

Propensity Score Matched Study of Tri-Weekly vs. Weekly Platinum-Based Chemotherapy Concurrent with Radiotherapy in the Treatment of Locally Advanced Cervical Cancer

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ABSTRACT

Objective: To compare tumor control and toxicity between tri-weekly chemotherapy and weekly platinum-based chemotherapy in locally advanced cervical cancer using the propensity score matching method.

Materials and Methods: DESIGN: Retrospective cohort with propensity score matched population. SETTING: Four university hospitals. PARTICIPANTS: 781 advanced local cervical cancer patients. INTERVENTION: tri-weekly platinum-based chemoradiotherapy versus weekly chemoradiotherapy OUTCOMES: Overall survival (OS), local recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), distant metastasis-free survival (DMFS), and toxicity, including hematological and renal toxicity.

Results: Overall median follow-up time was 59.5 months. After the propensity score matching process was completed, 326 patients were analyzed (163 in each group). The five-year OS was 66% and 64% (p 0.630); five-year LRFS was 85% and 81% (p 0.209); five-year RRFS was 89% and 94% (p 0.307); and five-year DMFS was 75% and 79% (p 0.420) in the tri-weekly and weekly groups, respectively. The patients in the tri-weekly and the weekly group had grade 2-3 neutropenia (10.5% vs 2.5%). The other toxicities appeared to be similar in both groups in terms of white blood count, platelet and creatinine.

Conclusion: There was a potential small benefit of local control (4%) and overall survival (2%) with the tri-weekly regimen but we could not demonstrate statistical significance. However, this came at the price of an increase of 7% to 8% in grade 2-3 neutropenia.

Keywords: Cervical cancer; chemotherapy; radiotherapy; weekly regimen; tri-weekly regimen (Siriraj Med J 2022; 74: 245-255)

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INTRODUCTION

A 1999 US National Cancer Institute announcement defined concurrent platinum-based chemotherapy with radiotherapy as the standard of care for women with locally advanced cervical cancer due to approximately 10% added survival benefit after five years without a significant increase in late toxicities.¹ This was based on the results of five randomized controlled trials.^{2-4,5,6}

Despite this, the frequency of the platinum-based regimen remains heterogeneous and routine chemotherapy is different among hospitals. For example, some hospitals administer weekly chemotherapy sessions whereas others give tri-weekly chemotherapy. To compare these treatment methods, many randomized controlled have been carried out.⁷⁻¹⁴ Interestingly, most of the evidence remains conflicting in terms of both tumor control and toxicity. For example, a randomized controlled trial from the University of Ulsan, Korea in 2008¹³ showed that the weekly regimen not only improved compliance but was comparable with the tri-weekly regimen in response and survival rate. On the other hand, a collaborative randomized controlled trial by the Korea Institute of Radiological and Medical Sciences, Dongnam Institute of Radiological and Medical Sciences and National Cancer Institute, Korea¹² showed that the tri-weekly regimen was 20% more effective in terms of overall survival and had less grade 3-4 neutropenia than the weekly regimen.

Moreover, evidence from meta-analyses looking at the same question is also conflicting. Zhu J et al,¹⁵ carried out a meta-analysis based on six randomized controlled trials and two retrospective studies. It showed that the tri-weekly regimen was superior to the weekly regimen only in local recurrence but not overall survival. The same results were reported in a recent meta-analysis¹⁶ based on eight randomized controlled trials. Meanwhile, a meta-analysis was also carried out by Petrelli et al,¹⁷ based on four randomized controlled trials and four retrospective studies. Its results showed that the platinum-based combined therapy should be the preferred treatment over weekly regimen due to benefits in overall survival.

As a result, there are different policies for the weekly and tri-weekly regimen. The routine regimen at the Radiation Oncology Division at Siriraj Hospital is weekly cisplatin (40 mg/m²) or carboplatin (AUC2), but some hospitals have a routine tri-weekly regimen of cisplatin (75-100 mg/m²) (or carboplatin AUC5) with or without 5FU. We are still waiting for high-quality evidence, notably results of the Tri-weekly Cisplatin Based Chemoradiation in Locally Advanced Cervical Cancer (TACO) trial (Clinical Trials.gov Identifier: NCT01561586). In the meantime,

we still require evidence for solving this issue. Hence, we collected data from a multicenter in Thailand where locally advanced cervical cancer patients underwent concurrent chemoradiotherapy. This could help provide a suitable answer to a controversial issue with the help of advanced statistical analysis, such as propensity score matching that can simulate pseudo randomization by matching pre-treatment variable factors.

MATERIALS AND METHODS

We used retrospective cohort data from a multicenter in Thailand (Siriraj Hospital (SI), Ramathibodi Hospital (RA), King Chulalongkorn Memorial Hospital (CU) and Songklanagarind Hospital (PSU)). We recruited patients with squamous cell carcinoma, adenocarcinoma, or adenosquamous carcinoma of locally advanced cervical cancer who were definitively treated with concurrent chemoradiotherapy between Jan 2007 to Dec 2015. For staging purposes, all patients underwent a CT scan with contrast media of the whole abdomen, chest X-ray and cystoscopy. Diagnostic radiologists in each hospital newly reviewed the lymphadenopathy status according to the pelvic lymphatic pathway.^{18,19} Depending on the policy of each hospital, a weekly or tri-weekly regimen of cisplatin or carboplatin concurrently with radiotherapy was given to the patient. Generally, 46-50 Gy of external beam radiotherapy and 4 fractions of each 6.5 to 7.0 Gy high dose rate brachytherapy were routinely prescribed. For chemotherapy, usually, the clinical policy of SI, CU and PSU is to give cisplatin weekly whereas RA gives cisplatin tri-weekly. Additionally, Siriraj Hospital may also adhere to the weekly carboplatin regimen as it is the preference of some radiation oncologists regardless of the patient's performance status. The main outcome of this study was overall survival. The secondary outcomes were local-recurrence free survival, regional-recurrence free survival and distant metastasis-free survival, which were defined as first day of radiotherapy to the date of first failure at cervical area, regional pelvic or paraaortic lymph node and visceral distant metastases or lymph node metastases above the diaphragm respectively. Hematological toxicity (hemoglobin, white blood cell count, neutrophil count and platelet) and renal toxicity in the maximum grade of each patient were also reported.

Sample size

A randomized controlled trial from Korea¹² showed that the tri-weekly regimen was more effective in overall survival. This study reported a hazard ratio of 0.375. When using this hazard ratio, 0.05 type I error and 80% statistical power, the sample size contained only 38

patients in each arm. However, we planned to include more patients as per our data availability.

Statistical analysis

In order to eliminate the selection bias of weekly or tri-weekly chemotherapy regimen, we performed a propensity score-matching analysis. This method is based on balancing baseline characteristics of patients to simulate randomization. Theoretically, the best propensity score came from factors that clinicians unfairly selected in the weekly or tri-weekly regimen, such as patient or tumor characteristics before treatment, especially pelvic or para-aortic lymph nodes. In this study, we used the new 2018 FIGO stage, which included pelvic and para-aortic lymphadenopathy status, histology, tumor grade, tumor size, age, initial hemoglobin and hydronephrosis status. For this purpose, we used MatchIt package version 3.02 in R software version 4.05. Logistic regression with the factors above was used to predict the linearized propensity score. We then used this score in the MatchIt function with the nearest method with varying caliper distances. We further proved whether this procedure worked by comparing baseline characteristics before and after the propensity score-matched procedure.

After we got the matched population, we also explored whether the factors after the start of the treatment were well-balanced, especially the chemotherapy regimen (cisplatin or carboplatin). We aimed to control this additional confounder in non-parametric analysis. For time-to-event analysis, we used the Kaplan Meier method and log-rank test to determine the hypothesis. Non-parametric analysis was performed to show a difference with 95% confidence interval. For toxicity comparison, we used the Fisher exact test to test the hypothesis.

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Faculty of Medicine Siriraj Hospital, Mahidol University (Si 312/2016).

RESULTS

The patient characteristics before and after the propensity score matching process is shown in [Table 1](#). Missing data were in only histopathological grade, which was available 80%. Before the matching process, a total of 781 patients (618 in the weekly group and 163 patients in the tri-weekly group) were compared. The patients in the tri-weekly group seemed to have a better prognosis in terms of 2018 FIGO stage. For example, less pelvic lymph node metastases (stage IIIC1, 20.2%) were

observed in the tri-weekly group, compared with the weekly group (stage IIIC1, 34.3%). After the propensity score matching process was completed (163 patients in the weekly group and 163 patients in the tri-weekly group), there was a similar prognosis, especially in terms of FIGO staging. The pelvic lymph node metastases were only 20.2% in both the weekly and tri-weekly groups. Also, the proportion of histology was very similar in terms of adenocarcinoma (22.1% in the weekly group and 22.7% in the tri-weekly group). Furthermore, age, tumor type, tumor size, tumor grade, initial hemoglobin and also any side effects of hydronephrosis were better balanced in both groups ([Table 1](#)). Despite the balance in these prognostic factors, the chemotherapy regimens (cisplatin or carboplatin) were different in both groups. Cisplatin was given to half of the patients (56%) in the weekly group, but almost all the (96%) patients in the tri-weekly group. This difference was then further adjusted in a statistical analysis.

The overall median follow-up time was 59.5 months. The follow-up rate for disease recurrence status and for death status was 87% and 100% respectively. For tumor control outcome, the tri-weekly group showed an unadjusted non-statistically small benefit in overall survival ([Fig 1A](#)). This small benefit was only 2%-3% as per the follow-up time ([Supplementary Fig S1](#)). After chemotherapy regimen (cisplatin or carboplatin) adjustment, this small difference disappeared and the survival curve seemed to cross each other ([Fig 1B](#)). Interestingly, the tri-weekly group showed better local recurrence-free survival ([Fig 2A](#)). This difference was about 6%-7% in the first two years of follow-up and about 3%-4% in the third to fifth year ([Supplementary Fig S2](#)). Unfortunately, with our limited sample size, a statistical difference could not be detected. Again, after chemotherapy regimen adjustment, this difference disappeared ([Fig 2B](#)). For regional recurrence-free survival ([Fig 3A](#)) and distant metastasis-free survival ([Fig 4A](#)), the difference between the weekly group and tri-weekly group was small and not consistent with the follow-up time ([Fig 3B and Fig 4B](#)). Also, the adjustment of chemotherapy regimen ([Supplementary Fig S3 and Fig S4](#)) showed no significant change from unadjusted analysis.

Toxicity outcome was available for 96% of study population. For grade 2 or greater toxicity ([Table 2](#)), the patients in the tri-weekly group had more absolute neutrophil count toxicity (10.5%), when compared to patients in the weekly group (2.5%). On the other hand, patients in the tri-weekly group seemed to have less hemoglobin toxicity (29.4%) when compared to patients in the weekly group (33.8%). These results are

TABLE 1. Patient characteristics before and after propensity score matching.

Patient Characteristics	Before Propensity score Matching			After Propensity score Matching		
	Weekly n=618	Tri-weekly n=163	p-value	Weekly n=163	Tri-weekly n=163	p-value
Age	53.8 (11.7)	54.1 (10.6)	0.80	54.7 (11.7)	54.1 (10.6)	0.59
Stage: I-II	132 (21.4%)	51 (31.3%)	0.004	51 (31.3%)	51 (31.3%)	0.92
IIIa-b	180 (29.1%)	55 (33.7%)		53 (32.5%)	55 (33.7%)	
IIIc1	212 (34.3%)	33 (20.2%)		33 (20.2%)	33 (20.2%)	
IIIc2	82 (13.3%)	20 (12.3%)		24 (14.7%)	20 (12.3%)	
IVa	12 (1.9%)	4 (2.5%)		2 (1.2%)	4 (2.5%)	
Type: Exophytic type	428 (69.3%)	129 (79.1%)	0.015	120 (73.6%)	129 (79.1%)	0.30
Ulcerative type	190 (30.7%)	34 (20.9%)		43 (26.4%)	34 (20.9%)	
Tumor size	4.43 (1.54)	4.15 (1.37)	0.036	4.21 (1.41)	4.15 (1.37)	0.72
Histology: SCC	475 (76.9%)	121 (74.2%)	0.50	122 (74.8%)	121 (74.2%)	1.00
Adenocarcinoma	117 (18.9%)	37 (22.7%)		36 (22.1%)	37 (22.7%)	
Adenosquamous carcinoma	(4.2%)	5 (3.1%)		5 (3.1%)	5 (3.1%)	
Differentiation: Well	119 (19.3%)	37 (22.7%)	<0.001	38 (23.3%)	37 (22.7%)	0.96
Moderate	227 (36.7%)	30 (18.4%)		30 (18.4%)	30 (18.4%)	
Poorly	153 (24.8%)	61 (37.4%)		64 (39.3%)	61 (37.4%)	
Unknown	119 (19.3%)	35 (21.5%)		31 (19.0%)	35 (21.5%)	
Initial Hb	11.5 (1.8)	11.6 (1.6)	0.38	11.5 (1.9)	11.6 (1.6)	0.76
Hydronephrosis: No	550 (89.0%)	143 (87.7%)	0.68	143 (87.7%)	143 (87.7%)	1.00
Yes	68 (11.0%)	20 (12.3%)		20 (12.3%)	20 (12.3%)	

approximately the same when we categorized to cisplatin and carboplatin ([Supplementary Table S1](#)). The other toxicities appeared to be very similar in both groups in terms of white blood count, platelet and creatinine. The compliance towards chemotherapy in both groups was very good (79.14% in five cycles or more in the weekly group and 89.6% in two cycles or more in the tri-weekly group).

DISCUSSION

The standard treatment for locally advanced cervical cancer is concurrent platinum-based chemotherapy and radiotherapy.¹ The frequency of the chemotherapy regimen is either weekly or tri-weekly administration

according to clinical practice guideline of some institution in Thailand.²⁰ The weekly regimen is easy to manage in terms of no requirements for patient admission and possibly fewer side effects, however, there is still the concern that the weekly regimen might not be enough in terms of tumor control. Therefore, any additional evidence may potentially provide a benefit in routine management of chemotherapy in this setting.

Our results show that the tri-weekly group experienced 8% more neutrophil count grade 2 or greater toxicity than the weekly group. This effect led to no significant reduction in compliance. Interestingly, our results also showed a potential 6%-7% benefit in local control and possibly a small benefit (2%-3%) in overall

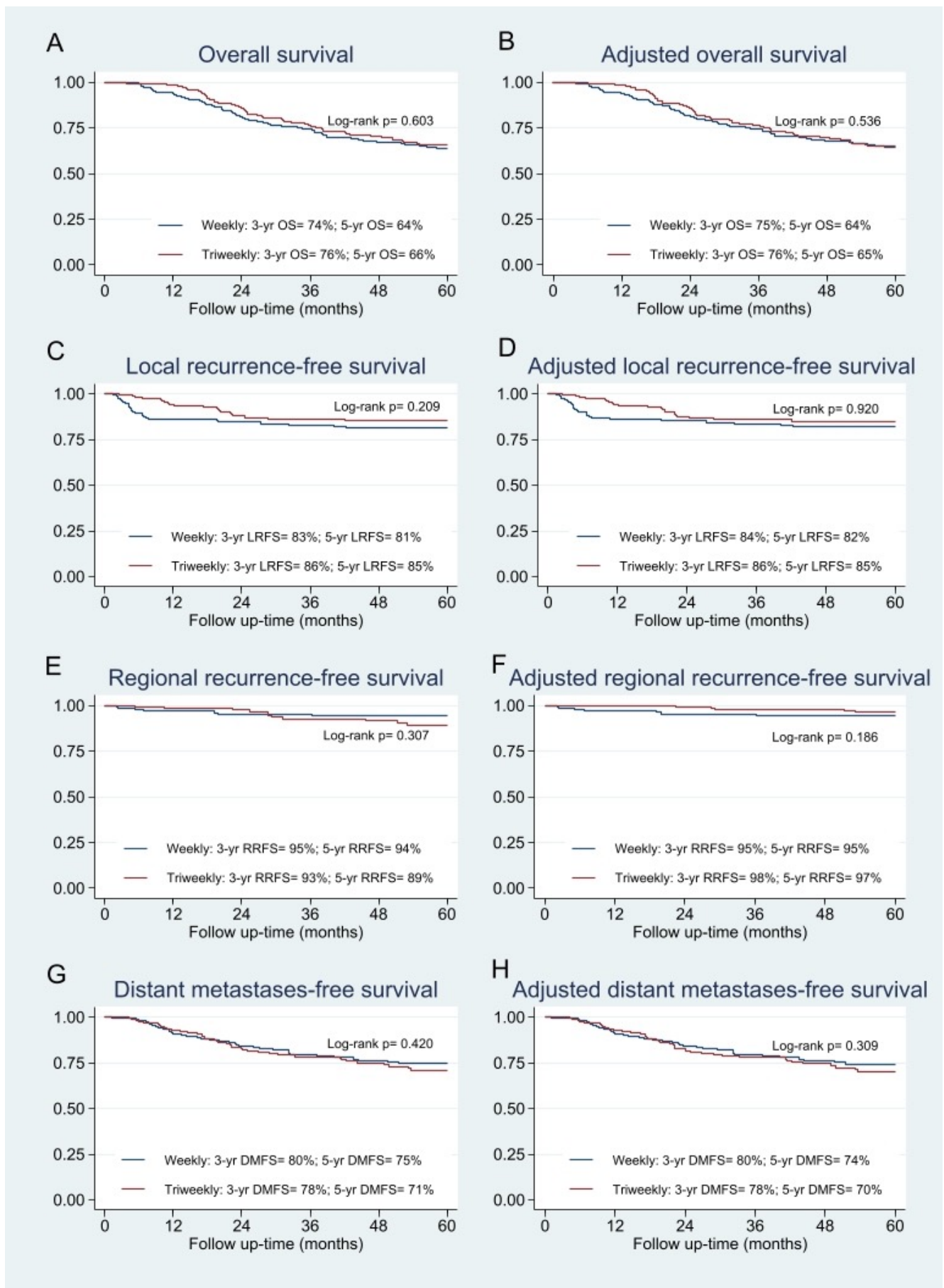
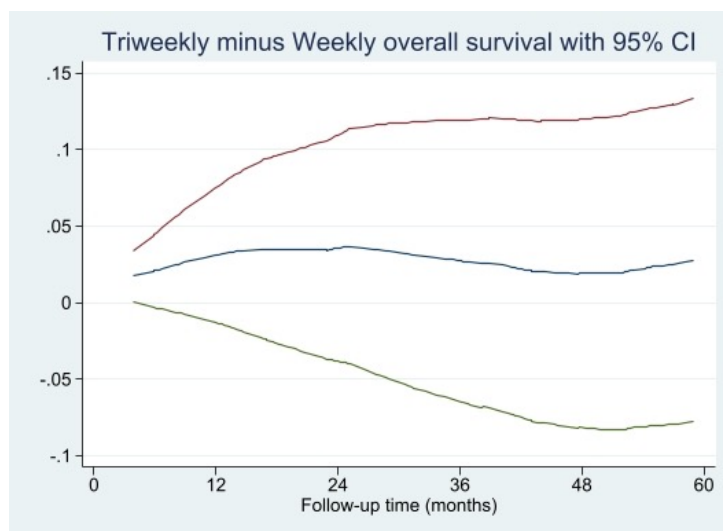
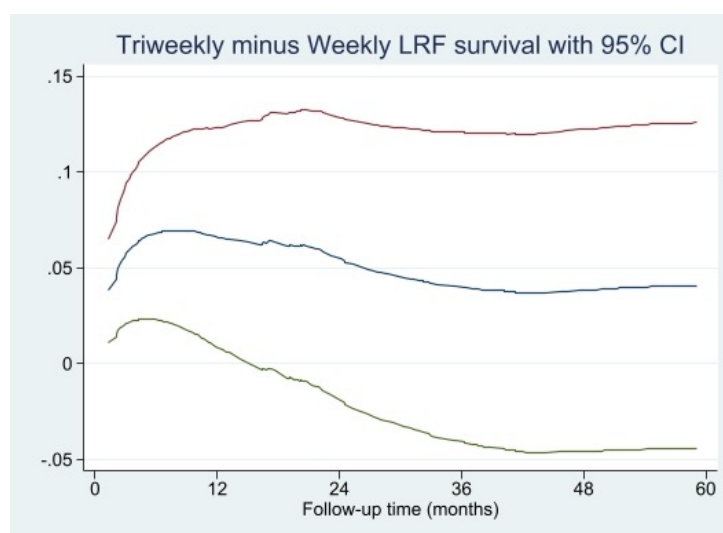


Fig 1. Kaplan-Meier survival estimate comparison between weekly and tri-weekly chemotherapy, unadjusted curve (left) and adjusted by chemotherapy regimen (carboplatin or cisplatin) (right).



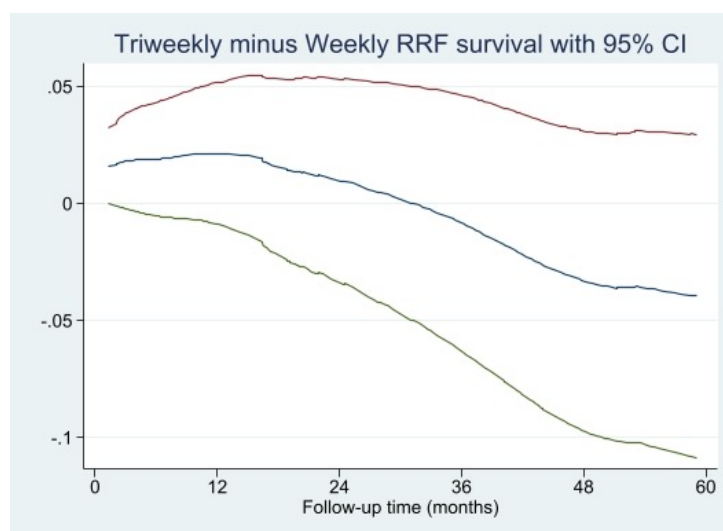
	Absolute difference
3-yr OS	0.03% (-0.7% to 1.2%)
5-yr OS	0.03% (-0.8% to 1.3%)

Supplementary Fig S1. Absolute difference of overall survival with 95% confidence interval.



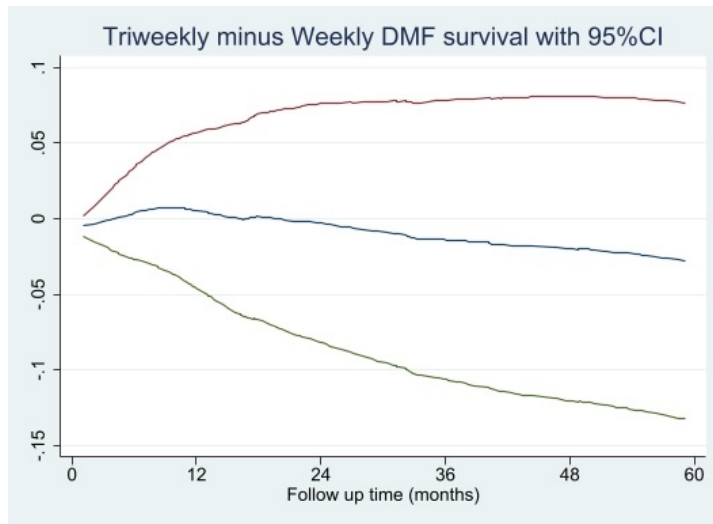
	Absolute difference
3-yr OS	0.04% (-0.04% to 0.12%)
5-yr OS	0.04% (-0.04% to 0.13%)

Supplementary Fig S2. Absolute difference of local recurrence-free survival with 95% confidence interval.



	Absolute difference
3-yr OS	-0.01% (-0.06% to 0.05%)
5-yr OS	-0.04% (-0.11% to 0.03%)

Supplementary Fig S3. Absolute difference of regional recurrence-free survival with 95% confidence interval.



Absolute difference	
3-yr OS	-0.01% (-0.11% to 0.08%)
5-yr OS	-0.03% (-0.13% to 0.08%)

Supplementary Fig S4. Absolute difference of distant metastasis-free survival with 95% confidence interval.

TABLE 2. Toxicity and compliance between weekly and triweekly chemotherapy.

		Weekly n=163	Tri-weekly n=163	p-value
Compliance				
No of cycle	1	2 (1%)	14 (9%)	Not applicable
	2	8 (5%)	132 (81%)	
	3	2 (1%)	14 (9%)	
	4	20 (12%)	-	
	5	91 (56%)	-	
	6	38 (23%)	-	
	7	1 (1%)	-	
	Missing data	1 (1%)	3 (1%)	
Toxicity				
Hemoglobin	0	44 (27.0%)	25 (15.3%)	0.011
	1	60 (36.8%)	81 (49.7%)	
	2	51 (31.3%)	40 (24.5%)	
	3	4 (2.5%)	8 (4.9%)	
	Missing data	4 (2.5%)	9 (5.5%)	
White blood cell	0	51 (31.3%)	45 (27.6%)	0.43
	1	77 (47.2%)	73 (44.8%)	
	2	28 (17.2%)	29 (17.8%)	
	3	3 (1.8%)	7 (4.3%)	
	Missing data	4 (2.5%)	9 (5.5%)	
ANC	0	123 (75.5%)	102 (62.6%)	0.009
	1	32 (19.6%)	35 (21.5%)	
	2	4 (2.5%)	12 (7.4%)	
	3	0	5 (3.1%)	
	Missing data	4 (2.5%)	9 (5.5%)	
Platelet	0	109 (66.9%)	145 (89.0%)	<0.001
	1	50 (30.7%)	14 (8.6%)	
	2	1 (0.6%)	1 (0.6%)	
	3	0	0	
	Missing data	3 (1.8%)	3 (1.8%)	
Creatinine	0	139 (85.3%)	141 (86.5%)	0.80
	1	19 (11.7%)	14 (8.6%)	
	2	1 (0.6%)	2 (1.2%)	
	3	0 (0.0%)	1 (0.6%)	
	Missing data	4 (2.5%)	5 (3.1%)	

SUPPLEMENTARY TABLE S1. Toxicity and compliance between weekly and triweekly cisplatin and carboplatin.

		Cisplatin			Carboplatin		
		Weekly n=92	Tri-weekly n=157	P value	Weekly n=71	Tri-weekly n=6	p-value
Compliance							
No of cycle	1	0(0%)	13(8%)	NA	2(3%)	1(17%)	NA
	2	3(3%)	128(82%)		5(7%)	4(67%)	
	3	2(2%)	13(8%)		0(0%)	1(17%)	
	4	11(12%)	-		9(13%)	-	
	5	49(53%)	-		42(59%)	-	
	6	26(28%)	-		12(17%)	-	
	7	0(0%)	-		1(1%)	-	
	Missing data	1(1%)	3(2%)		0(0%)	0(0%)	
Toxicity							
Hemoglobin	0	28(30%)	24(15%)	0.003	16(23%)	1(17%)	0.553
	1	30(33%)	78(50%)		30(42%)	3(50%)	
	2	31(34%)	39(25%)		20(28%)	1(17%)	
	3	1(1%)	8(5%)		3(4%)	0(0%)	
	Missing data	2(2%)	8(5%)		2(3%)	1(17%)	
WBC	0	22(24%)	44(28%)	0.417	29(41%)	1(17%)	0.085
	1	43(47%)	71(45%)		34(48%)	2(33%)	
	2	23(25%)	27(17%)		5(7%)	2(33%)	
	3	2(2%)	7(4%)		1(1%)	0(0%)	
	Missing data	2(2%)	8(5%)		2(3%)	1(17%)	
ANC	0	66(72%)	99(63%)	0.285	57(80%)	3(50%)	0.025
	1	20(22%)	34(22%)		12(17%)	1(17%)	
	2	4(4%)	11(7%)		0(0%)	1(17%)	
	3	0(0%)	5(3%)		0(0%)	0(0%)	
	Missing data	2(2%)	8(5%)		2(3%)	1(17%)	
Platelet	0	61(66%)	141(90%)	<0.001	48(68%)	4(67%)	1.000
	1	29(32%)	12(8%)		21(30%)	2(33%)	
	2	1(1%)	1(1%)		0(0%)	0(0%)	
	3	0(0%)	0(0%)		0(0%)	0(0%)	
	Missing data	1(1%)	3(2%)		2(3%)	0(0%)	
Creatinine	0	81(88%)	137(87%)	0.842	58(82%)	4(67%)	0.413
	1	9(10%)	12(8%)		10(14%)	2(33%)	
	2	1(1%)	2(1%)		0(0%)	0(0%)	
	3	0(0%)	1(1%)		0(0%)	0(0%)	
	Missing data	1(1%)	5(3%)		3(4%)	0(0%)	

survival. These results could lead to potential benefits in individual clinical judgment, especially in the context of a university hospital in Thailand while we wait for stronger evidence.

Nowadays, strong evidence to clearly support weekly or tri-weekly platinum-based chemotherapy with radiotherapy in locally advanced cervical cancer is limited. Two famous randomized controlled trials from Korea provide conflicting results and different points (Table 3). The first study from Korea¹³ showed a comparable tumor control effect and more compliance with weekly chemotherapy. The reasons behind this could be that the tri-weekly combined chemotherapy regimen with cisplatin and 5FU has poor compliance due to 15% grade 4 hematological toxicity, compared

with only 2% in the weekly group. Therefore, the weekly group in this study might display a similar effect because of inadequate chemotherapy in the tri-weekly group due to toxicity. On the other hand, the second randomized controlled trial from Korea¹² showed that the tri-weekly regimen was 20% more effective in terms of overall survival and had less grade 3-4 neutropenia than the weekly regimen. Less toxicity can be explained by the fact that the regimen in this study was only cisplatin without 5FU. Interestingly, even with planned randomization, the baseline characteristics in this second study were not well-balanced. The patients in the weekly chemotherapy group had much poorer prognosis. For example, the patients in the weekly group had an advanced stage of disease (stage III and stage IVA 45.1%), compared with

TABLE 3. Comparison of two Korean randomized controlled trials and this study.

Study	Kim et al ¹³ (RCT)		Ryu et al ¹² (RCT)		Our study (PS matched)	
	Weekly (Cis) (n=77)	Tri-weekly (Cis+5FU) (n=78)	Weekly (Cis) (n=51)	Tri-weekly (Cis) (n=53)	Weekly (Cis, carbo) (n=163)	Tri-weekly (Cis, carbo) (n=163)
Patient characteristics	Stage II =58(75%)	Stage II =52(67%)	Stage II =28(55%)	Stage II =34(64%)	Stage I-II =51(31.3%)	Stage I-II =51(31.3%)
	Stage III-Iva =19(25%)	Stage III-Iva =26(33%)	Stage III-Iva =23(45%)	Stage III-Iva =19(36%)	Stage III-Iva =112(68.7%)	Stage III-Iva =112(68.7%)
	Pelvic LN+ =31(40%)	Pelvic LN+ =32(41%)	Pelvic LN+ =29(57%)	Pelvic LN+ =27(51%)	Pelvic LN+ =33(20%)	Pelvic LN+ =33(20%)
			PAN + =7(14%)	PAN + =5(9%)	PAN + =24(15%)	PAN + =20(12%)
Chemotherapy compliance	>80% planned dose = 64(83%)	>80% planned dose = 47(60%)	>=5 cycles = 98%	>=2 cycles = 94%	>=5 cycles = 80%	>=2 cycles = 90%
Hematological toxicity	Grade 3-4 =19(25%)	Grade 3-4 =32(41%)	Neutropenia	Neutropenia	Neutropenia	Neutropenia
	Grade 4 =2(3%)	Grade 4 =15(19%)	Grade 3-4 =20(39%)	Grade 3-4 =12(23%)	Grade 3-4 =0(0%)	Grade 3-4 =5(3%)
			Thrombocytopenia	Thrombocytopenia	Thrombocytopenia	Thrombocytopenia
			Grade 3-4 =4(8%)	Grade 3-4 =3(6%)	Grade 3-4 =0(0%)	Grade 3-4 =0(0%)
Overall survival	4 year : 67%	4 year : 70%	5 year : 67%	5 year : 89%	5 year : 64%	5 year : 66%

the tri-weekly group (stage III and stage IVA 35.9%). Moreover, positive pelvic and paraaortic lymph nodes were more frequent in the weekly group (70.6%) than in patients in the tri-weekly group (61.3%). This also could be a reason why the weekly group had poorer tumor control.

Our study had some strengths. First, it included real-world data from a multi-centered study from university hospitals in Thailand, meaning it was more generalized than a single-institute study. Second, we used advanced statistical analysis to match patients who showed well-balanced baseline characteristics. Third, this study had adequately long-term follow-up time. However, there were several limitations of this study as well. First, our data came from the two-dimensional brachytherapy era. Nowadays, many hospitals use three-dimensional brachytherapy, which likely leads to more local control of the primary site. Therefore, the benefit of tri-weekly chemotherapy might be less than that seen in this study. Also, our sample size was not large enough to detect any actual difference.

CONCLUSION

In summary, the tri-weekly chemotherapy regimen showed a non-statistically potential benefit over the weekly regimen in terms of local control and overall survival but with more neutrophil toxicity. Further evidence with adequate sample size could validate this result. In the meantime, individual judgment using this data can be discussed with patients.

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REFERENCES

1. Concurrent chemoradiation for cervical cancer. Clinical announcement, [press release]. Washington, D.C., February 22 1999.
2. Keys HM, Bundy BN, Stehman FB, Muderspach LI, Chafe WE, Suggs CL, 3rd, et al. Cisplatin, radiation, and adjuvant hysterectomy compared with radiation and adjuvant hysterectomy for bulky stage IB cervical carcinoma. *N Engl J Med*. 1999;340(15):1154-61.
3. Rose PG, Bundy BN, Watkins EB, Thigpen JT, Deppe G, Maiman MA, et al. Concurrent cisplatin-based radiotherapy and chemotherapy for locally advanced cervical cancer. *N Engl J Med*. 1999;340(15):1144-53.
4. Morris M, Eifel PJ, Lu J, Grigsby PW, Levenback C, Stevens RE, et al. Pelvic radiation with concurrent chemotherapy compared with pelvic and para-aortic radiation for high-risk cervical cancer. *N Engl J Med*. 1999;340(15):1137-43.
5. Whitney CW, Sause W, Bundy BN, Malfetano JH, Hannigan EV, Fowler WC, Jr., et al. Randomized comparison of fluorouracil plus cisplatin versus hydroxyurea as an adjunct to radiation therapy in stage IIB-IVA carcinoma of the cervix with negative para-aortic lymph nodes: a Gynecologic Oncology Group and Southwest Oncology Group study. *J Clin Oncol*. 1999;17(5):1339-48.
6. Peters WA, 3rd, Liu PY, Barrett RJ, 2nd, Stock RJ, Monk BJ, Berek JS, et al. Concurrent chemotherapy and pelvic radiation therapy compared with pelvic radiation therapy alone as adjuvant therapy after radical surgery in high-risk early-stage cancer of the cervix. *J Clin Oncol*. 2000;18(8):1606-13.
7. Mittal S, Chauhan A, Kaur P, Verma YP. Comparing Weekly versus Three Weekly Schedules of Cisplatin Concomitant with Radical Radiotherapy in Locally Advanced Carcinoma Uterine Cervix. *Gynecol Obstet (Sunnyvale)*. 2017;7(1).
8. Panda N, Bag S, Samantaray S. Randomised Clinical Trial of Weekly vs. Triweekly Cisplatin Based Chemotherapy Concurrent with Radiotherapy in the Treatment of Locally Advanced Cervical Cancer. *J Med Sci Clin Res*. 2017;5(4):4.
9. Sharma K, Kumar P, Singh DP. Weekly versus tri-weekly concurrent cisplatin with radiotherapy in the treatment of cervical cancer: a study comparing efficacy and toxicity. *SRMS Journal of Medical Sciences*. 2016;1(2):66-72.
10. Preety J, Fareed K, Amit A. Comparative study of weekly versus three weekly cisplatin in advanced cases of carcinoma cervix alone with radiotherapy. *Journal of Evolution of Medical and Dental Science*. 2015;4(88):8. DOI: <http://dx.doi.org/10.14260/jemds/2015/2177>
11. Nagy VM, Ordeanu C, Coza O, Alin CR, Traila A, Todor N. Randomized phase 3 trial comparing 2 cisplatin dose schedules in 326 patients with locally advanced squamous cell cervical carcinoma: long-term follow-up. *Int J Gynecol Cancer*. 2012; 22(9):1538-44.
12. Ryu SY, Lee WM, Kim K, Park SI, Kim BJ, Kim MH, et al. Randomized clinical trial of weekly vs. triweekly cisplatin-based chemotherapy concurrent with radiotherapy in the treatment of locally advanced cervical cancer. *International journal of radiation oncology, biology, physics*. 2011;81(4):e577-81.
13. Kim YS, Shin SS, Nam JH, Kim YT, Kim YM, Kim JH, et al. Prospective randomized comparison of monthly fluorouracil and cisplatin versus weekly cisplatin concurrent with pelvic radiotherapy and high-dose rate brachytherapy for locally advanced cervical cancer. *Gynecol Oncol*. 2008;108(1):195-200.
14. Rose PG, Ali S, Watkins E, Thigpen JT, Deppe G, Clarke-Pearson DL, et al. Long-term follow-up of a randomized trial comparing concurrent single agent cisplatin, cisplatin-based combination chemotherapy, or hydroxyurea during pelvic irradiation for locally advanced cervical cancer: a Gynecologic Oncology Group Study. *J Clin Oncol*. 2007;25(19):2804-10.
15. Zhu J, Ji S, Hu Q, Chen Q, Liu Z, Wu J, et al. Concurrent

- weekly single cisplatin vs triweekly cisplatin alone with radiotherapy for treatment of locally advanced cervical cancer: a meta-analysis. *Cancer Manag Res*. 2018;10:1975-85.
16. Zhu J, Zhang Z, Bian D, Chen Q, Hu Q, Ji S, et al. Weekly versus triweekly cisplatin-based concurrent chemoradiotherapy in the treatment of locally advanced cervical carcinoma: An updated meta-analysis based on randomized controlled trials. *Medicine (Baltimore)*. 2020;99(1):e18663.
17. Petrelli F, De Stefani A, Raspagliesi F, Lorusso D, Barni S. Radiotherapy with concurrent cisplatin-based doublet or weekly cisplatin for cervical cancer: a systematic review and meta-analysis. *Gynecol Oncol*. 2014;134(1):166-71.
18. Paño B, Sebastià C, Ripoll E, Paredes P, Salvador R, Buñesch L, et al. Pathways of lymphatic spread in gynecologic malignancies. *Radiographics*. 2015;35(3):916-45.
19. Mao Y, Hedgire S, Praprutam D, Harisinghani M. Imaging of Pelvic Lymph Nodes. *Current Radiology Reports*. 2014;2(11):70.
20. Ieumwananonthachai N, Pataranutraporn P, Chasilpa Y, Sangruchi S, Verasan V, Suntornpong N, et al. Results of Cervical Cancer Patients Treated According to Clinical Practice Guidelines in Siriraj Hospital. *Siriraj Med J*. 2003;55(12):695-703.