ORIGINAL RESEARCH

Californium-252 Intracavitary Radiotherapy for Primary Vaginal Carcinoma: A Retrospective Clinical Study

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ABSTRACT

Objective • To investigate the therapeutic effect of Cf-252 neutron intracavitary brachytherapy (ICBT) in the treatment of primary vaginal carcinoma of stage I-III, along with advanced complications.

Methods • Between August 2009 and August 2013, 41 patients with intact primary vaginal carcinoma based on the histological diagnosis at the Second Cancer Hospital of Heilongjiang Province (Beidahuang Group General Hospital) and the Daping Hospital of the Third Military Medical University were included in this study. Among them, 32 patients were squamous cell carcinoma, and 9 adenocarcinomas. Stage I patients were treated with ICBT alone. Patients at stages II and III were treated using ICBT combined with external beam radiotherapy (EBRT).

Results • The mean age, the rate of the 5-year local control, the rate of the 5-year overall survival was increased. The rate of the 5-year tumor-free survival was 56.1%, and the incidence of advanced serious complications (grade II and above radiation cystitis, proctitis, etc.) was 29.3%. Compared to later stages, early-stage patients are in better physical shape, so they are better able to withstand the toxic side effects of treatment. The local control (LC), overall survival (OS), or disease-free survival (DFS) rate in stage III patients was significantly lower than those in stage I and stage II. The rate of OS in stage I patients was 90.9% (10/11), which was significantly higher than that in all patients (56.1%; 23/41). Moreover, the mean survival time was significantly different between stage III and stage I. In addition, the survival status of squamous cell carcinoma and adenocarcinoma was also very different.

Conclusion • In summary, the use of Cf-252 ICBT radiotherapy resulted in a higher rate of local control of vaginal cancer and a lower rate of recurrence, better-shrinking effect, and efficacy for advanced tumors, and has clinical prospects. (*Altern Ther Health Med.* [E-pub ahead of print.])

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INTRODUCTION

Primary invasive vaginal cancer is rare, accounting for only about 2% of gynecological malignancies.[1,2] The general age of onset ranges from 55 to 75 years. Its etiology has not been understood yet and may be related to HPV (human papilloma virus) infection or vaginal hygiene.[3] Due to the rarity of occurrence of this disease, standardized therapeutic approaches have not yet evolved, and only few centers have an extensive experience with these tumors. The treatment of primary vaginal cancer is very challenging because the disease is not characterized by early symptoms and is often not diagnosed until late in life. Due to the special anatomy of the vagina, surgical resection is very limited and therefore surgical treatment is not the method of choice. Chemotherapy and radiotherapy are the main treatments available.

Currently, the commonly used treatments include radiation therapy, radiation therapy combined with chemotherapy, and surgical resection combined with radiation therapy. Radiotherapy is one of the main treatment methods but due to the high sensitivity of vaginal tissues to radiation, radiotherapy can cause serious adverse effects, including cervical stenosis and pathologic fractures. Therefore, the dose and regimen of radiotherapy need to be formulated very carefully.

Treating primary vaginal cancer is a very challenging task. Doctors need to formulate a personalized treatment plan according to the patient's specific situation in order to achieve the best therapeutic effect. At the same time, patients also need to actively cooperate with the treatment and provide timely feedback to doctors on the adverse effects of the treatment so that the treatment plan can be adjusted in time.

Due to the thinness of the recta-vaginal or vaginal bladder diaphragm, the tumor easily penetrates the bladder, urethra, or rectum. The complete resection of primary vaginal carcinoma in about 1/3 of vaginal cancer patients is challenging to achieve, especially in stage II and III patients.[4,5] In general, the radiation therapy is preferred in the treatment of primary vaginal carcinoma involving the middle and lower 1/3rd vagina.[6]

Californium (Cf)-252 neutrons have unique radiobiological properties and are high-line energy conversion or linear energy transfer (LET) rays.[7,8] They have great biological effects, including low periodic dependence on cells and are independent of tissue oxygen levels. These characteristics make the use of these rays a promising method in cancer treatment, theoretically. In the late 1970s, Professor Maruyama first reported the treatment of cervical cancer using Cf-252, demonstrating good therapeutic efficacy.[9] Intraluminal radiotherapy equipment using Cf-252 is less used because of its high cost and the large size of the radionuclide raw material Cf-252, which has a cylindrical-shaped neutron source of 3 mm × 18 mm dimension.[10] It is challenging to operate, and there is a high risk of bleeding from interstitial implants. Moreover, intracavitary brachytherapy (ICBT) combined with external beam radiotherapy (EBRT) is the main treatment for vaginal cancer. Conventional radiation ICBT has already been reported in the treatment of vaginal cancer.[11–14] Also, Cf-252 neutron ICBT has been reported in the treatment of cervical cancer.[15] However, it has not yet been reported in the treatment of vaginal cancer.

In this study, we retrospectively analyzed 41 patients with primary vaginal cancer who received Cf-252 neutron ICBT treatment. Through the study, we evaluated the efficacy of Cf-252 neutron ICBT combined with EBRT in the treatment of primary vaginal carcinoma. The purpose of our study was to demonstrate that treatment with Cf-252 neutron ICBT combined with EBRT improves local control of vaginal cancer, decreases the recurrence rate, and demonstrate the efficacy and safety of Cf-252 neutron ICBT combined with EBRT in the treatment of primary vaginal cancer.

MATERIALS AND METHODS

Patients

Between August 2009 and August 2013, 41 patients with intact primary vaginal carcinoma based on the histological diagnosis at the Second Cancer Hospital of Heilongjiang Province (Beidahuang Group General Hospital) and the Daping Hospital of the Third Military Medical University were included in this study. The presence of vaginal squamous cell carcinoma or vaginal adenocarcinoma was confirmed by histopathology. The patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) clinical staging system (2009), with stage I-III vaginal cancer.[16]

All patients were evaluated for distant metastasis using B-ultrasound examination or computed tomography (CT) scans. The magnetic resonance imaging (MRI) tests were used to define staging and lymph node metastases. The study was approved by the ethics review board of Beidahuang Group General Hospital (BDAJTZYY-2021–003-LW). The privacy rights of human subjects were considered throughout the experiment.

Radiotherapy characteristics

Facilities. ZH-1000 Cf-252 neutron brachytherapy devices (made in China). The mean energy of the Cf source was 2.3 Mev, the half-life was 2.65 years, and the activity was 400–98 μg. The size of the source was as follows: active portion: φ1.4 × 5 mm, shell: φ3 × 10 mm. The equated emission rate was: 2.3×10^9/s (neutron) and 1.3×10^{10}/s (gamma). Dose conversion was calculated according to DGY-eq (relative biological dose) = neutron relative biological effect value·neutron dose + gamma biological effect value·gamma dose. Neutron relative biological effect (RBE) values were between 2 and 6.[17,18]

EBRT (external beam radiotherapy). The Elekta linac was used for EBRT. The upper edge of external irradiation was located at the upper edge of the fifth lumbar spine. External beam radiotherapy included a prescription dose of 45 to 46 Gy in 23 to 25 fractions to the planning target volume (PTV), followed by a boost dose of 8 to 14 Gy in 4 to 7 fractions to the parametrial lesion and metastasis lymph nodes. When 40 Gy external irradiation was provided, the vagina was covered to protect the bladder and rectum near the vagina. Brachytherapy was prescribed as 30 to 40 Gy in 4 to 5 times/week, while chemotherapy was allowed. The radiotherapy techniques included two-field radiotherapy, four-beam box field radiotherapy, or 3D conformal radiation therapy (3DCRT).

Cf-252 neutron ICBT. Stage I patients were treated with ICBT alone. The lesions involving the upper 1/3rd of the vagina were treated with a single-channel applicator of the uterine cavity and two oval single-channel applicators. The dose reference points were defined on point A and vaginal mucosal surface, respectively. The total dose was 30–36 Gy, once a week, and 8–12 Gy each time. The lesions involving the lower 2/3rd of the vagina were treated with a single-channel vaginal cylinder or a four-channel cylinder of diameters 30 mm and 35 mm. The total dose was 30-40 Gy, once a week, and 8-12 Gy each time.

Before the treatment using Cf-252 intraluminal radiotherapy, the cervix and vagina were examined visually, the applicator was placed in the uterine cavity and vagina, and fixed after catheterization. A rectal marker ruler was inserted from the anus, and a catheter was inserted in the bladder (7 mL of contrast fluid injected into the balloon) and other centers, to take pelvic orthogonal films. This was done

to determine the placement of the applicator, the setting of the treatment point, and the reference point for normal organ dosing. The lowest point of the catheter balloon was considered as the bladder acceptance reference point, and five reference points (1 cm interval) were made in the anterior wall of the rectum near the cervical orifice shown by barium enema, while the maximum acceptance point was used as the rectal acceptance reference point (Figure 1).

Follow-up

Patients returned to the hospital for a cervical smear, CT, or MRI for gynecological examinations one month after the end of chemoradiation. Then the patients were followed up every 3 months for the first 2 years, after the completion of the treatment and every 6 months thereafter. One patient was lost to follow-up. The clinical re-examination of the pelvis and vaginal cytology was performed at each follow-up. Suspected lung and liver metastases in patients were subjected to CT or MRI for further diagnosis. Biopsy of confirmed isolated metastasized lesions was performed when necessary. The relapse of the primary tumor and pelvic lymph node in the external irradiation region was defined as recurrence. Disease-free survival (DFS) was defined as patients without vaginal local recurrence or distant metastasis. Late radiation proctitis was defined as rectal complications caused by patients receiving radiation therapy or after radiation therapy, including erosions, ulcers, or bleeding of the rectal mucosa. Cystitis was defined as patients with hematuria that were treated for 2 years after the end of radiotherapy according to the acute and chronic radiation injury grading standards of the Radiation Oncology Therapy Group (RTOG).[19] The mean follow-up time was 61.39 months (range 6-123 months).

Statistical analysis

The statistical analysis was performed using the statistical software SPSS version 13.0 (SPSS Inc., Chicago, IL). Kaplan-Meier method, log-rank, R×2 contingency, or Fisher's exact test were used to analyze the rate of local control (LC), overall survival (OS), disease-free survival (DFS), and serious late complication (LAC) (≥G2), as well as survival time. *P* values of ≤ .05 were considered statistically significant.

RESULTS

Patient characteristics

41 patients with intact primary vaginal carcinoma were included in the study. The mean age of the patients was 57.7 ± 15.40 years (Table 1). Among them, 11 patients had stage I cancer, 19 were in stage II, and 11 were in stage III. 32 patients had vaginal squamous cancer and 9 had vaginal adenocarcinomas. 12 patients developed relapses of primary vaginal cancer. The primary tumor relapse rate was 29.3%. Three patients had persistent vaginal lesions. Only one patient showed recurring pelvic lymph nodes. The rate of pelvic lymph node relapse was 2.4%. Eleven patients suffered from distant metastases (4 cases in the lung, 2 in the liver, 2 in both lung and liver, 1 in the brain, and 2 in adjacent organs). The most common sites for metastases were the lung and liver.

Figure 1. Schematic Diagram of the Operation. (A, B) Catheterization for Cf-252 Intraluminal Radiotherapy. (C-E) X-Ray Positioning of the Hysterical Catheter. (F) Vaginal Catheter X-Ray Positioning with Dose Graph.

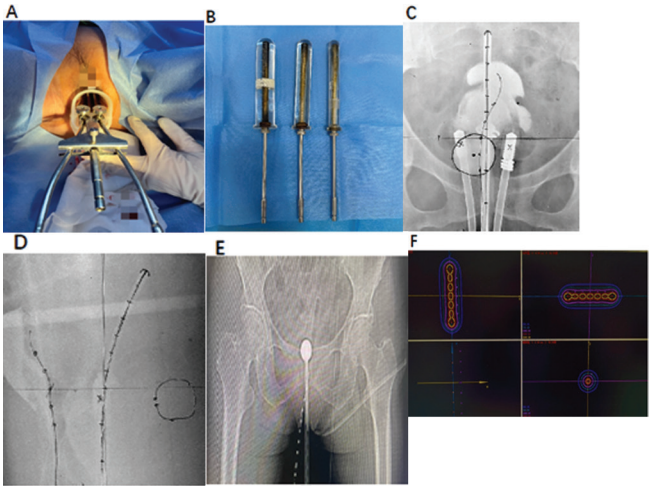


Table 1. The Characteristics of the Patients

Characteristic	No. of patients
Age (years)	
30-40	5
41-50	11
51-60	7
61-70	8
71-80	10
Mean age (years)	57.7
Stage	
I	11
II	19
III	11
Whole	41
Pathology	
Squamous	32
Adenocarcinoma	9
Location	
Upper 1/3	11
Anterior wall	3
Posterior wall	8
Middle 1/3	10
Anterior wall	5
Posterior wall	5
Lower 1/3	11
Anterior wall	3
Posterior wall	4
Entire vagina	4

Survival rates

The rates of OS and DFS in patients with vaginal cancer were significantly different between different stages (Figure 2). The rate of OS in stage I patients was 90.9% (10/11), which was significantly higher than that in the all patients (56.1%; 23/41) (P = .005, Table 2). The OS in patients with vaginal squamous cancer was significantly different between different stages (Figure 3), with the rate of OS in stage I vaginal squamous cancer being significantly higher than that in the whole-vaginal cancer patients. The rates of OS in vaginal squamous cancer stages I and II were not significantly different from those in the all patients (Figure 4). Similar results were observed in the case of DFS. The survival time in stage I patients was 112.1 months, which was significantly higher than that in stage III patients (39.4 months) (Table 3).

Figure 2. Kaplan-Meier Curves of Overall Survival for Different Stage in Vaginal Cancer Patients

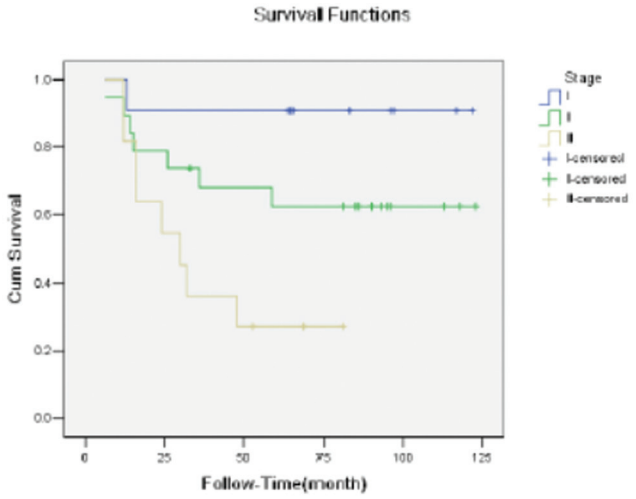
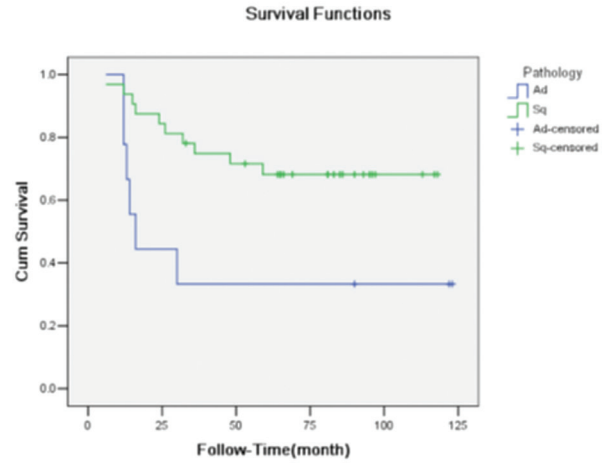


Table 2. The Results for Vaginal Cancer

	N	LC	DFS	OS	LAC
vaginal cancer					
I	11	90.9% (10/11)	90.9% (10/11)	90.9% (10/11)	27.3% (3/11)
II	19	73.7% (14/19)	57.9% (11/19)	57.9% (11/19)	26.3% (5/19)
III	11	45.5% (5/11)	18.2% (2/11)	18.2% (2/11)	36.4% (4/11)
Wh	41	70.7% (29/41)	56.1% (23/41)	56.1% (23/41)	29.3% (12/41)
χ^2		5.238	9.145	9.224	0.496
P value		.039	.005	.005	.453
vaginal squamous cancer					
I	9	100% (9/9)	100% (9/9)	100% (9/9)	22.2% (2/9)
II	16	75% (12/16)	62.5% (10/16)	56.3% (9/16)	18.8% (3/16)
III	7	57.1 % (4/7)	42.9% (3/7)	42.9% (3/7)	42.9% (3/7)
Wh	32	78.1% (25/32)	68.8% (23/32)	65.6% (21/32)	25.0% (8/32)
χ^2		4.342	6.828	0.011	1.626
P value		.052	.011	.011	.245
vaginal adenocarcinoma	9	44.4% (4/9)	33.3% (3/9)	33.3% (3/9)	44.4% (4/9)
vaginal squamous cancer	32	78.1% (25/32)	65.6% (21/32)	68.8% (22/32)	34.4% (8/32)
χ^2		3.849	3.018	3.703	1.283
P value		.064	.089	.063	.232

Abbreviations: Wh, whole patients; N, number; LC, local control rate; DFS, progression free survival rate; OS, overall survival rate; LAC, late complication rate

Figure 3. Kaplan-Meier Curves of Overall Survival for Vaginal Adenocarcinoma and Squamous Patients.



Abbreviations: Ad, adenocarcinoma; Sq, squamous

Figure 4. Kaplan-Meier Curves of Overall Survival for Different Stage in Vaginal Squamous Patients

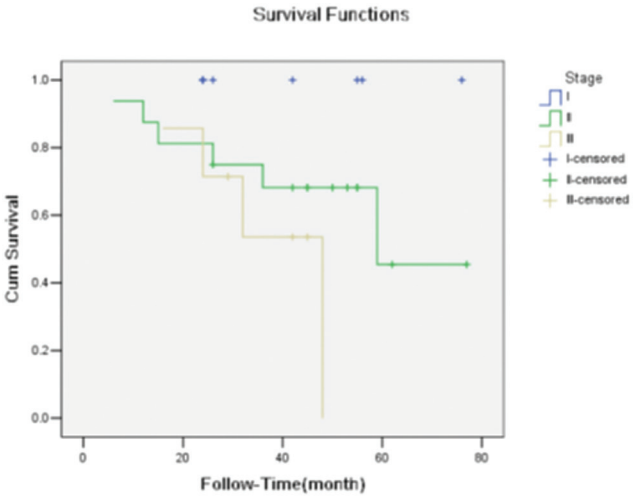


Table 3. The Mean and Median Survival Time (Month) for Vaginal Cancer

	Mean ± SE	95%CI	Median ± SE	95%CI
I	112.1 ± 9.5	93.6, 130.6		
II	85.9 ± 11.3	63.7, 108.1		
III	39.4 ± 8.3	23.2, 55.5	30 ± 8.8	12.7, 47.3
Wh	83.7 ± 7.8	68.6, 99.0		
vaginal adenocarcinoma	42.4 ± 12.5	17.9, 67.0	16.0 ± 3.0	10.2, 21.8
vaginal squamous cancer	68.6 ± 5.6	57.6, 80.0		

Abbreviations: Wh, whole patients; CI, confidence interval; SE, standard error

The survival time varied significantly between patients depending on the stage of disease ($\chi^2 = 9.173$, $P = .010$). The survival time in stage I patients was significantly higher than that in stage II or III patients. Moreover, the survival time in stage III patients was significantly lower than that in stage I and II. Furthermore, the survival time was significantly different between patients with squamous cell cancer and adenocarcinoma ($\chi^2 = 5.830$, $P = .016$). For all patients who survived throughout follow-up, the survival time could not be calculated (Table 2 and Figures 2 and 3).

Tumor local control (LC)

The rates of LC in stages I, II, and III were 90.9% (10/11), 73.7% (14/19), and 45.5% (5/11), respectively (Table 2). The rate of LC in patients with vaginal cancer was significantly different between different stages ($P = .039$). Furthermore, the rate of LC in stage III patients was significantly lower than that observed in patients in other stages. The rates of LC in stages I and II of vaginal cancer were not significantly different from those in the whole-vaginal cancer patients.

Adverse Events

The rate of serious LAC (radiation proctitis and cystitis, ≥G2) did not differ significantly between patients with squamous cell cancer and adenocarcinoma (Table 2). Three patients suffered from either proctitis or cystitis. Two patients suffered from recto-vaginal fistula within 1–2 years after

treatment. None of the patients suffered from vaginal necrosis, and the rate of heavy vaginal stenosis was only 14.6%.

There were no significant differences in the rates of adverse events in patients with squamous cell carcinoma and adenocarcinoma (radiation proctitis, radiation cystitis, ≥G2; Table 4). The rate of complications after radiation therapy for G1 and G2 was higher, while that after radiotherapy for G3 varied between 2.4% and 24.4%. Symptoms could be controlled after the traditional Chinese medicine retention enema therapy, treatment with mucosal repair agents, and bacterial culture after antibiotic treatment. In the two years after discharge, vaginal dilation was performed at home, 5 times a week for 10 min each time, which could effectively control vaginal stenosis.

Table 4. The Complication Rate

	G1	G2	G3	G4	G5
Radiation cystitis	100% (41/41)	73.2% (30/41)	4.9% (2/41)	0	0
Radiation proctitis	92.7% (38/41)	63.4% (26/41)	12.2% (5/41)	0	0
Radiation urethritis	100% (41/41)	85.4% (35/41)	2.4% (1/41)	0	0
Radiation vaginal mucosal injury	100% (41/41)	100% (41/41)	24.4% (10/41)	0	0

DISCUSSION

Although definitive radiotherapy is the main treatment strategy for vaginal cancer, it is difficult to accumulate sufficient information on radiotherapy due to the low incidence of vaginal cancer.[20,21] Information on radiotherapy for vaginal cancer is mostly obtained from cases at multiple centers. EBRT combined with ICBT can reduce the exposure of normal tissues to EBRT and increase the exposure of primary vaginal tumors.[22] Furthermore, this strategy can improve the rate of LC and decrease the incidence of complications. Recently, conventional radiation ICBT technology has been reported to treat vaginal cancer with high-dose Ir-192 or low-dose Cs-137 radionuclides, with a 5-year LC rate of about 70% and an OS rate of about 60–70%.[14,23] The Cf-252 neutron possesses unique radiobiological properties, such as a high relative biological effect (RBE) and low oxygen enhancement ratio (OER).[11] Moreover, the use of Cf-252 neutron ICBT combined with EBRT has been reported previously for the treatment of cervical and endometrial cancer.[24] However, none of the existing studies answer questions about the efficacy and safety of Cf-252 neutron ICBT combined with EBRT in the treatment of primary vaginal carcinoma. Our study demonstrates for the first time that treatment with Cf-252 neutron ICBT combined with EBRT improves the LC rate of vaginal cancer, reduces the recurrence rate, and, to some extent, answers the questions about the efficacy and safety of Cf-252 neutron ICBT combined with EBRT in the treatment of primary vaginal cancer.

There are significant differences in survival and LC rates among patients with different stages of vaginal cancer, and the reasons for these differences can be analyzed at several levels, as discussed below:

Biological mechanisms: The stage of cancer is closely related to the biology of the tumor. Early-stage tumors are usually smaller, more confined, and may have a lower pathologic grade and slower growth rate. Biologically, these tumors are more likely to retain certain normal tissue properties, including a more regular network of blood vessels, which can increase the efficiency with which the drugs of chemotherapy and radiotherapy reach the tumor area. On the other hand, advanced tumors may have developed microscopic or macroscopic metastases that involve more lymph nodes or other tissues and respond relatively poorly to treatment.

Differences in LC rates: Related to biological mechanisms, early-stage tumors are more completely surgically resected due to their small size, leaving less tumor residue, and therefore radiotherapy is more effective for local control. On the contrary, advanced tumors may have penetrated into adjacent structures, such as the pelvic wall or distant organs, making it difficult for both surgery and radiotherapy to completely eliminate the lesions, thus leading to a higher rate of local recurrence.

Treatment advantage: Among the different stages of vaginal cancer treatment, early-stage patients may receive the benefit of more treatment options. For example, early-stage tumors may only require local surgical resection or single-modality treatment, whereas patients with advanced tumors often require a combination of treatments, including radiation, chemotherapy, and possibly surgery. Survival rates are typically higher for early-stage patients because treatment is more focused and targeted. For patients with advanced disease, although combination therapy may improve survival, the overall prognosis is still not as good as that of patients with earlier stages.

Tolerance of treatment and side effects: Early-stage patients usually tolerate treatment better and are in better physical shape, so they are better able to withstand the toxic side effects of treatment. In contrast, patients in later stages may have poorer tolerance to treatment and more complex side effects due to the systemic effects of the disease and potential comorbidities.

This study reports that the 5-year LC and OS rates for squamous cell patients are 78.1% and 68.8%, respectively. The occurrence of serious LAC (radiation proctitis and cystitis, ≥G2) following conventional radiation ICBT techniques for vaginal cancer range from 15% to 25%. Regarding the late complications following treatment of vaginal cancer using the combination of Cf-252 neutron ICBT with EBRT, the rate of serious radiation proctitis and cystitis was 29.3% in patients with whole-vaginal cancer, including those with squamous cell cancer and adenocarcinoma. This rate was 34.4% for patients with squamous cell carcinoma. Generally, the stage of vaginal cancer can affect the prognosis and outcome of treatment. The results of this study indicate that the rates of OS and DFS differed significantly across different cancer stages, in patients with either whole-vaginal or squamous cell cancer. Furthermore, the rates of OS and DFS in stage I patients were significantly higher than those in whole-vaginal cancer

patients. Besides, the rates of OS and DFS in patients with stage III cancer were significantly lower than those in whole-vaginal cancer patients. This indicates that the stage of vaginal cancer can affect the outcome of the Cf-252 neutron ICBT combined with EBRT. These results highlight the efficacy of Cf-252 neutron ICBT combined with the EBRT in the treatment of primary vaginal carcinoma.

Moreover, since we used an off-axis three or four-channel applicator with a diameter of 3 or 3.5 cm to treat vaginal cancer, none of the patients suffered from vaginal necrosis. Also, the rate of heavy vaginal stenosis was 29.3%. Moreover, as the off-axis four-channel applicator could stay near the vaginal mucosa, the dose administered to the vaginal lesion was more accurate than a thin single-channel applicator. Besides, the use of an off-axis four-channel applicator decreased the exposure of the rectum or bladder. Particularly for patients with stage I squamous cell cancer, either the LC, OS, or DFS was 100% after treatment with Cf-252 neutron ICBT alone. This may be attributed to the use of off-axis intravaginal applicators. Since sufficient dose could be delivered to the vaginal lesion, a high rate of LC and a low rate of LAC were observed.

Most vaginal lesions (80%) are squamous cell carcinomas. Adenocarcinoma commonly metastasizes from other primary sites (e.g., uterus, colon, ovary, kidney, and breast), except for primary clear cell carcinomas.[25] True primary vaginal adenocarcinomas are rare. The detailed treatment results of primary adenocarcinoma have not been reported yet, except for sporadic case reports. The use of Cf-252 neutron ICBT for the treatment of primary vaginal adenocarcinoma in this study resulted in LC, OS, and LAC rates of 44.4%, 33.3%, and 33.3%, respectively. Although these rates did not differ significantly between squamous and adenocarcinoma patients, the mean survival time was significantly different (68.6 vs. 42.4 months). The reason for this was that vaginal adenocarcinoma patients often died soon after definitive radiotherapy (the median survival time was only 16 months).

In the case of vaginal cancer ICBT, it is difficult to deliver a precise dose to lesions. The primary difficulty is the selection of the vaginal applicator, which is essential when the tumor involves the upper 1/3rd of the vagina. This needs the combined use of intrauterine tandem and ovoid applicators, along with vaginal cylinder applicators and interstitial implants. Under such a situation, it is easy to present a cold-dose spot at the fornix and a hot-dose spot at the lower section of the vagina where the two applicators overlap. Generally, one fraction of the interstitial implant needs to be delivered to the fornix to supplement the deficient dose in some patients. In the case of lesions in the lower 2/3rd of the vagina, despite the availability of single-channel applicators of a diameter of 25 mm and eccentric four-channel vaginal cylinders of diameters of 30 mm or 35 mm, it is difficult to deliver a precise dose to the vaginal lesion because of the variable vaginal tightness. Secondly, it is difficult to define common composite dose reference points when the tumor involves the upper 1/3rd of the vagina. Three different dose reference points should be selected: the first one at point A when the lesion is treated with intrauterine tandem and ovoid applicators, the second one on the vaginal mucosa surface when the lesion is treated with vaginal cylinder applicators, and the third one at a point 5 mm from the source center when the persistent lesion is treated with the interstitial implant. Thus, it is difficult to calculate a precise dose for the vaginal tumor at a common composite dose reference point. Moreover, the Cf-252 source is larger than the conventional one, due to which, the size of the applicator is larger than that of the conventional one. Therefore, it is difficult to select the vaginal applicator. Furthermore, it is easier to present a cold-dose spot and more difficult to deliver an interstitial implant at the fornix than the conventional one.

In the treatment of vaginal cancer, Cf-252 neutron therapy is potentially advantageous because it can provide more precise and deeper radiation therapy for deep-seated tumors, especially in cases where the anatomical location is complex, difficult to resect, or responds poorly to conventional radiotherapy. Compared with conventional radiotherapy, Cf-252 neutron therapy has a high LET, which enhances the biological effect of radiation therapy and improves the killing efficiency of tumor cells.

When combined with chemotherapy, neutron capture can enhance the killing effect of chemotherapeutic agents on cancer cells, because radiotherapy can induce the sensitivity of tumor cells to chemotherapeutic agents, which improves the local control rate of the treatment and increases the overall survival rate of the patients through the combined effect.

The use of Cf-252, a rare and expensive radioisotope, in ICBT could provide a new therapeutic avenue for local control and potentially improve survival. This type of radiotherapy utilizes high LET alpha particles and neutron beams produced by Cf-252, which cause damage to DNA that is difficult to repair, to effectively kill cancer cells.

Combined EBRT can provide whole-pelvis treatment designed to ablate or control microscopic lesions and tumor cells that may be present. EBRT acts as a whole-body treatment by delivering an effective dose of radiation to areas that are difficult to reach directly with ICBT. ICBT, on the other hand, is able to precisely send high doses of radiation to tumor tissue with as little damage as possible to surrounding normal tissue.

Prospects for Cf-252 neutron simple ICBT combined with EBRT in patients with vaginal cancer include: (1) Advantage of local control: the high LET properties of Cf-252 mean that it can provide enhanced local control, especially for tumors that are difficult to remove or reach with radiotherapy. (2) Treatment of recurrent vaginal cancer: for patients with recurrent vaginal cancer, Cf-252 ICBT in combination with EBRT may offer a new treatment option, especially when conventional treatment options have been exhausted. (3) Deep Tumors: Cf-252 may have a unique advantage in treating deep tumors because of its ability to

generate deep neutron penetration, which may be effective in treating deep tumor tissue. (4) Side effect assessment: The side effects and long-term outcomes of Cf-252 neutron radiotherapy combined with EBRT need to be further evaluated to ensure efficacy while minimizing the impact on patients' quality of life.

Future research directions may include: (1) Dose effect and toxicity studies: to assess the efficacy of different doses of Cf-252 ICBT combined with EBRT and the toxic effects of these treatments on normal tissues. (2) Biomarker studies: to better predict response and tolerability, it may be valuable to study biomarkers associated with Cf-252 ICBT. (3) Treatment strategy optimization: segmenting patient populations and customizing treatment regimens based on tumor size, location, stage, and overall patient health. (4) Combination of other therapeutic modalities: Investigate the effect of using Cf-252 ICBT in combination with other therapeutic modalities such as chemotherapy, immunotherapy, or targeted therapy. (5) Clinical trials: Conduct additional prospective, randomized clinical trials to validate the safety and efficacy of Cf-252 ICBT in combination with EBRT, as well as the impact on quality of life.

Although the combination of Cf-252 neutron ICBT with EBRT for the treatment of vaginal cancer patients is effective and a high LAC rate is acceptable, the neutron source is large and expensive. Moreover, calibration of the precise biological-equivalent dose of Cf-252 neutron is difficult to implement. Cf-252 neutron ICBT is rarely used compared to Ir-192 and Cs-137 ICBT, particularly in Western Europe and North America. Due to the large population of China, the number of primary vaginal cancers is significant compared to other countries. Furthermore, it is more important to deliver a customized dose to each vaginal cancer patient. This strategy somewhat makes up for the shortcoming of Cf-252 neutron ICBT. We accumulated information on 41 patients over 5 years. As the results of Cf-252 neutron ICBT for the treatment of vaginal cancer are closely related to the experience of radiation oncologists, the obtained experience is valuable and further data needs to be collected. Therefore, the results of Cf-252 neutron ICBT for the treatment of vaginal cancer need to be monitored and improved further.

CONCLUSION

In summary, the use of Cf-252 neutron ICBT combined with EBRT treatment resulted in a higher rate of local control of vaginal cancer and a lower rate of recurrence. Thus, this combination therapy is expected to improve the long-term survival rate, and has clinical prospects.

AUTHOR DISCLOSURE STATEMENT

Authors have no conflict of interest.

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DATA AVAILABILITY

All data generated or analyzed during this study are included in this published article.

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