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A Phase II Study of Neoadjuvant Chemotherapy Followed by Extended Field Concurrent Chemoradiotherapy for Para-aortic Lymph Node Positive Cervical Cancer

YUKO SHIMOJI[1], YUTAKA NAGAI[1#], TAKAFUMI TOITA[2*], TAKURO ARIGA[2¥], JOICHI HEIANNA[2], TADAHARU NAKASONE[1], YUSUKE TAIRA[1], YOSHIHISA ARAKAKI[1], TOMOKO NAKAMOTO[1], TAKUMA OOYAMA[1], WATARU KUDAKA[1], ITOMI KANESHIMA[1], KUMIKO NISHIHIRA[1], KEIKO MEKARU[1] and YOICHI AOKI[1]

[1]*Department of Obstetrics and Gynecology, Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan;*
[2]*Department of Radiology, Graduate School of Medicine, University of the Ryukyus, Okinawa, Japan*

Abstract. *Background/Aim: We conducted a phase II study of neoadjuvant chemotherapy followed by extended field concurrent chemoradiotherapy in patients with cervical cancer with para-aortic node metastasis. Patients and Methods: Thirty-seven women with stage IB1-IVA cervical cancer were enrolled. Results: The median age was 52 years. Thirty-four patients other than 3 progressive disease, proceeded to extended field concurrent chemoradiotherapy. The 3-year overall survival and progression-free survival rates were 70.1% and 48.5%, respectively. The 3-year overall survival according to stages was significantly worse in stage IIIB. Twelve of the 17 patients with stage IIIB died of the disease. Conclusion: Neoadjuvant chemotherapy followed by extended field concurrent chemoradiotherapy may improve the prognosis of patients with stages IB and II cervical cancer with positive para-aortic node. However, new strategies should be investigated to improve a poor prognosis in stage IIIB disease with positive para-aortic node.*

Present address: [#]Department of Obstetrics and Gynecology, Okinawa Prefectural Nanbu Medical Center and Children's Medical Center, Okinawa, Japan; *Department of Radiation Therapy Center, Okinawa Chubu Hospital, Okinawa, Japan; [¥]Health Information Management Center, University of the Ryukyus Hospital, Okinawa, Japan.

Correspondence to: Yoichi Aoki, Department of Obstetrics and Gynecology, Graduate School of Medicine, University of the Ryukyus. 207 Uehara Nishihara, Okinawa 903-0215, Japan Tel: +81 988951177, Fax: +81 988951426, e-mail: yoichi@med.u-ryukyu.ac.jp

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It is currently accepted that para-aortic lymph nodes (PAN) metastasis is an important prognostic factor in patients with locally advanced cervical cancer and the existence of such is clinically very important in choosing the appropriate therapy (1). According to a Gynecologic Oncology Group (GOG) study, PAN involvement confirmed by biopsy was found in 5% of patients with the International Federation of Gynecology and Obstetrics (FIGO) stage IB, 17% of patients with stage IIB, and 25% of patients with stage IIIB. Poor survival rates were reported in these patients (2).

Optimal treatment is required for cure in patients with locally advanced cervical cancer with positive PAN at the time of initial diagnosis. Several studies reported encouraging results of extended field radiotherapy for treating PAN metastasis with a 5-year overall survival ranging from 29%-50% and tolerable side effects (3-6). However, these studies warranted more research on multimodalities to further improve the prognostic results. The impact of extended field concurrent chemoradiotherapy (EF-CCRT) was studied in a few trials, with 5-year overall survival varying from 29%-39% (7-10). Some patients who underwent EF-CCRT achieved long-term remission. This is because PAN metastasis is different from other distant metastases in systemic diseases. Studies also confirmed the safety of this treatment and acceptable late toxicities despite increased acute toxicities (7). However, patients with locally advanced cervical cancer with PAN metastasis still have poor prognoses when compared with those without PAN metastasis.

We conducted phase II study of neoadjuvant chemotherapy followed by EF-CCRT in patients with locally advanced cervical cancer with PAN and/or common iliac lymph nodes.

Patients and Methods

A prospective study was conducted at the University of the Ryukyus Hospital to investigate the efficacy and adverse effects of neoadjuvant chemotherapy followed by EF-CCRT, and high dose rate intracavitary brachytherapy on locally advanced cervical cancer patients with PAN and/or common iliac lymph nodes. The Institutional Board Committee approved the study on April 20, 2010 (#H22 3-9), and all patients gave written informed consent. Between 2010 and 2017, 37 women with both clinical staging classification the FIGO 2009 stages IB1-IVA biopsy-proven carcinoma of the uterine cervix were enrolled in the study after getting written informed consents. The common iliac and PAN enlargement were defined as the enlargement over a short axis diameter of 10 mm as measured by computed tomography or magnetic resonance imaging. Patients with a history of hysterectomy, abdominal or pelvic radiotherapy were excluded. All patients satisfied an Eastern Cooperative Oncology Group performance status of ≤2, were age ≤75 years, and had adequate hematological parameters (white blood cell count, 3,000-10,000/μl, hemoglobin ≥9.0 g/dl, and platelet count ≥100,000/μl). The hepatic parameters were: bilirubin level ≤1.5 mg/dl and aspartate aminotransferase/alanine aminotransferase ≤2.5× the upper limit of normal. The renal parameters were: creatinine clearance, ≥60 ml/min and the electrocardiographic findings were normal.

Initially, two courses of 50 mg/m^2 of cisplatin and 175 mg/m^2 of paclitaxel were administered intravenously at 21-day intervals. Appropriate hydration and antiemetics were given before and after the cisplatin and paclitaxel administration. Response to the chemotherapy was assessed using Response Evaluation Criteria in Solid Tumor ver. 1.1 criteria. Patients with complete response, partial response, and stable disease were forwarded to EF-CCRT, while patients with progressive disease were treated with palliative radiotherapy, chemotherapy, or best supportive care. Patients were treated with EF-CCRT as follows: starting with the four-field technique of EF-RT. The pelvic and para-aortic areas were treated as a continuous area, with a superior field border at the space between Th12 and L1. Then, with anterior–posterior and posterior–anterior parallel-opposed ports technique of extended field external beam radiotherapy was delivered at a total dose of 45 Gy in 25 fractions. A midline block (midline block; 4 cm width at the midline) was inserted into the center of the pelvic field after 39.6 Gy was delivered. Whole pelvic with midline block irradiation, after extended field external beam radiotherapy, was delivered (5.4 Gy in three fractions). Boost external beam radiotherapy doses of 6-10 Gy (three to five fractions) were applied to nodal enlargement for patients and/or with nodular parametrial involvement. Three fractions of high-dose rate-intracavitary brachytherapy with a single dose of 6 Gy were delivered at point A once a week. The patients received 50 mg/m^2 cisplatin every three weeks and 50 mg/m^2 paclitaxel weekly during EF-CCRT (11, 12).

The primary end point of the study was 3-year progression-free survival (PFS). PFS was defined as the time from study entry to the date of disease progression. Secondary end points were 3-year overall survival (OS), complete response rate, 3-year local disease-free survival, 3-year distant disease-free survival, and safety. 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 criteria, respectively. Follow-up examinations were conducted every month for the first year, every other month for the second year, and then every 3-6 months subsequently.

All statistical analyses were performed using the JMP software version 15.0 (SAS Institute, Cary, NC, USA). The Kaplan–Meier method and the log-rank test were used to assess the survival rate. Furthermore, *p*-values of <0.05 were considered significant.

Table I. *Patient characteristics (N=37).*

Median age (range) (years)	52 (27-70)
FIGO stage	
IB1	1
IB2	8
IIB	10
IIIB	17
IVA	1
Histology	
Squamous cell carcinoma	34
Adenocarcinoma	3
Median tumor size (range) (mm)	54 (20-99)
Lymph node enlargement	
COM	18
COM+PAN	15
PAN	4
Median pretreatment Hb (g/dl)	11.9 (4.2-14.8)
Median pretreatment SCC (ng/ml)	4.4 (0.8-283)

FIGO: International Federation of Gynecology and Obstetrics; COM: common iliac lymph node; PAN: para-aortic lymph node.

Results

Table I presents patient and treatment characteristics. The median follow-up period was 38 months (range=7-91 months). During EF-CCRT, the median total doses of cisplatin and paclitaxel were 200 mg/m^2 (range=100-300 mg/m^2) and 300 mg/m^2 (range=150-450 mg/m^2), respectively. The median overall irradiation time was 48 days (range=37-68 days).

Of the 37 patients who received two courses of paclitaxel and cisplatin chemotherapy, 28 patients showed partial response, six patients had stable disease, and three patients had progressive disease. Accordingly, 34 patients other than the 3 progressive disease patients proceeded to EF-CCRT. Thirty-two (86.5%) of these patients completed EF-CCRT. Of the remaining two patients, one developed acute phlegmonous esophagitis during the course of EF-CCRT and was changed to radiotherapy alone, and the other experienced disease progression on EF-CCRT and was changed to transcatheter arterial chemoembolization. After completing the protocol treatment, 28 patients (75.7%) achieved complete response, while four patients had persistent disease. Of these four patients, two underwent hysterectomy and achieved NED (Figure 1).

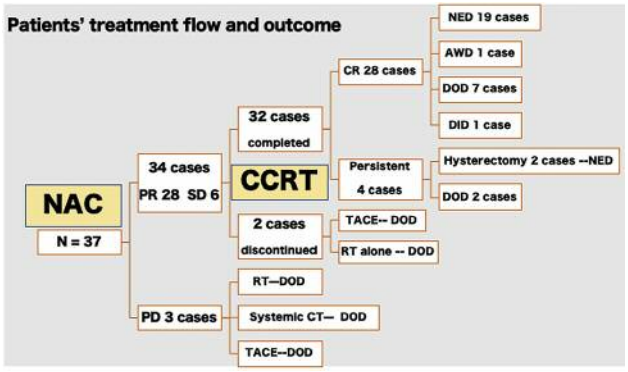

Figure 1. *Treatment flow and outcome in the 37 enrolled patients. PR: Partial response; SD: stable disease; CCRT: concurrent chemoradiotherapy; RT: radiotherapy; CT: chemotherapy; DOD: dead of disease; CR: complete response, TACE: transcatheter arterial chemoembolization; NED: no evidence of disease; AWD: alive with disease; DID: dead of intercurrent disease.*

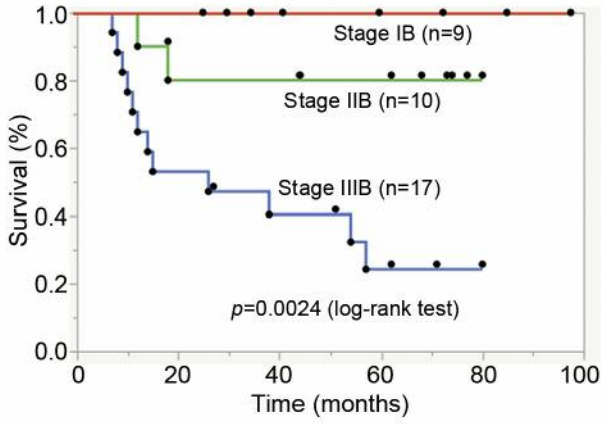

Figure 3. *Kaplan–Meier curves for overall survival according to stage. The 3-year overall survival according to stages were 100% in stage IB (n=9), 80.0% in stage IIB (n=10), and 47.1% in stage IIIB (n=17), which was significantly worse in stage IIIB (p=0.0024).*

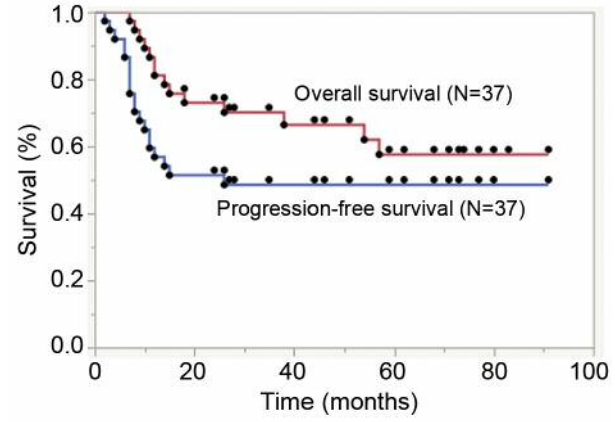

Figure 2. *Kaplan–Meier curves for overall survival and progression-free survival in all patients. The 3-year overall survival and progression-free survival rates were 70.1% and 48.5%, respectively.*

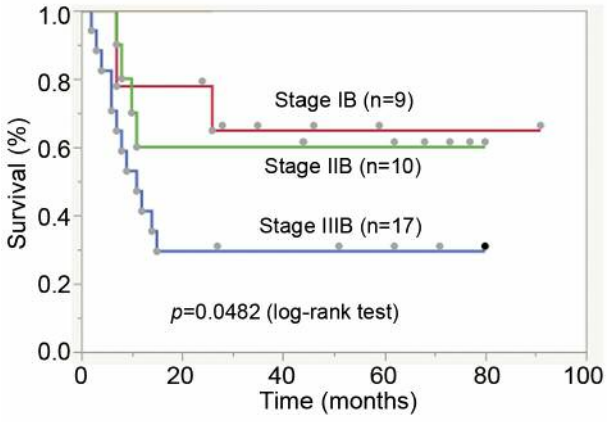

Figure 4. *Kaplan–Meier curves for progression-free survival according to stage. The 3-year progression-free survival according to stages were 64.8% in stage IB (n=9), 60.0% in stage IIB (n=10), and 29.4% in stage IIIB (n=17), which was significantly worse in stage IIIB (p=0.0482).*

The 3-year OS and PFS rates were 70.1% and 48.5%, respectively (Figure 2). The 3-year OS according to FIGO stages were 100% in stage IB (n=9), 80.0% in stage IIB (n=10), and 47.1% in stage IIIB (n=17), which was significantly worse in stage IIIB (p=0.0024) (Figure 3). The 3-year PFS according to clinical stages were 64.8% in stage IB (n=9), 60.0% in stage IIB (n=10), and 29.4% in stage IIIB (n=17), which was significantly worse in stage IIIB (p=0.0482) (Figure 4). The 3-year local PFS and distant p PFS rates were 61.5% and 64.3%, respectively. However, there were no significant differences in distant PFS and local PFS according to clinical stages. Nine patients (24.3%) had persistent disease and 11 patients (29.7%) experienced recurrence. Regarding an initial recurrence, one patient experienced locoregional recurrence, and five patients had both distant and locoregional recurrences, and five patients showed distant metastases. In 17 patients with stage IIIB disease, 12 patients died of the disease. Of these patients, three had progressive disease in neoadjuvant chemotherapy, one had progressive disease in EF-CCRT, one had residual disease after EF-CCRT, and the remaining seven had distant failure. The most frequent initial sites of distant recurrence were supraclavicular lymph nodes.

During the course of neoadjuvant chemotherapy, four patients (10.8%) had grade 3 neutropenia and two patients (5.4%) developed neutropenic fever. On EF-CCRT, six

patients (17.6%) had grade 3 and one grade 4 neutropenia, and grade 3 anemia and grade 4 thrombocytopenia were also observed in one of each patient. Regarding nonhematologic adverse events, grade 2 diarrhea was observed in 3 (8.1%) patients. In terms of late adverse events, no patient had grade 3 or worse adverse events on the basis of toxicity criteria of the Radiation Therapy Oncology Group/European Organization for Research and Treatment of Cancer. No death due to toxicities occurred during the study period.

Discussion

Patients with cervical cancer with PAN metastasis can develop distant failure. As such, these patients have poor prognoses when compared with those without PAN metastasis. Grigsby *et al*. (13) reported that the 3-year and 5-year OS rates of 43 patients treated with extended field radiotherapy were 37% and 32%, respectively. Forty percent (n=17) of the patients developed distant metastases with or without pelvic failure. Because of the poor prognosis of patients treated with extended field radiotherapy alone, several studies using concurrent chemoradiotherapy were conducted. GOG conducted a multicenter trial of concurrent chemoradiotherapy to evaluate the feasibility of EF-CCRT with 5-fluorouracil and cisplatin. Distant metastases occurred in 41.9%, while pelvic failure was observed in 31.4% of the patients. The 3-year OS and PFS were 39% and 34%, respectively (7). Ayman *et al*. (14) recently reported on the treatment outcomes of cervical cancer patients with PAN who were treated with extended field radiotherapy with or without chemotherapy. The 3-year pelvic node and PAN control rates were 100% and 42.2%, respectively, (p=0.03), while the 3-year distant control rates with and without chemotherapy were 81.8% and 46.2% (p=0.5), respectively. These results thereby indicated that the addition of concurrent cisplatin-based chemotherapy to extended field radiotherapy for this subset of patients appeared to improve the pelvic and PAN control rates, but not the rate of distant metastasis and survival. All the patients with recurrent disease died as a result of distant metastases. This suggests that a more effective systemic therapy should be explored.

Several studies have demonstrated the efficacy of neoadjuvant chemotherapy followed by concurrent chemoradiotherapy for the treatment of head and neck cancer. These studies concluded that the treatment decreased distant metastasis by 20% and improved the prognosis (15-17). For the treatment of locally advanced cervical cancer, in a single-arm phase II trial, 46 patients received dose-dense carboplatin and paclitaxel weekly for six cycles followed by concurrent chemoradiotherapy with weekly cisplatin. Although only 11% of the enrolled patients had positive PAN, this treatment regimen was reported to be feasible as evidenced by the acceptable toxicity of neoadjuvant chemotherapy and by the high compliance to radiotherapy (18). In a randomized phase II trial, patients with locally advanced cervical cancer were randomly assigned to three cycles of neoadjuvant chemotherapy with cisplatin and gemcitabine followed by standard concurrent chemoradiotherapy or to standard concurrent chemoradiotherapy alone, showing that the addition of neoadjuvant chemotherapy consisting of cisplatin and gemcitabine to standard concurrent chemoradiotherapy was possibly inferior to concurrent chemoradiotherapy alone. However, there was no information on PAN status in these groups of patients (19).

Accordingly, we introduced neoadjuvant chemotherapy to decrease distant metastasis in PAN/common iliac lymph nodes-positive patients with carcinoma of the cervix. The adverse effects of NAC and EF-CCRT were tolerable and 32 patients (86.5%) completed their planned treatments. There was good compliance with our protocol. The 3-year OS and PFS rates were relatively better when compared to the previous reports. Patients with stages IB and IIB had better OS, although the prognosis in stage IIIB was similar to the previous reports. Eight patients had persistent disease and 11 patients experienced recurrence or persistent disease, in which half was distant disease. The distant DFS by stages was also significantly worse in stage IIIB. Our treatment strategy seemed to decrease distant failure in patients with stages IB and II, but failed in patients with stage IIIB.

According to the previous reports regarding OS by the FIGO 2009 stage, patients in stage I with PAN involvement had 36-month OS rates of 15.6%, while patients in stages II to IV with PAN involvement had 0% OS (20). The 5-year cause-specific survival for stages I and II group of patients was 54%, and for patients with stages III and IVA was 26% (21). In patients undergoing extended field concurrent chemoradiotherapy, the 5-year OS was reported to be 50% and stages III-IV were independent predictors of lower cause-specific survival. The only prognostic factors of cause-specific survival were stages III-IV (22). GOG study reported that the 3-year OS rates were 50% for stage I, 39% for stage II, and 38% for stage III/IVA in patients with cervical carcinoma metastatic to PAN treated with EF-CCRT (7). Furthermore, the recent NCDB data showed that the 5-year OS rates in patients with PAN-positive cervical cancer were 36.8% in T1B, 42.2% in T2, and 31.4% in T3 patients. The NCDB data also showed that there was no difference in survival for T4A disease based on nodal status (23). In our patients, the 5-year OS was 100% for stage IB, 80.0% for stage IIB, and 24.4% for stage IIIB. Because of the small number of patients, the efficacy of neoadjuvant chemotherapy followed by EF-CCRT is unclear; however, the patients with stages IB and IIB were alive without recurrence for over a year. Owing to its feasibility and potential efficacy, neoadjuvant chemotherapy followed by

EF-CCRT may improve the prognosis of patients with stages IB and II cervical cancer with positive PAN.

However, we continued to observe a poor prognosis in stage IIIB disease with positive PAN. Twelve of 17 patients with stage IIIB disease died from the disease. Of these patients, three had progressive disease in neoadjuvant chemotherapy, one had progressive disease in EF-CCRT, one had residual disease after EF-CCRT, and the remaining seven had distant failure. Other effective strategies, such as bevacizumab (24) and immune check point inhibitors (25, 26), should be investigated for a subset of patients with stage IIIB disease.

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. YS, YN, TT, WK, and YA made substantial contribution to the conception, designed methods, interpreted the results, and wrote the manuscript. TA, JH, TN, YT, YA, TN, TO, WK, IK, KN, KM, and YA engaged in data acquisition and analyzed the data. YS and YA substantively revised the manuscript. All Authors treated patients, have read the manuscript, and have approved this submission.

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