The Selection of Time Interval Between Surgery and Adjuvant Therapy in Early Stage Cervical Cancer

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Objectives: The optimal interval between surgery and adjuvant treatment has not yet been found in cervical cancer. And whether patients with different FIGO stage should choose different interval is unknown. The purpose of this study was to evaluate whether interval has a different effect on oncologic outcome for patients with different tumor stages.

Methods: We performed a retrospective study of 226 cervical cancer patients who were treated by surgery and adjuvant therapy from May 2005 to August 2015. All patients were divided into 2 groups according to the interval of 5 weeks. Overall survival (OS) and disease-free survival (DFS) were compared between patients with interval shorter and longer than 5 weeks in the whole group and subgroups. Recurrence patterns were also analyzed. Multivariate analysis was performed to explore clinical factors significantly associated with DFS, local recurrence-free survival and distant metastasis-free survival for patients with stage IB2–IIA.

Results: For patients with stage IA2–IB1, the 5-year OS and DFS were similar between groups of short and long interval with also the comparable results of local and distant failure. For patients with IB2–IIA, both the OS and DFS in the short-interval group were higher than that in the long-interval group. Besides, the rates of local recurrence were found higher in the group of long interval compared with short interval. Multivariable analysis indicated that time interval was an independent predictor of DFS and local recurrence-free survival for patients with stage IB2–IIA.

Conclusions: In cervical cancer patients, time interval between surgery and adjuvant therapy may have different effects on the prognosis in different FIGO stages.

Key Words: Cervical cancer, Radiotherapy, Chemotherapy, Time interval

The standard of care for early-stage cervical cancer is surgery, and definitive radiotherapy (RT) serves as an alternative if surgery is not suitable to be administered or is refused by patients.[1] After surgery, some pathological findings, including metastasis-positive pelvic nodes, surgical margins, and/or positive parametrial involvement (PI) are regarded as indicating a high risk of recurrence, and postoperative chemo-RT is suggested for patients with these findings.[2] Moreover, patients with tumors that display a combination of intermediate-risk factors, such as large size, lymphovascular space involvement (LVSI), or deep

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The authors declare no conflicts of interest.
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stromal invasion (DSI), are also considered to be at risk of recurrence and require postoperative pelvic RT.[3]

Currently, adjuvant RT or chemo-RT for early-stage uterine cervical cancer is usually initiated 4 to 6 weeks after radical hysterectomy, allowing time for wound healing. However, there is no robust evidence supporting that, and the optimal interval between surgery and adjuvant therapy has not yet been fully determined.[4] Besides, various reports have suggested that the time interval (TI) from surgery to adjuvant therapy may have an impact on survival in patients with many types of cancer, including breast, colorectal, endometrial, and head and neck cancers.[5–8] It is reasonable to consider that this TI may also influence survival in patients with cervical cancer. Thus, we performed our present study with the aim to investigate whether the interval between surgery and adjuvant therapy influences oncologic outcomes, which may help us to optimize individual treatments.

MATERIALS AND METHODS

Ethics Statement

This research was approved by the ethics committee of Sun Yat-sen Memorial Hospital, and written informed consent was obtained from every patient included in the study.

Patients and Procedures

The data were extracted from a prospectively collected database that enrolled all patients who underwent surgical treatment at Sun Yat-sen Memorial Hospital between May 2005 and August 2015. The database included information on patient characteristics, operative findings, pathologic reports, adjuvant treatment, and follow-up data. The selection criteria for the study were as follows: (1) pathologically confirmed uterine cervical cancer; (2) received surgery, followed by adjuvant RT or adjuvant chemo-RT; (3) normal liver and renal function; (4) no evidence of distant metastases during the treatment; and (5) no concurrent malignancy or prior history of RT to the pelvis. Patients with only one intermediate-risk factor were not included because adjuvant treatment for them is controversial in our hospital. Finally, 226 patients met the inclusion criteria and were analyzed in the present study after reviewing the clinical data.

Chemotherapy

Patients who were classified in the high-risk group were administered with adjuvant chemotherapy. A regimen containing paclitaxel and cisplatin was administered to the patients every 3 weeks. Details of the dose are as follows: paclitaxel, 135 mg/m^2 over 3-h IV on day 1; and cisplatin, 70 mg/m^2, 2-h IV infusion on day 1. The median number of administered cycles in patients who received chemotherapy was 3 (2–4). In addition, patients within the intermediate-risk group were recommended to undergo adjuvant RT alone and chemotherapy was not administered to each of them.

External Beam Radiotherapy

All the patients received a standard protocol of postoperative radiation with three-dimensional conformal RT. The prescribed dose to the whole pelvis was 45 to 50 Gy, which was delivered in 1.8- to 2.0-Gy fractions once daily for 5 days per week. The clinical target volume included the primary tumor bed, supravaginal portion, paracervical tissue, common iliac lymph nodes, internal and external iliac lymph nodes, obturator lymph nodes, and sacral lymph nodes. Roughly, the superior border of the clinical target volume was the bottom of L4, and the inferior border was the lower margin of the obturator. The anterior border was the posterior margin of the bladder. When lateral fields were used, the posterior border encompassed S2.

Follow-Up Evaluation

In our hospital, patients were recommended to be evaluated every 3 months for the first 2 years, every 6 months during the following 3 years, and annually thereafter. Complete

TABLE 1A. Patient demographics, baseline tumor characteristics, type of surgery, and pathologic outcome

Variable	Interval ≤ 5 wk (n = 104)	Interval > 5 wk (n = 122)	P
Age, y			0.041
Median	54	57	
Stage			0.644
IA2	3 (2.9%)	4 (3.3%)	
IB1	56 (53.8%)	71 (58.2%)	
IB2	43 (41.4%)	42 (34.4%)	
IIA	2 (1.9%)	5 (4.1%)	
Histology			0.492
SCC	62 (59.6%)	82 (67.2%)	
AC	31 (29.8%)	30 (24.6%)	
ASC	11 (10.6%)	10 (8.2%)	
LVSI			0.506
Yes	60 (57.7%)	65 (53.3%)	
No	44 (42.3%)	57 (46.7%)	
DSI			0.292
Yes	62 (59.6%)	81 (66.4%)	
No	42 (40.4%)	41 (33.6%)	
Lymph node metastasis			0.639
Yes	22 (21.2%)	29 (23.8%)	
No	82 (78.8%)	93 (76.2%)	
PI			0.573
Yes	28 (26.9%)	37 (30.3%)	
No	76 (73.1%)	85 (69.7%)	
Vaginal involvement			0.534
Yes	26 (25.0%)	35 (28.7%)	
No	78 (75.0%)	87 (71.3%)	
Adjuvant therapy			0.477
RT	42 (40.4%)	55 (45.1%)	
Chemo-RT	62 (59.6%)	67 (54.9%)	

Values are presented as number (%) except for age.

TABLE 1B. Correlation between the different features investigated and the survival rates for the whole group

Variable	No. Patients (%)	5-y DFS	P	5-y OS	P
Age, y			0.188		0.876
≤55	108 (46.9%)	82.33%		88.39%	
>55	118 (53.1%)	74.25%		83.64%	
Stage			0.161		0.173
IA2	7 (3.1%)	85.71%		85.71%	
IB1	127 (56.2%)	83.79%		90.87%	
IB2	85 (37.6%)	70.14%		82.54%	
IIA	7 (3.1%)	53.57%		64.29%	
Histology			0.498		0.908
SCC	144 (63.7%)	80.44%		88.17%	
AC	61 (27.0%)	72.50%		86.86%	
ASC	21 (9.3%)	80.95%		85.71%	
LVSI			0.833		0.947
Yes	125 (55.3%)	77.38%		85.84%	
No	101 (44.7%)	79.30%		86.51%	
DSI			0.041		0.058
Yes	143 (63.3%)	74.06%		82.52%	
No	83 (36.7%)	86.65%		93.79%	
Lymph node metastasis			0.030		0.026
Yes	51 (22.6%)	66.58%		79.99%	
No	175 (77.4%)	82.40%		88.09%	
PI			0.003		0.048
Yes	65 (28.8%)	62.41%		80.79%	
No	161 (71.2%)	85.02%		87.91%	
Vaginal involvement			0.067		0.095
Yes	61 (27.0%)	73.57%		81.81%	
No	165 (73.0%)	81.64%		89.36%	
Risk group			0.033		0.528
Intermediate-risk group	97 (42.9%)	87.21%		89.96%	
High-risk group	127 (57.1%)	71.84%		83.64%	

blood cell counts, biochemical routines, squamous cell carcinoma (SCC) antigen, and physical examinations were the routine evaluations during each visit. Vaginal cytology assessments were also performed for the detection of lower genital tract neoplasia. Chest radiography and computed tomography or magnetic resonance imaging of the abdomen and pelvis were conducted every 6 months with the aim of detecting possible recurrent disease. If recurrent signs were suspected in a patient, biopsy was performed whenever possible. Disease-free survival (DFS) and overall survival (OS) were defined from the date of diagnosis to the date of recurrence or metastasis and to the date of death, respectively. For surviving patients, they were defined to the date of the last follow-up.

Statistical Analysis

All statistical analyses were performed using SPSS software, version 19.0. Categorical variables were analyzed
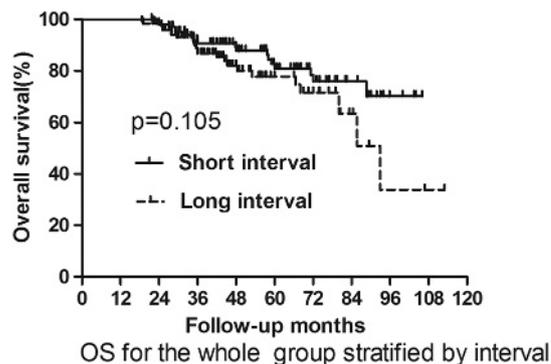
FIGURE 1. OS for the whole group stratified by interval. No significant difference was found in OS between patients with short and long interval for whole group ($P = 0.105$).

TABLE 2. Survival for the whole group of patients

Group	Interval ≤ 5 wk (n = 104)		Interval > 5 wk (n = 122)		P
	3-y	5-y	3-y	5-y	
OS	90.65%	86.70%	80.85%	77.74%	0.105*
DFS	88.06%	82.61%	83.68%	73.68%	0.322*

*Calculated by Kaplan–Meier method.

using the χ^2 test or Fisher exact test. Continuous variables were analyzed using the Student t test or the Mann–Whitney U test. The Kaplan–Meier method was used to compare DFS and OS rates. Multivariate analysis of DFS, local recurrence-free survival (LRFS), and distant metastasis-free survival (DMFS) were performed using Cox proportional hazards regression, and the Cox proportional hazards model was performed using a forward conditional selection of variables. Variables with P values less than 0.2 were entered into the Cox model. P value of less than 0.05 was considered to be statistically significant.

RESULTS

Clinical Characteristics

In total, 226 patients were enrolled in our present study. The median interval time between surgery and adjuvant therapy was roughly 5 weeks (2–8 weeks); this was chosen as the cut-off value to separate all the patients into 2 groups. A total of 104 patents received adjuvant therapy less than 5 weeks after surgery, whereas the remaining 122 patents received adjuvant therapy more than 5 weeks after surgery. Compared with patients with longer intervals between adjuvant therapy and surgery, those with short intervals presented no differences in histology, tumor stage, LVSI, DSI, PI, lymph node metastasis, vaginal involvement, and adjuvant therapy. However, patients in the long interval group were significantly older than those in the short interval group (Table 1a).
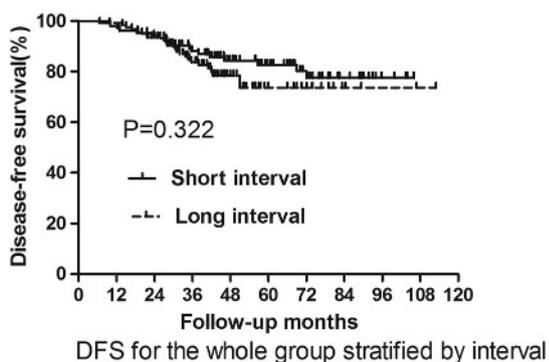
FIGURE 2. DFS for the whole group stratified by interval. No significant difference was found in DFS between patients with short and long interval for whole group ($P = 0.322$).

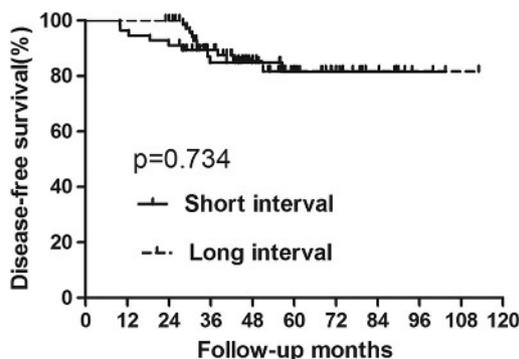OS for patients with stage IA2-IB1 stratified by interval
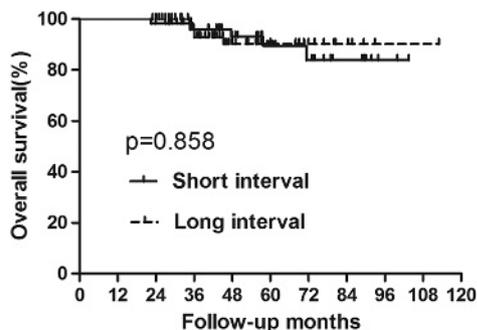
FIGURE 3. OS for patients with stage IA2–IB1 stratified by interval. No significant difference was found in OS between patients with short and long interval for the subgroup ($P = 0.858$).

Survival Analysis for All Patients

Among all patients, 24 died during follow-up. On univariate analysis, the clinical factors associated with decreased OS were lymph node metastasis($P = 0.026$) and PI ($P = 0.048$) (Table 1b). And the 5-year OS rates in the short and long interval groups were 86.70% and 77.74%, respectively (Fig. 1, Table 2). No significant difference was found in the 5-year OS between the 2 groups ($P = 0.105$). Recurrence was found in 42 patients. Among them, 10 patients developed local recurrence and 26 patients presented with distant metastasis. Besides, 6 patients developed both local and distant failure. The clinical factors correlated with worse DFS on univariate analysis were positive parametrial invasion, lymph node metastasis, DSI, and high-risk group (Table 1b). As for the clinical factor of TI, the 5-year DFS rates in the short and long interval groups were 82.61% and 73.68%, with no significant difference between the 2 groups ($P = 0.322$) (Fig. 2, Table 2).

Survival Analysis for the Subgroups

For patients with stage IA2 to IB1 cervical cancer, 10 died during follow-up and 19 developed recurrence. Three patients only recurred locally and 14 patients only developed

DFS for patients with IA2-IB1 stratified by interval

FIGURE 4. DFS for patients with stage IA2–IB1 stratified by interval. No significant difference was found in DFS between patients with short and long interval for the subgroup ($P = 0.734$).

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TABLE 3. Survival for patients with stage IA2–IB1

| Group | Interval ≤ 5 wk (n = 56) | | Interval > 5 wk (n = 78) | | |
	3-yr	5-yr	3-yr	5-yr	P
OS	95.88%	89.48%	92.84%	90.20%	0.858*
DFS	84.79%	81.53%	89.37%	81.63%	0.734*

*Calculated by Kaplan–Meier method.

FIGURE 5. OS for patients with stage IB2–IIA stratified by interval. No significant difference was found in OS between patients with short and long interval for the subgroup (P = 0.050).

distant metastasis. In addition, 2 patients presented with both local and distant metastases. The 5-year OS and DFS rates in the short and long interval groups were 89.48% and 90.20% and 81.53% and 81.63%, respectively (Figs. 3, 4, Table 3). No significant differences were found in both OS and DFS rates between the 2 groups (P = 0.858 and P = 0.734, respectively). The recurrence pattern was further analyzed with results showing that there were no differences in both the local and distant failure rates between patients in the short and long interval groups (Table 4).

For patients with stage IB2 to IIA cervical cancer, 23 developed recurrence, of which 14 died because of tumor recurrence. Specifically, 7 patients developed only local recurrence and 12 presented with only distant metastasis. Four patients developed both local and distant metastases. The 5-year OS rate in the short interval group was significantly greater than that in the long interval group (89.20% vs 72.14%, P = 0.050) (Fig. 5, Table 5). As for the 5-year DFS rates, it was also found that patients in the short interval group acquired better DFS compared with those in the long interval group (83.77% vs 59.65%, P = 0.034) (Fig. 6, Table 5). Deeper analysis was performed on recurrence patterns, and we found that the rate of local recurrence was significantly higher in the long interval group than that in the short interval group. Meanwhile, no difference was shown in the distant metastasis between the 2 groups (Table 6).

Clinical Predictors for DFS, LRFS, and DMFS in Patients With Stage IB2 to IIA Cervical Cancer

In multivariable analysis, both the TI and lymph node metastasis were independent predictors of DFS in patients with stage IB2 to IIA cervical cancer. In additions, the TI was especially associated with LRFS, although it did not predict
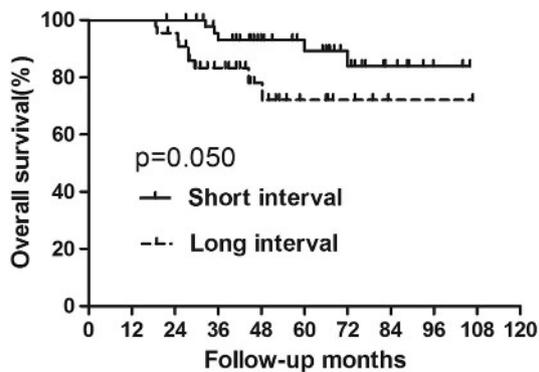
DMFS significantly. Besides, PI also predicted poor LRFS, and lymph node metastasis was significantly correlated with impaired DMFS (Table 7).

CONCLUSIONS

In our present study, we demonstrated that the TI between surgery and adjuvant RT (chemo-RT) may have different effects on oncologic outcomes in patients with cervical cancer of different International Federation of Gynecology and Obstetrics (FIGO) stages. In detail, for patients with stage IB2 to IIA cervical cancer, the patients in the long interval group achieved poorer DFS than those in the short interval group. However, in patients with stage IA2 to IB1 cervical cancer, no significant differences were found in DFS and OS between patients in the long and short interval groups. Further analysis was performed on the recurrence patterns in patients with stage IB2 to IIA cervical cancer, and we found that long intervals resulted in poorer local control, thus leading to impaired DFS and OS. Multivariable analysis was also performed, which showed that long intervals significantly predicted poorer LRFS. A possible explanation is that the micrometastases or residual cancer cells may proliferate during the interval from surgery to adjuvant therapy and the increased time may have offered the chance for increased proliferation.[9,10] It has been reported that surgery may lead to early accelerated growth of micrometastases and the conversion of dormant tumor cells into

TABLE 4. Recurrence patterns for patients with stage IA2–IB1

| Group | Interval ≤ 5 wk (n = 56) | | Interval > 5 wk (n = 78) | | |
	3-y	5-y	3-y	5-y	P
LR	2 (3.6%)	2 (3.6%)	3 (3.8%)	3 (3.8%)	0.951*
SM	6 (10.7%)	8 (14.3%)	4 (5.1%)	7 (9.0%)	0.637*

Values are presented as number (%).
*Calculated by Kaplan–Meier method.
LR indicates local recurrence; and SM, systemic metastases.

TABLE 5. Survival for the patients with stage IB2–IIA

| Group | Interval ≤ 5 wk (n = 48) | | Interval > 5 wk (n = 44) | | |
	3-y	5-y	3-y	5-y	*P*
OS	93.07%	89.20%	83.36%	72.14%	0.050*
DFS	91.53%	83.77%	73.94%	59.65%	0.034*

*Calculated by Kaplan–Meier method.

rapidly proliferating ones.[11] Besides, long intervals between the surgical removal of primary tumors and administration of chemotherapy may weaken the cytotoxic effects of the chemotherapeutic agents, leading to a decrease in the proliferative index of tumor cells.[12] Thus, it seems rational to initiate the administration of adjuvant treatments after surgery as soon as possible if the patients' general condition permits.

Currently, few studies have investigated the impact of TIs between surgery and adjuvant treatment on the prognosis of cervical cancer. In a study performed by Hanprasertpong et al, 110 patients with stage IA2 to IB1 cervical cancer who underwent radical resection and adjuvant therapy were included, and they were divided into 2 groups based on the cut-off TIs of 4 and 6 weeks, respectively. The results showed that, according to the TI (≤4 vs >4 weeks, and ≤6 vs >6 weeks), no statistical differences were found in 5-year recurrence-free survival (RFS) (89.2% vs 81.0%, and 83.2% vs 100.0%, respectively) or 5-year OS rates (90.9% vs 97.2%, and 93.2% vs 100.0%, respectively). However, it was found that the delay in initiating adjuvant therapy after surgery beyond 4 weeks might result in poorer RFS in patients with SCC, whereas patients with adenocarcinoma (AC) or adenosquamous cell carcinoma (ASC) did not show any detriments from delayed administration of adjuvant therapy.[4] In another study conducted by Kim et al, 98 patients with pelvic lymph node metastasis, positive resection margins, and/or parametrial invasion who received adjuvant chemo-RT were included. The first cycle of platinum-based adjuvant chemotherapy was initiated within
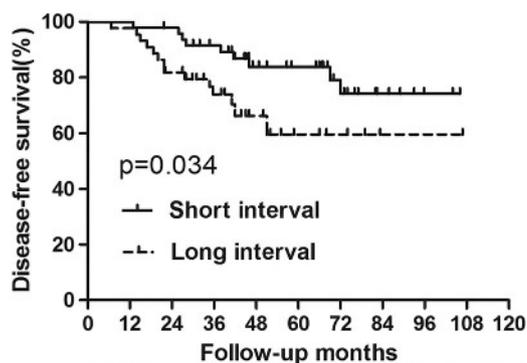
FIGURE 6. DFS for patients with stage IB2–IIA stratified by interval. No significant difference was found in DFS between patients with short and long interval for the subgroup (*P* = 0.034).

2 to 3 weeks after surgery (median, 12 days) and continued every 4 weeks for a total of 4 cycles. Adjuvant RT was performed during the second and third cycles of chemotherapy. Their results showed that the oncologic outcomes were quite favorable with 5-year RFS and cancer-specific survival rates of 87.6% and 90.6%, respectively.[13] Besides, Jhawar et al performed an analysis based on data including 3051 nonmetastatic cervical cancer patients undergoing hysterectomy followed by adjuvant chemoradiation. Their results also indicated that a longer interval between surgery and adjuvant chemoradiation leads to impaired survival. Thus, they suggested a TI (surgery to adjuvant chemoradiation) of less than 8 weeks should be attempted whenever clinically feasible.[14] In our present study, the 5-year OS and DFS rates were slightly lower than those discussed earlier; this was due to patients with stage IB2 and IIA cervical cancer also being included in the analysis. The new finding in our report was that we discovered the TI that may impart different effects in patients with cervical cancer of different FIGO stages.

The TI from surgery to adjuvant therapy can have an impact in other types of cancer. It was reported that a delay in RT of more than 9 weeks was an independent significant predictor for poor disease-specific survival (*P* < 0.005) in patients with endometrial cancer who received postoperative RT.[15] In a study by Klein et al, 1827 patients with stage III colonic cancer were included; their results showed that adjuvant therapy that was initiated within 4 and 8 weeks improved survival when compared with initiating adjuvant therapy later than 8 weeks (hazard ratio [95% confidence interval]: 1.7 [1.1–2.6]; *P* = 0.024 and 1.4 [1.07–1.8]; *P* = 0.013, respectively).[9] However, several other studies have found that TI is not associated with clinical outcomes in patients with breast cancer, soft tissue sarcoma, and gastric cancer.[16–18] This simply indicates that the TI may have different impacts on survival in different cancers at different stages, and some intrinsic factors, although not fully determined, may play a role.

When adjuvant therapy was administered earlier, the possible increase in treatment-related toxicities should be considered because of inadequate recovery from surgery. Kim et al reported that the incidences of grade 3 to 4 hematologic and gastrointestinal toxicities were 37.8% and 14.3%, respectively, in patients who received adjuvant treatment within 2 to 3 weeks after surgery.[13] Moreover, they suggested that early administration of adjuvant concurrent chemo-RT was safe

TABLE 6. Recurrence patterns for patients with stage IB2–IIA

| Group | Interval ≤ 5 wk (n = 48) | | Interval > 5 wk (n = 44) | | |
	3-y	5-y	3-y	5-y	*P*
LR	1 (2.1%)	2 (4.2%)	5 (11.4%)	8 (18.2%)	0.021*
SM	3 (6.3%)	6 (12.5%)	8 (18.2%)	9 (20.5%)	0.187*

Values are presented as number (%).
*Calculated by Kaplan–Meier method.
LR indicates local recurrence; and SM, systemic metastases.

TABLE 7. Multivariate analyses of DFS, LRFS, and DMFS for patients with stage IB2–IIA

Variable	DFS		LRFS		DMFS	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
TI						
≤5 wk vs >5 wk	0.325 (0.145–0.879)	0.027	0.138 (0.015–0.963)	0.042	0.434 (0.168–1.095)	0.064
Lymph node metastasis						
No vs yes	0.216 (0.117–0.850)	0.018	0.211 (0.121–1.083)	0.055	0.309 (0.116–0.963)	0.042
PI						
No vs yes	0.556 (0.280–1.106)	0.095	0.209 (0.042–0.972)	0.047	0.703 (0.304–1.449)	0.516
Age						
>55 vs ≤55	1.420 (0.738–2.733)	0.293	0.797 (0.267–2.381)	0.685	1.522 (0.710–3.261)	0.303
LVSI						
Yes vs no	1.108 (0.551–2.230)	0.773	0.926 (0.297–2.890)	0.895	1.497 (0.649–3.452)	0.344
DSI						
Yes vs no	2.065 (0.954–4.474)	0.066	3.531 (0.932–6.530)	0.053	1.390 (0.615–3.141)	0.429
Vaginal involvement						
Yes vs no	2.011 (0.860–3.413)	0.072	3.247 (0.862–5.768)	0.057	1.416 (0.637–3.275)	0.387
Histology						
SCC vs AC	0.685 (0.229–2.047)	0.498	0.239 (0.056–1.025)	0.058	1.126 (0.252–5.037)	0.876
ASC vs AC	0.945 (0.301–2.965)	0.923	0.394 (0.082–1.316)	0.070	1.590 (0.345–7.328)	0.288

because the incidence of severe toxicities (grade 3–4) was comparable with that in patients with longer interval times.[19–21] In our present study, the incidence of severe diarrhea was higher in patients with short intervals than in those with long intervals, whereas other types of toxicities were similar between the 2 groups (Table 8).

There were some limitations, such as the short follow-up and retrospective design in our study. Another important limitation was that the small sample size in the different subgroups may have affected the reality of the results to some extent. Although we have suggested that a longer interval may lead to impaired survival for patients with stage IB2 to IIA cervical cancer, the optimal interval for the patients still needs to be investigated. A large study including sufficient cases might address this question.

TABLE 8. Severe toxicity (Grade ≥ 3) of adjuvant therapy

Toxicity Type (Grade ≥ 3)	Interval ≤ 5 wk (n = 104)	Interval > 5 wk (n = 122)	P
Abdominal pain			
Nausea	4 (3.8%)	4 (3.3%)	0.818
Vomiting	3 (2.9%)	3 (2.5%)	0.843
Enteritis	2 (1.9%)	2 (1.6%)	0.872
Diarrhea	16 (15.4%)	9 (7.4%)	0.056
Constipation	2 (1.9%)	2 (1.6%)	0.872
Hemoglobin	3 (2.9%)	2 (1.6%)	0.526
Platelets	1. (1.0%)	2 (1.6%)	0.657

In conclusion, our study indicated that the FIGO stage should be considered when deciding when to administer adjuvant therapy for patients with cervical cancer after surgery. Although we suggested that long intervals may result in poorer survival for patients with stage IB2 to IIA cervical cancer, further larger-scale cohort studies are still warranted to confirm our results. We strongly suggest the tailored selection of TIs for different patients.

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