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An evaluation comparing Californium^{252} neutron brachytherapy with neoadjuvant intra-arterial embolism chemotherapy assisted surgery effect for treating advanced cervical carcinoma patients

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Summary

Purpose of investigation: To compare the therapeutic and side effects of using Californium^{252} (^{252}Cf) neutron brachytherapy with neoadjuvant intra-arterial embolism chemotherapy in combination with surgery for treating Stage Ib2-IIb cervical cancers (CCs). *Materials and Methods:* Thirty-two Stage Ib2-IIb CC patients were enrolled and randomly divided into two groups from January 2007 to April 2010 in the present Hospital. Prior to surgery within four weeks, a total of 17 cases were treated with ^{252}Cf neutron brachytherapy (700-800 cGy doses at point A) once a week (Group A), and 15 cases were treated by neoadjuvant intra-arterial embolism chemotherapy using a combination of bleomycin, carboplatin, and cyclophosphamide twice (Group B). The clinical symptoms and signs, side effects, and relapse condition follow up until July 2013 were compared between the two groups for the perioperation. *Results:* Reductions in tumor mass and CR+PR were not significantly different between the groups before the surgery ($p > 0.05$). Abdominal pain and pelvic adhesions were significantly more severe in Group B ($p < 0.05$). There were no significant differences in surgical time, blood loss or the other side effects between Groups A and B ($p > 0.05$). The percentage of pelvic tumor recurrences in Group A was lower than that of the patients in Group B (11.8% *vs* 20.0%) although with no significant difference at present. No distant metastasis has been found in both two groups. *Conclusion:* Except for less abdominal pain and pelvic adhesions, ^{252}Cf neutron brachytherapy has perioperative effects similar to those of neoadjuvant intra-arterial embolism chemotherapy.

Key words: Advanced cervical cancer; Neoadjuvant intra-arterial embolism chemotherapy; Californium^{252} neutron brachytherapy.

Introduction

Cervical cancer (CC) is the second most common cancer in women worldwide and is a leading cause of cancer-related deaths in women in underdeveloped countries. CC is one of the most common cancers affecting a woman's reproductive organs. In China, epidemiological research in the central and western regions has shown that CC is becoming a major health concern for women in the countryside. Nearly 100,000 cases of CC are diagnosed annually, with approximately 20,000 deaths in 2001 alone in China [1-2].

Surgery for CC may be an option in the early stages when the tumor is confined, while radiotherapy, chemotherapy or radiochemotherapy is used in the late stages of CC. No significant increases in curative rates have been observed from photon radiotherapy, despite important progress in radiotherapy techniques and quality assurance. Among the reasons for this lack of effect is the varying radiosensitivity of different tumor subpopulations. Treatment with Californium^{252} (^{252}Cf), as a source of gamma/neutron radiation in brachytherapy, provides new treatment modalities to overcome this limitation [3-5]. However, its effects when combined with surgery need to be reevaluated. In addition, neoadjuvant chemotherapy combined with surgery for CC has recently become an important treatment for advanced CC, especially Stage IIb disease [6-7]. Intra-arterial embolism chemotherapy based on cisplatin or carboplatin has become the most common form of neoadjuvant chemotherapy. The primary purpose of this study was to compare the perioperative therapeutic effects of ^{252}Cf neutron brachytherapy and neoadjuvant intra-arterial embolism chemotherapy when they are used with surgery to treat advanced Stage Ib-IIb CC. The relapse sites and survival were also analyzed.

Materials and Methods

Patients

From January 2007 to April 2010, a randomized study of 64 women with bulky or locally advanced Stage Ib–IIb CC was performed at the Department of Obstetrics and Gynecology of the First Affiliated Hospital of Sun Yat-sen University. The disease stage was determined according to the FIGO classification sys-

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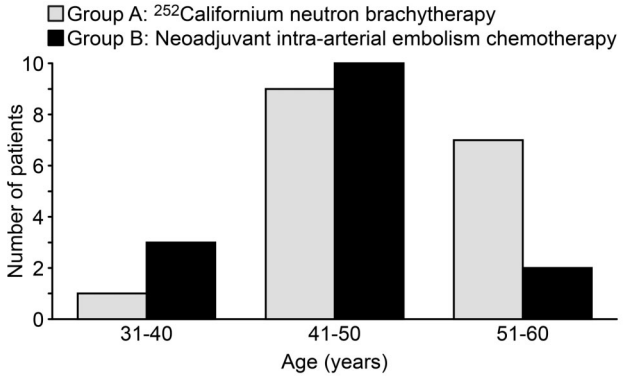

Figure 1. — Comparison of the distribution of patients with Stage IB2 to IIB cervical carcinomas by age in the two treatment groups.

Table 1. — *Distribution of the two patient groups by stage, grade, and histopathology.*

Group A	n	Squamous cell carcinoma	Adenocarcinoma	G1	G2	G3
Ib2	12	12	0	1	1	10
IIa	3	2	1	0	1	1
IIb	2	2	0	2	0	0
Total	17	16	1	3	2	11

Group B	n	Squamous cell carcinoma	Adenocarcinoma	G1	G2	G3
Ib2	10	9	1	0	2	6
IIa	4	3	1	0	1	2
IIb	1	0	1	1	0	0
Total	15	12	3	1	3	8

*Group A: ^{252}Californium neutron brachytherapy.
*Group B: Neoadjuvant intra-arterial embolism chemotherapy.

tem (2000) [8] on the basis of the following examinations: inspection, palpation, biopsy, cystoscopy, liver sonography, chest X-ray, and hematological/biochemical examination of the blood. Lymphography of the retroperitoneum and pelvis using magnetic resonance imaging (MRI) was also performed. Eleven cases with internal diseases or a history of pelvic surgeries, 14 cases that were being treated by intravenous chemotherapy, four cases that were treated by chemoradiation, and three missed cases were eliminated. The remaining 32 cases (22 in Stage Ib, seven in Stage IIa, and three in Stage IIb) were enrolled in the study. The ages of the patients ranged from 32 to 57 years, and the average age was 46 years. The patients were allocated to treatment groups using random selection. The ages of the patients by group are shown in Figure 1. Two cases presented with vaginal hemorrhage. No patient had to be withdrawn from the study during treatment or monitoring. All of the tumor diameters were greater than four cm when measured by colposcopy, ultrasound examination, and MRI before treatment. Twenty-eight cases were squamous carcinomas, and four cases were adenocarcinomas. The staging, histopathological type, and grading of the cervical carcinomas by group are shown in Table 1. The patient's age, stage, and tumor grade served as the criteria for a stratified randomization. These criteria were considered during the allocation of the patients into the treatment groups, and there were no significant differences between the groups as a result. This protocol was approved by the First Affiliated Hospital of Sun Yat-sen University Ethical Review Committee, and all recruited patients provided informed written consent.

Methods

The patients had normal hepatic, pulmonary, and cardiac function and no chemotherapy or radiotherapy contraindications. The 32 patients were randomized into two groups. Seventeen cases (Group A) were treated with identical 700-800 cGy doses of ^{252}Cf neutron brachytherapy at point A in the paracervical space once a week. The doses were administered by intracavitary insertion once a week continuously over four weeks in a specialized intracavitary ^{252}Cf therapy room of the outpatient department at Wu Jing Zong Dui Hospital of Guangdong Province. The intracavitary ^{252}Cf neutron component was administered in one uterovaginal application using a disposable cervical tube. Fifteen cases (Group B) were treated with two continuous courses of neoadjuvant intra-arterial embolism chemotherapy (consisting of a combination of 45 mg bleomycin, 0.35/m^2 carboplatin, and 0.6/m^2 cyclophosphamide) that were administered every three weeks. The examination, therapy, and short-term monitoring were performed by the same team of physicians (gynecologists and radiation oncologists).

The effects and side effects were evaluated following chemotherapy or radiotherapy prior to surgery. Ultrasound and MRI examinations were performed before and after the administration of chemotherapy or radiotherapy to evaluate the change in tumor size. A radical hysterectomy with pelvic lymphadenectomy was performed three weeks after chemotherapy or radiotherapy in all the patients. The surgical effects and relapse condition were also compared between the two groups.

Therapeutic effect criteria

The therapeutic effects were judged by the changes in tumor size before and after the chemotherapy or radiotherapy. The following criteria of the Union for International Cancer Control (UICC) were used: complete remission (CR) consisted of a tumor that completely disappeared macroscopically and no new lesions; partial remission (PR) consisted of a reduction in tumor size of $\geq$ 50% and no new lesions; stable disease (SD) consisted of a reduction in tumor size of $\leq$ 50% and no new lesions; and progressive disease (PD) consisted of no reduction in tumor size or the appearance of new lesions. CR and PR were considered to indicate effective treatment, and SD and PD were considered to indicate ineffective treatment. The patients who died for reasons other than cervical carcinoma and had no evidence of disease at the most recent checkup were included when calculating the overall survival rate.

Statistical analysis

A statistical comparison of the treatment results between the groups was performed with SPSS Version 13.0 using the Kaplan-Meier method for survival analysis and the log-rank test and Mann-Whitney nonparametric tests for side effects rates. The *t*-test and χ^2 test in SPSS 13.0 were also used. A p value <0.05 was considered significant.

Results

Comparison of therapeutic effect between the two groups

Group A was treated with four courses of ^{252}Cf neutron brachytherapy, and Group B was treated with two courses of neoadjuvant intra-arterial embolism chemotherapy at the same intervals. The tumor sizes in the two groups before

Table 2. — *Comparison of cervical tumor diameter (in mm) before and after chemotherapy and radiation between the two groups.*

	Group A	Group B	*p* value
Before therapy	48.8 ± 5.7	50.3 ± 10.9	0.156
After therapy	18.6 ± 4.7	20.7 ± 6.6	0.257
p value	0.000	0.002	

Tumor diameter: means of the maximal diameter, as measured by ultrasound examination and MRI.

Table 3. — *Comparison of the late efficacy rates between the two groups before surgery.*

	Group A	Group B	*p* value
CR	17.6% (3/17)	20.0% (3/15)	0.911
PR	64.7% (11/17)	60.0% (9/15)	0.823
SD	11.8% (2/17)	20.0% (3/15)	0.710
PD	5.9% (1/17)	0.0% (0/15)	0.794
CR + PR	82.3 (14/17)	80.0% (12/15)	0.911

Table 5. — *Comparison of operative conditions between the two groups.*

	Group A	Group B	*p* value
Mean blood loss (ml)	673 ± 26	450 ± 15	0.238
Mean surgical time (minutes)	288 ± 38	276 ± 20	0.317
Pelvic adhesions	0/17	10/15	<0.001

Table 6. — *Relapse patterns in patients with cervical carcinoma after treatment in the two groups.*

	Stage IB2	Stage IIA	Stage IIB	Total
Group A				
Recurrence in the pelvis	0/17	1/17	1/17	2/17
Distant metastasis	0/17	0/17	0/17	0/17
Group B				
Recurrence in the pelvis	0/15	2/15	1/15	3/15
Distant metastasis	0/15	0/15	0/15	0/15

The percentage of recurrence in the pelvis in Group A was lower than that of the patients in Group B (11.8% *vs* 20.0%) although with no significant difference.

and after chemotherapy and radiotherapy were comparable, with no significant difference between the two groups ($p > 0.05$). The tumor sizes were significantly reduced after chemotherapy or radiotherapy in each group ($p < 0.05$). The tumor sizes before and after chemotherapy and radiotherapy are shown in Table 2.

According to the UICC therapeutic effect criteria, before surgery, CR occurred in three cases, PR in 11 cases, and PD in one case for Group A. The efficacy rate (CR+PR) of Group A was 82.3%. The tumor disappeared completely with presenting an erosion in three cases. The pathology of one PD case was adenocarcinoma. In Group B, CR occurred in three cases, PR in nine cases, and SD in three cases. The efficacy rate (CR+PR) was 80.0%. The tumor disappeared completely, presenting an erosion, in three cases. Vaginal hemorrhage occurred in two cases and was immediately controlled through neoadjuvant intra-arterial embolism chemotherapy. The pathology of one SD case was adenocarcinoma. The efficacy rates were not significantly different between the two groups (Table 3).

Side effects

Usual side effects such as abdominal pain, symptoms of gastrointestinal, fever, vaginal bleeding, renal dysfunction, and bone inhibition were compared between the two groups, and routine blood tests and hepatic-renal function were monitored in the two groups after chemotherapy or radiotherapy. The curative effects and complications after therapy are shown in Table 4.

The side effects rates for abdominal pain in Group A were significant lower than those in Group B. There was almost no recent toxicity reaction in Group A, except for one case of hematuria caused by contamination from vaginal bleeding. The hemoglobin level did not change after radiotherapy even in two cases with moderate anemia (Hbs of 64g/l and 80 g/l). There was no significant hepatic or renal dysfunction in each group.

Comparison of the following surgery

All patients had radical hysterectomies with adnexectomy and pelvic lymphadenectomy. The blood loss ranged from 400 to 1,500 ml and from 200 to 1,500 ml with averages of 673 ml and 450 ml in Groups A and B, respectively ($p > 0.05$). Group A had a slightly longer mean surgical time (288 minutes) than Group B (276 minutes; $p > 0.05$). During the procedures, no pelvic adhesions were found in Group A, but ten cases of different degrees of tissue necrosis and pelvic adhesions were noted in Group B. Of these ten cases, three were severe adhesions manifested by bilateral adhesion of the ureters, iliac ar-

Table 4. — *Comparison of side effects and complications between the two groups before sugery.*

	n	Abdominal pain	Vomit	Fever	Vaginal bleeding	Renal dysfunction	Bone inhibition
Group A	17	0	0	0	1	1	1
Group B	15	10	3	4	2	0	5
p value		0.001	0.350	0.202	0.737	0.794	0.189

tery, and surrounding tissue. Most cases of tissue necrosis around the ureters were formulated at the ureteral tunnel with adhesions that led to surgical difficulties. The pelvic adhesion rate of Group B was significantly higher than that of Group A ($p < 0.001$) (Table 5).

Follow-up of relapse and survival

Throughout the study period from January 2007 to July 2013, two cases in Stage Ib2 in Group A were lost to follow-up during 2011, and the remaining 15 patients in Group A were alive at the end of the study. All the patients in Group B were alive. The relapse patterns in both treatment groups are shown in Table 6.

In the patients treated with ^{252}Cf pre-surgery, the percentage of pelvic tumor recurrences was 11.8% (2/17), which was lower than that of the patients treated with neoadjuvant intra-arterial embolism chemotherapy (20.0%, $p = 0.87$, $p > 0.05$) although with no significant difference at present.. All the relapses were characterized as new lesions or vaginal residuals in the pelvis without distant metastasis.

Discussion

The therapeutic outcome and survival of patients with bulky or locally advanced CC remains poor because of the large amount of bleeding during surgery, surgical difficulties, and tumor residuals, which lead to pelvic lymph node metastasis. To reduce the tumor volume, decrease tumor cell activity, prevent dissemination, and improve the surgical resection possibility and survival rate, a comprehensive therapeutic regimen of combined surgery, radiotherapy, and chemotherapy has been developed according to FIGO 2003 guidelines [9]. Intra-arterial chemotherapy may increase the tumor's exposure to high drug concentrations in the local pelvis, which can be four to 22 times that of intravenous chemotherapy, while decreasing systemic drug delivery to tissues. Combined with embolization, intra-arterial chemotherapy may prolong the response time of the chemotherapy, simultaneously increase ischemia, and necrosis of the tumor tissues themselves, and can also effectively control large vaginal hemorrhages [10-11]. All of the above considerations have identified to increase the surgical possibilities and success rates. In recent years, the efficacy rate and CR rate of platinum-combination chemotherapy have been >80% and 9% to 18%, respectively, in cases of advanced CC [12]. In the present study, intra-arterial embolism chemotherapy combined with cisplatin, bleomycin, and cyclophosphamide prior to surgery was given to patients with advanced Stage Ib2-IIb bulky and locally CC. The efficacy rates were the same (80%), but CR rate increased to 20%; these values are similar to other previously reported chemotherapy regimens.

The discovery of ^{244}Cf as a neutron/gamma radiation source in 1950, followed by the discovery of its radionuclide ^{252}Cf in 1956, which opened up the possibility of high linear energy transfer rays (high-LET) brachytherapy in tumor treatment. In early studies showed that, depending on the method of administration, the inclusion of ^{252}Cf in tumor brachytherapy often produced better results than conventional brachytherapy, thereby opening the prospect of improved therapeutic outcomes [13, 14]. These investigations on ^{252}Cf demonstrated that during high-LET irradiation, the section of the cell survival curve that benefits from the repair of sublethal damage is practically nonexistent. The lethal effects caused by the single-hit, irreparable damage of the neutron component become prominent. During ^{252}Cf tumor therapy, therefore, there is no need for prolonged irradiation to achieve the desired biological effect [15]. The ability of X-rays and γ-rays to kill cancer cells decreases because of increased cellular hypoxia and decreased radiation sensitivity in locally advanced cervical carcinoma, which causes cancer cell residual and recurrence of the tumor due to hypoxia. From the mechanism and clinical trials, ^{252}Cf neutron rays allow for more rapid regression of tumor tissues, a higher local control rate, and less recurrence due to their ability to kill hypoxic and aerobic cells. A decreased reliance on the cell cycle for the further biological effects of high-LET radiation leads to a lower oxygen enhancement rate (OER) [16], inhibition of sublethal and potentially lethal cell damage repair [17], and a minimal dependence of radiation sensitivity on the cell cycle. A previous study has reported that three courses of ^{252}Cf neutron brachytherapy were effective in 72% of patients with locally advanced Stage Ib2 CC. This study concluded that ^{252}Cf is more effective for ray-resistant tumors by comparing 117 cases of ^{252}Cf brachytherapy to 110 cases of γ-ray brachytherapy. More than 90% of the radiation reached the target organs [18]. In the present study with advanced CC, the therapeutic efficacy rate of ^{252}Cf brachytherapy was found to be 82.4%, which is similar to that of intra-arterial embolism chemotherapy. Although the mechanisms of ^{252}Cf brachytherapy are completely different from those of intra-arterial embolism chemotherapy, the clinical therapeutic effects at the same time intervals were similar to each other.

According to this research, the incidence of abdominal pain was significantly higher in patients treated with intra-arterial embolism chemotherapy, which may have been caused by local tissue ischemia. Although pain control was often needed in some cases, there was obvious improvement by the following day. The high incidence of fever was found in the intra-arterial embolism chemotherapy group, which may have been related to the invasive nature of the procedure and the absorption of embolic agents. It should be noted in this study, however, that ^{252}Cf brachytherapy allows the direct interaction of neutrons with the cells of the tumor population, thus minimizing

the postradiation damage to healthy tissues [19]. The present authors found that ^{252}Cf neutron brachytherapy caused no obvious abdominal pain and fever even bone marrow inhibition; as a result, the patients could be treated as outpatients, and even patients with the moderately anemic tolerated the therapy.

In subsequent surgeries, the incidence of pelvic adhesions was significantly higher in the intra-arterial embolism chemotherapy group, perhaps because the blocked vessels in the tumor led to tumor tissue ischemia and necrosis, hyperemia, and adhesions caused by the subsequent collateral circulation. However, in this study, the pelvic adhesions did not significantly increase the blood loss or surgical time, and no risk of injury around organs was found. By contrast, fewer pelvic adhesions were found in the continuous surgeries following ^{252}Cf brachytherapy.

No deaths occurred in either the ^{252}Cf neutron brachytherapy or the neoadjuvant intra-arterial embolism chemotherapy groups, perhaps because of the limited follow-up times, which currently range from 34 to 73 months. Further research is needed to compare the survival rates.

^{252}Cf brachytherapy improves surgical therapeutic effects similar to those of intra-arterial embolism chemotherapy in bulky or local cervical carcinomas while causing fewer pelvic adhesions and less discomfort, such as abdominal pain.

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