High Dose Rate Brachytherapy in the treatment of Uterine Cervical Cancer: Incidence of Late Radiation proctitis and cystitis among different schedules.

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ABSTRACT

Purpose: This retrospective study at Mahavachiralongkorn hospital aims to explore the survival rate and incidence of radiation proctitis as well as cystitis in patients with uterine cervical cancer treated by high dose rate (HDR) intracavitary brachytherapy (ICRT) and also to compare the late complications among patients receiving different HDR schedules.

Methods and materials: A hundred and sixty-eight patients with uterine cervical cancer stage IB-IIIB treated by external beam radiotherapy (EBRT) with a median dose of 5000 cGy followed by Iridium 192 HDR brachytherapy, 500 cGy/F x 5 fractions (57 cases), 600 cGy/F x 4 fractions (59 cases) and 700 cGy/F x 3fractions (52 cases) were enrolled in the study from January 2005 to June 2008. Most patients were assessed by physical examination during the follow-up period.

Results: Median age of the patients in this study was 53 years (range of 28-87 years) and median follow-up time was 63 months. Five-year overall survival was 69.0% (95% confidential interval of 64.4%-73.7%). There was no significant difference in survival among the three HDR schedules (500 cGy/F x 5F, 600cGy/F x 4F and 700cGy/F x 3F), 67.0%, 68.0% and 65.0% respectively.

The overall late radiation proctitis and cystitis rates were 17.8% and 2.3%, respectively. The incidence of late radiation procitis in 500 cGy/F x5F group was 12.3% which is lower than those in the other two groups, 600 cGy/Fx4F (20.3%)and 700 cGy/Fx3F (21.1%). Majority of the patients with late radiation proctitis presented with grade 1-2, and majority of late radiation cystitis presentation was grade1. There was no severe complication among these patients.

Conclusions: In this study, there was no significant difference of 5- years overall survival and incidence of late radiation proctitis and cystitis among three HDR schedules.

INTRODUCTION

Worldwide, invasive uterine cervical cancer is the second most common malignancy in women (after breast cancer) and accounts for nearly 500,000 cases and 250,000 case deaths per year [1]. In Thailand, uterine cervical cancer was the second most common cancer among Thai women (after breast cancer) with estimated 19,011 new cases in 2001-2003. The incidence was about 18.1 per 100,000 women [2]. It was also the second most common female cancer in Mahavachiralongkorn hospital, 163 new cases, in the year 2004-2006 [3]. Radiation therapy (RT) has an important role in the management of the carcinoma of the uterine cervix.

Definitive RT gives high rate of tumor control in patients with early-stage disease and is the standard approach in patients with locally advanced disease. The treatment typically involves a combination of external beam irradiation (EBRT) delivered to the whole pelvis and followed by intracavitary radiation therapy (ICRT). Overall, reported 5-years survival rates of patients treated with RT alone were approximately 75% to 85% for International Federation Gynecology and Obstetrics staging of the Cervix (FIGO) stage IB, 65% to 75%, 30% to 50% and 10% to 20% for stage II, III and IVA, respectively [4]. According to some previous studies about the complications of cervical cancer treatment, overall incidence rate of urinary bladder complication ranged from 8 to 12%. Severe urinary bladder complication was about 2-6% [5-10], while the incidence rate of severe proctitis was 4-13%, depending on the maximal radiation dose [11]

For the past four decades, the remote control after loading high-dose-rate (HDR) intracavitary brachytherapy has become an acceptable treatment technique and has increased rapidly in the recent years, since this technique has now made it possible to deliver intracavitary radiation in minutes instead of hours. Moreover, with remote control after loading equipment, radiation exposure to the personnel is eliminated. The patients do not have to be hospitalized for treatment, providing possible economic advantage and delivery of treatment in several short fractions may permit greater control over the position of sources during treatment. The most important concern of treatment with large HDR fractions is the reduction of the opportunity for recovery of sublethal normal tissue injury and therefore it may narrow the therapeutic ratio between tumor control and complication [12].

In Mahavachiralongkorn hospital, the patients with carcinoma of uterine cervix in radiation therapy department are treated by EBRT to the whole pelvis followed by ICRT with different HDR schedule (500 cGy/F x 5F, 600 cGy/F x 4F and 700 cGy/F x 3F). This study was conducted to explore treatment outcomes of these different schedules in terms of overall survival rate and late complications of treatment (radiation proctitis and radiation cystitis).

METHODS AND MATERIALS

Patient population

Retrospective data collection was performed by medical record review. Three hundred and twelve stage 0-IVB patients were referred to the Mahavachiralongkorn hospital from January, 2005 to June, 2008. Of these, 144 patients were excluded from the study (13 lost to follow-up before treatment, 30 palliative intent, 6 treatment denial, 5 treatment from other institutes, 2 referred to other institute, 10 postoperative radiotherapy, 2 double primary cancer, 2 HIV positive, 1 stage 0, 42 stage IV, 29 persistent tumor after treatment, and 2 with inadequate information). The cases with persistent tumor after radiotherapy were excluded from this study due to variation of further treatment, such as total hysterectomy, pelvic exenteration, chemotherapy and most of the cases were referred back to local hospitals for supportive treatment. Some patients lost to follow-up and changed to alternative medicines. These caused limitation in evaluation of radiation complications.

One hundred and sixty-eight patients with uterine cervical carcinoma stage IB- stage IIIB were treated by definitive RT intent. All patients underwent a combination of EBRT followed by three to five HDR intracavitary insertions (700 cGy/F x 3F = 52 cases, 600cGy/F x 4F=59 cases, 500cGy/F x5F =57 cases). The patients and tumor characteristics are shown in Table 1. Median follow-up time of all patients was 63 months (in the range of 6-90 months).

Table 1. Baseline characteristics

Characteristics	N	%
No. Patients	168	100
Age (years)	53 (28-87)	
Median		
Range 20-29	1	0.5
30-39	10	5.9
40-49	40	23.8
50-59	46	27.4
60-69	42	25
70-79	21	12.5
80-89	8	4.9
Performance status	120	71.4
ECOG 0	15	8.9
1	33	19.7
not specify		
Stage IB	7	4.1
IIA	2	1.2
IIB	112	66.7
IIIA	2	1.2
IIIB	45	26.8
Histology		
Squamous cell carcinoma	141	83.9
Adenocarcinoma	21	12.5
Adenosquamous carcinoma	6	3.6
Grading		
Well-differentiated	12	7.2
Mod-differentiated	19	11.3
Poorly-differentiated	19	11.3
Not specify	118	70.2

Teletherapy

All patients were treated by EBRT with a cobalt 60 teletherapy unit at 80-cm source axis distance or 6-10 MV linear accelerators at 100-cm source axis distance. The treatment schedule included a program of 180-200 cGy/fraction/day, five days per week. The whole pelvic total dose ranged from 4500 to 5040 cGy, with a median dose of 5000 cGy. The majority of patients were treated with a dose of 5000cGy, some patients were midline blocked and parametrium boosted to 5400-6000 cGy. The technique employed was AP//PA or four-field box technique with anterior, posterior and two lateral fields. The usual field borders for anterior and posterior fields were at the L4-L5 interspaces superiorly, at the lower border of ischial tuberosity inferiorly and laterally 1.5 to 2 cm lateral to the bony pelvic wall. Lateral fields had anterior border at the symphysis pubis and the posterior border at the S3-S4 interspaces.

Brachytherapy

For HDR intracavitary brachytherapy (Microselectron HDR Ir-192, Veenendaal, Netherland) treatment was administered with a Henschke or Rotterdam applicator. The ICRT was performed weekly after completion of EBRT. In cases of good tumor regression, HDR brachytherapy was performed during the last week of EBRT course. The applicator system consisted of a full set of intrauterine tandem and pair of ovoids or intrauterine tandem alone. Types of applicator system were selected based on the individual's anatomy (roomy or cone shape vagina), and the attending staff's preference.

The dose per fraction was prescribed in range of 500 cGy/F x 5F, 600 cGy/F x 4F and 700 cGy/F x 3F. HDR brachytherapy and EBRT were never given on the same day. During each insertion, anterior and posterior vaginal packing were used to maximize the distance between the sources and posterior bladder wall or anterior rectal wall. The Foley's catheter was applied and filled with radiopaque solution in the balloon. The sponge embedded with metallic seeds was applied in rectum for identification of the anterior rectal wall.

HDR brachytherapy dosimetric planning was performed for every insertion by semi-orthogonal system with box. The computerized planning program used was the PLATO system, developed by Nucletron. Semi-orthogonal films were taken to verify the placement of the applicators and to perform the dosimetric plan. The prescribed dose was computed at point A, which was defined at 2 cm above the flange of the uterine tandem and 2 cm lateral from the axis of uterine tandem. The rectal reference point was located by metallic seeds, obtained from the radiographs. The bladder reference point was located at the posterior surface of the balloon, which was filled with 7-10 cc of radiopaque solution and pulled downward against the urethra.

Equivalent dose for use in HDR brachytherapy

For the combination of dose from EBRT and HDR ICRT, this study used the program developed by Nag S and Gupta N. This program was designed to calculate the tumor and late responding tissue equivalent doses for different HDR brachytherapy regimens [13]. This program was developed by incorporating the Linear Quadratic (LQ) formula to calculate the biologically equivalent dose (BED). To express the BED in more familiar terms, it was reconverted to equivalent dose as if given as fractionated irradiation at 2 Gy/fraction.

Since doses giving to normal tissue (urinary bladder and rectum) in HDR brachytherapy treatments are different from those given to tumor, a normal tissue dose modifying factor (DMF) was applied in this calculation for more realistic equivalent normal tissue effects (DMF=0.7).

The LQ equation was used to calculate the BED of different doses fractionation schemes, using the α/β ratio=3 Gy for normal tissue or late effect and α/β ratio=10 Gy for tumor or early reacting tissue [14].

Scoring of complication

The acute radiation complication criteria used in this study was according to the Radiation Therapy Oncology Group (RTOG) [15]. The late radiation complication criteria used in this study was the European Organization for Research and Treatment of Cancer (EORTC) the SOMA scale [16]. These scales include four separate elements, representing

Table 2. Staging distribution of the three HDR schedules

Stage	500cGyx5F (57 cases)	600 cGyx4F (59 cases)	700 cGyx3F (52 cases)
IB	3 (5.3%)	3 (5.1%)	1 (1.9%)
IIA	0 (0%)	0 (0%)	2 (3.9%)
IIB	42 (73.7%)	38 (64.4%)	32 (61.5%)
IIIA	0 (0%)	0 (0%)	2 (3.9%)
IIIB	12 (21.0%)	18 (30.5%)	15 (28.8%)
Total	57 (100%)	59 (100%)	52 (100%)

Subjective, Objective, Management and Analytical evaluation of injury.

Grade 1 represents the most minor symptoms that require no treatment.
Grade 2 represents moderate symptoms, requiring only conservative treatment.
Grade 3 represents severe symptoms, which have a significant negative impact on daily activities and which require more aggressive treatment.
Grade 4 represents irreversible functional damage, necessitating major therapeutic intervention.

The acute complication criterion was used to score/grade toxicity from radiation therapy. The criterion was relevant from day 1, the commencement of therapy, through day 90. Thereafter, the SOMA scale of Late Radiation Effect was utilized.

In both scoring criteria, "0" means an absence of the radiation effects and "5" means the effects lead to death. The "mild" toxicity was reported as Grade 1 and "moderate" toxicity was reported as Grade 2. The "severe" toxicity was reported as grade 3 and 4 together.

When the scores were reported in range, such as "Grade 1-2" or "Grade 2-3", the higher score of the ranges were used for data collection.

RESULTS

One hundred and sixty-eight patients had a median age of 53 years (range of 28-87 years). Most of the cases were stage IIB, about 66.7%. Baseline characteristics are detailed in table 1 and 2. Median follow-up time of all patients was 63 months (the range of 6-90 months). The overall five-year survival was 69.0% (stage II and stage III were 70.0% and 55.0%, respectively) (Figure 1,2).

The five-year survival rates among the three HDR schedules (500 cGy/F x 5F, 600cGy/F x 4F and 700cGy/F x 3F) were 67.0%, 68.0% and 65.0% respectively (Figure 3). There was no significant difference in survival among the three HDR schedules.

Acute gastrointestinal complications

Ninety-nine patients (58.5%) developed acute gastrointestinal (GI) complications. According to RTOG scoring, mild (grade 1) complications were observed in 25 patients (14.8%), moderate (grade 2) complications in 71 patients (41.9%). and severe (grade 3) complications in 3 patients (1.8%), respectively. The most common complication in 62 patients (36.6%) was diarrhea requiring parasympatholytic drug. Most of the symptoms could be controlled by oral medication. There were two patients (1.2%) who required parenteral fluid. These symptoms occurred in a median time of 2.3 weeks after the start of treatment (2 days - 10.6 weeks).

Acute genitourinary complications

Forty-four patients (26%) developed acute genitourinary (GU) complications. Mild (grade 1) complications were observed in 12 patients (7.1 %), moderate (grade 2) complications in 31 patients (18.3%), and severe (grade 3) complications in one patient (0.6%). The most common symptom was

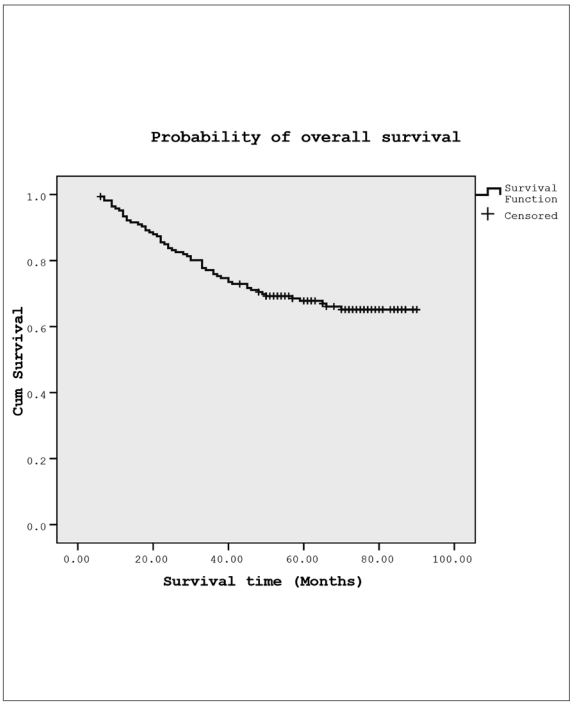

FIGURE 1 *: OVERALL SURVIVAL*

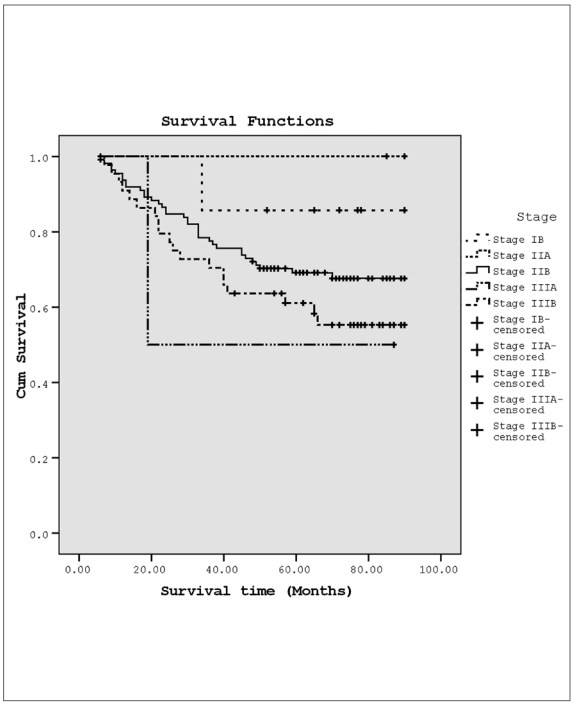

FIGURE 2 *: OVERALL SURVIVAL COMPARISION AMONG STAGE GROUPS (168 cases)*

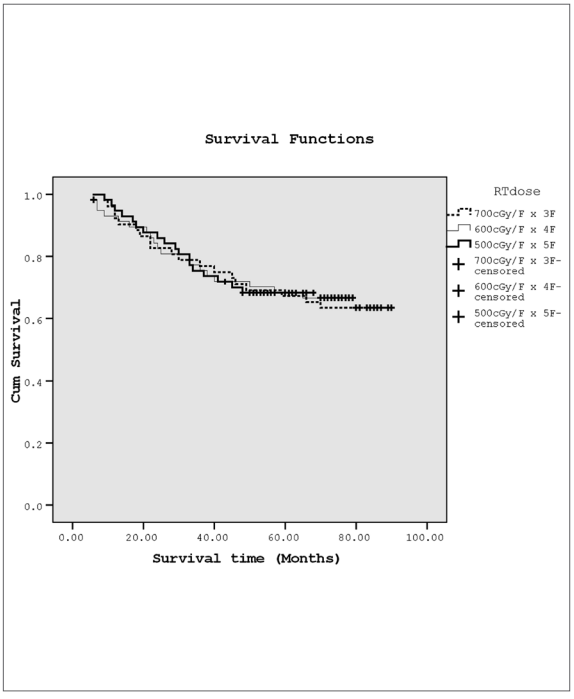

FIGURE 3 *: OVERALL SURVIVAL COMPARISION AMONG THREE HDR SCHEDULES*

500cGyX5F (57 cases) VS 600cGyX4F (59 cases) VS 700cGyX3F (52 cases)

dysuria or urgency requiring local anesthetic drugs (17.1%). The median time to developed acute GU complications was 3.5 weeks after the start of radiotherapy (5 days- 11.2 weeks).

Late gastrointestinal complications

Thirty patients (17.9%) developed radiation proctitis, the most common symptom was slight rectal discharge or bleeding (12.5%). There was no severe late GI complication in the study. Two patients without definite diagnosis in medical records were categorized as “unknown” group (Table 3).

There were seven patients (12.3%) with late radiation proctitis in 500cGy/F x 5F group, which were less than in other two groups, 12 cases (20.3%) in 600 cGy/F x 4F and 11 cases (21.1%) in 700 cGy/F x3F, respectively (Table 4).

Late genitourinary complications

Four patients (2.4 %) developed late radiation cystitis, the most common symptom was dysurea and frequency. All of them were in mild degree (grade I) which could be controlled by medication.

One patient without definite diagnosis in medical records was categorized as "unknown" group (Table 3).

There was one patient (1.5%) with late radiation cystitis in 500 cGy/F x 5F group, which were less than 3 cases (5.8%) in 700cGy/F x 3F group. No severe late complications were detected in this study (Table 5).

DISCUSSION

In this study, we found that there was no significant difference in five-year survival rate among three HDR schedules. The acute GI complication rate was 58.5%, which was rather high. However, all of the symptoms could be controlled by supportive treatment and the patients could continue the whole course of irradiation.

Table 3. Late Gastrointestinal (GI) and Genitourinary (GU) complications in 168 cases

Complication	Proctitis (%)	Cystitis (%)
Mild	21 (12.5%)	4 (2.4%)
Moderate	9 (5.4%)	0 (0%)
Severe	0 (0%)	0 (0%)
Unknown	2(1.2%)	1 (0.6%)
Total	32 (19.1%)	5 (3.0%)

Table 4. Late Gastrointestinal (GI) complications among three HDR schedules

Late radiation proctitis	500 cGyx5F (57 cases)	600 cGyx4F (59 cases)	700 cGyx3F (52 cases)
Mild	5 (8.8%)	6 (10.2%)	10 (19.2 %)
Moderate	2 (3.5%)	6 (10.2%)	1 (1.9%)
Severe	0	0	0
Unknown	0	1 (1.7%)	1 (1.9%)
Total	7 (12.3%)	13 (22.1 %)	12 (23.0%)

Table 5. Late Genitourinary (GU) complications among three HDR schedules

Late radiation cystitis	500cGyx5F (57 cases)	600 cGyx4F (59 cases)	700 cGyx3F (52 cases)
Mild	1 (1.5%)	0	3 (5.8 %)
Moderate	0	0	0
Severe	0	0	0
Unknown	1 (1.5%)	0	0
Total	2 (3.5%)	0	3 (5.8%)

The incidence of late radiation proctitis in 500cGy/F x 5F group was less than in other two groups, 600 cGy/F x 4F and 700 cGy/F x3F. This might be due to lower dose per fraction which causes less late complications.

According to the previous study of Wiboonpol-prasert and Tangcharearnsatient [17], 115 cases of cervical cancer (stage I-IV) treated at Ramathibodi Hospital during January 1977 to September 1981 by EBRT followed by LDR Ra-226 ICRT showed overall late GI and GU complication rates of 80.0% and 58.0%, respectively. These were higher than the results of this study. We reported the late GI and GU complications of 17.8% and 2.4%, respectively. Sangruji studied 372 cases of stage II and 324 cases of stage III carcinoma of uterine cervix during 1981-1986 treated by EBRT followed by LDR Cs-137 at Siriraj Hospital. They found that overall incidence rates of radiation procitis and cystitis were 27.6% and 15.6%, respectively. Severe procitis occurred in 5.1% and severe cystitis in 0.7% of the cases [18].

According to the previous study of Tharavichitkul et al [19], 377 cases of locally advance carcinoma of uterine cervix treated by concurrent chemoradio-therapy followed by two different HDR schedules Group I: 720 cGyx3 F and Group II: 600cGyx4 F at Chiang Mai University, from January 2004 to 2006 were studied. Overall survival rate for group I and II were 98.8% and 97.3%, respectively. Five and six patients developed grade 3-4 late GI toxicities, respectively. No patient developed grade3-4 late GU toxicities in Group I while two patients developed grade 3-4 late GU toxicities in Group II.

At the present, 500 cGy/F x 5F schedule is a standard ICRT regimen for cervical cancer treatment in our daily practices at Mahavachiralongkorn hospital. In the cases that the patients have got long waiting queues for ICRT, the attending radiation oncologists may change the schedule from "500 cGy/F x 5F" to "600 cGy x 4F" or "700 cGy x 3F" in order to shorten the waiting list. One limitation of this study is some incomplete important data because it is retrospective study. However, our team has made the best attempt to minimize any biases in this study. This study supports our practices that there is no significant difference in survival outcome and late complications among these three HDR schedules.

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