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ORIGINAL ARTICLE

Outcome of cervix uteri cancer patients: Clinical treatment results and toxicity profile in a retrospective study from Saudi Arabia

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Abstract

***Aim*:** This study evaluated the survival outcome, pattern of failure and prognostic factors in cervix uteri cancer patients.

***Methods*:** We reviewed the data of 60 patients with stages IB-IVA cancer who were treated between January 2004 and December 2010.

***Results*:** Most patients ($n = 50$; 83%) had squamous cell carcinoma. Stage IIB was the most common presentation ($n = 41$; 68%). Forty-seven patients (78%) received Cisplatin concurrent with radiotherapy (CRT). The 2- and 4-year overall survival (OS) was 82% and 79%, respectively. Prolongation of the overall treatment time (OAT) for greater than 56 days, advanced stage and pretreatment hemoglobin (Hb) levels (<10 g/dL) negatively predicted OS ($P = 0.039$, $P = 0.044$ and $P = 0.008$, respectively). The 2- and 4-year disease-free survival (DFS) rates were 80% and 69%, respectively. Vaginal infiltration and brachytherapy (orthogonal versus CT-based planning) were significant factors for the prediction of relapse ($P = 0.048$ and $P = 0.049$, respectively). The 2- and 4-year loco-regional control (LRC) rates were 78% and 70%, respectively, and the distant metastasis-free survival (DMFS) rates were 82% and 79%, respectively. Vaginal infiltration was the only negative predictive factor for LRC ($P = 0.045$), and pathological tumor grade was the only factor indicative of distant metastases ($P = 0.037$). Grade 3 or 4 late rectal reactions were reported in two patients (3%), and no patients developed grade 3 or 4 urinary reactions.

***Conclusion*:** The treatment results in our cervix uteri cancer patients and the prognostic factors are comparable to those of previous reports. Orthogonal brachytherapy planning and vaginal infiltration negatively predicted relapse.

Key words: cancer in Saudi Arabia, cervix uteri cancer, concurrent chemo-radiotherapy, high-dose rate brachytherapy

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INTRODUCTION

Cervix uteri cancer is the fourth most common cancer in women worldwide and the most common cancer affecting women in sub-Saharan Africa, Central America and south-central Asia.[1]

The incidence of cervical cancer in Saudi women is low. The current estimates indicate that 152 women are newly

diagnosed with cervical cancer and 55 women will die from their disease in Saudi Arabia annually.[2,3]

High dose rate intracavitary brachytherapy (HDR-ICBT) in combination with external beam irradiation (EBRT) is the standard treatment for localized cervix uteri cancer.[4,5]

The National Cancer Institute (NCI) issued an alert in 1999 after the publication of five trials recommending that concomitant chemo-radiotherapy should be considered instead of radiotherapy alone in women with cervical cancer. This alert led to a worldwide change in the treatment of cervix uteri cancer.[6,7] Two subsequent reviews reported improvements in survival, progression-free survival and recurrence rates with the use of chemo-radiotherapy.[8,9]

The Cochrane Gynecological Group performed a meta-analysis and reached the following conclusions: there was a 6% improvement in 5-year survival rates with chemo-radiotherapy (hazard ratio [HR] = 0.81, $P \leq 0.001$); and significant survival benefit for platinum-based (HR = 0.83, $P = 0.017$) and non-platinum based (HR = 0.77, $P = 0.009$) chemo-radiotherapy. Chemo-radiotherapy also reduced local and distant recurrence and improved disease-free survival.[10]

This study evaluated the survival outcome, pattern of failure and prognostic factors of the use of EBRT with or without chemotherapy and HDR-ICBT in cervix uteri cancer patients in the Saudi population.

METHODS AND MATERIAL

The medical charts of 60 patients with newly diagnosed cervix uteri cancer who were treated between January 2004 and December 2010 at the radiation oncology department of King Faisal Specialist Hospital and Research Center, Jeddah and King Abdulaziz University Hospital, Jeddah, Saudi Arabia, were retrospectively reviewed and analyzed.

All patients were initially evaluated by clinical examination under anesthesia (EUA), biopsy with cystoscopy and proctoscopy, computerized tomography (CT) scan and/or magnetic resonance images (MRI) of the pelvis, and underwent appropriate staging work ups (e.g., chest X-ray, CT chest, abdomen, and bone scan). Basic laboratory examinations (e.g., CBCD, renal profile and hepatic profile) were performed for all patients.

Treatment began with external beam radiotherapy (EBRT) using four fields (AP-PA and two lateral), a high-energy photon beam (15–18 MV) for a dose of 45 Gy in 25 fractions for 5 weeks. Planning was done using the Eclipse planning system. Dose volume histograms were generated for the rectum and bladder. EBRT was given concurrently with weekly intravenous Cisplatin (40 mg/m^2) unless contraindicated.

HDR-ICBT began within 1 week of EBRT completion. The applicator was inserted under general anesthesia. The HDR-ICBT schedule before 2006 was 6 Gy weekly for 4 weeks with the dose prescribed to point A. The schedule was changed to 7 Gy weekly for 3 weeks because of a tight anesthesia schedule and to shorten the overall treatment time.

MRI/CT-compatible Fletcher Suit Device (FSD) was used with a central tandem and two ovoids of different sizes according to the patient's geometry. Treatment was delivered using a high dose rate (HDR) remote after loading of the brachytherapy machine using a single Iridium192 source (^{192}Ir). Planning was done using Brachy-Vision, V.7.3.10. Orthogonal films were used until 2006. CT-based planning became the standard practice in our department after the establishment of the CT simulator in 2007. Each fraction was delivered with a separate plan.

Point A, which was the point doses for the rectum and bladder, were determined according to ICRU 38 [11] and used for orthogonal film calculation. GEC-ESTRO recommendations were used for three-dimensional planning using 2 cc of the bladder and rectum CT volumes instead of the ICRU points [12] for the reporting of bladder and rectum doses. Patients were seen weekly during treatment to assess acute side effects with weekly CBCD and renal profiles.

Regular follow-up was performed every 3–4 months after treatment. Pelvic MRI was performed every 6 months for the 1st 3 years, then annually. Cervical cytology was performed 3–4 months after the end of radiotherapy, every 6 months for the 1st 3 years, then annually. The median follow-up period was 24 months (range: 6–77 months).

STATISTICAL METHODS

The Statistical Package for Social Science program version 16 (SPSS, Chicago, IL, USA) was used for analysis. Survival rate was calculated using the Kaplan–Meier method.[13] The log-rank test evaluated the prognostic factors. Univariate analysis (UVA) was performed using the Cox proportional hazards regression model [14] for age, FIGO stage, tumor grade, pathological type, lymph node, pretreatment Hb level, vaginal infiltration, parametrial extension, fractionation of the HDR-ICBT, orthogonal versus CT planning of the brachytherapy and the use of chemotherapy. Multivariate analysis (MVA) was performed for the significant and borderline significant

factors in UVA. P value < 0.05 was considered statistically significant. DFS, loco-regional control (LRC), DMFS, and OS were measured from the time to diagnosis (biopsy) until the time of the events, relapse (loco-regional and/or distant) or death. Acute and late reactions were recorded using RTOG/EORTC criteria.[15]

RESULTS

Forty-seven patients (78%) received Cisplatin concomitant with EBRT, and 13 patients (22%) received EBRT alone because of their medical problems (e.g., impaired renal function or advanced age). These patients included 9, 2, 1 and 1 patients in stages IIB, IB, IIIB and stage IVA disease, respectively (Table 1).

Eleven patients (18%) received HDR-ICBT at a dose of 6 Gy, four times, for a total dose of 24 Gy (up to 2006). From 2007 onwards, 45 patients (75%) received a dose of 7 Gy, three times, for a total dose of 21 Gy. Four patients (7%) received a dose of 9 Gy, twice, for a total dose of 18 Gy. These patients were elderly, and they were risky for repeated general anesthesia.

A total of 187 applications were performed in our 60 patients. The mean dose to point A was 6.9 ± 1.1 Gy per fraction, the difference between Point A right relative to point A left was greater than 10% in six patients (10%), and the difference was less than 10% in the remaining 54 patients (90%).

The mean total physical dose to the point A from HDR-ICBT was 21 ± 3.8 Gy, and the mean total physical dose to point A from EBRT was 45 ± 4 Gy.

The maximal point dose to the bladder from EBRT and HDR-ICBT ranged between 49.4 and 68.1 Gy, with a mean value of 57.7 ± 4.3 Gy.

The maximal point dose to the rectum from EBRT and HDR-ICBT ranged between 49.1 and 65.2 Gy with a mean value of 56.2 ± 4 Gy.

Conversion of these physical doses to the biologically effective dose was performed using the linear quadratic model. The iso-effective total dose (EBRT+ HDR-ICBT) and EQD2 (total doses given in 2 Gy and α/β of 10 Gy for the tumor and 3 Gy for the rectum and bladder) was equivalent to 74.9 Gy to point A (mean dose), 73.1 Gy was the maximal dose to the bladder, and 67.4 Gy was the maximal dose to the rectum.

The following constraints were used for the bladder and rectum during the HDR-ICBT application in orthogonal planning: the bladder ICRU point received less than 80% of the prescribed dose, and the rectum ICRU point received less than 70% of the prescribed dose. The following constraints in the CT-based planning were used: the 2 cc of the bladder and 2 cc of the rectum CT volumes received less than 80% and 70% of the prescribed dose, respectively.

Surgery with total abdominal hysterectomy and bilateral salpingo-oophorectomy was performed after HDR-ICBT in four patients after 4–6 weeks because of the radiological persistence of bulky disease after HDR-ICBT. No residual tumor was detected pathologically in one patient. However, the residual tumor site in the other three patients was detected in the cervix in one patient, the cervix and pelvic lymph nodes in another patient, and the cervix, pelvic lymph nodes and para-aortic lymph node in the third patient.

All patients tolerated their treatment well without reported acute grade 3 or 4 skin, urinary, rectal, gastrointestinal or hematological toxicities. Most patients reported grade 1 or 2 reactions, and they were treated with appropriate supportive measures.

Three patients (5%) developed late urinary reactions in the form of grade 1 or 2 dysuria, increased frequency of micturition with radiological thickening of the bladder wall. However, no grade 3 or 4 late urinary bladder reactions were reported.

Six (10%) patients had late rectal reactions: grade 1 or 2 in four patients (7%), and grade 3 or 4 in two patients (3%). One patient developed grade 3 proctitis, and another patient developed recto-vaginal fistula (grade 4). Vaginal adhesion was reported in only one patient (1.7%).

Fifteen patients (25%) relapsed during the follow-up period. Five patients had isolated loco-regional recurrence, and 10 patients had loco-regional recurrences associated with distant relapse simultaneously. The median time to relapse was 22 months (range 2–69 months). Nine patients (15%) died of their disease at the end of the follow-up period, 4–6 months after relapse and progression of their disease. The median time to death from diagnosis was 12 months (range, 6–24 months). The 2- and 4-year OS rates were 82% and 79%, respectively (Table 2).

Three patients underwent salvage surgery for their loco-regional recurrence. Palliative radiotherapy to the brain and bone was given to four patients, and palliative chemotherapy was used in two patients. Only supportive treatment was given to six patients because of their poor general condition (Tables 3 and 4).

The UVA analysis revealed that pretreatment Hb level <10 mg /dL ($P = 0.008$), overall treatment time greater than 56 days ($P = 0.039$) and the presence of advanced stages ($P = 0.044$) were significant negative prognostic factors for OS. The OS in patients with pretreatment

Table 1 Patient characteristics (60 patients, 100%)

Age	Mean 49 years (range 31–85 years) ($n = 60$)		
ECOG performance status [16]	0	5	8%
	1	53	88.5%
	2	2	3.5%
Pathological type	Squamous	50	83%
	Adeno-carcinoma	6	10%
	Others	4	7%
Pathological grade	Grade 1	12	20%
	Grade 2	30	50%
	Grade 3	12	20%
	Grade 4	6	10%
FIGO stage	IB	3	5%
	IIA	2	3%
	IIB	41	69%
	IIIA	3	5%
	IIIB	9	15%
	IVA	2	3%
Lymph node (LN)	Pelvic LN	22	37%
	Para-aortic LN	5	8%
	both	1	2%
	No LN	32	53%
Vaginal extension	Yes	14	23%
	No	46	77%
Parametrial infiltration	Unilateral	38	63%
	bilateral	10	17%
	No parameterial	12	20%
Mean pretreatment Hb	11 ± 1.5 g/dL (range 7–14)		
	≤10	15	25%
	10.1–12	31	52%
	>12	14	23%
Mean EBRT dose	45.8 Gy ± 2		
	45 Gy	52	89%
	50 Gy	8	11%
Brachytherapy techniques	Orthogonal planning	29	48%
	CT based planning	31	52%
HDR-ICBT schedule	6 Gy × 4	11	18%
	7 Gy × 3	45	75%
	9 Gy × 2	4	7%
Mean point A dose	21 Gy ± 3.8		
Chemotherapy	Yes	47	78%
	No	13	22%
Over all treatment time	≤56 days	16	17%
	>56 days	44	73%

Hb levels <10 mg/dL was 80%, and OS was 85% for patients with Hb levels ≥10 mg/dL ($P = 0.008$). Patients with an overall treatment time longer than 56 days had lower survival than patients who completed their treatment within 56 days (75% *vs* 89%, $P = 0.039$).

The OS in patients with stages III and IV was lower than the OS in patients with stage IIB (77% *vs* 87%, $P = 0.044$). None of the factors significantly affected OS in MVA.

The OS of patients who received concurrent chemotherapy and radiotherapy therapy compared to the

Table 2 Mean survival times (±standard error [SE] and [95% confidence interval, CI]) were estimated using the Kaplan–Meier procedure and SE for cumulative survival proportions at 2 and 4 years

Event	*N*	Mean survival times (MONTHS)	SE†	95% CI
Death	9	64.84	3.64	57.7–72.0
Relapse (total)	15	51.80	3.80	44.4–59.3
Loco-regional	15	51.72	3.83	44.2–59.2
Distant	10	64.27	3.90	56.6–71.9

		2 years cumulative survival		4 years cumulative survival	
Event/Hazard	*N*	Proportion (%)	SE†	Proportion (%)	SE†
Death	9	82	0.053	79	.064
Relapse (total)	15	80	0.054	70	.073
Loco-regional	15	78	0.058	70	.072
Distant	10	82	0.054	79	.063

† Mean (±SE [95% CI]) survival times and standard errors of cumulative survival proportions were estimated using the Kaplan–Meier procedure.

patients received radiotherapy alone was 87% versus 77% ($P = 0.220$), and the rate of relapse was 21% versus 38%, respectively ($P = 0.153$).

The 2- and 4-year DFS rates were 80% and 69%, respectively. Vaginal infiltration was the only negative predictor factor for relapse in the UVA. The incidence of relapse was 43% in patients with vaginal infiltration versus 20% in patients without infiltration ($P = 0.048$). MVA analysis revealed that the presence of the vaginal infiltration and the use of the orthogonal brachytherapy planning were the only significant factors that negatively affected DFS ($P = 0.032$ and 0.049, respectively). The rate of relapse was 38% in patients treated with orthogonal planning versus 13% in patients treated with CT-based planning.

The 2- and 4-year LRC rates were 78% and 70%, respectively, and the median time to loco-regional recurrence was 19 months (range: 2–69 months). The presence of vaginal infiltration emerged as the only negative prognostic factor in the UVA for loco-regional control rate. The LRC was 57% versus 80% in patients with versus without vaginal infiltration ($P = 0.045$).

The 2- and 4-year DMFS rates were 82% and 78%, respectively. Patients with tumor grade 3 or 4 had a higher incidence of distant metastases (35%) than patients with grade 1 or 2 (9%) in the UVA ($P = 0.037$). None of the factors were significant for the LRC or DMFS in MVA.

DISCUSSION

This study evaluated the efficacy of definitive radiotherapy (EBRT and HDR-BT) with and without chemotherapy and the prognostic factors in 60 patients with cervix uteri cancer (Table 5).

The OS in patients with pretreatment Hb levels <10 g/dL was 80% versus 85% for patients with Hb levels ≥10 mg/dL in the current study ($P = 0.008$). This result is consistent with the results of Teh *et al.*,[26] who found that the nadir and pretreatment Hb levels less than 10 g/dL were associated with poorer DFS and OS. However, Parker *et al.*[19] did not find any association between Hb levels and prognosis in their study. This difference may be attributed to their practice of transfusing patients when Hb levels dipped below 11 g/dL. Chen *et al.* reported similar results.[22]

One proposed hypothesis for the lower therapeutic effect in patients with low Hb levels is that low Hb results in tumor hypoxia, which increases radio-resistance. A different potential mechanism of action is that the anemia was a result of a more biologically aggressive disease due to bleeding and the release of cytokines that suppresses erythroid progenitor cells and/or impair the response of erythroid progenitors to erythropoietin.[23] The reversal of anemia using blood transfusion is of great interest, and blood transfusion in patients with anemia remains the standard of care in certain institutions despite the conflicting evidence.[17]

Prolonged overall treatment time also impacts disease control because of an accelerated repopulation of clonogenic cells during radiotherapy.[18] Perez *et al.*[24] retrospectively reviewed 1224 patients in stage IIB–III and found that treatment prolongation significantly reduced pelvic tumor control by 0.85% daily over 7 weeks.

Table 3 Univariate regression analysis of survival and relapse predictors (Cox regression)

Covariate (predictor)	Death		Relapse (loco-regional or distant)		Loco-regional relapse		Distant relapse	
	B (coeff.)	*P*-value	*B* (coeff.)	*P*-value	*B* (coeff.)	*P*-value	*B* (coeff.)	*P*-value
Patient factors								
Age (≤50 years *vs* >50 years)	−0.813	0.443	−0.223	0.730	−0.206	0.750	−0.170	0.830
Pretreatment HB level (≤10 *vs* >10)	2.196	**0.008**†	−1.377	0.184	−1.396	0.178	−3.388	0.301
Performance status (0 *vs* 1)	−0.454	0.669	0.208	0.841	0.225	0.829	−0.265	0.802
Tumor factors								
Pathology type (squamous *vs* others)	−0.510	0.631	0.240	0.710	0.237	0.713	−0.705	0.504
Stage (IB1–IIA *vs* IIB *vs* III–IV)	1.274	**0.044**†	0.393	0.448	0.390	0.451	0.056	0.929
Pathological grade (1 and 2 *vs* 3 and 4)	0.116	0.870	0.807	0.119	0.820	0.113	1.350	**0.037**†
Parametrial invasion (yes *vs* no)	3.320	0.372	3.338	0.254	3.340	0.252	3.336	0.335
Lymph node positive (yes *vs* no)	0.908	0.199	−0.906	0.099‡	0.910	0.970	0.692	0.285
Vaginal extension (yes *vs* no)	1.061	0.114‡	1.048	**0.048**†	1.061	**0.045**†	−0.550	0.426
Treatment factors								
Brachytherapy technique (orthogonal *vs* CT based)	−1.322	0.099‡	−1.065	0.071‡	−1.071	0.069‡	−1.504	0.057‡
Chemotherapy (yes *vs* no)	−0.874	0.220	−0.784	0.153	−0.797	0.147	−1.112	0.086‡
Overall treatment time (≤56 *vs* > 56 days)	−1.656	**0.039**†	−0.967	0.064‡	0−.974	0.062‡	−1.142	0.072‡

†Significant for *P*-value <0.050.
‡Predictor reanalyzed in multivariate model.

Treatment prolongation time more than 56 days in this study was associated with lower OS (75%) than in patients who completed their treatment within 56 days (89%; $P = 0.039$). Lim and Sia[17] found that a treatment time longer than eight weeks was significantly associated with increased relapse and death. Parker *et al.*[19] found that a minimum treatment time of 57 days subsequently reduced the number of HDR-ICBT from 4 to 3 by increasing the dose per fraction. This result is similar to our current treatment policy. We further attempted to reduce the treatment time by starting HDR-BT from the third or fourth week of EBRT if possible technically and omitting EBRT on the day of brachytherapy, as recommended by the American Brachytherapy Society (ABS).[25]

This study and others demonstrated that an overall treatment time longer than 8 weeks (56 days) was associated with an increased risk of relapse and decreased OS. This period is slightly longer than Perez *et al.*[24] However, patients in that group did not receive chemotherapy. The optimal overall treatment time in patients receiving combined chemotherapy and radiotherapy was not elucidated. It is not clear whether similar treatment time restrictions for radiotherapy alone should be used, but caution should be applied using this approach because of the potential for increased toxicity.[17]

The 2- and 4-year DFS rates in this study were 80% and 69%, respectively. Lim and Sia[17] reported that the 24- and 48-month DFS rates were 59.4% and 56.7%,

Table 4 Multivariate regression analysis of survival and relapse predictors (Cox regression)

Event (dependent variable)	Predictors	*B* (coeff.)	Significance (*P*-value)
Over all survival	Vaginal extension (− vs +)	0.788	0.262
	Overall treatment time (≤56 or >56 days)	0.0887	0.061
	Stage (IB1–IIA *vs* IIB *vs* III–IV)	1.272	0.060
	Pretreatment Hb level ≤10 *vs* >10 ng/dL	0.680	0.354
	Brachytherapy technique (orthogonal *vs* CT based)	−1.489	0.072
Relapse (loco-regional and/or distant)	Vaginal extension (yes *vs* no)	1.184	**0.032**†
	Lymph node positive (yes *vs* no)	0.0987	0.079
	Brachytherapy technique (orthogonal *vs* CT based)	−1.190	**0.049**†
	Overall treatment time (≤56 days *vs* >56 days)	−0.590	0.264
Loco-regional relapse	Vaginal extension (yes *vs* no)	1.077	0.110
	Brachytherapy technique (orthogonal versus CT based)	−0.700	0.192
	Overall treatment time *(≤56 vs > 56 days)*	−1.029	0.084
Distant relapse	Pathological grade (1 and 2 *vs* 3 and 4)	1.077	0.110
	Brachytherapy technique (orthogonal *vs* CT based)	−0.851	0.187

†Significant for *P*-value <0.050.

Table 5 Summaries of the previously published series of chemo-radiotherapy incorporating HDR-BT in cervix uteri cancer patients

Study	Country	Numberof patients	FIGO stage I–IV patients	OS (%) (5 years unless stated)	LRC rate (%) (5 years unless stated	Median follow-up in, months	Grade 3 or 4 late reaction
Lim A and Sia S 2011 [17]	Western Australia	69	18, 28, 17, and 1	61(4 years)	70.1 (4 years)	27	4(5.8)
Teh *et al.* 2010 [18]	Singapore	120	7, 53, 36, and 4	65	81.7	50	5(4%)
Parker *et al.* 2009 [19]	UK	92	8, 63, 26, and 0	55	67	26	4(4%)
Atahan *et al.* 2007 [20]	Turkey	100†/183	10, 64, 26, and 0	55	74	45	8(8%)
Novetsky *et al.* 2007 [(21]	United Sates	100	60 (I and II) and 40 (III and IV)	82	88% for stage I and II, 65% for stage III/IV	42	5(6%)
Chen *et al.* 2006 [22]	Taiwan	70	0, 69, 31, and 0	74 (4 years)	87%	43	11(14.3%)
This study	Saudi Arabia	60	3, 43, 12, and 2	79 (4 years)	70 (4 years)	24	2(3%)

†100 of 180 patients received concomitant chemo-radiotherapy.

respectively. Teh *et al.* demonstrated that the 5-year DFS was 57.3%.[18]

Vaginal infiltration was a negative predictive factor for relapse in this study. The incidence of relapse was 43% in patients with vaginal infiltration versus 20% in patients without infiltration ($P = 0.038$). Atahan *et al.*[20] found that vaginal infiltration was associated with a nonsignificant increase in loco-regional relapse and nonsignificant decreases in DFS and OS.

The LRC rates at 2 and 4 years were 78% and 70%, respectively, and the 2- and 4-year distant metastasis-free survival rates were 82% and 78%, respectively. Chen *et al.*[22] reported slightly superior results; the 4-year pelvic relapse and distant metastases-free survival rates were 87% and 75%, respectively. Parker *et al.*[19] reported 5-year local control and distant control rates of 67% and 48%, respectively. In contrast, Novetsky *et al.* reported a superior 5-year distant control rate of 92%, compared to a 5-year local control rate of 80%.[21]

No significant differences in OS and rate of relapse rates were observed between patients who received concurrent chemotherapy and radiotherapy therapy and patients who received radiotherapy alone in this study (had an of 87% *vs* 77%, $P = 0.220$ and 21% *vs* 38%,

$P = 0.153$, respectively). However, the small sample size did not preclude the significance level. Improvements in OS and DFS with the use of chemotherapy with radiotherapy confirmed the meta-analyses results of the NCI and the Cochrane Gynecological Group.[8–10]

Fifteen patients (25%) in this study relapsed during the follow-up period, and five of these patients (8%) developed loco-regional relapse alone. The other 10 relapsed patients (17%) suffered simultaneous loco-regional with systemic relapse.

This study revealed a relatively high proportion of loco-regional recurrence. Fifteen of our 60 patients (25%) exhibited loco-regional recurrence, with most of the relapse occurring at the primary site. The reasons for this observation may be multifactorial. The failure at the primary site despite completion of the planned brachytherapy may reflect inadequate brachytherapy target volumes or target dose. The HDR-ICBT dose was prescribed to point A before 2007, and planning was based on the orthogonal films and standard two-dimensional planning. Therefore, the dose prescribed may not have adequately encompassed the tumor volume. MVA analysis demonstrated that orthogonal-based planning was a predictor for relapse in our patients ($P = 0.049$). The use of CT-based planning significantly reduced the rate of relapse (from 38% with orthogonal planning to 13% with CT-based planning). This difference may be further improved using MRI to ensure that the brachytherapy treatment volume sufficiently encompasses the tumor.

Potter *et al.*[26] described the impact of MRI-based brachytherapy planning on clinical outcome. Patients who underwent MRI-based planning had a 3-year continuous complete remission rate of 92%, compared with 83% in the group that did not use MRI, and greater benefit was observed in tumors larger than 5 cm. This result was also reflected in the 3-year OS rates, which were 58% and 28% in the MRI-based group compared to the group that did not undergo MRI planning, respectively.

The total dose to point A could be another factor for loco-regional failure. The calculated dose to point A in our current regimen was 74.9 Gy biologically (EQD2) to high-risk (HR) volume, which is lower than the dose recommended by the ABS and GEC-ESTRO recommendations (range of 85–90 Gy). One way to overcome this low dose is to increase the fraction number to 4×7 Gy or increase the dose of the fraction to 8-8.5 Gy x 3F. Huerta[27] used a schedule of 8.5 Gy x 3 fractions in 116 cervix uterine cancer patients and demonstrated no significant difference in the late morbidity compared to traditional fractionation schemes.

Our results demonstrated that vaginal infiltration was the only significant factor for loco-regional failure in the UVA. This result means that our use of the standard FSD applicator, which has limitation of delivering the optimal dose to the disease site, should be revisited. The use of applicators that allow better optimization, especially in the direction of the vaginal infiltration and parametrium, is encouraged.

CONCLUSION

Our retrospective study has an inherent bias, but it displayed the efficacy of radiotherapy (EBRT and HDR-ICBT) with or without chemotherapy in our cancer cervix patients with acceptable rectal and bladder toxicities. The relevant prognostic factors for LRC and survival are consistent with the published literature. Local and distant failures are not solved in this group of patients, and ongoing research and advances in image-guided (MRI based HDR-ICBT) and intensity-modulated radiotherapy and progress in systemic therapy are promising methods in the future. The limitations of this study are the small sample size with the wide range of tumor stages treated and the inclusion of different methods of brachytherapy fractionation and planning methods. These concerns limit the results of the multivariate analysis. National studies that include data from across the country and all the centers are highly appreciated and desired.

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