

Prognostic factors affecting survival and recurrence in patients with early cervical squamous cell cancer following radical hysterectomy

Journal of International Medical Research
48(4) 1–13

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DOI: 10.1177/0300060519889741

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Abstract

Objective: This study aimed to investigate the clinical and histological features affecting the survival of patients with early cervical squamous cell cancer treated with radical hysterectomy.

Methods: We retrospectively analyzed clinical and histological data for patients with stage IB-IIA cervical cancer treated by radical hysterectomy at Zhejiang Cancer Hospital from August 2008 to January 2013.

Results: A total of 1435 patients were included in the study. Cox regression analysis identified tumor size >4 cm, lymphovascular space involvement (LVSI), lymph node ratio (LNR), and squamous cell carcinoma antigen (SCC-Ag) >2.65 ng/mL as independent prognostic risk factors. Among 1096 patients without high pathological risk factors, the 5-year local recurrence rates for SCC-Ag ≤2.65 and >2.65 ng/mL were 6.6% and 25.7%, respectively. Among 332 patients with lymph node positivity, the overall survival rates for LNR ≤0.19 and >0.19 were 87.8% and 55.6%, respectively.

Conclusions: LVSI, tumor size >4 cm, LNR >0.19, and SCC-Ag >2.65 ng/mL may predict a poor prognosis in patients with early cervical squamous cell cancer treated with radical hysterectomy. SCC-Ag >2.65 ng/mL may be a useful prognostic factor guiding the use of postoperative radiotherapy in patients without pathological risk factors.

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Keywords

Lymph node ratio, squamous cell carcinoma, antigen, uterine cervical neoplasm, prognosis, tumor size, radiotherapy

Date received: 11 August 2019; accepted: 30 October 2019

Introduction

Cervical cancer is one of the most common malignancies in women, and the second most commonly diagnosed cancer and third-leading cause of cancer-related death in developing countries. The estimated numbers of new cases and related deaths were 102,000 and 30,000 (3.61%), respectively, according to the 2014 data from the National Central Cancer Registry.¹ Squamous cell carcinoma is the most common pathological type of cervical cancer, accounting for approximately 80% of cases.² Radical surgery is the standard treatment for early cervical cancer, followed by adjuvant radiotherapy (RT) to improve local control in patients with pathologic risk factors; however, 10% to 20% of patients still have a poor prognosis.^{3–5} According to National Comprehensive Cancer Network (NCCN) guidelines, several factors have been recognized as high-risk factors, including lymph node (LN) metastasis, parametrial invasion, and positive vaginal margins. In patients without postoperative high-risk factors, tumor size (any, ≥ 2 cm, ≥ 4 cm, ≥ 5 cm), lymphovascular space invasion (LVSI) (positive or negative), and deep stromal invasion (DSI) (deep, middle, and superficial thirds, respectively) are considered as medium-risk factors according to Sedlis standards.⁶ However, the use of adjuvant therapy based on the combination of medium-risk factors remains controversial.² We searched the Elsevier, SpringerLink, and PubMed databases between 2008 and 2018 for English-language reports on prognostic models of survival in patients with surgically treated

early-stage cervical cancer, using keywords related to early-stage cervical cancer and prognostic factors. Several prognostic factors, including age, International Federation of Gynecology and Obstetrics (FIGO 2009) stage, squamous cell carcinoma antigen (SCC-Ag), removed LNs (RLNs), LN metastasis, parametrial involvement, surgical margin, DSI, LVSI, and tumor size have been identified.⁷ Among these, LN metastasis, parametrial involvement, and surgical margin have been identified as high-risk factors for recurrence.^{8,9} LN metastasis is an important prognostic factor, and LN status, including positive LN number, size, and position, can predict the prognosis and recurrence of early cervical cancer.^{10,11} The ratio between the number of positive LNs and RLNs is an important prognostic factor in esophageal,⁷ gastric,¹² colorectal,¹³ breast,^{14,15} and other cancers, though information on the value of this LN ratio (LNR) in cervical cancer is lacking. The GOG092 trial⁶ enrolled patients with at least two of the following risk factors: more than a third stromal invasion, LVSI, and large clinical tumor diameter. Although the analysis indicated a significant (47%) reduction in the risk of 2-year recurrence (odds ratio (OR)=0.53, $P=0.008$) among the RT group, there was no significant difference in overall survival (OS). Given the lack of consensus regarding the risk factors for cervical cancer after surgery, we evaluated the impacts of various clinicopathological features on OS in patients with early-stage cervical cancer treated with radical hysterectomy and pelvic LN dissection.

Materials and methods

Patients

We retrospectively analyzed the medical records of patients with biopsy-proven cervical cancer treated at the Departments of Gynecology and Radiation Oncology at Zhejiang Provincial Cancer Hospital between August 2008 and January 2013. All patients were staged according to the International Federation of Gynecology and Obstetrics (FIGO 2009)¹⁴ staging system. The inclusion/exclusion criteria are indicated in Figure 1. The study was conducted following an expedited review by the Medical Ethics Committee of

Zhejiang Cancer Hospital on October 29 2018. This retrospective study posed no potential risk to the subjects, and the subjects' personal privacy was protected. The study was approved by the Ethics Committee (Ethical approval document: IRB-2018-195).

Treatment regimens

Patients with stage IB–IIA cervical cancer underwent radical hysterectomy and pelvic and/or para-aortic lymphadenectomy. According to NCCN guidelines, either laparotomy (open surgery) or laparoscopy (minimally invasive surgery performed with either conventional or robotic

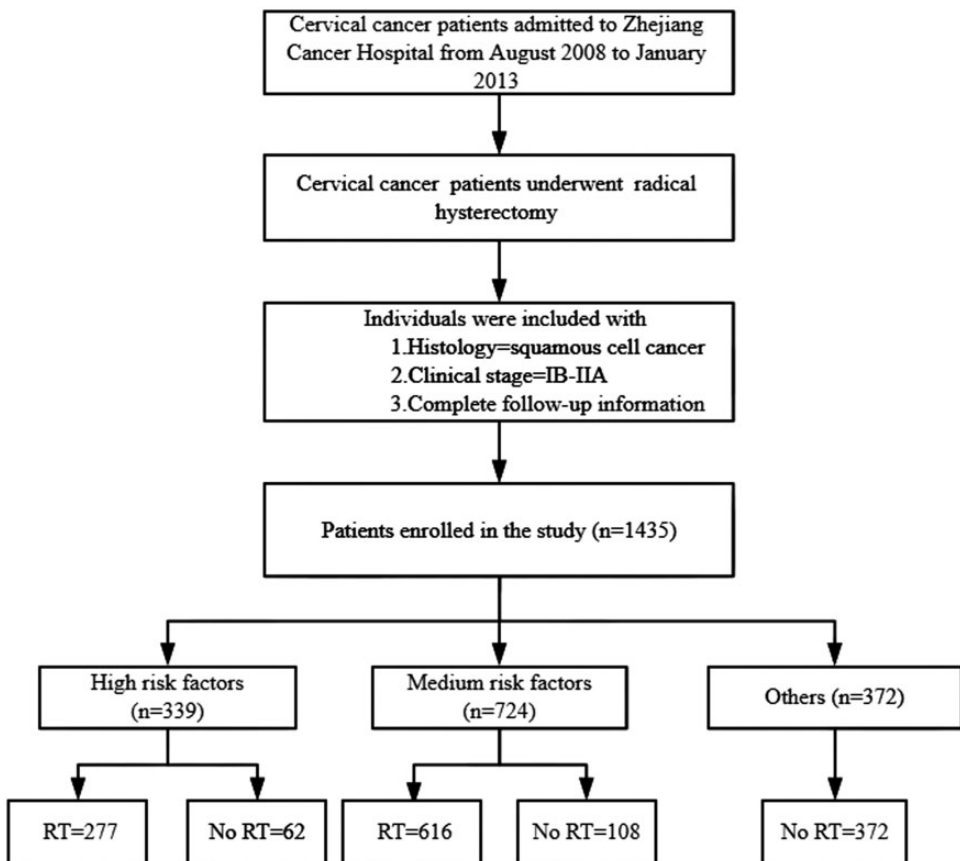


Figure 1. Study workflow. RT, radiotherapy.

techniques) is an acceptable approach to radical hysterectomy in patients with early-stage (IA2–IIA) cervical cancer. In the current study, the choice of surgical methods was based on the patient's condition and the doctor's preferred approach.¹⁶ Among the patients without high-risk factors, patients in the high- and medium-risk groups were defined according to the NCCN guidelines.¹⁷ Patients with postoperative pathological risk factors also received pelvic RT, including external-beam RT or intensity-modulated RT with or without intracavitary brachytherapy, at a dose of 1.8 to 2 Gy per fraction for 25 fractions (45–50 Gy). The pelvic treatment fields generally extended superiorly to include L5. The clinical target volume was defined as the area of potential microscopic disease and included the supravaginal portion, paracervical tissue, common iliac, internal and external iliac, obturator, and sacral LNs. Patients with common iliac and para-aortic LN metastasis were treated with RT in the para-aortic region (the upper boundary of irradiation was renal vascular level) at a dose of 45 Gy. Some patients in the RT groups also received concurrent platinum-based chemotherapy.

Clinical follow-up

Patients were evaluated every 3 months for 2 years, every 6 months during the following 3 years, and annually thereafter until December 2018. Complete physical examination, detailed gynecological examination, laboratory tests, and imaging techniques were performed during all follow-up visits. OS was calculated from the date of diagnosis until the date of death or the date of the last follow-up for surviving patients. Cause of death due to cervical cancer was confirmed by telephone or medical record review. No patient died of adverse effects. Surviving patients were censored on the date of the last follow-up.

Statistical analysis

All analyses were performed using SPSS for Windows, Version 19.0 (IBM Corp., Armonk, NY, USA). Differences between two or multiple groups were analyzed by χ^2 tests. Receiver operating characteristic (ROC) curves were used to determine the best cut-off values of SCC-Ag level and LNR for predicting prognosis. Survival outcomes were assessed with respect to age, FIGO stage, SCC-Ag, tumor size, pelvic LNs, common iliac/para-aortic LN metastasis, LNR, DSI, and LVSI. Survival analyses were performed using the Kaplan–Meier method and compared using the log-rank test. Multivariate analysis was performed using the Cox proportional hazards model and logistic regression model, using all factors identified as significant by univariate analysis. A *P* value of 0.05 was considered statistically significant.

Results

Patient outcomes

A total of 1435 patients with biopsy-proven cervical cancer were included in the study. A total of 893 patients with high- and medium-risk postoperative pathological risk factors received pelvic RT and 503 patients in the RT groups also received concurrent platinum-based chemotherapy (Figure 1).

The patient characteristics are summarized in Table 1. The median follow-up time was 77 (range, 4–110) months, until October 30 2017. The mean age of the patients was 47 years. The 5-year OS was 91.1%. An LNR of 0.19 was identified as the optimal cut-off point (OS, area under the ROC curve = 0.658, *P* < 0.05) (Figure 2) and used to assess the prognostic value. The sensitivity and specificity were 41.4% and 89.1%, respectively, and the positive and negative predictive values

Table 1. Demographic and clinical characteristics of eligible patients, including 5-year overall survival.

Variable	n(%)	5-y OS	χ^2	P
Age, years				
≤ 35	127 (8.9)	89.0%	0.841	0.359
> 35	1308 (91.1)	91.4%		
Tumor size, cm				
≤ 4	1265 (88.2)	92.4%	23.387	<0.001
> 4	170 (11.8)	81.8%		
FIGO Stage				
IB	908 (63.3)	93.6%	5.425	0.066
IIA	527 (36.7)	89.0%		
Differentiation grade				
Well	107 (7.5)	97.2%	8.574	0.014
Moderate	815 (56.8)	91.8		
Poor	513 (35.7)	88.9%		
DSI				
$\leq 1/2$	591 (41.2)	95.4%	22.919	<0.001
$> 1/2$	844 (58.8)	88.2%		
LVSI				
Negative	686 (47.8)	94.9%	23.222	<0.001
Positive	749 (52.2)	87.7%		
Pelvic LN metastasis				
0	1103 (76.9)	93.7%	75.477	<0.001
1-2	205 (14.3)	89.3%		
> 2	127 (8.8)	71.7%		
Common iliac metastasis				
Negative	1366 (95.2)	92.3%	51.910	<0.001
Positive	69 (4.8)	68.1%		
Para-aortic LN metastasis				
Negative	305 (21.2)	88.5%	45.651	<0.001
Positive	24 (1.7)	62.5%		
unknown	1106 (77.1)	92.4%		
LNR				
≤ 0.19	1381 (96.2)	92.5%	100.404	<0.001
> 0.19	54 (3.8)	55.6%		
SCC-Ag(ng/ml)				
≤ 2.65	922 (64.3)	93.8%	22.961	<0.001
> 2.65	513(35.7)	86.4%		

FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; DSI, deep stromal invasion; LN, lymph node; LNR, lymph nodes ratio; SCC-Ag, Squamous cell carcinoma antigen.

were 44.4% and 92.5%, respectively. An SCC-Ag of 2.65 ng/mL was identified as the optimal cut-off point (OS, area under the ROC curve = 0.704, $P < 0.05$) (Figure 3) for predicting pelvic LN metastasis, with a sensitivity and specificity of 60.8% and 71.8%, respectively, and

positive and negative predictive values of 14.25% and 61.3%, respectively.

Survival analysis

Univariate analysis showed that prognosis was significantly correlated with tumor size,

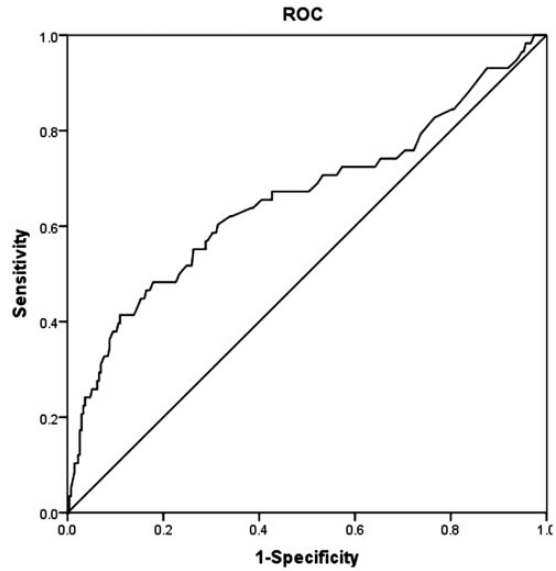


Figure 2. Receiver operating characteristic curve for predicting survival according to lymph node ratio. ROC, receiver operating characteristic curve.

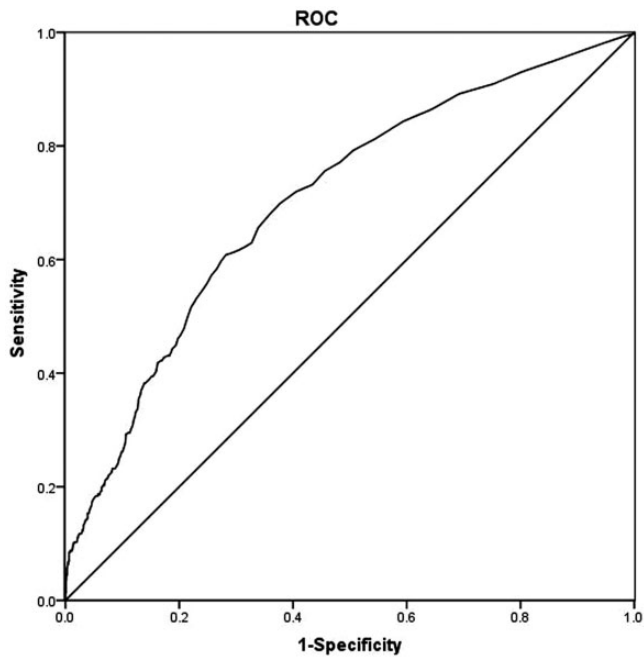


Figure 3. Receiver operating characteristic curve for predicting pelvic lymph node metastasis according to serum squamous cell carcinoma antigen. ROC, receiver operating characteristic curve.

Table 2. Multivariate Cox proportional hazards regression analysis of predictors of overall survival.

Variable	B	SE	Wald	P	HR	95%CI
Tumor size>4 cm	0.753	0.212	12.616	<0.001	2.124	1.402–3.218
LVSI+	0.571	0.218	6.881	0.009	1.770	1.155–2.713
LNR >0.19	0.997	0.318	9.836	0.002	2.709	1.453–5.051
Pelvic LN +>2	0.276	0.155	3.184	0.074	1.318	0.973–1.784
SCC-Ag >2.65 ng/mL	0.471	0.198	5.677	0.018	1.502	1.087–2.359

B, regression coefficient; Wald, χ^2 value equal to B^2 divided by its standard error; LVSI, lymphovascular space invasion; LN, lymph node; LNR, lymph nodes ratio; SCC-Ag, squamous cell carcinoma antigen; HR, hazard ratio; CI, confidence interval; SE, standard error.

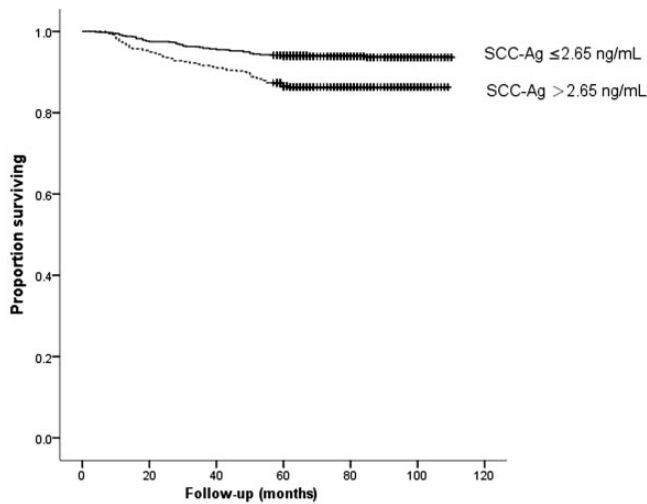


Figure 4. Kaplan–Meier curves for overall survival according to squamous cell carcinoma antigen (SCC-Ag) level. SCC-Ag ≤ 2.65 ng/mL was associated with significantly longer survival than SCC-Ag > 2.65 ng/mL ($P < 0.001$).

differentiation grade, DSI, LVSI, pelvic LN metastasis, common iliac or para-aortic LN metastasis, LNR, and SCC-Ag (all $P < 0.05$) (Table 1). In addition, Cox regression analysis identified tumor size > 4 cm, LVSI, pelvic LN metastasis > 2 , LNR, and SCC-Ag > 2.65 ng/mL as independent prognostic risk factors (Table 2). The OS rates in patients with SCC-Ag ≤ 2.65 and > 2.65 ng/mL were 93.8% and 86.4%, respectively ($P < 0.001$) (Figure 4). OS among 332 patients with positive LNs was 82.5%, and the OS rates in patients with LNRs ≤ 0.19 and > 0.19 were

87.8% and 55.6%, respectively ($P < 0.001$) (Figure 5). The OS rates among 1096 patients without high pathological risk factors and SCC-Ag ≤ 2.65 and > 2.65 ng/mL were 95.0% and 90.7%, respectively ($P = 0.001$).

Recurrence analysis

At the end of the follow-up period, the 5-year recurrence rate among 1096 patients without high-risk factors was 14.0%: 132 patients (12.7%) had locoregional failure and 55 patients (5%) experienced distant

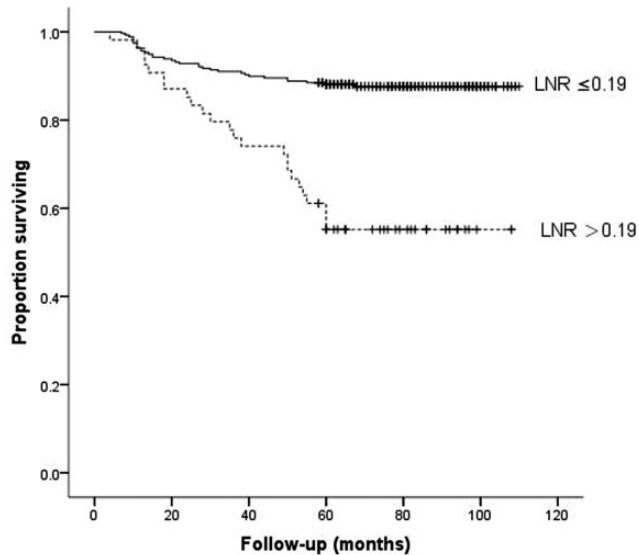


Figure 5. Kaplan–Meier curves for overall survival according to lymph node ratio (LNR). LNR ≤ 0.19 was associated with significantly longer survival than LNR > 0.19 ($P < 0.001$).

metastasis. Univariate analysis showed that recurrence was significantly correlated with tumor size, FIGO stage, DSI, and SCC-Ag level (all $P < 0.05$) (Table 3). FIGO stage and SCC-Ag > 2.65 ng/mL were independent risk factors for recurrence (Table 4). The 5-year local recurrence rates in patients with SCC-Ag ≤ 2.65 and > 2.65 ng/mL were 6.6% and 25.7%, respectively ($P < 0.001$). Of the 480 patients who did not receive adjuvant RT, 414 and 66 patients had SCC-Ag ≤ 2.65 and > 2.65 ng/mL and 5-year local recurrence rates of 7.5% and 37.9%, respectively ($P < 0.001$). In contrast, among the 616 patients with medium-risk factors who received adjuvant RT, 371 and 245 had SCC-Ag ≤ 2.65 and > 2.65 ng/mL and 5-year local recurrence rates of 5.7% and 22.4%, respectively ($P < 0.001$).

Discussion

Patients with cervical cancer with high-risk factors after surgery are administered adjuvant therapy, consisting of RT or concurrent chemoradiation therapy, to decrease

the risk of recurrence and improve survival.¹⁶ Tumor size, LVSI, and DSI are identified as medium-risk factors according to NCCN guidelines, but there is currently no agreement with regard to adjuvant RT in these patients. The results of our Cox regression analysis suggested that tumor size > 4 cm, LVSI, LNR > 0.19 , and SCC-Ag > 2.65 ng/mL were significant factors affecting OS. Although LN metastasis is the most important indicator of poor prognosis in patients with early-stage cervical cancer undergoing radical hysterectomy, recent studies indicated that tumor size¹⁷ and DSI¹⁸ were also related to OS. However, the standard of cervical stromal depth was not consistent, and results have therefore differed. Furthermore, the prognostic significance of LVSI is controversial. In a previous meta-analysis of 25 articles, only three (12%) identified LVSI as an independent risk factor.¹⁹ Furthermore, LVSI is subject to interpretation by the observer and depends on the histological processing, making its use as the sole

Table 3. Univariate analysis of recurrence in 1096 patients without postoperative high-risk factors.

Variable	n	5-year recurrence (%)	χ^2	P
Age, years				
≤ 35	84	8.3	1.182	0.277
> 35	1012	12.4		
Tumor size, cm				
≤ 4	986	11.3	5.732	0.017
> 4	110	19.1		
FIGO stage				
IB	718	14.5	16.623	< 0.001
IIA	378	17.5		
SCC-Ag (ng/mL)				
≤ 2.65	785	6.6	76.705	< 0.001
> 2.65	311	25.7		
Differentiation grade				
Well or moderate	728	11.6	0.455	0.500
Poor	368	13.0		
DSI				
$\leq 1/2$	535	7.9	17.350	< 0.001
$> 1/2$	561	16.0		
LVSI				
Negative	625	11.8	0.057	0.811
Positive	471	12.3		

FIGO, International Federation of Gynecology and Obstetrics; LVSI, lymphovascular space invasion; DSI, deep stromal invasion; SCC-Ag, squamous cell carcinoma antigen.

Table 4. Multivariate logistic analysis of recurrence factors in 1096 patients without postoperative high-risk factors.

Variable	B	SE	Wald	OR	95%CI	P
FIGO stage	0.513	0.187	7.561	1.671	1.159–2.409	0.006
SCC-Ag > 2.65 ng/mL	1.502	0.196	58.960	4.490	3.059–6.590	< 0.001

B, regression coefficient; Wald, χ^2 value equal to B^2 divided by its standard error; FIGO, International Federation of Gynecology and Obstetrics; SCC-Ag, squamous cell carcinoma antigen; HR, hazard ratio; CI, confidence interval; SE, standard error.

factor determining the use of RT after radical hysterectomy questionable. Our study demonstrated that the 5-year OS rates of patients with negative LNs, non-common iliac pelvic LN, pelvic LN, common iliac LN, and para-aortic LN metastasis were 93.7%, 86.3%, 82.5%, 68.1%, and 62.5%, respectively. Overall, LN metastasis and anatomic extension of the metastatic site increased the risk of death. Our findings

were in good agreement with previous results.^{20,21} In postoperative patients, the number of positive LNs is reportedly affected by the number of RLNs and is related to prognosis.²² Uno and colleagues²³ reported 5-year OS rates for patients with no, one, and two or more positive pelvic LN metastases of 89%, 83%, and 58%, respectively ($P = 0.007$). Conversely, a prospective Gynecologic Oncology Group (GOG-49)

study found no increased risk of recurrence in relation to the number of postoperative positive LNs.²⁴

The number of LN metastases depends on surgical technique and level of pathological examination, and the use of LNR can reduce the difference in lymph node assessments between different surgeons and pathologists. Polterauer et al.²⁵ reported a series of 88 consecutive node-positive patients and found that patients with a LN density >10% had poorer disease-free survival (HR = 2.2, 95%CI: 1.1–4.7, $P=0.01$) and OS rates (HR = 2.2, 95%CI: 1.0–4.8, $P=0.05$) compared with patients with a LN density $\leq 10\%$. Their definition of LN density was the same as the LNR in the current study. In a series of 2269 node-positive early-stage (stages I–II) cervical cancer patients, Zhou et al.²⁶ found that LNR >0.16 was associated with poor cervical cancer-related survival (CCSS) (HR = 1.376, 95%CI: 1.082–1.750; $P < 0.001$) and OS (HR = 1.287, 95%CI: 1.056–1.569; $P = 0.012$), and postoperative RT was only associated with survival benefits in patients with LNR >0.16 (CCSS, $P < 0.001$; OS, $P < 0.001$) but not in those with LNR ≤ 0.16 (CCSS, $P = 0.620$; OS, $P = 0.167$). Moreover, these trends were not affected by the number of removed LNs. A higher LNR is associated with poorer survival in LN-positive cervical cancer. Nicole et al.²⁷ reported that an LNR >6.6% was associated with poorer progression-free survival (HR = 2.97, 95%CI: 1.26–7.02, $P = 0.01$) and that an LNR >7.6% was associated with shorter OS (HR = 3.96, 95%CI: 1.31–11.98, $P = 0.01$) in patients ($n = 82$) with at least 10 removed LNs. Our study found that the 5-year OS rates in patients with none, up to two, and more than two LN metastases were 93.7%, 89.3%, and 71.7% ($P < 0.001$), respectively, while the 5-year OS rates in patients with positive LNs ($n = 332$) and LNR ≤ 0.19 and >0.19 were 87.8% and 55.6%, respectively

($P < 0.001$). These results suggest that patients with more than two LN metastases or LNR >0.19 should be treated with postoperative adjuvant therapy.

There are currently no tumor markers that can be used to predict prognosis and therapy in patients with cervical cancer, such as CA125 in ovarian cancer. However, numerous studies have found that SCC-Ag is associated with the prognosis and recurrence of cervical cancer. For example, Salvatici et al.²⁸ reported that SCC-Ag levels in 197 patients with stage I or II cervical squamous carcinoma were an independent and significant prognostic factor for OS (HR = 6.3, 95%CI: 3.4–11.6, $P < 0.001$) and progression-free survival (HR = 5.5, 95%CI: 3.2–9.3, $P < 0.001$). The median time intervals between the SCC-Ag test and diagnosis of recurrence were 0.3 and 1.8 months in patients with SCC-Ag >1.5 and <1.5 ng/mL, respectively ($P = 0.01$). Van et al.²⁹ also found that SCC-Ag levels >1.1 ng/mL were associated with a poor prognosis, and that OS ($P = 0.025$) and DFS ($P = 0.011$) were higher in LN-negative patients with SCC-Ag ≤ 1.1 ng/mL compared with those with SCC-Ag >1.1 ng/mL.

The current findings were in good agreement with previous results. In the total study population, an SCC-Ag cut-off value of 2.65 ng/mL was significantly associated with a poor prognosis. Furthermore, the 5-year recurrence rate was 14.0% and pelvic local recurrence was the main site in the 1096 patients without high-risk factors. FIGO stage (OR = 1.671, 95%CI: 1.159–2.409, $P = 0.006$) and SCC-Ag >2.65 ng/mL (OR = 4.490, 95%CI: 3.059–6.590, $P < 0.001$) were independent risk factors for recurrence, and recurrence was more frequent in patients with elevated pre-treatment SCC-Ag (25.7%) than in those with normal SCC-Ag levels (6.6%, $P < 0.001$). Among these patients with postoperative RT, the 5-year recurrence rates

for SCC-Ag >2.65 and ≤ 2.65 ng/mL were 22.4% and 5.7%, respectively ($P < 0.001$), while the equivalent rates in patients without postoperative RT were 37.9% and 7.5%, respectively ($P < 0.001$). Preoperative serum SCC-Ag >2.65 ng/mL was significantly correlated with recurrence in patients with early-stage squamous cell carcinoma cervical cancer, and can thus be used as a criterion for postoperative RT in patients without high-risk factors. A report³⁰ showed that, among 337 patients with early-stage cervical cancer, adjuvant RT was administered for classic indications in 110 (33%) (pelvic LN metastases, parametrial involvement, tumor-positive resection margins, and a combination of these three). In patients without indications for adjuvant RT at the Ib1 stage, the 2-year recurrence rates in patients with elevated and normal SCC-Ag levels were 15% and 1.6%, respectively ($P = 0.02$). Serum SCC-Ag levels thus appear to identify a subgroup of LN-negative patients with occult disease, allowing for a more refined preoperative estimation of the value of adjuvant RT. In addition, SCC-Ag levels can identify patients at high risk of recurrence when treated with surgery alone.³⁰

This study was limited by the relatively small sample size, and further studies with larger samples are needed to verify the conclusions.

In conclusion, our study showed that tumor size >4 cm, LVSI, pelvic LN metastasis >2 , LNR >0.19 , and SCC-Ag >2.65 ng/mL were independent prognostic risk factors in patients with early cervical squamous cell cancer treated with radical hysterectomy. Patients with LN metastasis and an LNR >0.19 should be treated with postoperative adjuvant therapy, while pretreatment serum SCC-Ag level is a strong predictor of OS and recurrence, and may thus be useful for selecting a subgroup of patients requiring more aggressive therapy.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

This research was funded by the Medical and Health Technology Platform Project of Zhejiang Province (2017ZD012).

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