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Postoperative chemoradiation therapy using high dose cisplatin and fluorouracil for high- and intermediate-risk uterine cervical cancer

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ABSTRACT

The purpose of this retrospective study was to analyze data in patients with stage IB–IIB uterine cervical cancer who were treated with concurrent chemoradiotherapy (CCRT) with high dose cisplatin and fluorouracil as postoperative adjuvant therapy. Between February 2003 and November 2011, 76 patients with FIGO stage IB–IIB cervical cancer were analyzed. Seventy patients were treated with postoperative CCRT and 6 patients were treated with radiation therapy alone. Data related to overall survival (OS), disease-free survival (DFS), toxicity, and failure pattern were analyzed. The median patient age was 45 years (range, 20–80 years). The median follow-up duration was 63 months (range, 10–125 months). Fifty-eight patients (76.3%) had a squamous cell histologic type, 55 patients (72.4%) had lymphovascular invasion, 31 patients (40.8%) had parametrial invasion, and 28 patients (36.8%) had lymph node metastases. Five-year OS and DFS were 96% and 92%, respectively. Five-year DFS in stage IB1 patients was significantly higher than in stage IB2–IIB patients ($p = 0.022$). Nineteen patients (25%) had grade 3 or 4 neutropenia, 13 patients (17.1%) had grade 3 anemia, and 2 patients (2.6%) had grade 3 thrombocytopenia, but none of these patients died from the disease. Three patients experienced chronic toxicity: one had bladder perforation, one had hydronephrosis, and one experienced ileus. CCRT as postoperative adjuvant therapy resulted in good survival and outcome without severe toxicity.

Key Words: Uterine cervical cancer, Hysterectomy, Concurrent chemoradiotherapy, Cisplatin, 5-FU.

INTRODUCTION

Cervical cancer is the most common gynecologic malignancy in the world.[1)] In Japan, an estimated 10,908 new cases of invasive cervical cancer were diagnosed in 2012, and there were 2,902 cancer-related mortalities in 2014.[2)]

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It has been well documented that patients with early-stage cervical cancer have survival rates of approximately 90%, whether treated with radical hysterectomy or radiation therapy alone. However, in 15% to 20% of patients with early-stage disease, the disease has either spread to the lymph nodes, there is involvement of the parametrium, or there are positive surgical margins at the time of radical hysterectomy. When one or more of these factors is found, the 5-year survival rate drops to 50% to 70%.[3)]

The majority of patients with early-stage cervical cancer who undergo surgical treatment with radical hysterectomy will receive postoperative adjuvant therapy based on the analysis of surgical-pathological risk factors. Recurrence risk factors for cervical cancer after surgery include pelvic lymph node metastasis, parametrial invasion, tumor size, deep stromal invasion, lymphovascular space invasion, histological types, and degree of differentiation.[4-6)] In general, patients with positive pelvic nodes, parametrial invasion, or a positive surgical margin are classified as high risk. Patients with large tumors, deep stromal invasion, or lymphovascular space involvement to ≥2 are classified as intermediate risk.[6-8)]

Currently, concurrent chemoradiotherapy (CCRT) is recommended for high-risk patients and radiation therapy alone for intermediate-risk patients. The Gynecologic Oncology Group Study 92 (GOG 92) showed that pelvic radiotherapy (RT) after surgery significantly reduces the risk of recurrence and prolongs disease-free survival (DFS) in patients with Stage IB cervical cancer with ≥2 of the following features: deep stromal invasion, lymphovascular space involvement, and tumor diameter ≥4 cm.[9,10)] A Southwest Oncology Group (SWOG) phase III study (8797) showed that the addition of cisplatin/fluorouracil-based chemotherapy (CT) to postoperative RT in high-risk patients improved the survival rate.[11)] CCRT is now approved as standard therapy for cervical cancer. Some studies have shown that, in high-risk patients with early cervical cancer, prognosis after surgery is improved by the addition of CT to pelvic RT over radiation treatment alone.[12, 13)] At our institution, CCRT after surgery is provided to patients of intermediate or high risk in accordance with the Japan Society of Gynecologic Oncology guidelines 2011 for the treatment of uterine cervical cancer.

The purpose of this retrospective study was to investigate the effect of treatment among patients with early cervical cancer who were treated with CCRT after radical hysterectomy in terms of overall survival (OS), DFS, and treatment complications. We also examined various prognostic risk factors, including tumor size, deep stromal invasion, lymphovascular space involvement, positive pelvic nodes, parametrial invasion, and positive surgical margins.

METHODS AND MATERIALS

This study was approved by the Institutional Review Board of the Nagoya University Hospital, and all patients provided written informed consent.

Patients

From February 2003 to November 2011, 80 consecutive patients with FIGO stage IB1–IIB cervical cancer who received chemoradiotherapy or radiation alone after radical hysterectomy and pelvic lymphadenectomy at the Nagoya University Hospital were selected from patient medical records. Four patients were excluded from this analysis because of histopathological small cell carcinoma. No patients underwent CT and/or RT before operation.

RT plus concurrent CT after surgery was performed in patients with at least one of the following risk factors: pelvic lymph node metastasis, parametrial invasion, large tumor size, deep stromal invasion, lymphovascular space invasion, or positive surgical margins. The decision to

perform post-operative treatment was determined by the cancer board at our hospital.

Radiotherapy

Adjuvant RT was started 4–6 weeks postoperatively. Patients underwent external beam RT to the whole pelvis. Pelvic RT was performed using 10 MV x-rays delivered from a linear accelerator with a four-field box technique. The superior border of the radiation field was the top of the fifth lumbar vertebra, and the inferior border was the inferior margin of the pelvic bone. External irradiation was delivered to the whole pelvis at 1.8 Gy per fraction once daily, 5 fractions a week over 5–6 weeks.

According to the policy at our institution, para-aortic lymph node irradiation was performed in patients under 35 years old who had one positive lymph node region in the pelvis, and patients over 35 years old who had >2 positive lymph node regions in the pelvis. To reduce side effects, para-aortic lymph node irradiation was performed after pelvic irradiation was completed. External irradiation was delivered to the para-aortic lymph node at 2 Gy per fraction once daily, 5 fractions a week, and the total radiation dose was 46 Gy in 23 fractions.

Chemotherapy

CT was generally administered concurrently with RT and repeated for 3 cycles. Each cycle of CT consisted of cisplatin at a dose of 70 mg/m^2 on Day 1 and 5-fluorouracil (5-FU) at a dose of 700 mg/m^2 per day given as a continuous infusion over 96 h on Days 1–4. The second cycle of CT began on day 22. The third cycle of CT commenced after completion of RT on Day 43.

Follow-up and evaluation

The patients were followed up in an outpatient clinic every month in the first year, every 2 months in the second year, every 3 months in the third year, every 4 months in the fourth year, every 6 months in the fifth year, and annually thereafter for 10 years after treatment. After the completion of treatment, patients underwent clinical surveillance such as a clinical history, physical examination, laboratory examinations, Papanicolaou smear, and radiographic studies.

Statistical analysis

Statistical analysis was performed using SAS software (SAS Institute Inc., Cary, NC, USA). Survival curves were computed using the Kaplan-Meier method and comparison of survival rate was performed by log-rank test. Multivariate analysis was performed by Cox regression analysis to assess prognostic factors in predicting DFS. Univariate and multivariate analysis were performed for DFS. P values of <0.05 were considered statistically significant.

Complications

Toxicity was defined according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0.

RESULTS

Seventy-six patients were postoperatively treated with CCRT or RT alone. Of these, 47 patients belonged to the high-risk group (a positive lymph node or parametrial invasion), and 29 patients belonged to the intermediate-risk group (a large tumor, deep stromal invasion, or lymphovascular space involvement). The characteristics of the patients pre- and post-treatment are shown in Table 1 and Table 2. The median patient age was 45 years (range, 20–80 years). Fifty-eight patients

(76.3%) had a squamous cell histologic type, 55 (72.4%) had lymphovascular invasion, 31 (40.8%) had parametrial invasion, and 28 (36.8%) had lymph node metastases. Fourteen patients (18.4%) had a maximum tumor diameter > 4 cm.

In postoperative treatment, 56 patients received 3 cycles of cisplatin (70 mg/m^2 on Day 1) and 5-FU (700 mg/m^2 on Days 1–4). Thirteen of these patients were not able to complete all 3 cycles (Table 2). Six patients received radiotherapy alone because of underlying diseases, such as renal impairment. The median dose of external irradiation to the whole pelvis was 45 Gy (range 41.4–50.4 Gy), and the median dose of irradiation to the para-aortic lymph node was 46 Gy (range 40–46 Gy). Two patients received intracavitary brachytherapy of 15 Gy in 3 fractions below the vaginal mucosa after external beam radiotherapy. One patient had a positive surgical margin and the other patient was treated with radiation therapy alone after surgery because of renal impairment.

Recurrence and Survival Analysis

The median follow-up was 63 months (range 10–125 months). Recurrence occurred in 9 patients (11.8%). Table 3 shows recurrence by histologic type in each group. In the high-risk group, 3 patients (6.4%) developed pelvic recurrence and 4 patients (8.5%) developed distant metastases. Of the patients who developed pelvic recurrence, 1 case was in the pelvic lymph node region and 2 cases were stump recurrence. Among the patients who developed distant metastasis, 1 case was metastasis to the lung, 2 cases were para-aortic lymph node metastasis, and 1 case was mediastinal lymph node metastasis. In the intermediate-risk group, distant metastases were observed in 2 patients (8.7%), both to the lungs. Of the 17 patients who received radiation to the para-aortic region according to our policy, there were no cases of recurrence in the para-aortic region. However, of the remaining 30 patients in the high-risk group who did not receive radiation to the para-aortic region, 2 patients (6.7%) showed recurrence in this region.

The 5-year OS and DFS of the patients were 96% and 92%, respectively. Five-year OS and DFS were 97% and 97% in the intermediate-risk group, respectively (n = 29), and 96% and 89% in the high-risk group, respectively (n = 47) (p = 0.71 for OS, p = 0.054 for DFS). Five-year DFS in patients with stage IB1 tumors was 95% in the intermediate-risk group (n = 22) and 100% in the high-risk group (n = 34) (p = 0.14) Five-year DFS in patients with stage IB2–IIB tumors was 100% in the intermediate-risk group (n = 7) and 62% in the high-risk group (n = 13) (p = 0.08). Five-year DFS in patients with stage IB1 tumors was significantly higher than in patients with stage IB2–IIB tumors (p = 0.022) (Table 4).

Clinical and pathologic risk factors for predicting DFS were evaluated by univariate and multivariate analysis. In the univariate analysis, T-stage (p = 0.017), tumor size (p = 0.032), and margin status (p = 0.007) were significant risk factors for DFS (Table 5). However, in the multivariate analysis, T-stage (p = 0.019) was the only significant risk factor for DFS (Table 5).

Complications

Evaluation of adverse events was performed using the CTCAE ver. 4.0. Treatment related-death was not observed in all patients. Acute and late toxicities are summarized in Table 6.

Acute toxicities of grades 3 or 4, neutropenia, anemia, thrombocytopenia, and diarrhea were observed, with hematological toxicities being the most frequently observed. Seventeen patients (22.4%) showed grade 3 neutropenia, and 2 patients (2.6%) showed grade 4 neutropenia. Thirteen patients (17.1%) showed grade 3 anemia, 3 patients (3.9%) developed grade 3 thrombocytopenia, and 2 patients (2.6%) developed grade 3 diarrhea. Eighteen patients had G3–4 adverse events of the bowel system (5 patients (28.8%) receiving chemoradiation plus para-aortic radiation vs. 13 patients (72.2%) receiving pelvic chemoradiation alone, p = 0.053). Eighteen patients had G3–4

hematological complications (7 patients (38.8%) who received chemoradiation plus para-aortic radiation vs. 11 patients (61.1%) who received pelvic chemoradiation alone, p = 0.054).

There were no grade 4 late toxicities in any of the patients. Grade 3 bladder perforation occurred in 1 patient (1.3%) and grade 3 hydronephrosis occurred in 1 patient (1.3%). Grade 3 ileus occurred in 1 patient (1.3%).

Table 1 Patient characteristics pre-treatment

	n	(%)
Number of patients	76	
Mean age (range)	45 years (20–80)	
Performance status		
0	52	68.4
1	24	31.6
FIGO Stage		
T stage		
IB1	56	73.7
IB2	9	11.8
IIA	8	10.5
IIB	3	3.9
Tumor size (cm)		
≤4	62	81.6
>4	14	18.4
Histology		
Squamous cell carcinoma	58	76.3
Adenosquamous carcinoma	8	10.5
Adenocarcinoma	5	6.6
Mucinous adenocarcinoma	5	6.6
Pretreatment Hemoglobin (g/dL)		
<11	37	48.7
>11	39	51.3

Table 2 Surgical, pathology, and postoperative treatment characteristics

	n	(%)
Type of surgery		
Radical hysterectomy	75	98.7
Modified radical hysterectomy	1	1.3
Positive lymph nodes		
0	48	63.2
1	14	18.4
2	5	6.5
≥ 3	9	11.8
Parametrial invasion		
No	45	59.2
Yes	31	40.8
Lymphovascular invasion		
No	21	27.6
Yes	55	72.4
Deep stromal invasion		
No	70	92.1
Yes	6	7.9
Margin status		
Negative	73	96.1
Positive	3	3.9
Chemotherapy[a)]		
Yes	70	92.1
No	6	7.9
Cycles of chemotherapy		
0	6	7.9
1	2	2.6
2	12	15.8
3	56	73.7
Extent of radiotherapy		
Whole pelvic and para-aortic	17	22.3
Whole pelvic only	57	75.0
Whole pelvic and local boost	1	1.3
Whole pelvic and brachytherapy	1	1.3

a) Cisplatin + 5-fluorouracil regimen

Table 3 Patterns of failure by histologic type

Recurrence site	Pelvis (%)	Distant (%)	Total (%)
High-risk group (n =47)	3 (6.4)	4 (8.5)	7 (14.9)
SCC (n = 35)	2 (5.7)	3 (8.6)	5 (14.3)
Non-SCC (n = 12)	1 (8.3)	1 (8.3)	2 (16.7)
Intermediate-risk group (n = 29)	0 (0)	2 (6.9)	2 (6.9)
SCC (n = 23)	0 (0)	2 (8.7)	2 (8.7)
Non-SCC (n = 6)	0 (0)	0 (0)	0 (0)

SCC: squamous cell carcinoma

Table 4 Five-year overall and disease-free survival according to stage and risk group

	IB1 vs. IB2–IIB	IM vs. HR (all stages)	IM vs. HR in IB1	IM vs. HR in IB2–IIB
5-OS (%)	98 vs. 90	97 vs. 96	–	–
p-value	0.33	0.71	–	–
5-DFS (%)	98 vs. 75	97 vs. 89	95 vs. 100	100 vs. 62
p-value	0.022[a)]	0.54	0.14	0.08

IM: Intermediate-risk group, HR: High-risk group, 5-OS: 5-year overall survival, 5-DFS: 5-year disease-free survival
a) A p-value of 0.022 is statistically significant.

Table 5 Univariate and multivariate analysis of factors associated with disease-free survival

Variable		Univariate P-value[a)]	Multivariate P-value[b)]
		DFS	DFS
Age	≥45 vs. <45	0.78	–
Stage	IB2–IIB vs. IB1	0.017	0.019
Tumor size	>4 cm vs. ≤4 cm	0.032	0.45
Hb	≥11 g/dL vs.<11 g/dL	0.15	–
Cycles of chemotherapy	>3 vs. ≤3	0.59	–
Period to RT start	≥30 days vs. <30 days	0.94	–
Irradiation to PAN	(yes vs. no)	0.43	–
Parametrial invasion	(yes vs. no)	0.97	–
Lymphovascular invasion	(yes vs. no)	0.30	–
Deep stromal invasion	(yes vs. no)	0.75	
Margin status	(yes vs. no)	0.007	0.27
Histology	non-SCC vs. SCC	0.74	–
Lymph nodes in pelvis	(yes vs. no)	0.13	–

DFS: disease-free survival, Hb: Hemoglobin, RT: radiotherapy, PAN: para-aortic lymph node, SCC: squamous cell carcinoma.
a) As determined by log-rank test.
b) As determined by backward selection for Cox proportional hazards model.

Table 6 Acute and chronic toxicity[a] of postoperative concurrent chemoradiotherapy

Acute toxicity	Grade 3 (%)	Grade 4 (%)
Diarrhea	2 (2.6)	0
Hematologic		
Neutropenia	17 (22.4)	2 (2.6)
Anemia	13 (17.1)	0
Thrombocytopenia	3 (3.9)	0
Chronic toxicity		
Bladder perforation	1 (1.3)	0
Hydronephrosis	1 (1.3)	0
Ileus	1 (1.3)	0

a) Defined as grade ≥3, CTCAE ver. 4.0.

DISCUSSION

In this study, the 5-year OS at all stages was very high; therefore, there were no significant differences by stage. However, the difference in 5-year DFS between stage IB1 and stage IB2–IIB was statistically significant ($p = 0.022$). In the univariate analysis, T-stage ($p = 0.017$), tumor size ($p = 0.032$), and margin status ($p = 0.007$) were significant risk factors for DFS (Table 5). However, in the multivariate analysis, T-stage ($p = 0.019$) was the only significant risk factor for DFS (Table 5).

We can point to several factors for the high survival rates seen in this study. First, the number of patients with lymph node metastasis was lower than previously reported, with the rate of node negative status being 63.2%. Additionally, the rate of ≥2 positive nodes was 14.4%, compared to a rate of 44% in SWOG (8797).[11] Second, triweekly CT consisting of cisplatin and 5-FU was more effective than weekly cisplatin-only CT,[14, 15] although we applied CCRT as modified by the procedure of Peters *et al.*[11] (cisplatin was administered every 3 weeks at a dose of 70 mg/m^2 by 2-hour intravenous infusion during RT). CT consisted of bolus infusion of cisplatin (70 mg/m^2) and a 96-hour infusion of 5-FU at 1000 mg/(m^2·day) every 3 weeks for 4 cycles. It has been reported that chemoradiotherapy after cervical cancer surgery reduces the risk of recurrence and extends DFS for patients with high risk. Additionally, it has been reported that the outcome of chemoradiotherapy after surgery was better than with radiation alone.[16-19] Third, para-aortic lymph node irradiation was performed in patients with positive lymph nodes in the pelvis. In our study, there was no recurrence in the para-aortic lymph nodes in patients who received preventive irradiation of the para-aortic lymph node area. Analysis of the sites of recurrence showed that patients who received CCRT tended to show distant metastasis and para-aortic lymph node metastasis rather than intrapelvic recurrence. Another strategy may be required to prevent distant metastasis and recurrence outside of the irradiated areas. Effective systemic CT and preventive irradiation of the para-aortic lymph node area might be considered for reducing distant metastasis.

Although it has been reported that the incidence of complications over 10 years is elevated in patients receiving para-aortic lymph node irradiation,[20] there has not been an increase in adverse events in our study population. With postoperative chemoradiation, an increase in adverse events

is a concern.[21, 22] Since adverse events in our study were within the acceptable range, it can be determined that chemoradiation is relatively safe, although it may be better to have a reduced dose of 5-FU (700 mg/m^2).

Previous reports have shown that severe gastrointestinal toxicity was more common than we observed, despite use of the same regimen. The treatment regimen was carried out to 4 courses in that study,[23] whereas patients received only 3 courses of CT in our study. This may be one of the reasons that gastrointestinal toxicity was more severe. A reduction in adverse events is expected with the use of intensity-modulated radiotherapy (IMRT) as the irradiation method.[24, 25] Adverse events can also be expected in a dose-dependent manner when using IMRT. IMRT was the choice of post-operative irradiation in this study.

Our study has several limitations. First, the number of cases analyzed in this study was small. Second, this is a retrospective study thus lack a control group. Third, although the median follow-up was 63 months, a much longer follow-up is needed for the evaluation of late adverse complications.

In conclusion, CCRT using high dose cisplatin and 5-FU as the postoperative adjuvant therapy for uterine cervical cancer resulted in good survival outcome without severe toxicity.

CONFLICTS OF INTEREST

The authors declare that they have no competing interests.

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