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Prognostic value of lymphovascular space invasion in patients with early stage cervical cancer in Jilin, China

A retrospective study

Wenxing Yan, PhD[a], Shuang Qiu, PhD[b], Yaming Ding, PhD[a], Qi Zhang, PhD[a], Lihui Si, PhD[b], Sha Lv, PhD[b], Linlin Liu, PhD[a,*]

Abstract

The metastasis of cervical carcinoma is associated with the lymphovascular spread. The primary objective of the present study was to determine the prognostic value of lymphovascular space invasion (LVSI) in patients with early-stage cervical cancer in Jilin, China.

In this retrospective cohort study, patients with early-stage cervical cancer (stage IB-IIA) at the Second Hospital of Jilin University from February 2014 to December 2016 were included in the analysis. All included participants underwent radical hysterectomy with pelvic lymphadenectomy. LVSI was identified by hematoxylin and eosin (H&E) staining. The primary outcomes are overall survival (OS) and progression-free survival (PFS). Kaplan–Meier curves were used to calculate the patient's survival. Survival was compared using the log-rank test, while risk factors for the prognosis were assessed by Cox regression analysis.

The incidence of LVSI was positively associated with the depth of stromal invasion ($P = .009$) and lymph node metastasis (LNM, $P < .001$). LVSI is an independent factor that affects OS ($P = .009$) and PFS ($P = .006$) in patients with early stage cervical cancer. LNM status is an independent factor that affects postoperative OS ($P = .005$).

The incidence of lymphatic vessel infiltration is positively associated with the depth of stromal invasion and LNM. LVSI is an independent risk factor for the prognosis of early cervical cancer. The results suggest that further large-scale studies are needed to improve the treatment for patients with LVSI.

Abbreviations: CT = chemotherapy, FIGO = International Federation of Gynecology and Obstetrics, H&E = hematoxylin and eosin, HPV = human papillomavirus, LNM = lymph node metastasis, LVSI = lymphovascular space invasion, NFT = no further therapy, OS = overall survival, PFS = progression-free survival, RT = radiotherapy, TCT = ThinPrep cytology test.

Keywords: cervical carcinoma, chemotherapy, lymphovascular space invasion, overall survival, progression-free survival, radical hysterectomy, radiotherapy

Editor: Surinder Kumar.

Precis: In this retrospective cohort study, the incidence of LVSI was positively associated with the depth of stromal invasion (P=.009) and lymph node metastasis (LNM, P<.001).

The authors have no conflicts of interests to disclose.

Supplemental Digital Content is available for this article.

[a] Radiotherapy Department of Oncology, Second Hospital of Jilin University,, [b] Department of Epidemiology and Biostatistics, School of Public Health, Jilin University, Changchun, Jilin, China.

[*] Correspondence: Linlin Liu, Deputy Director of Radiotherapy Department, Second Hospital of Jilin University, Changchun 130021, Jilin, China (e-mail: 2660424632@qq.com).

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How to cite this article: Yan W, Qiu S, Ding Y, Zhang Q, Si L, Lv S, Liu L. Prognostic value of lymphovascular space invasion in patients with early stage cervical cancer in jilin, China. Medicine 2019;98:40(e17301).

Received: 13 January 2019 / Received in final form: 12 June 2019 / Accepted: 27 August 2019

http://dx.doi.org/10.1097/MD.0000000000017301

Key Points

- Highlights: The incidence of lymphatic vessel infiltration is positively associated with the depth of stromal invasion and LNM. LVSI is an independent risk factor for the prognosis of early cervical cancer.
- A large of consecutive postoperative patients who had early-stage cervical cancer in recent years were retrospectively analyzed, although the study time was short, these patients received relatively uniform treatment modalities in short time.
- LVSI is an independent factor that affects OS ($P = .009$) and PFS ($P = .006$) in patients with early stage cervical cancer, which may better reflect the impact of different risk factors on the prognosis.

1. Introduction

Cervical cancer is one of the common malignant tumors of the female reproductive system with an estimate of 527,000 new

cases in 2018.[1,2] The 5-year survival rate of early cervical cancer surgery is approximately 65%, in which more than 30% of patients will develop recurrence disease.[3] There are many risk factors that can influence the prognosis of the patients with early stage of cervical cancer. The incidence of early cervical cancer can be reduced by HPV prophylactic vaccine, which safety has been confirmed by the World Health Organization.[4,5] Patients accepting Laparoscopic surgery may be associated with poor prognosis compared with the open approach in early-stage cervical cancer patients.[6] Patients with pathological risk factors (e.g., LNM, tumor-positive surgical margins, depth of invasion, vascular thrombosis, interstitial infiltration depth, tumor stage, and tumor differentiation) have a higher frequency of recurrence when compared to patients without those factors.[7] At the same time, especially recent studies have found that the size of tumors over 2 cm may also be a poor prognostic factor,[8–12] which has a certain correlation with the depth of invasion of tumors. Hence, it is vital to analyze the influence of different risk factors on the prognosis of patients with early-stage cervical cancer, which also decides how to plan adjuvant treatment after surgery.

According to NCCN guidelines, patients with cervical cancer after surgery must undergo concurrent chemoradiotherapy if they have high-risk factors.[13,14] However, patients with only intermediate risk factors do not have standard treatment methods, and some clinicians plan therapeutic principles according to the Sedlis standard.[15] There are no strict standards for those group of patients yet, and it needs evidence from clinical trials to support it. With the physical progress of radiotherapy (RT), the clinical outcome has been improved, and toxicity was significantly reduced.[16,17] As well as the renewal of chemotherapeutic drugs, the new application mode of RT and chemotherapy (CT) is worth re-exploring for patients with only intermediate risk factors.

It remains controversial whether lymphovascular space invasion (LVSI) is an independent prognostic factor in patients with early-stage cervical cancer. Some studies have shown that LVSI is a high-risk factor for regional LNM and is associated with local recurrence and distant metastasis after surgical treatment for early-stage cervical cancer.[18–21] On the contrary, other studies have shown that LVSI is not an isolated prognostic factor for cervical cancer.[22,23] However, it is presently considered that the spread of tumor thrombus through blood vessels and lymphatic vessels is the basis of tumor metastasis.[24] In the process of metastasis of malignant tumors, the first step is the formation of tumor blood vessels. The blood vessels and lymphatic vessels from stroma have been supplying the growth of tumors. The deeper the infiltrating stroma, the more LVSI will appear. When tumor cells exfoliate and invade the interstitium, then enter the vascular system, the tumor thrombus will be formed. When tumor thrombus spread to various tissues and organs of the body, it leads to metastasis of tumors. Therefore, LVSI is the basis of tumor metastasis. When the differentiation of tumors is worse, the malignancy of the cancer is higher; the more likely LVSI will occur. Therefore, the investigators explored whether an association exists between lymphatic vessel infiltration and LNM, and furthermore, whether LVSI is associated with poor prognosis in patients with early-stage cervical cancer in China.

Consecutive postoperative patients who had early-stage cervical cancer in the Second Hospital of Jilin University in recent years were retrospectively analyzed, to evaluate the prognostic value of LVSI in patients with early-stage cervical cancer in China.

2. Materials and methods

The ethical approval for this retrospective cohort study was obtained from the Second Hospital of Jilin University. Consecutive patients with early-stage cervical cancer (International Federation of Gynecology and Obstetrics [FIGO] stage IB-IIA) at the Second Hospital of Jilin University from February 2014 to December 2016 were included into the present study. The FIGO staging is based on tumor size, parametrial involvement, and distant metastasis.[25] The early-stage of cervical cancer was defined according to FIGO stage IB-IIA, which indicated that patients have no parametrial involvement or distant metastasis. All patients were treated with hysterectomy and pelvic lymphadenectomy. Furthermore, all included patients with risk factors (e.g., LNM, tumor-positive surgical margins, depth of invasion, vascular thrombosis, interstitial infiltration depth, tumor stage, and tumor differentiation) underwent C-type radical surgery and pelvic lymphadenectomy for cervical cancer. The dissected lymph nodes included internal iliac lymph nodes (including obturator lymph nodes), external iliac lymph nodes, common iliac lymph nodes, and presacral lymph nodes. Exclusion criteria:

(1) patients who received adjuvant CT or radiation therapy before the surgery;
(2) patients with positive parametrial extension;
(3) patients with positive surgical margins;
(4) patients with para-aortic lymph nodes metastasis;
(5) patients who have no risk factors.

Patients who meet these conditions may only account for a small proportion but would affect the treatment results of all patients.

The baseline information of these patients was retrieved from patient files, which included age, gender, FIGO stage, and clinical tumor size. A pathological examination was performed for each patient after the surgery. The following pathological data were collected for the present study: tumor differentiation grade, vascular tumor thrombus, tumor size, stromal invasion (>50%), and the number of positive lymph nodes. The LVSI of each patient was identified by 2 senior pathologists. Using hematoxylin and eosin (H&E) staining, LVSI positivity was defined as the presence of tumor cells in the luminal space, which is lined by endothelial cells.

The postoperative therapy for these patients was mainly dependent on their postoperative pathology reports and the subjective wishes of the patients and their family. In patients with pelvic lymph node involvement and tumor size >4 cm, postoperative adjuvant RT combined with CT was recommended. In patients with poor differentiation, LVIS positive, or stromal invasion (>50%), postoperative RT or CT was recommended. However, the ultimate determination for the treatment was referred to the wishes and economic conditions of the patients and their families.

All patients were followed up after the surgery until July 31, 2018. Information on recurrence, metastasis, or death were recorded. The primary endpoints of the present study were overall survival (OS), which was defined as the time from surgery to death or the most recent follow-up, and progression-free survival (PFS), which was define as the time from surgery to clinically proven relapse.

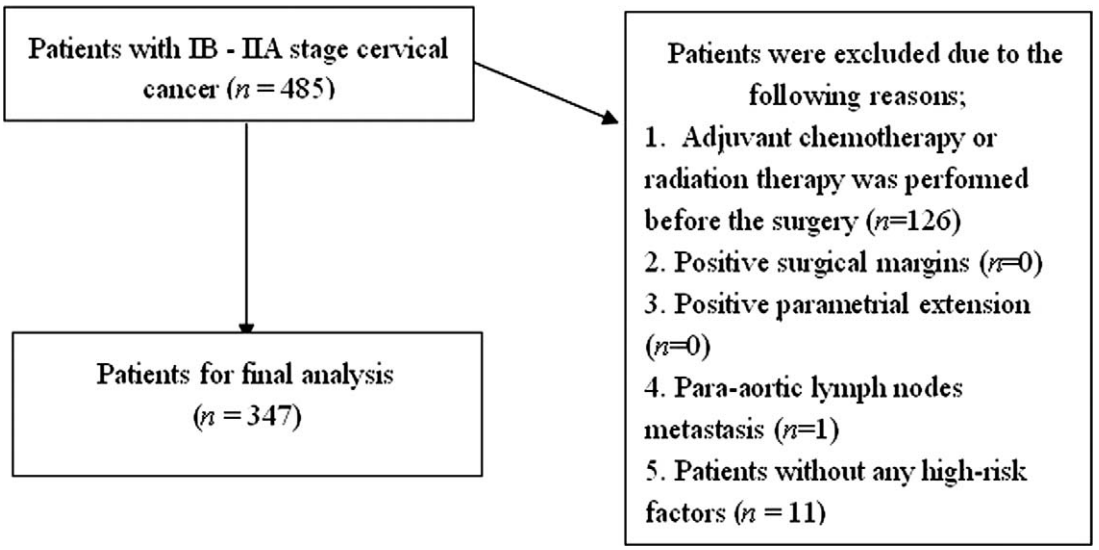

Figure 1. Workflow diagram for the present study.

3. Statistical analysis

Differences between categorical variables were determined using the X^2 test. Differences between numerical variables were determined by t test. $P < .05$ was considered statistically significant. The survival curves were evaluated using the Kaplan–Meier method. Survival rates were compared using the Log-rank test, and risk factors for the prognosis were assessed by Cox regression analysis. All analyses were performed using SPSS 19.0 (IBM Corp., Armonk, NY).

4. Results

From 2014 to 2016, 485 patients with stage IB-IIA cervical cancer were identified (Fig. 1). According to the eligible criteria, a total of 347 patients were included for the final analysis.

Among the 347 patients, 97 patients were stage IB_1 (28.0%), 63 patients were stage IB_2 (18.2%), 166 patients were stage IIA_1 (47.8%), and 21 patients were stage IIA_2 (6.0%). These patients underwent radical hysterectomy with pelvic lymphadenectomy. Furthermore, among these 347 patients, 49 (14.1%) patients were under usual care without any treatment, 61 (17.6%) patients were treated with RT alone, 38 (11.0%) patients were treated with CT alone, and 199 (57.3%) patients were treated with RT and CT. For all included patients, LVSI ($P < .001$), lymph node positive ($P = .042$), stromal invasion ($P = .003$), and tumor differentiation ($P = .013$) are significantly different. The details of the clinical characteristics of the included patients are presented in Supp. Table 1, http://links.lww.com/MD/D261. The incidence of LVSI was significantly associated with FIGO stage ($P = .008$), the depth of stromal invasion ($P < .001$), lymph node-positive metastasis ($P < .001$), and treatment after surgery ($P < .001$). Patient characteristics according to LVSI status are presented in Table 1.

Patients were followed up from 28 months to 55 months, with a median of 36.4 months. Among the 347 patients in the present study, 22 patients died. The OS rates were significantly lower for patients with LVSI, when compared to patients without LVSI (9.2% vs 2.1%; $P = .009$), and for patients with LNM, when compared to patients without LNM (12.7% vs 4.5%; $P = .01$). The survival comparison according to LVSI and LNM status is presented in Figure 2 and Supp. Figure 1, http://links.lww.com/MD/D261. Furthermore, 19 of the 22 patients who died had LVSI. As shown in Table 2, the univariate analysis revealed that LNM positive was an independent prognostic factor that affected OS ($P = .01$). Meanwhile, the multivariate analysis (including age, FIGO stage, lymph node status, depth of stromal invasion, vascular tumor thrombus, tumor differentiation, and treatment) revealed that LNM positive was still an independent prognostic factor for OS ($P = .04$). It was found that LVSI was an independent prognostic factor that affected OS not only by univariate analysis ($P = .009$), but also by multivariate analysis (.041). Treatment was not an independent prognostic factor for OS ($P > .05$).

During the follow-up period, 30 patients developed recurrence diseases, and 25 (12.1%) of these recurrent patients had LVSI. Furthermore, the PFS rates were significantly lower for patients with LVSI, when compared to patients without LVSI (12.1% vs 4.5%; $P = .006$), and for patients with LNM, compared to patients without LNM (16.5.7% vs 6.3%; $P = .005$). The PFS comparison according to LVSI and LNM status is presented in Figure 3 and Supp. Figure 2, http://links.lww.com/MD/D261. As shown in Table 3, the univariate analysis revealed that LNM positive was an independent prognostic factor that affected PFS ($P = .005$). However, the multivariate analysis revealed that this was not an independent prognostic factor ($P = .128$). It was found that that LVSI was an independent prognostic factor that affected PFS by not only the univariate analysis ($P = .006$), but also the multivariate analysis ($P = .030$). However, treatment was not an independent prognostic factor for PFS ($P > .05$).

Finally, a treatment analysis was performed according to the characteristics of these patients. As mentioned above, these patients were treated by four different adjuvant postoperative therapies:

(1) CT only;
(2) RT only;
(3) CT + RT;
(4) no further therapy (NFT).

Table 1

Patient characteristics according to LVSI status.

Clinical characteristics	Number of patients	LVSI negative, number (%)	LVSI positive, number (%)	X^2	*P* value
Age					
>50	221	97 (43.9)	124 (56.1)		
≤50	126	44 (34.9)	82 (65.1)	2.677	.102
FIGO Stage					
IB1	97	26 (26.8)	71 (73.2)		
IB2	63	27 (42.9)	36 (57.1)		
IIA1	166	80 (48.2)	86 (51.8)		
IIA2	21	8 (38.1)	13 (61.9)	11.808	.008
Tumor differentiation					
Good	3	1 (33.3)	2 (66.7)		
Moderate	301	122 (40.5)	179 (59.5)		
Poor	37	13 (35.1)	24 (64.9)		
Others	6	5 (83.3)	1 (16.7)	4.863	.171*
LNM					
Negative	268	126 (47.0)	142 (53.0)		
Positive	79	15 (19.0)	64 (81.0)	19.869	<.001
Stromal invasion					
>50%	257	94 (36.6)	163 (63.4)		
≤ 50%	90	47 (52.2)	43 (47.8)	6.765	.009
Treatment after surgery					
NFT	49	32 (65.3)	17 (34.7)		
RT	61	31 (50.8)	30 (49.2)		
CT	38	13 (34.2)	25 (65.8)		
RT + CT	199	65 (32.7)	134 (67.3)	20.879	<.001

* Fisher exact test.

CT = chemotherapy, FIGO = International Federation of Gynecology and Obstetrics, LNM = lymph node metastasis, LVSI = lymphovascular space invasion, NFT = No further treatment, RT = radiotherapy.

It was found that there was a significantly different therapy format according to the status of LNM, stromal invasion, LVSI and tumor differentiation. Patients with positive LNM, LVSI, >50% stromal invasion, and moderate to poor tumor differentiation achieved more RT + CT (Supp. Table 2, http://links.lww.com/MD/D261).

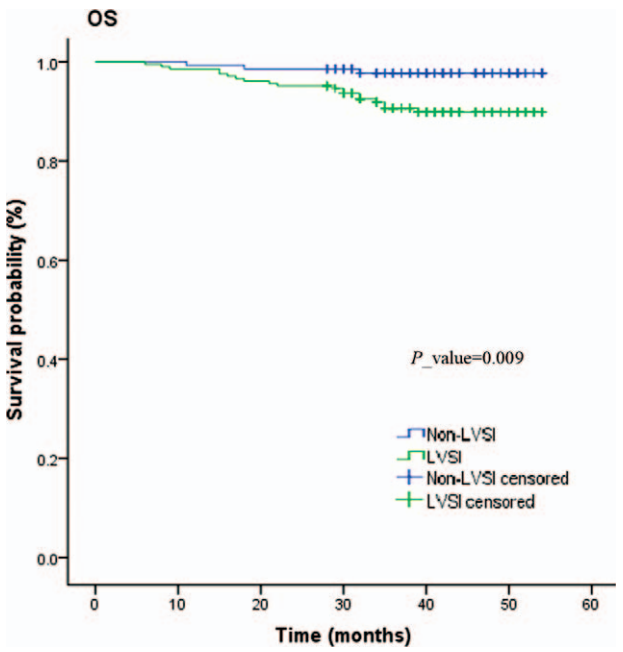

Figure 2. Overall survival proportions according to the status of the lymphovascular space invasion.

5. Discussion

Nowadays, due to the popularity of the ThinPrep cytology test (TCT) and human papillomavirus test (HPV test), most cervical cancers can be detected early and treated early.[26] However, 30% to 40% of patients with early cervical cancer continue to have a recurrence, and patients with risk factors can have a higher risk of recurrence.[27] Due to the side effects of RT and CT, (e.g., lower extremity edema, radiation enteritis, and bone marrow suppression), most patients refuse to receive postoperative adjuvant CT and RT. One of the therapy goals is to develop an appropriate adjuvant therapy for patients according to their postoperative risk factors.

In the process of tumor recurrence and metastasis, the growth of the tumor mainly depends on the lymphatic vessel expansion and angiogenesis.[24] The exfoliated cancer cells can enter into the vasculature(s) and form a tumor thrombus with the results of metastasis.[24] Therefore, LVSI may be a necessary component for cervical cancer metastasis. LNM is presently considered as an independent prognostic factor for early cervical cancer, which can significantly reduce the 5-year survival rate of early cervical cancer.[28–30] However, there is controversy on the association of LVSI with prognosis, which has led to various treatment strategies. For instance, Singh et al considered that LVSI is an independent risk factor for OS and DFS in patients with early-stage cervical cancer.[31] Yu et al stated that LVSI positive indicates poor prognosis in patients with cervical cancer after surgery.[32] Wang et al revealed that LVSI is an independent predictor of pelvic LNM by multivariate analysis, but there is no evidence directly indicating the prognostic significance of LVSI for early cervical cancer.[33] Ryu et al studied 2158 patients with IB-IIA stage cervical cancer and media risk, who underwent radical hysterectomy. They randomly arranged the 4 factors, including

Table 2

Univariate and multivariate analyses for overall survival in the 347 included patients with early-stage cervical cancer.

			Overall survival			
			Univariate analysis		Multivariate analysis*	
Covariate	Number of patients	Number of deaths (%)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age						
>50	126 (36.3)	9 (7.1)	1.000			
≤50	221 (63.7)	13 (5.9)	0.827(0.353–1.935)	.660		
FIGO Stage						
IB1	97 (28.0)	7 (7.2)	1.000			
IB2	63 (18.2)	7 (11.1)	1.512 (0.530–4.310)	.227		
IIA1	166 (47.8)	8 (4.8)	0.661 (0.240–1.823)			
IIA2	21 (6.0)	0 (0.0)	NA			
LNM						
Negative	268 (77.2)	12 (4.5)	1.000			
Positive	79 (22.8)	10 (12.7)	2.877 (1.243–6.660)	.010	2.495 (1.045–5.956)	.040
Tumor differentiation						
Good	3 (0.9)	0 (0.0)	1.000			
Moderate	301 (86.7)	18 (6.0)	NA	.601		
Poor	37 (10.7)	4 (10.8)	NA			
Others	6 (1.7)	0 (0.0)	NA			
LVSI						
Negative	141 (40.6)	3 (2.1)	1.000			
Positive	206 (59.4)	19 (9.2)	4.410 (1.305–14.904)	.009	4.175 (1.167–14.934)	.041
Stromal invasion						
≤50%	90 (25.9)	2 (2.2)	1.000			
>50%	257 (74.1)	20 (7.8)	3.548 (0.829–15.182)	.068		
Treatment after surgery						
NFT	49 (14.1)	4 (8.2)	1.000		1.000	.267
RT	61 (17.6)	3 (4.9)	0.583 (0.130–2.604)	.063	0.392 (0.086–1.784)	.226
CT	38 (11.0)	4 (10.5)	1.224 (0.306–4.901)		0.771 (0.188–3.167)	.718
RT + CT	199 (57.3)	11 (5.5)	0.654 (0.208–2.055)		0.354 (0.108–1.156)	.085

CI = confidence interval, CT = chemotherapy, HR = hazard ratio, LNM = lymph node metastasis, LVSI = lymphovascular space invasion, NFT = no further treatment, RT = radiotherapy.
* The variables (*P* value less than .1 in univariate analysis) were included in multivariate analysis.

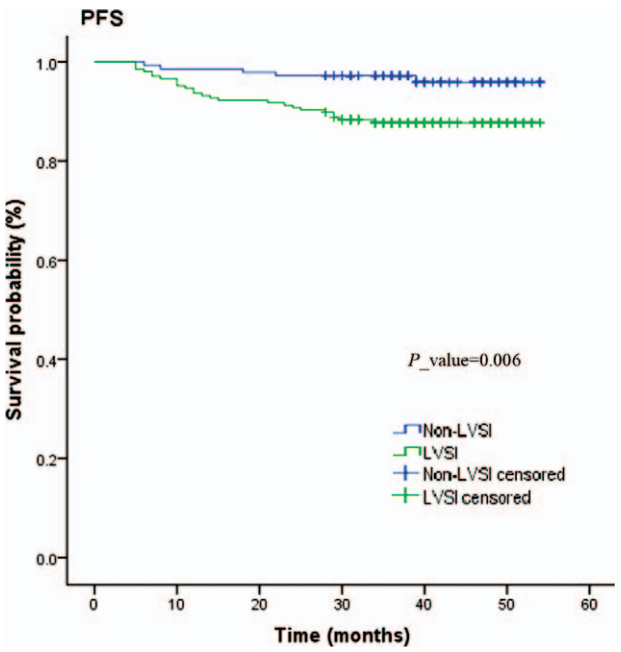

Figure 3. Progression-free survival proportions according to the status of the lymphovascular space invasion.

histological type, tumor size, depth of stromal invasion, and positive vascular invasion, into deferent groups, and found that the combined effects of any 2 of these 4 factors were significantly associated with tumor recurrence, suggesting that LVSI is one of the risk factors for tumor recurrence.[34] There were also studies that revealed that LVSI may be associated with the lymphatic metastasis of cervical cancer, while lymphatic metastasis is directly correlated to the prognosis of patients with cervical cancer.[21,32]

At present, for patients with recurrent risk factors, such as LVSI positive or interstitial infiltration, there is no standard postoperative adjuvant therapy. The present study retrospectively analyzed 367 patients with risk factors in our hospital from January 2014 to April 2016. The results revealed that the depth of stromal invasion and lymph node-positive metastasis was significantly associated with the occurrence of LVSI, with a *P* value of .009 and <.001, respectively. This result confirms the hypothesis on the relationship of LVSI with LNM. We also found that the incidence of LVSI was significantly associated with treatment after surgery ($P < .001$). As the LVSI evaluation relies on the tumor removed by the initial surgery, it should not have anything to do with further treatment. The significant association we found between the incidence of LVSI and treatment after surgery may due to the causal relationship with the association between the patient's cancer stage and the LVSI.LVSI is a medium-risk factor, and LNM is a high-risk factor. According to NCCN guidelines, patients with cervical cancer after surgery

Table 3

Univariate and multivariate analyses for progression-free survival in the 347 included patients with early-stage cervical cancer.

			Progression free survival			
			Univariate analysis		Multivariate analysis*	
Covariate	Number of patients	Number of deaths (%)	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age						
>50	126 (36.3)	14 (11.1)	1.000			
≤50	221 (63.7)	16 (7.2)	0.638 (0.311–1.306)	.214		
FIGO Stage						
IB1	97 (28.0)	12 (12.4)	1.000			
IB2	63 (18.2)	8 (12.7)	1.031 (0.421–2.522)			
IIA1	166 (47.8)	10 (6.0)	0.479 (0.207–1.109)			
IIA2	21 (6.0)	0 (0.0)	NA	.102		
LNM						
Negative	268 (77.2)	17 (6.3)	1.000		1.000	
Positive	79 (22.8)	13 (16.5)	2.710 (1.316–5.579)	.005	1.804 (0.844–3.858)	.128
LVSI						
Negative	141 (40.6)	5 (3.5)	1.000		1.000	
Positive	206 (59.4)	25 (12.1)	3.559 (1.362–9.297)	.006	3.026 (1.111–8.241)	.030
Tumor differentiation						
Good	3 (0.9)	0 (0.0)	1.000			
Moderate	301 (86.7)	26 (8.6)	NA			
Poor	37 (10.7)	4 (10.8)	NA			
Others	6 (1.7)	0 (0.0)	NA	.784		
Stromal invasion						
>50%	90 (25.9)	2 (2.2)	1.000		1.000	
≤ 50%	257 (74.1)	28 (10.9)	5.073 (1.209–21.298)	.013	3.969 (0.907–17.370)	.067
Treatment after surgery						
NFT	49 (14.1)	5 (10.2)	1.000		1.000	.425
RT	61 (17.6)	4 (6.6)	0.637 (0.171–2.371)		0.479 (0.128–1.798)	.276
CT	38 (11.0)	4 (10.5)	1.027 (0.276–3.828)		0.696 (0.185–2.626)	.593
RT + CT	199 (57.3)	17 (8.5)	0.822 (0.303–2.228)	.888	0.441 (0.159–1.224)	.116

CI = confidence interval, CT = chemotherapy, HR = hazard ratio, LNM = lymph node metastasis, LVSI = lymphovascular space invasion, NFT = No further treatment, RT = radiotherapy.
* The variables (*P* value less than .1 in univariate analysis) were included in multivariate analysis.

must undergo concurrent chemoradiotherapy if they have high-risk factors. However, patients with only moderate risk factors do not have standard treatment methods, and we planned the therapy according to the experience of the clinicians.

For the 30 patients with recurrence, 25 (83.3%) patients were positive for LVSI, while for the 38 patients who died, 25 (65.8%) patients were positive for LVSI. The present study revealed that LVSI is an independent factor that affect postoperative OS ($P=.009$) and PFS ($P=.006$) in early cervical cancer. However, lymph node positivity was merely an independent factor that affected postoperative PFS ($P=.005$) in early cervical cancer. Furthermore, in the present study, no statistically significant difference was found in prognosis after 4 different postoperative treatments. The reason for this result may lie in the more intensive treatments (RT and CT) performed to patients with LNM and positive LVSI. Therefore, it was speculated that combination CT with RT has a reduced impact on postoperative recurrence in patients with LNM and lymphatic vessel infiltration.

In addition, the present study revealed that poor tumor differentiation was not an independent prognostic factor ($P=.698$). However, the tumor differentiation patients (67.6%) in the present study were more likely to receive chemo-radiotherapy. Wang et al considered that there is no significant correlation between histological differentiation and the recurrence of patients with early cervical cancer. Hence, postoperative adjuvant therapy should not be performed to these patients.[33] Furthermore, Ramirez et al found that patients with postoperative histological grade G3 should be actively given adjuvant treatments to improve their prognosis.[34] Therefore, there is a need to pay more attention to patients with poor tumor differentiation when they have other high-risk factors. From the collect data, it was considered that CT combined with RT may benefit these patients.

There were strengths and limitations in the present study. Although the study time was short, the number of cases was large. Furthermore, the treatment methods are more uniform, which may better reflect the impact of different risk factors on the prognosis.

Overall, the results of the present study add more evidence to the prognostic value of LVSI for patients with early stage of cervical cancer in China and provides some clue on the postoperative therapy choice. More robust studies on effective interventions are needed to determine their effect on the prognosis of patients.

6. Conclusion

In conclusion, although the adjuvant treatment of early cervical cancer should be based on the comprehensive consideration of tumor stage, mass size, tumor differentiation, surgical margin and LVSI, the present study revealed that LVSI is associated with the depth of stromal invasion and LNM, and that it is an independent prognostic factor for PFS and OS. The combination of RT and CT have a reduced effect on postoperative recurrence in patients with lymph node positive and LVSI.

Author contributions

Conceptualization: Wen-Xing Yan, Linlin Liu.
Data curation: Wen-Xing Yan, Linlin Liu.
Formal analysis: Wen-Xing Yan, Shuang Qiu, Linlin Liu.
Funding acquisition: Wen-Xing Yan, Shuang Qiu, Ya-Ming Ding, Li-Hui Si, Linlin Liu.
Investigation: Wen-Xing Yan, Ya-Ming Ding, Li-Hui Si, Linlin Liu.
Methodology: Shuang Qiu, Ya-Ming Ding, Li-Hui Si.
Project administration: Qi Zhang.
Resources: Sha Lv.
Software: Qi Zhang, Sha Lv.
Validation: Qi Zhang, Sha Lv.
Writing – original draft: Qi Zhang.

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