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Impact of different post-operative treatment modalities on long-term outcomes in International Federation of Gynecology and Obstetrics (FIGO) 2018 stage IIICp cervical cancer

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► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ijgc-2022-004234).

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Received 15 December 2022
Accepted 16 March 2023

To cite: Soochit A, Zhang C, Feng Y, *et al. Int J Gynecol Cancer* Published Online First: [please include Day Month Year]. doi:10.1136/ijgc-2022-004234

ABSTRACT

Objective This retrospective study aimed to evaluate the survival outcomes in International Federation of Gynecology and Obstetrics (FIGO) 2018 stage IIICp cervical cancer patients receiving different adjuvant treatment modalities after radical hysterectomy.

Methods From January 2008 to December 2012, patients diagnosed with cervical cancer who underwent radical hysterectomy plus retroperitoneal lymphadenectomy with pathologically confirmed positive lymph nodes, and received either radiotherapy, concurrent chemoradiation, or sequential chemoradiation, were included in this study. Survival analysis was performed according to different adjuvant treatment modalities and after adjustment using propensity score matching.

Results A total of 192 stage IIICp cervical cancer patients were eligible. In multivariate analysis, only sequential chemoradiation versus radiotherapy was associated with both overall survival (HR 0.44, 95% CI 0.21 to 0.94, p=0.035) and disease-free survival (HR 0.26, 95% CI 0.11 to 0.57, p<0.001). The 5-year overall survival for radiotherapy, concurrent chemoradiation, and sequential chemoradiation was 71.6%, 81.7%, and 81.5%, respectively. No significant difference in overall survival was noted between the three groups (radiotherapy vs concurrent chemoradiation, p=0.15; radiotherapy vs sequential chemoradiation, p=0.09; concurrent chemoradiation vs sequential chemoradiation, p=0.95). However, sequential chemoradiation significantly increased disease-free survival compared with radiotherapy alone (79.2% vs 63.1%, p=0.028). After propensity score matching in the baseline characteristics, both overall survival (88.0% vs 71.6%, p=0.028) and disease-free survival (88.0% vs 63.1%, p=0.021) were improved in the sequential chemoradiation group compared with radiotherapy alone; no significant differences were noted between sequential chemoradiation and concurrent chemoradiation (overall survival 88.0% vs 83.8%, p=0.50; disease-free survival 88.0% vs 75.8%, p=0.28).

Conclusion In this cohort of FIGO 2018 IIICp cervical cancer patients, post-operative sequential chemoradiation was associated with higher survival compared with radiotherapy alone after propensity matching. Future prospective studies are required to further elucidate the optimal modality in node-positive cervical cancer.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Patients with lymph node metastasis after radical hysterectomy are considered to have 'high-risk' disease, and concurrent chemoradiation is the recommended adjuvant modality. The risk of recurrence is higher in those with positive lymph nodes, and optimal treatment after radical surgery needs further investigation.

WHAT THIS STUDY ADDS

⇒ Post-operative sequential chemoradiation significantly improved survival compared with radiation alone, especially in node-positive patients with negative surgical margins, no parametrial involvement, and no vaginal involvement.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Sequential chemoradiation is associated with higher survival compared with radiation alone in FIGO 2018 stage IIICp cervical cancer patients after radical hysterectomy.

INTRODUCTION

Retroperitoneal lymph node metastasis is one of the most significant prognostic factors in cervical cancer, and patients with positive nodes have a higher risk of recurrence.[1–3] In 2018, for the first time nodal status was included in the International Federation of Gynecology and Obstetrics (FIGO) staging system; according to the new system, women with pelvic or para-aortic lymph node metastasis are classified into stage IIIC.[4 5]

In patients with high-risk factors, the addition of chemotherapy proved to be beneficial compared with radiation alone.[6] Concurrent chemoradiation is the recommended option for node-positive patients after radical surgery.[7] However, relapse will still occur in about 20–30% of patients.[6 8] Consolidation chemotherapy after concurrent chemoradiation is another option that still needs further validation due to heterogenous results in high- or intermediate-risk

patients.[9 10] The recently published STARS trial comparing different post-operative adjuvant treatments in early-stage cervical cancer reported an improved disease-free survival in patients receiving sequential chemoradiation compared with radiotherapy and concurrent chemoradiation.[11] Optimal treatment for node-positive cervical cancer after radical surgery needs further investigation. In our institution, radiotherapy, concurrent chemoradiation, and sequential chemoradiation were the three adjuvant modalities for high- and intermediate-risk cervical cancer after radical surgery. Thus, we conducted this retrospective study to evaluate the long-term outcomes following different treatment modalities in FIGO 2018 stage IIICp cervical cancer patients after radical hysterectomy.

METHODS

Eligibility and Clinical Information

In this study, consecutive patients diagnosed with cervical cancer between January 2008 and December 2012 at Sun Yat-sen University Cancer Center were retrieved. Patients who underwent radical hysterectomy plus lymphadenectomy with confirmed positive retroperitoneal lymph nodes and had received either radiotherapy, concurrent chemoradiation, or sequential chemoradiation were eligible. Patients with synchronous malignancies, other malignancies prior to the study, neuroendocrine tumors, or had received neoadjuvant chemotherapy were excluded. The study was conducted in conformity with the Declaration of Helsinki[12] and was approved by the Ethics Committee of Sun Yat-sen University Cancer Center. The clinical and pathological data of eligible patients were retrieved and analyzed. Apart from external pelvic radiation, patients were given extended field radiation to the para-aortic region when the common iliac or para-aortic lymph nodes were involved. For concurrent chemoradiation, weekly cisplatin was administered during radiation. Sequential chemoradiation consisted of two cycles of platinum-based chemotherapy plus paclitaxel before and after radiation, forming a 'sandwich' modality.

Statistical Analysis

The entire cohort (unmatched population) and a matched population with an equal number of patients in each treatment group were analyzed. The propensity score matching method was used to minimize potential selection bias in the matched population. Two propensity scores were estimated using the multivariate logistic regression model followed by two 1:1 optimal matching without replacement through a common referent group (radiotherapy group). The variables used for the propensity score were diameter of tumor, tumor grade, depth of stromal invasion, lymphovascular space invasion, parametrial involvement, surgical margins, vaginal involvement, involvement of the common iliac lymph node, and number of positive lymph nodes. The quality of matching was evaluated by comparing the standardized mean difference (SMD) between matched and unmatched cohorts; an SMD <0.1 was considered negligible.

All statistical analysis and graphics were generated in RStudio, version 4.0.3 (R Foundation). Disease-free survival was defined from the date of surgery to the date of first recurrence or the date of death from any cause, whichever occurred first. Overall survival was the duration from the date of surgery to the date of death from any cause or the last follow-up. Survival analysis were carried out using the Kaplan-Meier (log-rank) method. Cox's regression model was used for univariate and multivariate analysis. The baseline characteristics in the unmatched population were assessed with one-way analysis of variance (ANOVA) for means and χ^2 test for categorical variables. A p value <0.05 was set as the threshold for statistical significance.

RESULTS

Clinicopathological Characteristics

The baseline characteristics of the 192 eligible patients are listed in Table 1. The average age at diagnosis was 48.0±9.2 years old, and most patients underwent laparotomy (97.9%) for a radical hysterectomy with pelvic lymph node dissection. The stage distribution according to the FIGO 2009 staging system was stage IB1 (56.8%), IB2 (4.2%), IIA1 (37.5%), and IIA2 (1.6%). The median tumor size was 3.5 cm (range 0.5–7.5 cm). The average number of lymph nodes retrieved and positive lymph nodes was 24.3±8.9 and 3.5±5.5, respectively. A total of 107 (55.7%) patients had more than one involved lymph node. In patients (n=40) who had a pelvic lymph node dissection plus para-aortic lymph node dissection, 15 had positive para-aortic lymph nodes with synchronous positive pelvic lymph nodes; no isolated para-aortic lymph node metastasis was detected. A total of 82 (42.7%) patients participated in the STARS clinical trial.[11] After surgery, a majority of patients received sequential chemoradiation (66.1%) as adjuvant therapy compared with concurrent chemoradiation (20.8%) and radiotherapy alone (13.0%).

Oncologic Outcome and Associated Risk Factors

The mean follow-up time was 89.0 (95% CI 82.7 to 95.4) months. The 5-year overall survival and 5-year disease-free survival for the entire cohort were 80.2% and 75.4%, respectively. The results of univariate and multivariate cox regression analysis for factors associated with disease-free survival are shown in Table 2. In univariate analysis, parametrial involvement (HR 2.93, 95% CI 1.24 to 6.90, p=0.014), positive surgical margins (HR 2.56, 95% CI 1.23 to 5.29, p=0.011), vaginal involvement (HR 2.94, 95% CI 1.46 to 5.91, p=0.003), positive common iliac lymph node (HR 2.02, 95% CI 1.03 to 3.96, p=0.042), and sequential chemoradiation versus radiotherapy (HR 0.45, 95% CI 0.22 to 0.94, p=0.034) were risk factors for recurrence. After multivariate analysis, only vaginal involvement (HR 3.13, 95% CI 1.29 to 7.58, p=0.011) and sequential chemoradiation versus radiotherapy (HR 0.26, 95% CI 0.11 to 0.57, p<0.001) were the two independent factors affecting recurrence. For overall survival (Online supplemental table S1), despite a significant association with tumor size (>2 cm to ≤4 cm vs ≤2 cm; HR 3.70, 95% CI 1.11 to 12.28, p=0.033) and deep stromal invasion (HR 2.36, 95% CI 1.00 to 5.55, p=0.050) as prognosticators in univariate analysis, only radiotherapy was a factor associated with worse survival compared with sequential chemoradiation (sequential chemoradiation vs radiotherapy; HR 0.44, 95% CI 0.21 to 0.94, p=0.035) in multivariate analysis. During the follow-up, 48 deaths (radiotherapy 10; concurrent chemoradiation 10; sequential chemoradiation 28) and 47 recurrences (radiotherapy 10; concurrent chemoradiation 11; sequential chemoradiation 26) occurred. No differences were observed between the three groups for local (p=0.09) or distant site (p=0.99) recurrences (Online supplemental table S2).

Table 1 Baseline characteristics of the 192 eligible cervical cancer patients

Characteristics	Number (%)
Number of patients	192
Age (years)*	48.0±9.2
Stage (FIGO 2009)	
IB1	109 (56.8)
IB2	8 (4.2)
IIA1	72 (37.5)
IIA2	3 (1.6)
Diameter of tumor (cm)	
≤2	28 (14.6)
>2 to ≤4	107 (55.7)
>4	57 (29.7)
Histology	
SCC	162 (84.4)
AC	16 (8.3)
ASC	14 (7.3)
Tumor grade	
Grade 1~2	59 (30.7)
Grade 3	132 (68.8)
Unknown	1 (0.5)
Depth of stromal invasion	
<1/2	43 (22.4)
≥1/2	149 (77.6)
LVSI	
No	116 (60.4)
Yes	75 (39.1)
Unknown	1 (0.5)
Parametrial involvement	
No	182 (94.8)
Yes	10 (5.2)
Surgical margins	
Negative	173 (90.1)
Positive	19 (9.9)
Surgical approach	
Laparotomy	188 (97.9)
Laparoscopic	4 (2.1)
Para-aortic LN dissection	
No	152 (79.2)
Yes	40 (20.8)
Vaginal involvement	
No	173 (90.1)
Yes	19 (9.9)
Number of LN removed*	24.3±8.9
Number of positive LN	
Mean*	3.5±5.5
1	85 (44.3)
≥2	107 (55.7)
Location of positive LN	
Only pelvic	177 (92.2)
Pelvic+para-aortic	15 (7.8)
Common iliac LN	
Negative	161 (83.9)
Positive	31 (16.1)
Adjuvant treatment	
RT	25 (13.0)
CCRT	40 (20.8)
SCRT	127 (66.1)

*Value is mean (±SD).
AC, adenocarcinoma; ASC, adenosquamous carcinoma; CCRT, concurrent chemoradiation; FIGO, International Federation of Gynecology and Obstetrics; LN, lymph node; LVSI, lymphovascular space invasion; RT, radiotherapy; SCC, squamous cell carcinoma; SCRT, sequential chemoradiation.

Impact of Different Post-operative Adjuvant Therapy on Survival

The baseline characteristics of the entire cohort and the matched cohort according to different adjuvant therapies are shown in Table 3. No statistical differences were observed among the characteristics in the unmatched cohort (p>0.05). However, significant differences were noted in most of the characteristics between each treatment group (SMDs >0.1). After matching, each treatment group had 25 patients, and SMDs were <0.1, indicating good quality matching, except for the number of positive lymph nodes (SMD 0.108), tumor grade (SMD 0.134), the status of common iliac lymph node (SMD 0.146), and diameter of tumor (SMD 0.292). The concurrent chemoradiation and sequential chemoradiation groups had a higher number of patients with two or more positive lymph nodes (radiotherapy 13; concurrent chemoradiation 15; sequential chemoradiation 15), grade 3 tumors (radiotherapy 19; concurrent chemoradiation 20; sequential chemoradiation 21), and larger tumors (>2 cm: radiotherapy 19; concurrent chemoradiation 21; sequential chemoradiation 22) compared with the radiotherapy group (Table 3).

The Kaplan-Meier analysis according to different treatment modalities for the entire cohort is shown in Figure 1A (overall survival) and Figure 1B (disease-free survival). The 5-year overall survival for radiotherapy, concurrent chemoradiation, and sequential chemoradiation was 71.6%, 81.7%, and 81.5%, respectively. No differences in overall survival were noted between any of the three groups (radiotherapy vs concurrent chemoradiation, p=0.15; radiotherapy vs sequential chemoradiation, p=0.09; concurrent chemoradiation vs sequential chemoradiation, p=0.95).

The differences observed between radiotherapy and concurrent chemoradiation (63.1% vs 71.7%, p=0.31) or concurrent chemoradiation and sequential chemoradiation (71.7% vs 79.2%, p=0.34) did not reach statistical significance for 5-year disease-free survival. Nevertheless, there was a significant increase in 5-year disease-free survival

Table 2 Univariate and multivariate Cox regression for factors associated with disease-free survival

	Univariate		Multivariate	
Characteristics	**HR (95% CI)**	**P value**	**HR (95% CI)**	**P value**
Diameter of tumor (cm)				
≤2				
>2 to ≤4	3.02 (0.92 to 9.91)	0.069	2.83 (0.81 to 9.88)	0.102
>4	2.61 (0.75 to 9.01)	0.130	2.46 (0.66 to 9.22)	0.179
Tumor grade				
Grade 1~2				
Grade 3	1.01 (0.54 to 1.88)	0.987	0.89 (0.46 to 1.74)	0.742
Depth of stromal invasion				
<1/2				
≥1/2	2.22 (0.94 to 5.22)	0.069	1.51 (0.59 to 3.88)	0.392
LVSI				
No				
Yes	1.16 (0.65 to 2.06)	0.625	1.07 (0.59 to 1.96)	0.815
Parametrial involvement				
No				
Yes	2.93 (1.24 to 6.90)	**0.014**	1.28 (0.35 to 4.59)	0.709
Surgical margins				
Negative				
Positive	2.56 (1.23 to 5.29)	**0.011**	1.37 (0.44 to 4.27)	0.589
Vaginal involvement				
No				
Yes	2.94 (1.46 to 5.91)	**0.003**	3.13 (1.29 to 7.58)	**0.011**
Number of positive LN				
1				
≥2	1.68 (0.92 to 3.08)	0.090	1.29 (0.65 to 2.53)	0.465
Common iliac LN				
Negative				
Positive	2.02 (1.03 to 3.96)	**0.042**	1.49 (0.65 to 3.41)	0.349
Adjuvant treatment				
RT				
CCRT	0.64 (0.27 to 1.50)	0.303	0.48 (0.20 to 1.17)	0.107
SCRT	0.45 (0.22 to 0.94)	**0.034**	0.26 (0.11 to 0.57)	**<0.001**

CCRT, concurrent chemoradiation; LN, lymph node; LVSI, lymphovascular space invasion; RT, radiotherapy; SCRT, sequential chemoradiation.

in the sequential chemoradiation group compared with the radiotherapy group (79.2% vs 63.1%, p=0.028). Furthermore, the survival outcomes between treatment groups were compared in the matched cohort and are shown in Figure 1C (overall survival) and Figure 1D (disease-free survival). After matching (Table 3), patients in each group had negative surgical margins, no parametrial involvement, and no vaginal involvement. The 5-year overall survival (88.0% vs 71.6%, p=0.028) and disease-free survival (88.0% vs 63.1%, p=0.021) for sequential chemoradiation were higher compared with radiotherapy. No statistically significant survival differences were observed between concurrent chemoradiation and radiotherapy (overall survival, 83.8% vs 71.6%, p=0.11; disease-free survival, 75.8% vs 63.1%, p=0.19) or concurrent chemoradiation and sequential chemoradiation (overall survival, 83.8% vs 88.0%, p=0.50; disease-free survival, 75.8% vs 88.0%, p=0.28).

DISCUSSION

Summary of Main Results

In the current study, parametrial involvement, positive surgical margins, vaginal involvement, positive common iliac lymph node, and sequential chemoradiation versus radiotherapy were

Table 3 Baseline characteristics of patients according to different adjuvant treatment modalities before and after matching

	Unmatched cohort (n=192)					Matched cohort (n=75)			
Variables	RT (n=25)	CCRT (n=40)	SCRT (n=127)	SMD	P value	RT (n=25)	CCRT (n=25)	SCRT (n=25)	SMD
Age (years)*	48±10.6	49±9.5	47±8.8	0.115	0.613	48±10.6	47±8.9	47±9.0	0.071
Diameter of tumor (cm)				0.270	0.439				0.292
≤2	6	6	16			6	4	3	
>2 to ≤4	13	25	69			13	17	16	
>4	6	9	42			6	4	6	
Tumor grade				0.232	0.325				0.134
G1-2	6	16	37			6	5	4	
G3	19	24	89			19	20	21	
Depth of stromal invasion				0.125	0.744				0.061
<1/2	7	8	28			7	7	6	
>1/2	18	32	99			18	18	19	
LVSI				0.125	0.724				0.056
No	17	23	76			17	16	17	
Yes	8	16	51			8	9	8	
Parametrial involvement				0.278	0.237				–
No	25	39	118			25	25	25	
Yes	0	1	9			0	0	0	
Surgical margins				0.349	0.195				–
Negative	25	36	112			25	25	25	
Positive	0	4	15			0	0	0	
Vaginal involvement				0.391	0.062				–
No	25	38	110			25	25	25	
Yes	0	2	17			0	0	0	
Common iliac LN				0.228	0.232				0.146
Negative	21	37	103			21	22	20	
Positive	4	3	24			4	3	5	
Number of positive LN				0.074	0.908				0.108
1	12	17	56			12	10	10	
≥2	13	23	71			13	15	15	

*Value is mean (±SD).
CCRT, concurrent chemoradiation; LN, lymph node; LVSI, lymphovascular space invasion; RT, radiotherapy; SCRT, sequential chemoradiation; SMD, standardized mean difference.

prognosticators for recurrence in univariate analysis; however, only vaginal involvement and sequential chemoradiation versus radiotherapy were the two independent factors affecting recurrence in multivariate analysis. Furthermore, sequential chemoradiation versus radiotherapy alone was also the only factor associated with overall survival in multivariate analysis. No significant difference was noted in overall survival among the three treatment modalities; however, sequential chemoradiation showed higher disease-free survival compared with radiotherapy alone. In the matched cohort that included patients with negative surgical margins, no parametrial involvement, and no vaginal involvement in each treatment group, the sequential chemoradiation group had a higher 5-year overall survival and disease-free survival compared with radiotherapy alone.

Results in the Context of Published Literature

In recent years many studies evaluated the impact of different adjuvant therapy in both high- and intermediate-risk cervical cancer patients. Patients with lymph node metastasis, parametrial involvement, and positive margins are considered to have 'high-risk' disease.[7] For these patients, concurrent chemoradiation is the recommended option which significantly improves overall survival.[6] The Gynecologic Oncology Group (GOG) Study 109, which evaluated radiation and chemoradiation in node-positive, margin positive,

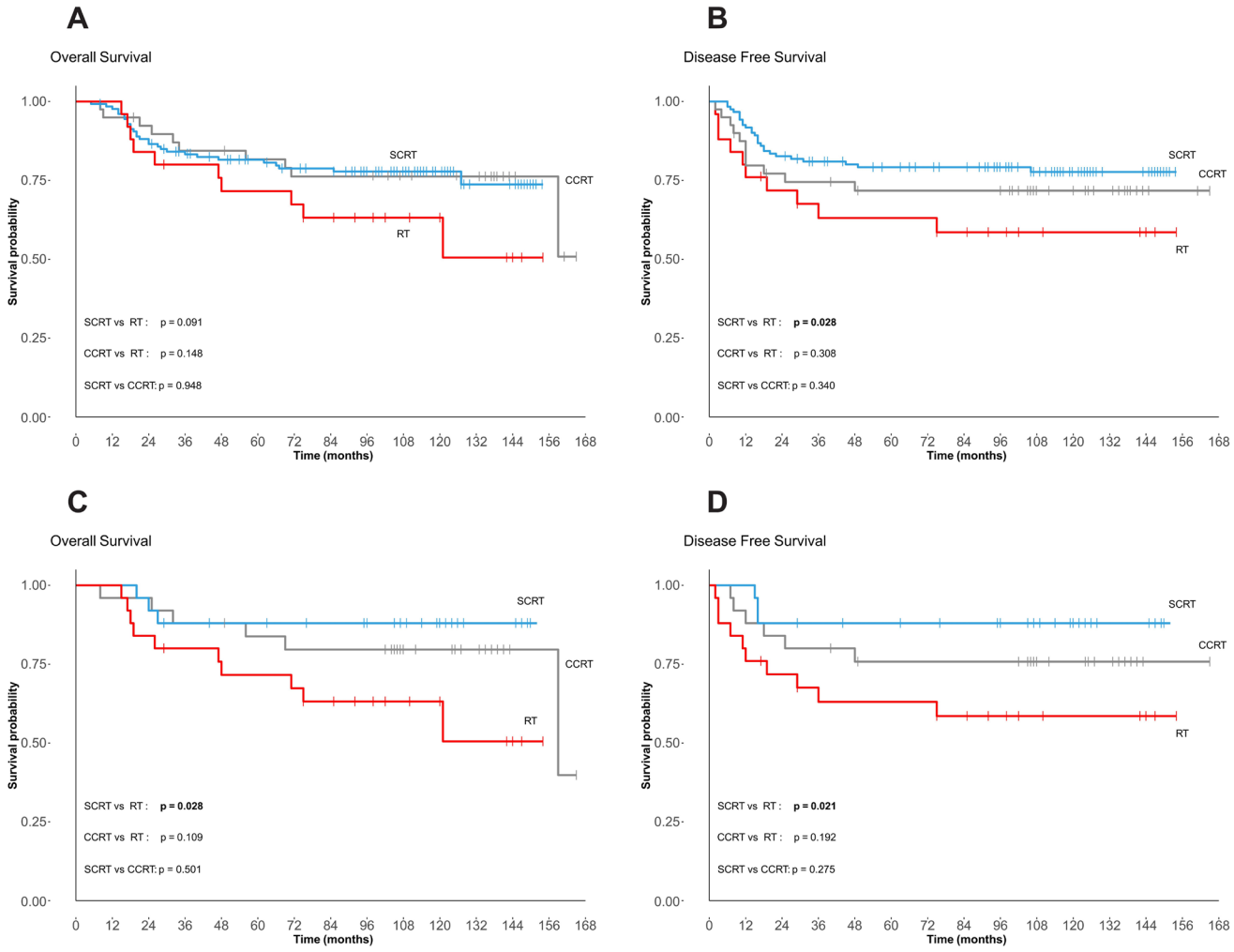

Figure 1 Overall survival and disease-free survival according to different post-operative treatment modalities in the unmatched (A, B) and matched cohort (C, D). CCRT, concurrent chemoradiation; RT, radiotherapy; SCRT, sequential chemoradiation.

and/or microscopic parametrial involvement after radical surgery, reported a substantially improved disease-free survival and overall survival in the chemoradiation group.[6] The re-evaluated findings from this study further validate the survival benefit of chemoradiation; however, the best result was restricted to node-positive patients.[8]

Even though lymph node involvement and number of positive lymph nodes were associated with survival,[13–17] limited evidence is available for the treatment strategy in FIGO 2018 stage IIICp after radical hysterectomy. The optimal treatment option for node-positive with or without other high-risk factors remains uncertain. Consolidation chemotherapy is another option that was evaluated in node-positive cervical cancer after radical hysterectomy; it showed improved survival in patients with more than three positive nodes or more than two positive nodes with lymphovascular space invasion and stromal invasion greater than 1/3.[10] In another study, Kim et al reported that additional chemotherapy after post-operative concurrent chemoradiation did not improve survival in high- or intermediate-risk patients (disease-free survival, p=0.539; overall survival, p=0.121); however, a significantly higher number of patients with lymph node metastasis were in the study group (72.1%) compared with the control group (46.0%).[9] Although insufficient data suggest the benefit of consolidation chemotherapy, a phase III open-label randomized trial and other retrospective studies reported improved survival in locally advanced cervical cancer.[18–21]

The recently published phase III randomized controlled STARS trial investigated the clinical benefit of radiotherapy, concurrent chemoradiation, or sequential chemoradiation as adjuvant therapy in FIGO 2009 stage IB-IIA cervical cancer (n=1048) with high- or intermediate-risk after radical hysterectomy; the trial showed that sequential chemoradiation significantly improved 3-year disease-free survival compared with radiotherapy (90% vs 82%, p=0.01) and concurrent chemoradiation (90% vs 85%, p=0.04).[11] After adjustment for lymph node status, sequential chemoradiation further reduced the risk of recurrence and improved the 5-year risk of death compared with radiotherapy (92% vs 88%).[11] However, no difference was observed in terms of disease-free survival or cancer risk death between the concurrent chemoradiation and radiotherapy group.[11]

Unlike the STARS trial, the present study recruited only lymph node-positive cervical cancer patients after radical hysterectomy and showed that sequential chemoradiation versus radiotherapy alone significantly improved disease-free survival (unmatched and

matched cohorts) and overall survival (matched cohort). However, no survival differences were noted between sequential chemoradiation and concurrent chemoradiation in either cohort. Based on a longstanding hypothesis, radiotherapy is believed to have an important role in controlling locoregional recurrences, while the addition of chemotherapy helps in reducing extra pelvic recurrence.[6 22] In the STARS trial, the sequential chemoradiation group had a lower distant recurrence rate compared with concurrent chemoradiation or radiotherapy alone (6.5%, 11%, and 10.6%; p=0.037); no statistically significant difference was noted for local recurrence among the three different treatments.[11] In the present study, locoregional and distant site recurrences were not statistically significant among the different treatment groups, despite a lower number of locoregional failures in the sequential chemoradiation group. The site of recurrence might have been influenced as a higher number of patients with other risk factors (positive surgical margin, parametrial involvement, or vaginal involvement) were present in the concurrent chemoradiation and sequential chemoradiation group.

When considering chemoradiation or additional chemotherapy, the choice of regimens could be a factor that influences response and tolerability. Despite good survival outcomes, the 5-fluorouracil and cisplatin combination in the GOG 109 trial was unpopular in practice due to toxicity and its inconvenience in administration.[23] However, the platinum and taxane combination has been preferred for its response and tolerable toxicities.[24 25] In previous studies, the results of additional chemotherapy after concurrent chemoradiation were conflicting and might have been due to inconsistency in agents or regimens administered.[9 10] In contrast, the STARS trial and the present study were consistent in the regimens for both concurrent chemoradiation and sequential chemoradiation.[11] Besides, the toxicities associated with sequential chemoradiation were similar to concurrent chemoradiation (grade 3 or 4 hematological toxicities, 19.1% vs 18.8%, p=0.93).[11] However, gastrointestinal toxicities and discontinuation (37.4% vs 23.8%) due to chemotherapy-related toxicities or intolerability were more frequent with concurrent chemoradiation compared with sequential chemoradiation.[11]

The interval between surgery and adjuvant therapy for cervical cancer patients is crucial. There has been consensus that a time gap, usually within 6 weeks between surgery and initiation of radiotherapy, was related to better survival.[26 27] Nevertheless, in low-income countries where the incidence of cervical cancer is high,[28] the waiting period for oncologic treatment is generally much longer.[29 30] Sequential chemoradiation could be an alternative that reduces the time gap as chemotherapy can be administered while waiting for radiation, especially when resources are limited.

In light of our current findings, we believe that sequential chemoradiation is an option that can be further explored in high-risk cervical cancer, but it is well-acknowledged that concurrent chemoradiation is the standard of care compared with radiotherapy alone based on the GOG 109 trial. Thus, future prospective studies comparing these two modalities (concurrent chemoradiation and sequential chemoradiation) are warranted for node-positive cervical cancer.

Strengths and Weaknesses

Our study specifically evaluated lymph node-positive cervical cancer patients from a single institution with a consistent treatment pattern for each post-operative modality. It also provided data regarding sequential chemoradiation which was less studied in cervical cancer. There were some limitations in this study due to its retrospective nature. The number of patients in each treatment group was not balanced, and even after adjustment, bias was not completely avoidable and could have influenced the results. The majority of patients received sequential chemoradiation as post-operative adjuvant therapy and could be subject to bias as factors influencing the clinicians for this choice were not available. Since para-aortic lymph node dissection was not a routine procedure at the time of treatment, only a small proportion of patients underwent a para-aortic lymph node dissection, and the extent was not well documented in certain cases. Surgery that is not currently recommended by international guidelines for locally advanced disease was performed, as during that period, the waiting time for radiotherapy was much longer due to limited resources in certain local hospitals. Lastly, insufficient data were available to compare the toxicities associated with each treatment modality.

Implication for Practice and Future Research

In this cohort of high-risk cervical cancer patients with positive lymph nodes, sequential chemoradiation could be an alternative post-operative treatment modality that provides better survival than radiotherapy alone. Future studies are required with international collaboration to further elucidate the optimal therapeutic modality in node-positive cervical cancer with other risk factors. The final results of the RTOG-0724 (NCT00980954) clinical trial evaluating additional chemotherapy in high-risk early-stage cervical cancer treated with radical hysterectomy are awaited with great interest.

CONCLUSION

In this cohort of FIGO 2018 IIICp cervical cancer patients, post-operative sequential chemoradiation was associated with higher survival compared with radiotherapy alone. Future prospective studies are required to further elucidate the optimal modality in node-positive cervical cancer.

Contributors All authors meaningfully contributed to the study. AS: Conceptualization; data acquisition; statistical analysis; writing; review and editing. CZ: Conceptualization; data acquisition; visualization; project administration; review and editing. YF, XL, HH: Visualization; review and editing. JL: Supervision; funding acquisition; review, editing, and is responsible for the overall content as the guarantor.

Funding This study was funded by Sun Yat-sen University (Clinical Research 5010 Program (No. 2007041)).

Competing interests None declared.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. Data are available upon reasonable request. Please contact the corresponding author.

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