# Clinical Report on Californium-252 Neutron Intraluminal Brachytherapy Combined with External Irradiation for Cervical Carcinoma Treatment

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**OBJECTIVE** To observe the curative effects and complications of californium-252 ($^{252}$Cf) neutron intraluminal brachytherapy (IBT) combined with external irradiation (EI) for treatment of cervical carcinoma.

**METHODS** From December 2000 to December 2004, 128 cases of cervical carcinoma staged into IIA~IIIB according to the International Federation of Gynecology and Obstetrics (FIGO) standards were treated with $^{252}$Cf neutron IBT using 8~10 Gy per fraction, once a week. The total dose at reference A point was 36~40 Gy in 4~5 fractions. From the second day after $^{252}$Cf neutron IBT treatment, the whole pelvic cavity was treated with $^{60}$Co γ-ray EI, applying 2 Gy per fraction, 4 times per week. After 20~25 Gy of EI, the center of the whole pelvic field was blocked with 4 cm of lead in width. The total dose of EI was 45~50 Gy.

**RESULTS** The short-term therapeutic effects were CR 95.3% and PR 4.7%. The 3 and 5-year local control rates were 93.5% and 87.9%. The overall 3-year survival rate was 87.5% and for Stages II and III , 90.9% and 81.5% respectively; the overall 5-year survival rate was 70% and for Stages II and III, 76.2% and 61% respectively. The rate of radiation complications was 4.7% for radiation cystitis, 7.8% for radiation proctitis, 6.3% for vagina contracture and adhesion and 5.5% for protracted radiation proctitis.

**CONCLUSION** An combination of $^{252}$Cf neutron IBT with EI for treatment of cervical carcinoma can be well-tolerated by cervical carcinoma patients. The rate of local tumor control is high and radiation complications are few.

**KEYWORDS: californium-252 neutron, brachytherapy, radiotherapy, cervical carcinoma.**

Radiotherapy is used to treat patients in all stages of cervical carcinoma, especially in stages later than IIA. With the use of high-energy radiation, afterloading techniques and computer technology in the clinic, radiotherapy treatments for cervical carcinoma have been unceasingly improved, but the survival rate of these patients has shown little improvement. Gamma radioactive nuclides such as $^{60}$Co, $^{137}$Cs, $^{192}$Ir, etc. are often used as a radioactive source to treat cervical carcinoma patients with intraluminal brachytherapy. Gamma rays provide low linear energy transfer (LET), their curative effects are influenced by the oxygen content in the tumor tissue and by the cell cycle of the tumor. Because of these variables, irradiation of a tumor may only result in sublethal or potentially lethal cell damage, leaving the tumor out of control and prone for relapse. Neutron rays produce high

linear energy transfer, which have particular radiobiological characteristics. In the late 1960s, $^{252}Cf$ neutron radiation was used for intraluminal brachytherapy and interstitial implants in treating gynecological malignant tumors in America, the Former Soviet Union and Japan. Early results showed the advantages of neutron radiation for tumor treatment. From December 2000 to December 2004, 128 cervical carcinoma patients were treated with $^{252}Cf$ neutron radiation using intraluminal brachytherapy combined with external $^{60}Co$ γ-ray irradiation, in order to explore the therapeutic effects and complications of $^{252}Cf$ neutron radiation for treatment of cervical carcinoma. This report summarizes our results.

## MATERIALS AND METHODS

### Clinical data

In our study, 128 cervical carcinoma patients were 32 to 80 years of age, with a mean age of 49. Karnofsky (KPS) scorese ≥ 70 points, with clinical symptoms of irregular colporrhagia, leukorrhagia, inferior abdominal gas pains and lumbodynia. All the patients were definitely diagnosed by pathological diagnosis; hemograms and liver and kidney function were normal. The extent of the disease was defined by means of a chest X-ray, abdominal B type ultrasound and pelvic cavity CT scan. The stage of disease was determined according to the FIGO (1997) standard classification. The distribution of histopathologic type, size and stage of cervical carcinoma of patients are listed in Table 1. All patients were treated with first-time radiotherapy.

### Treatment

The patients on the first day were treated with $^{252}Cf$ neutron intraluminal brachytherapy and then from the second day with external irradiation.

$^{252}Cf$ neutron was applied by means of a $^{252}Cf$ neutron afterloading system (LZH-1000 type, produced by the Lin Den Science and Technology Co, Shenzhen). The source intensity of $^{252}Cf$ neutrons was 678.3 ug (measured on April 26, 2000), half-life period of $^{252}Cf$ neutrons was 2.65 years. Neutron rays and gamma rays were emitted during the time of decay, the average energy of $^{252}Cf$ neutrons was 2.13 MeV, the emissivity of $^{252}Cf$ neutrons were $2.4\times10^{6}n.s^{-1}.g^{-1}$ and gamma rays were $1.3\times10^{7}\gamma.s^{-1}.g^{-1}$.

The conversion of $^{252}Cf$ doses to Gy-equivalents (Gy-eq) was made using the following formula: $Gy\text{-}eq=N^{0.2}RBEn.Dn+D\gamma$.

Dn=$^{252}Cf$ neutron component dose

Dγ=$^{252}Cf$ γ component dose

RBEn=relative biological effectiveness of neutrons

N=number of treatments

The RBE of the $^{252}Cf$ neutron component had the value of 2~3.

When the patients were treated with $^{252}Cf$ neutron intraluminal brachytherapy, we inserted a tri-cavity applicator without $^{252}Cf$ in their uterine cavity and the two fornices, then took a X-ray orthogonal radiograph of their pelvic cavity and according to the extent and size of the tumor, developed a personal treatment plan by means of a treatment planning system. The reference dose point was A point, the dose to bladder and rectum was less than 60% of A point and the dose ratio of the cervix to the vagina was 1:1. $^{252}Cf$ neutron intraluminal brachytherapy was administered once a week, 8~10 Gy per fraction. The total dose of reference A point was 36~40 Gy in 4~5 fractions.

External irradiation was given by $^{60}Co$ γ-ray beams with the position and tumor target being determined by a CT scan. The applied dose of 45~50 Gy, 2 Gy per fraction, 4 times per week was administered with two opposite fields in divided doses of 20~25 Gy in full and split fields to the pelvis. The upper edge of the field was at the level of the L4~L5 region, the lower edge was at the inferior border of the obturator foramen, the side edges were at 2 cm outside of the pelvis and the width of the central shield of the split field was 4 cm.

There was no change of therapy for any patient due to intolerance of treatment or any other reason during the course of treatment.

During the course of treatment, clinical symptoms and signs of patients were observed every day, routine blood and biochemical examinations were conducted each week and a B type ultrasound of the pelvic cavity was administered each week to measure the regression

**Table 1. The distribution of histopathologic type, size and stage of cervical carcinomas**

| Histopathologic Type | | Size | | Stage | | | |
|---|---|---|---|---|---|---|---|
| Squamous carcinoma | Adenocarcinoma | ≥ 4 cm | < 4 cm | IIA | IIB | IIIA | IIIB |
| 122 | 6 | 105 | 23 | 19 | 58 | 32 | 19 |

of the tumor.

### Follow-up

Follow-up started 3 weeks following completion of treatment, including once per 3 months as an out-patient for a clinical check-up in the first year, and once per 6 months for a check-up from the second year on. The check-ups consisted of a routine gynecological examination, B type ultrasound examination of the pelvic cavity, cervical scraping and biopsy in the area where a possible doubted tumor remnant may be or relapse may occur.

The patients were followed-up over a 1 to 5 year period with a follow-up rate of 96% and ended in December 2005.

### Statistics

A statistical comparison of the treatment results was performed according to the Log-Rank test and Kaplan-Meier method for survival rates (SPSS Version 13.0 for Windows).

## RESULTS

### Curative effects

The remission rate of vaginal bleeding was 100% and bleeding ceased after two treatments with the $^{252}Cf$ neutron intraluminal brachytherapy. The remission rate of leukorrhagia, inferior abdominal gas pains and lumbodynia was 95.3% (82/86), 100% and 91.4% (53/58) respectively. These symptoms were relieved at the end of the treatment.

According to the WHO standards relating to solid tumor therapeutic effects, the effects are categorized as complete response (CR), partial response (PR), no change (NC) and progressive disease (PD). We consider CR and PR as effective. After treatment, CR was 95.3% (122/128), PR was 4.7% (6/128), the objective effective rate (CR+PR) was 100%.

The 3-year local control rate was 93.5% (73/78) and the 5-year local control rate was 87.9% (29/33).

### Rate of radiation complications

Early radiation complications occurred in the 3rd or 4th week of radiotherapy, especially in the 5th week. The rate of radiation cystitis was 4.7% (6/128), causing frequent, urgent micturition and odynuria with no hematuria. The rate of radiation proctitis was 7.8% (10/128), resulting in tenesmus, anus gas pains, and mucous stool. A decrease in appetite was seen in 85.2% (109/128) of the patients. Leukocyte degression was grade 1 in 88.3% (113/128) and grade 2 in 7.8% (10/128). Changes in blood biochemical assays were not significant.

The late radiation complications were 6.3%(8/128) for vagina contracture and adhesion, 5.5%(7/128) for protracted radiation proctitis. Radiation proctitis occurred 9 months after completion of radiotherapy and vagina contracture and adhesion occurred 1 year after completion of radiotherapy.

### Survival rate

The 3 and 5-year overall survival rates were 87.5% and 70%, whereas the 3 and 5-year survival rates for Stage II were 90.9% and 76.2% and for Stage III were 81.5% and 61% respectively. When comparing Stage II and Stage III patients for the 3 and 5-year survival rates, there was no statistically significant difference ($\chi^2$=1.154, $P$>0.05, Fig.1).

The 3 and 5-year survival rates for patients with tumors of diameter <4 cm were 87.6% and 71.4% and for those with tumors of diameter ≥ 4cm were 86.7% and 65% respectively. Comparing cases with tumor diameter ≥ 4 cm and < 4cm for the 3 and 5-year survival rates, there was no statistically significant difference ($\chi^2$=0.023, $P$>0.05, Fig.2).

## DISCUSSION

$^{252}Cf$ spontaneously releases neutron rays, which cause high linear energy transfer, resulting in radiobiological effects such as high relative biological effective (RBE) value, low oxygen enhancement rate (OER), inhibition of sublethal and potentially lethal cell damage repair and minimal dependency of radiation sensitivity on the cell cycle. Because neutron fission energy is low and the penetrating power is poor, neutron rays are suited for intraluminal brachytherapy and interstitial implantation rather than for external irradiation.[1] Much experience has been gained from studies using $^{252}Cf$ to treat cervical carcinoma. Maruyama et al.[2] used $^{252}Cf$ neutron brachytherapy combined with surgery and gamma ray external irradiation to treat 218 non-randomized cervical carcinoma patients in Stages IB~III during the years 1976~1983. The 5 and 10-year overall survival rates were 87%, 62%, 33% and 82%, 61%, 25% respectively. Marjina [3] reported studies from 345 cases of cervical carcinoma in Stages II~III who were treated with $^{252}Cf$ neutron intraluminal brachytherapy and external irradiation. The 5-year survival rates for both Stages II and III were 72.3%. Zheng et al.[4] studied cellular effects of $^{252}Cf$ neutron

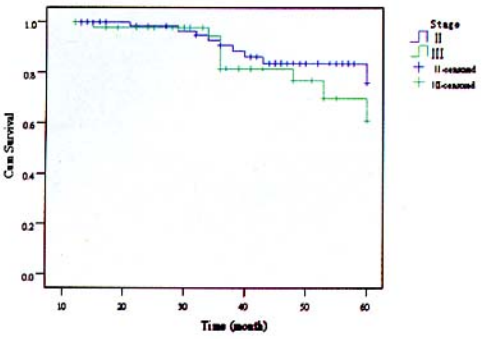


**Fig.1.** Comparison of Stage II and Stage III patients for 3 and 5-year survival rates.

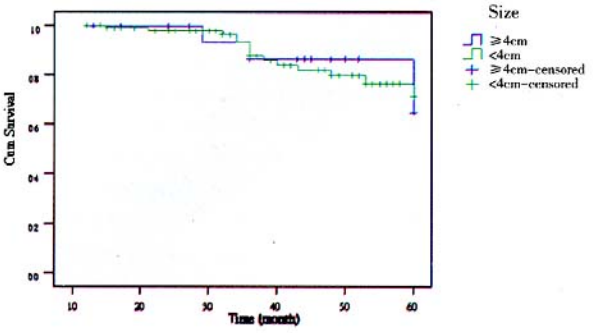


**Fig.2.** Comparision of patients with tumor diameter ≥ 4 cm and < 4 cm for 3 and 5-year survival rates.

rays on cervical carcinoma, showing that $^{252}Cf$ induced apoptosis and inhibited proliferation of the tumor cells. Our choice of intracavitary $^{252}Cf$ therapy as the procedure to be used in this study was based on Maruyama's empirical findings [2,5] Initial application of neutrons as a source of irradiation during therapy in combination with subsequent external gamma irradiation serves to immediately eliminate a large or radioresistant tumor, promote reoxygenation of the tumor cells, increase blood supply to the tumor, boost radiosensitivity to photons and improve the local control and survival rates. Maruyama[6] analyzed 41 cases of cervical carcinoma in Stage IIB. They showed that normal tissue showed little damage if the external irradiation to the pelvic cavity was administered after $^{252}Cf$ neutron brachytherapy, the radiation complication rate was 3%. In contrast when the $^{252}Cf$ neutron brachytherapy was applied after external irradiation, the radiation complication rate raised significantly (40%). Furthermore, with prolonged therapy time , the probability of tumor repopulation increased with poorer therapeutic tumor control. Therefore, $^{252}Cf$ neutron radiation should not be used in a later period of therapy. In using time-dose fractions, it is better to apply $^{252}Cf$ neutron brachytherapy at a higher fraction dose (10~20 Gy_eq) with less frequency. The reason is that, a sufficient dose administered over a short time can kill hypoxic and radioresistant tumor cells, reduce tumor repopulation and radioresistant colon cells, thereby boosting the local control rate. In comparing single therapy with multiple therapy, the relative biological effective (RBE) value to normal tissue is reduced by 2.5 times, resulting in fewer normal-tissue complications. $^{252}Cf$ neutron therapy is suited to higher fraction and a shorter course of treatment. In our study, the 128 patients were treated with $^{252}Cf$ neutron intraluminal brachytherapy once a week on the first day of treatment with 8~10 Gy per fraction in 4~5 fractions. Then they received external irradiation 4 times per week. All the patients tolerated the therapy well, illustrating that the treatment scheme is feasible.

In this study, the patients had irregular colporrhagia, leukorrhagia, inferior abdominal gas pains and lumbodynia before treatment. After radiotherapy, the remission rates of vaginal bleeding, leukorrhagia, inferior abdominal gas pains and lumbodynia were 100% , 95.3%, 100% and 91.4% respectively. These results show that $^{252}Cf$ neutron intraluminal brachytherapy for cervical carcinoma can relieve the symptoms of bleeding and pain and improve patients' quality of life.

After treatment, CR was 95.3%, PR was 4.7% and the objective effective rate was 100%. These results make clear that $^{252}Cf$ neutron radiation for cervical carcinoma produces satisfactory short-term therapeutic effects, even for cervical adenocarcinoma which is resistant to conventional photon radiation. In studies reported by Luo et al., [7] $^{252}Cf$ neutron intraluminal brachytherapy combined with external irradiation for cervical carcinoma, the 2-year local control rate was 100%. In our study, the 3 and 5-year local control rates were 93.5% and 87.9% , showing that $^{252}Cf$ neutron brachytherapy can result in a satisfactory local control rate. Zhou et al.[8] showed that, using $^{192}Ir$ intraluminal brachytherapy combined with external irradiation for cervical carcinoma, the 3-year survival rate was 83.1%, 87.5% for Stage II and 76.1% for Stage III. In

our study, the 3-year overall survival rate was 87.5% and for Stages II and III, 90.9% and 81.5% respectively, which is better than previous reports. Using $^{192}$Ir intraluminal brachytherapy combined with external irradiation for cervical carcinoma, Wang et al.[9] reported the 5-year survival rate was 64.2% and for Stages II and III, 73.2% and 55.7% respectively. In other studies,[10] $^{252}$Cf neutron brachytherapy treatment for cervical carcinoma produced a 5-year survival rate of 70~80%. Our results showed that the 5-year overall survival rate was 70% and for Stages II and III, 76.2% and 61% respectively, which was better than that of conventional afterloading brachytherapy, indicating that $^{252}$Cf neutron radiation for cervical carcinoma can produce a better long-term survival rate. In comparing the 3 and 5-year survival rates for Stage II and III patients in our findings, there was no statistically significant difference. As our study lacked Stages I and IV cases, the efficacy of $^{252}$Cf neutron rays on different stages of cervical carcinoma needs to be further studied.

Conclusions drawn from a study of 267 cases of cervical carcinoma[11] indicated that the tumor size was an important index of prognosis. But in our study, we saw no significant correlations between the tumor size and prognosis. One of the possible reasons is that, in the bigger tumors, there is a higher proportion of hypoxic cells inside the tumor, causing enhanced resistance to routine radiotherapy. As the oxygen enhancement rate (OER) is low, neutron rays have more power to kill hypoxic cells, thus raising the local control and survival rates. In that our follow-up period for the patients was short, the influence of tumor size on prognosis should be further observed.

In another study,[8] $^{192}$Ir intraluminal brachytherapy was combined with external irradiation to treat cervical carcinoma patients. The rates of radiation cystitis and radiation proctitis were 5.9% and 13.6% at an early time and later 4.2% and 15.3%, but formation of rectum vaginal fistulas was only 0.9%. Tacev et al.[12] published a 5-year randomized study, showing that treatment of cervical carcinoma with $^{252}$Cf neutron intraluminal brachytherapy resulted in rates of radiation cystitis, radiation proctitis and rectal ulcers that were 16.2%, 18% and 0.8% respectively. There was no indication of cystelcosis. However, by using photon ray intraluminal brachytherapy for cervical carcinoma, the rates of radiation complications noted above were 14.6%, 54% and 5.5% respectively and the rate of cystelcosis was 3.6%. In our study, early radiation complications were radiation cystitis (4.7%) and radiation proctitis (7.8%), but symptoms improved using antiinflammatory and other appropriate treatments. The late radiation complication was mainly vaginal contracture and adhesion, at a rate of 6.3%, which was lower than the 16.39% previously reported.[13] The major site where vaginal contracture and adhesion occurred was in the upper 1/3 of the vagina or fornix. The reasons may be the following: first, the cervix and fornix were the regions of highest radiotherapy dosage, which served for good tumor control, but resulted in irreversible normal tissue damage; second, the vaginas were not flushed thoroughly during or after radiotherapy. Vaginal flushing will clean the vagina, prevent infection and adhesion and promote epithelial healing. Therefore, a vaginal flush should be conducted at the beginning of radiotherapy.

Another late radiation complication was protracted radiation proctitis, with an incidence of 5.5%. Two patients who suffered from protracted radiation proctitis were relieved of this problem using antiinflammatory treatments and hemostasis. Another five patients need an enema with an antibiotic mixed with dexamethasone to achieve relief. Important measures to reduce bladder and rectum damage is to ensure that the rectum is empty, pack the vagina with bandages before therapy so as to push the rectum and bladder away from radioactive source. It's clear that, by employing $^{252}$Cf neutron intraluminal brachytherapy to treat cervical carcinoma, the complications are no higher than that with conventional gamma afterloading intracavitary brachytherapy, the side effects are mild and the patients tolerate the therapy well.

Five patients died from local tumor relapse and another 13 patients died from tumor metastasis: of which 6 were in the lungs metastasis, 4 in the liver and 3 in bones. Metastatic patients were all in Stage III, indicating that patients in late clinical stages (III~IV) should be treated with radiotherapy combined with chemotherapy.

The use of $^{252}$Cf neutron intraluminal brachytherapy for cervical carcinoma has distinct advantages such as less radiation complications, a higher local control rate and fewer relapses, pointing to more potential clinical applications. However the period of $^{252}$Cf use has been short, so further studies are needed to examine the best fraction dose and the suitable time of therapy as well as the long-term radiation complications which now are under observation.

## REFERENCES

1 Martin RC, Knauer JB, Balo PA. Production, distribution

and applications of californium-252 neutron sources. Appl Radiat Isot. 2000;53:785-792.
2 Maruyama Y, Nagell V, Yoneda J. A review of californium-252 neutron brachytherapy for cervical cancer. Cancer. 1991;68:1189-1197.
3 Marjina L A. High dose rate $^{252}Cf$ neutron intraluminal brachytherapy for treatment of cervical carcinoma and corpus carcinoma. Chin J Radiat Oncol. 1997;6:145-146.
4 Zheng X H, Chen Z Q, Li L, et al. The effect of $^{252}Cf$ neutron radiation on apoptosis and proliferation of uterine cervical carcinoma cells. Chong Qing Medicine. 2005;34: 885-887.
5 Maruyama Y, Feola JM, Wierzbicki J. Study of biological effects of varying mixtures of Cf-252 and P radiation on the acute radiation syndromes: relevance to clinical radiotherapy of radioresistant cancer. Int J Radiat Oncol Biol Phys. 1993;27:907-914.
6 Maruyama Y, van Nagell JR, Yoneda J, et al. Schedule in Cf-252 neutron brachytherapy: complications after delayed implant therapy for cervical cancer in a phase II trial. Am J Clin Oncol. 1993;16:168-174.
7 Luo G, Zheng CW, Shan JL, et al. The Preliminary report of cervical cancer treated with californium 252 neutron afterloading intracavitary radiotherapy. Chin J Obstet Gynecol. 2001;36:742-744.
8 Zhou CH, Lv WC, Chen HJ, et al. $^{192}Ir$ afterloading intracavitary brachytherapy and external beam radiotherapy for carcinoma of uterine cervix. Chin J Radiat Oncol. 2002; 11:235-236.
9 Wang YW, Li AL, Yao X, et al. Intracavitary brachytherapy and external beam radiotherapy for 367 cases of cervical carcinoma. J Prac Diagn Ther. 2003;17:302-303.
10 Marjina L, Uymanov VA, Nechshkin MI. Interstitial irradiation in vulvar cancer. Herald Cancer Research Center AMS Russia. 1997;1:42-48.
11 Sheng XG, Hou XT, Li HQ, et al. Approach of death causes of cervical carcinoma with stage II and III within 2 years after radiotherapy: analysis of 267 cases. Tumor. 2000;20:48-50.
12 Tacev T, Ptackova B, Stmad V. Californium-252 ($^{252}Cf$) versus conventional gamma radiation in the brachytherapy of advanced cervical carcinoma. Strahlenther Onkol. 2003; 179:377-384.
13 Zeng D H, Liang Y X, Tian Q. Intracavitary brachytherapy combined with external beam radiotherapy for 183 cases of cervical carcinoma. Journal of Youjiang Nationalities Medical College. 2005;2:208-209.