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Long-term Outcomes of Cervical Adenocarcinoma Treated With Concurrent Chemoradiotherapy Using Paclitaxel and Cisplatin

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Abstract. *Background/Aim: We retrospectively analyzed the locally advanced adenocarcinoma (AC)/adenosquamous carcinoma (ASC) of the uterine cervix treated with concurrent chemoradiotherapy using cisplatin plus paclitaxel (TP-CCRT). Patients and Methods: Thirty patients with stage IB–IVA AC/ASC were treated with whole pelvis external beam radiotherapy. A high-dose-rate intracavitary brachytherapy was delivered once per week at a fractional dose of 6 Gy. For TP-CCRT, the patients received cisplatin and paclitaxel. Results: A complete response was achieved in 17 patients (77.3%) in the TP-CCRT group and 4 patients (50.0%) in the P-CCRT group. The 5-year OS rate in the TP-CCRT and P-CCRT groups was 74.2% and 25.0% (p=0.0094), the central DFS rate was 58.0% and 12.5% (p=0.0267), and the distant DFS rate was 63.6% and 12.5% (p=0.0042), respectively. Conclusion: TP-CCRT achieves a considerably better disease control for AC of the cervix, leading to a better OS.*

Of all cervical cancer cases, adenocarcinoma (AC) and adenosquamous carcinoma (ASC) only accounts for around 10%-20% (1, 2). AC/ASC has worse prognosis than squamous cell carcinoma of the cervix, because AC/ASC is less sensitive to radiotherapy (RT) and chemotherapy, and has a tendency to invade into the lymphovascular space even at an early stage (3-6). Recent reports have mentioned that AC/ASC subtypes are independent prognostic factors in patients treated with definitive RT and are related to poor treatment outcomes compared with those with SCC of the cervix. More effective treatments to improve the prognosis of cervical AC/ASC are desired (7-12).

Regarding concurrent chemoradiotherapy (CCRT) for AC of the cervix, it has been reported that the 5-year disease free survival (DFS) rate for stage III AC of the uterine cervix treated with RT alone (25%) was worse than that for the SCC (59.1%) (13). A retrospective survey of 61 patients with stage IIIB AC of the uterine cervix treated with RT alone showed that the 5-year overall survival (OS) rate was 20.2% of all the patients (14). Our previous study (15) has shown that only 50.0% of the patients with cervical AC achieved a complete response (CR). Hence, RT alone is not appropriate treatment for a favorable prognosis of AC of the cervix.

A previous retrospective study of 94 patients with advanced disease stage (7) has shown that there were no significant differences in the 5-year relapse-free, disease-specific, local relapse-free, or distant relapse-free survival rate of patients treated with RT alone and those treated with CCRT using cisplatin (P-CCRT), demonstrating that P-CCRT did not improve the outcomes of patients with AC/ASC. In our previous study (15), P-CCRT did not improve the outcomes of patients with AC of the cervix. Thus, P-CCRT is unlikely to result in favorable treatment outcomes for cervical AC. P-CCRT was a routinely used treatment until 2002, however, it was changed to the TP-CCRT, because P-CCRT could not achieve favorable outcome. Our preliminary results have shown that CCRT using cisplatin plus paclitaxel (TP-CCRT) achieved considerably good local control of cervical AC, leading to a decrease in locoregional recurrence (15).

In the current study, we analyzed more patients for a longer period to provide useful definite information on the TP-CCRT treatment for the locally advanced AC of the uterine cervix.

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Key Words: Locally advanced, cervical adenocarcinoma, paclitaxel/cisplatin, concurrent chemoradiotherapy.

Table I. *Patient characteristics*.

	TP-CCRT (n=22)	P-CCRT (n=8)	*p*-Value
Median age (range) (years)	59 (34-74)	51 (33-61)	0.417
FIGO stage (2009)			
IB2	2	0	
IIB	5	3	
IIIB	13	5	
IVA	2	0	1.000
Median tumor size (range) (mm)	51 (26-88)	56 (42-76)	0.537
Lymph node enlargement	12 (54.5%)	3 (37.5%)	0.682
Median course of chemotherapy (courses)	2 (2-3)	2 (1-3)	NA
Median overall treatment time (days)	51 (45-67)	48 (37-68)	0.135
Median follow up period (range) (months)	51 (6-144)	19.5 (5-189)	0.0461

Table II. *Complete response and recurrence*.

	TP-CCRT (n=22)	P-CCRT (n=8)	*p*-Value
Complete response	17 (77.3%)	4 (50.0%)	0.1954
Local recurrence	6 (27.2%)	7 (87.5%)	0.0094
Distant recurrence	8 (36.3%)	7 (87.5%)	0.0352

TP-CCRT: Paclitaxel and cisplatin concurrent chemoradiotherapy; P-CCRT: cisplatin concurrent chemoradiotherapy.

Table III. *Acute and late toxicity (Grade 3)*.

	TP-CCRT (n=22)	P-CCRT (n=8)
Acute toxicity[a]		
Neutropenia	4 (18.0%)	2 (25.0%)
Anemia	2 (9.1%)	0
Thrombocytopenia	1 (4.5%)	0
Nausea	0	3 (37.5%)
Diarrhea	3 (13.6%)	0
Myalgia	0	0
Peripheral neuropathy	0	0
Late toxicity[b]		
Small/large intestine	1	0
Urinary bladder	1	0

[a]Common Terminology Criteria for Adverse Events (CTCAE) version 4.0; [b]Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) Radiation Toxicity Grading (late radiation morbidity). TP-CCRT: Paclitaxel and cisplatin concurrent chemoradiotherapy; P-CCRT: cisplatin concurrent chemoradiotherapy.

Patients and Methods

Clinicopathological data from the records of 30 patients with stage IB–IVA (FIGO 2009 classification) cervical AC who were treated with CCRT between 1997 and 2016 at our institute were retrospectively analyzed. We excluded patients with para-aortic lymph node (LN) enlargement (short axis diameter higher than 10 mm measured by computed tomography or magnetic resonance imaging) in this study. All the patients satisfied previously described criteria (15). Patients treated with P-CCRT were used as the historical control for TP-CCRT in this study.

The patients were treated as previously described (15, 16). Briefly, whole pelvis external beam radiotherapy (WP-EBRT) with 50 Gy (25 fractions) were performed using a center shield at mid-line after delivering 40-Gy dose. A high-dose-rate intracavitary brachytherapy (HDR-ICBT) and boost EBRT doses were applied. The patients received 20 mg/m^2 cisplatin for 5 days every 3 weeks in the course of P-CCRT (15, 16) and the patients received 50 mg/m^2 cisplatin every 3 weeks and 50 mg/m^2 paclitaxel weekly in the course of TP-CCRT (15, 17).

Acute and late toxicities were graded according to the Common Terminology Criteria for Adverse Events version 4.0 and the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer (RTOG/EORTC) criteria, respectively. Follow-up examinations were conducted every month for the first year, every other month for the second year, and subsequently every 3-6 months (15).

Statistical analyses were performed using the JMP Statistical Discovery Software ver. 15.0 (SAS Institute, Inc., Cary, NC, USA). Kaplan–Meier curves were used for the survival curves, and the difference was analyzed by the log-rank test. *p*-Values<0.05 were considered significant.

Written informed consent regarding the treatment was obtained from all the patients. All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. This retrospective study was approved by the Institutional Review Board of our university (#1394 on Feb 7, 2019).

Results

Patient characteristics (n=30) are shown in Table I. Eight patients were treated with P-CCRT between 1997 and 2002, and 22 were treated with TP-CCRT after 2003. The median age was 59 years (range=34-74 years) in the TP-CCRT group and 51 years (range=33-61 years) in the P-CCRT group. The median follow-up period was 51 months (range=6-144 months) in the TP-CCRT group and 19.5 months (range=5-189 months) in the P-CCRT group. There were no statistically significant differences in the distribution of stage, LN status, or other clinicopathological variables. The median number of chemotherapy courses was 2 in both TP-CCRT (range=2-3

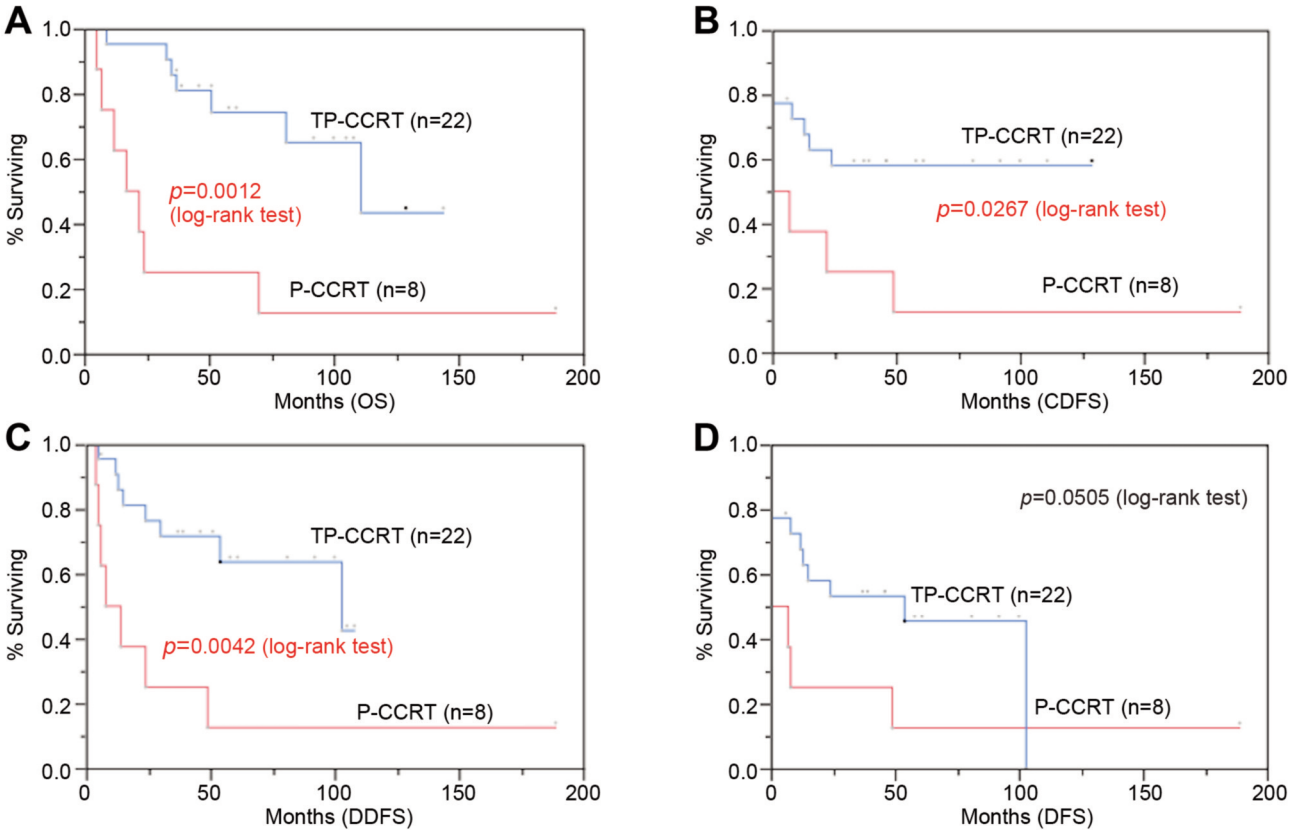

Figure 1. *Kaplan-Meier curves for survival rate analysis. The 5-year overall survival rates of the patients in the TP-CCRT and P-CCRT groups were 74.2% and 25.0% (p=0.0094) (a), the central disease-free survival (DFS) rates were 58.0% and 12.5% (p=0.0267) (b), and the distant DFS rates were 63.6% and 12.5% (p=0.0042) (c), respectively. The 5-year DFS rates in the TP-CCRT and P-CCRT groups were 45.5% and 12.5%, respectively (p=0.0505) (d).*

courses) and P-CCRT (range=1-3 courses) groups; the median overall treatment time, including HDR-ICBT and boost EBRT, was 51 days (range=45-68 days) in the TP-CCRT group and 48 days (range=40-68 days) in the P-CCRT group.

CR was defined as the absence of clinically or pathologically viable cancer cells assessed by magnetic resonance imaging and needle biopsy 3 months after the completion of CCRT. A clinical and pathological CR was achieved in 17 of the 10 patients (77.3%) in the TP-CCRT group and 4 of the 8 patients (50.0%) in the P-CCRT group, respectively. Six of the 22 patients in the TP-CCRT group and 7 of the 8 patients in the P-CCRT group experienced locoregional recurrence. Furthermore, 8 of the 22 patients in the TP-CCRT group and 7 of the 8 patients in the P-CCRT group experienced distant recurrence (Table II). The 5-year OS rate in the TP-CCRT and P-CCRT groups was 74.2% and 25.0% (p=0.0094) (Figure 1a), the central DFS rate was 58.0% and 12.5% (p=0.0267) (Figure 1b), and the distant DFS rate was 63.6% and 12.5% (p=0.0042) (Figure 1c), respectively. However, the 5-year DFS rate in the TP-CCRT and P-CCRT groups was 45.5% and 12.5%, respectively (p=0.0505) (Figure 1d).

The acute adverse events in patients treated with TP-CCRT are as follows: only four patients (18.0%) had grade 3 neutropenia without febrile episodes, and no septic deaths were noted (Table III). TP-CCRT was interrupted because of grade 3 diarrhea in 1 patient. Regarding late adverse events of TP-CCRT, two out of the 22 patients (9.1%) suffered grade 3 late intestinal toxicity or grade 3 radiation cystitis and no grade 4 toxicities were observed during the follow-up period, according to the RTOG/EORTC scoring criteria (Table III).

Discussion

This study focused on the long-term outcomes of TP-CCRT-treated patients with AC of the cervix. A CR was achieved in 77.3% of the patients in the TP-CCRT group, indicating a considerably better result than that observed in the patients in the P-CCRT group (12.5%). Six out of the 22 patients experienced locoregional recurrence and 8 out of the 22 patients experienced distant recurrence. The 5-year OS, central DFS, distant DFS, and DFS rates of patients in the

TP-CCRT group were 74.2%, 58.0%, 63.6%, and 45.5%, respectively, which were significantly higher than those in the P-CCRT group; however, the 5-year DFS rate was marginal (p=0.0505). Therefore, TP-CCRT is highly effective and feasible, and it is a promising strategy for the therapy of AC of the cervix even after a long-term follow-up.

Paclitaxel arrests cell cycle in the radiosensitive G2M phase, demonstrating its radio-sensitization *in vitro* (18, 19). A phase I study demonstrated radiosensitization to paclitaxel (17), revealing that 50 mg/m^2 weekly in combination with 50 mg/m^2 cisplatin every 3 weeks resulted in a 93% response rate. In 2002, the chemotherapy regimen of CCRT for AC of the cervix was changed to TP-CCRT in our institute.

Regarding TP-CCRT, 50 mg/m^2 cisplatin every 3 weeks and 50 mg/m^2 paclitaxel weekly were administered in our institute according to the study by Chen et al. (17). Several phase I/II trials of concurrent RT with cisplatin–paclitaxel have been reported. The results of a phase I study of concurrent RT with weekly administration of cisplatin–paclitaxel in 18 patients with cervical cancer have shown that the maximum tolerated dose (MTD) of paclitaxel was 50 mg/m^2/week with 30 mg/m^2/week cisplatin in CCRT; meanwhile, diarrhea was the dose-limiting side effect (20). The Gynecologic Oncology Group phase I/II study of 35 patients with stage IB2 to IVA cervical cancer of TP-CCRT has determined that the MTD was weekly administration of 40 mg/m^2 cisplatin and 40 mg/m^2 paclitaxel (21). A Japanese phase I study has also reported that CCRT with weekly administration of 30 mg/m^2 cisplatin and 50 mg/m^2 paclitaxel can be tolerable for the treatment in Japanese women with locally advanced cervical cancer (22). Another phase I trial of CCRT with paclitaxel and cisplatin (30 mg/m^2/week) has found that the MTD of paclitaxel was 40 mg/m^2 (23). Therefore, there is need to investigate the appropriate dose of paclitaxel and cisplatin for cervical AC.

We should consider the addition of systemic chemotherapy to CCRT to overcome AC of the cervix, such as the OUTBACK trial (24), INTERLACE trials (25) and so on (26, 27). A well-designed prospective, randomized trial is necessary to develop a novel CCRT strategy for the treatment of locally advanced AC of the cervix. Furthermore, other effective strategies, such as bevacizumab (28) and immune check point inhibitors (29, 30), should be investigated for a subset of patients with AC of the cervix.

Conclusion

The current study, although a retrospective analysis with a small number of patients, demonstrates that TP-CCRT achieves a considerably better disease control for AC of the cervix, leading to a better OS. These results might provide useful information for the development of appropriate treatment strategies. Prospective trials involving a larger number of patients undergoing TP-CCRT, as well as other novel therapies, are urgently warranted.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

The work presented here was carried out in collaboration among all authors. YA, TA, JH, KM, and YA made substantial contribution to the conception, design of methods, interpretation of the results, and writing of the manuscript. YS, TN, YT, TN, TO, WK, IK, and KN engaged in data acquisition and analysis. YA, TA, KM, and YA substantively revised the manuscript. All authors treated patients, have read the manuscript, and have approved this submission.

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