

# The Combination of External Beam Radiotherapy with Cf (Californium)-252 Neutron Intracavitary Brachytherapy is Significantly Effective than with Ir (Iridium)-192 Gamma Intracavitary Brachytherapy in Controlling Stage IIB Cervical Adenocarcinoma: A Matched Pair Analysis

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## Research

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# Abstract

**Background:** To assess the efficacy of combined external beam radiotherapy (EBRT) and intracavitary brachytherapy (ICBT) with Cf-252 neutrons versus Ir-192 photons in matched pairs for stage IIB adenocarcinoma of the uterine cervix (AC).

**Methods:** Patients with stage IIB AC were matched into 19 pairs between January 2005 and March 2013 and were divided into neutron ICBT (NICBT) and photon ICBT (PICBT) groups. Pelvic EBRT was administered with 2 Gy/fraction, 4 fractions/week, to a total dose of 50–54 Gy, with the center of pelvic field blocked by 4 cm in width after 20–36 Gy in both groups. NICBT and PICBT were administered with 10.5–13 Gy-eq/fraction vs. 10–13 Gy/fraction, to a total dose of 42–53.2 Gy-eq vs. 40–51 Gy at point A. Radiotherapy was administered concurrently and sequentially with 2–4 cycles of chemotherapy, consisting of cisplatin, or carboplatin, and paclitaxel only in PICBT groups. Survival data and late complication rates were assessed using the Kaplan-Meier method, log rank, t test, and 2 × 2 contingency analysis.

**Results:** The 5-year OS and DFS rate in the NICBT group were significantly higher than those of the PICBT group. Early treatment toxicity and late complications were mild in both groups.

**Conclusion:** The combination of EBRT and Cf-252 neutron ICBT alone is more effective than the combination of EBRT and Ir-192 photon ICBT with concurrent and sequential chemotherapy for stage IIB AC patients.

## Background

While cervical cancer incidence has declined steadily over the past four decades since the introduction of Papanicolaou smear screening, cervical cancer remains the second-most commonly diagnosed female cancer and a leading cause of cancer-related mortality in China[1]. In contrast with the marked decrease in squamous cell carcinoma(SCC) incidence, both the absolute incidence and relative proportion of adenocarcinoma(AC) have increased significantly, accounting for approximately 5–20% of all cervical cancers in the past two decades[2-4]. However, the treatment paradigm for patients with AC remains the same as for patients with SCC, and the combination of concurrent or sequential chemotherapy with definitive radiotherapy continues to be used for locally advanced AC[5-7]. In addition, the prognosis remains worse than that of SCC [8, 9]. One possible explanation for this difference is that AC typically presents with a bulky tumor that has invaded the uterine corpus and contains a large number hypoxic cells [10, 11]. Furthermore, AC is less sensitive to conventional radiotherapy (RT) and/or chemotherapy than is SCC, which may lead to more frequent local recurrence and distant metastasis[12, 13].

Previously, we reported that although patients with AC have a worse treatment response rate and survival than do SCC patients, the combination of Cf-252 neutron intracavitary brachytherapy (ICBT) and EBRT was more effective than conventional ICBT for both SCC and AC [14, 15]. Combined EBRT and ICBT with concurrent chemotherapy is the current standard of care for patients with locally advanced cervical

cancer, and the most commonly used isotopes for ICBT for cervical cancer are  $\gamma$ -emitting cobalt-60, cesium-137, and iridium-192[16]. However, because of its particular histology, AC is less sensitive to conventional  $\gamma$ -ray ICBT. Chiefly, we found that Cf-252 neutron ICBT combined with EBRT was more effective than conventional ICBT radiation in treating cervical cancer[14]. Because the incidence of advanced stage AC is low, it is difficult to conduct randomized controlled trials comparing  $\gamma$ -emitting isotopes with neutron-emitting Cf-252 ICBT. To address this question, we treated equal proportions of patients with FIGO stage IIB AC with either Cf-252 neutron or Ir-192 gamma ICBT and EBRT using a matched-pair design, such that each pair consisting of a patient in the former (NICBT) group and a patient in the latter (PICBT) group. We then evaluated the local disease control (LC), overall survival (OS), disease-free survival (DFS), and severe late complication (LAC,  $\geq$ G2) rates in these patients.

## Patients And Methods

### Patients

From January 2005 to March 2013, 19 patients with Stage IIB AC treated with a combination of Cf-252 neutron ICBT and EBRT were enrolled in this study. Subsequently, 19 patients with AC of the same stage who were treated with a combination of Ir-192 gamma ICBT and EBRT were matched according to tumor size ( $\leq$ 4 vs.  $>$ 4 cm), hemoglobin level (60–90, 90–110, and  $>$ 110 g/L), pelvic lymph node metastasis, and age (31–40, 41–50, 51–60, 61–70 and  $>$ 70 years old), which are all known prognostic factors for Stage IIB AC. All patients were previously untreated. Of these 38 patients with AC, 12 had pelvic lymph node metastasis and 26 had a tumor size larger than 4 cm, while hemoglobin levels below 90 g/L occurred in only 4 patients. The Eastern Cooperative Oncology Group (ECOG) score of all patients was less than 2 (Table. 1).

### Radiotherapy

Pelvic EBRT was administered with 2 Gy/fraction, 4 fractions/week, as described in our previous study[15]. The total dose of EBRT administered to the whole pelvis was 50–54 Gy; the central band (4 cm wide) of the pelvic field was blocked after 20–36 Gy of pelvic RT in both the NICBT and PICBT groups.

Cf-252 neutron ICBT was administered at 10.5–13 Gy-eq/fraction with a total dose of 42–53.2 Gy-eq at point A. Ir-192 photon ICBT was administered with 10–13 Gy/fraction with a total dose of 40–51 Gy at point A. (Fig. 1, Fig. 2).

### Chemotherapy

In PICBT patients, radiotherapy was administered concurrently and sequentially with 2–4 cycles of chemotherapy consisting of cisplatin, 75 mg/m<sup>2</sup>/day, or carboplatin, AUC 5–7.5 mg/mL, and paclitaxel, 135–175 mg/m<sup>2</sup>/day, given intravenously on day 1. Chemotherapy was administered every 3 weeks. No chemotherapy was administered to the NICBT patient group.

## **Patient follow-up**

The patients were followed up regularly, once a month after the initial treatment, and then every 3 months in the first 2 years posttreatment and every 6 months thereafter. At each follow-up visit, patients were subjected to a pelvic re-examination and cervical cytology. LAC morbidity from cystitis and proctitis was assessed according to the Radiation Therapy Oncology Group criteria.

## **Statistics analysis**

The SPSS 20.0 software package (SPSS, Inc., Chicago, IL) was used to conduct all statistical analyses. All reported p values were two-sided, with a significance level of  $p \leq 0.05$  considered to be statistically significant. Continuous data summarized as means  $\pm$  standard deviations, and discrete data are reported as frequencies. The LC, OS, DFS, and serious LAC (radiation proctitis and cystitis,  $\geq$  grade 2) rates, as well as mean survival time in groups NICBT and PICBT were assessed using the Kaplan-Meier method, log-rank, t test, and  $2 \times 2$  contingency analysis.

# **Results**

## **Patient characteristics**

The demographic and clinical characteristics of our study population are summarized in Table 1. As planned, the age compositions of the NICBT (mean age =54.8 years; range, 31–81 years) and PICBT (mean age= 54.4 years; range, 31–81years) groups were similar. Of the 38 total patients with AC in this study, 12 had pelvic lymph node metastasis, 26 had a tumor greater than 4 cm in diameter, and 4 had a hemoglobin level less than 90g/L. All patient ECOG scores were below 2. The paired PICBT group and NICBT group patients were matched for clinicopathological features (Table 1).

## **Treatment response**

All patients completed their scheduled treatments. The complete response rate was 94.74% (18/19) in the NICBT group and 78.95% (15/19) in the PICBT group, where in complete response was noted if a pelvic CT scan showed that the patient's tumor had regressed completely.

## **Local regional control and distant metastasis**

The overall 5-year local regional control rate was 28/38 (73.7%), with not differing significance for each group. Overall, distant metastases were detected in 4/38 patients (10.5%). Distant metastasis was observed more frequently in the PICBT patient group than in the NICBT patient group. A total of 4 patients had developed distant metastasis in the lung only, including 3 patients in the PICBT group and 1 patient in the NICBT group.

## **Survival and failure pattern**

At the time of last follow up, 14/19 patients in the NICBT group and 8/19 patients in the PICBT group were still alive. Moreover, the mean overall survival time(OS) was  $92.7\pm 8.8$  months in NICBT group, which was  $77.4\pm 13.4$  months in PICBT group. (Figure 3) The NICBT group also had a greater mean disease survival time (DFS,  $87.4\pm 10.4$  months; 95%CI, 67.0–107.8 months) than the PICBT group ( $63.5\pm 13.8$  months; 95%CI, 36.5–90.6 months). The median DFS was  $36.0\pm 20.3$  months in PICBT group, which did not reach the end point in the NICBT group. (Figure 4) The 5-year OS rate of NICBT group was 73.7% vs. 42.1% in PICBT group, which were significantly greater than those of the PICBT( $P=0.014$ ), and the 5-year DFS rate of NICBT group was 68.4% vs. 42.1% in PICBT group, which were significantly greater than those of the PICBT( $P=0.025$ ).

## Treatment toxicity

Early toxicity was mild in both groups of patients, and all patients completed RT with grade 1–2 gastrointestinal toxicity. Late complication rates after RT were similar for the two groups (Table 2), consisting mainly of radiation-induced proctitis and cystitis, with 1 patient in the PICBT group and 2 patients in the NICBT group developing severe grade 2 LAC. Regarding type of grade 2 LACs observed, grade 2 late radiation cystitis occurred in 1 patient in the NICBT group and no patients in the PICBT group, grade 2 late radiation proctitis occurred in 1 patient in each group. No patients, in either group, developed Grade 3 or higher complications.

## Discussion

Although cervical cancer incidence continues to decline, effective tumor control remains a challenge for patients with locally advanced disease, especially for different tumor histologies, such as adenocarcinoma. Our previous study had already confirmed that the combination of Cf-252 neutron ICBT and EBRT was more effective than conventional ICBT radiation for management of both SCC and AC. However, advanced-stage AC cervical cancers are so frequent that it is difficult to conduct a randomized, controlled trial to compare  $\gamma$ -emitting isotopes with neutron-emitting Cf-252 ICBT[14, 15]. Thus, in the current study, we assessed the outcomes of combined EBRT and Cf-252 neutron vs. Ir-192 gamma ICBT in patients with AC using a matched-pair study design. We observed a possible trend in 5-year regional local control rate in favor of NICBT over PICBT, though the difference was not significant, perhaps due to the relatively small sample examined in this study. Although a large sample of AC patients would be difficult to assemble, due to the relative rarity of AC histology clinically, a larger sample size might yield a significant difference for this comparison. Compared with the NICBT group, the PICBT group had more distant metastasis; correspondingly, the PICBT group had a significantly shorter mean survival time than the NICBT group. The 5-year OS rate and 5-year DFS rate were also significantly shorter in the NICBT group than in the PICBT group.

Unlike conventional photon rays, Cf-252 neutrons employed in NICBT provide high linear energy transfer radiation that damages tumor cell genomic DNA regardless of cell cycle phase, causing a high rate of DNA double-strand breaks[17, 18]. Thus, AC cells that were resistant to conventional  $\gamma$ -ray PICBT were

probably sensitive to Cf-252 NICBT. Furthermore, NICBT has radiobiological characteristics, such as higher relative biological effectiveness and lower oxygen enhancement than photon radiotherapy [19].

Cf-252 NICBT has been reported previously to be more effective than conventional radiation ICBT in controlling advanced or bulky cervical cancer (hypoxic IIIb) [16, 20]. These prior studies focused on therapies other than neutron intracavitary brachytherapy in patients with SCC histology, leaving the NICBT for AC uncertain. In this study, although we did not obtain a significant group effect in the analysis of our cancer control data, our survival data analysis nevertheless did yield significant outcomes in favor of NICBT over PICBT in patients with AC. Thus, the current data support the use of Cf-252 neutron ICBT combined with external beam radiotherapy for patients with cervical AC.

Some studies reported that the combination of EBRT and ICBT with concurrent chemotherapy is more effective than the same treatment without chemotherapy for controlling cervical cancer [21, 22]. However, the isotopes most commonly used for ICBT of cervical cancer all have a low linear energy transfer, and the major histology type evaluated thus far has been SCC[23, 24]. As discussed above, because AC is more difficult to control than SCC, treatment for AC should be more aggressive. The data from our former study suggested that concurrent platinum-based chemotherapy provided an efficacy similar to that of pelvic EBRT combined with Cf-252 neutron ICBT for the treatment of locally advanced cervical cancer. Although it did not improve the local tumor control rate, OS, or DFS, relative to treatment without concurrent platinum-based chemotherapy, it did increase the incidence of serious LAC significantly. In the current study, it is noteworthy that patients in the NICBT group achieved better survival outcomes than the PICBT group despite the fact that they were not given concurrent and/or sequential chemotherapy for stage IIB adenocarcinoma of the uterine cervix.

Furthermore, the acute treatment toxicity was mild in both groups of patients, and all patients completed the RT schedule with only grade 1–2 gastrointestinal toxicity. Late complications after RT included only radiation-induced proctitis and cystitis. The total dose of ICBT at point A received by NICBT group patients was higher than that received by the PICBT group, which likely explains why the late radiation proctitis rate was slightly, albeit not significantly, higher in the NICBT group than in the PICBT group. Nevertheless, the late complications experienced were considered acceptable in both groups.

This study has some limitations. For example, it was a retrospective investigation, and the number of patients is quite small, which can lead to bias. Nonetheless, we observed a better outcome for patients treated with NICBT.

## Conclusion

Based on survival outcome data, the combination of EBRT and Cf-252 neutron ICBT alone was found to be more effective than the combination of EBRT and Ir-192 photon ICBT with concurrent and sequential chemotherapy for stage IIB uterine cervical AC. A prospective study with a larger number of patients is needed to confirm the presently suggested advantage of NICBT over PICBT in patients with stage IIB uterine cervical AC.

# Declarations

## Compliance with Ethical Standards

### Funding:

This study was funded by National Natural Science Foundation of China (grant number 81902671).

### Conflict of Interest:

We declare that we have no conflict of interest.

### Ethical approval:

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

### Informed consent:

Informed consent was obtained from all individual participants included in the study.

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## Tables

Table 1.

Base line characteristics of 19 patient pairs.

<b>Characteristic</b>	<b>N</b>
Mean age, y (PICBT vs. NICBT)	54.4 vs. 54.8
<i>Distribution across age bands, y</i>	
31–40	2
41–50	4
51–60	8
61–70	4
>70	1
<i>Tumor size</i>	
≥4 cm	13
<4 cm	6
<i>Hemoglobin, g/L</i>	
>110	16
90–109	1
60–89	2
<i>Pelvic lymph node metastasis</i>	
Negative	13
Positive	6
<i>Chemotherapy(PICBT group only)</i>	
Concurrent	10
Sequential	5
None	4
PICBT: photon intracavity brachytherapy	

Table 2.

Comparison of outcomes between the NICBT and PICBT groups.

Outcome variable	PICBT	NICBT	<i>P</i>
LC	68.4%(13/19)	78.9%(15/19)	.157
OS	42.1%(8/19)	73.7%(14/19)	.014
DFS	42.1%(8/19)	68.4%(13/19)	.025
LAC ( $\geq$ G2)	5.26%(1/19)	10.5%(2/19)	.317

PICBT: photon intracavity brachytherapy; NICBT: neutron intracavity brachytherapy; LC: local control; OS, overall survival; DFS: disease-free survival; LAC( $\geq$ G2): late complication  $\geq$  grade 2

## Figures

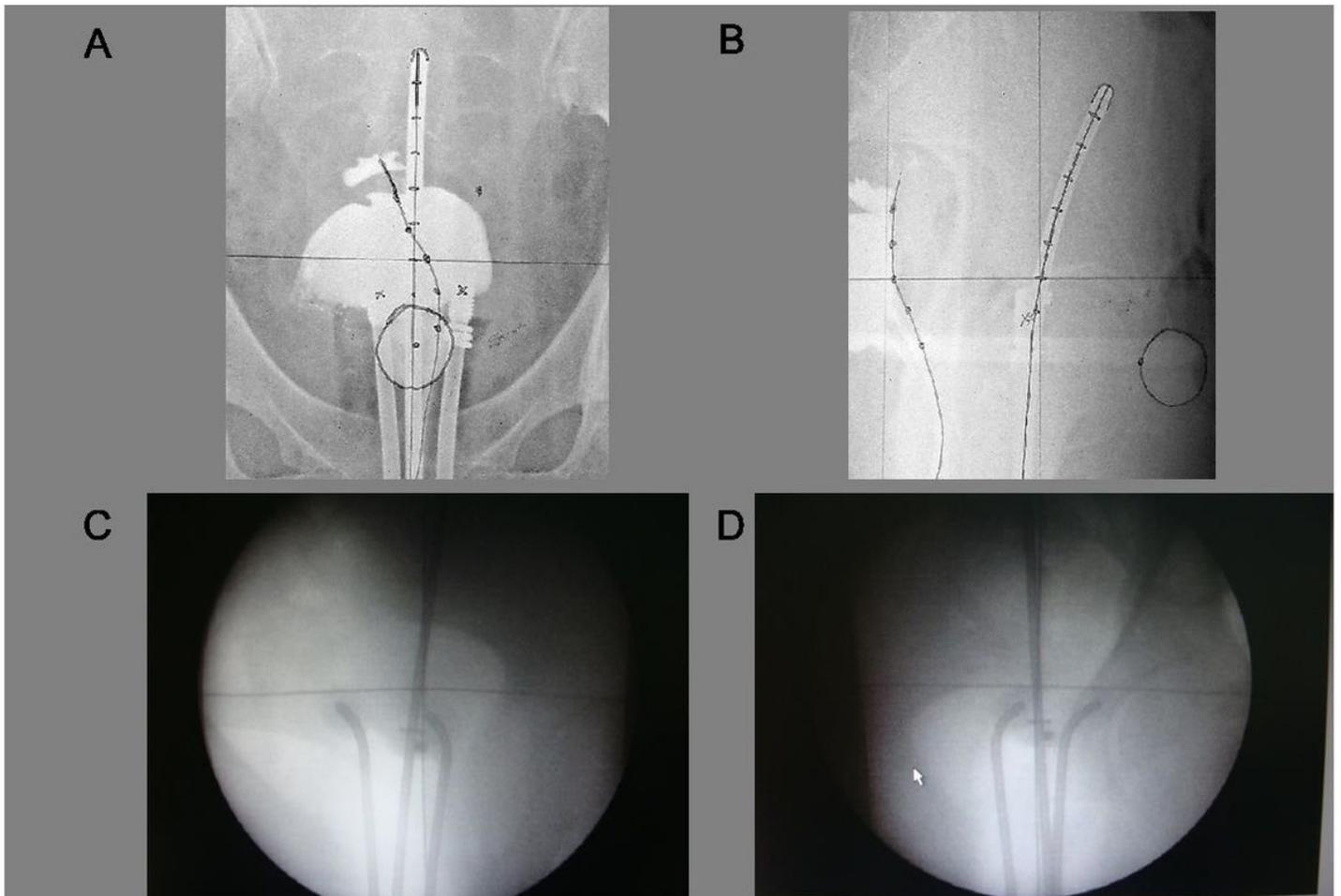
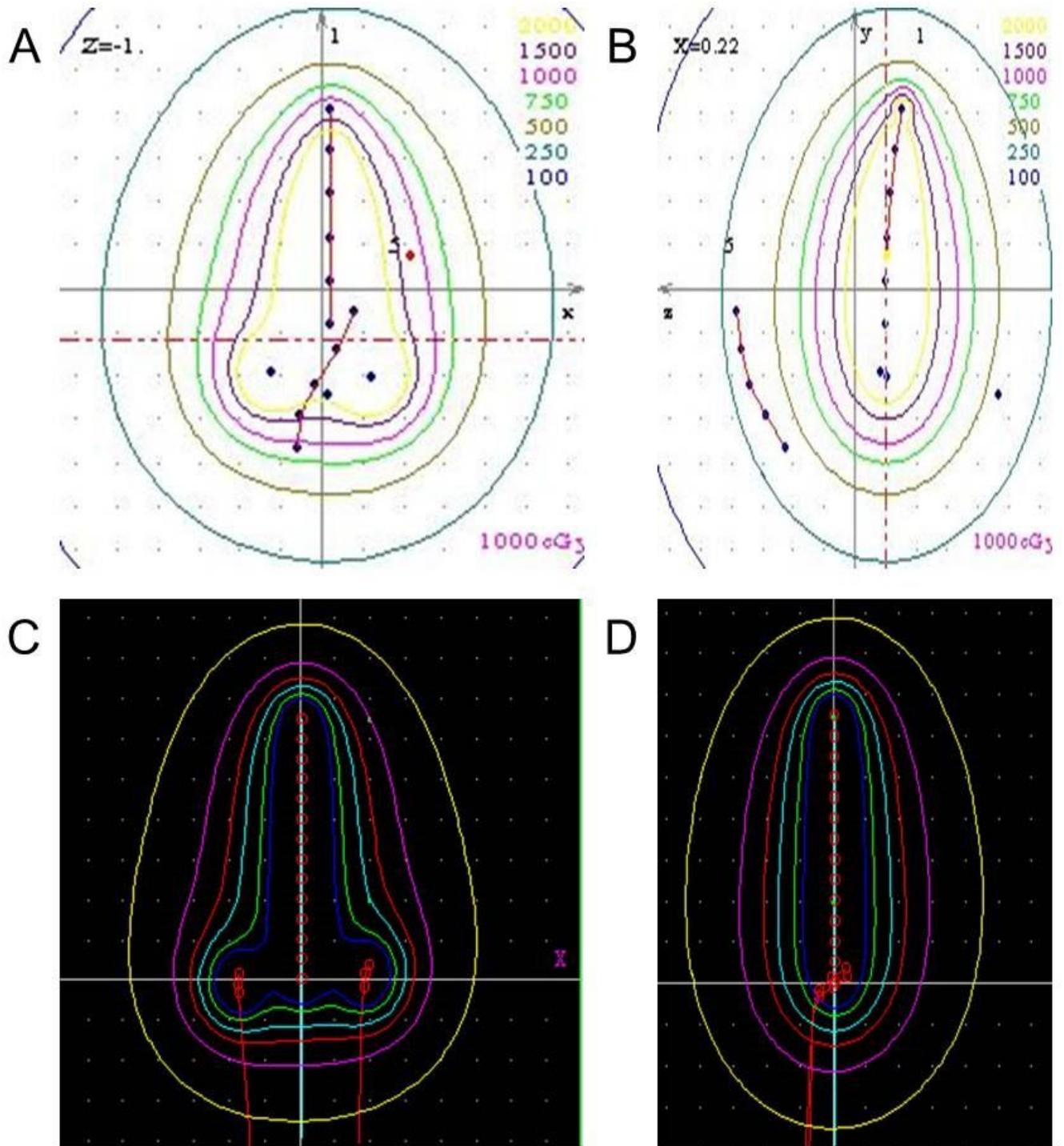


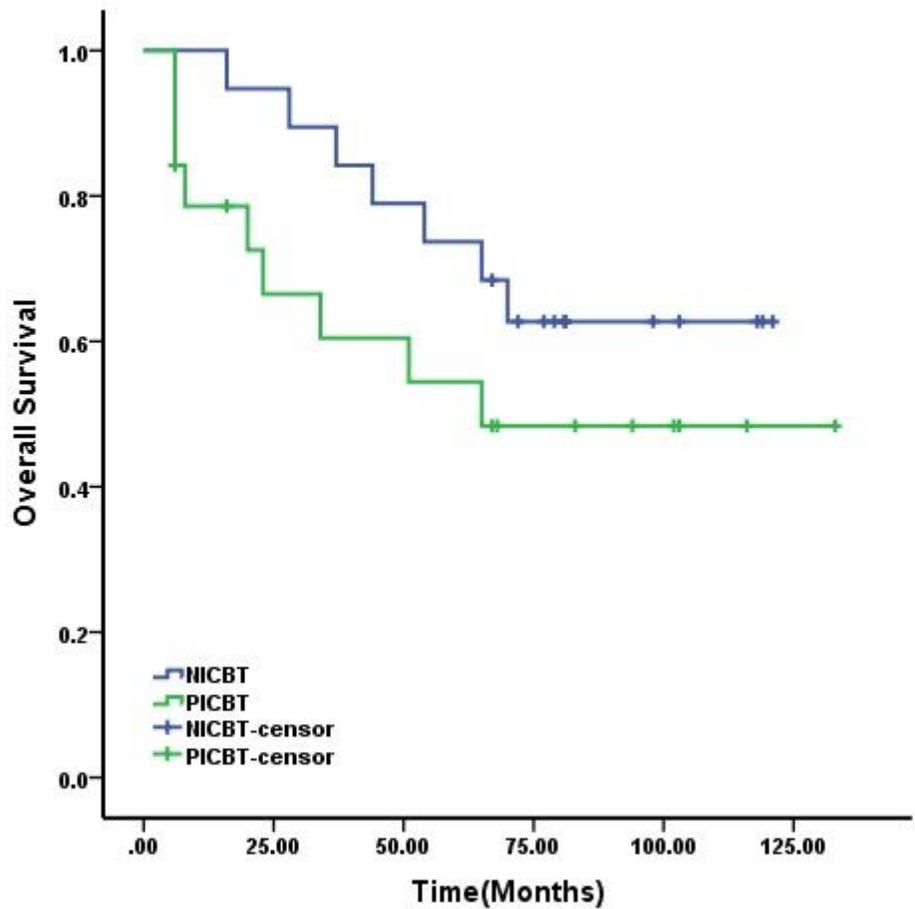
Figure 1

Pelvic orthographs of patients undergoing ICBT treatment. A and B is for Cf -252 neutron ICBT, C and D is for Ir-192 photon ICBT.



**Figure 2**

Isodose distribution for patients undergoing ICBT treatment. A and B are for Cf -252 neutron treatment plan, and the isodose curves are 2000cGy, 1500 cGy, 1000 cGy, 750 cGy, 500 cGy, 250 cGy, 100 cGy from inside to outside. C and D are for Ir-192 treatment plan, and the isodose curves are 200cGy, 150 cGy, 100 cGy, 75 cGy, 50 cGy, 25 cGy from inside to outside.



**Figure 3**

Kaplan-Meier analysis of OS stratified by type of ICBT, NICBT vs. PICBT. At the time of last follow up, most of the patients were still alive, therefore, median OS would not be analysed. The mean overall survival time (OS) was  $92.7 \pm 8.8$  months in NICBT group, which was  $77.4 \pm 13.4$  months in PICBT group. ( $P=0.218$ ) However, possible trend observed in OS was in favor of NICBT over PICBT.

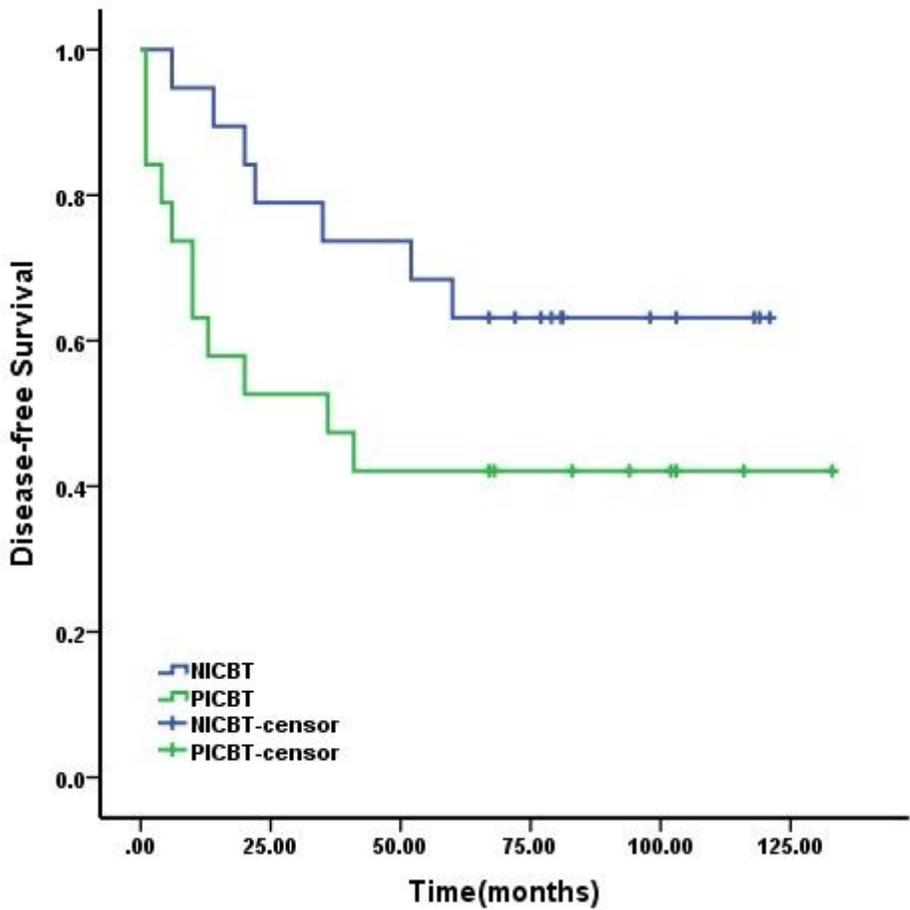


Figure 4

Kaplan-Meier analysis of DFS stratified by type of ICBT, NICBT vs. PICBT. The mean DFS was  $87.4 \pm 10.4$  months in NICBT group vs.  $63.5 \pm 13.8$  months in PICBT group. ( $P=0.102$ ) The median DFS was  $36.0 \pm 20.3$  months in PICBT group, which did not reach the end point in the NICBT group.