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ORIGINAL ARTICLE

Long-term outcomes of postoperative taxane/platinum chemotherapy for early stage cervical cancer: a retrospective study

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Abstract

Background Taxane/platinum (TP)-based combination chemotherapy is standard for the treatment of metastatic or recurrent cervical cancer. The aim of this study was to investigate the efficacy of postoperative TP therapy in early stage cervical cancer.

Methods A retrospective review of patients with FIGO IB–IIB stage cervical cancer who were treated with radical hysterectomy and displayed surgical-pathological risk factors was performed. 122 patients were identified between 2003 and 2012. Survival was analyzed by Kaplan–Meier method and compared by the log-rank test. The Cox proportional hazards model was used to investigate predictors of survival.

Results The median follow-up period was 82.4 months. The postoperative adjuvant therapy was TP in 82 (67.2%) patients, other chemotherapies in 10 (8.2%), radiotherapy (RT) in 25 (20.5%), and no further therapy (NFT) in 5 (4.1%). Survival was analyzed using 4 subgroups according to the postoperative adjuvant therapy. The estimated 5-year overall survival was 95.1% in the TP group, 90.0% in the other chemotherapy group, 78.9% in the RT group, and 100% in the NFT group. No significant difference of survival was observed in the subgroups. However, when analyzing only patients who displayed high-risk factors, non-TP adjuvant therapy (including RT and other chemotherapies) was independently associated with shorter survival on multivariate analysis. In the TP group, multivariate analysis revealed that a positive surgical margin was a significant predictor of shorter survival.

Conclusions Postoperative TP is effective in patients with surgically treated early stage cervical cancer. In these populations, a positive surgical margin could be associated with poor prognosis.

Keywords Cervical cancer · Recurrence · Survival · Adjuvant therapy · Radical hysterectomy · Taxane/platinum

Introduction

Uterine cervical cancer is the fourth most frequent cancer in women with an estimated 530,000 new cases worldwide in 2012 [1]. Cervical cancer is most commonly diagnosed at early stage, with the highest incidence rates being in younger women [2, 3]. The majority of early stage cervical cancer patients who undergo surgical treatment with radical hysterectomy receive adjuvant therapy based on surgical–pathological risk factors [4].

Risk factors for recurrence after radical hysterectomy have been evaluated in many studies [5–17]. Positive lymph nodes, positive surgical margins, and parametrial invasion are classified as high-risk factors [5], while a large tumor size, lymphovascular space involvement (LVSI), and deep cervical stromal invasion are categorized as intermediate-risk factors [8]. Pelvic external beam radiotherapy (RT) with or without concurrent cisplatin-containing chemotherapy has been a standard adjuvant treatment for patients with these risk factors since the 2000s [4, 18–20]. Although the improvement in survival for early stage cervical cancer has been confirmed, severe complications, including lower-limb lymphedema, bowel obstruction, radiation cystitis, and urinary disturbance, have also been reported [5, 8, 21–23]. RT-induced complications are not easy to treat and related

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to a poor quality of life. Moreover, for young patients who received ovary-sparing surgery, postoperative RT leads to early menopause. RT often causes a fibrosis of the vagina [24], making it difficult for patients to retain a sexual function after treatment. One possible solution for these problems would be to use chemotherapy as an alternative adjuvant treatment.

Recently published data from phase III randomized trials suggested that taxane/platinum (TP)-based combination chemotherapy, such as paclitaxel/cisplatin, paclitaxel/carboplatin, and paclitaxel/cisplatin/bevacizumab, was the most effective treatment for metastatic or recurrent cervical cancer [25–27]. Despite no randomized trials of TP chemotherapy in the adjuvant setting, several retrospective studies demonstrated the efficacy and safety of postoperative TP for patients with early stage cervical cancer [28–34]. These studies strongly suggest that TP may be an alternative adjuvant treatment to RT. However, because the follow-up in these studies was relatively short (33–46.8 months), the value of adjuvant TP chemotherapy remains to be determined.

The aim of this study is to evaluate the long-term outcomes of patients with FIGO IB–IIB stage cervical cancer who received postoperative adjuvant TP after radical hysterectomy.

Patients and methods

Patients

Permission to proceed with the data acquisition and analysis was obtained from the National Hospital Organization Shikoku Cancer Center's Institutional Review Board. A list of 437 patients who received primary treatment for the International Federation of Gynecology and Obstetrics (FIGO) stage IB–IIB cervical cancer at National Hospital Organization Shikoku Cancer Center from January 2003 to December 2012 was generated from our institutional tumor registry. Through a chart review, 164 patients who were treated with radical hysterectomy were identified (Supplemental Fig. 1). Patients who received neoadjuvant chemotherapy, those who received non-radical surgery, and those who received RT or chemotherapy as their primary treatment were excluded. At our institution, the histological classification of cancer is performed by two independent pathologists, and histology, LVSI, tumor size, marginal status, parametrial involvement, deep stromal invasion (> 50%), and lymph node metastasis were routinely recorded. The patients were clinically staged according to the FIGO staging criteria.

Treatment

All the patients who were enrolled in the current study underwent with type C radical hysterectomy and pelvic lymphadenectomy [35]. The lymphadenectomy procedure included complete bilateral pelvic lymphadenectomy with the aim of removing all of the external iliac, internal iliac, common iliac, obturator, and presacral lymph nodes. When para-aortic lymph node (PALN) metastasis was suspected on the preoperative computed tomography scan or by intraoperative palpation, a para-aortic lymphadenectomy was performed. Seven patients with histologically confirmed PALN metastasis were not included in this study (Supplemental Fig. 1).

Postoperative adjuvant therapy is indicated when a patient's pathological report displays any of the following high-risk prognostic factors: parametrial invasion, pelvic lymph node metastasis, or a positive surgical margin, or one of the following intermediate-risk prognostic factors: deep stromal invasion, LVSI, or a large tumor (over 4 cm in diameter). Pathological reports revealed at least one risk factor in 122 patients (Supplemental Fig. 1). We provided these patients with information on adjuvant RT or adjuvant chemotherapy. Patients could then choose the modality of adjuvant therapy.

Follow-up

Once treatment ended, the patients were followed up regularly by gynecological oncologists. The median duration of the follow-up was 82.4 months (range 7.1–176.1 months).

Statistical analysis

Overall survival (OS) was defined as the time from radical hysterectomy to death or the latest observation. Recurrence-free survival (RFS) was defined as the time from radical hysterectomy to the date of clinically proven recurrence. Univariate analyses were performed by comparing Kaplan–Meier curves using the log-rank test. The Cox proportional hazards regression model was employed to investigate predictors of survival. Kruskal–Wallis test and Mann–Whitney U test were used to compare groups. P values of < 0.05 were considered statistically significant. MedCalc (MedCalc Software, Mariakerke, Belgium) was used for all analyses.

Results

Patient characteristics

One-hundred and twenty-two patients who underwent radical hysterectomy and had any surgical-pathological risk factors were evaluated for the analysis. The clinical–pathological

demographics of the patients are shown in Table 1. There were 82 (67.2%) patients who received TP as an adjuvant chemotherapy and 10 (8.2%) patients who received other regimens (irinotecan/nedaplatin or tegafur/uracil) (Table 1 and Supplemental Fig. 1). Twenty-five (20.5%) patients received adjuvant RT. The remaining 5 (4.1%) patients received no further therapy (NFT) at the patient's request.

The median number of dissected lymph nodes was 38 (range 14–117) and 37 (30.3%) patients had lymph node metastasis. For the majority of the prognostic factors, such as age, FIGO stage, parametrial invasion, surgical margin, LVSI, and maximum tumor diameter, the distribution of patients was not significantly different according to the modality of adjuvant therapy (Table 1). However, the proportion of patients who had squamous cell carcinoma (SCC) was significantly higher in patients who received RT than in patients who received TP ($P = 0.008$). Patients who received other chemotherapies were more likely to have lymph node metastasis ($P = 0.03$) and shallow stromal invasion ($P = 0.03$) than patients who received TP.

Table 1 Patient characteristics

Modality of adjuvant therapy	Chemotherapy				RT		NFT		*P* value*
	TP		Other regimens						
	No. of patients	(%)	No. of patients	(%)	No. of patients	(%)	No. of patients	(%)	
Total	82		10		25		5		
Age (year)									
Median (range)	50 (24–68)		42 (36–53)		54 (36–66)		53 (43–56)		0.10
FIGO stage									
IB1	54	65.9	5	50.0	14	56.0	2	40.0	0.41
IB2	18	22.0	2	20.0	4	16.0	2	40.0	
IIA	5	6.1	3	30.0	4	16.0	1	20.0	
IIB	5	6.1	0	0	3	12.0	0	0	
Histology									
SCC	48	58.5	7	70.0	22	88.0	4	80.0	0.048
Non-SCC	34	41.5	3	30.0	3	12.0	1	20.0	
Lymph node metastasis									
Negative	61	74.4	4	40.0	15	60.0	5	100	0 04
Positive	21	25.6	6	60.0	10	40.0	0	0	
Parametrial invasion									
Negative	66	80.5	10	100	18	72.0	5	100	0.18
Positive	16	19.5	0	0	7	28.0	0	0	
Surgical margin									
Negative	81	98.8	10	100	23	92.0	5	100	0.25
Positive	1	1.2	0	0	2	8.0	0	0	
Stromal invasion									
Less than one-half	10	12.2	4	40.0	1	4.0	2	40.0	0.01
More than one-half	72	87.8	6	60.0	24	96.0	3	60.0	
LVSl									
Negative	7	8.5	3	30.0	5	20.0	2	40.0	0.053
Positive	75	91.5	7	70.0	20	80.0	3	60.0	
Maximal tumor diameter (mm)									
Median (range)	35 (13–82)		27 (11—45)		35 (13–92)		30 (21–43)		0.74
Surgical-pathological risk									
High	30	36.6	6	60.0	13	52.0	0	0	0.08
Intermediate	52	63.4	4	40.0	12	48.0	5	100	
Number of dissected lymph nodes									
Median (range)	42 (15–117)		34 (21–63)		35 (19–68)		43 (14–66)		0.31

TP taxane/platinum, *RT* radiotherapy, *NFT* No further therapy, *SCC* squamoɪs cell carcioma, *LVSI* lymphovascular space involvement

*Kruskal-Wallis test

Among 122 patients who were evaluated in the current study, 49 (40.2%) displayed high-risk prognostic factors. Meanwhile, 73 (59.8%) patients displayed intermediate-risk prognostic factors. The distribution of patients who displayed high- or intermediate-risk factors was not significantly different according to the modality of adjuvant therapy (Table 1).

Postoperative chemotherapy

In 9 of the 64 patients who initially received paclitaxel/cisplatin, the regimen was changed to paclitaxel/carboplatin because of inadequate renal function (8 patients) or severe gastrointestinal symptoms (1 patient). In 2 of the 18 patients who initially received paclitaxel/carboplatin, the regimen was changed to docetaxel/carboplatin because of an allergic reaction to paclitaxel or severe peripheral neuropathy. In our standard chemotherapy, paclitaxel/cisplatin consists of paclitaxel (175 mg/m^2 on day 1) plus cisplatin (50 mg/m^2 on day 1) triweekly, or paclitaxel (80 mg/m^2 on day 1, 8, and 15) plus cisplatin (25 mg/m^2 on day 1, 8, and 15) weekly. Paclitaxel/carboplatin consists of paclitaxel (175 mg/m^2 on day 1) plus carboplatin (at area under the curve of 5 mg/mL/min on day 1) triweekly. Docetaxel/carboplatin consists of docetaxel (60 mg/m^2 on day 1) plus carboplatin (at area under the curve of 5 mg/ml/min on day 1) triweekly. Nine patients received irinotecan/nedaplatin which consists of irinotecan (60 mg/m^2 on day 1 and 8) plus nedaplatin (80 mg/m^2 on day1) triweekly. One patient received tegafur/uracil (600 mg/day) for 90 days.

The median number of postoperative chemotherapy cycles was 5 (range 3–6). The total number of cycles of chemotherapy was 385; paclitaxel/cisplatin comprised 238 cycles, paclitaxel/carboplatin comprised 97 cycles, docetaxel/carboplatin comprised 8 cycles, and irinotecan/nedaplatin comprised 42 cycles.

Postoperative radiotherapy

Among 25 patients who received adjuvant RT, 14 patients were treated with external beam pelvic RT plus concurrent chemotherapy and 11 patients were treated with pelvic RT alone. The external irradiation was delivered to the whole pelvis at 1.8 Gy per fraction for a total of 28 fractions (50.4 Gy). Cisplatin (40 mg/m^2) was employed as a radiosensitizing agent and administered intravenously during the course of pelvic RT.

Treatment outcomes

Among 122 patients who underwent radical hysterectomy and had surgical–pathological risk factors, 15 (12.3%) developed recurrent disease and 12 (9.8%) died of their disease after a median follow-up of 82.4 months. The estimated 5-year OS and RFS rates were 91.7 and 87.5%, respectively (Supplemental Figs. 2A and 2B).

Survival was analyzed using 4 subgroups divided by the modality of adjuvant therapy (TP, other chemotherapies, RT, and NFT). The estimated 5-year OS and RFS rates were, respectively, 95.1 and 90.2% in the TP group, 90.0 and 90.0% in the other chemotherapy group, 78.9 and 75.3% in the RT group, and 100 and 100% in the NFT group. No significant differences in OS and RFS were observed between the TP and other chemotherapy groups (OS, $P = 0.81$; RFS, $P = 0.96$), between the TP and RT groups (OS, $P = 0.058$; RFS, $P = 0.053$), and between the TP and NFT groups (OS, $P = 0.53$; RFS, $P = 0.48$) (Fig. 1a and b). Similar results were observed in the analysis of patients who displayed intermediate-risk factors (TP vs. other chemotherapy, OS, $P = 0.53$, RFS, $P = 0.49$; TP vs. RT, OS, $P = 0.34$, RFS, $P = 0.70$; TP vs. NFT, OS, $P = 0.52$, RFS, $P = 0.44$) (Fig. 1c and d). However, when analyzing only patients who displayed high-risk factors (Fig. 1e and f), both OS and RFS were significantly shorter in the RT group compared to the TP group (OS, $P = 0.003$; RFS, $P = 0.006$). No significant difference in survival was observed between the TP group and the other chemotherapy group (OS, $P = 0.47$; RFS, $P = 0.38$) (Fig. 1e and f). Table 2 shows univariate and multivariate analysis, investigating prognostic factors for survival in the high-risk patients. The univariate analysis identified surgical margin and modality of adjuvant therapy (TP vs. non-TP therapy [including RT and other chemotherapies]) as statistically significant variables for both OS and RFS. On the multivariate analysis, non-TP adjuvant therapy was independently associated with shorter OS and RFS (Table 2).

Prognostic factors for survival in patients who received postoperative TP

To investigate prognostic factors for survival in patients who received adjuvant TP, survival analyses were performed in the TP group (Fig. 2). OS and RFS were not significantly different between the intermediate- and high-risk patients (estimated 5-year OS rate 94.2% vs. 94.6%, hazard ratio [HR] 1.03, 95% confidence interval [CI] 0.23–4.62, $P = 0.85$; estimated 5-year RFS rate 88.5% vs. 89.2%, HR 1.14, 95% CI 0.34–3.76, $P = 0.48$) (Fig. 2a and b). As shown in Table 3, on univariate analysis in the TP group, a positive surgical margin and non-SCC histology were significantly associated with shorter OS and RFS. In a multivariate model, a positive surgical margin remained significantly correlated with shorter OS and RFS.

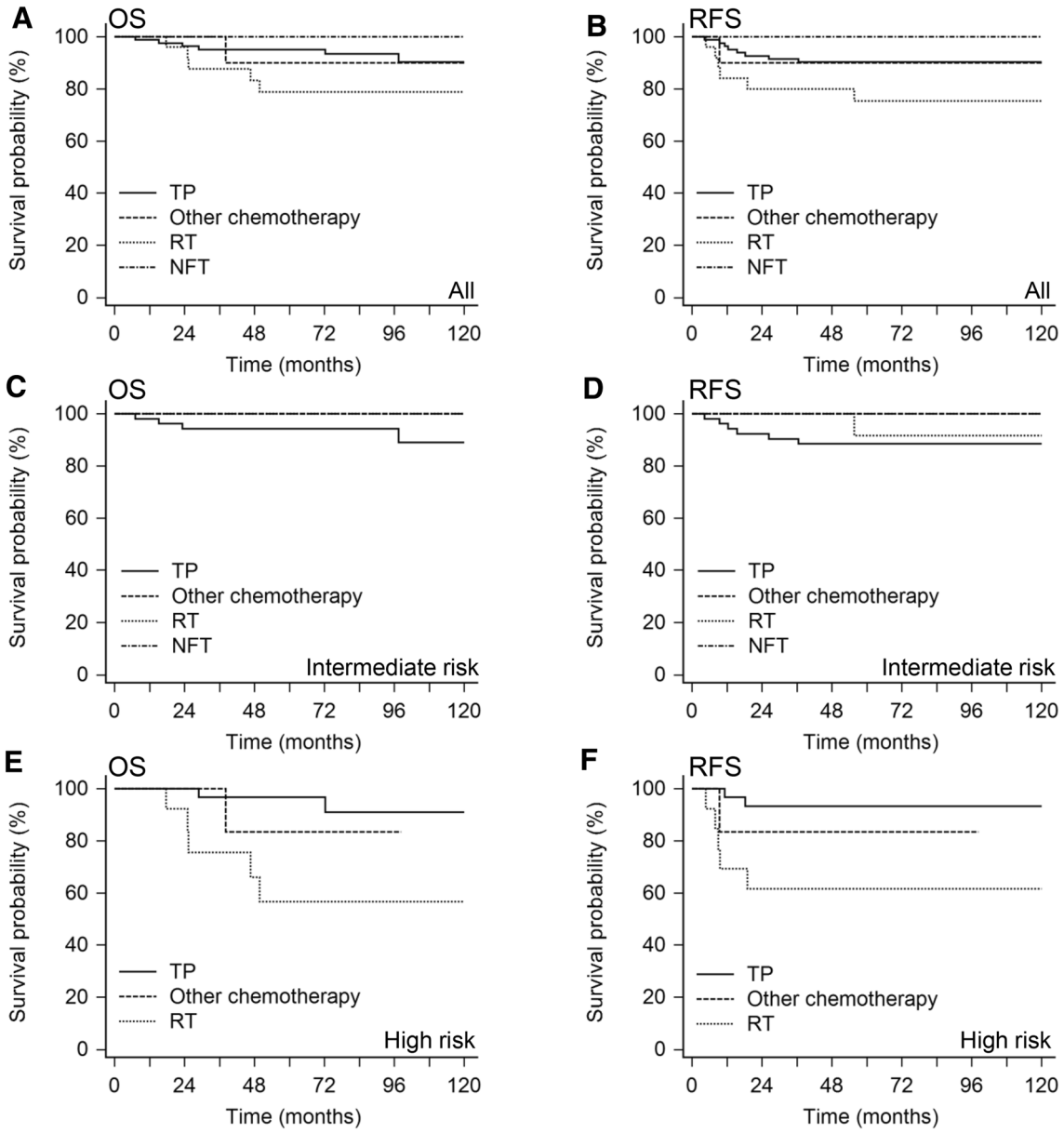

Fig. 1 Survival curves in patients who received radical hysterectomy and displayed surgical–pathological risk factors using 4 subgroups according to the postoperative adjuvant therapy. **a** Overall survival (OS) in all patients. **b** Recurrence-free survival (RFS) in all patients. In the analysis of all patients, no significant difference of OS and RFS was observed in the subgroups. **c** OS in patients with intermediate-risk factor. **d** RFS in patients with intermediate-risk factor. In the analysis of patients with intermediate-risk factor, no significant difference of OS and RFS was observed in the subgroups. **e** OS in patients with high-risk factor. **f** RFS in patients with high-risk factor. In the analysis of patients with high-risk factor, both OS and RFS were significantly shorter in the RT group than TP group. No significant difference was observed between the TP and other chemotherapy groups. *TP* taxane/platinum, *RT* radiotherapy, *NFT* no further therapy

Pattern of recurrence

As shown in Table 4, recurrence was observed in 8 (9.8%) patients in the TP group, 1 (10.0%) patient in the other chemotherapy group, and 6 (24.0%) patients in the RT group. No recurrence was observed in the NFT group. The sites of recurrence are shown in Table 4. Recurrences were considered local if to the pelvis or vagina and distant if to extrapelvic locations. Local recurrence was seen in 2 (2.4%) patients, distant recurrence in 5 (6.1%) patients, and local and distant recurrence in 1(1.2%) patient in the TP group. One (10%) patient had local recurrence in the other chemotherapy group. Local recurrence was seen in 4 (16.0%) patients, distant recurrence in 1 (4.0%) patient, and local and distant recurrence in 1 (4.0%) patient in the RT group. The TP group had a significantly lower local

Table 2 Univariate and multivariate analysis for OS and RFS in patients with high-risk prognostic factors

Covariate	No. of patients	OS				RFS			
		Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
		HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age									
> 50	24	1	NS			1	NS		
< 50	25	0.97 (0.24–3.87)				0.99 (0.25–3.96)			
FIGO stage									
IB	36	1	NS			1	NS		
IIA-IIB	13	0.37 (0.08–1.77)				0.90 (0.19–4.31)			
Histology									
SCC	35	1	NS			1	NS		
Non-SCC	14	1.53 (0.33–7.17)				1.50 (0.32–6.97)			
Lymph node metastasis									
Negative	12	1	NS			1	NS		
Positive	37	2.41 (0.49–11.79)				2.30 (0.46–11.47)			
Parametrial invasion									
Negative	26	1	NS			1	NS		
Positive	23	1.82 (0.45–7.27)				2.01 (0.50–8.09)			
Surgical margin									
Negative	46	1	0.003			1	0.01		
Positive	3	7.84 (0.24–260.35)				6.48 (0.26–161.11)			
Stromal invasion									
Less than one-half	4	1	NS			1	NS		
More than one-half	45	0.63 (0.05–7.81)				0.60 (0.05–7.83)			
LVSI									
Negative	1	NA	NS				NS		
Positive	48								
Maximum tumour diameter(mn)									
< 40	24	1	NS			1	NS		
> 40	25	1.59 (0.40–6.34)				1.72 (0.43-6.90)			
Modality of adjuvant therapy									
TP	30	1	0.01	1		1	0.02	1	
Non-TP therapy[a]	19	5.88 (1.36–25.47)		43.76 (3.57–536.20)	0.003	5.62 (1.31–24.10)		16.58 (1.72–159.70)	0.02

OS overall survival, *RFS* recurrence free survival, *HR* haz and ratio, *95% CI* 95% confidence interval, *SCC* squamous cell carcinoma, *LVSI* lymphovascular space involvement, *TP* taxane/platinum, *NS* not significant, *NA* not available

[a]Non-TP therapy included radiotherapy and other chemotherapies

recurrence than the RT group (Fig. 3a) (5-year cumulative recurrence rate 3.7 vs. 21.1%; HR 0.17, 95% CI 0.03–0.90, $P = 0.006$). Meanwhile, the frequency of distant recurrence in the TP group was similar to that in the RT group (Fig. 3b) (5-year cumulative recurrence rate 7.4 vs. 8.0%; HR 0.87, 95% CI 0.17–4.59, $P = 0.87$).

Surgical–pathological risk factors in patients who developed recurrence are also shown in Table 4; a positive surgical margin was seen in 1 patient in the TP group and 1 patient in the RT group.

Adverse effects of postoperative TP

Overall, postoperative TP was well tolerated. The most frequently observed grade 3–4 hematological toxicity was neutropenia (19 patients, 29.7%). Thirteen (20.3%) patients

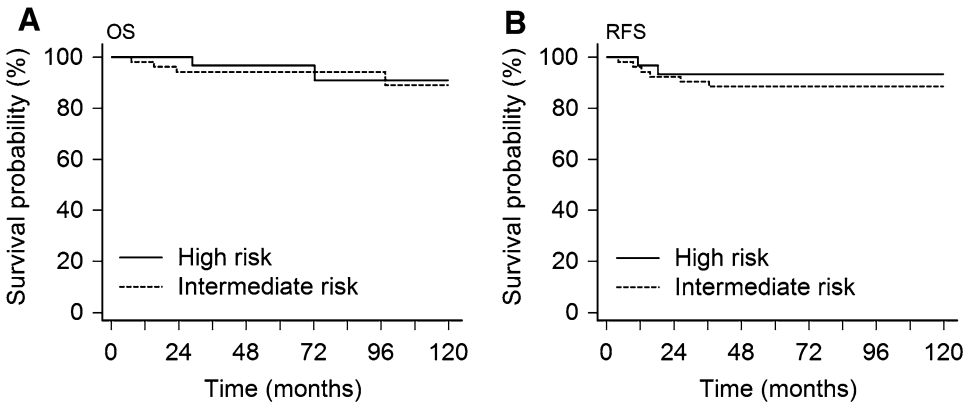

Fig. 2 Survival curves based on surgical–pathological risk factor in patients who were treated with radical hysterectomy and adjuvant TP chemotherapy. **a** Overall survival (OS). **b** Recurrence-free survival (RFS). OS and RFS were not significantly different between the intermediate- and high-risk patients

Table 3 Univariate and multivariate analysis for OS and RFS in the cervical cancer patients who were treated with radical hysterectomy and adjuvant TP

Covariate	No. of patients	OS				TP			
		Univariate analysis HR (95% CI)	*P* value	Multivariate analysis HR (95% CI)	*P* value	Univariate analysis HR (95% CI)	*P* value	Multivariate analysis HR (95% CI)	*P* value
Age									
> 50	40	1	NS			1	NS		
<5 0	42	0.98 (0.20–4.87)				1.64 (0.41–6.58)			
FIGO stage									
IB	72	1	NS			1	NS		
IIA–IIB	10	1.46 (0.13–17.03)				0.98 (0.12–7.81)			
Histology									
Sec	48	1	0.04			1	0.04		
Non-SCC	34	7.20 (1.41–36.62)				4.57 (1.11–18.85)			
Lymph node metastasis									
Negative	61	1	NS			1	NS		
Positive	21	1.39 (0.23–8.52)				0.97 (0.20–4.73)			
Parametrial invasion									
Negative	66	1				1	NS		
Positive	16	0.82 (0.11–6.18)				0.57 (0.10–3.21)			
Surgical margin									
Negative	81	1	< 0.001	1	0.01	1	0.001	1	0.01
Positive	1	17.39 (0.01–32965.94)		18.18 (2.02–163.56)		14.99 (0.01–19425.58)		15.69 (1.83–134.37)	
Stromal invasion									
Less than one-half	10	NA	NS			1	NS		
More than one-half	72					1.01 (0.12–8.14)			
LVSI									
Negative	7	NA	NS			NA	NS		
positive	75								
Maximum tumor diameter (mm)									
< 40	50	1	NS			1	NS		
> 40	32	1.59 (0.31–8.23)				0.91 (0.22–3.76)			

TP taxane/platinum, *OS* overall survival, *RFS* recurrence-free survival, *HR* hazard ratio, *95% CI* 95% confidence interval, *SCC* squamous cell carcinoma, *LVSI* lymphovascular space involvement, *NS* not significant, *NA* not available

Table 4 Patients who developed recurrence

Modality of adjuvant therapy	Patient	RFS (month)	Site of recurrence							Surgical- pathological risk factor						
			Vagina	Intrapelvic site	PLN	PALN	Lung	Liver	Other site	LNM	PMI	PSM	DSI	LVSI	LTD	Non-SCC
TP	#1	4.2		•	•								•	•		•
	#2	9.4					•	•					•	•		•
	#3	11.2			•	•		•		•			•	•		•
	#4	12.4					•						•	•		
	#5	15.5					•		Brain, mediastinal LN				•	•		•
	#6	18.3		•						•	•	•	•	•	•	•
	#7	26.4					•							•		
	#8	36.5					•						•	•		•
Other chemotherapies	#1	9.4			•					•			•	•		
RT	#1	4.7				•				•	•		•	•	•	
	#2	7.9	•								•		•	•		
	#3	9.0		•						•	•	•	•	•	•	•
	#4	9.6			•					•				•		
	#5	19.0			•	•				•	•		•	•	•	
	#6	55.6	•										•			

RFS recurrence-free survival, *PLN* pelvic lymph node, *PALN* para-aortic, *LN* lymph node, *LNM* lymph node metastasis, *PMI* parametrial invasion, *PSM* positive surgical margin, *DSI* deep stromal invasion, *LVSI* lymphovascular space involvement, *LTD* large tumor diameter, *SCC* squamous cell carc inoma, *TP* taxane/platinum, *RT* Radiothrapy

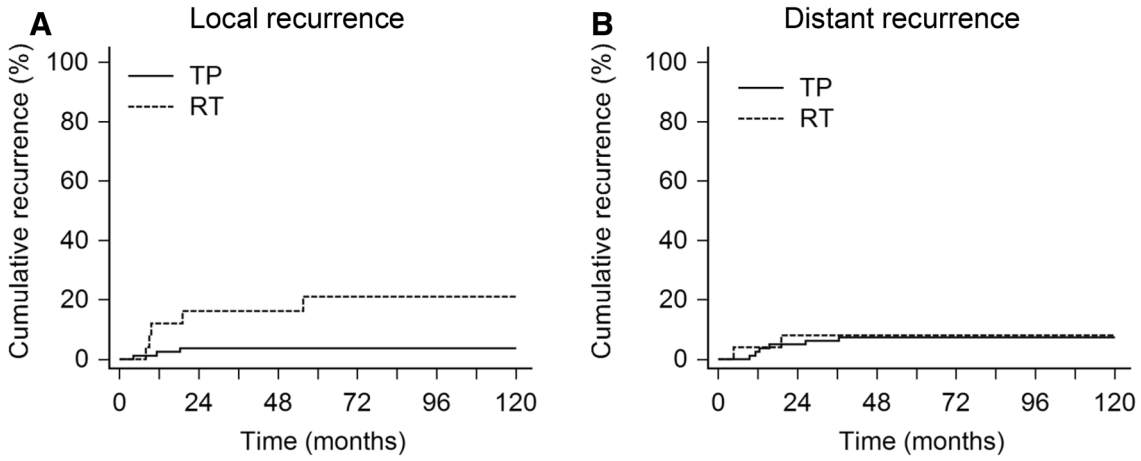

Fig. 3 Cumulative incidence curves for local (**a**) and distant pelvic recurrence (**b**) based on adjuvant treatment types. The TP group had a significantly lower local recurrence than the RT group. Meanwhile, the frequency of distant recurrence in the TP group was similar to that in the RT group. *TP* taxane/platinum chemotherapy, *RT* radiotherapy

developed grade 3–4 anemia and 2 (3.1%) patients developed grade 3–4 thrombocytopenia. Bowel obstruction was the only grade 3–4 non-hematological toxicity (grade 3 in 1 patient, 1.6%).

Discussion

The current study demonstrated that postoperative adjuvant TP chemotherapy improved the survival outcome for patients with FIGO IB–IIB stage cervical cancer who had been treated with radical hysterectomy.

Based on the results of recent studies investigating the efficacy of systemic chemotherapy as an adjuvant treatment for early stage cervical cancer, the survival outcome for patients who received adjuvant chemotherapy is similar to that of patients who underwent adjuvant RT or concurrent chemoradiotherapy (CCRT) [28, 31, 33, 34]. A large-scale retrospective study, in which 1074 patients with node-positive stage IB–IIB cervical cancer who underwent radical hysterectomy received postoperative chemotherapy, RT, or CCRT, showed that those who received postoperative chemotherapy exhibited similar survival outcomes to those who received CCRT [36]. Other studies also reported that patients receiving adjuvant chemotherapy had an equivalent survival outcome to those receiving adjuvant RT or CCRT (3-year OS 100% [33], 5-year OS 86.5% [31], 5-year OS 95.5% [37], 4-year OS 76.0% [28]). In the current study, stage IB–IIB cervical cancer patients with surgical–pathological risk factors who received postoperative TP had an estimated 5-year OS of 95.1%. These results strongly support the efficacy of adjuvant chemotherapy for patients with FIGO IB–IIB stage cervical cancer who had been treated with radical hysterectomy. Moreover, the long-term good survival outcome and less severe adverse events in the current study indicate that TP chemotherapy has activity and tolerance not only for recurrent or advanced disease but also in the adjuvant setting for cervical cancer.

The pattern of recurrence in patients who underwent radical hysterectomy and received adjuvant chemotherapy has been reported in several studies, showing that adjuvant chemotherapy was effective in regional tumor control as well as distant control [28–32, 34]. In contrast, a recent study reported that the utility of adjuvant chemotherapy was independently associated with decreased distant recurrence, but it was also associated with increased local recurrence compared with adjuvant RT in patients with node-positive cervical cancer [36]. However, a TP regimen was not used as adjuvant chemotherapy in all patients in these studies. In the current study, the TP group showed significantly fewer local recurrence than the RT group. Despite the small sample size, these findings could indicate the efficacy of adjuvant TP on regional tumor control in patients who undergo radical hysterectomy. Recently, neoadjuvant chemotherapy has been tried before surgery in bulky or locally advanced cervical cancer in an attempt to reduce tumor volume. Several studies reported the efficacy of TP in the neoadjuvant setting, where it showed a response rate of 90–95% [38–40]. The biological mechanism underlying how TP handle tumor regrowth in the pelvis is unclear. However, these findings indicate that TP may be active in pelvic lesions in cervical cancer.

In previous studies, the 5-year survival of early stage cervical cancer patients who have high-risk factors and received adjuvant CCRT was 71–81% [9, 41, 42]. In the current study, high-risk patients received TP had similar survival outcomes to those with intermediate-risk factors; the estimated 5-year OS and RFS were 94.6 and 89.2%, respectively. Furthermore, in patients who displayed high-risk factors, the

multivariate analysis revealed that non-TP adjuvant therapy was independently associated with shorter survival. Our findings may indicate the impact of adjuvant TP chemotherapy on patients with high-risk factors, as well as adjuvant CCRT. However, it is possible that the good outcome in the TP group was not caused by the benefit of adjuvant TP, but by the effect of surgical treatment. In the current study, the median number of resected lymph nodes was 38. Generally, the number of resected lymph nodes in systematic lymphadenectomy for cervical cancer has been reported to be 13 to 56.4 [43]. A significant relationship between the number of resected lymph nodes and survival outcome has also been reported [44]. It is possible that the good outcome in the TP group was mainly because of the quality of surgery in the current study.

Interestingly, a positive surgical margin was the only independent prognostic factor correlated with shorter OS and RFS in patients who received adjuvant TP. To our knowledge, no factor has been detected that is associated with poor survival in patients who received adjuvant chemotherapy following radical hysterectomy. Our finding indicates that surgically treated patients who display a positive surgical margin may need to receive additional treatment, such as CCRT. A recent study reported that paclitaxel/carboplatin-based CCRT followed by paclitaxel/carboplatin-based consolidation chemotherapy was feasible and effective in patients with surgically treated early stage cervical cancer with high-risk factors [45]. The use of paclitaxel/carboplatin concurrently with RT or as consolidation chemotherapy might be effective in this population.

The limitations of the current study need to be addressed. The first is that it involved a relatively small sample size and was retrospective. Potential biases may have influenced the results, such as the heterogeneity of the patient population and selection bias exercised by physicians. Secondly, although the current study showed the promising activity of postoperative TP, it remains uncertain whether patients with intermediate-risk factors could obtain a survival benefit with adjuvant chemotherapy. The GOG92 study, in which adjuvant RT versus no further treatment was tested, showed that adjuvant RT was significantly associated with prolonged RFS [46]. However, the improvement in OS did not reach statistical significance [46]. The results of this study indicate that the role of adjuvant therapy for patients with intermediate-risk factors is still controversial. The role of adjuvant RT/CCRT in intermediate-risk patients is currently being evaluated in an international phase III randomized trial (GOG263) [47].

In summary, postoperative TP could be an alternative adjuvant treatment for patients with FIGO IB–IIB stage cervical cancer who are treated with radical hysterectomy. Future randomized trials are needed to verify the efficacy of this treatment.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflicts of interest.

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