Preliminary report of a single-channel applicator in high dose rate afterloading brachytherapy for cervical cancer

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Funding information
Science and Technology Department in Sichuan province, Grant/Award Number: LY-86

The aim of this study was to evaluate whether a patented single-channel applicator, which was modified from the traditional tandem applicator and wrapped with an oval-shield alloy around the source channel, has the same clinical efficacy and safety as the standard Fletcher-type applicator in high dose rate (HDR) brachytherapy for carcinoma of the cervix. Between December 2011 and February 2017, 299 patients with pathologically confirmed International Federation of Gynecology and Obstetrics (2009) stage Ib2–IVa cervical cancer were recruited to the trial and finished the allocated intervention. Of the first 151 patients, 71 were allocated to the Fletcher group and 80 to the single-channel group, satisfying the criteria for a preliminary analysis. All but 3 patients were treated with concurrent cisplatin chemotherapy and external beam radiotherapy followed by HDR brachytherapy. The 2-year overall survival, progression-free survival, and locoregional failure-free survival was 80.3%, 77.5%, and 78.9%, respectively, for the Fletcher group, and 86.3%, 82.5%, and 83.8%, respectively, for the single-channel group. The seriousness of acute treatment-related toxicities was similar in the 2 groups. The cumulative rate of late rectal complications of grade 3–4 in the Fletcher group and the single-channel group was 2.8% and 2.5%, respectively. The cumulative rate of grade 3 bladder complications was 2.8% for the Fletcher group and 1.3% for the single-channel group. The preliminary results of our study show that the patented single-channel intracavitary applicator might be able to provide protection for the rectum and bladder and seems to have the same clinical efficacy as the standard Fletcher-type 3-channel applicator in HDR brachytherapy for carcinoma of the cervix. This trial was registered with the Chinese Clinical Trial Registry (registration no. ChiCTR-TRC-12002321).

Keywords
Cervical carcinoma, clinical trial, concurrent chemoradiotherapy, high dose rate brachytherapy, radiotherapy

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Cervical cancer is the fourth most common cancer diagnosed in women worldwide. Of these, nearly 85% occur in low- and middle-income countries (LMIC), which causes considerable social and economic impact. Concomitant cisplatin-based chemoradiotherapy followed by high dose rate (HDR) brachytherapy (BT) represents the standard of care in patients with tumors larger than 4 cm, that is, from stage Ib2 to stage IVA. Brachytherapy is an integral component of definitive radiation for cervical cancer, and proper positioning of intracavitary applicators has been singled out as the most important prognostic factor in improving local control (LC) of disease.

The BT component of treatment can be undertaken using an intracavitary (IC), interstitial (IS), or hybrid (IC and IS) implant. The guidelines from the American Brachytherapy Society (ABS) recommend HDR ISBT for cervical cancer patients in certain clinical situations such as bulky lesions, a narrow vaginal apex, inability to enter the cervical os, extension to the lateral parametria or pelvic sidewall, and lower vaginal extension. Compared to the ICBT technique, ISBT with special dosimetric advantages is more invasive and complex, involving individualized catheter placement and image guidance, and higher requirements for doctors and patients. Consequently, it is difficult to enable ISBT to be equally accessible nationwide. To attempt to reach optimum dose distribution from ICBT for carcinoma of the uterine cervix with conditions such as narrow vaginal apex and lower vaginal extension in LMIC, we designed a single-channel applicator (China Patent no. 200710050108.1), wrapped with an oval-shield alloy around the source channel, which was modified from the traditional tandem applicator. The patented single-channel applicator effectively decreases the high-dose coverage on the anterior-posterior axis and has the same dose contributions to bladder and rectum points with Fletcher applicators (Figure 1). We speculated that this single-channel applicator might also be useful for other patients who do not have narrow vagina and lower vaginal extension. As it has a simpler structure, this method could simplify implantation procedures and spare time in source-channel reconstructions, and could be an alternative option for resource-poor settings. A phase I clinical trial in China has confirmed that the toxicity was acceptable. A retrospective study by Kagei et al. suggested the similarity in the clinical outcome of single-channel applicator HDR afterloading BT. To evaluate whether the patented single-channel applicator has the same clinical efficacy and safety as the standard Fletcher-type applicator in HDR brachytherapy for carcinoma of the cervix, we undertook a prospective randomized phase II clinical trial. In this report, we present our preliminary results of this ongoing trial, focusing on the early and late rectal/bladder toxicities as well as the survival outcomes.

**FIGURE 1** Sectional relative dose distributions of the single-channel intracavitary applicator, tested using Mapcheck. A prescribed dose of 70 cGy was delivered to point A following optimized planning with a 6 cm effective length and a 1 cm step size. The ratio of the time between each spot was 13.9%, 11.0%, 6.8%, 8.3%, 15.5%, 22.5%, and 22.0%, respectively. A, Diagram showing the lead thicknesses in the anteroposterior and lateral directions. B, Dose distributions in cross-sectional view. C, Dose distributions in coronal view. D, Dose distributions in sagittal view.
2 | MATERIAL AND METHODS

2.1 | Study design

This was a single blind, prospective, parallel randomized trial. No patient was informed of the type of applicator used before treatment, but the doctor was aware. This trial was registered in the Chinese Clinical Trial Registry (No. ChiCTR-TRC-12002321). The noninferiority test was used to calculate the sample size. Considering factors such as patient drop-out, we expanded the sample by 20%, to 310 women. All the eligible patients were randomized by random computer generation to 1 of 2 treatment groups: the patented single-channel applicator group (single-channel group) or the Fletcher applicator group (Fletcher group). The structure of the intracavitary applicators is shown in Figure 2. Patients in both groups were treated with concurrent cisplatin chemotherapy and external beam radiotherapy (EBRT) followed by HDR BT (not including IIa1).

A preliminary analysis was planned for when at least 150 patients had achieved a minimum follow-up of 2 years. A flow diagram of the progress of the trial is summarized in Figure 3.

2.2 | Patient eligibility criteria

To be eligible, patients had to be between the ages of 18 and 70 years, with a Karnofsky performance status ≥70, normal electrocardiography, adequate bone marrow reserve, and normal liver function and renal function test results. Patients with small-cell carcinoma and carcinosarcoma histology, inability to enter the cervical os, or synchronous/metachronous malignancy, or those who were pregnant, were excluded. The study was approved by the institutional ethics committee. All patients provided informed consent.

FIGURE 2 Structure of the intracavitary applicators. A, Fletcher applicator sets (left) and single-channel applicator (right) that comprises an internally lead-shielded region, surrounded with an outer tube for placement and special canular structure to reduce artifacts (middle). B, Inner tube with lead-shielding from a vertical view. The front and back direction of the lead should be consistent with the direction of the urinary bladder and the rectum.

Pretreatment workup included a medical history, gynecologic examination, complete blood count, liver and kidney function tests, chest radiography or contrast-enhanced computed tomography (CT), and MRI or CT of the abdomen and pelvis. Magnetic resonance imaging was the first choice for the primary tumor unless there was a contradiction or financial difficulties. Cystoscopy and sigmoidoscopy were carried out only in cases with clinical or radiologic suspicion of involvement in the bladder, rectum, or both. Patients were staged clinically on the basis of the pretreatment workup in a multidisciplinary clinic comprising a radiation oncologist, a medical oncologist, and a gynecologist.

2.3 | External beam radiotherapy

A photon beam of 6 MV was used for EBRT. Parallel opposed anteroposterior-posteroanterior beams and a 4-field technique were both permitted. In patients with documented common iliac and/or para-aortic nodal involvement, extended-field pelvic and para-aortic radiotherapy (RT) was recommended, up to the level of the renal vessels. The prescribed dose of EBRT to the pelvis was 46-50 Gy, consisting of 23-25 fractions 5-6 weeks apart. The midline block of 4 cm wide was inserted at 30 Gy. Intensity-modulated radiation therapy was not allowed. Boost EBRT of 10-14 Gy per 5-7 fractions was applied for patients with nodal metastases (≥10 mm in shortest diameter).

2.4 | Chemotherapy

The patients received cisplatin chemotherapy at a dose of 40 mg/m² once a week 5 times during the RT period. According to the Cervical Cancer National Comprehensive Cancer Network guidelines, patients with stage IIa1 do not necessarily need to receive concurrent cisplatin chemotherapy; therefore, those patients only received EBRT followed by HDR BT. The first cisplatin treatment was on day 1 of the RT. Cisplatin treatment was withheld for 1 week until adverse events resolved to the following: Karnofsky performance status, ≥70; temperature, <38.0°C; neutrophil count, ≥1000/mm³; and platelet count, ≥75 000 or more. When grade 4 hematological toxicity was observed, complete blood count was tested more frequently and all treatment stopped.

2.5 | Brachytherapy

Five to 6 fractions with a dose of 7 Gy per fraction of ICBT once a week were given to all patients after the third week of pelvic irradiation. Standard Fletcher applicators or the patented single-channel applicators were used according to the random number. A Foley’s catheter was placed in the bladder and filled with 7 mL diluted contrast media. The vagina was packed with gauze to fix and increase the distance between the radiation source, and the rectum and bladder. In order to prevent the rotation of the applicator during treatment, a special rubber plug is applied to fix the depth of the single tube applicator. There is a direction mark in the tube that indicates the front and back direction of the lead, which should be consistent.
with the direction of the urinary bladder and the rectum before packing. Then the intracavitary applicator is attached to the treatment table by means of a special fixed device. External beam RT was interrupted for each day of HDR BT insertion. After the intracavitary insertions, all patients were transferred to the CT simulator and the position of the applicators was checked. The equivalent dose in 2 Gy (EQD2) (assuming an α/β ratio of 10) to point A ranged from 80.0 to 90.0 Gy. Standard (point-based) HDR ICBT with CT scans was planned with the Oncentra planning system, version 4.3 (Elekta, Stockholm, Sweden) and administered with an iridium-192 source (microelectron HDR remote afterloading unit; Elekta, Veenendaal, The Netherlands) for all patients. The doses to point A, the rectum, and the bladder were calculated according to ICRU 38 recommendations. All patients were treated without sedation except 1 patient in the Fletcher applicator group.

2.6 | Follow-up and evaluation of toxicity

After completion of treatment, patients in both groups were followed up the first month after the end of treatment, then once every 3 months in the first 2 years, 6 months in the third and fifth years, and annually thereafter, alternating between a radiation oncologist and gynecology oncologist. At each visit, a complete history, clinical examination, and blood work, including a complete blood count and blood chemistry profile, were obtained. A Papanicolaou smear was undertaken 1 month after the completion of treatment and at each subsequent follow-up visit. An MRI/CT scan of the abdomen and pelvis was obtained at the 3-month follow-up visit, then at the 6-month visit, and chosen according to each patient’s condition, including other imaging tests. Tumor response was evaluated by gynecologic examination, Papanicolaou smear, and MRI/CT scan of the abdomen and pelvis 3-6 months after treatment. Magnetic resonance imaging was the first choice to evaluate the treatment response unless there was a contradiction or financial difficulties. Tumor response was classified according to RECIST 1.1 criteria. Confirmation of complete response and partial response is required to ensure tumor response rates. Patients in both groups were assessed throughout treatment and until 90 days after completion of treatment for acute gastrointestinal, rectal, genitourinary, and hematologic toxicities in accordance with the Radiation Therapy Oncology Group criteria. After 90 days, late toxicities were graded during follow-up according to the Radiation Therapy Oncology Group criteria.
Patients were followed for outcomes including locoregional failure-free survival (LRFFS), progression-free survival (PFS), and overall survival (OS), as well as post-treatment toxicities. Local recurrence was defined as biopsy-proven disease or clinical progression in the true or central pelvis (cervix and adjacent tissues). Progression-free survival was measured from the initiation of concurrent chemoradiation therapy to the first event of disease progression. Overall survival was measured from the initiation of concurrent chemoradiation therapy to death of any cause. Patients without an event or lost to follow-up were censored at the time of the last follow-up visit. The LRFFS, PFS, and OS were estimated by the Kaplan-Meier method. To compare the 2 treatment groups, \( \chi^2 \) analyses were used; Fisher’s exact test was used for binary variables when sample sizes were small. SPSS software, version 17.0 (SPSS, Chicago, IL, USA), was used for all data analyses, and all \( P \) values were based on a 2-sided hypothesis. A value of \( P < 0.05 \) was considered statistically significant.

## RESULTS

### 3.1 Patient characteristics

Between December 2011 and February 2017, 315 patients with pathologically confirmed International Federation of Gynecology and Obstetrics (2009) stage Ib2-IVa carcinoma of the cervix were recruited. As Figure 3 shows, of 315 eligible patients, 299 patients received and finished the allocated intervention. As of February 2017, the last patients had enrolled in this trial, and the minimal duration of follow-up of the first 151 patients recruited into the trial was approaching 2 years in July 2017. The following is a report based on the first 151 patients randomly allocated to each of the 2 applicator groups. The patient characteristics are described in Table 1. The patients in 2 groups for preliminary analysis showed compatible clinical characteristics.

### 3.2 Feasibility and acute adverse events

Two patients (2.8%) in the Fletcher group and 1 (1.3%) patient in the single-channel group did not receive concurrent chemotherapy. Chemotherapy was given for 5 or more courses in 31 patients (43.7%)
in the Fletcher group, and 26 patients (32.5%) in the single-channel group. The median number of chemotherapy cycles in both groups was 4, and the majority of reasons for delays in chemotherapy administration was grade 3-4 hematological toxicity. The response rate was 97.2% in the Fletcher group, and 96.3% in the single-channel group. Table 2 summarizes the acute hematological toxicity and nonhematologic toxicity in both groups. No significant differences were observed for the acute toxicities between the 2 groups. Sixty-nine patients (97.2%) in the Fletcher group and 78 (97.5%) patients in the single-channel group received 6 fractions of ICBT. Total prescribed point A doses (external beam irradiation without central block + total cumulative HDR ICBT) for the 2 groups ranged from 65.0 to 72.0 Gy (median, 72.0 Gy). The EQD2 to point A ranged from 80.0 to 90.0 Gy (median, 90.0 Gy). One patient in the single-channel group was given extended-field pelvic and para-aortic radiotherapy because of para-aortic nodal metastasis.

### 3.3 Follow-up outcomes

Up to October 2017, the median duration of follow-up was 40 months (Fletcher group, 39 months; single-channel group, 41 months), ranging from 7 to 70 months. Nine patients were lost to follow-up, 4 patients in the Fletcher group, and 5 in the single-channel group. The follow-up rate was 94.0%. Figure 4 showed that there was no significant difference in OS, PFS, and LRFFS between the 2 treatment groups. The 2-year OS survival was 80.3% for the Fletcher group and 86.3% for the single-channel group (P = 0.169). The 2-year PFS was 77.5% for the Fletcher group and 82.5% for the single-channel group (P = 0.289). The 2-year LRFFS was 78.9% for the Fletcher group and

| TABLE 3 | Outcomes of patients treated with Fletcher or single-channel applicators of high dose rate brachytherapy for carcinoma of the cervix |
|----------|----------------------------------------------------------|
|          | Fletcher group, n = 71 | Single-channel group, n = 80 |
| Alive without disease | 50 | 63 |
| Alive with disease | | |
| Local failure | 0 | 2 |
| Distant metastasis | 3 | 2 |
| Both | 0 | 0 |
| Died of disease | | |
| Local failure | 4 | 3 |
| Distant metastasis | 7 | 2 |
| Both | 2 | 1 |
| Died of complication | 0 | 0 |
| Died of intercurrent disease | 1 | 2 |
| Lost to follow-up | 4<sup>a</sup> | 5<sup>b</sup> |

<sup>a</sup>Two patients that were lost to follow-up in the Fletcher group had distant metastasis.

<sup>b</sup>Four patients that were lost to follow-up in the single-channel group had local failure, and 1 patient had distant metastasis.
TABLE 4 Late complications in patients treated with Fletcher or single-channel applicators of high dose rate brachytherapy for carcinoma of the cervix

|                     | Fletcher, % (n: n = 71) | Single-channel, % (n: n = 80) |
|---------------------|-------------------------|-----------------------------|
|                     | Grade 1-2 | Grade 3-4 | Grade 1-2 | Grade 3-4 | P value |
| Radiation proctitis | 52.1 (37) | 2.8 (2)   | 52.5 (42) | 2.5 (2)   | 1.000   |
| Radiation cystitis  | 28.2 (20) | 2.8 (2)   | 30.0 (24) | 1.3 (1)   | 0.593   |

83.8% for the single-channel group (P = 0.369). The outcomes of the 2 groups of patients are listed in Table 3.

3.4 | Late toxicity

Table 4 summarizes the late complications for both treatment groups at the median follow-up of 40 months. No treatment-related deaths occurred. The cumulative rate of grade 3-4 rectal complications was 2.8% for the Fletcher group and 2.5% for the single-channel group. No grade 4 bladder complications were observed in the 2 groups. The cumulative rate of grade 3 bladder complications was 2.8% for the Fletcher group and 1.3% for the single-channel group. No significant differences were identified for late radiation proctitis and cystitis between the 2 groups.

4 | DISCUSSION

The main objective of radiation therapy is to deliver a precise dose of irradiation to a defined tumor volume while keeping the damage to surrounding healthy tissue as minimal as possible. This concept is especially important in the presence of surrounding dose-limiting organs, such as the rectum and bladder, in the treatment of gynecological cancers where initial EBRT is given to the whole pelvis. Intracavitary BT offers the best possibility to decrease the dose to normal tissues while prescribing a curable dose to the target volume in gynecological cancers.

The dose distribution of an IC application depends on a number of parameters, such as the type, size, and geometry of the applicators, fixation procedures, packing technique, anatomical variations, and the prescription of reference points. Image-guided BT in locally advanced cervix cancer has recently been introduced and shown to provide improvements in dose volume parameters, which allows changing the size and the shape of the classical pear-shaped isodose according to the target volume. This improvement in target coverage and reduction in dose to critical organs has been shown to improve LC and decrease toxicities. However, in many low-resource settings where 3D imaging, and in some cases 2D imaging, is not possible at the time of applicator placement, volume-based contouring is not realistic, only a 25% volume-based dose.

Thus, for these settings, a high-quality implant is mainly determined by the patient anatomy, tumor geometry, and the brachytherapist’s experience. In the absence of appropriate sedation and analgesia, which was unexpectedly found in many LMIC, most patients will experience discomfort and strong pain during ICBT. This can also lead to inappropriate applicator placement, such as: short or long active tandem length in the uterus, narrow or asymmetric ovoid separation, and different sagittal levels of the ovoids. A technically poor implant was reported more frequently in narrow vaginal vault and asymmetric vaginal fornices. These patients might be best treated using an interstitial approach; however, such ISBT should only be carried out at institutions with appropriate experience and expertise. If this is not available, a tandem and cylinder applicator could be used, which results in lower parametrial doses and higher bladder and rectal doses relative to tumor, with a possible increase in complications and pelvic failures. In addition, because of economic reasons, there are limited choices of applicator in low-resource settings, and for Asian women, the size of the vaginal mold is always large and more suitable for non-Asian women. Oversized ovoids can result in displacement of the applicator in the vagina, which causes the quality of the dosimetry to deteriorate and leads to undesirably low doses to the cervix.

How can we improve the quality of implant in BT when 3-channel applicators are not appropriate in many LMICs where ISBT is not very popular? Moving to an experienced hospital is a solution, but it usually means a long waiting time for treatment. As Fletcher emphasized in his textbook of RT, “the axis of the tandem should be equidistant from the colostats and bisect their height.” Therefore quality of implant colostats is the most important issue for a standard ICBT. If treatment with a single-channel intrauterine applicator was available with the same dose contributions as a 3-channel applicator, the BT implant would become simple and the uncertainty of the applicator geometrical arrangements would also be reduced. For this goal, we designed a single-channel applicator, wrapped with an oval-shield alloy around the source channel, which was modified from the traditional tandem applicator. The oval-shield alloy is thin on the side and thick on the middle, which was intended to reduce the doses in the ventral and dorsal directions, thereby shielding the bladder base and the anterior wall of the rectum. Iridium-192 is a radiation source with lower gamma energy; the effective energy is approximately 384 keV and the half value layer is 3 mm in lead. So the shielding material can be very thin, but it does not affect the structure of the intrauterine applicator. For its oval-shield alloy, the shape of the sagittal views of the reference dose distribution through point A was pear shape, as in the classical Manchester system. Enlarging the upper part of the pear shape isodose envelope can increase the dose of point A, but the dose of the rectum and bladder will not increase as sharply as a single tandem applicator. A phase I study found that, of 20 patients with cervical carcinoma treated with the patented single-channel applicator, 15 (75.0%)
achieved clinical complete response. The acute treatment-related toxicities were 10% for both rectal reaction and genitourinary effect, and most were grade 1-2.

The preliminary results of a phase II clinical trial showed that there was no significant difference in 2-year OS, PFS, or LRFSS between the 2 treatment groups. Parker et al. reported that the OS rate was 72% and the LC rate was 76% at 2 years for concurrent chemoradiotherapy in cervical cancer, which was a little lower than in the present study. The RT schedules in this study gave a total EQD2 of 76.25 Gy to point A, which was lower than in the present study and do not correspond to the ABS recommendation that 80–85 Gy be used for early stage disease and 85–90 Gy for advanced stage. In addition, the EQD2 to point A ranged from 80.0–90.0 Gy (median, 90.0 Gy) in the present study, and only 4 patients had 5 brachytherapy insertions (EQD2, 80 Gy). This means that as high as 97.3% of patients in our study accepted a total EQD2 of 90 Gy to point A. But because of the 1-week BT schedule, the median total treatment time was more than 8 weeks, which was recommended by ABS.

The severity of acute treatment-related toxicities was similar in the Fletcher group and the single-channel group. Thirty-five (49.3%) patients in the Fletcher group and 42 (52.5%) in the single-channel group had acute grade 3-4 hematologic toxicity, which was higher than in other reports. No grade 4 acute nonhematologic toxicity was observed in the 2 groups. Because of the high treatment-related hematologic toxicity, only a small number of patients received 5 or more courses of concurrent cisplatin chemotherapy. The acute rectal/bladder toxicity was comparable with earlier reports.

In order to reduce the influence of artificial factors, this study gave the majority of patients (97.3%) the same high dosing parameters (EQD2, 90 Gy) and the late rectal/bladder toxicities were the focus of our observation. The cumulative rate of grade 1-2 rectal/bladder complications for all patients was higher than another study; nevertheless, the cumulative rate of grade 3-4 rectal/bladder (1.3%–2.8%) complications was acceptable, compared with the other reports of 6%–23.3% late grade 3 and 4 toxicities. No significant differences were observed for late radiation proctitis or cystitis between the 2 groups.

In conclusion, the preliminary results of the present study suggest that the patented single-channel IC applicator might be able to provide protection for the rectum and bladder and seems to have the same clinical efficacy as the standard Fletcher-type 3-channel applicator in HDR BT for carcinoma of the cervix. Further studies are needed to assess long-term outcomes and associated toxicities.

ACKNOWLEDGMENTS

This work was supported by the Science and Technology Department, Sichuan Province (LY-86).

CONFLICT OF INTEREST

The authors have no conflict of interests to declare.

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How to cite this article: Li D, Wen E, Zhang Y, et al. Preliminary report of a single-channel applicator in high dose rate afterloading brachytherapy for cervical cancer. Cancer Sci. 2018;109:3953-3961. https://doi.org/10.1111/cas.13845