

Adjuvant chemotherapy for early-stage cervical cancer

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Abstract

The aim of this review is to address the current status of adjuvant chemotherapy alone in early-stage cervical cancer treatments in the literature. At present, the therapeutic effect of adjuvant chemotherapy alone after radical surgery (RS) has not yet been established, and radiation therapy (RT) or concurrent chemoradiotherapy (CCRT) is recommended as the standard adjuvant therapy after RS for early-stage cervical cancer in various guidelines. The main purpose of adjuvant therapy after RS, however, should be to reduce extrapelvic recurrence rather than local recurrence, although adjuvant RT or CCRT has survival benefits for patients with intermediate- or high-risk factors for recurrence. Moreover, several studies reported that adjuvant therapies including RT were associated with a higher incidence of complications, such as lymphedema, bowel obstruction and urinary disturbance, and a lower grade of long-term quality of life (QOL) or sexual functioning than adjuvant chemotherapy alone. The effect of adjuvant chemotherapy alone for early-stage cervical cancer with intermediate- or high-risk factors for recurrence were not fully investigated in prospective studies, but several retrospective studies suggest that the adjuvant effects of chemotherapy alone are at least similar to that of RT or CCRT in terms of recurrence rate, disease-free survival, or overall survival (OS) with lower incidence of complications. Whereas cisplatin based combination regimens were used in these studies, paclitaxel/cisplatin (TP) regimen, which is currently recognized as a standard chemotherapy regimen for patients with metastatic, recurrent or persistent cervical cancer by Gynecologic Oncology Group (GOG), had also survival benefit as an adjuvant therapy. Therefore, it may be worth considering a prospective randomized controlled trial (RCT) of adjuvant chemotherapy alone using TP regimen versus adjuvant RT as an alternative adjuvant therapy. Because early-stage cervical cancer is a curable condition, it is necessary that the therapeutic strategies should be improved with considering adverse events and QOL for long-term survivors.

Keywords: Adjuvant chemotherapy; cervical cancer; quality of life (QOL); survival; intermediate-risk disease

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Introduction

Cervical cancer is the fourth most common cancer in women, and there are nearly 500,000 new cases of cervical cancer each year, accounting for around 12% of all cancers diagnosed in women worldwide (1). Due to significant advances in the screening and treatment of cervical dysplasia, 5-year overall survival (OS) were about 60% in all stages (2), and 70-90% in early-stage cervical cancer (3). Therefore, it is necessary that the therapeutic strategies for cervical cancer

should be improved with considering adverse events and quality of life (QOL) for long-term survivors.

An adjuvant therapy is a supplementary treatment that is given to decrease the risk of the cancer recurrence after a main treatment. In various guidelines including the National Comprehensive Cancer Network (4), the National Cancer Institute (5), the European Society of Medical Oncology (6), and the Japan Society of Gynecologic Oncology (7), radiation therapy (RT) or concurrent chemoradiotherapy (CCRT), but not chemotherapy alone is recommended as

the standard adjuvant therapy after radical surgery (RS) for early-stage cervical cancer. Indeed, adjuvant RT or CCRT after RS can reduce the risk of local recurrence, but the main purpose of adjuvant therapy after RS is to reduce extrapelvic recurrence rather than local recurrence. Because RS including extensive pelvic lymphadenectomy should be enough for local disease control even without adjuvant RT or CCRT in cases without gross residual tumors, adjuvant chemotherapy alone after RS may be an alternative strategy for the patients undergoing primary RS. Another possible reason to utilize adjuvant chemotherapy alone is that chemotherapy can reduce adverse effects of RT or CCRT. Adjuvant RT or CCRT is associated with an increased risk of severe acute complications, described below. And several studies suggest that QOL and sexual functioning of cervical cancer survivors treated with therapy including RT are worse than surgery alone or surgery followed by chemotherapy without RT (8,9). Moreover, when chemotherapy is applied for the patients with extrapelvic recurrence (mainly distant metastasis) after adjuvant RT or CCRT, we often encounter adverse effects (severe hematologic toxicity) because of impairment of bone marrow function by RT or CCRT, resulting in reduction of dose intensity of chemotherapy and inadequate treatment for recurrent disease. Thus, if overall adjuvant effect of chemotherapy alone is at least similar to that of RT or CCRT, it is quite reasonable to apply chemotherapy alone, but not RT or CCRT as an adjuvant therapy after RS.

In Japanese institutions, postoperative adjuvant chemotherapy is widely employed for the patients undergoing RS, due to nationwide use of Okabayashi radical hysterectomy, which corresponds to class IV hysterectomy in Piver's classification, and has maximal efficacy for local disease control. A recent survey of the Japanese Gynecologic Oncology Group (JGOG) reported that at 33.1% of JGOG member institutions, patients with intermediate-risk cervical cancer were treated by adjuvant chemotherapy alone, which was the most common adjuvant therapy for intermediate-risk patients in Japan (adjuvant CCRT and RT were applied for 26.5%, and 28.3% of the institutions, respectively), although CCRT was the most common adjuvant therapy (57.9%) (adjuvant chemotherapy alone and RT alone were 19.9% and 9.0%, respectively) for high-risk patients (10).

Chemotherapy for cervical cancer is widely used for advanced and/or recurrent disease, but not considered as an adjuvant therapy after RS worldwide. That is because there is no high quality of randomized controlled trials (RCTs)

Table 1 The pathological risk factors for early-stage cervical cancer

Risk group	Risk factors
High risk disease	Any of following factors Lymph node metastasis (LNM) Parametrial invasion (PI)
Intermediate risk disease	Any of following factors without LNM or PI Deep stromal invasion (DSI) Lymph vascular space involvement (LVSI) Bulky tumor (BT) (tumor diameter >4 cm)
Low risk disease	Without anything described above

for postoperative adjuvant chemotherapy in comparison with adjuvant RT or CCRT, although several RCTs showed that a larger survival advantage might appear to occur when adjuvant chemotherapy was administered after primary CCRT (11). The aim of this review is to address the current status of adjuvant chemotherapy alone in cervical cancer treatments in the literature, and finally discuss the possibility of prospective study to compare the adjuvant effect of RT/CCRT with that of chemotherapy alone after RS in the future.

The RCTs for post-surgical adjuvant therapy

The therapeutic strategies for cervical cancer depend on pretreatment disease status according to International Federation of Gynecology and Obstetrics (FIGO) stage, and for early-stage cervical cancer (FIGO stage IA2 to IIB), both CCRT and RS are considered as the standard treatments. At many institutions in Japan, early-stage cervical cancer (FIGO stage IA2-IIB) is treated with RS because of widespread acceptance of Okabayashi method for radical hysterectomy. Adjuvant therapy is added when postoperative pathological examinations reveal risk factors for recurrence, including lymph node metastasis (LNM), parametrial invasion (PI), deep stromal invasion (DSI), lymph vascular space involvement (LVSI), and bulky tumor (BT, tumor diameter >4 cm) (Table 1). High-risk factors for recurrence are positive LNM and/or PI, and intermediate-risk factors are BT, DSI, and/or LVSI without LNM or PI (7).

Table 2 summarized the results of several major RCTs for postoperative adjuvant therapies. Rotman *et al.* showed for intermediate-risk patients, RS followed by RT were superior to RS alone in recurrence rate and progression or death (14). Peters *et al.* showed that adjuvant CCRT for high-risk patients was superior to RT alone after RS in

Table 2 The RCTs on postoperative therapy for early-stage cervical cancer with high- or intermediate-risk factors for recurrence

Author	Year	No. of patients	Recurrent rate (%)	DFS/OS (month)
Curtin <i>et al.</i> (12)	1996	CT alone: 44; CCRT: 45	20; 22	3-y: 80/85; 3-y: 70/75
Peters <i>et al.</i> (13)	2000	CCRT: 127; RT: 116	Not described	4-y: 80**/81**; 4-y: 63/71
Rotman <i>et al.</i> (14)	2006	RT: 137; OBS: 140	HR, 0.54*; 90% CI, 0.35-0.81	Not described
Sehouli <i>et al.</i> (15)	2012	CT followed by RT: 132; CCRT: 131	Not described	2-y/5-y: 87.2/85.8; 2-y/5-y: 81.8/78.9

RCT, randomized controlled trial; CCRT, concurrent chemoradiation therapy; RT, radiation therapy; CT, chemotherapy; OBS, observation; DFS, disease free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval. *, P<0.05; **, P<0.01.

Table 3 The major complications of adjuvant therapy after radical surgery

Complications	Incidence (%) after adjuvant therapy including RT	Incidence (%) after adjuvant chemotherapy alone
Bowel obstruction (19,20)	24.5-31.0	3.1-3.6
Urinary disturbance (19,20)	34.7-38.1	7.1-15.6
Lower-limb lymphedema (18-21)	22.4-31.6	11.4-14.3
Locoregional infection (18)	Not described	4.6

RT, radiation therapy.

both OS and progression free survival (PFS) (13). Cochrane reviews suggest that adjuvant RT may decrease the risk of disease progression compared with no further treatment in stage IB cervical cancer (16), and the addition of platinum-based chemotherapy to adjuvant RT (CCRT) may improve survival in women with early-stage cervical cancer (IA2-IIA) with risk factors for recurrence (17).

The complications of adjuvant RT or CCRT

The complications of adjuvant RT or CCRT were not fully documented in previous studies, but several studies reported that RS followed by RT or CCRT was associated with a relatively high incidence of morbidity (18) (Table 3). Barter *et al.* reported that 30% of patients treated with RT had serious complications, and in particular small bowel obstruction has been one of the major problems of that treatment combination (22). Soisson *et al.* reported that the incidence of lymphedema requiring medical therapy was significantly increased from 5.2% in patients treated with surgery alone to 22% in those receiving surgery plus adjuvant pelvic RT (23). Hosaka *et al.* in their retrospective study pointed that the incidence of bowel obstruction and urinary disturbance increased in adjuvant RT group compared with adjuvant chemotherapy alone group; the incidence of bowel obstruction and urinary disturbance

were 3.6% *vs.* 31.0% (P=0.0026), and 7.1% *vs.* 38.1% (P=0.0016) in adjuvant chemotherapy alone *vs.* adjuvant RT, respectively (19). Adjuvant chemotherapy alone may potentially reduce adverse events, because the majority of severe adverse events have relation with RT. Ohba *et al.* (24) and Oda *et al.* (25) investigated the risk factors for lower-limb lymphedema (LLL) and persistent low bladder compliance (PLBC) after RS, respectively, and showed that adjuvant RT was an independent risk factor for LLL [Odds ratio (OR), 3.7; 95% confidence interval (CI), 1.2-10.9, P=0.019] and PLBC (OR, 10.3; 95% CI, 2.5-43.5, P=0.0013), whereas adjuvant chemotherapy alone was not associated with both complications. Recently, several studies contrived reduction of adverse effects of RT: a sequential strategy of systemic chemotherapy followed by RT, and intensity modulated radiation therapy (IMRT). Sehouli *et al.* found out that different profiles of toxicity existed between CCRT versus a sequential strategy of chemotherapy followed by RT and tolerability appeared to favor the use of the sequential strategy (15). Moreover, several studies investigated the feasibility of IMRT after RH in 2000's (26,27), and recent studies showed that IMRT after RS reduced gastrointestinal complications even combined with chemotherapy (28). However, it is quite reasonable to apply chemotherapy alone but not RT as an adjuvant therapy after RS, if adjuvant effect is similar between chemotherapy

Table 4 Retrospective studies for early stage cervical cancer with intermediate-risk

Author	Year	No. patients	Regimen [courses]	No (%) recurrences	DFS	OS
Takeshima <i>et al.</i> (18)	2006	30	BOMP [3]	1 (3.3%)	5-y 93.3%	Not described
Hosaka <i>et al.</i> (19)	2008	27	BOMP [3]	1 (3.7%)	3-y 96.3%	Not described
Lee <i>et al.</i> (29)	2008	38	PF or TP [3]	3 (7.9%)	5-y about 88%	incomplete
Angioli <i>et al.</i> (21)	2012	61	TP [3]	6 (9.8%)	5-y 81%	5-y 88%
Hosaka <i>et al.</i> (20)	2012	32	TP [3-6]	7 (21.9%)	3-y 78.1%	3-y 93.8%
Lee <i>et al.</i> (30)	2013	78	PF or EP [1-6]	Not described	Not described	5-y 94.9%
Li <i>et al.</i> (31)	2013	1010	TP, BVP, PF, BP, CP or PFM [2-6]	167 (16.5%)	5-y 84.5%	5-y 86.5%

DFS, disease free survival; OS, overall survival; BOMP, bleomycin/vincristine/mitomycin/cisplatin; TP, paclitaxel/cisplatin; PF, cisplatin/5-fluorouracil; EP, etoposide/cisplatin; BVP, bleomycin/vincristine/cisplatin; BP, bleomycin/cisplatin; CP, irinotecan/5-fluorouracil; PFM, cisplatin/mitomycin/5-fluorouracil.

alone and RT/CCRT.

The retrospective studies for adjuvant chemotherapy without radiation therapy (RT)

Whereas adjuvant chemotherapy alone was not enough discussed in RCTs, small sized RCT by Curtin *et al.* showed chemotherapy alone compared favorably with CCRT in OS or disease free survival (DFS) (12). Furthermore, several retrospective studies showed that adjuvant chemotherapy using cisplatin (CDDP) based combination regimens alone had at least equal survival benefit compared with adjuvant RT for patients with intermediate-risk for recurrence.

Table 4 summarized some of retrospective studies for adjuvant chemotherapy alone after RS for patients with intermediate-risk factors. Takeshima *et al.* demonstrated that adjuvant chemotherapy using CDDP with bleomycin (BLM), vincristine (VCR), and mitomycin (MMC) combination regimen (BOMP regimen) reduced recurrent rate and had survival benefits; the incidence of recurrence was only 3.3%, and estimated 5-year DFS was 93.3% for intermediate-risk patients (18). Hosaka *et al.* retrospectively compared the clinical efficacy between adjuvant chemotherapy alone and pelvic RT, and showed that chemotherapy has the equivalent therapeutic effect as RT with fewer postoperative complications for patients with intermediate-risk factors [BOMP: the 3-year DFS was 82.6% *vs.* 96.3% with RT *vs.* chemotherapy alone, $P=0.16$ (19); paclitaxel (PTX) plus CDDP (TP): the 3-year DFS was 67.3% *vs.* 78.1% ($P=0.23$), and 3-year OS was 69.4% *vs.* 93.8% ($P=0.02$) with RT *vs.* chemotherapy alone, respectively (20)]. Other retrospective studies also reported

that adjuvant chemotherapy (CDDP based combination regimens) alone showed favorable prognosis without severe complications (21,29-31). Although some previous studies showed that the survival benefits of adjuvant chemotherapy alone for high-risk patients with LNM and/or PI were similar to those of adjuvant RT, CCRT is considered the best treatment of node-positive cervical cancer, especially for adenocarcinomas, at present (32).

The appropriate regimens for adjuvant chemotherapy

Adjuvant chemotherapy alone may potentially reduce adverse events with same efficacy as RT. Although standard chemotherapy regimen has not yet been established for cervical cancer in adjuvant setting, TP regimen may be better as an adjuvant chemotherapy for early-stage cervical cancer after RS because the efficacy were investigated in phase III trials for advanced cervical cancer. *Table 5* summarized clinical trials of Gynecologic Oncology Group (GOG) for advanced or recurrent cervical cancer (33-35). Because of severe toxicity of topotecan combined with CDDP in GOG179, TP regimen (PTX 135 mg/m², CDDP 50 mg/m², 3 weeks) is currently recognized as a standard chemotherapy regimen by GOG for patients with metastatic, recurrent or persistent cervical cancer. In fact, Hosaka *et al.* investigated the clinical efficacy of adjuvant TP regimen, and they showed that TP regimen might be more beneficial than adjuvant RT because 3-year OS in the TP group (93.8%) were significantly better than that in the RT group (69.4%, $P=0.02$), and the incidence of postoperative complications were reduced, especially bowel obstruction

Table 5 The response rate of each regimen for advanced or recurrent cervical cancer

Clinical trial	Regimen	RR (%)	PFS (month)	OS (month)
GOG169 (33)	PTX + CDDP	36.0**	4.8**	9.7
	CDDP alone	19.0	2.8	8.8
GOG179 (34)	CDDP alone	13.0	2.9	6.5
	topotecan + CDDP	27.0*	4.6*	9.4*
GOG204 (35)	GEM + CDDP	22.3	–	10.3
	topotecan + CDDP	23.4	–	10.3
	vinorelbine + CDDP	25.9	–	10.0
	PTX + CDDP	29.1	–	12.9

GOG; Gynecologic Oncology Group; RR, response rate; PFS, progression free survival; OS, overall survival; PTX, paclitaxel; CDDP, cisplatin; GEM, gemcitabine; *, P<0.05; **, P<0.01.

in their retrospective study (20). Other possible regimens are BOMP (36), CDDP with VCR and BLM (VBP) (37), and nedaplatin plus irinotecan (38), which were reported to have favorable response rate in neoadjuvant chemotherapy (NAC). Although the long-term efficacy of NAC is now controversial, it would be reasonable to consider the combination with NAC, because NAC followed by RS has the advantage of being able to evaluate therapeutic effects of NAC regimen pathologically and individually. Indeed, Landoni *et al.* showed in their retrospective study that when RS were performed after NAC, patients with suboptimal response and intra-cervical residual disease could receive favors by additional cycles of chemotherapy after the surgery (39). Furthermore, adjuvant chemotherapy using TP combined with bevacizumab may need to be explored. In GOG240 phase III trial, Tewari *et al.* newly evaluated the effect of addition of bevacizumab (15 mg/kg) to TP regimen (CDDP 50 mg/m², PTX 135 or 175 mg/m²) in patients with recurrent, persistent or metastatic cervical cancer, and they showed that it was associated with increased OS (17.0 *vs.* 13.3 months; HR for death, 0.71; 98% CI, 0.54 to 0.95; P=0.004) (40). Because all data from trials using bevacizumab combined with CCRT for cervical cancer, including Radiation Therapy Oncology Group (RTOG) 0417 (41), and the study of Zigelboim *et al.* (42) are consistent with significant toxicities, particularly grade 3-4 bleeding, thromboembolic events, and gastrointestinal fistulas, it may be possible to add bevacizumab to adjuvant TP therapy but not to adjuvant RT/CCRT.

The possibility of future studies

Because early-stage cervical cancer is a curable condition, the therapeutic strategies should be established with reducing adverse events and not impairing QOL for long-

term survivors. Although adjuvant RT and CCRT after RS have survival advantages, these therapies often result in severe complications. There are three directions for the possibility of future studies. First, reducing adverse events of adjuvant RT itself: a sequential strategy of adjuvant chemotherapy followed by RT or adjuvant IMRT with or without chemotherapy may reduce complications. Second, adjuvant therapy without RT: adjuvant chemotherapy alone may have similar therapeutic effects to adjuvant RT/CCRT with reduction of severe complications. Although several regimens were investigated, it is worth considering a RCT for comparing adjuvant chemotherapy alone using TP regimen versus RT as an alternative adjuvant therapy. Finally, improving adjuvant chemotherapy alone: postoperative adjuvant chemotherapy combined with NAC or addition of bevacizumab may expect additional survival advantages especially for high-risk patients. Thus, further studies are needed including adverse events and long-term QOL in comparison with adjuvant CCRT.

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Footnote

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