Review Article

Concurrent chemoradiotherapy for cervical cancer: background including evidence-based data, pitfalls of the data, limitation of treatment in certain groups

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Abstract: Concurrent chemoradiotherapy (CCRT) is regarded as the standard treatment for locally advanced uterine cervical cancer (LACC), including stage Ib2-IVa disease [International Federation of Gynecology and Obstetrics (FIGO) staging]. However, approximately a third of eligible patients in previous studies died of LACC despite receiving CCRT. The therapeutic significance of CCRT alone in stage III-IVa disease has not yet been confirmed. Effective treatment of some LACC is beyond the scope of CCRT. The objective of the present review is to highlight some challenging work aimed at overcoming this seemingly intractable disease. CCRT with increased peak concentrations of cisplatin (CDDP), surgery following CCRT, adjuvant chemotherapy (CT) following CCRT, and neoadjuvant CT followed by CCRT are strategies expected to enhance the therapeutic efficacy of CCRT. If patients with LACC were divided into those with low-risk or high-risk systemic disease or prognoses, novel strategies should be assessed in the group with high-risk disease.

Keywords: Concurrent chemoradiotherapy (CCRT); locally advanced cervical cancer (LACC); adjuvant chemotherapy (CT)

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Introduction

Among women worldwide, cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death, accounting for 8% [275,100] of total cancer deaths among women in 2008 (1). In China, cervical cancer is the seventh most commonly diagnosed cancer and the eighth leading cause of cancer death in women, accounting for 2.6% of total cancer deaths among women in 2010 (2). More than a decade ago, several randomized controlled trials (RCTs) reported significant survival advantages for patients who received concurrent chemoradiotherapy (CCRT) compared with those who received radiation therapy (RT) alone (3-6). CCRT has also become a standard treatment for locally advanced cervical cancer (LACC) in Japan. However, CCRT was introduced differently in Japan than in Western countries. Because of the nationwide use of Okabayashi radical hysterectomy (corresponding to class IV hysterectomy in Piver's classification), patients who present with International Federation of Gynecology and Obstetrics (FIGO) stage Ib disease rarely receive CCRT; surgery is the treatment of choice for stage IIb disease in Japan (7). Whereas previous RCT populations mainly had stage I-II disease (3-6,8), Japanese patients who undergo CCRT often have stage III-IVa disease. Therefore, Japanese studies may offer useful findings regarding the therapeutic limit of CCRT. In this manuscript, there are two issues to be discussed: (I) the therapeutic limit of CCRT; and (II) a new treatment strategy for high-risk LACC.

Indications for CCRT according to the clinical guidelines

CCRT is the standard treatment for stage III-IVa cervical

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Table 1 Literature review of prognostic factors for patients treated with CCRT

Author	Year of publication	Patient number	Stage III/IV rate (%)	Prognostic factors
Parker *et al*. (17)	2009	92	29	Tumor size (>4 cm), pretreatment hemoglobin
Lim *et al*. (18)	2009	69	26	Nodal involvement, pretreatment hemoglobin, completion of BRT
Kim *et al*. (20)	2012	174	32	Stage, tumor size (>4 cm), clinical response
Kudaka *et al*. (21)	2012	99	100	Tumor size (>5.5 cm), pretreatment hemoglobin
Endo *et al*. (19)	2014	85	81	Tumor size (>6 cm), pelvic lymph node enlargement, distant metastasis

CCRT, concurrent chemoradiotherapy; BRT, brachytherapy.

cancer in various guidelines including: the National Comprehensive Cancer Network (NCCN) (9); the National Cancer Institute (10); the European Society of Medical Oncology (11); the Arbeitsgemeinschaft fur Gynakologische Onkologie (12); and the Japan Society of Gynecologic Oncology (7). Among them, the description in the NCCN clinical guidelines is noteworthy; surgical staging, namely extraperitoneal or laparoscopic lymph node dissection is listed as an alternative for stage IB2-IVA patients. Unless surgical staging is performed, the guideline instructs physicians to consider resection of radiologically enlarged lymph nodes. In a nutshell, the NCCN clinical guidelines imply that some LACC with lymph node metastasis cannot be cured by CCRT alone.

Pitfalls of clinical evidence regarding CCRT

Systematic reviews have reported that CCRT is therapeutically superior to RT alone in treating LACC (13,14). However, most positive trials of CCRT had small percentages of patients with stage III-IV disease. In contrast, fewer than 16% of Japanese institutions offer CCRT to patients with stage IB2/IIA bulky disease (15). As for stage IIB disease, 32% and 17% of Japanese institutions offer CCRT to patients with squamous and non-squamous cell carcinoma; respectively (15). Large percentages of patients in Japan with stage IB2-IIB LACC had radical hysterectomies with regional lymphadenectomies. As a result, a higher percentage of patients treated with CCRT in Japan have stage III-IV disease than in other countries.

In western countries, patients with involved para-aortic lymph nodes have been excluded from some relevant RCTs. On the other hand, surgical staging, namely resection of para-aortic lymph nodes before CCRT, is rarely performed in Japan. Some negative trials of CCRT did not require eligible patients to undergo surgical staging for para-aortic lymph nodes (8,16). Therefore, both the smaller percentage of patients with stage III-IV disease and elimination of those with para-aortic node involvement may have led to more positive results for CCRT in previous meta-analyses. No evidence has supported therapeutic superiority for CCRT over RT alone in Japanese women. One of the findings reported by systematic reviews is noteworthy; it implied that there was a smaller beneficial effect in trials involving a high proportion of stage III/IV patients (13,14). The relative effect of CCRT on survival has been suggested to decrease as stage increases, with estimated absolute 5-year survival benefits of 10% at stages Ia-IIa, 7% at stage IIb, and 3% at stages III-IVa (14). CCRT may have room for improvement as standard treatment for stage III-IV patients.

Therapeutic limit of CCRT

Lymph node enlargement (17-19), tumor diameter (17,19-21), pretreatment hemoglobin level (17,18,21) and clinical stage (20) have been confirmed as prognostic factors for patients with cervical cancer who are treated with CCRT (*Table 1*). Overall treatment period (22) was confirmed as a prognostic factor for patients who are treated with RT.

As described above, CCRT is therapeutically limited by high clinical stage, as is tumor size. Kim *et al*. showed that tumor size was a prognostic factor independent of clinical stage (20); and Kudaka *et al*. showed that tumor size was a prognostic factor in patients with stage III/IV disease (21). Also, larger tumors usually destroy the normal structure of the cervical canal, which may complicate implementation of intracavitary brachytherapy (BRT). What is a reasonable cut-off value for tumor size as a therapeutic limit of CCRT? According to patients with mostly advanced disease, tumors of 5.5-6.0 cm in size are a plausible therapeutic limit for CCRT (19,21).

Lymph node enlargement may also be a therapeutic limit

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Table 2 Literature review of outcomes of surgery after CCRT

Author	Year of publication	Patient number	Radical surgery	Stage III/IV rate (%)	Pathological CR rate (%)	Recurrence rate (%)	Morbidity rate (%) [severe (%)]	Intraoperative complication rate (%)
Azria *et al*. (26)	2005	10	7	0	0	70	70 [40]	NA
Houvenaeghel *et al*. (27)	2005	35	34	54	46	37	14	NA
Distefano *et al*. (28)	2005	100	95	24	45	18	13	6
Classe *et al*. (29)	2006	175	175	22	38	29	26 [7]	NA
Ferrandina *et al*. (30)	2007	161	152	21	44	21	33 [10]	9
Delpech *et al*. (31)	2007	73	24	0	51	33	38 [11]	NA
Huguet *et al*. (32)	2008	92	92	0	55	12	23 [4]	NA
Motton *et al*. (33)	2010	171	43	17	50	32	17	NA
Legge *et al*. (34)	2013	268	268	16	70*	20	25 [8]	NA
Sun *et al*. (35)	2014	192	81	100	86	17	20	NA

*, complete response+microscopic disease; NA, not available. CCRT, concurrent chemoradiotherapy.

of CCRT, as lymph node enlargement adversely affects prognosis independent of cervical tumor size because of differences in maximal radiation doses to lymph node areas and cervical tumor areas. In cases with enlarged lymph nodes, relevant areas will receive varying radiation doses, some of which will be considerably less than optimal.

LACC might be divided into two categories by prognosis: low-risk and high-risk. Novel tactics are needed to improve outcomes for high-risk disease.

Novel treatment strategies for high-risk locally advanced disease

What can be done besides CCRT for patients with large tumors and radiologically enlarged lymph nodes? Potential strategies include (I) increased peak concentration of cisplatin (CDDP); (II) surgery following CCRT; (III) adjuvant chemotherapy (CT) following CCRT; and (IV) neoadjuvant CT before CCRT.

First, concomitant use of definitive RT and CDDP using a higher dose of one medication than standard might be a promising approach. Tumor response to CDDP has been shown to depend on its peak concentration up to 100 mg/m^2 (23,24). However, deterioration in prognosis was observed when treatment was temporarily suspended during CCRT. Side effects that lead to treatment delay are the greatest concern of this strategy. A RCT in which two CCRT regimens were compared in patients with stage IIB-IVA cervical cancer showed a significant survival advantage for patients who had received triweekly CDDP CT (75 mg/m^2 in 3 cycles) concurrent with RT compared with those who received weekly CDDP CT (40 mg/m^2 in 6 cycles) concurrent with RT (5-year overall survival: 89% *vs*. 67%; hazard ratio: 0.375; 95%CI, 0.154-0.914) (25). Higher peak concentrations may be more critical in enhancing the synergy of CCRT than weekly CDDP exposure. The percentage of distant failure in the higher peak group was less than in the lower peak group (17% *vs*. 26%) (25). Higher peak concentrations may also be more effective in eliminating metastatic tumor cells. Compliance between the two groups did not significantly differ (higher peak group: 93%; lower peak group: 86%) (25). Grade 3/4 neutropenia was rather frequent in the lower peak group (39% *vs*. 23%, P=0.03) (25). CCRT with increased peak CDDP concentration might be useful and feasible in LACC, although further study is needed to validate its efficacy.

Second, surgery following CCRT has been evaluated with varying results (*Table 2*) (26-35). Surgical morbidity is the greatest concern of this strategy. Acceptable morbidity was observed in extrafascial hysterectomy (33,35), type II radical hysterectomy (32,33), and type ≥III radical hysterectomy (28,30,34). However, further study is needed to confirm feasibility of type ≥III radical hysterectomy following CCRT. Some studies failed to show a survival advantage for radical hysterectomy over extrafascial hysterectomy (33,35). Sun *et al*. showed that survival in patients who underwent extrafascial hysterectomy was better than that in patients who underwent radical hysterectomy (35). They identified extrafascial hysterectomy with pelvic lymph node dissection as the most feasible surgical approach, even in a population consisting exclusively of

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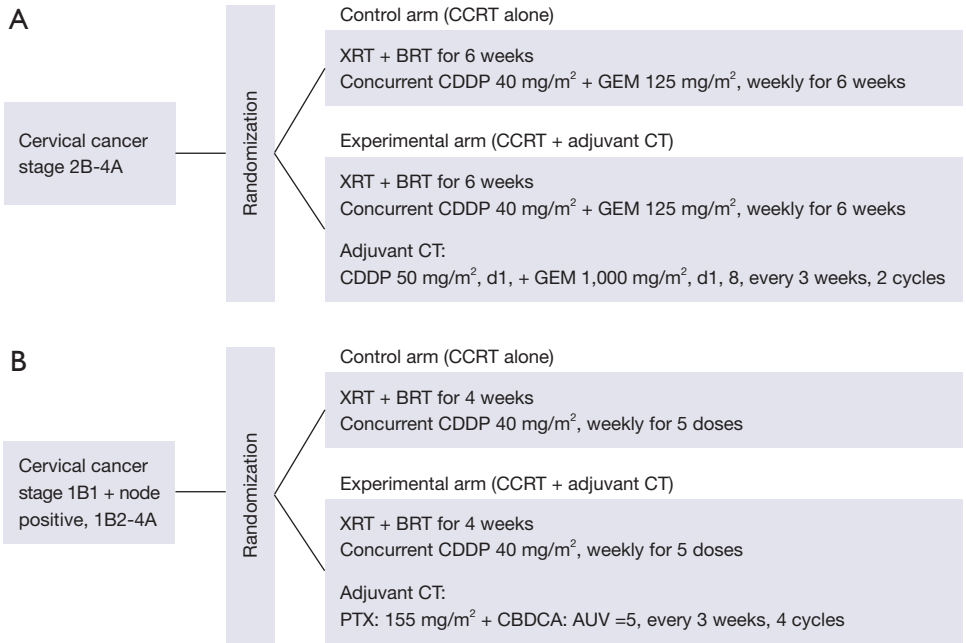

Figure 1 Protocol designs of two randomized controlled studies that CCRT alone with CCRT followed by adjuvant CT. (A) Multinational B9E-MC-JHQS, (B) OUTBACK trial. CCRT, compare concurrent chemoradiotherapy; CT, chemotherapy; XRT, external-beam radiation; BRT, brachytherapy; CDDP, cisplatin; GEM, gemcitabine; PTX, paclitaxel; CBDCA, carboplatin.

stage III/IV patients. Patient selection may also be critical to implement this strategy. Huguet *et al*. reported that type II radical hysterectomy after CCRT for operable bulky stage I/II cervical cancer and negative lymph node metastasis on imaging can be used with acceptable toxicity and good tumor control (32). Residual tumor in resected specimen was seen in 14-100% of patients who underwent surgery after CCRT. Surgery following CCRT undoubtedly leads to improved local control rates. However, distant failure often occurs in LACC. A prospective randomized study should be conducted to assess the survival benefit of this strategy.

Third, adjuvant CT following CCRT appears to be the most promising treatment for advanced cervical cancer. A RCT in which CCRT, with and without adjuvant chemotherapy, was compared in patients with stage IIB-IVA cervical cancer showed a significant survival advantage for patients who underwent CCRT in combination with adjuvant chemotherapy (3-year progression-free survival rates, 74% *vs*. 65%; P=0.029; *Figure 1A*) (36). A meta-analysis suggested a survival advantage for patients who received adjuvant chemotherapy following CCRT compared with those who were treated with CCRT alone (14). However, these data were based on only two trials, one of which investigated totally different CCRT regimens (intravenous mitomycin C and oral 5-fluorouracil) and different CT (oral 5-fluorouracil) from the standard at present. Therefore, the most recent systematic review concluded that no sufficient evidence supports use of adjuvant CT after CCRT (37). Taking these results into consideration, a RCT (the OUTBACK trial) in which CCRT with and without adjuvant CT is compared in LACC is now ongoing (*Figure 1B*).

Fourth, another novel strategy involving the metachronous CT at a sufficient level to control distant metastasis has recently attracted attention. In 2013, a group from the UK published results of a phase II study of neoadjuvant CT before CCRT for LACC (CxII trial) (38). In this trial, 46 patients received dose-dense carboplatin (CBDCA) (AUC2) and paclitaxel (PTX) (80 mg/m^2) weekly for 6 cycles before standard CCRT and achieved good response rates (70% at the end of neoadjuvant CT and 85%, 12 weeks after completing CCRT). In view of the CxII trial results, a RCT (the INTERLACE trial) that compares CCRT in LACC with and without prior neoadjuvant CT is now ongoing (*Figure 2*). Neoadjuvant CT before CCRT is a novel strategy for potentially systemic (i.e., high-risk) LACC. However, patients with FIGO stage IB2-IIA disease are eligible for the INTERLACE trial, although those with radiologically enlarged lymph nodes above the aortic

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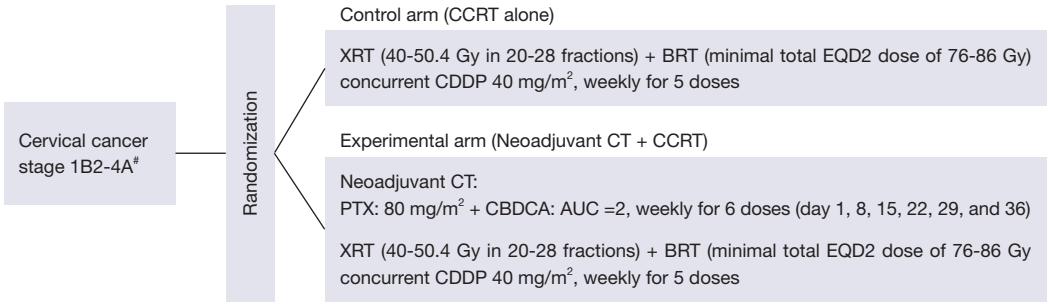

Figure 2 Protocol designs of INTERLACE trial studies, which compared CCRT alone with neoadjuvant CT followed by CCRT. #, Exclusion criteria includes FIGO IIIA disease and positive lymph nodes (imaging or histological) above the aortic bifurcation. CCRT, compare concurrent chemoradiotherapy; XRT, external-beam radiation; BRT, brachytherapy; CT, chemotherapy; CDDP, cisplatin; PTX, paclitaxel; CBDCA, carboplatin.

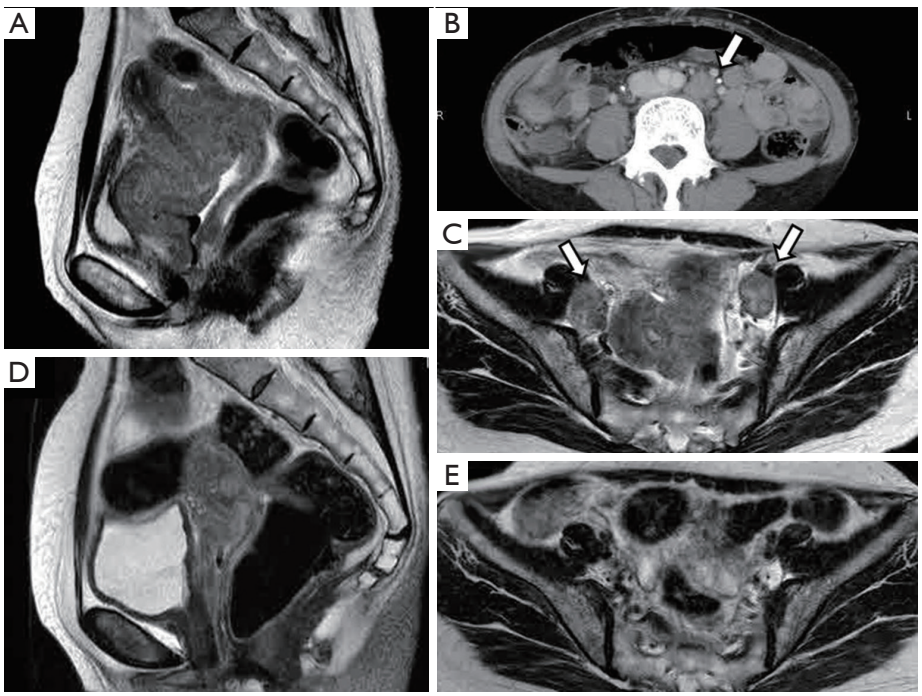

Figure 3 Neoadjuvant CT was remarkably efficacious in a patient who had a large-sized cervical tumor (A), para-aortic lymph node enlargement (B: arrow) and multiple pelvic lymph node enlargement (C: arrow). After one course of combined CT (PTX 180 mg/m^2 and cisplatin 60 mg/m^2), the size of local disease was extremely reduced (D) and multiple lymph node enlargement disappeared (E). The patient received CCRT after two cycles of neoadjuvant CT and achieved a long-term disease-free survival period of 72 months. CT, chemotherapy; PTX, paclitaxel; CCRT, compare concurrent chemoradiotherapy.

bifurcation are ineligible. We are concerned that so few patients with high-risk systemic disease are represented in the INTERLACE trial. If most INTERLACE patients are low-risk, the results will mainly reflect the responses of low-risk patients and may imply that less invasive treatments should be the standard of treatment. Therefore, RCTs carried out in Western countries may reach conclusions disadvantageous to high-risk patients, although high-risk patients require more effective treatments, regardless of invasiveness. For example, we present a case of high-risk LACC: our patient had a large tumor that involved the lower third of her vagina, with pelvic and para-aortic lymph

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node metastasis (*Figure 3A-C*). It responded remarkably well to neoadjuvant CT (*Figure 3D,E*). The patient then received modified CCRT with extended-field irradiation and achieved a long-term disease-free survival period. Such a case cannot be entered in the INTERLACE trial, although chemo-sensitive cervical cancer is not unusual. Neoadjuvant CT before CCRT for high-risk cases of LACC certainly merits wider testing.

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