

Analysis of the Survival Rate with Cervical Cancer Using ^{137}Cs and ^{192}Ir Afterloading Brachytherapy

Guixia Zhou
Guoxiong Chen
Demei Ma
Jianping Sun
Lin Ma

Department of Radiotherapy, the General Hospital of PLA, Beijing 100853, China.

OBJECTIVE To analyze and compare the survival rate for stages II and III cervical cancer treated by external irradiation plus ^{137}Cs or ^{192}Ir .

METHODS The patients with cervical cancer were treated by external irradiation plus ^{137}Cs (group A, 427 patients) or plus ^{192}Ir (group B, 156 patients). There were 170 stage II cases and 413 stage III cases. The number of cancer types were as follows: squamous cell carcinoma, 524; adenocarcinoma, 34; and adenosquamous cell carcinoma, 25. The two groups received the same external irradiation using 8 or 10 MV of X-ray. After the whole pelvis received 25–35 Gy, the focus was given a total of 45–55 Gy by four divided fields. Intracavitary irradiation was performed with one fraction of 6–7 Gy in reference dose at A point every week and a total dose of 40–60 Gy with 6–8 fractions for group A; every fraction of 5–6 Gy in reference dose of A point and total dose of 30–42 Gy with 5–7 fractions for group B.

RESULTS The 5-year survival rate of stage II and III, and total were 82.9%, 62.2%, and 67.2% for group A respectively and 85.1%, 61.5% and 69.2% for group B respectively. There were significant differences between stage II and III in each group ($P < 0.05$) but there were no differences in the 5-year survival rate between the two groups ($P > 0.05$). The late complications of the therapy were rectitis and urocystitis and with an incidence rate of 7.3% and 6.3% for group A and 9.6% and 9.0% for group B ($P > 0.05$).

CONCLUSION The long-term survival rate and complications of stages II and III cervical cancer are similar when treated with external irradiation plus ^{137}Cs or plus ^{192}Ir .

KEYWORDS: cervical cancer, radiotherapy, intracavitary irradiation, ^{137}Cs and ^{192}Ir .

From May 1985 to December 1994, 637 patients with cervical carcinoma were treated by performing external irradiation plus afterloading radiotherapy in our General Hospital of the PLA. Out of the 637 cases, there were 583 with sufficient data in stage II and III to allow retrospective analysis in terms of different afterloading brachytherapy radioactive sources, pathological types and forms, clinical stages and long term survival rates.

MATERIALS AND METHODS

Clinical data

The age of all patients were from 26 to 82 years (mean age 57

Received April 11, 2004; accepted May 20, 2004.

Chinese Journal of Clinical Oncology
Email: COCR@eyou.com Tel(Fax): 86-22-2352-2919

Table 1. Pathological type and form and clinical stages (cases)

Group	Cases	Pathological types			Clinical stages				Pathological appearances				
		SCC	ADC	ADSC	IIa	IIb	IIIa	IIIb	Cauli-flower	Nodule	Ulcer	Erosion	Cervical canal
A	427	384	25	18	21	102	129	175	173	125	60	57	12
B	156	140	9	7	5	42	39	70	54	42	24	31	5
Total	583	524	34	25	26	144	168	245	227	167	84	88	17

SCC: squamous cell carcinoma ADC: adenocarcinoma ADSC: adenosquamous cell carcinoma

years), of which 16.8% (98/583) were 40~49, 38.4% (224/583) were 50~59 and 29.8% (174/583) were 60~69. Five hundred-twenty four cases (89.9%) were squamous cell carcinoma, 34 (5.8%) cases adenocarcinoma and 25 (4.3%) adenosquamous cell carcinoma. The detailed pathological type and form and clinical stages are shown in Table 1.

Treatment methods

With the exception of few of the massive-hemorrhage patients who first received radiotherapy 1-2 times with an afterloading device, most of the patients were irradiated by conventional external beam therapy with 8 or 10 MV X-ray; the whole pelvis received 25~35 Gy (25~30 Gy for stage II and 30~35 Gy for stage III), then the patients were treated with a combination of four-field irradiating and intracavitary radiotherapy. Group A was treated with a ^{137}Cs three-canal afterloading system, (Buchler, Germany) with the activity of radioactive source being 6~10 Ci. We obtained differential dose-distribution curves by a complete program and most of them had upright pear-shaped curves, followed by cylinder-shaped curves. Point A was irradiated with 6~7 Gy per fraction, once a week and total dose of 40~60 Gy with 6~8 fractions. For group B, Chinese WD-HDR18 ^{192}Ir afterloading system was adopted with the activity of radioactive source in the range of 2.1~6.8 Ci. Point A was treated with a total dose of 30~42 Gy (5~7 fractions, 5~6 Gy/fraction, once a week). The patients who had larger cervical tumors or difficulty in afterloading into the uterine cavity at the first treatment were primarily treated with tissue implantation or applicators of 2 radiation boxes, and the distance of the reference point was 1.5~2cm away from radioactive source with a dose of

8~15 Gy per fraction.

RESULTS

Long-term survival rates

All the patients were followed up over 5 years. The follow-up rates was 91.1% (531/583) taking into account that 52 of the missed follow-up patients had died. The overall 5-year survival rates for group A and group B were 67.2% (287/427) and 69.2% (108/156) respectively. The differences in the 5-year survival rate of the same pathological type between the two groups were not statistically significant ($P>0.05$).

There were significant differences between squamous cell carcinoma and adenocarcinoma plus adenosquamous cell carcinoma for two groups were statistically significant (group A: $\chi^2=6.81$, $P<0.01$. group B: $\chi^2=3.97$, $P<0.05$), as shown in Table 2. Table 3 shows the relationship between clinical stages and survival rates. The overall 5-year survival rates of group A for stage II and III were 82.1% and 61.2% respectively ($\chi^2=6.09$, $P<0.05$), and for group B they were 85.1% and 61.5% respectively ($\chi^2=6.43$, $P<0.05$). The differences in the overall 5-year survival rate of the same stage between the two groups were insignificant ($\chi^2=1.57$, $P>0.05$). With respect to pathological appearance, erosion and cauliflower types resulted in good prognosis, significantly different from the nodule and ulcer types, as seen in Table 4. Results of the prognostic difference between various pathological types were as follows: In group A, erosion and ulcer type: $\chi^2=6.04$, $P<0.05$; erosion and nodule type: $\chi^2=9.5$, $P<0.005$; cauliflower and ulcer type: $\chi^2=4.38$, $P<0.05$; group B: erosion and ulcer type: $\chi^2=4.42$, $P<0.05$.

Table 2. Relationship between pathological type and survival rate (cases %)

Group	Cases	SCC	ADC&ADSC
A	427	384(70.1)	43(41.9)
B	156	140(72.1)	16(43.8)
Total	583	524(70.6)	59(42.4)

Table 3. Relationship between clinical stages and survival rate (cases %)

Group	IIa	IIb	IIIa	IIIb
A	19/21(90.5)	82/102(80.4)	85/129(65.9)	101/175(57.7)
B	5/5(100)	35/42(83.3)	27/39(69.2)	41/70(58.6)
Total	24/26(92.3)	117/144(81.3)	112/168(66.1)	142/245(58.0)

Table 4. Relationship between pathological form and survival rate (cases %)

Group	Cauliflower	Nodule	Ulcer	Erosion	Cervical canal
A	134/173(77.5)	76/125(60.8)	31/60(51.7)	46/57(80.7)	0/12
B	42/54(77.8)	26/42(61.9)	13/24(54.2)	26/31(83.9)	0/5
Total	176/227(77.5)	102/167(61.1)	44/84(52.4)	72/88(81.8)	0/17

Radiotherapeutic complications

With regard to radiotherapeutic complications, rectal complications occurred the most frequently and were the earliest in the process of radiotherapy, the incidence rates being 22.7% and 29.5% for group A and group B, respectively, (no significant difference, $\chi^2 = 2.27, P > 0.05$). Increasing frequency of defecation and mucous stool were the main symptoms. Vesical complications from radiotherapy were less frequent, with urethral irritation as its main symptom. The incidence rate of urethral irritation for group A was 5.4%, and for group B 6.4%, with no significant difference between the two groups ($\chi^2 = 1.39, P > 0.05$). The late complications in the late period included mild, moderate radiation proctitis (7.3% for group A, 9.6% for group B), radiation cystitis (6.3% and 9.0% for group A and group B, respectively) and colpatesia (0.7% for group A, 0.6% for group B), but there was no incidence of rectovaginal fistulas or vesicovaginal fistulas occurred. Colpostenosis and contracture of the vagina, however, had a high incidence rate of 90.7% (529/583).

Cause of death

In group A, 101 deaths included 50 patients (49.5%) who died from local recurrence, 29 (28.7%, 29/101) from metastasis, 14 from other diseases and 8 from other unknown causes; In group B, 36 deaths included 18 patients (50.0%) from local recurrence, 8 from metastasis, 7 from other diseases and 3 from other unknown causes. For the 68 local recurrence cases, the majority were nodule type (44.1%, 30/68), 35 cases (51.5%, 35/68) occurred within two years after radiotherapy and 48 cases (70.6%, 48/68) within three years. The regional and central recurrences comprised the major percentage of 48.5% (33/68).

DISCUSSION

Cervical cancer has had a high incidence rate in China [11] with the 5-year survival rate of after an early operation and radiotherapy alone achieving up to 95.0% ~ 100%. Previously, the main radioactive sources of brachytherapy were ^{226}Ra , ^{137}Cs and ^{60}Co . Yet, with the development of a high-dose rate ^{192}Ir mini-afterloading system in the early 1990s, most Chinese hospitals have replaced the old afterloading system with the new one. However, few reports have been published relating to the differences in long-term therapeutic effects of various radiation dose rates. Therefore, we hopefully expected our study would have some future value in clinical treatment for hospitals which are using a median-dose-rate or high-dose-rate afterloading system.

Radiobiological effects of various radiation dose rates

Experiments have shown that radiobiological effects of various radiation rates were diverse, but the dose-effect was most obvious in the range of 1 ~ 100 cGy/min [12]. In the search for various dose-rate effects on cervical cancer animal models, the ratio of the biological effect between the dose rate of 100 cGy/min and 1.5 cGy/min was found to be approximately 1:0.7. But if the patients were treated with 80 ~ 100 cGy/min, the therapeutic effect in point A with 50 Gy/5w was similar to that with 70 Gy/5w (1.5 cGy/min) which was low dose rate. High-dose-rate irradiation can be defined as trying to make the dose rate high enough to complete the irradiation

in less than 1 hour (shorter than the repair for sublethal injury), consequently to achieve the dose-effect required in 1 min or 5 min has no significant difference. Owing to the repair of sublethal damaged cells over the duration of the low-dose-rate irradiation period, the two dose-rates had a differential biological effect. ^{137}Cs , one of the median-dose-rate radioactive sources, caused lower radiobiological effects than the high-dose-rate with ^{192}Ir use in the identical irradiation dosage. Therefore, in order to obtain the identical biological effect, the irradiation dosage should be increased. In addition, the isoeffect correction coefficient of various dose rates was 0.5~0.8, which can serve as a dosage conversion reference when irradiating with various dose rates. Although the external irradiation dosage and conditions for the two groups were similar in the present study, due to application of differential dose-rates for the two radioactive sources, we decreased the intracavity irradiation dose by 10~30 Gy using ^{192}Ir to acquire the same long-term therapeutic effect as ^{137}Cs .

Relationship between various irradiation dose-rates and late complications

At the end of radiotherapy we can evaluate the irradiation dosage of the rectum because of the monitoring for rectal dose when the patients were treated by ^{137}Cs afterloading system. So, in our research, the total dose of rectal irradiating for patients in group A, who had late rectal complications, was over 30 Gy, even up to 55 Gy with intracavitary radiotherapy. On the contrary, we could not determine the exact dosage by using a ^{192}Ir device due to the lack of a detector for rectal irradiation dosage. Inferred from the results that group B had higher incidence rates of late rectal complications than group A, the rectal irradiation dose and effective biological dose by the ^{192}Ir radioactive resource was higher than that by ^{137}Cs . Some researchers also reported that late complications of high-dose-rate intracavitary radiotherapy were more than that caused by median and low dose rates, but there were no statistical differences^[3,4]. The incidences of late complications will increase remarkably if the dose of external irradiation for the whole pelvis is over 40 Gy or the dose of point A per fraction is over 8 Gy. Therefore, presently in our clinical application, to lessen the

irradiation dosage of the rectum, ribbon gauze packing was applied to enlarge the distance between the rectum and the radioactive resource. But at the same time, this method lowered the irradiation dosage in the upper segment of vagina. Besides, most of the patients suffered from decrease of vaginal elasticity and colpostenosis, which made it difficult to enlarge the distance between rectum and radioactive resource, and thus made the rectum receive a higher dose. To decrease the incidence of late complications, we suggest application of the following methods: 1) the irradiation dosage for the whole pelvis should be lower than 40 Gy; 2) for point A, the single dose should be not beyond 6 Gy and the total dose should not beyond 36 Gy using ^{192}Ir intracavitary irradiation, respectively, or not beyond 6 Gy and 36 Gy by ^{192}Ir ; 3) interstitial therapy should be administered for eccentric or large tumor to increase the rate of tumor elimination and indirectly decrease the irradiation dosage of rectum.

Factors influencing the long-term survival rate

The significant prognostic factors of cervical cancer proved to be the clinical stage, pathological type and appearance. Some reports revealed that the 5-year survival rate in stage II was 75.8~86.7%, and in stage III 40.7%~63.6%^[5,6]; if combined with chemotherapy, the 5-year survival rate in stage III can be elevated from 51.2% which was the rate of radiotherapy alone to 72.9% ($P<0.05$)^[7,9].

In addition, the prognosis of differential pathological types obviously varied. According to some references^[10-12], the 5-year survival rate of adenocarcinoma was lower by 20% than that of squamous cell carcinoma. While, in our study the prognosis of squamous cell carcinoma was much better than that of adenocarcinoma and adenosquamous cell carcinoma with significant differences. The reason may be due to lower radiosensitivity and early metastasis of adenocarcinoma. From the point of pathological appearances we found that patients with a cervical-canal type tumor had poorer prognosis compared to an ulcer type. Among 11 patients with a cervical-canal type tumor in our study, none of them survived for 5 years. But the prognosis of erosion-type tumor patients was best and following was cauliflower because of

their greater intracavitary radiosensitivity and late lymphatic metastasis.

In a word, this article demonstrated that there were not significant differences in 5-year survival rates or radiological complications between high-dose-rate ^{192}Ir and median-dose-rate ^{137}Cs under the similar condition of external irradiation and properly adjusted afterloading dose. But compared with ^{137}Cs , ^{192}Ir had some advantages such as short treatment time, multiform radioactive applicator, the use of a thin pipe for uterine cavity and little pain for patients etc. In present circumstances, quite a few hospitals continue to use a ^{137}Cs afterloading system, which was shown in this study to be of the same long-term effect as this modern brachytherapeutic system.

REFERENCES

- 1 Li LD, Lu FZ, Zhang SW, et al. Analysis of cancer mortality and distribution in China from 1990~1992. An epidemiological study. *Chin J Oncol*. 1996;6:403.
- 2 Liu TF, Senior editor. *Modern radiation oncology*. Shanghai: Fudan Press. 2001:257-266.
- 3 Chun M, Kang S, Kil HJ, et al. Rectal bleeding and its management after irradiation for uterine cervical cancer. *Int J Radiat Oncol Biol Phys*. 2004;58:98-105.
- 4 Vjitswanathan FR, Varghese C, Peedicayil A, et al. Hyperfractionation in carcinoma of the cervix: tumor control and large bowel complications. *Int J Radiat Oncol Biol Phys*. 1999; 45:653-656.
- 5 Cao ZY, Chief editor. *Gynecological Oncology*. Beijing: Beijing Press. 1998:585-686.
- 6 Toita T, Kakinohana Y, Ogawa K, et al. Combination external beam radiotherapy and high-dose-rate intracavitary brachytherapy for uterine cervical cancer. *Int J Radiat Oncol Biol Phys*. 2003;56:1344-1353.
- 7 Lorvidhaya V, Chitapanarux I, Sangruchi S, et al. Concurrent mitomycin C, 5-FU, and radiotherapy in the treatment of locally advanced carcinoma of the cervix: a randomized trial. *Int J Radiat Oncol Biol Phys*. 2003;55: 1226-1232.
- 8 Eifel PJ. Chemoradiation for carcinoma of the cervix: advances and opportunities. *Radiat Res*. 2000;153:229-236.
- 9 Pignata S, Frezza P, Tramontana S, et al. Phase I study with weekly cisplatin-paclitaxel and concurrent radiotherapy in patients with carcinoma of the cervix uteri. *Ann Oncol*. 2000; 11:455-459.
- 10 Kagei K, Tokuyue K, Okumura T, et al. Long-term results of proton beam therapy for carcinoma of the uterine cervix. *Int J Radiat Oncol Biol Phys*. 2003;55:1265-1271.
- 11 Dong ZL, Yang L. Long urative effect of cervical cancer in the treatment of ^{60}Co afterloading intra cavity plus extracorporeal irradiation. *Chinese J Radio Oncol*. 1998; 7: 115-117.
- 12 Maduro JH, Pras E, Willemse PHB, et al. Acute and long-term toxicity following radiotherapy alone or in combination with chemotherapy for locally advanced cervical cancer. *Cancer Treatment Reviews -December*. 2003;29:471-488.