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The Results of High-dose Rate Intracavitary Brachytherapy for Uterine Cervical Carcinoma in Ramathibodi Hospital.

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Abstract

Objectives: To study results of high-dose-rate brachytherapy (HDR-BCT) for the treatment of cervical cancer patients in Ramathibodi Hospital in terms of tumor control, survival and treatment complications and to identify factors that may impact on local control.

Materials and Methods: Retrospective analysis was performed on patients with stage IA-IVA cervical cancer treated with a combination of external beam radiotherapy (EBRT) and HDR-BCT in Ramathibodi hospital during March 1999 to June 2001. The Kaplan-Meier method was used for survival analysis. Univariate and Multivariate analysis was performed using log-rank test and Cox proportional hazard regression model to identify factors associated with local control rates.

Results: There were 263 patients included in this study (5.3% stage I, 52.8% stage II, 41.8% stage III). The median follow-up time was 66 months (3-113 months). Seventy-one patients (27%) were lost to follow-up. Chemotherapy was delivered in 45 patients. Early stage patients received 40-50.4 Gy whole pelvic EBRT plus 3-4 intracavitary brachytherapy sessions with a fraction size of 3-7 Gy. Patients with advanced stage underwent EBRT to the pelvis to a dose of 40-60 Gy followed by 2-4 sessions of HDR-BCT of 4-7.5 Gy. Median low-dose-rate equivalent dose at point A was 73 Gy and 75 Gy in early and advanced stage, respectively. The 5-year overall survival, disease-free, and local control rates for all patients were 70%, 70%, and 80%, respectively. The 5-year LC rates according to stage were 92% in early stage and 77% in advanced stage. Stage and quality of brachytherapy were independent prognostic factors of local control. Severe (grade 3 and 4) late GI and GU complication rates were 3.1%, and 1.6%, respectively.

Conclusion: the combination of EBRT and HDR-BCT, as used in Ramathibodi hospital, can produce favorable outcome and acceptable rates of late complication when compared to other centers in treatment of cervical cancer.

Keywords: cervical cancer, radiotherapy, brachytherapy

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Introduction

Cancer of the uterine cervix is the second most common female cancer with at least 400,000 new cases diagnosed throughout the world each year. Eighty percent of these cases occur in developing countries. In Thailand, cervical cancer is the most common cancer in female. In 1999, approximately 6,746 new cases were identified.[1] According to 2003-2005 Ramathibodi Cancer Registries, there were 174-208 new cases each year, which accounted for 12-17% of new cancer cases.[2]

Radiotherapy (RT) plays an important role in the treatment of cervical cancer. Combination of megavoltage external beam radiotherapy (EBRT) and intracavitary brachytherapy (IBCT) is the standard mode of treatment. IBCT has an advantage of delivering a high dose of radiation to the central tumor and a lower dose to surrounding normal tissues, resulting in high local control with low risk of normal tissue complication. Traditionally, low-dose-rate brachytherapy (LDR-BCT) had been used due to its biological advantage in sparing late-responding normal tissues.[3] However, this modality has some drawbacks such as radiation exposure to involved medical personnel, physical and psychological stress to the patients because of the long treatment time, and difficulty in maintaining good applicator geometry during treatment. As the result, high-dose-rate brachytherapy (HDR-BCT) was developed to overcome these drawbacks. Several studies have compared the results of HDR to LDR-BCT in cervical cancer.[4-7] Most of them have shown comparable local control, survival, and treatment complication rates.

HDR-BCT has been widely used for more than 30 years. However, wide variation of dose and fractionation schedules exists for a combination of EBRT and HDR-BCT.[4,5,7-14] There is no consensus about the optimal dose/fractionation schemes. The American Brachytherapy Society (ABS) published the recommendations for the use of HDR-BCT in cervical carcinoma. When EBRT and HDR-BCT are combined, the goals are to treat point A to an LDR equivalent doses of 80-85 Gy (BED = 96-102 Gy10) for early staged disease and 85-90 Gy (BED = 102-108 Gy10) for advanced stage. They recommended that the HDR fraction size should not exceed 7.5 Gy and the number of fractions ranges from 4-8 fractions.[15] However, these recommendations have not been tested.

In Japan, several studies delivered point A doses lower than the ABS recommendation.[12,14] These regimens produced a favorable outcome when compared to the large LDR series. In Ramathibodi hospital, Iridium-192 (Ir-192) HDR-IBCT system (Microselectron, Nucletron) has been used since 1999. Clinical practice guideline was developed by the Radiation Oncology and Gynecologic Oncology units for gynecologic cancers. Patients with stage I and II diseases were to be treated with 40 Gy whole pelvis plus 4 fractions of 6 Gy HDR-BCT (equivalent dose at point A = 72 Gy_{10}). A dose to whole pelvis 50 Gy combined with 3 fractions of HDR brachytherapy 6.5 Gy (equivalent dose at Point A = 76 Gy_{10}) were to be delivered in stage III/bulky patients. From our guidelines, the doses delivered to point A were much lower than those recommended by the ABS, therefore it was necessary to investigate the treatment outcomes. We utilized our previous data to analyze the results, especially in terms of local control and the subsequent complications from radiation.

Materials and methods

Patients

We searched for the histologically proven carcinoma of the uterine cervix patients who received curative treatment with the combination of EBRT and HDR-IBCT from the medical database in Ramathibodi Hospital. The information was obtained from the medical-record review, telephone-interviews, and the death reports.

During March 1999 to June 2001, there were

311 patients with carcinoma of the uterine cervix treated by the combination of EBRT and HDR-IBCT. Forty-eight patients were excluded from this study, including 13 patients with post-operative RT, 4 patients with recurrent cervical cancer, 5 patients with EBRT from other hospitals, 4 patients with stage IVB, 8 patients with palliative treatment, and 14 patients with follow-up less than 3 months. Therefore, 263 patients were eligible for analysis. All patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO) clinical staging system.[16] All patients were categorized in early and advance-stage disease. Early-stage disease were patients with stage I, II and tumor size ≤ 4 cm. Patients with stage III, IV or tumor size more than 4 cm were classified as advanced stage.

Treatment

Patients were treated with whole pelvic RT followed by HDR-IBCT. In case of parametrial boost was administered, HDR-BCT was performed prior to the completion of EBRT. EBRT was withheld on the day of BCT.

External beam irradiation

All patients were treated by mega-voltage EBRT to the pelvis using either ^{60}CO machine or 6 or 10 MV X-ray. Radiation was delivered to the whole pelvis through anterior and posterior parallel-opposed field (AP/PA) or four-field box technique. The upper border of the whole pelvic field was at the L4 and L5 interspace, and the lower border was at inferior border of the obturator foramen or at least 2-3 cm below the lowest tumor extension. The lateral border of AP/PA field was 2 cm lateral to pelvic inlet. Whole pelvic dose ranged from 40-50.4 Gy in stage I-II, and 50.4 Gy in stage III/bulky lesions, given at a dose of 1.8-2.0 Gy/F, 1 F/day and 5 F/wk. When patients had bulky parametrial tumor, an additional 5-10 Gy was applied to the parametrium to a total of 55-60 Gy.

Brachytherapy

Brachytherapy was performed using remote afterloading HDR unit with Ir-192. (Microselectron, Nucletron). The intracavitary doses were prescribed at Point A, defined on x-ray as being 2 cm above the external os and 2 cm lateral from the axis of the intrauterine tandem, according to the International Commission of Radiation Units and Measurements (ICRU), Report 38.[17] Vaginal gauze packing was performed to keep rectal and bladder wall away from a high dose region. A barium-filled Foley catheter balloon and rectal sponge with radiopaque markers were used to define bladder and anterior rectal wall in order to calculate the absorbed dose. According to the protocol, four intracavitary placements with a fraction size of 6.0 Gy at point A would be given in early stage, and 3 fractions of 6.5 Gy would be for advanced stage.

Dose calculation

Total LDR equivalent dose to point A was the summation of the whole pelvic dose and HDR-BCT dose, using linear-quadratic equation. Biological equivalent dose (BED) for tumor effect was calculated using α/β = 10 and analyzed in terms of equivalent dose given at 2 Gy per day (EQD).[18]

Chemotherapy

Chemotherapy was given to the patients at the discretion of the treating radiation oncologist and gynecologic oncologist, not used in routine. Chemotherapy was applied in bulky tumor or in tumor that did not respond to radiation. Cisplatin-based regimens were used at that time.

Follow-up

After the treatment was completed, patients were followed by a radiation oncologist and a gynecological oncologist. Physical examination, pelvic examination, and Pap smear were performed for every visit. Other

investigations were applied if clinically indicated. Patients were examined every 3-4 month for the first 2-3 years, then every 4-6 month in year 4^{th}-5^{th}, and once or twice a year thereafter. Suspected persistent or recurrent diseases were confirmed by imaging or histology when possible. Late complications (3 month after radiotherapy) were recorded and graded according to the RTOG/EORTC late radiation morbidity scoring scheme, especially for bladder and bowel complications.[19]

Clinical endpoints

This study was undertaken to analyze long-term outcomes. LC and late GI, GU complication rates were primary endpoints. Secondary endpoints were DF and OS rates. The disease or treatment related factors with impact on local control rate were also identified.

OS was defined from the date of diagnosis to the date of death (death from any cause as the only event) or the most recent follow-up. LC was defined from the date of diagnosis to the date of first documented local recurrence or the most recent follow up. DF rate was measured from the date of diagnosis to the date of first documented any disease failure or the most recent follow-up. Disease failures were classified as local for recurrence in the pelvis (cervix, vagina, and parametrium) or persistent lesions, and as distant for recurrence outside the pelvic region. Patients who were still in remission at the last follow up or at death are considered as censored cases. Late GI and GU complication was defined as the event occurred more than 90 days after the finish of treatment.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences for Windows version 16.0. OS, DF and LC rates were calculated using Kaplan-Meier method. Univariate analysis was evaluated by log-rank test. Multivariate analysis was performed using Cox proportional hazard regression model. A p-value of < 0.05 was considered to indicate statistical significance.

Results

Patients and treatment characteristics

The median age was 54 (29-89) years. Most patients had stage IIB and IIIB (233 patients, 88.6%) and 53 patients (20%) had tumor size larger than 4 cm. Squamous cell carcinoma was the most common cell type (212 patients, 80%). Other patient and tumor characteristics are described in Table 1.

Most patients were treated with ^{60}CO machine (158 patients, 60%). 2-field technique was used as often as 4-field-box technique. In early stage, median dose 45 Gy (range 40-50.4 Gy) was delivered to the whole pelvis plus 3-4 intracavitary placements with a fraction size of 3-7 Gy. Patients with advanced stage received 40-60 Gy whole pelvis EBRT followed by 2-4 sessions of HDR-IBCT of 4-7.5 Gy at point A. Therefore, median cumulative EQD at point A was 73 and 75 Gy in early stage and advanced stage, respectively. Inadequate BCT, defined as improper position of tandem and ovoid, was observed in 10 patients (3.8%). In these patients, tumors were large at the time of first BCT. Disease stages were either at stage IIB or IIIB and histologic subtype of these tumors were adenocarcinoma. Almost all of ten patients received concurrent or adjuvant cisplatin-based chemotherapy. Other treatment characteristics were summarized in Table 2.

Treatment outcomes

The median follow-up time for all 263 patients was 66 months (3-113 months). Seventy-one patients (27%) were lost to follow-up. For the purpose of survival analysis, we assumed dead in all 34 patients who had residual or recurrent disease at the time of last follow-up.

Table 1 Patient and tumor characteristics

Characteristic	Patient, n (%)
Age (yrs)	
Range (median)	29-89 (54)
Kanofsky performance status (KPS)	
90	225 (85.6)
80	30 (11.4)
70	8 (3)
Stage	
IB	14 (5.3)
IIA	13 (4.9)
IIB	126 (47.9)
IIIA	3 (1.1)
IIIB	107 (40.7)
Histology	
Squamous cell carcinoma	212 (80.6)
Adenocarcinoma	44 (16.7)
Adenosquamous carcinoma	4 (1.5)
Other	3 (1.1)
Grade	
Well differentiated	59 (22.4)
Moderate differentiated	34 (12.9)
Poorly differentiated	117 (44.5)
Not specified	53 (20.2)
Tumor size	
≤ 4 cm	210 (79.8)
> 4 cm	53 (20.2)
Pre-treatment hemoglobin level (g/dl)*	
≥ 10	194 (73.8)
< 10	35 (13.3)
Not specified	34 (12.9)
Concomitant disease	
None	183 (69.6)
DM	13 (4.9)
HT	30 (11.4)
DM and HT	23 (8.7)
Others	14 (5.3)
Smoking	
No	254 (96.6)
Yes	9 (3.4)
Previous abdominal surgery	
No	229 (87.1)
Yes	34 (12.9)

Table 2 Treatment characteristics

Characteristic	Patient, n (%)
External beam irradiation	
Machine	
Cobalt-60	158 (60.1)
Linac 6 MV	15 (5.7)
Linac 10 MV	90 (34.2)
Technique	
AP//PA	124 (47.1)
4-field box	139 (52.9)
Dose whole pelvis (Gy):	
range (median)	
Early stage	40-50.4 (45)
Advanced stage	40-60 (50)
Dose parametrium	
Range	45-60 (50)
Brachytherapy	
Dose/Fraction (Gy/F) : Range	
Early stage	3-7
Advanced stage	4-7.5
number of fraction : Range	
Early stage	3-4
Advanced stage	2-4
LDR-equivalent dose at Point A (Gy):	
Range (median)	
Early stage	64-81 (73)
Advanced stage	66-87 (75)
Improper brachytherapy	10 (3.8)
Overall treatment time (day)	
Range (median)	38-132 (60)
Chemotherapy	45 (17.1)
Concurrent chemotherapy	39 (14.8)
Cisplatin + 5-FU + IFN	9 (3.4)
Cisplatin + 5-FU	10 (3.8)
Cisplatin alone	20 (7.6)
Adjuvant chemotherapy	20 (7.6)
Cisplatin + 5-FU + IFN	1 (0.4)
Cisplatin + 5-FU	11 (4.2)
Cisplatin alone	8 (3.0)
Post-RT surgery	22 (8.4)

Overall survival

At last follow up, 173 of patients were alive, 171 patients were free of disease and only 2 patients were alive with disease (both with distant metastases). Eighty-one patients died from cervical cancer, 9 (10%) died from other causes. The 5-year OS rate was 70% (Figure 1). The 5-year OS rates according to stage were 79% for stage I, 78% for stage II and 58% for stage III, p=0.02.

Disease failure

Eighty-three patients (31.6%) had disease failures. Twenty-five patients (9.5%) had local failure in the pelvis only and 17 patients (6.5%) had both local and distant failures. Forty-one patients (15.6%) had only distant metastasis. Sites of distant metastases include paraaortic lymph nodes (48.3%), lung (39.7%), supraclavicular lymph nodes (22.4%), bone (22.4%), liver (6.9%) and other sites (10.3%). The 5-year DF rate was found to be 70% (Figure 2). The 5-year DF rates according to stage were 79%, 78% and 60% for stage I, II and III, respectively (p=0.03).

Forty-two patients (16%) had locoregional recurrence, including 2 patients in stage I, 16 and 24 patients in stage II and III, respectively. Most patients (35/42 patients, 83.3%) developed local recurrence in the first 3 years after treatment. The 5-year LC rate was 84% (Figure 3). The 5-year LC rates according to stage were 93%, 90% and 76% for stage I, II and III, respectively (p=0.04).

Factors associated with local control

From univariate analysis, stage (I/II vs III/bulky lesion), improper BCT (no vs yes), and EQD at point A (<74 vs ≥74 Gy) were statistically significant correlated with the local control rate. Patients with advanced stage had worse local control than early stage (77% vs 92%, p=0.003). Decreasing of LC rate in patients who received improper BCT (57% vs 85%, p= 0.04) and cumulative dose at point A ≥74 Gy (79% vs 89%, p=0.05) were found (Figure 4-6). Other factors were also analyzed and summarized in Table 3. On multivariate analysis, advanced stage (HR=2.20, 95% CI 1.11-4.36, p=0.024) and improper BCT (HR=3.74, 95% CI 1.22-11.45, p=0.021) were found to be significant worse prognostic factors for local control.

Complications

Fifty-two (19.8%) and 19 (7.2%) patients developed late gastrointestinal (GI) and genitourinary

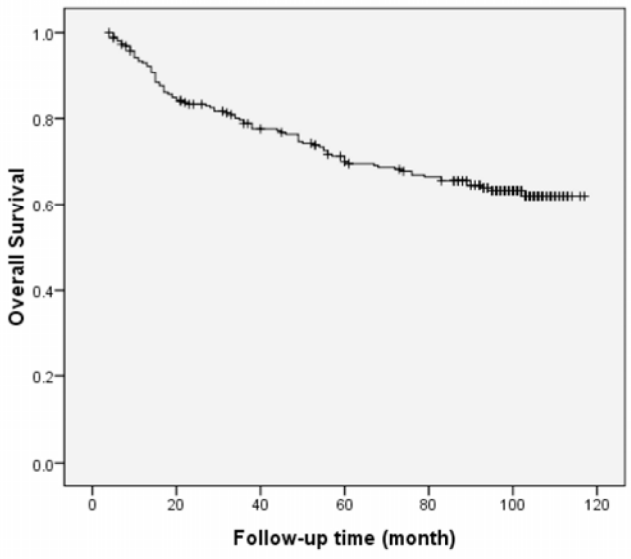

Fig.1 *Overall survival curve*

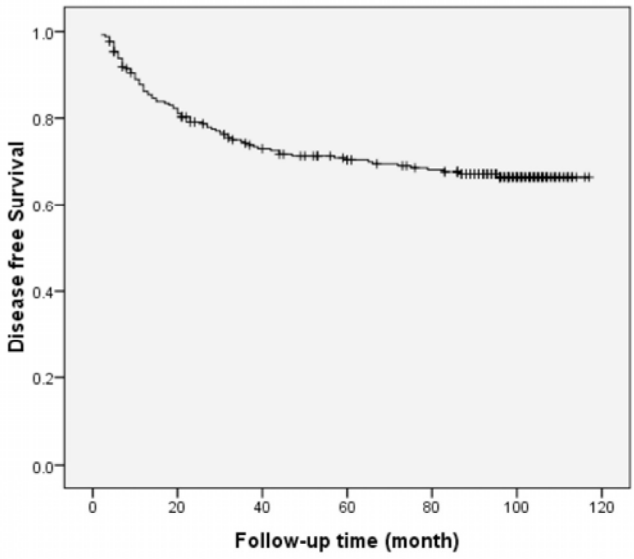

Fig.2 *Disease free rate curve*

Table 3 Univariate analysis; The prognostic factors for local control rate

Variable	n	5-yrs LRFS (%)	P-value
Age (yr)			
≤ 35	12	82	0.87
35-70	232	84	
> 70	19	88	
KPS			
≥ 80	255	84	0.84
< 80	8	83	
Stage			
Stage I,II	132	92	0.003
Stage III or bulky lesion	131	77	
Histological type			
Squamous cell CA	212	86	0.14
Adenocarcinoma	44	76	
Grade			
Well differentiated	93	85	0.78
Poorly differentiated	117	83	
Tumor size			
≤ 4 cm	210	86	0.21
> 4 cm	53	77	
Hemoglobin level (g/dl)			
< 10	35	81	0.30
≥ 10	194	88	
Improper BCT			
No	253	85	0.04
Yes	10	57	
Concurrent chemo			
No	224	84	0.66
Yes	39	86	
Total treatment time			
≤ 56 days	102	87	0.34
> 56 days	161	82	
Surgery post RT			
No	241	83	0.13
Yes	22	94	
EQD at point A (Gy)			
< 74	141	89	0.05
≥ 74	122	79	

EQD= low dose rate equivalent dose at point A

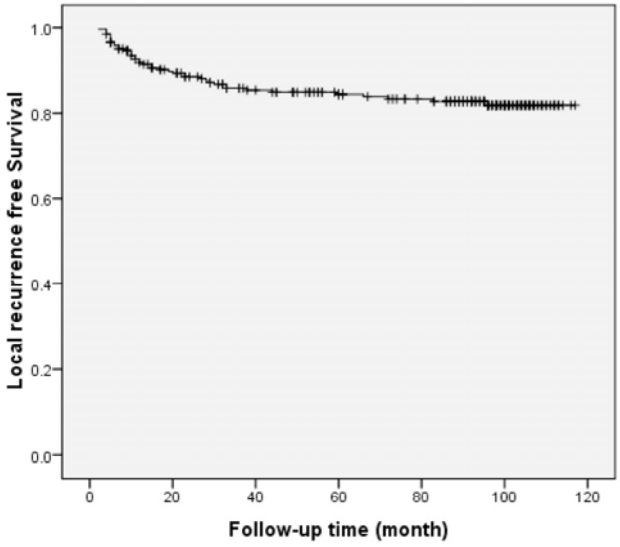

Fig.3 *Local control rate curve*

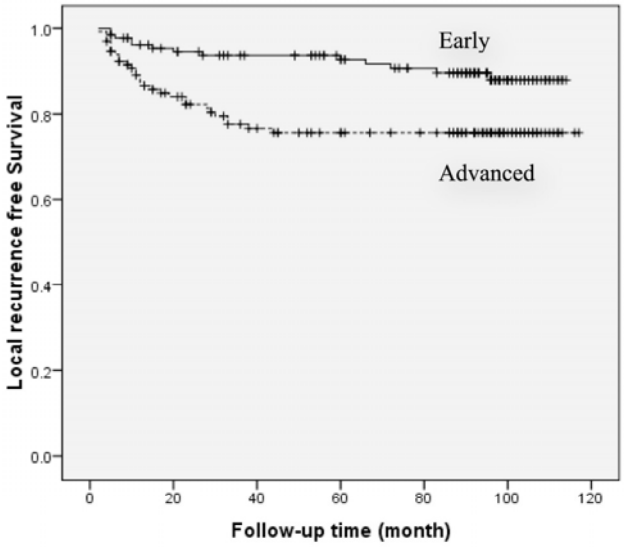

Fig.4 *Local control rate curve according to disease stage*

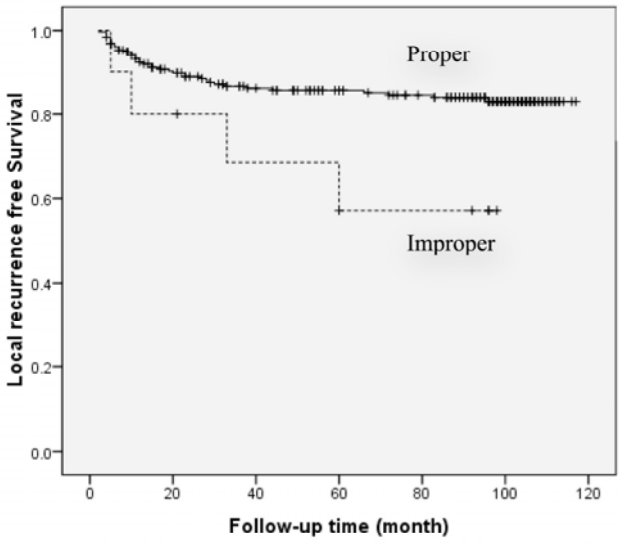

Fig.5 *Local control rate curve according to improper brachytherapy*

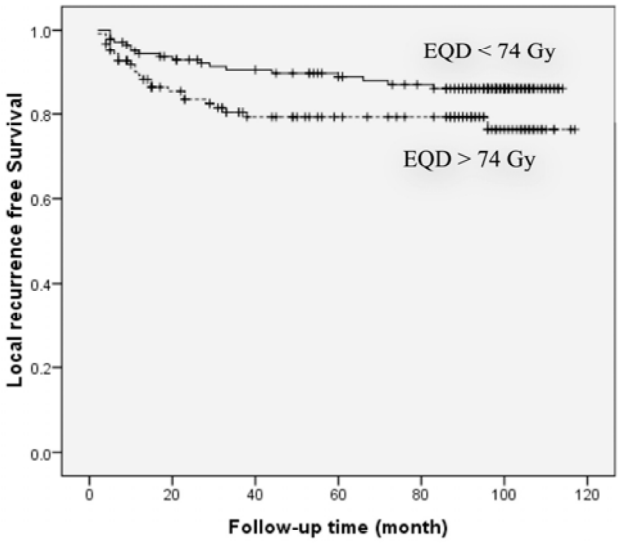

Fig.6 *Local control rate curve according to EQD at point A*

(GU) complications, respectively. Most GI complications (81%) occurred within the first 3 years after treatment. Forty-four patients (16.7%) developed grade I-II complications. Most patients presented with slight rectal bleeding. All symptoms were improved after medication and conservative treatment. Severe complications (grade III-IV) were found in 8 patients (3.1%). Two patients (0.8%) developed rectovaginal fistula. Argon plasma laser coagulating treatment was necessary in 6 patients (2.2%) due to the severe rectal bleeding. Most GU complications (70%) developed during the first 5 years after treatment. Grade I-II complications were reported in 15 patients (5.7%). All patients presented with microscopic or

macroscopic hematuria. The symptoms were improved after conservative treatment. Four patients (1.5%) developed severe complication, including vesicovaginal fistula (1 patient), urethral stricture (1 patient), severe urinary incontinence (1 patient) and severe hematuria (1 patient). These patients were treated by invasive procedures consisting of surgery in 2 patients, urethral dilatation in 1 patient and another one underwent formalin instillation in the bladder via cystoscopy. No grade V complication was found in this study.

Discussion

The use of HDR-BCT in the treatment of uterine cervical cancer has been increasing worldwide for more than 30 years; still there is no consensus about the optimal dose-fractionation. The studies from USA and Europe frequently delivered cumulative dose to point A following the ABS recommendation. As seen in report from Ferrigno et al[9], they used whole pelvic dose 50 Gy plus brachytherapy 24 Gy in 4 fractions (EQD at point A = 82). Falkenberg et al[8] also applied EQD at point A 85-90 Gy to patients with advanced stage. On the other hand, studies from Asia, especially Japan, commonly delivered lower point A dose than the ABS recommendation. They applied EQD 40-50 Gy to point A in early stage and 50-70 Gy in advanced stage patients.[4,7,12] In our study, median EQD at point A in early and advanced stage were 73 (64-81) and 75 (66-87) Gy, respectively. It was similar to report from Lertsanguansinchai et al, Patel et al, and Han et al.[5,10,13]

Petereit and Pearcy reviewed 24 articles using HDR-BCT in the treatment of cervical cancer, median EQD at point A was 80 Gy. The median 5-year pelvic control rates for stage I, II, III were 91%, 82% and 71%, with survival rates of 85%, 68% and 47%, respectively, at 5 years.[20] It is clear that results from studies in Asia also achieved favorable outcome. As seen in our results, the 5-year local control rate in stage I, II, and III was 93%, 90%, and 76% with OS rate of 79%, 78%, and 58%, respectively. However, variation of treatment outcomes from different institutions could be because of the differences in patients and tumor characteristics.

From univariate analysis of our data, high FIGO stage, improper BCT and EQD at point A higher than 74 Gy all adversely affected local control. Patients who received EQD at point A dose > 74 Gy mostly presented with advanced stage (82/122 patients, 70%). Therefore, only diseased stage and optimal of BCT remained statistically significant independent prognostic parameters in this study.

Stage is the most important parameter influencing local control in all population data base studies.[11,21-23] As seen in this study patient with advanced stage had a greater risk of local recurrence than early stage patients. Most reports, when analyzing the prognostic value of stage, also concluded that tumor size per stage was a better prediction of failure rate. Barillot et al, reported influence of tumor size in stage I/II. Stage IIB patient with 5 cm cervix tumor diameter had a relative risk of local and/or distant failure twice as higher as a stage IIB patient with a 3 cm cervix diameter.[24] In this study, tumor size was not a significant prognostic factor, only in patients with stage I/II the correlation between tumor size and local control was significantly demonstrated (size< 4 cm vs > 4 cm = 92% vs 75%, p=0.05). The lack of correlation in stage III/IV might not be surprising as the tumor size was difficult to be accurately evaluated under pelvic examination. It might be easy to underestimate the true tumor size.

The other prognostic factor was improper BCT. In this group, the tumor did not respond well to EBRT, the tumor size was still large at the time of the first IBCT session. Therefore, it was difficult to properly insert tandem and ovoids.

In 1999, cisplatin-based chemotherapy was introduced to improve local control in locally advanced cervical cancer by combination with radiation.[25-27] In

this study, effect of concurrent chemotherapy was not correlated with the local control because concurrent chemotherapy was applied in only 25% of the patients with advanced stage and in most patients chemotherapy was started after the beginning of radiation. Not until 2005 that our institute adopted the protocol to combine cisplatin-based chemotherapy with radiotherapy in locally advanced cervical cancer. It would take some more time before we can fully explore the efficacy of combining chemotherapy on the local control and overall survival.

Of additional interesting factor is the overall treatment time. When treatment duration exceeded the expected threshold, the local control and overall survival had been shown to decreased about 1% per day.[28-30] Grigiene et al reported decreased local control in the group with overall treatment time exceeding than 56 days.[31] However, our study did not show the effect of overall treatment time on local control.

Girinsky et al reported hemoglobin less than 10 g/dl during or before radiation treatment to be associated with reduced locoregional control and transfusion during treatment did not change the prognosis.[32] On the other hand, several studies showed that transfusion requirement was a true significant factor for pelvic relapse, not the initial hemoglobin level.[22,33] In our series, however, initial hemoglobin was not a statistically significant variable for local control. This was probably due to the missing data.

The overall incidence of late GI complication in our patient was higher than GU complication (19.8% vs 7.2%). Most of these complications were Grade 1-2 and could be improved by conservative treatment. Severe late complications in our study were 3.1% and 1.5% in the GI and GU system. Nakano et al reported rates of major GI and GU complication of 3.8% and 0.8%, respectively.[12] Fu and Phillips reviewed the treatment results of HDR-BCT in the literature[34], the major rectal and bladder complication rates ranged from 1.4-10% and 0.3-4%, respectively. Hence, compared with these studies, the complication rates of this current study were considered to be acceptable.

Major limitation of this study was the missing data reflective of its retrospective nature. And other limitation of this study included the non-uniform distribution of variables and non-randomized nature.

Conclusion

The combination of external beam radiotherapy and high-dose rate intracavitary brachytherapy, as used in Ramathibodi hospital, can produced favorable outcome and acceptable rates of late complication when compared to other centers in treatment of cervical cancer. Now, there are variety ways to improve local control in this disease, including the use of concomitant chemotherapy with radiotherapy, staging with MRI or CT imaging, more conformal dose distributions with 3-D planning or IMRT. In the future we will investigate efficacy of these ways.

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