The clinical practice of ^{252}Cf neutron brachytherapy devices on malignant tumor in China

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Abstract: The ^{252}Cf neutron brachytherapy devices were designed and manufactured after solving those problems: the shield difficulties for ^{252}Cf neutron; the method and facilities for ^{252}Cf neutron source deliver; the dose calculation and measurement for ^{252}Cf neutron. From 1999 to 2009, more than twenty ^{252}Cf neutron brachytherapy devices had been installed in China. The Chinese radiation oncologists implemented the ^{252}Cf neutron brachytherapy on more than 5 000 different kinds of cancer patients, including cervix cancer; endometrium cancer and achieved ideal results. For special presentation, they had breakthrough on radical treatment for low lying rectal adenocarcinoma with sphincter preservation and melanoma patients after the modification of ^{252}Cf neutron intracavitary applicator and dose calibration.
Key words: ^{252}Cf neutron; ^{252}Cf neutron brachytherapy device; cervix cancer; rectal adenocarcinoma; melanoma; applicator; dose calibration

1 Introduction

Radiotherapy is a main modality for malignant tumor treatment. Although IMRT (intensity modulated radiotherapy), IGRT (image guided radiotherapy) have developed rapidly for recent decades, the phenomena that tumor cells are not sensitive enough or radio-resistant to conventional photons was still difficulties for contemporary radiotherapy. ^{252}Cf has been found effective for radiotherapy and posses radiobiological advantages for treatment of radioresistant advanced or bulky tumors. The high linear energy transfer (LET) radiation has higher radiobiological effectiveness (RBE) and a lower oxygen enhancement ratio (OER) against photon radioresistance. Fast neutrons also inhibit sublethal or potentially lethal damage (SLD or PLD) repair. All these factors, combined with the low integral dose used in the brachytherapy result in a high therapeutic gain factor for ^{252}Cf neutrons.

2 The design and manufacture of ^{252}Cf neutron brachytherapy devices

There have been valuable researches about Californium neutron brachytherapy in China since 1997. Shenzhen Linden Science & Technology Develop Co., Ltd. developed the first Californium Neutron Remote Afterloading treatment system in 1998 named "ZH—1000 Linden Neutron Knife". Its principle is explained as follow: utilizing the neutrons eradiated by radioactive isotope neutron source—^{252}Cf, neutron knife is specially characterized by its great execution to hypoxic cells in tumor through irradiation even without any lethal or sublethal damage and the low recurrence rate. Applying modern remote-controlled afterloading technology, a tailor-made source applicator is inserted into human cavity (or organs) near to the focuses of tumor, and then, according to the treatment plan, the neutron sources will be transported through autocontrolled device and source-transportation setup into the source applicator. So the neutron sources actuate brachytherapy on the focuses to cure the tumor.

The first facility was set up in Daping Hospital in Chongqing, China. A neutron source with 526 μg of ^{252}Cf, Φ 3 mm × 16 mm, was imported from Russia and loaded into storage within the facility and the clinical trial was started in Feb. 1999. This is the first time that China used a ^{252}Cf source for cancer treatment.

The facility structure includes five parts: neutron source, applicator, mainframe, treatment control system and treatment planning system.

Since 1999, ^{252}Cf neutron brachytherapy in China has developed rapidly. Currently, twenty high dose rate Californium source units ("Linden Neutron Knife") have been operated (initial source content from 520 ~ 904 μg and Φ 3 mm × 11 mm).

There are the dosage parameters about "neutron

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(a) Mainframe

(b)Treatment control system

(c) Treatment planning system

Fig. 1 Pictures of "Neutron knife"

knife":

1) Real capacity of ^{252}Cf at loading: ≤1 000 μg, Equated emission rate: neutron 2.3×10^{9}/s, gamma 1.3×10^{10}/s;

2) Size of the source: shell is Φ 3 mm × 11 mm; active portion is Φ 1.4 mm × 5 mm;

3) Leakage of radiation: the equivalent dose rate of radiation at any position which is 1 m far from the touchable surface of the mainframe is less than 10 μSv/h;

4) Half life of ^{252}Cf source is 2.65 years; the cycle of replacing source is 5 years;

5) Dose error of treatment planning system: ≤5 %.

The following are the mainframe parameters about "neutron knife":

1) Measurement (length × width × height): 3 925 mm × 2 332 mm × 2 145 mm;

2) Total weight (approx.): 8 t;

3) Number of source channel: 12;

4) Minimal radius of curvature of the channel: ≤ 100 mm;

5) Range of vertical motion of treatment couch: 700 ~ 1 000 mm;

6) Range of horizontal motion of treatment couch: 1 000 mm;

7) Weight of treatment couch: 200 kg;

8) Locating precision and relocating precision: ±1 mm;

9) Stepping motion precision: ±1 mm;

10) Treatment timer precision: ±1 s;

11) The maximal distance of source can be transferred: 1 500 mm;

12) The time of delivering source or retracting source: ≤15 s;

13) The operation noise (A): ≤65 dB.

3 The clinical practice of ^{252}Cf neutron brachytherapy

3.1 Cervical cancer

Combined external beam radiotherapy (EBRT) and intracavitary radiotherapy (ICBT) constitute the main treatment modalities for the management of cervical cancer, especially in the advanced stages. As ICBT in the treatment of cervical cancer, high-does-rate ICBT has been widely used in the world.

Although high-does-rate ICBT has been used to treat cervical cancer for more than 40 years, the potential for local control rate of advanced stage, especially in III, IVa stage and the increase risk for late complication are major concern.

From December 1998, we have used californium-252 ICBT to treat locally advanced cervical cancers. Our objectives is to present the survival rate, local control rate and late complication in bladder and rectum, and prognosis factor of californium-252 ICBT in advanced cervical cancers.

3.1.1 Methods and materials

3.1.1.1 Staging and inclusion criteria Between Jan. 1999 and Dec. 2002, 115 patients with histologically diagnosed cervical cancer were selected according to FIGO staging system. The mean age of the patients was 39.56 years old (range 22 ~ 78).

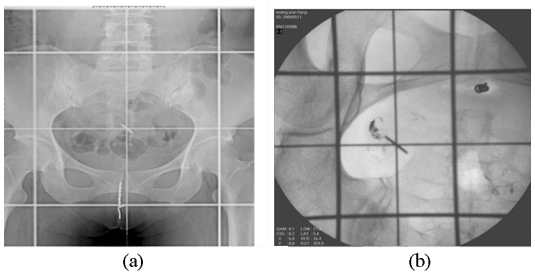
115 patients had stage IIa 20, stage IIb 45, stage IIIa 22, stage IIIb 18, stage IVa 10 respectively. The histologic type was squamous cell carcinoma in 105 patients, adenocarcinoma in 10 patients. Kamlfsky P Status > 70.

3.1.1.2 Radiotherapy EBRT: EBRT was delivered using a 6 MV or 8 MV linear accelerator. The technique was used by AP and PA fields. The total dose of EBRT to the whole pelvis was 44 ~ 52 Gy (2 Gy/ f/ d). Central shielding, with the placement of a 4 cm rectangular midline block of 5 half value layer at the anterior and posterior fields, was designed after 20 ~ 40 Gy pelvis RT (Fig 2(a)).

If necessary, followed by a parametrial boost dose of 8 ~ 12 Gy in three to four fractions. The dose of the parametrial boost ranged from 8 ~ 12 Gy (Fig 2(b)).

3.1.1.3 ^{252}Cf ICBT During each application insertion, the utrine was dilated firstly. The anterior and posterior vaginal packing was done after the insertion. Every patient was adopted to rectal lead wire insertion (in the early study) or rectal barium enema (in the late study).

The barium was pulled out as much as possible af-



(a) (b)

Fig. 2 Pelvic A-P field portal image(a) and parametrial portal image(b)

ter radiography. The urine catheter was inserted into bladder and the 3 mL contrast was injected into Foley sac. Then, the pelvis was filmed isocentric orthogonaly respectively(Fig 3).

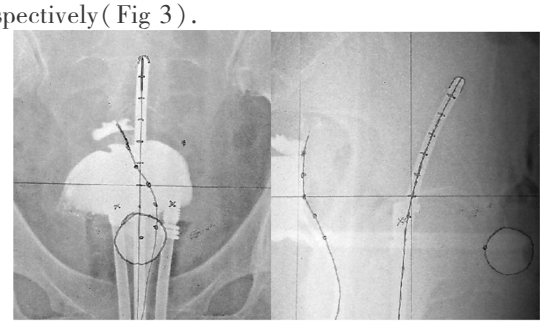


Fig. 3 X-ray films for ^{252}Cf ICBT

Point A was defined on X-ray films as being 2 cm superior(along the tandem) to the flange abutting external cervical and 2 cm lateral from the axis of the tandem. The rectal reference points was defined the along the lead wire or rectum(Fig 4).

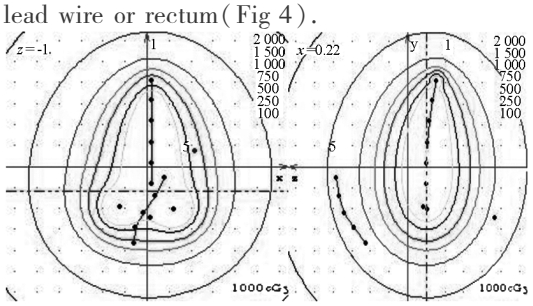


Fig. 4 Dose distribution

The bladder reference points were defined the lowest point of Foley. The dose of reference point A of every patient is given 7 ~ 12 Gy. ICBT was delivered in 2 ~ 3 hours per session and performed three to four times. The total ICBT dose to point A was 29 ~ 45 Gy-eq.

For ICBT, sealed ^{252}Cf neutron sources were used. Cf emits both fast neutrons with mean energy of 2.3 MeV and high energy gamma rays. The dose of Cf was calculated taking into account the neutron dose (Dn) and gamma ray does(Dγ).

RBE compared to an identical dose of gamma radiation was assumed to be 2 ~ 3 for neutrons in normal tissues. The neutron sources activity was 560 ~ 540 μg.

$$DGy\text{-}eq = RBEn \times Dn + RBE\gamma \times D\gamma$$

3.1.2 Follow-up

Patient follow-up was performed every 3 months in the first 2 years after treatment completion and every 6 months thereafter. The clinical pelvic examination and cervical cytology were performed at each follow-up visit. To observe the 5 years overall survival rate, local control rate and late complication rate in bladder and rectum according to the Radiation Therapy Oncology Group criteria.

Statistics analysis: K-P test and X^2 test were used. Statistical significance was considered P value < 0.05.

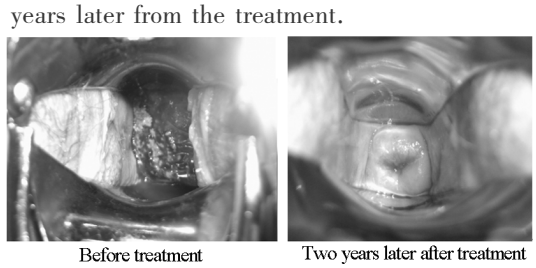
3.1.3 Results

All patients have being followed-up for more than 3 years, the 5 years overall, survival rate, local control rate was 79.1 % and 82.6 % respectively(Fig. 5 and Fig. 6).

Table 1 Survival rate and local control rate for different stage respectively

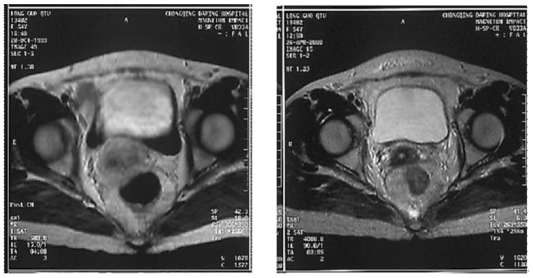
Stage	Survival rate/ %	Local control rate/ %
Ⅱa	90 (18/20)	100 (20/20)
Ⅱb	88.9 (40/45)	91.1 (41/45)
Ⅲa	77.3 (17/22)	81.8 (18/22)
Ⅲb	72.2 (13/18)	72.2 (13/18)
Ⅳa	30 (3/10)	30 (3/10)
Total	79.1 (91/115)	82.6 (95/115)

Distant metastases were frequent and were observed in liver for 3 patients, lung for 7 patients, and bone for 3 patients. The lost patient was defined as death. Tumor stage was the most significant prognosis factor. The late complication rate (>G2) was 3.5 % (4/15) for cystitis, 6.96 % (8/15) for proctitis. A patient suffered from sigmoid and vaginal fistula after two years later from the treatment.



Before treatment Two years later after treatment

Fig. 5 The figures of colposcopy for cervical cancer



Before treatment　　Six months after treatment

Fig. 6　The images of MRI for cervical cancer

3.1.4 Discussion

Advanced cancers of the cervix (especially stage III) are resistant to photon or γ irradiation; it is wide believed that tumor hypoxia is responsible for this. Radioresistance is manifested clinically by failure of local tumor control and low cure rate seen with conventional photon therapy.

Cf has been found effective for radiotherapy and possesses radiobiological advantages for the treatment of radioresistant advanced or bulky tumors. The high LET radiation has higher RBE and lower OER against photon radioresistance. Fast neutrons also inhibit sublethal or potentially lethal damage (SLD or PLD) repair.

The 5 years overall, local control rate for all patients were 79.1 % (91/115) and 82.6 % (95/115) respectively. They were 90 % (18/20), 100 % for IIa respectively; 88.9 % (40/45), 91.1 % (41/45) for Ⅱb respectively; 77.3 % (17/22), 81.8 % (18/22) for Ⅲa respectively; 72.2 % (13/18), 72.2 % (13/18) for Ⅲb respectively; 30 % (3/10), 30 % (3/10) for Ⅳa respectively. Of the adenocarcinoma patients, it was 80 %, 90 % respectively. The late complication rate was 3.5 % (4/115) for cystitis, 6.96 % (8/115) for proctitis.

Tumor stage, the volume of tumor before the radiotherapy and the age were the most significant prognosis factor for advanced cervical cancer of patients.

The combination ^{252}Cf brachytherapy and EBRT may be effective and well-tolerated on advanced cervical cancer. The survival rate for Ⅱa and Ⅱb patients with ^{252}Cf brachytherapy were higher slightly than the one of HDR ^{192}Ir brachytherapy. The survival rate for III IV and adenocarcinoma patients with ^{252}Cf brachytherapy was higher significantly than the one of HDR ^{192}Ir brachytherapy.

^{252}Cf brachytherapy has good perspective for advanced cervical cancers.

3.2　Rectal cancer

Adenocarcinoma of the colon and rectum is one of the most common internal malignancies. In most situations, the usual treatment for low-lying rectal adenocarcinoma (lower limit of tumor at < 6 cm from the anal verge) is abdominoperineal resection (APR) and proctectomy. Although the APR served to decrease the local recurrence rate and improve long-term survival, the associated morbidity and inconvenience of a colostomy made sphincter-saving options more of a viable alternative as surgical management of rectal cancer evolved. A series of sphincter preservation resections and straight colo-anal anastomosis were used by surgeons. But low-lying rectal adenocarcinoma (lower limit of tumor at < 6 cm from the anal verge) was still used APR.

To improve local control and possibly increase sphincter preservation, combined approaches with the addition of RT have become more popular. ^{252}Cf neutron ICBT and EBRT with or without ^{252}Cf neutron rectal interstitial implant (solving the deep tissue dose deficient) can provide a conservative alternative to proctectomy too. This study report three years survival rate and late side effect of ^{252}Cf neutron ICBT and EBRT or rectal interstitial implant on the treatment of T1-3 low-lying rectal adenocarcinoma with sphincter preservation.

3.2.1 Methods and materials

3.2.1.1　Radiotherapy

1) Staging and inclusion criteria: Patients were accrued between August 2006 and July 2008 into this pilot study. All patients were examined by one of us and underwent a careful digital rectal examination (DRE) in the knee chest position with an empty rectal ampulla followed by rigid proctoscopy in the same position.

All patients presented with biopsy-proven rectal adenocarcinoma that measured < 6 cm from the anal verge involving less than 2/3 circumference. Tumors were staged with transrectal ultrasound B. T1-3: 12, 22, 26 respectively (Fig. 7). All patients were examined by colonoscopy, liver ultrasonography, chest X ray, full blood count, and serum biochemistry. All patients were considered to be free of metastases. The median age of patients was 58 years, ranged 31 ~ 81 years.

2) External beam radiotherapy　For T2 patients, the anterior and posterior fields were centered on the tumor and measured 7 cm × 10 cm using 8 MV or 15 MV photons. The total dose was 37.4 ~ 39.1 Gy, 2.2 ~ 2.3 Gy/ f / d. For T3 patients, firstly, the patients were irradiated with 2 fields (anterior and posterior pelvic opposed fields) to 20 ~ 21 Gy, 2.2 ~ 2.3 Gy/ f / d using 8 MV or 15 MV photons. Then, AP-PA fields (7 cm × 10 cm size) were given to 19.8 ~ 20.7 Gy, 2.2 ~ 2.3 Gy/ f / d. The total does was

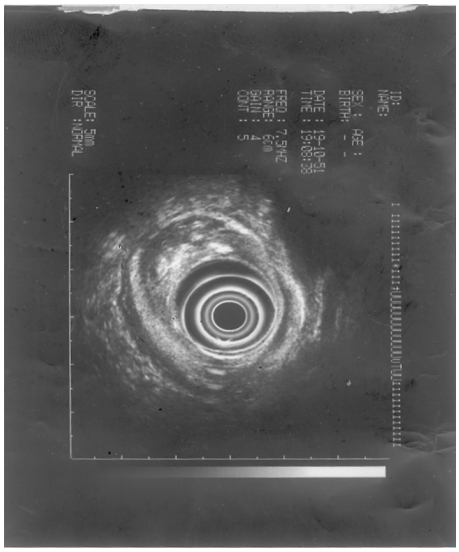


Fig. 7 Transrectal ultrasound B image

39.8 ~ 41.7 Gy.

3.2.1.2 ^{252}Cf neutron ICBT

1) ^{252}Cf neutron dose calibration for rectal cancer To irradiate the rectal cancer cells with different doses of ^{252}Cf neutron and high energy X ray to set up dose-survival curve using clonogenic assay. It could be yielded the RBE of ^{252}Cf neutron contrast X ray and α/β ratio of ^{252}Cf neutron and X ray respectively. ^{252}Cf neutron biological effectiveness dose(BED) on rectal adenocarcinoma cells were calibrated with the RBE and α/β ratio respectively.

2) The modification of the off-axis four channel ^{252}Cf neutron intrarectal applicator To modify and manufacture the off-axis four channel ^{252}Cf neutron intrarectal applicator which was 3 cm and 3.5 cm for the diameter respectively (Fig. 8).

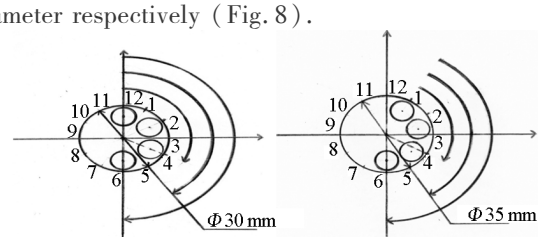


Fig. 8 The transsections of off-axis four channel for ^{252}Cf neutron intrarectal applicator

After the EBRT was delivered 1 week, 3 fractions of ^{252}Cf neutron ICBT were implemented every week. T1 patients were treated with ^{252}Cf ICBT alone.

Firstly, the peri-anal anesthesia was implemented with 2 % lidocaine 20 ~ 30 mL. Then, the pelvis of the patient was filmed isocentric orthogonaly respectively. From the orthogonal radiographs, The reference therapeutic points were defined as the surface of the rectal mucosa (Fig. 9).

T1 patients: the total does was 58 ~ 62 Gy, 14 ~ 16 Gy/f, 4 fractions.

T2 patients: the total does was 43 ~ 45 Gy, 14 ~ 15 Gy/f, 3 fractions.

T3 patients: the total does was 41 ~ 43 Gy, 13 ~ 15 Gy/f, 3 fractions.

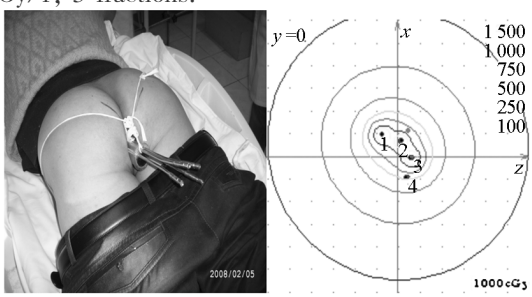


Fig. 9 The off-axis four channel ^{252}Cf neutron intrarectal applicator and its dose distribution

3.2.1.3 ^{252}Cf rectal interstitial implant After a 3 ~ 4-week interval completed the combination Cf ICBT and EBRT, ^{252}Cf rectal interstitial implant were delivered a completion dose of 14 ~ 17 Gy to the residue tumor for ten T3 patients (Fig. 10).

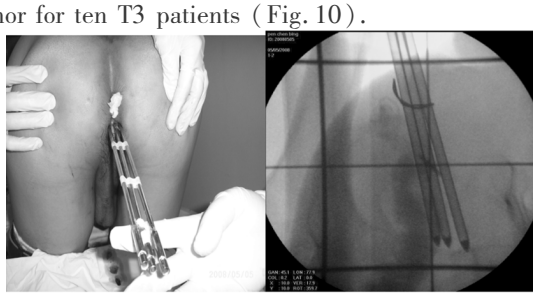


Fig. 10 ^{252}Cf rectal interstitial implant

3.2.2 Follow-up

The patients were followed for disease status including cases of deaths. No patient was lost to follow-up. Events were defined as local or nodal failure and distant metastases. To observe the morbidity and grade of acute and late side effects of rectum, bladder and the perianal skin. RTOG acute and late toxicity scoring system was used for this study.

The anal function was evaluated according to a function questionnaire Memorial Sloan-Kettering Cancer Center scoring system.

3.2.3 Results

The calibrated RBE was 1.8 ~ 2.2 for ^{252}Cf compared with X ray. The α/β ratio of ^{252}Cf neutron for rectal cancer cells was 2.2 Gy. The α/β ratio of X ray was 9.6 Gy (Fig. 11 and Fig. 12). The 41 ~ 45 Gy was equivalent to 71 ~ 76 Gy for rectal cancer cells according to formula.

DGy-eq = RBEn × Dn + RBEγ × Dγ

The 45 Gy was equivalent to 350 Gy for ^{252}Cf neutron according to formula (15 Gy/f, 3 fractions)

BEDn = nd[1 + d/α/β] = 45 × 7.8 = 350 Gy

The 90 Gy was equivalent to 350 Gy for contact X ray according to formula (30 Gy/f, 3 fractions)

BEDx = nd[1 + d/α/β] = 90 × 4.1 = 360 Gy

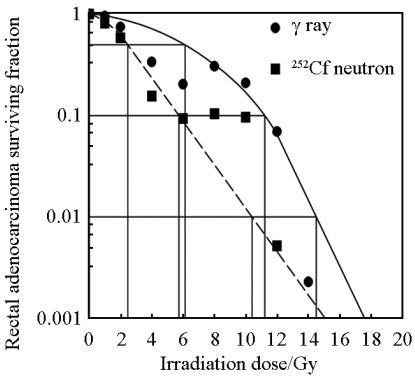


Fig. 11 Dose survival curve of γ rays and neutrons for RBE

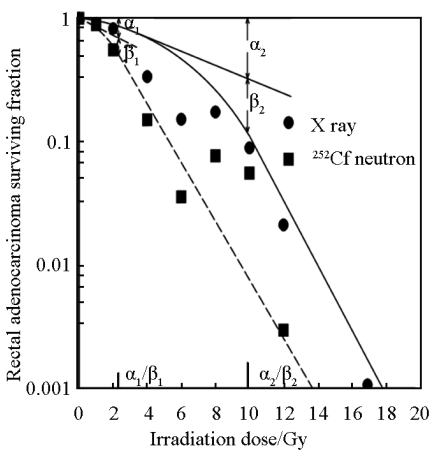
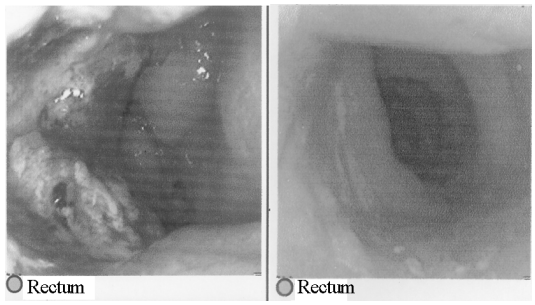


Fig. 12 Dose survival curve of X rays and neutrons for α/β ratio

1) 3-years local control rate All the patients completed treatment according to the protocol. After the radiotherapy, all lesions regressed completely. The primary local control rate was 81.7 % (49/60), of the patients, T1 was 100 %, T2 was 81.8 % (18/22), and T3 was 73.1 % (19/26) respectively, after salvage surgery, the T2 ultimate pelvic control was 91 %, T3 was 88.4 % (Fig. 13).

2) Distant metastases In 6 patients, a distant metastasis in the liver were detected. In 3 patients, a distant metastasis in the lung was detected. Metastasis was seen in association with local failure in the pelvis.

3) 3-years survival rate With a median follow-up time of 30 months, the 3-years survival rate was



Before the radiotherapy Six months later after the radiotherapy

Fig. 13 Figures of colonoscopy for rectal cancer

83.3 %. The 3-years survival rate was 100 %, 86.4 % (19/22) and 73 % (19/26) for T1, T2 and T3 stage patients respectively.

4) Morbidity Early toxicity: The acute side effect of rectum was moderate among all the patients. The morbidity of acute side effects of bladder was moderately high only among the male patient. The dermatitis around the perianal skin was severe only among the anal tumor patient who can fulfill the treatment without break.

Late complications: The 3-year rectal bleeding, severe rectal sensation of mass (> G2) rate were 23.3 %. Among them, T1 was 8.3 % (1/12); T2 was 22.7 % (5/22,); T3 was 30.8 % (8/22).

Prognostic factors: The T stage was a strong prognostic factor, with a 3-years survival rate of 100 %, 90 % and 77.2 % for T1, T2 and T3 lesions, respectively.

Sphincter function: It was scored as excellent in 40 patients, good in 10 patients and fair in 10 patients, mainly because of rectal bleeding with urgency. No patient required colostomy for fair anal function.

3.2.4 Discussion

The methods of radiotherapy alone treating rectal adenocarcinoma included contact X ray alone, the EBRT alone, the combination of EBRT and ICBT, the combination of contact X ray and EBRT, the combination of contact X ray and ICBT, the combination of contact X ray, EBRT and ICBT.

Many reports have suggested that contact X ray alone therapy can achieve local control in 85 % ~ 90 % of T1N0 rectal tumors patients and that tolerability is good in most with preservation of good anorectal function and no severe late toxic effects.

On the other hand, the results of T2, T3 stage rectal adenocarcinoma using RT alone remained controversy. Between 1977 and 1996, Papillon treated 71 patients who had T1 ~ T3 lesions with cobalt-60 arc therapy (30 Gy in ten fractions over 2 weeks) and one

session of contact therapy (25 Gy) given 6 weeks later. A final boost of 25 Gy was given 3 weeks after contact therapy by use of ^{192}Ir brachytherapy. Tumors close to the anal canal were generally excluded. Local control was achieved in 84 % of patients, and 5-year disease-free survival was 53 %. There were no severe late rectal toxic effects. Horiot and colleagues used the same approach to treat 42 patients with T2 ~ T3 lesions. Local failure was observed in 28 % of patients. Two patients required a colostomy for grade-3 rectal necrosis.

During the treatment with endocavitary contact X ray and EBRT, some T2, T3 stage adenocarcinoma have tumor residua, these patients had to undergo salvage surgery. The tumor response on day 21 (after two sessions of contact X-ray treatment) was particularly important prognostic factors.

EBRT in accelerated doses or concurrent with chemotherapy has shown a poor long-term local control even in small tumors. These phenomenon presented that the rectal adenocarcinoma was radioresistant to photons(X ray and γ ray) at sometimes compared with squamous cell carcinoma of the anal canal, head and neck, even adenocarcinoma of the breast and prostate.

On the other hand, Cf has been found effective for radiotherapy and posses radiobiological advantages for treatment of radioresistant advanced or bulky tumors. The high linear energy transfer(LET) has higher RBE and a lower oxygen enhancement ratio(OER) against photon radioresistantance.

Fast neutrons also inhibit sublethal or potentially lethal damage repair. All these factors, combined with the low integral dose used in the brachytherapy treatment result in a high therapeutic gain factor for Cf neutrons.

Firstly, our results represented that the rectal lesion can be regressed completely after the ^{252}Cf neutron ICBT and EBRT. Secondly, the primary local tumor control rate was 88 %, of the patients, T1 was 100 %, T2 was 90 %, and T3 was 72.2 % respectively, after salvage surgery, the T2 ultimate pelvic control was 100 %, T3 was 87 %. The 3-years survival rate was 88 %, of the patients, T1 was 100 %, T2 was 90 % and T3 was 77.2 % respectively. The anal function was evaluated as excellent in most patients.

The main limiting factor in increasing doses of radiotherapy is the tolerance of normal tissues. Delivery of doses higher than 50 Gy to rectum over 5 weeks to a large field (treated volume greater than 2 L) is difficult. If the field is reduced, the dose can be increased to 60 ~ 70 Gy over 6 ~ 7 weeks.

On a small surface (or volume) of the rectum a dose of 70 ~ 75 Gy can be given without any severe late effects other than rectal urgency and bleeding. According to these principals, our findings in this study demonstrated that the morbidity of rectal late complications with off-axis rectal applicator was low.

Late toxic effects are the limiting factor of dose escalation in radiotherapy.

Rectal ulcers with sometimes persistent bleeding leading to chronic anaemia have been reported. These complications can necessitate permanent colostomy in some cases.

The 3-year severe rectal bleeding, sensations of mass rate were 8.3 %, 22.7 %, 30.8 % in T1, T2, T3. As to partly mobile or tethered T3 stage lesions, although the local control rate was satisfactory due to high dose irradiation, the rectal bleeding occurred in most patients. Two cases had persistent bleeding leading to chronic anaemia.

After that 5 % formol was used to burn the rectal bleeding spot, the rectal persistent bleeding was coagulated. Because the sense of anal squamous epithelium was distributed by spinal nerves, high dose of radiation to anal squamous epithelium, will lead to intolerable sensation of mass. The bowel ungency occurred in most patients whose tethered T3 lesions located less than 3 cm from the anal verge in our study.

Our study represent that, the response of rectal adenocarcinoma were satisfactory to the ^{252}Cf ICBT and EBRT with or without ^{252}Cf rectal interstitial implant.

The acute side effect is acceptable. The anal function was evaluated as excellent in most patients. Because both 3-year local control and survival rate were high and the late complication rate was low for T1 and T2 stage patients, T1 and T2 rectal adenocarcinoma can be treated by a combination of ^{252}Cf neutron ICBT and EBRT. Because s rectal bleeding (> G2), severe rectal sensation of mass rate occurred high in T3 lesions, these patients should be carefully selected for adopting a combination of ^{252}Cf neutron ICBT and EBRT with or without ^{252}Cf rectal interstitial implant.

3.3 Melanoma

Malignant melanoma which has a highly malignant potential is a tumor of the melanocytes of the skin and mucosal membranes. Primary anal melanoma is an uncommon malignancy, accounting for 0.25 % ~ 1.6 % of all rectal neoplasms, 24 % of mucosal melanomas and less than 1 % of all melanomas, and the mucosal form of the disease has a very poor prognosis, despite curative local treatment[1]. There are less than 2 years with a mean survival[2]. Most patients die from complications of metastases. It was radio-resistant to conventional photon radiation.

To research the improved sphincter preservation ^{252}Cf neutron intracavitary brachytherapy (ICBT) results on anal and rectal malignant melanoma after the modification of ^{252}Cf neutron intracavitary applicator.

3.3.1 Material and methods

3.3.1.1 The modification of the symmetry and off-axis four channel ^{252}Cf neutron intrarectal applicator To modify and manufacture the symmetric and off-axis four channel ^{252}Cf neutron intrarectal applicator which was 3 cm and 3.5 cm for the diameter respectively.

3.3.1.2 ^{252}Cf neutron dose calibration for melanoma To irradiate the melanocytes with different dose of ^{252}Cf neutron and high energy X ray to set up dose-survival curve using clonogenic assay. It could be yielded the RBE of ^{252}Cf neutron contrast X ray and α/β ratio of ^{252}Cf neutron and X ray respectively. ^{252}Cf neutron biological effectiveness dose(BED) on malignant melanoma were calibrated with the RBE and α/β ratio respectively.

3.3.1.3 Case report Three anal malignant melanoma patients who were T1 staged by UICC were delivered using ^{252}Cf neutron ICBT alone with the symmetric and off-axis ^{252}Cf neutron intrarectal four channels applicator. The total dose was 70 Gy and 68 Gy respectively for anal melanoma patient to surface of mucosa as the reference point. One rectal malignant melanoma patient who was T2a was delivered using ^{252}Cf neutron ICBT with the off-axis four channels ^{252}Cf neutron intrarectal applicator and ^{252}Cf neutron rectal interstitial implant solving the deep tissue dose deficient. The total dose was 60 Gy as the same reference point plus rectal interstitial implant 16 Gy. It were used two contradictal ones of symmetry four channels for anal melanoma lesions located in the clockwise of 6:00 and 12:00 respectively. It was used three or four channels of off-axis four channels for anal or rectal melanoma lesion according to the area of melanoma lesion. To observe the tumor regression; local control; survival time and late complications (Fig. 14 ~ Fig. 16).

3.3.2 Results

They could yield high dose to anal or rectal melanoma lesion, otherwise spare the normal tissue with low dose using the modified symmetric and off-axis four channel ^{252}Cf neutron intrarectal applicators. The calibrated RBE was 2.2 ~ 2.5. The α/β ratio of ^{252}Cf neutron for melanocytes was 2 Gy. The α/β ratio of X ray was 10.5 Gy. The 70 Gy was equivalent to 145 Gy for melanocytes according to formula $DGy\text{-}eq = RBEn \times Dn + RBE\gamma \times D\gamma$. The anal and the rectal melanoma lesions were complete regression. One year local control rate were 100 %, one anal melanoma patient have survived for more than 36 months and others survived

Fig. 14 Colonoscopy for melanoma (before the radiotherapy)

Fig. 15 Morphological figure of anal melanoma

Fig. 16 The symmetric four channel ^{252}Cf neutron intrarectal applicator

for 24 months respectively. The rectal melanoma patient survived for 18 months. Most patients died from complications of metastases. The metastatic site was liver and lung. Three anal melanoma patients have slight frequent urgency for G1 late radiation proctitis according to RTOG criteria. The rectal melanoma patient has slight rectal bleeding for G1 late radiation proctitis (Fig. 17 and Fig. 18).

3.3.3 Discussion

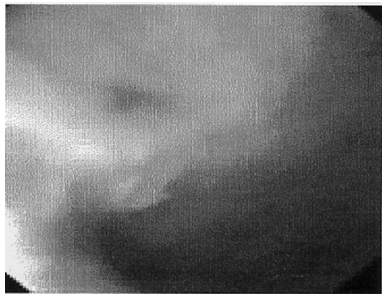


Fig. 17 Colonoscopy for melanoma (six months later after the radiotherapy)

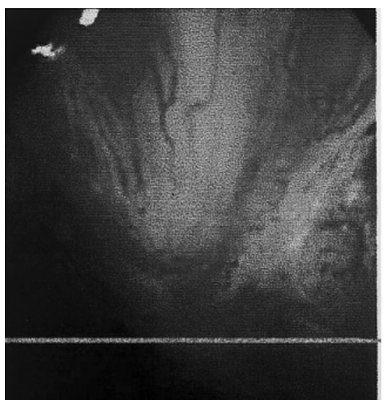


Fig. 18 Colonoscopy for melanoma (two years later after the radiotherapy)

Anal melanoma should be surgically excised. The surgical procedure of choice, APR versus local excision, is controversial for anal melanoma. A retrospective review from memorial sloan-kettering Cancer Center concluded that APR with pelvic lymphadenectomy lead to significantly higher chance of 5-years survival as compared to local excision. The conclusion was that APR with pelvic lymphadenectomy should be considered in patients with small localized anorectal melanoma without evidence of nodal metastases. Conversely, experience from the Mayo Clinic concluded that wide local excision with a negative margin of at least 1 cm was the treatment of choice. APR was advocated only for tumors unsuitable for local excision or as palliative treatment of large obstructive lesions. This multiple anal melanoma patient is difficult to preserve the sphincter function by local excision after an extensive discussion with general surgeon. The associated morbidity and inconvenience of APR and proctectomy made the life quality of patient decrease sharply, so most of patients refuse it firmly.

Malignant melanoma is a kind of tumor that resist to conventional photon radiation. It is controversy that large fraction photon EBRT may have some degree of effect to malignant melanoma[3]. Fast neutron is high linear energy transfer (LET) radiation. It has higher radiobiological effectiveness (RBE) and a lower oxygen enhancement ratio (OER) against photon radioresistant. Fast neutrons also inhibit sublethal or potentially lethal damage (SLD or PLD) repair. It has higher rate of DNA double-Strand break after radiation[4], so the repair rate of potentially lethal damage and sublethal damage are low, that's to say, we can get a higher local control rate and made the tumor hard to recurrence. From this we know that the malignant melanoma is not sensitive to normal photon but sensitive to neutron. The fast neutron generated by circular accelerator just only proper to surface tumor and it can damage the normal tissue if applied to cavitary tumor, but ^{252}Cf generated fast neuron can approach to cavitary tumor for after-loading treatment. Neutron damage the tumor cell but damage the normal tissue at the same time, moreover, anal and rectum is a small radiation tolerance organ, but the tolerance volume is closely related to the radiation area, that is, the smaller of the area, the bigger of the tolerance. On a small surface (or volume, 3 cm × 3 cm) of the rectum a dose of 100 Gy can be given without any severe late effects. According to these principals, we designed and manufactured this 3 cm-diameter four channels rectal applicator (have applied for patent right), let two of the four channels approach to the two therapy area which size is 1.768 cm × 4.45 cm and 1.616 cm × 4.35 cm respectively, this can remarkably decrease the radiation area of anal and rectum because of the other two channels are free, thus the two of melanoma at the anal are eliminated completely and just only have G1 late radiation proctitis. Our method proves that multiple and small area invaded anal & rectum malignant melanoma can be cured by ^{252}Cf neutron ICBT through special applicator and didn't have serious complications.

Thus ICBT neutron radiation therapy using high activity ^{252}Cf sources was first applied for the treatment of anal & rectum malignant melanoma. Dosimetric, morphological and clinical studies allow to consider ^{252}Cf neutron ICBT to be one of prospective trends in radotherapy of anal & rectum malignant melanoma with sphincter preservation after the modification of applicator.

The anal and rectal melanoma can be achieved local control without serious late complications because the received doses of normal tissue for anal and rectum were decreased remarkably after the modification of ^{252}Cf neutron intracavitary applicator. ^{252}Cf neutron ICBT was one of prospective trends in radiation therapy of early stage anal & rectum malignant melanoma.

4 Conclusion

Up to now, 5 000 patients received treatment with ^{252}Cf in China. 3 000 of these treatments were for cervical cancer, 500 for endometrium, 80 for vagina, 1 000 for esophagus, 400 for rectum, 50 for skin, and 30 for malignant melanoma. From the report of Chongqing Neutron Knife Center, the 5 years local control rate at and survival rate were perfect. These data is quite exciting. The challenge will be to develop a neutron source with high ^{252}Cf content and smaller size for HDR/MDR interstitial brachytherapy.

Neutron knife is the production of modern high-technology combined with multi-disciplines such as nuclear physics, radiobiology, tumor radiology, electro-mechanical integration, computer software. It is the world leader in advanced radiotherapy devices and supplied a gap in Chinese and even the world's cancer treatment field.

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