

Neoadjuvant chemotherapy for locally advanced cervical cancer

Takashi Iwata¹, Azumi Miyauchi¹, Yukako Suga¹, Hiroshi Nishio¹, Masaru Nakamura¹, Akiko Ohno¹, Nobumaru Hirao¹, Tohru Morisada¹, Kyoko Tanaka¹, Hiroki Ueyama¹, Hidemichi Watari², Daisuke Aoki¹

¹Department of Obstetrics and Gynecology, Keio University School of Medicine, Tokyo, Japan; ²Department of Obstetrics and Gynecology, Hokkaido University Graduate School of Medicine, Sapporo, Hokkaido, Japan

Correspondence to: Takashi Iwata, MD, PhD. Department of Obstetrics and Gynecology, Keio University School of Medicine, 35 Shinanomachi, Shinjuku-ku, Tokyo, Japan. Email: iwatakashi@1995.jukuin.keio.ac.jp.

Abstract: Neoadjuvant chemotherapy followed by surgery (NCS) has not been fully evaluated clinically. Currently, the main regimen of neoadjuvant chemotherapy (NAC) used in NCS includes cisplatin. The antitumor effects of NAC reduce lymph node metastasis and the tumor diameter in patients prior to surgery, and this can reduce the number of high risk patients who require postoperative radiation therapy. Many randomized controlled trials (RCTs) have examined the long-term prognosis of NCS compared to primary surgery, but the utility of NCS remains uncertain. The advent of concurrent chemoradiotherapy (CCRT) has markedly improved the outcome of radiotherapy (RT), and CCRT is now used as a standard method in many cases of advanced bulky cervical cancer. NCS gives a better treatment outcome than radiation therapy alone, but it is important to verify that NCS gives a similar or better outcome compared to CCRT.

Keywords: Neoadjuvant chemotherapy (NAC); cervical cancer

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Introduction

Cervical cancer is the second most common cancer in females worldwide, with 500,000 new patients and 300,000 deaths due to this cancer reported globally each year (1). Among cervical cancer cases, 80% occur in developing countries (2) and about 70% are identified as advanced cancer (3). Treatment of cervical cancer is currently conducted based on the 2009 Federation of Gynecology and Obstetrics (FIGO) staging system (4), with FIGO stage IB1 and IIA1 cases treated by surgery or radiotherapy (RT) if no lymph node metastasis is observed. In contrast, the appropriate treatment for cervical cancer of stages IB2, IIA2, and IIB remains uncertain. Major treatment options include radical surgery with or without postoperative RT, neoadjuvant chemotherapy (NAC) followed by Radical surgery with or without postoperative RT, and concurrent chemoradiotherapy (CCRT). Radical surgery usually entails type III radical hysterectomy including pelvic lymphadenectomy with or without para-aortic lymphadenectomy (5). For stage IB2 and IIA2 cervical

cancer, the National Comprehensive Cancer Network clinical guidelines mainly recommend CCRT (category 1) and to a lesser degree radical hysterectomy with pelvic lymphadenectomy and para-aortic lymph node sampling (category 2b). Stage IIB or more advanced cases are treated by RT because surgery is not applicable in these cases. However, the prognosis is poor and the five-year survival rate is about 40% (6).

Cervical cancers are sensitive to chemotherapy, and thus trials of chemotherapy combined with radiotherapy or surgery continue to be performed. In 1999, the National Cancer Institute recommended CCRT as the standard approach for locally advanced cervical cancer, based on a 30-50% decrease in mortality (7-10). In Europe, Japan and Latin countries, NAC followed by surgery (NCS) has emerged as a valid alternative and several pilot studies have shown a large benefit over RT alone in terms of overall survival (OS) and disease-free survival (DFS) (11). The best evaluation of the addition of chemotherapy to surgery is through a direct comparison with surgery alone, But when compared with primary surgery, the efficacy of NCS has

not been determined in previous randomized controlled trials (RCTs) (5,12-14) or observational studies (15-17). Recent reviews of NCS for cervical cancer have shown no significant benefit in OS over surgery alone (18,19).

Advantages and disadvantages of neoadjuvant chemotherapy (NAC) for cervical cancer

The benefits of NCS are improvement of the radical cure rate, safety, a possible increase in the number of cases for which surgery is applicable due to the reduced tumor size, and suppression of remote metastasis by elimination of minute metastatic lesions. Zhang *et al.* (20) found that the rate of intrapelvic lymph node metastasis was significantly decreased in patients treated with NCS compared to those who underwent primary surgery because apoptosis in lymph nodes was induced by NAC. Further advantages of NCS include drugs reaching the tumor more easily because blood circulation to the tumor is not hampered by surgery or RT; and maintenance of hematopoiesis since there is no myelosuppression due to RT. In addition, NCS may be used as a substitute treatment in regions without facilities to conduct CCRT (21). However, NCS has disadvantages in that the treatment period is prolonged if chemotherapy is not successful, medical expenses are increased, patients may receive overmedication, and the tumor may progress before surgery. Autologous blood for autotransfusion also cannot be collected preoperatively in some cases and intraoperative blood transfusion may be needed due to anemia during chemotherapy. Therefore, the treatment approach should be selected after considering both the advantages and disadvantages of NCS.

Clinical research on the efficacy of NAC

NAC is more effective than RT alone based on a meta-analysis of RCTs (22), but comparison with surgery is required to clarify the efficacy of NCS. The following clinical studies performed a comparison of NCS with surgery alone (larify theRT) (Table 1).

(I) Sardi *et al.* (1997) (12)

A RCT was conducted for stage IB squamous cell carcinoma in NCS + RT and surgery + RT groups. The NAC regimen was cisplatin (CDDP) + vincristine (VCR) + bleomycin (BLM). There was no difference in the prognosis of patients with a tumor diameter ≤ 4 cm between the two groups, but the NCS group had a higher surgery completion rate in patients with a tumor diameter >4 cm.

These findings suggest that NCS can significantly prolong OS by reducing poor pathological prognostic factors.

(II) Napolitano *et al.* (2003) (13)

A RCT was conducted for IB-IIIB squamous cell cancers in NCS (\pm RT) and surgery (\pm RT) groups. The NAC regimen was CDDP + VCR + BLM. In the NCS group, extensive total hysterectomy was required in some cases. NAC contributed to prolonged survival in stage IB-IIIB cases, but there was no significant difference in stage IIB cases.

(III) Cai *et al.* (2006) (14)

A RCT was conducted for stage IB squamous cell cancer and adenocarcinoma in NCS (\pm RT) and surgery (\pm RT) groups. The NAC regimen was CDDP + 5-fluorouracil (5-FU). Antitumor effects of NAC were observed in 84.2% of the patients (CCR: 7.7%, PR: 76.9%, SD: 15.4%). The lymph node metastasis rate was much lower in the NCS group than in the surgery group (9.6% *vs.* 29.6%, $P=0.04$) and vascular space involvement was also significantly lower in the NCS group (9.6% *vs.* 27.8%, $P=0.024$). There was no significant difference in the incidence of parametrial invasion, but the five-year survival rate was significant higher in the NCS group compared to the surgery group (84.6% *vs.* 75.9%, $P=0.0112$). These results suggest that NCS significantly prolongs long-term survival through suppression of lymph node metastasis and reduction of poor pathological prognostic factors.

(IV) Katsumata *et al.* (2006) (5)

A RCT was conducted for stage IB2-IIIB squamous cell cancers in NCS (\pm RT) and surgery (\pm RT) groups. The NAC regimen was BLM + VCR + MitomycinC (MMC) + CDDP. The four-year survival rates were 74.6% in the NCS group and 74.4% in the surgery group, with no significant difference between the groups. It should be noted that termination of this trial was recommended during the trial since an interim analysis showed a low over all survival rate in patients receiving NAC.

(V) Eddy *et al.* (2007) (23)

A RCT (GOG141 study) was conducted for stage IB2 squamous cell cancer, adenosquamous carcinoma and adenocarcinoma in NCS (\pm RT) and surgery (\pm RT) groups. The NAC regimen was CDDP + VCR. There was no significant difference in recurrence and mortality rates, or in the total hysterectomy rate. Thus, this trial indicated no usefulness of NCS.

(VI) Chen *et al.* (2008) (24)

A RCT was conducted for stage IB2-IIIB squamous cell cancer, adenosquamous carcinoma and adenocarcinoma

Table 1 Demographic characteristics of 6 RCT studies

Author	FIGO stage	Histology	Comparison (No. of patients)	Regimen of NAC	Cycles of NAC
Sardi (1997) (12)	IB	SCC	NCS + RT [102] Surgery + RT [103]	CDDP 50 mg/m ² day 1 VCR 1 mg/m ² day 1 BLM 25 mg/m ² day 1-3	Every 10 days for 3 cycles
Napolitano (2003) (13)	IB-IIIB	SCC	NCS ± RT [106] Surgery ± RT [86]	CDDP 50 mg/m ² day 1 VCR 1 mg/m ² day 1 BLM 25 mg/m ² day 1-3	Every 21 days for 3 cycles
Cai (2006) (14)	IB	SCC AD	NCS ± RT [52] Surgery ± RT [54]	CDDP 75 mg/m ² day 1 5-FU 24 mg/kg day 1-5	Every 21 days for 2 cycles
Katsumata (2006) (5)	IB2-IIIB	SCC	NCS ± RT [29] Surgery ± RT [33]	BLM 7 mg/m ² day 1-5 VCR 0.7 mg/m ² day 5 MMC 7 mg/m ² day 5 CDDP 14 mg/m ² day 1-5	Every 21 days for 2 cycles
Eddy (2007) (23)	IB2	SCC AD, ASC	NCS ± RT [145] Surgery ± RT [143]	CDDP 50 mg/m ² day 1 VCR 1 mg/m ² day 1	Every 10 days for 3 cycles
Chen (2008) (24)	IB2-IIIB	SCC AD, ASC	NCS ± RT [72] Surgery ± RT [70]	CDDP 100 mg/m ² day 1 MMC 4 mg/m ² day 1-5 5-FU 24 mg/kg day 1-5	Every 14 days for 2-3 cycles

RCT, randomized controlled trial; FIGO, Federation of Gynecology and Obstetrics; NAC, neoadjuvant chemotherapy; SCC, squamous cell carcinoma; NCS, neoadjuvant chemotherapy followed by surgery; RT, radiotherapy; VCR, vincristine; BLM, bleomycin; AC, adenocarcinoma; ASC, adenosquamous carcinoma; 5-FU, 5-fluorouracil; MMC, MitomycinC.

in NCS (± RT) and surgery (± RT) groups. The NAC regimen was CDDP + MMC + 5-FU. The success rate of NAC [complete response (CR) + partial response (PR)] was 69.4%, and in the NCS group PFS was significantly prolonged and the recurrence rate was significantly reduced in CR + PR cases compared to stable disease (SD) + progression disease (PD) cases. The four-year survival rate was significantly greater in the NCS group compared to the surgery group (71.0% vs. 58.0%, $P=0.041$). However, in multivariate analysis, NAC was not an independent prognostic factor ($P=0.074$). The side effects of NAC were within the acceptable range, poor pathological prognostic factors were eliminated, and the prognosis was significantly improved in CR + PR cases with reduced tumor diameters.

Review articles

In the Cochrane review (18) conducted in 2010, 1,036 cases in six RCTs were analyzed, and the NCS group had better PFS compared to the surgery group. The local recurrence rate and remote metastasis rate were lower in the NCS group, but there was no significant difference and no improvement in OS. There was also no significant difference in the extended total hysterectomy rate. Thus, although NCS may improve the prognosis, these results did not prove greater efficacy of this method over primary surgery, and it was concluded that NSC should continue to be used only in clinical trials.

The Cochrane review was updated in 2012 (25) with addition of data for OS, local recurrence and remote

metastasis in the RCT conducted by Chen *et al.* (24) This analysis showed significantly better PFS and OS in the NCS group compared to the surgery group, and the local recurrence rate was also significantly decreased in the NCS group. Chemotherapy is a systemic treatment, in contrast to localized treatment with RT, and therefore it was expected that NCS would decrease the remote metastasis rate. However, there was actually no significant difference in this rate between the NCS and surgery groups. Moreover, since postoperative RT was conducted together with NCS in many studies, it could not be concluded that the decreased local recurrence was due only to NCS. The total hysterectomy rate was evaluable based on the effect of NCS alone, but this rate showed no significant improvement with NCS. However, the lymph node metastasis rate and the incidence of parametrial invasion were lower in the NCS group compared to the surgery group.

Markers reflecting the prognosis of NCS cases

The benefits of NCS have yet to be proven and the method also has disadvantages of a prolonged treatment period, increased medical expenses, and the possibility of tumor progression. Therefore, selection of patients for whom NCS is likely to be successful and improve the prognosis is particularly important. In an analysis of serum metabolites after performance of NCS in 38 stage 1B2-IIIB squamous cell cancer patients, Hou *et al.* found that L-valine and L-tryptophan were significantly higher in the pathological CR and PR groups compared to the SD group (26). The NAC regimen was PTX + CDDP.

Takatori *et al.* (27) investigated the effects of factors such as age, PS, clinical stage, histological type, tumor diameter, presence of lymph node metastasis before NCS, postoperative chemotherapy, squamous cell carcinoma antigen (SCC) levels before and after NCS, and success of anticancer drug therapy on prognosis after NCS. The regimen of NAC was irinotecan + CDDP. Among these factors, lymph node metastasis before treatment, SCC level after NCS, and the success rate of anticancer drug therapy were related to the prognosis. Thus, it was concluded that lymph node metastasis determined by CT is the most useful factor for selection of appropriate patients for NCS before the start of treatment.

Lu *et al.* (28) reviewed two RCTs and nine observational studies conducted from 1987 to 2012 to investigate whether the success rate of NCS is changed by histologic type. In patients in stage IIB and more advanced stages,

NCS significantly improved OS and PFS in squamous cell cancer compared to non-squamous cell cancers including adenocarcinoma.

NCS for cervical cancer in pregnancy

Cervical cancer in pregnancy accounts for about 2% of all cervical cancer cases and most of the cases are early-stage invasive cancers. Handling of continuation of pregnancy is unclear in these cases. If invasive cancer is found in the early stage, pregnancy may need to be terminated and total hysterectomy conducted. Alternatively, total hysterectomy can be delayed until the child is born, after the patient understands the risk of disease progression. In such cases, NCS can prevent progression of cancer and allow surgery to be delayed until the child is born. In an analysis of treatment outcomes in more than 47 pregnant females who underwent NSC, Zagouri *et al.* (29) found that the prognoses of mothers and babies were good. For NAC in pregnant women, drug administration after 14 weeks of pregnancy is recommended due to the reduced teratogenic risk after this period (30).

NCS using drugs other than CDDP

CDDP is currently the most important drug for cervical cancer and the regimen in many RCTs includes CDDP. However, clinical studies using drugs other than CDDP have also been reported. NCS has been performed using CDDP + PTX (31,32), but there has been no RCT of this treatment. The Japanese Gynecologic Oncology Group (JGOG) conducted a phase II multicenter clinical study on NCS in patients in stage Ib2-IVb (33). The success rate of NAC in CR + PR cases was 75.8% and the side effects were within an acceptable range. However, the success rate was not higher than that of NAC using CDDP + CPT-11 and there is currently no plan to conduct a phase III clinical trial.

Conclusions

The efficacy of NCS for cervical cancer has yet to be verified, but this treatment can reduce the risk factors of lymph node metastasis and vascular invasion and avoid the need for additional therapy such as postoperative RT. The prognosis may be improved by NCS in cases showing CR or those with elimination of lymph node metastasis by NAC. Thus, better treatment outcomes of NCS with a higher success

rate are likely through combination with chemotherapy. NCS gives better outcomes than RT alone (22), but CCRT combined with CDDP also results in a better prognosis than RT alone and is currently the standard therapeutic approach for advanced bulky cervical cancer. Thus, a RCT comparing NCS and CCRT is required to investigate the utility of NCS.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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