Late Rectal Complication in Patients Treated with High Dose Rate Brachytherapy for Stage IIB Carcinoma of the Cervix

Eun Ji Chung, M.D., Gwi Eon Kim, M.D., Chang Ok Suh, M.D.
Ki Chang Keum, M.D. and Woo Cheol Kim, M.D.

Department of Radiation Oncology, Yonsei Cancer Center, College of Medicine
Yonsei University, Seoul, Korea

= Abstract =

Purpose : This paper reports a dosimetric study of 88 patients treated with a combination of external radiotherapy and high dose rate ICR for FIGO stage IIB carcinoma of the cervix. The purpose is to investigate the correlation between the radiation doses to the rectum, external radiation dose to the whole pelvis, ICR reference volume, TDF, BED and the incidence of late rectal complications, retrospectively.

Materials and Methods : From November 1989 through December 1992, 88 patients with stage IIB cervical carcinoma received radical radiotherapy at Department of Radiation Oncology in Yonsei University Hospital. Radiotherapy consisted of 44-54 Gy(median 49 Gy) external beam irradiation plus high dose rate intracavitary brachytherapy with 5 Gy per fraction twice a week to a total dose of 30 Gy on point A. The maximum dose to the rectum by contrast(r, R) and reference rectal dose by ICRU 38(dr, DR) were calculated. The ICR reference volume was calculated by Gamma Dot 3.11 HDR planning system, retrospectively. The time-dose factor(TDF) and the biologically effective dose (BED) were calculated.

Results : Twenty seven(30.7%) of the 88 patients developed late rectal complications:12 patients(13.6%) for grade 1, 12 patients(13.6%) for grade 2 and 3 patients(3.4%) for grade 3. We found a significant correlation between the external whole pelvis irradiation dose and grade 2, 3 rectal complication. The mean dose to the whole pelvis for the group of patients with grade 2, 3 complication was higher, 4093.3±453.1 cGy, than that for the patients without complication, 3873.8±415.6 ($0.05<p<0.1$). The gradual increase in the frequency of grade 2, 3 rectal complication increased as a function of the dose of external beam therapy to the whole pelvis(midline shielding start dose) and total rectal dose. The mean total rectal dose by rectal barium(R) for the group of patients with grade 2, 3 rectal complication was higher, 7163.0±838.5 cGy, than that for the patients without rectal complication, 6772.7±884.0 ($p<0.05$). There was no correlation of the rate of grade 2, 3 rectal complication with the ICR rectal doses(r,dr), ICR

본 논문은 1995년 11월 4일 접수하여 1996년 2월 3일에 채택되었음.

reference volume, TDF and BED.

Conclusion : This investigation has revealed a significant correlation between the dose calculated at the rectal dose by ICRU 38(DR) or the most *anterior rectal dose by contrast*(R), *dose to the whole pelvis and the* incidence of grade 2, 3 late rectal complications in patients with stage IIB cervical cancer undergoing external beam radiotherapy and HDR ICR. Thus these rectal reference points doses and whole pelvis dose appear to be useful prognostic indicators of late rectal complication in high dose rate ICR treatment in cervical carcinoma.

Key Words : Cervical carcinoma, High dose rate(HDR), Intracavitary radiation (ICR), Late rectal complication

INTRODUCTION

Carcinoma of the uterine cervix is a potentially radiocurable tumor. Radiation therapy alone is the clear treatment of choice for the more advanced stages (IIB and III) for patients unsuited to surgery. Intracavitary radiation(ICR) with radioisotopes, used in combination with external beam irradiation, represents the standard approach for treatment of the uterine cervical cancer. Because of the steep dose gradient around the radioisotope source and because the rectum and bladder are close to the cervical tumor, these organs are at risk. The relationship between dose to the adjacent organs and frequency of late-occurring sequelae have been major subjects of discussion in the medical literature, with contradictory conclusions reported [1-17]. Although dose and volume specification for reporting intracavitary irradiation in cervical carcinoma was originally defined for low dose rate (LDR) ICR (ICRU 38), and as such are well established[18], their value as predictors of late complications has been controversial[7, 12, 14, 16, 17, 19-22]. With the increasing use of high dose rate (HDR) ICR which differs in biological effect and is frequently fractionated, the dose and volume specification for high dose rate treatments have come under further scrutiny[17, 21]. HDR-ICR has been used in the treatment of cervical cancer for more than 20 years, many studies have noted that the most common late complication site is the rectum[1-7, 15, 17, 21, 23-27]. Although numerous studies have been devoted to late rectal complication in intracavitary brachytherapy for cancer of the cervix, the multitude of dosimetric descriptions makes comparisons difficult. Several factors, such as: hypertension, diabetes, age, previous pelvic surgery, pelvic inflammatory disease, treatment technique, radiation dose to the critical organs, radiation volume, TDF and BED have been identified as responsible or contributing to the development of the late complications[7, 14, 15, 19, 28-34]. The opportunity of decreasing late rectal complication risk from an assessment of dose to the rectum, volume, and other affecting factors in each individual case prior to treatment with HDR-ICR is of prime importance.

RALSTRON (remote controlled afterloading system using high-dose rate Cobalt-60 radionuclides) was first installed in 1979 and the other HDR-ICR unit Gamma Med 12i (Iridium-192 radionuclides) was also installed in 1989 at Department of Radiation Oncology, Yonsei University Hospital. Since November 1989 about 500 patients have been treated with the Gamma Med HDR unit. This study was undertaken to retrospectively analyze the 88 patients with FIGO stage IIB cervical carcinoma treated with HDR-ICR Gamma Med to evaluate the incidence of late rectal complications, the interval between radiotherapy and the development of rectal complications, and the relationship between these complications and factors such as ICR and total reference rectal points; external whole pelvis dose; ICR reference volume; TDF and BED.

MATERIALS AND METHODS

1. Patient Population

Between November 1989 and December 1992, 115 patients of histologically proven cervical carcinoma of the intact uterus FIGO stage IIB were treated with external radiation and Gamma Med HDR-ICR at the Department of Radiation Oncology, Yonsei University Hospital. Among them 27 patients were excluded from this study because they were treated with combination chemotherapy, leaving 88 patients as the subjects for our study.

The hospital charts, treatment records, simulation and verification films, and dosimetry results were thoroughly reviewed in all the 88 patients, whose mean age was 57 years(range, 29-83 years). There were 84(95.5%) patients with squamous cell carcinoma and 4(4.5%) patients with adenocarcinoma. The patients were followed up every three months during the first two years and every six months thereafter. 86 of 88 patients (97.7%) were followed up for at least 2 years or until death (follow up range 24-68 months, median 40 months). In all of the 86 patients, follow-up consisted of review of institutional records, letter or telephone contact, and occasional direct communication with the patient or relatives. The T-test was done for comparison of mean doses between the group with grade 2, 3 late rectal complications and those without them.

2. Radiation Treatment

Prior to insertion of the radioactive Iridium 192 source, all patients underwent external beam irradiation to the whole pelvis with 10 MeV photons with or without midline shielding. The total external dose were 44-54 Gy(median 49 Gy) and the whole pelvis doses (midline shield doses) delivered to the midplane ranged between 25 and 45 Gy (median 36 Gy), with dose fractions of 1.8-2 Gy/day, 5/week. Port combination was usually 4 field box technique for whole pelvis radiation and AP/PA parallel opposed ports when using a 4 cm width midline shield. In some cases external parametrial boosts were given. HDR-ICR with Gamma Med was performed 2 weeks within completion of the external beam radiotherapy. In our hospital, each HDR-ICR treatment was performed with an outpatient setup without anesthesia or analgesics and took about 10-20 minutes for each treatment.

The Gamma Med system, which is a remotely controlled high dose rate afterloading radiation machine, was used for the delivery of HDR-ICR. The system contains Iridium 192 source with the radioactivity of 10 Curie(370 GBq) at installation. Rigid intrauterine tandems with curvatures of 0° 15° 20° 30° and lengths of 4, 5, 6, 7 cm were used in combination with pairs of ovoids of 2, 2.5 and 3 cm diameter which are partially shielded Manchester ovoids or modified Fletcher Suit applicators. HDR ICR with Gamma Med was given twice week. A single dose of 5 Gy was delivered at point A. Total doses of ICR at point A ranged from 25-40 Gy, with a median of 30 Gy. After insertion of the uterine tandem and ovoids, orthogonal AP and lateral films were taken with dummy sources. The bladder neck was identified by Foley catheter balloon filled with 7 cc of contrast material and the rectum was filled with 100 cc of barium.

3. Determination of Reference Rectal Points, ICR Reference Volume, TDF and BED

Retrospective treatment planning for ICRU 38 reference rectal point dose and ICR reference volume for each patient was carried out with current upgraded treatment planning system for Gamma Med(Gamma dot 3.11). The reference rectal points used in this study were two kinds of points. One is the rectal point defined by the ICRU 38[18]. In ICRU report 38, the point of reference for rectal dose is as follows. On the lateral radiograph, an anteroposterior line is drawn from the low end of the intrauterine source(tandem ring). The maximum rectal point(dr) is located on this line 5 mm behind the posterior vaginal wall. The posterior vaginal wall is visualized, depending

upon the technique, by means of an intravaginal mould or by opacification of the vaginal cavity with a radio-opaque gauze used for packing. We did not insert a radio-opaque gauze routinely because the vaginal cavity was not wide enough to insert a gauze for vaginal packing in many patients. On the AP radiograph, this reference point is at the lower end of the intrauterine source. The other reference rectal point(r) is the most anterior rectal mucosal point located at the same anteroposterior line on the lateral radiograph by barium contrast. In this report, DR and R mean the total rectal doses which were a combination of external beam irradiation to the rectum(whole pelvis dose) and ICR reference rectal doses(dr, r). The ICR reference volume was calculated by upgraded Gamma Dot 3.11 treatment planning system retrospectively. We were able to select the reference volume which was covering a specific dose in the planning system. We chose the ICR reference volume which covered the point A isodose line.

The modification doses of the cumulative reference rectal dose administered by whole pelvis external irradiation and HDR-ICR were calculated from the TDF(Time-Dose Factor) and BED(Biologically Effective Dose). Time-Dose Factor was defined by the formula:

$$TDF = ND^{1.538} X^{-0.169} 10^{-3},$$

where N is the number of fractions, D the dose of each fraction, and X the number of treatment days per fraction. The Time-Dose Factor could also be calculated for brachytherapy and for combined brachytherapy/fractionated therapy modalities[35, 36].

Biologically Effective Dose was defined by the formula:

$$BED = ND\left(1+\frac{D}{\alpha/\beta}\right)$$

We had assumed a value of α/β=3 Gy for late reactions[39]. A Biologically Effective Dose is equivalent to an Extrapolated Response Dose (which is the analog of TDF), and α/β is a tissue-specific, linear-quadratic (LQ) model parameter[37-39].

4. Grading System of Late Rectal Complication

The grading system for late rectal complications arising from radiation therapy was based on the Kottmeier's classification[29]. Grade 1 includes mild rectal bleeding requiring no treatment. Grade 2 includes moderate to severe rectal bleeding requiring medication and/or transfusion. Grade 3 includes severe rectal bleeding or fistula requiring surgical treatment.

RESULTS

Twenty seven patients(30.7%) developed rectal complications. Among them about half(12/27) of the patients presented with mild self limited grade 1 complications(12/88=13.6%), and fifteen patients developed grade 2, 3 complications(15/88=17%). Three patients with grade 3 complications had rectovaginal fistulae and 2 of the 3 died of sepsis which resulted from the complication.

The latent interval between the completion of radiation therapy and late rectal complications ranged from 4 to 43 months (mean 17.3 months, median 16 months). We found that at least 3/4 of rectal complications developed within 2 years after radical radiotherapy.

Table 1. represents the mean radiation doses and values in patients with and without rectal complications. There is no significant difference of treatment factors between the two groups. Therefore, we excluded the patients with grade 1 mild complications and analyzed major complications only(grade 2 and 3) for several factors (Table 2). The mean dose to the whole pelvis for the group of patients with grade 2, 3 rectal complication was higher than that for the patients without complications (4093.3±453.1 cGy vs 3873.8 ±415.6 cGy) ($0.05<p<0.1$). There was a gradual increase in the frequency of grade 2, 3 complications as a function of the dose of external beam therapy to the whole pelvis(midline shield start dose), ranging from 10% for patients receiving less than 36 Gy to 29.3% for patients

Table 1. Mean Radiation Doses and Mean Values in Patients with and without Rectal Complications (mean±SD)

Variables	Without Complication(n=61)	With Complication(n=27)
Whole pelvis dose (cGy)	3873.8±415.6	3944.4±428.4
Rectal dose by ICR (cGy)		
r	2965.3±771.5	3109.9±633.8
dr	3191.5±611.7	3435.9±924.0
Total rectal dose (cGy)		
R	6772.7±884.0	6889.5±731.5
DR	7028.2±713.8	7297.4±986.5
Total TDF	132.6±8.2	134.0±9.2
Total BED	115.8±15.4	118.6±8.8
ICR reference volume(cm^3)	699.9±106.9	686.2±144.5

Table 2. Mean Doses in Patients without Rectal Complication and with Grade 2, 3 Rectal Complication (mean±SD)

Variables	Without Complication(n=61)	With Grade 2, 3 complication(n=15)	P-value
Whole pelvis dose (cGy)	3873.8±415.6	4093.3±453.1	0.5-0.1
Rectal dose by ICR (cGy)			
r	2965.3±771.5	3137.1±713.8	N.S.
dr	3191.5±611.7	3438.1±870.9	N.S.
Total rectal dose (cGy)			
R	6772.7±884.0	7163.0±838.5	<0.05
DR	7028.2±713.8	7470.1±964.9	<0.05
Total TDF	132.6±8.2	136.3±8.3	N.S.
Total BED	115.8±15.4	121.4±7.7	N.S.
ICR reference volume(cm^3)	699.9±106.9	970.4±144.2	N.S

Table 3. Incidence of Grade 2, 3 Rectal Complication by Whole Pelvis Dose (p<0.05)

Whole pelvis dose (cGy)	No. of grade 2, 3 complication(%)
≤ 3600	5 / 50 (10.0)
3600 - 4000	3 / 14 (21.4)
≥ 4000	7 / 24 (29.3)

Table 4. Incidence of Grade 2, 3 Rectal Complication by ICR Rectal Dose(r, dr) (p<0.05)

ICR rectal dose by contrast ; r(cGy)	No. of grade 2, 3 complication(%)
< 2500	3 / 22 (13.6)
2500 - < 3000	3 / 28 (10.7)
3000 - < 3500	5 / 19 (26.3)
≥ 3500	4 / 19 (21.1)
ICR rectal dose by ICRU ; dr(cGy)	**No. of grade 2, 3 complication(%)**
< 2500	3 / 11 (27.3)
2500 - < 3000	2 / 20 (10.0)
3000 - < 3500	2 / 32 (6.3)
≥ 3500	8 / 25 (32.0)

receiving 40 Gy or more to the whole pelvis ($p<0.05$)(Table 2, 3). The mean ICR rectal dose for the group with grade 2, 3 complication were higher than those of the group without complication, but we could not find any correlation between grade 2, 3 complications and the ICR rectal reference point doses by contrast media or ICRU 38 (r, dr)(Table 2, 4). But we did find a similar significant correlation between the total rectal dose and grade 2, 3 rectal complications

Table 5. Incidence of Grade 2, 3 Rectal Complication by Total Rectal Dose(R, DR) (p<0.05)

Total rectal dose by contrase ; R(cGy)	No. of grade 2, 3 complication (%)
< 6500	4 / 38 (10.5)
6500 - 7500	5 / 29 (17.2)
≥ 7500	6 / 21 (28.5)
Total rectal dose by ICRU ; DR(cGy)	**No. of grade 2, 3 complication (%)**
< 6500	2 / 21 (9.5)
6500 - < 7500	5 / 41 (12.2)
≥ 7500	8 / 26 (30.8)

Table 6. Incidence of Grade 2, 3 Rectal Complication by TDF, BED and ICR Reference Volume (p>0.1)

ICR reference volume(cm^3)	No. of grade 2, 3 complication (%)
< 600	2 / 13 (15.4)
600 - < 700	7 / 33 (21.2)
700 - < 800	4 / 31 (12.9)
≥ 800	2 / 11 (18.1)
TDF	**No. of grade 2, 3 complication (%)**
< 130	6 / 52 (11.5)
130 - < 140	2 / 10 (20.0)
140 - < 150	6 / 21 (28.6)
≥ 150	1 / 5 (20.0)
BED	**No. of grade 2, 3 complication (%)**
< 115	6 / 52 (11.5)
115 - < 125	2 / 11 (18.2)
≥ 125	7 / 25 (28.0)

(Table 2, 5). The mean total rectal dose by contrast media(R) for the group of patients with grade 2, 3 rectal complications was higher than that for the uncomplicated patients (7163.0±838.5cGy vs 6772.7±884.0cGy) ($p<0.05$). The risk of grade 2, 3 complications increased as a function of total rectal dose ranging from 10.5% for patients receiving less than 6500 cGy to the rectum, to 28.5% for patients receiving 7500 cGy or more to the rectum. A similar correlation was also found for total reference rectal dose by ICRU 38(DR) and grade 2, 3 complication. The mean total rectal dose by ICRU 38(DR) for the group of patients with grade 2, 3 complications was higher than that for the patients without complication (7470.1±964.9 cGy vs 7028.2±713.8 cGy)($p<0.05$) and the grade 2, 3 complication rate was also increased from 9.5% for patients receiving < 6500 cGy to 30.8% for patients receiving >7500 cGy (Table 2, 5). Because we could not find any correlation between grade 2, 3 complications and the ICR rectal doses(r, dr), we thought the differences of total rectal doses came mainly from the dose distributed by the external whole pelvis dose. We also analyzed the relationship between the ICR reference volume, Time-Dose Factor(TDF), Biologically Effective Dose(BED), and the grade 2, 3 complications, we could not find any significant correlation of the rate of grade 2, 3 rectal complication with the ICR reference volume, TDF and BED (Table 2, 6).

DISCUSSION

The concept of a relationship between dose, treatment volume, and the risk of late complications is well established and has been thoroughly explored in external radiation therapy. In radiation therapy for the uterine cervix, however, the analysis of the risk of complications at specific anatomic sites is difficult because of the variations in the combinations of external radiation therapy and intracavitary radiation(ICR), the multitude of dosimetric descriptions, and the complexity of the anatomy.

High dose rate(HDR) ICR has been used in the treatment of carcinoma of the uterine cervix in Europe, Japan, and elsewhere for over a decade [1-7, 15, 17, 21, 23-27]. During recent years it has gained popularity in the United States. The most common site of late complications is the rectum. Many reports have been published on late rectal complication after external beam radiation and HDR ICR for carcinoma of the cervix. The incidence of rectal complication varied from one institution to another. The reported incidence of late rectal complications with HDR-ICR ranged from 0.7 to 52.2% for overall complications and from 1.4% to 14.9% for major complications[1-11, 15, 26]. The overall

incidence of late rectal complication in this study was 30.7% and this is comparable with the result of other institutions. In our study, Kottmeier's grade 1 complications were excluded in analysis of affecting factors. Because Kottmeier indicated that there was no correlation between grade 1 rectal injuries and several affecting factors[29].

Late rectal damage manifests from 6 months to 5 years after radiation treatment with a median latent interval of 19 months[13, 22]. In this study, most of the complications appeared within 30 months after radiation therapy and the median latent interval was 16 months.

Many reports have found various factors affecting the rectal complications including overweight, hypertension, retroversed uterus, previous medical or surgical history, treatment technique, rectal dose and radiation volume, and other radiation-related values[7, 12-15, 19, 22, 28-34, 40]. Among various factors affecting the rectal complications, the radiation dose to the rectum is the most important. Although numerous studies have been devoted to late rectal complications in intracavitary brachytherapy for cancer of the cervix, the multitude of dosimetric descriptions make comparisons difficult. So the use of improved reference points is necessary to ensure an accurate prediction of normal tissue tolerance in patients. In consequence, the first guidelines for measurement of bladder and rectal dose in low dose rate(LDR) ICR were established by the International Commission on Radiation Units and Measurements (ICRU);they proposed(ICRU Report 38) standardized system of dose reporting, using reference volumes and critical organ doses at two specified reference points on the anteroposterior and lateral projection radiographs obtained after insertion of the intracavitary devices[18].

Some authors define the rectal point according the ICRU 38 criteria[7, 12, 19-22]; others use barium contrast criteria[16, 41, 42]; or in vivo rectal measurements such as the use of intracavitary markers and computed tomography(CT)-assisted delineation of organ boundaries or in vivo thermoluminescent dosimeter(TLD) measurements and CT-assisted treatment planning[4, 14, 15, 25, 27, 41, 43-45]. In brachytherapy for cervical carcinoma, vaginal packing is sufficient to adequately increase the distance between the applicator and the anterior rectal wall, whether the applicator selected is appropriated. But the vaginal cavity was so narrow in many patients to insert gauze for packing that we could not pack the gauze routinely. We measured the two rectal reference points doses based on rectal barium contrast criteria and on the ICRU 38 criteria. In many patients, ICRU 38 reference rectal point would be similar to the maximum anterior rectal dose calculated using rectal barium contrast on lateral film.

Many reports found that the rectal doses on the anterior surface of the rectum and radiation volume served as the primary indicator for predicting rectal complications in both of LDR-ICR and HDR ICR[12, 13, 19, 22, 45]. The apparent threshold is a combined external beam and brachytherapy dose of 75 to 80 Gy, although this depends on ICR applicator type, dose rate and volume irradiated. The similar relationship of total radiation dose to the rectum and rectal complication was also observed in this study. The mean total rectal doses by contrast(R) and by ICRU 38 (DR) for the group with grade 2, 3 complications were significantly higher than those for the group without complications. We also found that grade 2, 3 rectal complication rate rose upto about 30% when the total rectal doses(R, DR) exceed 75 Gy. We concluded that total radiation doses to rectum are good predictors for major rectal complications.

Several researchers reported significant increase in complication of bladder and rectum with increasing the whole pelvis dose[12, 15, 28]. Hamberger et al. observed 3.1% incidence of severe complication with 40 Gy, 10% with 50 Gy and 20% with 60 Gy whole pelvis dose[28]. Pouquier et al also emphasized the whole pelvis dose, demonstrating that the highest risk of complication occurred above 45 Gy external dose to the whole pelvis[12]. But Kottmeier et al and Perez et al indicated that total dose contributed by both external and intracavitary irradiation to a given organ have a

greater predictive value in correlation with frequency of major complication than the dose by either modality alone[13, 29]. The grade 2, 3 rectal complication rate of 17% in present study is higher than that of 0.9% of our previous report[26] and others[7, 15] treated with HDR-ICR. The higher incidence of grade 2, 3 rectal complication might be due to higher whole pelvis dose by external irradiation as well as higher fraction size and higher weekly doses in Gamma Med HDR-ICR than Co-60 RALS. In the present study the midline shield was done usually after 36-45 Gy to the whole pelvis compared with previous midline shield at the level of 20-30 Gy to the whole pelvis. A single dose of HDR-ICR 5 Gy at point A and twice a week to total 30 Gy was given in present study, compared with 3 Gy per fraction on point A and 3 times a week to total 30-39 Gy was given with Co-60 HDR-ICR in previous study[26]. We didn't compare the effect of ICR single dose size(5 Gy vs 3 Gy) or ICR weekly dose (10 Gy vs 9 Gy) in two different HDR-ICR schemes because we didn't analyze the result of the patients treated with external beam radiation with the similar late midline shielding and Co-60 HDR ICR. But we considered those ICR factors might be important to increase the grade 2, 3 rectal complication rate. Therefore we are going to analyze the difference of treatment result between the Co-60 HDR-ICR and Ir-192 HDR-ICR group. When analyzed for the external radiation dose delivered to whole pelvis and rectal complication rate, external whole pelvis dose did significantly correlate with the incidence of grade 2, 3 complication. Now we are trying to start the midline shield earlier during the external pelvic irradiation. That is, whole pelvic external irradiation doses are individualized according to stage, tumor size, clinical tumor regression. And we could not find the significant relationship between the ICR rectal dose by contrast media(r) or by ICRU(dr) and the incidence of grade 2, 3 rectal complication. So we considered that the significant correlation between total rectal dose (R, DR) and the incidence of rectal complication was the influence of whole pelvis dose.

Esche and many authors[12, 14, 16, 19, 22, 41, 46] have suggested that, in low dose rate intracavitary brachytherapy(LDR-ICR), clinically significant injury may develop from relative small regions of high dose area in the rectum (hot spot), whereas Crook and Esche found that reference volumes are useful in defining the zones of risk of moderate and severe sequelae[19, 22]. Van Lancker et al. suggested that individual application volume and the cumulative volume are very good predictors for severe late complication, but that the value of the reference point can be questioned in HDR-ICR[21]. In contrast, Montana et al. noted that, of the two variables of volume and dose that have been implicated in rectosigmoid complications, the latter is more likely to be controlled in LDR-ICR[16]. Krishiman et al. described volume to be complex, and its applicability to the clinical setting in predicting or preventing complications is uncertain[47]. Pourquier et al. observed no correlation of volume with rectosigmoid complication in patients treated with LDR-ICR[12]. We did not calculate the reference volume in hwt, HWT by ICUR 38 recommendation but instead of them we calculated the ICR reference volume using upgraded Gamma Dot 3.11 HDR treatment planning system for Gamma Med, retrospectively. We selected the ICR reference volume which covered a prescribed point A isodose line. There was no correlation between the ICR reference volume in cm^3 and the rectal complication rate in this study.

Because the HDR-ICR doses at rectal reference points are much larger per fraction than the external doses for the whole pelvis, it is not possible to simply add the doses when late rectal complication is considered. Some researchers, therefore, use the TDF(Time-Dose Factor), which is related to normal tissue effect, as well as the BED(Biologically Effective Dose), which is related to late normal tissue effects, as another factor[7, 14, 15, 20, 42]. We also calculated the cumulative rectal dose administered by whole pelvis external irradiation and HDR-ICR using both TDF, BED because several reports identified a strong

correlation between the incidence of the late rectal complication and TDF or BED values in both LDR-ICR[14, 20] and HDR-ICR[7, 15, 42]. In this study, however, the TDF, BED value did not a predictor for rectal complication.

The optimal time/dose/fractionation regimen and technique for HDR remote afterloading intracavitary brachytherapy for cervical cancer has to be established. We plan to examine pretreatment and treatment factors affecting local control, survival and late complication. And we are going to compare the local control rate and the incidence of late complication between the patients treated with Co-60 RALSTRON HDR-ICR and the patients treated with Ir-192 Gamma Med HDR-ICR in terms of ICR fraction size(3 Gy vs 5 Gy on point A), ICR total dose(30 Gy vs 30-39 Gy) and other prognostic factors. Further analysis of these data might permit us to establish optimal integration of radiation therapy regimens for HDR-ICR to minimize the complication and to improve the cure rate in cancer of the uterine cervix.

CONCLUSION

This investigation has revealed a significant correlation between the total rectal dose calculated at the reference point by ICRU 38(DR) or at the most anterior rectal mucosa dose by rectal contrast(R), dose to the whole pelvis and the incidence of late rectal complications, especially grade 2, 3 in patients with stage IIB cervical cancer undergoing external beam radiotherapy and high dose rate ICR. Thus these reference rectal points (R, DR) and whole pelvis dose appear to be useful prognostic indicators of late rectal complications in high dose rate ICR treatment in cervical carcinoma.

REFERENCES

1. **Akine YA, Arimoto H, Ogino T, et al.** High-dose-rate intracavitary irradiation in the treatment of carcinoma of the uterine cervix: Early experience with 84 patients. Int J Radiat Oncol Biol Phys 1988; 14:893-898
2. **Fu KK, Phillips TL.** High-dose-rate versus low-dose-rate intracavitary brachytherapy for carcinoma of the cervix. Int J Radiat Oncol Biol Phys 1990; 19:791-796
3. **Joslin CAF.** High-activity source afterloading in gynecologic cancer and its future prospects. Endocuriether Hyperther Oncol 1989; 5:69-81
4. **Newman H, Jur B, James KW, Smith CW.** Treatment of cancer of the cervix with a high-dose-rate afterloading machine(the Cathetron). Int J Radiat Oncol Biol Phys 1983; 9:931-937
5. **Shigematsu Y, Nishiyama K, Masaki N, et al.** Treatment of carcinoma of the uterine cervix by remotely controlled afterloading intracavitary radiotherapy with high dose rate system. Int J Radiat Oncol Biol Phys 1983; 9:351-356
6. **Utley JF, Essen CF, Horn RA, Moeller JH.** High-dose-rate afterloading brachytherapy in carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 1984; 10:2259-2263
7. **Ogino I, Kitamura T, Okamoto N, et al.** Late rectal complication following high dose rate intracavitary brachytherapy in cancer of the cervix. Int J Radiat Oncol Biol Phys 1995; 31:725-734
8. **Taina E.** Complications following high and low dose rate intracavitary radiotherapy for stage I-II cervical carcinoma; A comparison of remotely afterloaded Co 60(Cathetron) and conventional radium therapy. Acta Obstet Gynecol Scand Suppl 1981; 103:39-49
9. **Orton CG, Seyedsadr M, Somnay A.** Comparison of high and low dose rate remote afterloading for cervix cancer and the importance of fractionation. Int J Radiat Oncol Biol Phys 1991; 21:1425-1434
10. **Himmelmann A, Holmberg E, Od'en A, et al.** Intracavitary irradiation of carcinoma of the cervix stage IB and IIA. A clinical comparison between a remote high dose-rate afterloading system and a low dose-rate manual system. Acta Radiol [Oncol] 1985; 24:139-144
11. **Sato S, Yajima A, Suzuki M.** Therapeutic results using high-dose-rate intracavitary irradiation in cases of cervical cancer. Gynecol Oncol 1983; 19:143-147
12. **Pourquier H, Dubois JB, Deelard R.** Cancer of the uterine cervix: Dosimetric guidelines for prevention of late rectal and rectosigmoid complications as a result of radiotherapeutic treatment. Int J Radiat Oncol Biol Phys 1982; 8:1887-1895

13. **Perez CA, Breaux S, Bedwinek JM, et al.** Radiation therapy alone in the treatment of carcinoma of the uterine cervix. Cancer 1984; 54:235-246
14. **Orton CG, Wolf-Rosenblum S.** Dose dependence of complication rates in cervix cancer radiotherapy. Int J Radiat Oncol Biol Phys 1986; 12:37-44
15. **Teshima T, Chatani M, Hata K, Inoue T.** High-dose rate intracavitary therapy for carcinoma of the uterine cervix. II. Risk factors for rectal complication. Int J Radiat Oncol Biol Phys 1988; 14:281-286
16. **Montana Gs, Fowler WC.** Carcinoma of the cervix: Analysis of bladder and rectal radiation dose and complications. Int J Radiat Oncol Biol Phys 1989; 16:95-100
17. **Clark BG, Souhami L, Roman TN, Evans MD, Pla C.** Rectal complications in patients with carcinoma of the cervix treatment with concomitant cisplatin and external beam irradiation with high dose rate brachytherapy: A dosimetric analysis. Int J Radiat Oncol Biol Phys 1994; 28:1243-1250
18. International Commission on Radiation Units and Measurements. Dose and volume specification for reporting intracavitary therapy in gynecology. ICRU Report 38. Bethesda, MD:International Commission on Radiation Units and Measurements, 1985
19. **Esche BA, Crook JM, Horiot JC.** Dosimetric methods in the optimization of radiotherapy for carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 1987; 13:1183-1192
20. **Perez CA, Fox S, Lockett MA, et al.** Impact of dose in outcome of irradiation alone in carcinoma of th uterine cervix: Analysis of two different methods. Int J Radiat Oncol Biol Phys 1991; 21: 885-898
21. **Van Lancker VM, Strome G.** Prediction of severe late complications in fractionated, high-dose-rate brachytherapy in gynecological applications. Int J Radiat Oncol Biol Phys 1991; 20:1125-1129
22. **Cook JM, Esche BA, Chaplain G, Isturiz J, Sentenac I, Horiot J.** Dose-volume analysis and the prevention of radiation sequelae in cervical cancer. Radiother Oncolo. 1987; 8:321-332
23. **Arai T, Nakano T, Morita S, et al.** High-dose-rate remote afterloading intracavitary radiation therapy for cancer of the uterine cervix. Cancer 1992; 69:175-180
24. **Koga K, Watanabe K, Kawano M, et al.** Radiotherapy for carcinoma of the uterine cervix by remotely controlled afterloading intracavitary system with high-dose rate. Int J Radiat Oncol Biol Phys 1987; 13:615-618
25. **Roman TN, Souhami LS, Freeman CR, et al.** High dose rate afterloading intracavitary therapy in carcinoma of the cervix. Int J Radiat Oncol Biol Phys 1991; 20:921-926
26. **Suh CO, Kim GE, Loh JJK.** Treatment of carcinoma of the uterine cervix with high-dose-rate intracavitary irradiation using Ralstron. J Korean Soc Ther Radiol 1990; 8:231-239
27. **Stuecklschweiger GF, Aruab-Schad KS, Poier E, Poscjauko J, Hackl A.** Bladder and rectal dose of gynecologic high-dose-rate implants: Comparison of orthogonal radiographic measurements with in vivo and CT-assisted measurements. Radiology 1991; 181:889-894
28. **Hamberger AD, Unal A, Gershenson DM, et al.** Analysis of the severe complications of irradiation of carcinoma of the cervix: Whole pelvis irradiation and intracavitary radium. Int J Radiat Oncol Biol Phys 1983; 9:367-371
29. **Kottmeier HL, Gray MJ.** Rectal and bladder injuries in relation to radiation dosage in carcinoma of the cervix. Am J Obstet Gynecol 1961; 82:74-82
30. **Van Nagell Jr, JR, Parke JC, Maruyama Y, Utley J, Luckett P.** Bladder or rectal injury following radiation therapy for cervical cancer. Am J Obstet Gynecol 1974; 119:727-732
31. **Chism SE, Keys HM, Gillin MT.** Carcinoma of the cervix: A time dose analysis of control and complications. Am J Roentgenol 1975; 123:84-90
32. **Jampolis S, Martin P, Schroeder P, Horiot JC.** Treatment tolerance and early complications with extended fields irradiation in gynecological cancer. Br J Radiol 1977; 50:195-199
33. **Jolles CT, Freedman RS, Hamberger AD, Horbelt DV.** Complications of extended-field therapy for cervical carcinoma without prior surgery. Int J Radiat Oncol Biol Phys 1986; 12:179-183
34. **Montana GS, Fowler WC, Varia MA, Walton LA, Mack Y.** Analysis of results of radiation therapy for stage II carcinoma of the cervix. Cancer 1985; 55:956-962
35. **Ellis F.** Low to high dose-rate by the TDF system. In: Bates TD, Berry RJ., eds. High dose-rate afterloading in the treatment of cancer of the uterus. London: Special Report No.17 of the Br J Radiol; 1978, 146-156
36. **Orton CG.** Time-dose factors(TDFs) in brachytherapy. Br J Radiol 1974; 47:603-607

37. **Dale RG.** The application of the linear-quadratic dose effect equation to fractionated and protracted radiotherapy. Br J Radiol 1985; 58:515-528
38. **Hall EJ.** Radiobiology for the radiologist, 3rd ed. Philadelphia, PA: J.B.Lippincott Co; 1988; 107-136
39. **Fowler JF.** The radiobiology of brachytherapy. In: martinez AA, Orton CG, Mould RF, eds. Brachytherapy HDR and LDR. Leersum, Netherlands: Nucletron International, B.J.; 1990; 121-137
40. **Combs PF, Daly MJ, Horiot JC, et al.** Results of radiotherapy alone in 581 patients with stage II carcinoma of the uterine cervix. Int J Radiat Oncol Biol Phys 1985; 11:463-471
41. **Cunningham DE, Stryker JA, Velkley DE, Chung CK.** Routine clinical estimation of rectal, rectosigmoid, and bladder doses from intracavitary brachytherapy in the treatment of carcinoma of the cervix. Int J Radiat Oncol Biol Phys 1981; 7:653-660
42. **Stitt JA, Fowler JF, Thomadsen BR, et al.** High dose rate intracavitary brachytherapy for carcinoma of the cervix: The madison system: I. Clinical and radiobiological considerations. Int J Radiat Oncol Biol Phys 1992; 24:335-348
43. **Million RR, Mauderli W, Bruno FP.** Modification of technique for bladder and rectal measurements in carcinoma of the cervix. Radiology 1966; 60:921-925
44. **Inoue TO, Inoue TA, Harada K, Hata K, Oxawa R, Kawanabe K.** A modified dose monitoring system in remote afterloading therapy of carcinoma of the uterine cervix using semi-conductor dosimeter. Strahlenther Onkol 1981; 157:400-404
45. **Yu WS, Sagerman RH, Chung CT, et al.** Anatomic relationships in intracavitary irradiation demonstrated by computed tomography. Radiology 1982; 143:537-541
46. **Perez CA, Breaux S, Madoe-Jones H, et al.** Correlation between radiation dose and tumor recurrence and complications in carcinoma of the uterine cervix: Stage I and IIa. Int J Radiat Oncol Biol Phys 1979; 5:373-382
47. **Krishinan L. Cytacki EP, Wolf CD, et al.** Dosimetric analysis in brachytherapy of carcinoma of the cervix. Int J Radiat Oncol Biol Phys 1990; 18:965-970
48. **Lee KH, Kagan AR, Nussbaum H, Wollin M, Winkley JH, Norman A.** Analysis of dose, dose-rate, and treatment time in the production of injuries by radium treatment for cancer of the uterine cervix. Br J Radiol 1976; 49:430-440

= 국문초록 =

FIGO병기 IIB 자궁경부암에서 고선량 강내 방사선치료후의 후기 직장 합병증

연세대학교 의과대학 치료방사선과학교실, 연세암센터

정은지 · 김귀언 · 서창옥 · 금기창 · 김우철

목 적 : 외부 방사선 치료(External Radiation Therapy) 및 Gamma-med (Iridium-192) 고선량 강내 방사선 치료를 받은 자궁 경부암 FIGO stage IIB 환자에서 직장 합병증 발생률 및 이와 관계있는 인자를 후향적으로 분석해 보았다.

대상 및 방법 : 1989년 11월부터 1992년 12월까지 연세암센터 치료방사선과에서 근치적 목적의 외부 및 강내 방사선치료를 받은 FIGO 병기 IIB 자궁경부암 환자 88명을 대상으로 방사선치료후 발생한 직장 합병증 및 이와 연관된 인자들을 분석하여 보았다. 환자들의 연령은 29-83세로 평균치, 중앙치 모두 57세였고 병리조직 분류상 편평상피세포암이 84예 선암이 4예였다. 방사선치료는 외부방사선을 골반 부위에 5-6주 동안 4500-5400cGy 치료하였으며 환자별로 중간 차폐를 시행하였고 고선량 Gamma-med ICR은 A점에 1회당 500cGy씩 1주 2회로 총 3000cGy 조사하였다. 외부 방사선치료시 중앙 차폐까지의 외부 조사량, ICR rectal dose(r) 및 total rectal dose(R), ICRU 38에 따른 ICR rectal dose(Dr)와 total Dr dose(DR), ICR reference volume, TDF, BED(Biologically Effective Dose)를 계산하고 분석해 합병증과의 연관성을 찾아보았다. 대상 환자 88명중 87명(98.9%)에서 최저 24개월 이상 추적 관찰이 가능하였으며 중앙치는 40개월(20-66개월)이었다.

결 과 : 직장 합병증은 27예에서 발생하였는데(30.7%) grade 1이 12예(13.6%), 2가 12예(13.6%), 3이 3(3.4%)예였고 합병증이 발생하는 시기는 방사선치료후 4-43개월(중앙치 16개월, 평균 17.3개월)이었다. 직장 합병증이 발생하지 않은 환자군의 *total rectal dose*(R)는 6772.67±884.02 로 grade 2-3 합병증이 발생한 15명의 R=7163.0±838.49와 유의한 차이를 보였으며 total Dr dose (DR)도 두 군간에 차이를 보였다. 또 grade 2-3인 직장 합병증 발생률은 중앙 차폐시 까지의 외부 방사선량과 관계가 있었는데 36Gy이하에서는 10%, 36-40Gy는 21.4%, 40Gy 이상에서는 29.3%의 직장 합병증이 발생하여 중앙 차폐까지 조사된 외부 방사선량이 증가할수록 직장 합병증이 증가함을 알 수 있었다. 직장에 조사된 총직장 조사량(R)에 따라 grade 2-3 합병증 발생률이 증가하였는데 65Gy 이하에서는 10.5%, 65-75Gy는 17.2%, 75Gy이상 조사된 환자군에서는 28.5%로 조사량이 증가할수록 직장 합병증이 증가하는 양상이었으며 ICRU 38 에 따른 total rectal dose (DR)에 대해서도 비슷한 양상이었다. ICR rectal dose(r, Dr)만 따로 분석해 보았는데 방사선량과 직장 합병증간에는 차이가 없었다. 그 외의 인자로 분석한 TDF 와 BED도 grade 2-3의 경우에는 그 값이 증가할수록 증가하는 양상을 보였으나 통계적인 유의성은 없었고 Gamma Dot 에서 계산되는 ICR reference volume도 분석해 보았으나 합병증과의 연관성을 발견할 수 없었다.

결 론 : 병기 IIB 자궁경부암 환자에서 외부 방사선치료 및 고선량 강내 방사선치료후 직장 합병증 발생률은 30.7%(grade 2-3: 15예 17%)였다. 직장 합병증 발생에 영향을 미치는 중요한 인자는 직장에 조사된 전골반 방사선량(중앙 차폐까지의 방사선량) 및 고선량 강내 방사선치료와 합한 총직장 방사선량(r, Dr)으로 나타났으며 이들이 증가할수록 합병증 발생률이 증가하였다.