COMPARATIVE STUDY OF STANDARD FRACTIONATION AND REDUCED FRACTIONATION RADIOTHERAPY IN UTERINE CERVICAL CANCER.

S. PENPATTANAGUL M.D.

ABSTRACT

During the first of January 1998 to 30th of September 2000, new uterine cervical cancer patients were double-blinded randomly devided into 2 groups to receive a daily radiation dose fraction of 200 cGy or 250 cGy. In the standard treatment group, 20 fractions of 200 cGy were given to the pelvis and 5 fractions of 200 cGy were given to the parametria in addition. Three more fractions were given to boost the parametrial doses in stage IIIB patients. In the reduced fractionation group 15 fractions were given for the whole pelvis and 4 fractions for the parametria. Two booster doses to the parametria were given in stage IIIB. Both groups were treated 5 fractions per week. Time-dose-fraction calculation formular (TDF) was used to determine the number of fractions. Both groups were given intracavitary radiation with Cesium LDR machine 24-26 Gy by single insertion. Residual tumor, local recurrent tumor, metastasis and complication were compared by T-test evaluation with 95 % confidence interval. The study showed worse local control in the reduced fractionation group in stage IIIB patients. Better local control in the reduced fractionation group in stage IB patients. No significant difference was seen in the early and late complication of radiation of both groups.

INTRODUCTION

Uterine cervical cancer is the most common cancer in female in THAILAND. Estimated number of new cases is 5590 cases per year.[1] Radiotherapy is the treatment of choice in both early and advanced stages of the patients. The result of treatment in advanced stages is poor.[2] There are about 21 radiotherapy centers in Thailand. 9 centers are in the capital city. The radiotherapy centers and number of beds for treatment of uterine cervix cancer is not enough. The patients have to wait about 3-12 weeks to start the treatment. Altered fractionation radiotherapy of tumor was studied in many centers from 1976 to 2000.[3,4,5,6,7] Table 1 shows each type of altered fractionation. The reduced fractionation was selected to be used in our department due to shortened total treatment time and we hope to get a better result with acceptable complication.

MATERIAL & METHOD

The study was started from 1st January 1998 to 30th September 2000. Only stage IB to stage IIIB patients were selected for double blind randomised study. Two groups were divided and treated by a standard fraction of 200 cGy/day and reduced fractionation of 250 cGy/day. In the 200-cGy group, 20 fractions were given to the whole pelvis and 5 fractions more were added to the parametria (midline block field). Three

DEPARTMENT OF RADIATION ONCOLOGY UDORN REGIONAL CANCER CENTER THAILAND

fractions of booster doses were added to the parametrium in stage IIIB. The 250-cGy group received 15 fractions to the whole pelvic and 4 fractions of midline blocked field. Two fractions of booster doses were added in stage IIIB. All cases received 5 fractions / week of AP and PA pelvic field alternatively with Cobalt teletheapy machine with additional brachytherapy by Cesium intracavitary insertion 24-26 Gy in single insertion. Table 2 shows the number of fractions, total doses and overall treatment time of each group. Table 3 shows the TDF of the treatment of each group. Amount of blood transfusion, level of cystitis and diarrhea for each case was recorded during irradiation period. The early response was evaluated at the last external irradiation day. The result of radiotherapy was evaluated at 3 months after Cesium insertion. The recurrent tumor and late complication were evaluated at 3-30 months follow-up period (the mean follow-up time is 19.65 months). Three significant late complications (subcutaneous fibrosis, radiation proctitis and radiation-cystitis) were grading with RTOG radiation morbidity scoring criteria. The T-test (Levene's Test of Equality of Variences) was used to evaluate the different results of both groups with 95 % confidence interval.

RESULTS

There are 234 uterine cervical cancer patients that received treatment at the radiotherapy unit Udorn Regional Cancer Center. 56 patients were not included in the study: 7 cases were recurrent or metastatic post treatment from other centers, 8 cases were post operation, 32 cases were stage IVA or IVB, 9 cases received external irradiation with other regimen due to severe bleeding.

After completion of the treatment, the number of patients for evaluation is 146 cases. 32 cases were excluded from the study: 1) no brachytherapy (19 cases), 2) delay brachytherapy (5 cases), 3) incomplete external irradiation (7 cases), 4) early death from other disease (1 case).

The patients in conventional dose group were 68 cases and in the reduced fractionation group were 78 cases (table 4). The result of the study was shown in table 5-8. Table 10 and table11 show the Radiotheapy Oncology Group (RTOG) criteria for grading of radiation morbidity. Severe complication grade 4-5 was not detected in both arms. No definite different in the number of blood transfusion and the complication of treatment in both groups. But there is significant difference in result of tumor control in stage IIIB patients. The number of residual tumor and recurrent tumor in the reduced fractionation group (250 cGy) is significantly higher (p value=0.005). Therefore, good result in the reduced fractionation group was seen in stage IB patients (p value = 0.002).

TABLE 1. Type of altered fractionation radiotherapy.

	Dose /F. (cGy)	F./day	Treatment days/week	Total dose (cGy)	Total time (days)
1. standard fractionation	180-200	1	5	6500-7000	45-56
2. hyperfractionation	110-125	2	5	More	Equal
	70-80	3	5	More	Equal
3. accelerated hyperfractionation	130-170	2	5	More	Less
4. accelerated fractionation	180-200	1	6-7	Less	Less
	180-200	2	5	Less	Less
5. hypofractionation	>210	1	<5	Less or equal	Less or equal
6. accelerated hypofractionation	>210	>1	1-5	Less	Less
7. concomittent boost field					
8. mixed fractionation					
9. split course external irradiation					
10. reduced fractionation	>200	1	5	less	less

TABLE 2. Radiation treatment plan of each group.

		Whole pelvis (fractions)	Parametrium (fractions)	Boost RT at Pm.	Total F.	Total dose (cGy)	Total day
Standard fraction	Stage IB, IIA, IIB, IIIA	20	5	-	25	4000+ 1000	33-35
	Stage IIIB	20	5	3	28	4000+ 1000+ 600	38
Reduced fractionation	Stage IB,IIA,IIB,IIIA	15	4	-	19	3750+ 1000	25
	Stage IIIB	15	4	2	21	3750+ 1000+ 500	29

TABLE 3. Time-dose-fractions table (TDF).

		Whole pelvis	parametrium	Boost Pm	Total TDF
Standard fraction	Stage IB,IIA,IIB,IIIA	65.36	16.34	-	81.70
	Stage IIIB	65.36	16.34	9.80	91.50
Reduced fractionation	Stage IB,IIA,IIB,IIIA	69.09	18.42	-	87.51
	Stage IIIB	69.09	18.42	9.21	96.72

TABLE 4. Staging of tumor.

	200 cGy	250 cGy
Stage IB	15	25
Stage IIA	25	28
Stage IIB	14	16
Stage IIIA	-	2
Stage IIIB	14	17
Total cases	68	78
age	31-68 years mean 48.59 ,SD 9.15	31-72 years mean 49.67,SD 10.75
no significant difference in stage (p= 0.95)		

TABLE 5. Number of local residual tumors and recurrent tumors.

	200 cGy		250 cGy		P value (95%CI)
	cases/total	%	cases/total	%	
Stage IB	4/15	26.7	2/25	8.0	.002*
Stage IIA	9/25	36.0	5/18	27.8	.26
StageIIB	5/14	35.7	5/16	31.3	.625
Stage IIIA	-	-	1/2	50.0	-
Stage IIIB	7/14	50.0	14/17	82.3	.005*
Total cases	25/68	36.7	27/78	34.6	.594

TABLE 6. Early complications and late complications.

		200 cGy	250 cGy	P value	95 %CI	
					lower	upper
1. early cystitis	Grade 1	36	38	.950	-.11	.27
	Grade 2	4	3			
	Grade 3	-	-			
2. early diarrhea	Grade 1	23	19	.378	-.41	.23
	Grade 2	17	28			
	Grade 3	6	6			
3. blood transfusion				.935	-.27	.25
4. subcutaneous fibrosis	Grade 1	10	18	.211	-.30	.12
	Grade 2	5	3			
	Grade 3	-	2			
5. late cystitis	Grade 1	6	2	.130	-5.48E-02	.13
	Grade 2	-	1			
	Grade 3	-	-			
6. late proctitis	Grade 1	10	12	.892	-.16	.17
	Grade 2	3	3			
	Grade 3	-	-			
7.comparing total late complications				.554	-.37	.28
*No grade 4,5 complication detected in this study						

TABLE 7. Number of metastatic cases (medium follow up time 19 months).

stage	200 cGy		250 cGy	
	Cases/total	%	Cases/total	%
All stage	6/68	8.8	7/78	9
Stage IB	2/15	13.3	0/25	0
Stage IIA	1/25	4	3/28	10.71
Stage IIB	2/14	14.28	0/16	0
Stage IIIA	-	-	0/2	0
Stage IIIB	1/14	7.1	4/17	23.5

TABLE 8. Survival of the patients (with and without tumor).

Stage	Survival	200 cGy		250 cGy	
		Cases/total	%	Cases/total	%
Stage IB	6 months	15/15	100	25/25	100
	12 months	15/15	100	18/18	100
	18 months	12/12	100	12/12	100
	24 months	6/6	100	5/5	100
Stage IIA	6 months	25/25	100	18/18	100
	12 months	21/22	95	15/16	94
	18 months	15/18	83	11/13	85
	24 months	7/8	87	2/3	67
Stage IIB	6 months	14/14	100	16/16	100
	12 months	9/10	90	10/11	91
	18 months	4/5	80	4/7	57
	24 months	2/3	67	1/3	33
Stage IIIA	6 months	-	-	2/2	100
	12 months	-	-	1/1	100
	18 months	-	-	1/1	100
	24 months	-	-	1/1	100
Stage IIIB	6 months	13/14	93	16/17	94
	12 months	11/12	92	12/12	100
	18 months	7/8	87	5/8	62
	24 months	4/5	80	3/4	75
All stages	6 months	67/68	98	77/78	99
	12 months	56/59	95	56/58	96
	18 months	38/43	88	33/41	80
	24 months	19/22	86	12/16	75

TABLE 9. Possible factor in pelvic failure [5]

Patient-related
1. low socioeconomic level
2. age younger than 35 years
3. anemia
4. Karnofsky performance status below 90
5. high stage of tumor
6. bulky tumor
7. nodal metastases
8. small cell histologic type
Treatment-related
1. low-energy teletherapy
2. lack of brachytherapy
3. single brachytherapy insertion versus two or more
4. prolong rest period between teletherapy and brachytherapy
5. insufficient radiation dose
6. persistent of tumor at end of radiation therapy

TABLE 10. Acute Radiation Morbidity Scoring Criteria (RTOG).

	Score	Clinical signs and symptoms
1. acute radiation cystitis	Grade 1	Frequency of urination or nocturia twice pretreatment habit; dysuria, urgency not requiring medication
	Grade 2	Frequency of urination or nocturia less frequent than every hour; dysuria, urgency, bladder spasm requiring local anesthetic.
	Grade 3	Frequency with urgency and nocturia hourly or more frequently; dysuria, pelvic pain, or bladder spasm requiring regular, frequent narcotic; gross hematuria with or without clot passage
	Grade 4	Hematuria requiring trasfusion; acute bladder obstruction not secondary to clot passage, ulceration, or necrosis
2.acute radiation proctitis	Grade 1	Increased frequency or change in quality of bowel habits not requiring medication; rectal discomfort not requiring analgesics
	Grade 2	Diarrhea requiring parasympatholytic drugs; mucous discharge not necessitating sanitary pads; rectal or abdominal pain requiring analgesics
	Grade 3	Diarrhea requiring parenteral support; severe mucous or blood discharge necessitating sanitary pads; abdominal distention (flat plate radiograph demonstrates distended bowel loops)
	Grade 4	Acute or subacute obstruction, fistula or perforation, GI bleeding requiring transfusion, abdominal pain or tenesmus requiring tube decompression or bowel diversion

TABLE 11. Late Radiation Morbidity Scoring Criteria (RTOG).

	score	Clinical signs and symptoms
1. subcutaneous fibrosis	Grade 1	Slight induration (fibrosis) and loss of subcutaneous fat
	Grade 2	Moderate fibrosis but asymptomatic, slight field contracture
	Grade 3	Severe induration and loss of subcutaneous tissue; field contracture> 10 % linear measurement
	Grade 4	necrosis
2. radiation cystitis	Grade 1	Slight epithelial atrophy, mild telangiectasia
	Grade 2	Moderate frequency, generalized telangiectasia, intermittent macroscopic hematuria
	Grade 3	Severe frequency and dysuria, sever generalized telangiectasia (often with petechiae), frequenct hematuria, reduction in bladder capacity
	Grade 4	Necrosis, contracted bladder (capacity< 100 cc), severe hemorrhagic cystitis
3. radiation proctitis	Grade 1	Mild diarrhea, mild cramping, bowel movement 5 times daily, slight rectal discharge or bleeding
	Grade 2	Moderate diarrhea and colic, bowel movement > 5 times daily, excessive rectal mucous or intermittent bleeding
	Grade 3	Obstruction or bleeding requiring surgery
	Grade 4	Necrosis, perforation, fistula

DISCUSSION

Uterine Cervical Cancer is the most common female cancer in Thailand. Early detection of the tumor is in the process of highly motivated in the attempt to reduce the number of advanced stage tumors. Poor result of radiotherapy is in the late stage cancer.[2] There are many new lines of treatment in the process of investigation to get better local control. Altered fractionation radiotherapy is used in many centers.[8,9] But the results are not satisfactory. Reduced fractionation radiotherapy was used in this study because of the benefit of decreasing the overall treatment time and the tumor response rate may be increased. In many studies no significant benefit had been shown.[8,9] The disadvantages of reduced fractionation with increased dose per fraction are the increasing of early and late complications of radiation. The 250 cGy dose /fraction that were used in our study is not a very high dose. The treatment was given daily as the conventional treatment. TDF calculation is used to decide the number of fractions. TDF of reduced fractionation in this study is slightly higher than standard fraction (table 3). The total treatment days were 10 days shorter than the standard group. Number of blood transfusion and degree of early

complications were in our interest during radiotherapy. But no significant difference was detected. Late complication of radiation at the time of evaluation also shows no significant differences.

The result of treatment in the advanced stage (IIIB) was opposite to our expectation. The lower total tumor doses that had been given may be the reason of the poor results in the late cases.

On the contrary a better result was seen in stage IB. In this study, we didnot take the sizes of the tumor as a criteria for evaluation of the result of the response to treatment. Tumor size is, in fact, one important factor of tumor control.[10] Larger dose fraction of reduce fractionation group may be more effective to the tumor than the standard dose fraction. The result of stage IB is different from the study of Perez.[11] Total number of patients in this study is not large enough. Further larger study is needed to confirm the result.

REFERENCES

1. Vatanasapt V, et al.: Cancer in Thailand 1988-1991. IARC Technical Report no 16,1993:59-60.
2. Jampolis S, Andras J, Fletcher GH: Pelvic failure in Ca Cervix after radiation: Radiology 1975; 115: 681-685
3. Greenberg M, Eisert DR, Cox JD: Initial evaluation of reduced fractionation in the irradiation of malignant epithelial tumors. Am J Roentgen Radium Ther Nucl Med 1976; 126: 268-278
4. Byhardt RW, Freenberg M, Cox JD: Local control of squamous cell carcinomas of the oral cavity and oropharynx with 3 vs 5 treatment fractions per week, Int J Radio Oncol Biol Phys 1977;2:415-420
5. Marcial VA: Radiation Therapy of cervical cancer: present at the National conference of Gynecologic Cancers, Orlando, Florida, April 2-4,1992
6. Harwood AR, Beale FA, Cummings JB, et al: Supraglottic laryngeal carcinoma: An analysis of dose-time-volume factors in 410 patients: Int J Radio Oncol Bio Phys 9:311,1983
7. Wang CC: Altered fractionation radiation therapy for gynecologic cancers. Cancer 60:2064-2067,1987
8. Marcial VA, Amato D, Marks RD, et al: Split-course versus continuous pelvis irradiation in carcinoma of the uterine cervix: A prospective randomized clinical trial of the radiation therapy oncology group. Int J Radiat Oncol Bio Phys 9:431-436,1983
9. Marcial VA, Komaki R, : Altered fractionation and extended field irradiation of carcinoma of cervix.Cancer 76 (suppli) : 2152-2158, 1995
10. Perez CA, Grigsby PW, Nene SM, Camel HM, Galalatos A, Kao MS, Lockett MA; Effect of tumor size on the prognosis of carcinoma of the uterine cervix treated with irradiation alone: Cancer 62: 2796-2806,1992
11. Perez CA, Breaus S, Madoc-Jones H, et al: Radiation therapy alone in the treatment of carcinoma of uterine cervix.I.Analysis of tumor recurrence. Cancer 51: 1393-1402,1983