption of the spacer gel in the body still needs further observation.

Interstitial brachytherapy is commonly used for larger tumors and advanced stages of cervical cancer. Previous studies have shown that combined intracavitary/interstitial applicator can increase the dose to the HRCTV without affecting the dose to OARs [21]. In this study, all 8 patients received intracavitary brachytherapy throughout, so we were unable to analyze the impact of the hydrogel on interstitial brachytherapy. Future trials could induce the analysis to observe whether the combined application of the spacer gel and interstitial brachytherapy can further optimize dose distribution and reduce adverse reactions.

The study has several limitations: Firstly, it included only eight patients, which is a small sample size and insufficient to adequately demonstrate the safety of isolation gel application and statistically significant reduction in rectal dose. Secondly, the follow-up period of the study was only nine months, allowing for dose-related comparisons but not direct evaluation of late toxicity. Additionally, the trial lacked a control group, and the method of comparing with previous literature is not convincing enough. Moreover, for patients with tumor involvement of the posterior vaginal wall, *trans*-vaginal vault puncture is not a suitable choice. Lastly, regarding sexual rehabilitation, as only one patient was sexually active during the follow-up period, a comprehensive evaluation could not be performed. To address these limitations, we are conducting a multicenter randomized Phase II clinical trial, with an expanded sample size and longer follow-up period, to observe differences in late toxicity. In the experimental group, both CT-guided and ultrasound-guided injections will be simultaneously employed to compare their differences.

5. Conclusion

The application of the hydrogel could effectively limit the rectal dose without increasing doses to other organs at risk. Only mild adverse effects were observed during the follow-up period, demonstrating the potential of this approach to reduce rectal toxicity reactions. Further

studies could be conducted to validate its long-term safety and efficacy.

6. Disclosures

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CRediT authorship contribution statement

Yuxuan Wang: Formal analysis, Writing – review & editing. **Hongnan Zhen:** Methodology, Writing – review & editing. **Ke Hu:** Supervision. **Lang Yu:** Methodology. **Jie Zhang:** Methodology. **Chunli Luo:** Project administration. **Lihua Yu:** Project administration. **Junfang Yan:** Conceptualization, Methodology, Writing – review & editing, Resources. **Fuquan Zhang:** Conceptualization, Data curation, Writing – review & editing, Resources, Funding acquisition.

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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