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ORIGINAL ARTICLE

The prognostic factors for locally advanced cervical cancer patients treated by intensity-modulated radiation therapy with concurrent chemotherapy

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KEYWORDS
cervical cancer;
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Background/Purpose: To identify the prognostic factors for locally advanced cervical cancer patients treated by intensity-modulated radiotherapy (IMRT) and concurrent cisplatin-based chemotherapy.
Methods: A total of 125 patients with stage IB2–III cervical carcinoma were treated with IMRT and concurrent cisplatin-based chemotherapy, plus high dose rate (HDR) brachytherapy between January 2004 and November 2010, in our institution. All patients received external irradiation of 45–54 Gy with the IMRT technique and concurrent cisplatin-based chemotherapy monthly or weekly. HDR brachytherapy of 20–30.5 Gy was prescribed to point A, as a local boost. Prognostic factors including age, histology, stage, lymph nodes metastasis, pretreatment hemoglobin level, serum squamous cell carcinoma antigen (serum SCC-Ag), chemotherapy regimens and the cumulative dose of weekly cisplatin, were analyzed. The endpoints were overall survival (OS), local failure-free survival (LFFS) and disease-free survival (DFS).
Results: The median follow-up time was 42 months. The 4-year OS, LFFS and DFS were 73.8%, 77.9% and 67.2%, respectively. Four (3.2%) patients developed ≥grade 3 acute gastrointestinal (GI) toxicity and 29 (23.2%) patients developed ≥grade 3 acute hematological toxicity. Five (4.0%) patients developed ≥grade 3 late GI toxicity and seven (5.6%) patients developed ≥grade 3 late genitourinary system toxicity. On univariate analysis, adenocarcinoma was a poor prognostic factor for OS ($p = 0.05$), LFFS ($p = 0.01$) and DFS ($p = 0.006$). Patients with lymph nodes metastasis at diagnosis had worse OS ($p = 0.02$). The high cumulative dose of cisplatin (>180 mg/m^2) had better OS ($p = 0.03$) and tended to have better survival on LFFS ($p = 0.13$) and DFS ($p = 0.10$). On multivariate analysis, adenocarcinoma was a significant independent

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prognostic factor for OS ($p = 0.001$), LFFS ($p = 0.005$) and DFS ($p < 0.001$). Initial lymph nodes metastasis was an independent predictor of OS ($p = 0.013$). Cumulative dose of weekly cisplatin significantly affected OS ($p = 0.041$), and high cumulative dose of cisplatin tended to have better LFFS ($p = 0.083$). Higher pretreatment hemoglobin level had better LFFS ($p = 0.034$).
Conclusion: Adenocarcinoma and lymph nodes metastases were poor prognostic factors for patients with locally advanced cervical cancer. Lower pretreatment hemoglobin level had poorer local control. Chemotherapy with a high cumulative dose of cisplatin tended to result in better survival.

Introduction

Five randomized studies[1–5] demonstrated that concurrent chemoradiotherapy (CCRT) improved overall survival (OS) and progression-free survival in patients with locally advanced cervical cancer. The use of radiotherapy with concurrent cisplatin-based chemotherapy has become the mainstay treatment in locally advanced cervical cancer.

Previous studies[6,7] on other pelvic malignancies found that intensity-modulated radiation therapy (IMRT) helped to achieve adequate target organ and lymph nodes coverage and decreased the dose to the small bowel, bladder and rectum. Traditional radiation therapy techniques, including three-dimensional conformal radiation therapy (3DCRT) with uniform radiation intensity and/or with simple beam fluence modifying devices, such as wedges, do not provide a method for sparing critical structures that push into and are partially or fully surrounded by a target or combination of targets. IMRT dose plan and treatment delivery used inverse or forward planning techniques for modulated beam delivery, and used a binary collimator, or with a conventional multileaf collimator (MLC) system, either sliding window (dynamic MLC) or step and shoot (segmented MLC) modes. IMRT had more conformal dose distributions of the radiation fields and reduction in the volume of critical organs. These advantages may diminish acute and late toxicity. However, the IMRT treatment had a longer treatment time than conventional radiotherapy and the possibility of organ motion. In our study,[8] we demonstrated that IMRT achieved good outcomes and was well tolerated, with favorable acute and late toxicity in locally advanced cervical cancer patients. In this retrospective study, we reviewed more patients and all patients received IMRT and high dose rate (HDR) brachytherapy; patients also had a longer follow up time. One purpose of our study was to demonstrate the longer treatment outcomes, including survival and toxicity, of IMRT with concurrent chemotherapy.

Many studies[9–15] have shown that some prognostic factors, such as concurrent cisplatin dose, histology, advanced stage, age, and anemia, have an effect on survival. Another purpose of this study was to identify the prognostic factors of cervical cancer and find the patients who need more aggressive treatment.

Methods and materials

Patients

A total of 125 stage IB2-III cervical cancer patients met the inclusion criteria, which were: (1) biopsy confirmation of adenocarcinoma or squamous cell carcinoma (SCC) of the cervix; (2) no evidence of distant metastasis initially; (3) completion of IMRT and concurrent cisplatin-based chemotherapy plus HDR brachytherapy boost; and (4) no previous surgery, chemotherapy or radiotherapy. All patients received definitive CCRT at the radiation oncology department of Taichung Veterans General Hospital in Taiwan, between January 2004 and November 2010. The pretreatment staging workup included a comprehensive medical history, clinical physical examination, bimanual pelvic and rectal examinations, cervical biopsy, a chest X-ray, diagnostic abdomen and pelvic computed tomography (CT) scan, complete blood cell count, blood chemistry profiles and serum SCC antigen (serum SCC-Ag). A positron emission tomography (PET) scan was elective for 20 patients with equivocal lymph node metastasis at CT scan. Magnetic resonance imaging was used for workup in two selected patients. The lymph node metastasis criteria including: (1) enlarged lymph node $\geq$0.8 cm and/or central necrosis on CT scan; (2) 2-deoxy-2-fluoro-D-glucose (FDG) increased uptake in the PET scan and compatible with the equivocal lymph node region by CT scan; and (3) the enlarged lymph node $\geq$0.8 cm and/or heterogeneous enhanced signal intensity on T1-weighted image, were considered as having clinical lymph node metastasis. Cystoscopy or proctoscopy was indicated if bladder or rectal invasion was suspected clinically. Clinical staging was defined according to the International Federation of Obstetrics and Gynecology (FIGO) staging system. Written informed consent was obtained from each patient before treatment. The study was approved by the Institutional Review Board at Taichung Veterans General Hospital.

IMRT technique and brachytherapy

All patients were scheduled to undergo IMRT and HDR intracavitary brachytherapy. The treatment planning system of Eclipse (Varian Medical Systems, Palo Alto, CA, USA) software program was used for treatment planning of IMRT. The IMRT treatment planning was delivered using a dynamic multileaf linear accelerator with photon energy of 10 MV. In general, a vacuum fixed pad was used to immobilize the patient and bladder filling was arranged before taking a CT image and daily treatment. The contrast-enhanced CT scan images were obtained using a radiopaque marker, to define the cervix and upper vagina before contouring. We checked the patients' position and V-films before IMRT treatment. If the patients could not fit the vacuum fixed pad, we would recheck the treatment centers and/or arrange repeat CT images and another IMRT plan.

Gross tumor volume (GTV) was defined as the cervix tumor and uterus. GTV-N was defined as pelvic lymph nodes ≥0.8 cm. The clinical target volume (CTV) of IMRT covered the pelvis and generally included a 0.5—1 cm margin to GTV radially, the upper half of the vagina, the parametrium and regional lymph nodes. The regional lymph nodes targeted by IMRT included the common iliac, internal iliac, external iliac and presacral area lymph nodes. The treatment field extended from the L4—5 interspace to 3 cm below the most distal vaginal or cervical site of disease. For 18 patients with enlarged para-aortic lymph nodes, the superior field border extended to the T12—L1 interspace. The CTV of para-aortic lymph nodes included enlarged para-aortic lymph nodes, plus a 0.5—1 cm margin radially and the vascular structures such as aorta and inferior vena cava.

The planned target volume (PTV) with a 0.7—1 cm margin superiorly, inferiorly, and radially, was given to the CTV. A total radiation dose of 50.4—54 Gy, 1.8 Gy/fraction, five fractions/week, was delivered to the GTV. GTV-N used a concomitant IMRT boost to 54—60 Gy to the involved lymph nodes. A dose of 45—48 Gy in 28—30 fractions was given to the CTV.

The dose constraint of normal tissues included the bladder, rectum and small bowel and colon. The rectum is usually defined as from the level of the anus to the sigmoid flexure and received a dose of V30 <40%. The small bowel loops and colon were outlined within the irradiated volume plus a 2 cm margin and a dose of V30 <15% was given.

The source used in HDR brachytherapy was iridium-192. A cumulative dose of 20—33.5 Gy to point A in four to seven fractions, two fractions/week, was prescribed. The median number of HDR brachytherapy was 6 fractions. The median day of IMRT and HDR brachytherapy was 64 days, ranging from 52 to 85 days.

Chemotherapy

Ninety-seven patients received concurrent weekly cisplatin 30—40 mg/m^2 and a maximum of six doses of cisplatin were given. The median cycle of weekly chemotherapy was five cycles, ranging from one to six cycles. All patients who received pelvic irradiation routinely received cisplatin 40 mg/m^2/week. Dose modifications of 30 mg/m^2/week might be prescribed for patients if: (1) patients received extended field irradiation; (2) Karnofsky performance status ≤70; (3) age ≥70 years old; and (4) grade 1 or 2 hematological toxicity occurred during chemoradiotherapy. If grade 3 or 4 hematological toxicity occurred, chemotherapy was held. Twenty-eight patients were treated with two courses of cisplatin 50—75 mg/m^2 day 1, plus fluorouracil 500—1000 mg/m^2 day 1～4, at weeks 1 and 5. Acute gastrointestinal (GI) and hematological toxicity of CCRT were assessed weekly using the Common Terminology Criteria for Adverse Events (CTCAE) v3.0. Dose modifications were prescribed for subsequent cycles, based on the acute toxicity grade. If a patient had grade 3 or 4 hematological toxicity, chemotherapy was held.

Statistical analysis

The endpoints were OS, local failure-free survival (LFFS) and disease-free survival (DFS). The OS was defined as the time from the initial date of CCRT, to the date of death from any cause or last follow-up. The LFFS was measured from the initial date of CCRT, to the date of any evidence of local recurrence or last follow-up. The DFS was calculated from the initial date of CCRT, to the date of any evidence of local recurrence, or distant metastasis or last follow-up. Survival analysis was estimated using the Kaplan-Meier method. A univariate comparison of subgroup survival curves was performed using the log-rank test. Age, histology, lymph node metastasis, the cumulative dose of weekly cisplatin, pretreatment hemoglobin level and stage were incorporated in the multivariate Cox proportional hazard model, to estimate the hazard ratio and 95% confidence intervals. The statistical analysis was performed using SPSS software, version 10.0. A p value <0.05 was regarded as statistically significant.

Results

Table 1 summarizes the patients' characteristics. The median age was 54 years, ranging from 29 to 77 years. One hundred and five patients had biopsy-proven SCC and 20 patients had adenocarcinoma. Ninety-four patients had clinically negative lymph nodes, and 31 patients had

Table 1 Patient characteristics (n = 125).

		No. of patients
Age	<54 y	58
	≥54 y	67
Histology	Adenocarcinoma	20
	Squamous cell carcinoma	105
Grade	3	77
	1 and 2	48
Tumor size	≤4 cm	52
	>4 cm	73
Clinical lymph node metastasis	Negative	94
	Pelvic node only	13
	Para-aortic and/or pelvic node	18
FIGO stage	IB2	6
	IIB	70
	IIIA	5
	IIIB	44
Serum SCC	<2 ng/mL	29
	≥2 ng/mL	76
Pretreatment hemoglobin level	≥11 g/dL	89
	<11 g/dL	36
Radiotherapy field	Pelvis	107
	Extended field	18
Point A dose	≤7440 cGy	58
	>7440 cGy	67
Chemotherapy	Monthly	28
	Weekly	97
Cumulative dose of weekly cisplatin	≤180 mg/m^2	50
	>180 mg/m^2	47

clinical pelvic and/or para-aortic lymph nodes involvement. Of 31 patients with clinical lymph node metastasis, 13 patients were pelvic lymph node metastasis only and received pelvic radiotherapy and 18 patients had enlarged para-aortic lymph nodes and received extended field radiotherapy. The cumulative dose of weekly cisplatin was calculated and the median cumulative dose of weekly cisplatin was 180 mg/m^2. We categorized patients into a high-dose chemotherapy group ($>$180 mg/m^2) and a low-dose chemotherapy group ($\leq$180 mg/m^2).

All patients completed the prescribed course of IMRT and concurrent chemotherapy, plus HDR brachytherapy boost. One hundred and eighteen patients (94.4%) had clinical complete response after external beam radiotherapy. Seven patients (5.6%) had persistent disease after external beam radiotherapy of 50.4 Gy and they completed the HDR brachytherapy course. Two (1.6%) still had residual tumor after the whole course of IMRT and HDR brachytherapy and they underwent salvage radical hysterectomy.

The median follow-up was 42 months, ranging from 5 to 92 months. The 4-year OS, LFFS, and DFS for all patients were 73.8%, 77.9%, and 67.2%, respectively. There were no treatment-related deaths in this study. At the end of follow-up, 35 patients (28.0%) experienced tumor relapse. Ten patients (8.0%) had locoregional recurrence, 12 patients (9.6%) experienced distant metastasis, and 13 patients (10.4%) had locoregional and distant metastasis. Of the 23 patients (18.4%) with locoregional relapse, primary site recurrence was the most common failure pattern. Of 18 patients who underwent extended field radiotherapy, one patient had para-aortic lymph node recurrence; of 107 patients received pelvis radiotherapy, two patients experienced para-aortic lymph nodes recurrence. Among the 25 patients (20.0%) with distant metastasis, distant metastasis sites included lung and mediastinum lymph nodes (8 patients), liver (5 patients), neck lymph nodes (3 patients), bone (4 patients), peritoneal (5 patients), and inguinal lymph nodes (2 patients). Of patients with distant metastasis, chemotherapy is the mainstay treatment. Of 10 patients with local regional relapse, three underwent salvage surgery and others received salvage radiotherapy or chemotherapy.

Acute toxicity was assessed weekly during radiotherapy and summarized in Table 2. Four patients (3.2%) developed $\geq$grade acute GI toxicity and 29 patients (23.2%) developed grade 3 or greater hematological toxicity. Table 3 showed late toxicity. Five patients (4.0%) developed $\geq$grade 3 chronic GI toxicity and seven patients (5.6%) developed $\geq$grade 3 genitourinary system toxicity.

Table 4 summarizes the univariate analysis. Adenocarcinoma was a significant prognostic factor of poor OS (Fig. 1, $p = 0.05$), LFFS ($p = 0.01$) and DFS ($p = 0.006$). Patients with lymph nodes metastases at diagnosis had worse OS (Fig. 2, $p = 0.02$). The higher cumulative dose of weekly cisplatin had better OS (Fig. 3, $p = 0.03$) and tended to be associated with better LFFS ($p = 0.13$) and DFS ($p = 0.10$). Advanced stage tended to have poor survival. The 4-year OS, LFFS and DFS for stage I + II and stage III were 76.2% versus 70.1% ($p = 0.35$), 80.4% versus 72.3% ($p = 0.59$) and 70.8% versus 60.7% ($p = 0.52$), respectively. The 4-year OS, LFFS and DFS for pretreatment hemoglobin level $\geq$11 g/dL and pretreatment hemoglobin level $<$11 g/dL were 74.6% versus 71.1% ($p = 0.94$), 81.0% vs. 69.5% ($p = 0.17$) and 70.1% vs. 59.3% ($p = 0.31$), respectively.

Table 5 summarizes the multivariate analysis. Adenocarcinoma was an independent factor of OS (HR = 7.83; 95% CI = 2.23–27.4; $p = 0.001$), LFFS (HR = 5.67; 95% CI = 1.68–19.1; $p = 0.005$) and DFS (HR = 6.47; 95% CI = 2.26–18.5; $p < 0.001$). The cumulative dose of weekly cisplatin was an independent predictor of OS (HR = 0.31; 95% CI = 0.10–0.63; $p = 0.041$) and higher cumulative cisplatin dose tended to be associated with better DFS (HR = 0.47; 95% CI = 0.19–1.16; $p = 0.102$) and LFFS (HR = 0.41; 95% CI = 0.15–1.12; $p = 0.083$). The lymph nodes metastasis was a significant predictive factor of OS (HR = 3.83; 95% CI = 1.33–11.0; $p = 0.013$). Pretreatment hemoglobin level was an independent factor for local control (HR = 0.33; 95% CI = 0.12–0.92; $p = 0.034$).

Table 3 Late toxicity of IMRT with concurrent chemotherapy ($n = 125$).

Grade	GI system	GU system
1	10	8
2	11	6
3	1	2
4	4	4
Total	26	20

GI = gastrointestinal; GU = genitourinary; IMRT = intensity-modulated radiotherapy.

Discussion

In this article, we had a longer median follow up time than a previous published study,[8] and all patients received uniform treatment, which consisted of IMRT with concurrent chemotherapy plus HDR brachytherapy.

Table 2 Acute toxicity of IMRT with concurrent chemotherapy ($n = 125$).

Grade	Nausea	Vomiting	Diarrhea	Dermatitis	Leukopenia	Anemia
1	18	9	27	8	21	18
2	3	1	9	5	39	15
3	0	0	3	3	28	0
4	0	0	1	0	1	1
Total	21	10	40	16	89	34

IMRT = intensity-modulated radiotherapy.

Table 4 Univariate analysis for OS, LFFS and DFS.

Parameter	Four-year rate (%)		
	OS	LFFS	DFS
Age			
<54 y (n = 58)	79.7	76.9	69.4
≥54 y (n = 67)	67.9	78.9	65.1
	p = 0.08	p = 0.66	p = 0.71
Histology			
Adenocarcinoma (n = 20)	47.2	55.4	45.3
SCC (n = 105)	77.4	83.9	71.3
	p = 0.05	p = 0.01	p = 0.006
Stage			
I + II (n = 76)	76.2	80.4	70.8
III (n = 49)	70.1	72.3	60.7
	p = 0.35	0.59	0.52
Lymph node metastasis			
Negative (n = 94)	79.1	78.0	70.0
Positive (n = 31)	56.4	78.7	58.1
	p = 0.02	p = 0.71	p = 0.13
Pretreatment hemoglobin level			
≥11 g/dL (n = 89)	74.6	81.0	70.1
<11 g/dL (n = 36)	71.1	69.5	59.3
	p = 0.94	p = 0.17	p = 0.31
Chemotherapy			
Monthly (n = 28)	78.3	86.3	70.6
Weekly (n = 97)	71.8	75.5	66.7
	p = 0.54	p = 0.19	p = 0.67
Cumulative dose of weekly cisplatin			
≤180 mg/m^2 (n = 50)	60.5	66.0	55.7
>180 mg/m^2 (n = 47)	81.9	84.7	77.2
	p = 0.03	p = 0.13	p = 0.10
Serum SCC-Ag			
≤2 ng/mL (n = 29)	68.8	75.8	63.8
>2 ng/mL (n = 76)	80.8	84.1	74.1
	p = 0.35	p = 0.33	p = 0.29

DFS = disease free survival; LFFS = local failure free survival; OS = overall survival; SCC = squamous cell carcinoma; serum SCC-Ag = serum squamous cell carcinoma antigen.

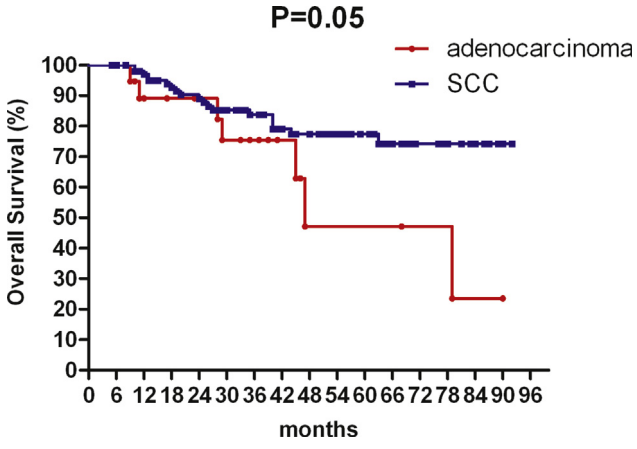

Figure 1 Overall survival (OS) according to histology.

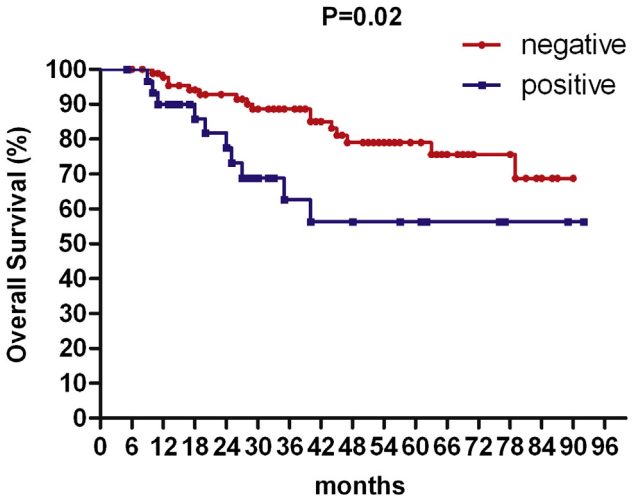

Figure 2 Overall survival (OS) according to lymph nodes metastasis.

The differences between IMRT and conventional radiotherapy are that IMRT has more conformal dose distribution and high dose gradients. These differences have potential benefits, including a higher dose to target and lower dose to critical organ, and may diminish acute and late toxicity. The theoretical drawbacks of IMRT are a longer treatment time, the possibility of organ motions, and the possibility of an inadequate coverage of targets. Patient immobilization, repeat check-up of patient positions and cautious target and critical organ delineation are important in IMRT treatment planning.

Five randomized trials[1–5] treated patients with conventional radiotherapy. They showed that the local regional recurrence rate was 19—20%. Our results demonstrated local a regional recurrence rate of 18.4%, after 4 years follow up. IMRT with delineating adequate target volume, and using adequate margins, could achieve compatible outcomes with conventional radiotherapy.

To our best knowledge, there were limited studies focused on the effect of the cumulative cisplatin dose.

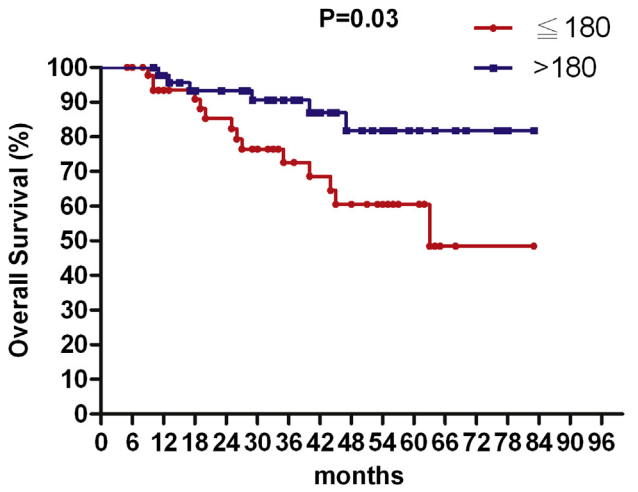

Figure 3 Overall survival (OS) according to cumulative dose of cisplatin.

Table 5 Multivariate analysis for OS, LFFS, DFS.

Variables	HR (95% CI)	*p*
OS		
Age (≥54 y vs. <54 y)	1.68 (0.58–4.86)	0.336
Histology (adenocarcinoma vs. SCC)	7.83 (2.23–27.4)	0.001
Lymph node metastasis (positive vs. negative)	3.83 (1.33–11.0)	0.013
Cumulative dose of weekly cisplatin (>180 mg/m^2 vs. ≤180 mg/m^2)	0.31 (0.10–0.96)	0.041
Pretreatment hemoglobin level (g/dL) (≥11 vs. <11)	1.33 (0.44–4.04)	0.616
Stage (III vs. I + II)	1.22 (0.44–3.42)	0.701
LFFS		
Age (≥54 y vs. <54 y)	1.02 (0.37–2.88)	0.965
Histology (adenocarcinoma vs. SCC)	5.67 (1.68–19.1)	0.005
Lymph node metastasis (positive vs. negative)	0.97 (0.32–2.91)	0.951
Cumulative dose of weekly cisplatin (>180 mg/m^2 vs. ≤180 mg/m^2)	0.41 (0.15–1.12)	0.083
Pretreatment hemoglobin level (≥11 vs. <11)	0.33 (0.12–0.92)	0.034
Stage (III vs. I + II)	1.20 (0.45–3.23)	0.721
DFS		
Age (≥54 y vs. <54 y)	1.11 (0.45–2.74)	0.819
Histology (adenocarcinoma vs. SCC)	6.47 (2.26–18.5)	<0.001
Lymph node metastasis (positive vs. negative)	1.87 (0.75–4.64)	0.180
Cumulative dose of weekly cisplatin (>180 mg/m^2 vs. ≤180 mg/m^2)	0.47 (0.19–1.16)	0.102
Pretreatment hemoglobin level (≥11 vs. <11)	0.66 (0.26–1.66)	0.374
Stage (III vs. I + II)	1.37 (0.57–3.31)	0.481

DFS = disease free survival; LFFS = local failure free survival; OS = overall survival; SCC = squamous cell carcinoma.

Torres et al[9] collected 302 patients with cervical cancer and showed that a cisplatin dose >200 mg/m^2 was an independent predictor of improved disease-specific survival. Our study used the median cumulative dose of weekly cisplatin as a cutoff point and found that a higher cumulative dose of weekly cisplatin (>180 mg/m^2) had a better OS and tended to be correlated with good outcomes in terms of DFS and LFFS.

Eifel et al[10] analyzed 229 patients with stage IB adenocarcinoma of the cervix. The 5-year survival rate was 72% versus 81% for SCC. The incidence of pelvic recurrence was similar (17% for adenocarcinoma and 13% for SCC). However, distant metastases were more frequent in patients with adenocarcinoma (37% vs. 21%; $p < 0.01$). The 4-year OS, LFFS and DFS rates in our patients, for adenocarcinoma and SCC, were 47.2% versus 77.4% ($p = 0.05$), 55.4% versus 83.9% ($p = 0.01$) and 45.3% versus 71.9% ($p = 0.006$), respectively.

Yamashita et al[11] reported that pelvic lymph nodes metastases and para-aortic lymph nodes metastases affected OS. Grigiene R et al[12] noted that a lymph node >10 mm on CT was significantly correlated with OS ($p = 0.03$) and local control ($p = 0.036$). In this study, we assessed lymph nodes status with CT scan. Our data showed that lymph nodes status affected the OS ($p = 0.02$). Esthappan et al[13] used PET/CT in patients with positive lymph nodes and treated patients with IMRT. PET/CT showed the potential to evaluate lymph nodes status, which could therefore allow for a more aggressive treatment of cervical cancer. In our institution, a PET scan was elective for patients with suspicion of lymph node metastasis. If PET scan showed a positive finding over lymph nodes, a higher radiation dose was given to the positive lymph nodes.

Haensgen et al[14] found that advanced stage had an effect on survival. In their study, FIGO stage IIIB was worse than FIGO stage IB and IIB. In our series, we showed that FIGO stage I + II tended to have better OS, LFFS and DFS than FIGO stage III, but the difference was not significant. The difference was not statistically significantly different, due to small number of patients of each FIGO stage.

Haensgen[14] et al found that a pretreatment hemoglobin level ≥11 g/dL had a better 3-year survival. In this study, pretreatment hemoglobin level was an independent factor of LFFS. If the hemoglobin level was lower than 10 g/dL during the treatment course, a blood transfusion was arranged. Blood transfusion may affect the hemoglobin level and diminish the pretreatment hemoglobin level effect.

Dattoli[15] et al showed that patients ≤40 years old had a poorer 5-year survival than patients > 40 years old. In our study, only seven patients were ≤40 years old. We used median age as a cutoff point and categorized patients into two groups. Our results showed that survival was not significantly different in these groups.

There were 105 patients with histologically proven SCC in this study. Seventy-six (72.3%) of these had elevated serum SCC. Previous studies[16–20] showed that the correlation between serum SCC and survival was controversial. Volgger et al[16] found that SCC-Ag < 2 ng/mL had a better OS ($p < 0.001$). Juang et al[20] used 1.5 as a cutoff value and revealed that serum SCC was a predictor of prognosis, but this did not reach statistically significant in multivariate analysis. Our data showed that the cutoff value 2 of serum SCC level had no significant difference on OS, DFS and LFFS.

This retrospective study had several limitations. First, the small number of patients limited our ability to perform

multiple adjustments for potential confounders and the power of our analysis to detect small differences. A large, multi-institutional study is needed to identify the prognostic factors of locally advanced cervical cancer. Second, a more precise system, such as image guided radiotherapy, is needed to deliver treatment planning.

Conclusion

Adenocarcinoma and initial lymph nodes metastases were poor prognostic factors for patients with locally advanced cervical cancer. Lower pretreatment hemoglobin levels had poorer local control. Chemotherapy, with a high cumulative dose of cisplatin, tended to be associated with better survival.

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