

Application of Intraoperative Radiotherapy for Cervical Cancer

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Abstract Objective To preliminarily assess the application effects of intraoperative radiation therapy (IORT) for cervical cancer. **Methods** To analyze retrospectively the effect of 181 cervical cancer patients with IORT. **Results** In 9 recurrence cases, 1 died in nine months after IORT because of multiple metastasis, 1 case relapsed at vagina Stump in fourteen months after IORT, the other seven cases have survived with free diseases up to now. In 172 patients in primy cervical cancer II b, 5-year disease free survival rate, 5-year survival rate and 5-year local control rate are 86.5%, 89.7% and 94.5% respectively. According to classification, the 5-year survival rate of squamous carcinoma, adenocarcinoma and adenosquamous carcinoma are 93.2%, 91.7% and 56% respectively. The complications dependent on IORT after operation were fewer and the most parts could be self-treated. **Conclusion** The effect of IORT for primary tumour is good. IORT not only is selected for recurrence of cervical cancer, but also suitable for primary cervical cancer II b. IORT can improve obviously 5-year survival rate of cervical carcinoma especially cervical adenocarcinoma. There are positive significance for patients of cervical cancer II b to choice "utero-adnexectomy + selective lymphadenectomy + IORT".

Key words Cervical cancer; Intraoperative radiotherapy; Lymphadenectomy

Cervical cancer is one of the most frequent malignant tumor in department of gynecology, its incidence is in the first place (70%~90%) in female genital organ tumor. There are about one hundred and thirty thousand ^[1]neopatiens of the disease developed in our country every year. About 30%~50% patients with cervical cancer emerge recurrence or metabasis whice induced treatment failure ^[2]. The great question what the clinical treatment is facing to is how to raise cure rate, prolong survive time and improve life quality of the patients. Intraoperative radiotherapy, IORT, is an efficient method to cure tumors by increasing local irradiation at one time in order to elevate local control rate. This is a close-up combination of operation and radiotherapy.

We analyses the results of 181 patients with cervical cancer who have accepted radiotherapy during operations. Consequences are as follows.

MATERIALS AND METHODS

Clinical data

From Februaey in 1997 to June in 2005, there are 181 patients with cervical cancer among 226 cases of female genital organ tumor accepted radiotherapy during the operations in the primary and secondary affiliated hospitals, medical college of Xian communication university. There are 172 initial finding and initial treatment cervical cancer II b [international department of gynaecology and obstetrics league (FIGO) clinical stage] specimen and 9 cases were center model cervical cancer palindromic patients. All specimen have got final diagnosis by pathology examination. The middle age of patients is 44 years old (ranged from 21~74). Pathology characteristics of cervical cancer are showed in table 1.

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There are 10 cases not yet ranked in squamous cancer examples, which were diagnosed by cervical biopsy in another hospital before and were pathologically demonstrated to be chronic inflammation in cervix uteri accompanied with superficial necrosis after operation and no cancer cells be found. Among the another 9 cases with recur cervical cancer, 8 were squamous cancer II degree examples, which all accepted radical radiation therapy; another one is poorly differentiated adenocarcinoma which was partly out of control example after complete hysterectomy in another hospital.

Internalize standards

Initial finding and initial treatment examples

- (1) Cervical cancer patients have got the final diagnosis by case history, physical examination and pathological examination. Gynecologic examination shows cancer have exceed cervix but not reached pelvic wall and it belongs to cervical cancer II b according to clinical stage;
- (2) Do not accept operation, radiotherapy or chemotherapy before diagnosis;
- (3) Preoperation radiotherapy is administered when the final diagnosis of cervical cancer II b is made, external exposure of cavitas pelvis + intracavitary afterloading radiotherapy in a short distance, the dose of point A is 30~34 Gy;
- (4) Do gynecologic examination after preoperation radiotherapy, the result showed cervical cancer extends no more than a half, the tumor can not be removed clearly by operation.

Recur cases

- (1) Recur tumour located in cavitas pelvis, isolated, centre form and limited relatively;
- (2) No medical proofs to show distant metastasis .

Contraindication

- (1) Cervical cancer II b and accept preoperation radiotherapy, gynecologic examination shows tumour extends more than a half of uterus;
- (2) The patients dont endure operation for the badly affections of heart, liver, kidney and so on;
- (3) The patients refuse to accept radiotherapy during op-

erations.

Therapy methods

Initial finding and initial treatment of cervical cancer II b

- (1) Preoperation radiotherapy: pelvic irradiation was administered in whole cavitas pelvis with accelerator linear, plane accumulated dose in cavitas pelvis is DT20Gy/10 times, matching radiotherapy in a short distance in point A in intracavitary DT:10~14Gy/ 2 times;
- (2) Style of operation and anaesthesia: operation and radiotherapy are done at the same time under continuous epidural anesthesia in 10~14 days after preoperation radiotherapy, the module of operation is the whole uterus and adnexectomy and selective absorbent gland removed;
- (3) radiotherapy during operation: all the things is done before embedding abdominal peritoneum. First, to sew a stitch by chorda serica chirurgicalis in vagina Stump as Drag, to raise Stump and establish vagina Stump and lymph drain area in cavitas pelvis to radiotherapy area under the cavitas pelvis calimator $\varphi=15\text{cm}$, the intestine and bladder were ensured to out of the radiotherapy area and the rectum was sheltered with lead board. Put a piece of absorbent gauze about 0.5cm thick on field dose in order to boost field dose. After examination, prepare accelerator linear and electrocardio monitor and then ray during operation (12Mev- β , DT 18~20Gy). Looking over radiotherapy area to make sure vagina Stump and intestinal canal are in right places. Unload calimator and lead backup, to end operation in order.

Center recurrence of cervical cancer after radical radiotherapy

- (1) Operation and anaesthesia style: operation accompanied with radiotherapy under persistent epidural anesthesia was performed, the operation style is whole uterus and adnexectomy through abdomen + tumorectomy of vaginal wall;
- (2) Radiotherapy during operation: put vagina stump to radiotherapy area to administer radiation with oval-shaped calimator $\varphi=8\text{cm}$ (9~12 Mev- β , DT 15~25Gy).

All patients must accept anti-infection sustain and hemostasis treatments, and take stitches out in 7~8 days

after operation.

Radiotherapy equipments during operation

(1) Calimator of cavitas pelvis: there are different calimators with different diameters can be choose. Calimator^[3] (patent number: ZL 97 2 39908.8) which $\phi = 15\text{cm}$ is used specially for cavitas pelvis. Its transverse section is oval-shap, contact prong with tissue is contour that well anastomosis with tissue of cavitas pelvis. Radiation field is from divarication of abdominal aorta to interspace between bladder and vagina (including vagina Stump 1cm), two sides including lymph area of ilio-blood vessel, but the small intestina, colon, bladder are excluded from radiation field, the rectum is protected by 6 mm lead strip. The distribution range of β -ray on tissue surface 12MeV of tube in our lab is 87 %~89 % of prescription dose. The deep range of D85 tissue is 0~4cm; when >4cm, ray dose decline to under 50% of prescription dose rapidly. Leak dose out of tube wall is 5 %~6 %. Oval-shap calimator which $\phi = 9\text{cm}$ wrap the vagina Stump into radiation areas.

(2) Accelerator linear: AMSCO -3080 operation table produced by Somo Company in USA, to match with therapeutic machine. Mevatron KD double photon linear accelerator and a complete set of supervising system produced by Siemens company in Germany.

(3) Condition in operating room: the special operating room for IORT was built in December in 1996, from high-energy linac treating room in radiotherapy department, therapeutic machine nose can adjoin in calimator top tightly, and provide all equipments needed in operating room and department of anesthesiology. Faculty leave when IORT begins.

(4) The requirements to doctors and physics master: the whole range of operation and IORT need to be done by the cooperation of radiotherapy department, department of anesthesiology and operating room. The operative procedure and radiotherapy plan are designed by tumor doctors in radiotherapy department, radiotherapy plan is finished under the supervision of radiotherapy physicists and the help of technicians.

Follow-Up and statistics

Follow-Up styles include patients' regular follow-

up, initiative telephone connection, and letters. Follow-Up time was 6~106 months and the mid-Follow-Up time was 36 months. of the total the survival follow-up time 6~106 months, ms-Follow-Up time 47 months. life span's calculation is from radiotherapy date during operation to death date or the last follow-up date, the live time to 2005-12-31 is the ending data. There are 4 patients out of touch, 2 patients accidentally died, Follow-Up rate is 96.7 %. There are 15 patients died of cervix cancer or complications. This is non-ending data. The extrem incident of existence without tumour is recurrence focus examined by pathology or imageology, without recurrence in areas during follow-up period is extrem data. The extrem incident of local control is tumor recurrence focus in radiotherapy area, not the distant diversion or un-recurrence in area, it is extrem data that without recurrence in radiotherapy area. we use SPSS12.0 statistical package, life table method to calculate survival rate, disease free survival, local control rate.

RESULTS

Follow-up information

In the 172 CACX II b patients who accept radiotherapy in the operation, 5 years survival rate is 89.71%, 5 years disease free survival is 86.46%, and 5 years local control rate is 94.5%. The 5 years survival rate, 5 years disease free survival, and 5 years local control rate of SC, AC and AdCa are showed on table 2. In 9 cervical cancer recurrence patients only one died of metastasis all over the body 9 months after radiotherapy during operation, which accepted complete hysterectomy and out of control partly in another hospital. Eight patients are cervix partly recurrence or vagina recurrence, only one patient vagina stump recurrence 14 months after accepting radiotherapy in the operation. 7 IORT are still alive without tumor up to now.

Tumor recurrence and the patients die

In 172 CACX II b patients who accepted radiotherapy during operation, pathological reports showed there were 21 uterus side infiltration (12.2 %), vagina Stump infiltration were 14 (8.1 %). Tumor recurrence after ra-

diatherapy during operation were 20 cases: SC 12/144 (8.3%), AC 3/16 (18.8%), AdCa 4/10 (40%), anaplastic carcinoma of mini cell 1/1. In these patients there were 13 distant metastasis: SC 7/144(4.9%), AC 3/16(18.8%), AdCa 2/10(20%), anaplastic carcinoma of mini cell 1/1. There were 7 patients recurrence in radiotherapy areas: SC5/144(3.5%), AdCa2/10(20%); 12 patients died: SC8/144 (5.56%), AC1/16 (6.25%), AdCa4/10 (40%), anaplastic carcinoma of mini cell 1/1. In the 9 cervix cancer recurrence patients, one patient who is partly out of control after complete hysterectomy in another hospital died in 9 months after radiotherapy during operation because of metastasis all over the body. Eight patients partly recur in cervix or vagina after radical radiation therapy, only one patient vagina stump recurrence in 14 months after radiotherapy during operation. Tumor recurrence and death type are in the following table 3. The time of tumour recurrence is 1~37 months after operation, meso time is 10 months. Among 8 instances that tumour recurrence in radiotherapy areas in cavitas pelvis, 6 instances' recurrence time no more than 8 months.

Complication

Complications happened in or after operations in 181 cervix cancer patients who accepted radiotherapy during operation include: vagina Stump phlegmonosis 10 cases, hydronephrosis 9 cases, rectum reaction 5 cases; lymphocyst in cavitas pelvis 2 cases; rectovaginal fistula 1 case. Besides 3 hydronephrosis needed operations, others healed by conservative treatment.

DISCUSSION

IORT is a kind of combined therapy which combine operation and radiotherapy and refer to many clinical speciality. Energetic electron beam have physical characteristics that attenuated rapidly after enter tissue. Consequently this not only for tumor bed after operation but also for tumor focus which couldnt be removed. With the rapid development of radiation oncology and radiotherapy equipments, IORT will be used moer and more widely in clinically treatments.

Characteristics of IROT

IROT is a kind of radiographic exposure with large dose at one time toward tumor bed, residual focus and correlated lymph drain areas. It can kill tumor cels, protect normal organ and tissue as much as possible^[4], because it definite coverage field under euthyphoria and choose suitable energy and dose. The merits of IROT are exact localization, high local dose, so it can eradicate local tumor efficiently, improve prognosis, no serious complications in the near future^[5,6]. There are 3 base theories of this therapy:(1)biological effects of large dose irradiation at one time are as 2~3 times as fractionated of routine dose irradiation;(2)exposure field in operation is just the place that tumor recurrence;(3) normal tissues which are restricted by radiation dose are excluded or blocked as much as possible^[7].

IORT of tumors in department of gynecology

Tumours in department of gynecology are largely in pelvic cavity, and the pelvic bases and pelvic walls are rugosity. But the butt end of shaping calimators are plane or inclined plane, which can not stick to tissue properly, so it can not irradiate tumour tissue in one exposure field, which limitates the application of radiotherapy during operation. Since 1996 we have been using "calimator to be used specially for cavitas pelvis operation "to do radiotherapy during operations of cavitas pelvis tumour, which satisfy the design equirements of IROT and clinical treatments by solving probles of "leak radiation"or"overlap radiation"existed in single field or multifield radiation.

Speaking to malignant tumor therapy, domestic and abroad scholars do IROT for cervical cancer and endometrial cancer in advanced stage or recurrence after operation, which affection limited relatively and no distant metastasis^[8-10]. There are less reports about operating IROT on mddle or advanced stage ervical cancer patients who are initial finding or accepting initial treatments. Gerard^[11]review and analysis 34 recurrence ervical cancers and carcinoma of corpus uteri patients who accept IORT, there are only 12 patients' tumour remove clearly. Total survival rate of 4 years is (32±8)%, 6 patients recur in IORT area. Martinez^[12] reports that 31 ervical cancer patients who are initial finding or ac-

cepting initial treatments, I b- II a12 patients, II b12 patients, III-IV a 7 patients survival rate of 10 years, Local Control rate are 58.0% and 92.8%; survival rate of 10 years, Local Control rate of 36 recur patients are 14%、46.4% respectively.

Our documents show: cervical cancer center recur patients who accept radical radiation therapy, just do tumorectomy+cavitas pelvis small area irradiation. One in eight patients vagina Stump recurrence 14 months after accepting radiation therapy during operation. 7 patients are still alive without tumour after accepting IORT. There are no statistically significance because of less case of a particular disease. Survival rate of 5-year, disease free survival rate of 5-year, local control rate of 5-year are 89.7%,86.5%,94.5% respectively in 172 CACX II b patients who accept radiotherapy. If we classify the tumour to SC, AC, AdCa, survival rate of 5 years are 93.2 %,91.7 %, 56.0 % respectively. The results mean: (1)radiotherapy during operation indeed has local control effect in primarily tumor area;(2)elevation 5-year survival rate of CACX especially AUC, which shows one time large dose IORT can improve AC sensitivity towards radioactive ray;(3)2 in 10 AdCa II b patients appear recurrence in irradiation area after radiotherapy, the reason may be that malignant of AdCa is hight and radiosensitiveness is low, radiotherapy dose (70~74Gy) both in and before operation can not eliminate cancer focus.

According to classics therapeutic regimen of CACX, II b patients can not accept rsection. But in our opinion that the operation and whole pelvic irradiation are performed at one time, and try to contract extent of radical operation and don't clear away lymphonode in cavitas pelvis, just to clear away swelled lymphonodes when doing adnexectomy through abdomen. This not only correspond with therapeutic principle that decrease relatively when using two treatments at one time but also with the points that keep lymph vessels in cavitas pelvis during operation^[13]. In operation we find that so-called encroachment to uterus side, decurtation and thickening of uterosacral ligament is because of inflammatory reaction actually, not cancer infiltration, cancer infiltration proved by patho-examination just 12.2%(21/172). Second II b patients often extend to fundus of vagina and

upper 1/3 of vagina, the removed extent of vagina in complete hysterectomy is limited (1~2 cm or so), so pathological report shows vagina stump attack by tumour are 8.1%(14/172), but not all patients appear vagina stump recurrence, this the evidence of clinical significance of radiographic exposure with large dose at one time .

All in all : (1) extent of operation can be reduced but therapeutic efficacy is good when you find no macroscopic tumour left in vagina stump and do radiotherapy at the same time, accumulated dose in radiotherapy is up to 70~74 Gy according to clinical practice of 8 years. (2) There are much difference between clinical stage and findings in operation, this may be related to personal experience and radiotherapy before operation, but it is necessary to rectify staging standards. It is much more meaningful to combine clinical stage and findings in operation. (3) patients need not worry about vagina stump, because dose perioperatively (30~34Gy) and in operation (37~40 Gy) can kill the tumour. (4)"small" operation"large" radiotherapy is not only corresponding with principle of combined therapy, but also with the demands of patients that to remove of infection quickly, shorten time of therapy, raise quality of life. (5)IROT is not only an effective therapy for CACX recurrence patients but also meaningful to initial CACX II b patients who accept large area IROT in cavitas pelvis.

The complications of IROT

Radiotherapy during operation is a kind of treatment that combine operation and radiotherapy by irradiating tumor bed or tumour at large dose one time. Some normal tissue man be included in exposure field in operation inevitably, too high dose may lead to complications in advanced stage also. These are complications related to radiotherapy after operation,such as vagina stump phlegmasia,hydronephrosis, rectum reaction, lymphocyst in cavitas pelvis. All patients fully recover from an illness or improve by expectant treatment except three hydronephrosis patients. The happening of hydronephrosis is related to fibrous degeneration of metanephric duct and post abdominal peritoneum because of irradiation in operation. In order to definite the

suitable dose of IORT, a great quantity of animal experiments were done in abroad, in order to find the relationship between dose and injure or patho—changes to AtV, intestinal canal, metanephric duct, nervous tissue and so on. According to this in clinical radiotherapy the dose are great vessels of post abdominal peritoneum $\leq 25\text{Gy}$; part small intestine $\leq 20\text{Gy}$; extrahepatic bile duct $\leq 20\text{Gy}$; half kidney $\leq 15\text{Gy}$; metanephric duct $\leq 30\text{Gy}$; peripheral nerve $\leq 15\text{Gy}$. The same dose when combine extracorporeal irradiation^[14]. But because of individual difference, protective measure of metanephric duct still need to be proved.

AT after IROT

Death and recurrence tumor data in this study showed: ①the 5 years survival rate of 10 AdCa II b patients is 56 %, disease free survival rate is 48%, Local Control rate is 72%;there were 4 patients died, 2 died of distant metastasis, and 2 died of recurrence in cavitas pelvis. ②the patho—consequence of cervix mini cell anaplastic carcinoma after IROT is:cervix chronic inflammation with local tumor superficial cellular necrosis, without tumor cell. It is possible that cancer focus has been killed by preoperation radiotherapy. The left lower limb of the patient appeared pain 14 months after operation,CT of abdominal cavity shows:paraortic lymph node diversion, to give hydroxycamptothecine vein chems+local radiotherapy, die of metastasis all over the body after half a year.③the patho—result of one patient die of AUC shows:AUC II and invade full—thickness, Right ovary and colic omentum diversion, cutting edge remains tumour. The patient die of liver metastasis 13 months later; ④death and tumor recurrence SC patient has high risk of cancer. To malignant cancer of the cervix, such as AdCa, mini cell anaplastic carcinoma, poorly differentiated SC and existing high risk factors after accepting"preoperation radiotherapy +operation + IROT"should give adjuvant chemotherapy. ⑤one patient die of metastasis all over the body 9 months after radiotherapy who partly out of control after accepting AUC complete hysterectomy in another hospital. So, it is the key to reach final diagnosis before accepting IORT for CACX recur patients.

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