Original Articles

Efficacy of neoadjuvant chemotherapy followed by radical hysterectomy in locally advanced non-squamous carcinoma of the uterine cervix: a retrospective multicenter study of Tohoku Gynecologic Cancer Unit

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Summary

Objective: Radical hysterectomy (RH) is a standard treatment for locally advanced non-squamous cell carcinoma (N-SCC) of the uterine cervix, but there have been no reports on whether neoadjuvant chemotherapy (NAC) followed by radical hysterectomy could improve the outcome of patients with this disease. *Materials and Methods:* This multicenter retrospective study enrolled 77 patients with Stage IB2 to IIB N-SCC of the uterine cervix. Of these, 27 patients were treated with NAC prior to radical hysterectomy (NAC group) and 50 with RH alone (RH group). The two-year recurrence-free survival (RFS) rate, progression-free survival (PFS), and overall survival (OS) were compared between the two groups. Clinical parameters such as clinical stage, histological type, and post-operative treatment were also examined between the groups. *Results:* While the two-year RFS rates were 81.5% and 70.0% in NAC and RH groups, respectively ($p = 0.27$) and the median PFS was 51 months and 35 months in NAC and RH groups, respectively ($p = 0.35$), the median OS was 58 months and 48 months in NAC and RH groups, respectively, which was significant ($p = 0.0014$). The median OS of patients with mucinous adenocarcinoma in NAC group was significantly higher than that in RH group: 58 months versus 37 months ($p = 0.03$). *Conclusion:* NAC prior to RH may offer the prognostic advantage of patients with locally advanced N-SCC of the uterine cervix, especially mucinous adenocarcinoma.

Key words: Uterine cervical carcinoma; Non-squamous cell carcinoma; Neoadjuvant chemotherapy; Radical hysterectomy; Outcome.

Introduction

Radical hysterectomy and radiotherapy are a traditional therapeutic modality for invasive carcinoma of the uterine cervix in Japan. Since some observations showed that chemo-radiotherapy with cisplatin offered the advantage of clinical outcome in locally advanced carcinoma of the uterine cervix, chemotherapy has become the treatment of preference of uterine cervical carcinoma [1-7]. The Italian multicenter randomized study, which enrolled patients with locally advanced Stage IB2 to IIB squamous cell carcinoma of the uterine cervix, showed that NAC prior to RH improved the patient outcome as compared to conventional radiation therapy alone [8]. Combination of docetaxel and carboplatin in the neoadjuvant setting for patients with advanced or recurrent uterine cervical malignancy showed complete or partial response in all of patients with uterine cervical adenocarcinoma, suggesting that the combination may be quite promising for treatment of uterine cervical adenocarcinoma [9]. However, there is no evidence that NAC improves the outcome of patients with uterine cervical adenocarcinoma. The aim of this multicenter study was to retrospectively evaluate whether NAC can improve the outcome of patients with locally advanced N-SCC of the uterine cervix.

Materials and Methods

This study enrolled 77 patients with Stage IB2 to IIB N-SCC of the uterine cervix who underwent RH at the institutions belonging to the Tohoku Gynecologic Cancer Unit (TGCU) between January 1996 and December 2008. Of these, 27 patients were treated with NAC prior to RH (NAC group), and 50 patients were treated with RH alone (RH group). The two-year recurrence-free survival (RFS) rate, progression-free survival (PFS), and overall survival (OS) were compared between the two groups. Clinical parameters, such as: clinical stage, histological type, and postoperative treatment were also examined between the groups.

The PFS and OS in the two groups were calculated by the Kaplan-Meier method, and the statistical significance of differences in the cumulative curves between the two groups was evaluated by log-rank test. Categorical variables comparisons were conduced by two-tailed Chi square or Mann-Whitney U test where appropriate. A result was deemed significant at $p < 0.05$.

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Results

Patient characteristics

The median age was 49 and 45 years in NAC and RH groups, respectively. Eleven (40.7%) and 29 (58.0%) patients had Stage IB2 disease in NAC and RH groups, respectively, and 16 (59.3%) and 21 (42.0%) patients had Stage II disease NAC and RH groups, respectively. In regard to the histological type, 13 patients had mucinous adenocarcinoma, four had endometrioid adenocarcinoma, three had clear cell carcinoma, and seven had adenosquamous carcinoma in the NAC group, while 27 patients had mucinous adenocarcinoma, nine had endometrioid adenocarcinoma, two had clear cell carcinoma, nine had adenosquamous carcinoma, and three had other types in RH group. Of the 27 patients in NAC group and 50 in RH group, 19 (70.4%) and 40 (80.0%) underwent any postoperative treatments, respectively (Table 1).

Table 1. — *Patient characteristics*.

Variable	NAC (n = 27)	RH (n = 50)	*p* value
Median age in years [range]	49 [30-63]	45 [25-76]	$p = 0.85$*
Stage			
IB2	11 (40.7)	29 (58.0)	$p = 0.15$**
II			
IIA	0	6 (12.0)	
IIB	16 (59.3)	15 (30.0)	
Histological type			
Adenocarcinoma			
mucinous	13 (48.1)	27 (54.0)	$p = 0.98$**
endometrioid	4 (14.9)	9 (18.0)	
clear cell	3 (11.1)	2 (4.0)	
Adenosquamous carcinoma	7 (25.9)	9 (18.0)	
Others	0	3 (6.0)	
Adjuvant therapy			
administered	8 (29.7)	10 (20.0)	$p = 0.34$**
not administered			
Chemotherapy	9 (33.3)	16 (32.0)	
Chemoradiation therapy	5 (18.5)	14 (28.0)	
Radiotherapy	5 (18.5)	10 (20.0)	

*Mann-Whitney U test, **Chi-square test, numbers of parenthesis represent %.

NAC regimens and number of cycles

Because this was a retrospective and multicenter study, the combination of anti-cancer agents utilized was heterogeneous as shown in Table 2. Of the 27 patients in NAC group, eight received DC: seven patients received two cycles and one patient received three cycles. Five patients received cisplatin alone. Four patients received MEP: one patient received one cycle, two patients received two cycles, and one patient received three cycles. Three patients received TC of two cycles. Three patients received FCAP: one patient received one cycle and two patients received three cycles. Other four patients received cisplatin/CPT-11 of two cycles, cisplatin/Adriamycin of two cycles, cisplatin/mitomycin C of three cycles, and carboplatin/actinomycin D of three cycles, respectively.

Table 2. — *List of NAC regimens*.

Regimen	No. of patients
DC (Docetaxel 70 mg/m^2, carboplatin AUC6 day 1 q21 days)	8
Cisplatin alone (total 200 mg/body for 3 days)	5
MEP (MMC 10 mg/m^2 day 1, etoposide100 mg/m^2 days 1,3,5, cisplatin 50 mg/m^2 day 1, q28 days)	4
TC (Paclitacel 175 mg/m^2, carboplatin AUC6 day 1 q21 days)	3
FCAP (5-FU 200 mg/body, CPM100 mg/body, cisplatin 20 mg/m^2 days 1-7, ADM 35 mg/m^2 day 7)	3
Cisplatin/CPT-11 (cisplatin 70 mg/m^2 day 1, CPT-11 70 mg/m^2 days 1,8 q21 days)	1
Cisplatin/ADM (cisplatin 100 mg/body, ADR 40 mg/body days 1,2 q21 days)	1
Cisplatin/MMC (cisplatin 50 mg/body, MMC 4 mg/body day 1 q21 days)	1
Carboplatin/Actinomycin D (Carboplatin 300 mg/body, Actinomycin D 1.5 mg/body day 1 q21 days)	1

MMC: mitomycin C; CPM: cyclophosphamide; ADM: adriamycin.

Comparison of clinical outcome between NAC and RH groups

The two-year RFS rate was 81.5% in NAC group and 70.0% in RH group ($p = 0.27$, Table 3). The median PFS was 51 months (range, 14-157 months) in NAC group and 35 months (range, 4-157 months) in RH group ($p = 0.35$, Table 3). On the other hand, the median OS was 58 months (range, 15-157 months) in NAC group and 48 months (range, 9-157 months) in RH group, which was significant ($p = 0.0014$, Table 3 and Figure 1A).

Table 3. — *Comparison of the clinical outcome between the two groups*.

	NAC (n = 27)	RH (n = 50)	*p* value
Two-year RFS rate	81.5% (22/27)	70.0% (35/50)	$p = 0.27$
Median PFS (range)	51 months (14-157)	35 months (4-157)	$p = 0.35$
Median OS (range)	58 months (15-157)	48 months (9-157)	$p = 0.0014$

RFS: recurrence free survival; PFS: progression-free survival; OS: overall survival.

Comparison of clinical outcome according to clinical parameters

There were no significant differences in the median PFS and OS between NAC and RH groups according to stage, histological type and adjuvant therapy, except mucinous adenocarcinoma (Table 4). While the median PFS of patients with mucinous adenocarcinoma was 58 months (range, 8-124 months) in NAC group and 33 months (range, 4-125 months) in RH group ($p = 0.34$), the median OS of those with mucinous adenocarcinoma was 58 months (range, 24-124 months) in NAC group and 37 months (range, 9-125 months) in RH group, which was significant ($p = 0.03$) (Table 4 and Figure 1B).

Clinical outcome according to therapeutic modality after NAC and radical surgery

The outcome of patients who underwent chemotherapy or chemoradiotherapy or radiotherapy after NAC and RH were compared. As shown in Table 5, chemotherapy after NAC and surgery prolonged PFS and OS, and increased

Table 4. — *Comparison of the clinical outcome according to clinical parameters.*

Clinical parameters	Median PFS			Median OS		
	NAC	RH	*p* value	NAC	RH	*p* value
Stage						
IB2	64 (11-157)	37 (9-157)	0.26	64 (15-157)	54 (12-157)	0.26
II	33 (4-124)	45 (4-92)	0.45	39 (16-124)	45 (9-92)	0.40
Histological type						
Adenocarcinoma						
mucinous	58 (8-124)	33 (4-125)	0.34	58 (24-124)	37 (9-125)	0.03
endometrioid	31 (10-97)	70 (14-97)	0.29	31 (10-97)	70 (20-97)	0.49
clear cell	22 (4-108)	64 (12-106)	0.89	22 (16-108)	83 (60-106)	0.41
Adenosquamous	36 (12-157)	45 (12-157)	0.11	43 (21-157)	46 (12-157)	0.31
Adjuvant therapy						
administered	77 (25-157)	31 (5-157)	0.18	77 (35-157)	32 (12-157)	0.24
not administered	33 (4-124)	47 (4-106)	0.66	39 (16-124)	51 (9-106)	0.61

Numbers show months: Parenthesis means range. PFS: progression-free survival; OS: overall survival.

Table 5. — *Clinical outcome according to therapeutic modality after NAC and radical surgery.*

	Chemotherapy (n = 9)	Chemoradiotherapy (n = 5)	Radiotherapy (n = 5)
PFS (months)	42 (10-108)	30 (4-76)	22 (8-97)
OS (months)	42 (19-108)	30 (16-76)	31 (22-97)
Two-year RFS rate	88.9%	60.0%	60.0%

PFS: progression-free survival; OS: overall survival; RFS: recurrence free survival.

the two-year RFS rate compared to chemoradiotherapy or radiotherapy after NAC and surgery, although they did not reach significance.

Discussion

Numerous phase II studies have reported the favorable effects of NAC in the treatment of locally advanced carcinoma of the uterine cervix. The authors have previously reported the efficacy and safety of NAC with cisplatin plus irinotecan in this disease [10]. However, few randomized clinical trials (RCT) have evaluated the effect of NAC in the clinical outcome of patients with this disease. Sardi *et al*. reported a significant improvement of the seven-year survival rate in patients treated by NAC and radical surgery and radiotherapy (65%), as compared with that in those treated by radical surgery and radiotherapy (41%) in a four-arm randomized controlled trial (RCT) (NAC and radical surgery and radiotherapy, radical surgery and radiotherapy, radiotherapy alone, and NAC and radiotherapy) [11]. However, the retrospective study did not show obvious improvement of the five-year survival rate in patients with Stage IB2 carcinoma of the uterine cervix treated by NAC prior to surgery, as compared with that in those treated by surgery alone (80% versus 69%) [12]. These two reports were conducted in patients with SCC of the uterine cervix. Since N-SCC of the uterine cervix has recently increased in Japan, it is an important issue to evaluate the effectiveness of NAC in the outcome of patients with N-SCC of the uterine cervix. Some evidence showed that the outcome of patients with N-SCC of the uterine cervix was poorer than that of patients with SCC of the uterine cervix [13, 14], because of the higher incidence of lymph node metastases at a relatively early stage of the disease, and a lower sensitivity to radiotherapy in N-SCC of the uterine cervix [15, 16]. Chemotherapy is therefore expected to have a greater beneficial effect on the outcome of patients with N-SCC than radiotherapy or chemoradiation therapy. Because the present study was conducted retrospectively in multicenters, the combination of anti-cancer agents used was heterogeneous. The NAC regimens used in this study invariably included one of platimun derivatives, such as cisplatin and carboplatin, so platimun agents seem favorable for chemotherapy prior to surgery in N-SCC of the uterine cervix.

The two-year RFS rate and the median PFS were better in NAC group than in RH group, which were not significant, whereas the median OS in NAC group was significantly longer than in RH group ($p = 0.0014$). Furthermore, prognostic analysis in clinical parameters showed that the median OS of patients with mucinous adenocarcinoma in NAC group was significantly longer than in RH group ($p = 0.03$), although other histological types and postoperative treatment did not significantly affect the prognosis of patients between NAC and RH groups. These results suggest that NAC may offer the prognostic advantage of patients with locally advanced N-SCC of the uterine cervix, especially mucinous adenocarcinoma. Because mucinous adenocarcinoma accounts for approximately 70% out of adenocarcinomas of the uterine cervix, NAC may improve prognosis of patients with N-SCC of the uterine cervix, although NAC should be used individually at the present time.

The present study showed that chemotherapy after NAC and surgery prolonged PFS and OS, compared to chemoradiotherapy or radiotherapy after NAC and surgery, which did not reach significance. Tattersall *et al*. reported that primary chemotherapy followed by radiotherapy significantly decreased the survival rate of patients with uterine cervical carcinoma compared to those who were treated by radiotherapy alone [17]; furthermore, meta-analysis showed that chemotherapy followed by radiotherapy did not improve the survival time

Fig. 1A

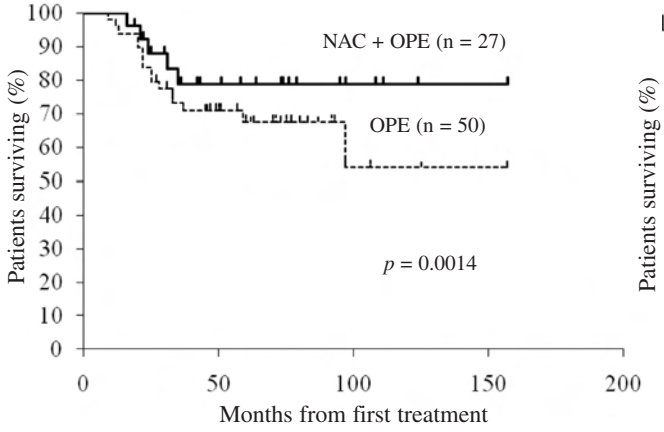

Fig. 1B

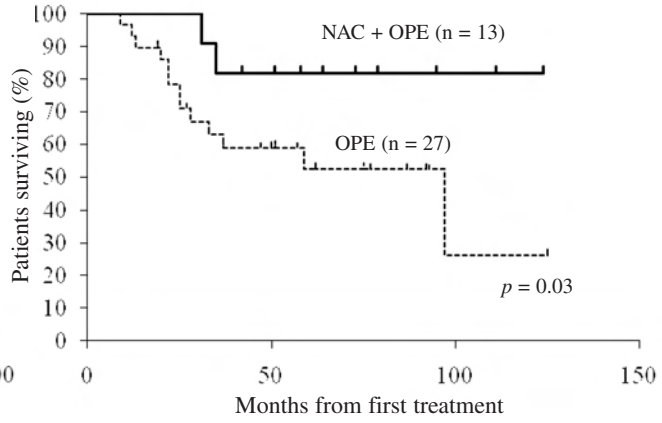

Figure 1. — 1A: overall survival in all patients who underwent neoadjuvant chemotherapy followed by radical hysterectomoy (NAC) or radical hysterectomy alone (RH). 1B: overall survival in patients with mucinous adenocarcinoma who underwent neoadjuvant chemotherapy followed by radical hysterectomoy (NAC) or radical hysterectomy alone (RH).

in uterine cervical carcinoma [18]. Considering these reports together with the present results, chemoradiotherapy or radiotherapy after NAC and surgery may contribute to unfavorable outcome of the patients with uterine cervical adenocarcinoma compared to chemotherapy after NAC and surgery, although further investigation is necessary to confirm the appropriate therapeutic modality follwing NAC and surgery.

The recent reports demonstrated that taxanes were used effectively in NAC for uterine cervical adenocarcinoma [19, 20]. Most of the institutions joining TGCU had adopted cisplatin-based regimens in the 1990s, and switched to the regimens combining taxanes and platinum derivatives after 2000. Despite the diverse NAC regimens and the small sample size, the authors believe that the present results have provided constructive ideas for the development of new therapeutic strategy for N-SCC of the uterine cervix. An effective chemotherapeutic regimen for N-SCC of the uterine cervix should be urgently integrated in a phase II study and then a RCT that compares a new single NAC and radical surgery with radical surgery alone, is warranted to confirm the present results.

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