Original Article

Long-Term Outcomes after Concurrent Chemoradiotherapy in Cervical Cancer

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Objective: To assess long-term survival outcomes and to identify prognostic factors for patients with cervical cancer treated with concurrent chemoradiotherapy [CCRT].

Materials and Methods: Cervical cancer patients who had CCRT in the Radiation oncology Unit, Department of Radiology, Faculty of Medicine Vajira Hospital between 2001 and 2017 were identified. Survival rate of the patients was analyzed by Kaplan-Meier method. Association between clinic-pathologic factors and survival were also studied using the log-rank test and Cox models.

Results: A total of 1310 cervical cancer patients were included in this study. The 5-year and 10-year disease free survival rates were 71.7% and 70.5%, respectively. The corresponding-5-year and 10-year overall survival rates were 74% and 68.5%, respectively. The 10-year overall survival decreased as stage advanced from 83.1% in stage I to 77.1%, 56.3% and 49.6 in stage II, III and IV, respectively. The poor factors which significantly associated with a lower survival rate included higher tumor grade, pre-treatment hemoglobin level <12g/dl, and higher clinical stage.

Conclusion: Cervical cancer patients who were treated with CCRT had a favorable long-term survival outcome. Survival rates did not change much between 5 and 10 years. Grade, hemoglobin level and clinical stage of cancer were significant prognostic factors for survival outcome.

Keywords: Cervical cancer, CCRT, Long term outcome

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Cervical cancer is the 9th most common cancer and is a major health problem for women worldwide. A global annual incidence of cervical cancer in 2015 was 526,000 new case with 239,000 deaths[1]. In Thailand, it is the second most common cancer with an estimated incidence rate of 14.4100,000 women and is the most common leading cause of cancer death among women[2].

Cervical cancer is a highly curable disease when discovered at early stage. Other prognostic factors aside from stage of cancer are age, tumor size, histology, pre-treatment hemoglobin levels and treatment modality[3-8]. Treatment for patients with non-bulky early stage disease can be treated with surgery or radiotherapy with yield comparable survival or recurrence outcomes[9]. On the other hand, the standard treatment for bulky early stage disease as well as locally advanced stage disease is concurrent chemoradiotherapy [CCRT] which has significant survival benefit over radiotherapy [RT] alone[10-16].

The present study assessed long-term outcomes of patients with cervical cancer who were treated with CCRT. Prognostic factors for survival were also studied.

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Materials and Methods

Study sample

The study was approved by the Ethics Committees of the institution. Patients diagnosed with

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cervical cancer and were treated by CCRT in the Radiation oncology unit, Department of radiology, Faculty of Medicine Vajira Hospital between 2001 and 2017 were identified. Inclusion criteria were patients who had stage IB2-IVA and completed CCRT. All patients were staged according to the FIGO 2009 staging system. The patients were excluded if they had; histopathology of neuroendocrine; clear cell or adenoid cystic carcinoma; history of cancer in others organ; uncontrolled medical illness, e.g. chronic renal failure; or HIV infection. The characteristics features of the patient, tumor and details of treatment were collected from the patient's medical record.

Treatment modalities

All patients were treated with chemotherapy concurrent with pelvic radiation. Radiation therapy was a combination of external beam radiotherapy and brachytherapy. Total dose given to point A was 80 to 90 Gy calculated based on EQD2Gy external beam plus EQD2Gy HDR brachytherapy. The chemotherapy drug was either single platinum agent or platinum containing combination regimens.

Outcome assessment

The primary outcomes were 5-year and 10-year overall survival [OS]. The secondary outcomes were 5-year and 10-year disease free survival [DFS], prognostic factors for survival, and complication rates. OS was obtained from the first day of treatment to the date of death from all causes or last follow-up. DFS was calculated from the first day of treatment until the date of disease progression, recurrence, or right-censored at the time of the last follow-up.

Acute complication of gastrointestinal system [GI] and genitourinary system [GU] were graded by the radiation oncologist during a course of treatment until 6 months after the completion of therapy. Late complications were graded after 6 months of treatment. All toxicities were recorded according to RTOG/EORTC toxicity criteria[18].

Statistical methods

Statistical analysis was performed with SPSS statistical analysis for Windows version 22.0 (IBM Corp, Armonk, NY). DFS and OS were analyzed by Kaplan-Meier method and were compared between groups with log-rank test. A value of $p<0.05$ was considered statistically significant. Multivariate analysis was performed using Cox proportional hazards regression analysis in a forward stepwise manner with a p-value of 0.05 as inclusion.

Results

Patients and primary tumor characteristics

A total of 1310 patients were included in the study. Characteristics of the patients are shown in Table 1. The median age at diagnosis was 52 years (range, 22 to 88 years). The majority of patients (74.6%) were older than 45 years and 66.5% had pretreatment hemoglobin level below 12 g/dl. Stage IB, IIA, IIB, IIIA, IIIB, and IVA were found in the following frequency: 3.6%, 1.6%, 50.9%, 2.1%, 38.2% and 3.6% respectively. Tumor size was greater than 4 cm in 52.5% (n = 688). Squamous cell carcinoma was most commonly found, 81.5% (n = 1068) with adenocarcinoma of only 16% (n = 210). Eighty-one percent of patients had well or moderately differentiated tumors.

Treatment characteristics

Details of treatment which the 1,310 patients received are shown in Table 2. The chemotherapy given in concurrent with radiation were carboplatin in 60.1%

Table 1. Patient and tumor characteristic

Characteristic	No. of patients	%
All patients	1,310	100
Median age (range), years	52 (22 to 88)	
Lesser than 45 years	333	25.4
Greater than or equal to 45 years	977	74.6
Histology type		
Squamous cell carcinoma	1,068	81.5
Adenocarcinoma	210	16.0
Adenosquamous	32	2.5
Tumor grade		
Well differentiated	365	27.9
Moderate differentiated	699	53.3
Poorly differentiated	246	18.8
Pretreatment hemoglobin level		
Lesser than 12 g/dl	871	66.5
Greater than or equal to 12 g/dl	439	33.5
Mean tumor size (range), cm	4.67 (0.5 to 10)	
Lesser than or equal to 4 cm	622	47.5
Greater than 4 cm	688	52.5
FIGO Stage		
IB2	42	3.6
IIA	21	1.6
IIB	667	50.9
IIIA	28	2.1
IIIB	501	38.2
IVA	47	3.6

and cisplatin in 39.9%. The median total treatment duration was 56 days (range, 33 to 129 days) and went beyond 56 days in 42.6%. The mean EBRT dose and mean total dose at point A EQD2 were 54 Gy (range, 43 to 60 Gy) and 30.72 Gy (range, 19.5 to 48 Gy) respectively.

Treatment outcomes

The median follow-up time was 89 months (range, 6 to 188 months). Recurrences were encountered in 350 patients (26.7%); 60 (17.1%) of the recurrences were loco-regional, 245 (70%) were distant, and 45 (12.9%) were combined loco-regional and distant. The results are summarized in Table 3. The 5-year and 10-year DFS rate were 71.7% and 70.5%, respectively.

During the follow-up period, 310 (23.7%) patients died. Approximately half of all deaths occurred during the first 2 years after treatment. The 5-year and 10-year OS rates were 74% and 68.5%, respectively. Several factors were studied in association with the overall survival (Table 4). Factors which significantly associated with lower rate of survival were: pretreatment hemoglobin level <12g/dl, higher clinical stage, tumor size >4 cm, and higher tumor grade. By a multivariate Cox regression analysis, we found tumor grade, pre-treatment hemoglobin level and clinical stage were statistically significant prognostic factors.

Table 2. Treatment delivered and complications

Characteristics	No. of patients	%
Concurrent chemotherapy		
Cisplatin	523	39.9
Carboplatin	787	60.1
Median RT duration (range), days	56 (33 to 129)	
Lesser than or equal to 56 days	752	57.4
Greater than 56 days	558	42.6
Mean total EBRT dose (range), Gy	54 (43 to 60)	
ICRT		
Mean total point A dose (range), Gy	30.72 (19.5 to 48)	
Mean bladder point dose, Gy	18.32 (6.66 to 33.38)	
Mean rectal point dose, Gy	19.28 (10 to 36)	

Table 3. Treatment outcomes

	No. of patients	%
Complete response		
Yes	1,298	99.1
No	12	0.9
Recurrence		
No	960	73.3
Loco-regional	60	4.6
Systemic	245	18.7
Combined loco-regional and systemic	45	3.4
Site of systemic failure		
Supraclavicular lymph node	49	3.7
Lung	41	3.1
Liver	25	1.9
Intra-abdomen	111	8.5
Bone	23	1.8
Multiple site	41	3.1

Treatment complications

Treatment related complications are shown in Table 5. Radiation toxicities ranged from 0.5% to 20.9%. Majority of the complications were mainly grade 1 or 2. Only 33 out of 461 (2.5%) gastrointestinal events and 7 out of 150 urologic events (0.5%) were grade 3 and grade 4.

Discussion

The median age of 52 years of our patients was close to data reported by the US surveillance, epidemiology, and end results program [SEER] statistics which showed the median age of 49 years. Our study also found squamous cell carcinoma (SCC) as the most common histopathology similar to previous reports which found 70 to 80% of cervical cancer were SCC[18,19]. Approximately half of our patients had stage IIB and nearly 40% had stage IIIB. Other previous studies also found these stage IIB and stage IIIB were more common[11,12]. Kid et al conducted a retrospective study of 560 cervical cancer patients with stage IA-IVB also found that IIB and IIIB were most common[20].

The 5-year and 10-year DFS rates in our study were 72% and 71% whereas the 5-year and 10-year OS rates were 74% and 69%. These rates were in the ranges which were reported in other studies[11-29]. The long-term analysis of this study demonstrated that the PFS and OS were rather stable after 5 years. These finding supported the standard surveillance program that longer interval of only annual follow-up after 5 years is recommended[12,18,19].

Various pathological and clinical features are recognized as prognostic factors in cervical cancer, such as, such as pretreatment hemoglobin level, clinical stage, tumor size, tumor histopathology, grade and overall treatment period[3-8]. In the present study, tumor grade, pretreatment hemoglobin level and clinical stage

Table 4. Univariate and Multivariate Cox analysis of Characteristic associated mortality

Factor	5-year OS (%)	10-year OS (%)	Univariate analysis	Multivariate analysis	
			p-value	HR	95% CI
Age			0.146		
Lesser than 45 years	75.8	68			
Greater than or equal to 45 years	73.6	68.9			
Histology type			0.116		
Squamous cell carcinoma	75	69.2			
Adeno & Adenosquamous	68.1	65.3			
Tumor grade (Gr1-2 vs. Gr3)			<0.001	1.28	1.13 to 1.45
Well differentiated	85.3	84.2			
Moderate differentiated	71.7	68.7			
Poorly differentiated	62.6	44.4			
Pretreatment hemoglobin level			<0.001	0.76	0.59 to 0.99
Lesser than 12 g/dl	71.8	64.6			
Greater than or equal to12 g/dl	78.5	76.4			
Mean tumor size (Range), cm			<0.001	1.14	0.9 to 1.46
Lesser than or equal to 4 cm	79.7	73.2			
Greater than 4 cm	68.5	64.1			
FIGO Stage (I & II vs. III & IV)			<0.001	2.32	1.79 to 3.01
Stage I	83.1	83.1			
Stage II	82.2	77.1			
Stage III	61.4	56.3			
Stage IV	59.6	49.6			
Chemotherapy regimen			0.785		
Cisplatin	74.7	70.9			
Carboplatin	68.5	68.9			
Treatment duration			0.666		
Lesser than or equal to 56 day	72.7	68			
Greater than 56 day	75.7	68.9			

Table 5. Gastrointestinal and urologic adverse events

Characteristic	No. of patients	%
Acute toxicity		
Gastrointestinal tract Gr 1-2	154	11.8
Genitourinary tract Gr 1-2	32	2.4
Late toxicity		
Gastrointestinal tract Gr 1-2	274	20.9
Gastrointestinal tract Gr 3-4	33	2.5
Genitourinary tract Gr 1-2	111	8.5
Genitourinary tract Gr 3-4	7	0.5

were independent prognostic factors.

There is still a controversy regarding histology as an independent prognostic factor for survival. Many reports suggested that adenocarcinoma was associated with a worse prognosis with 10 to 20% lower 5-year OS rate than squamous cell carcinoma. In contrast, other reports showed no survival difference between the 2 histopathologic cell types[19]. In this present study, neither 5-year OS nor 10-year OS was affected by the histopathology.

Anemia is frequently found in cervical cancer patients. It has multifactorial causes: for instance, bleeding, iron deficiency, inflammation and infection which were generally correlated with tumor stage. Anemia especially the hemoglobin level of less than 12 g/dl is a poor prognostic factor associated with a lower survival rate because the low oxygen level would impair the effect of radiation treatment. Also demonstrated in present series that the 10-year OS of patients with pretreatment hemoglobin level less than 12 g/ml was only 65% compared to 76% to those with higher hemoglobin level.

Theoretically, overall treatment duration is an important prognostic factor for patients treated with radiotherapy. The acceleration of the repopulation of tumor in cervical cancer can occur with a prolonged treatment duration, and it is important to keep this duration within a normal limit[21]. However, others reported that treatment duration had no significant impact on both OS and local relapse when treated with concurrent chemoradiation[22]. In this study, the OS was insignificantly affected by longer treatment duration (>56 days).

Study found survival rates decreased when the stages advanced. The 10-year overall survival rate for stage I, II, III and IV were 83%, 77%, 56% and 50%, respectively. Our findings confirmed that clinical stage is an important prognostic factor for overall survival rate[18].

Concurrent chemoradiation is the standard of care for locally advance cervical cancer. Many important randomized clinical trials (with long-term follow-up in some) have confirmed that concurrent chemoradiation reduced the risk of death up to 20% to 30% compared to radiation alone[10-15]. A systematic review and meta-analysis reported the chemotherapy yielded 6% absolute improvement in OS and 8% in DFS with the hazard ratios of 0.81 and 0.78 resepctively[16]. In the patients who may not tolerate cispaltin in the concurrent setting, carboplatin was an alternative option yielding no difference in OS than that found from cisplatin[16,23,24].

Regarding the late toxicity of radiation therapy, Nakano et al reported 10-year actuarial grade 3 to 5 complication rates: 4.4% in rectosigmoid colon, 3.3% in small intestine, and 0.9% in genitourinary tract[25]. Our study found 10-year grade 3 and 4 toxicity of only 2.5% gastrointestinal tract and 0.5% to genitourinary tract, respectively. These data should confirm low risk of late morbidities from CCRT.

Conclusion

Cervical cancer patients who were treated with CCRT had a favorable long-term survival outcome and toxicity. About 50% of all deaths occurred during the first two years. Treatment outcome did not change much between 5 and 10 years. Grade, hemoglobin level and clinical stage of cancer significantly affect the survival outcome.

What is already known on this topic?

The standard treatment for early stage bulky to locally advanced disease is concurrent chemoradiotherapy. Stage was the most important prognostic factors that survival rates are lower as stage advanced. Other prognostic factors are tumor size, histopathology, age, pretreatment hemoglobin levels and treatment modality.

What this study adds?

Tumor grade, pretreatment hemoglobin level and clinical stage are independent prognostic factors for survival of cervical cancer patients, After 5 years, the recurrence and deaths from cancer were not common with relatively unchanged 10-year survival rates from 5-year survival rates.

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Potential conflicts of interest

The authors declare no conflict of interest.

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