Validation of the 2018 FIGO Staging System for Predicting the Prognosis of Patients With Stage IIIC Cervical Cancer

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Xingtao Long[1*], Misi He[1*], Lingling Yang[2], Dongling Zou[1], Dong Wang[1], Yuemei Chen[1] and Qi Zhou[1]

[1]Chongqing Cancer Hospital, Chongqing University, Chongqing, China. [2]School of Medicine, Chongqing University, Chongqing, China.

ABSTRACT

BACKGROUND: Risk stratification of patients with cervical cancer accompanied by positive lymph nodes (stage IIIC) (the 2018 International Federation of Gynecology and Obstetrics [FIGO] new staging system) yields a clinically heterogeneous group. In this study, we investigated the prognostic performance of the 2018 FIGO staging system for stage IIIC cervical cancer.

METHODS: The study included patients with stage III cervical cancer based on the 2018 FIGO staging system, who visited Chongqing University Cancer Hospital between January 2011 and December 2014. Kaplan-Meier curves were generated to evaluate overall survival (OS), which was compared using the log-rank test. The Cox proportional hazard regression model was used for multivariable analysis.

RESULTS: A total of 418 patients were eligible for analysis. The 5-year OS was 54.1% for stage IIIC1, 43.3% for stage IIIA, 40.6% for stage IIIB, and 23.1% for stage IIIC2 ($P < .001$). Multivariable analysis revealed that compared with stages IIIA (hazard ratio [HR] 1.432, 95% confidence interval [CI] 0.867-2.366, $P = .161$) and IIIB (HR 1.261, 95% CI 0.871-1.827, $P = .219$), stage IIIC1 cancer was not significantly associated with an increased mortality risk. Stage IIIC2 was independently associated with an increased mortality risk compared with stages IIIA (HR 2.958, 95% CI 1.757-4.983, $P < .001$) and IIIB (HR 2.606, 95% CI 1.752-3.877, $P < .001$). We stratified patients with stage IIIC1 based on the T stage. The 5-year OS was significantly longer in patients with stage IIIC1 (T1) than in those with stage IIIA ($P = .004$) or IIIB ($P < .001$). Analysis of multiple factors revealed that the mortality risk was 2.75-fold higher in patients with stage IIIC1pN>2 than in patients with stage IIIC1pN1-2 (HR 2.753, 95% CI 1.527-4.965, $P = .001$).

CONCLUSIONS: Patients with stage IIIC1 cervical cancer showed heterogeneous clinical characteristics that reflected variable prognoses, depending on the T stage and the extent of pelvic lymph node metastases.

KEYWORDS: International Federation of Gynecology and Obstetrics, FIGO, staging, cervical cancer, prognosis

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CORRESPONDING AUTHOR: Qi Zhou, Chongqing Cancer Hospital, Chongqing University, 181 Hanyu Road, Shapingba District, Chongqing 400000, China. Email: qizhou9128@163.com

Introduction

Approximately 570 000 cases of cervical cancer were diagnosed and 311 000 deaths secondary to the malignancy were reported in 2018 worldwide.[1] Cervical cancer is the most frequent malignancy of the female genital tract in China.[2] In contrast to most solid tumors, cervical cancer has been historically clinically staged and is currently most commonly staged based on the International Federation of Gynecology and Obstetrics (FIGO) system, which is convenient and reliable and includes the most powerful prognostic factors.[3-5] Rapid advances in modern imaging technology and the availability of innovative surgical-pathological techniques have focused attention on deficiencies of the FIGO staging system.[6,7] In October 2018, the 22nd FIGO Annual Conference published a revised FIGO classification for cervical cancer.[8] A major revision to the 2018 FIGO stage III classification includes incorporation of nodal status that is determined using radiological imaging or histopathological evaluation.[8] For example, stages IIIC1 and IIIC2 include only metastatic pelvic lymph nodes (and) or para-aortic lymph node metastases, respectively.[8] Although lymph node metastasis is associated with a high risk of poor survival,[9] the 2018 FIGO classification of patients with stage IIIC does not include the size and extent of the primary tumor. Moreover, stratification of all patients with positive lymph nodes (stage IIIC) yielded a clinically heterogeneous group. Therefore, several clinicians have questioned the reliability of the 2018 FIGO staging system for stage IIIC cervical cancer.[10-12]

The extent of stage migration and the changes in survival outcomes remain largely unknown. In this study, we retrospectively investigated the prognostic performance of the 2018 FIGO staging system for stage IIIC cervical cancer and performed risk stratification with incorporation of additional prognostic factors.

*Xingtao Long and Misi He contributed equally to this work.

Materials and Methods

Patients

Clinicopathological characteristics and other relevant data (recorded between January 2011 and December 2014) were retrieved from the electronic medical record system of Chongqing University Cancer Hospital, Chongqing, China. This study was approved by the Ethics Committee of the hospital (project number: 2019[177]). Informed consent was obtained from all study participants to use their medical information for scientific purposes. Inclusion criteria were as follows: (1) aged ⩾18 years or ⩽85 years and (2) histologically confirmed cervical squamous cell carcinoma, adenocarcinoma, and adenosquamous carcinoma according to the fifth edition of the World Health Organization (WHO) Classification of Tumours of the Female Genital Tract (squamous cell carcinoma, human papillomavirus [HPV]-associated; squamous cell carcinoma, HPV-independent; squamous cell carcinoma not otherwise specified [NOS]; sdenocarcinoma NOS; sdenocarcinoma, HPV-associated). Pathological grading was assessed according to the fifth edition of the WHO Classification of Tumours of the Female Genital Tract,[13] (3) diagnosis of 2018 FIGO stage III cervical cancer, and (4) administration of standard treatment and completion of the recommended treatment regimen. Exclusion criteria were as follows: (1) aged <18 years or >85 years—patients younger than 18 or older than 85 years may not have received standard treatment, such as lymph node removal and adjuvant treatment after surgery; (2) unknown lymph node status; (3) a history of concomitant malignancies; (4) unknown tumor size; and (5) no treatment administered after recurrence. Diagnostic criteria for stage IIICr were as follows: (1) lymphadenectasis, short diameter ⩾1 cm confirmed using magnetic resonance imaging/computed tomography (CT) and diagnosis of lymph node metastasis confirmed by 2 experts, and (2) lymph node metastases confirmed using positron emission tomography (PET)-CT. In our study, 128 and 62 patients had histopathologically documented pelvic lymph node metastasis (IIIC1p) and radiological imaging–documented metastasis (IIIC1r), respectively. Notably, 40 and 26 patients had histopathologically documented para-aortic lymph node metastasis (IIIC2p) and radiologically documented para-aortic lymph node metastasis (IIIC2r), respectively. Of the 168 patients who underwent surgery, 87 (51.8%) patients with stage I (2009 FIGO staging) and 41 (24.4%) patients with stage II (2009 FIGO staging) were upstaged to IIIC1p based on the 2018 FIGO staging system, and 23 (13.7%) patients with stage I (2009 FIGO staging) and 17 (10.1%) patients with stage II (2009 FIGO staging) were upstaged to IIIC2p. Overall survival (OS) was defined as the interval between the date of initial diagnosis and death or the last follow-up. The follow-up deadline was set at October 25, 2019 (median follow-up of 58.96 months [range, 7-92 months]).

Treatments

All patients underwent standard first-line treatment as follows: (1) surgery, which included radical hysterectomy and bilateral pelvic lymphadenectomy with or without para-aortic lymphadenectomy, using standard open or minimally invasive surgery and adjuvant treatment after radical hysterectomy based on the guidelines and clinical practice; (2) radical radiochemotherapy with or without consolidation chemotherapy. Concurrent chemoradiation therapy is the preferred therapeutic option for locally advanced cervical cancer. Concurrent chemoradiation therapy includes external radiation and intracavitary brachytherapy with weekly cisplatin (30-40 mg/m^2) or cisplatin combined with paclitaxel (60 mg/m^2). Intracavitary brachytherapy was added during the later stage of external irradiation. Postoperative radiotherapy is indicated in patients with adverse pathological factors. Postoperative radiotherapy consists of whole-pelvis external beam radiotherapy to ensure coverage of the tumor bed and the draining lymph node areas. A dose of 45 to 50 Gy is usually prescribed. Local/regional recurrence and distant metastasis occurred in 105 (25.1%) and 133 (31.8%) patients, respectively. Notably, 23 (9.6%) patients underwent pelvic exenteration or excision of the local metastatic lesion, followed by postoperative chemotherapy; 181 (76.1%) patients received chemotherapy and/or bevacizumab; 21 (8.9%) patients received palliative radiotherapy and/or chemotherapy; and 13 (5.4%) others.

Statistical Analysis

Statistical analysis was performed using the SPSS 25 and GraphPad Prism 6.01 software. Numerical values are presented as rates. Multigroup comparisons were performed using the χ^2 or Kruskal-Wallis H test. Survival analysis was performed using the Kaplan-Meier method, and data were compared using the log-rank test. Multivariable analysis was performed using a Cox proportional hazard regression model (variables with $P \leqslant .1$ were included). A P value of $<.05$ (2-tailed) was considered statistically significant. The SPSS software was used to calculate Bonferroni-corrected P values for pairwise comparisons.

Results

Clinical Characteristics

Between 2011 and 2014, 503 patients with cervical cancer were clinically staged as stage III (2018 FIGO classification) in accordance with the inclusion criteria. We excluded 85 patients (27 who did not complete treatment, 3 with concomitant malignancies, 32 in whom imaging data regarding lymph node or tumor size were unavailable, and 23 who did not receive treatment after recurrence) (Figure 1); therefore, we analyzed data of 418 patients who were diagnosed with stage IIIA (n = 42, 10.0%), IIIB (n = 120, 28.7%), IIIC1 (n = 190, 45.5%),

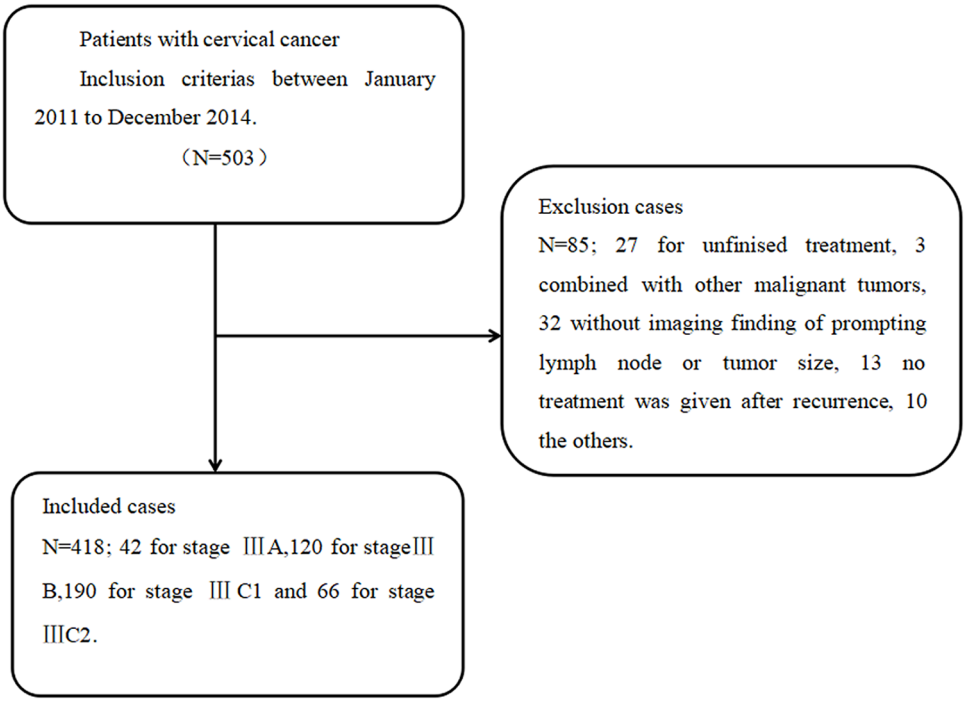

Figure 1. Flowchart of the protocol for patients' screening and recruitment.

or IIIC2 (n = 66, 15.8%) cancer. Patients with stage IIIC1 were younger than those with stage IIIA ($P < .001$) cancer. The histologic type, histopathological grading, tumor size, type of radiotherapy administered, and administration of consolidation chemotherapy were balanced across the different cancer stages ($P > .05$ for each). Differences between patients with stage IIIC1 or IIIC2 disease who underwent radical hysterectomy, minimally invasive surgery, or neoadjuvant chemotherapy were also balanced ($P > .05$ for each) (Table 1). Exclusive pelvic lymphadenectomy was performed in 106 patients (median number of pelvic lymph nodes removed was 25 [range, 11-42]). Pelvic and para-aortic lymphadenectomy was performed in 62 patients (median number of para-aortic lymph nodes removed was 5 [range, 2-11]). Histopathologically documented pelvic lymph node metastasis (IIIC1p) was detected in 128 patients and radiological imaging–documented metastasis (IIIC1r) in 62 patients. Histopathologically documented para-aortic lymph node metastasis (IIIC2p) was observed in 40 and radiological imaging–documented para-aortic lymph node metastasis (IIIC2r) in 26 patients. We performed para-aortic lymphadenectomy in 62 patients (most patients showed tumor size >4 cm [n = 46, 74.2%]). Preoperative radiological imaging (including PET-CT) revealed metastatic para-aortic lymph nodes in 51 (82.2%) patients, and metastatic para-aortic lymph nodes were detected intraoperatively in 9 (14.5%) patients.

Survival Outcomes

The 5-year OS rates were 54.1% (stage IIIC1) versus 43.3% (stage IIIA) versus 40.6% (stage IIIB) versus 23.1% (stage IIIC2) ($P < .001$) (Figure 2A). The OS was significantly shorter in patients with stage IIIC2 than in those with stage IIIC1 ($P < .001$). Increasing tumor size was associated with lower 5-year OS rates as follows: tumor diameter <4 cm (69.4%) and tumor diameter ⩾4 cm (36.5%) ($P < .001$). The 5-year OS rate was significantly higher in patients who underwent radical hysterectomy (72.1%) than in those who did not undergo this operation (48.3%) ($P < .001$). However, the histologic type, histopathological grading, neoadjuvant chemotherapy, type of radiotherapy, minimally invasive surgery, or consolidation chemotherapy did not affect 5-year OS rates ($P > .05$ for each) (Table 2). Variables that showed $P \leqslant .1$ on univariate analysis were subjected to multivariable analysis, which showed the following results: 2018 FIGO stage III was an independent risk factor. Stage IIIC2 was significantly associated with an increased risk of mortality compared with stages IIIC1 (hazard ratio [HR] 2.066, 95% confidence interval [CI] 1.438-2.969, $P < .001$), IIIB (HR 2.606, 95% CI 1.752-3.877, $P < .001$), and IIIA (HR 2.958, 95% CI 1.757-4.983, $P < .001$). Stage IIIC1 was not significantly associated with an increased risk of mortality compared with stages IIIA (HR 1.432, 95% CI 0.867-2.366, $P = .161$) and IIIB (HR 1.261, 95% CI 0.871-1.827, $P = .219$) (Table 2).

It is therefore reasonable to conclude that tumor size and local invasion affect prognosis. To test this hypothesis, we stratified patients diagnosed with 2018 FIGO stage IIIC1 on the basis of the T stage (T1/T2/T3) and compared intergroup survival rates. Tumor staging for cervical cancer was performed based on the American Joint Committee on Cancer staging system (9th Edition) as follows: T1: carcinoma strictly confined to the cervix, T2: carcinoma invasion beyond the uterus but not extending to the lower third of the vagina or the pelvic

Table 1. Patient demographics of 2018 FIGO stage III cervical cancer.

CHARACTERISTIC	STAGE IIIA	STAGE IIIB	STAGE IIIC1	STAGE IIIC2	*P* VALUE
	N = 42 (10.0%)	N = 120 (28.7%)	N = 190 (45.5%)	N = 66 (15.8%)	
Age, y					.003
<65	30 (71.4%)	98 (81.7%)	174 (91.6%)	56 (84.8%)	
⩾65	12 (28.6%)	22 (18.3%)	16 (8.4%)	10 (15.2%)	
Histology					.680
Squamous	29 (69.0%)	96 (80.0%)	152 (80.0%)	49 (74.3%)	
Adenocarcinoma	7 (16.7%)	13 (10.8%)	23 (12.1%)	8 (12.1%)	
Adenosquamous Carcinoma	6 (14.3%)	11 (9.2%)	15 (7.9%)	9 (13.6%)	
Grade					.279
3	6 (14.3%)	27 (22.5%)	37 (19.4%)	11 (16.7%)	
2	26 (61.9%)	68 (56.7%)	126 (66.3%)	46 (69.6%)	
1	5 (11.9%)	5 (4.2%)	6 (3.2%)	4 (6.1%)	
Unknown	5 (11.9%)	20 (16.6%)	21 (11.1%)	5 (7.6%)	
Tumor size(cm)					.727
<4	21 (50.0%)	49 (40.8%)	87 (45.8%)	30 (45.5%)	
⩾4	21 (50.0%)	71 (59.2%)	103 (54.2%)	36 (54.5%)	
Neoadjuvant chemotherapy					
Yes	0	0	51 (26.8%)	21 (31.8%)	.439[a]
No	42	120	139 (73.2%)	45 (68.2%)	
Radical hysterectomy					.319[a]
Yes	0	0	128 (67.4%)	40 (60.6%)	
No	42	120	62 (32.6%)	26 (39.4%)	
Minimally invasive surgery					.524[a]
Yes	0	0	23 (18.0%)	9 (22.5%)	
No	42	120	105 (82.0%)	31 (77.5%)	
Radiotherapy					.555
3-DCRT	19 (45.2 %)	48 (40.0%)	88 (46.3 %)	25 (37.9%)	
IMRT	23 (54.8 %)	72 (60.0%)	102 (53.7%)	41 (62.1%)	
Consolidation chemotherapy					.765
Yes	31 (73.8%)	89 (74.2%)	147 (77.4%)	47 (71.2%)	
No	11 (26.2%)	31 (25.8%)	43 (22.6%)	19 (28.8%)	

Abbreviations: 3-DCRT, 3-dimensional conformal radiotherapy; FIGO, International Federation of Gynecology and Obstetrics; IMRT, intensity-modulated radiotherapy.
[a]Stage IIIC1 vs stage IIIC2.

wall, and T3: carcinoma involving the lower third of the vagina and/or extension to the pelvic wall and/or associated hydronephrosis or non-functioning kidney.[14] Notably, the 5-year OS rates in the T1, T2, and T3 categories were 72.2%, 54.1%, and 18.6%, respectively ($P < .001$) (Figure 2B). We observed no significant difference between the 5-year OS rates based on age, histologic type, histopathological grading, type of radiotherapy administered, minimally invasive surgery, or consolidation chemotherapy ($P > .05$ for each). Variables that showed $P \leqslant .1$ on univariate analysis were subjected to multivariate analysis, which revealed that the T stage was an independent prognostic factor associated with survival in patients with stage IIIC1 cancer ($P < .001$) (Table 3). The 5-year OS rate was higher in patients with stage IIIC1 (T1) than in those with stage IIIA ($P = .004$) or IIIB ($P < .001$). Survival rates were similar between patients with stage IIIC1 (T2) and IIIA ($P = .522$) or IIIB ($P = .133$) cancer. The 5-year OS rates were lower in patients with stage IIIC1 (T3) than in patients with stage IIIA or IIIB cancer ($P = .001$ for each) (Figure 2C).

We further investigated the effects of the number of pelvic lymph node metastases (PLNMs) on prognosis in patients with stage IIIC1p (T1/T2a) cancer, who underwent radical hysterectomy and pelvic lymphadenectomy with or without para-aortic lymphadenectomy. We performed histopathological evaluation of PLNMs and observed that the number of PLNMs per patient ranged between 1 and 9. The 25th, 50th, and 75th percentiles represented 1, 2, and 3 PLNMs, respectively. The median value of the number of PLNMs represents the optimal prognostic cutoff value. The 5-year OS rate in patients with 1 PLNM was 89.1% versus 47.5% in those with

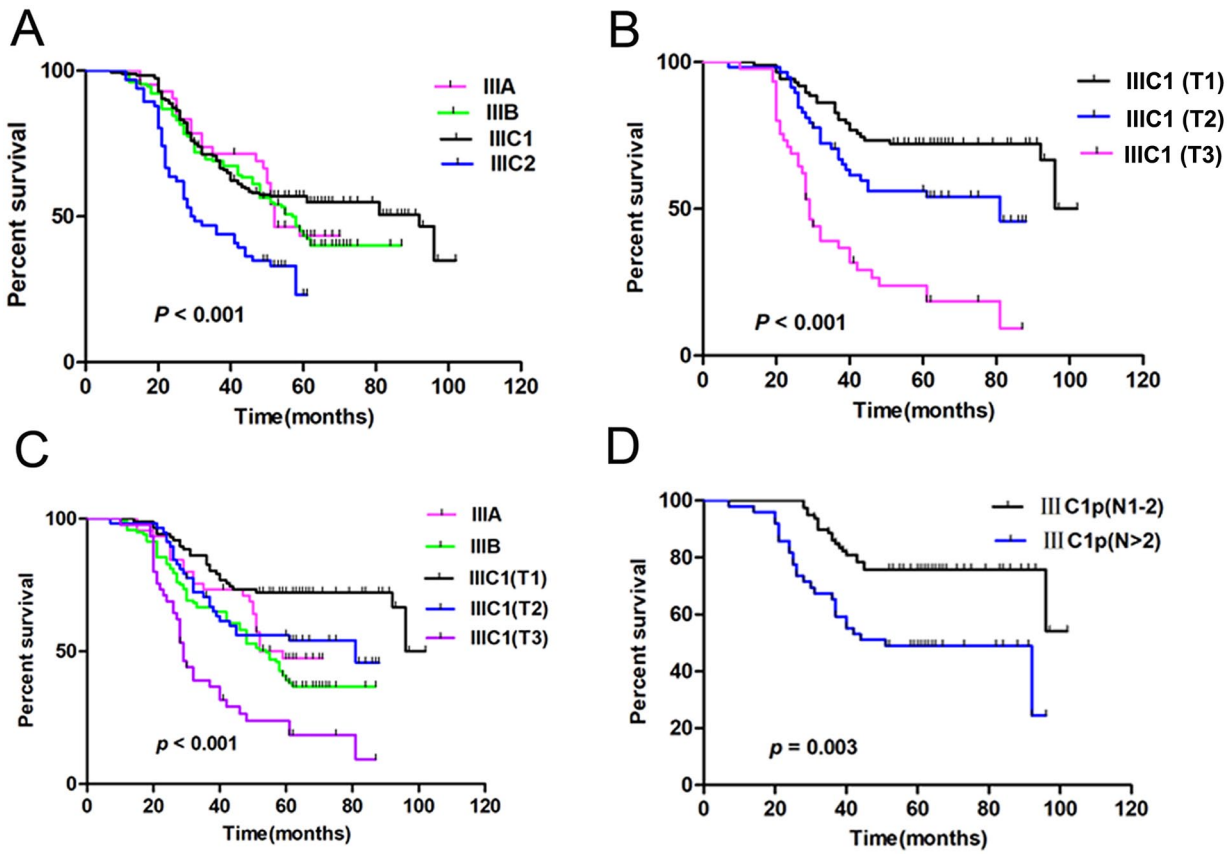

Figure 2. Kaplan-Meier curves based on the 2018 FIGO cancer staging system. Log-rank test for *P* values. Survival is shown for (A) stage III cervical cancer, (B) stage IIIC1 cervical cancer based on T stage, (C) stage IIIA, IIIB, and IIIC1 cervical cancer based on T stage, and (D) stage IIIC1p cervical cancer based on the number of metastatic pelvic lymph nodes.

>1 PLNM ($P < .001$). The 5-year OS rates were lower in patients with >2 PLNMs than in patients with 1 or 2 PLNMs (5-year OS rates, 47.9% vs 76.0%, $P < .001$). The 5-year OS rates in patients with >3 PLNMs were not significantly different from those with 1 to 3 PLNMs (59.3% vs 65.1%, $P = .337$). Univariate analysis revealed that survival in patients with IIIC1p (T1/T2a) was significantly associated with the number of PLNMs. Therefore, the 5-year OS rate was significantly higher in patients with stage IIIC1pN1-2 than in patients with IIIC1pN>2 (76.0% vs 47.9%, $P < .001$) (Figure 2D). However, age, histologic type, histopathological grading, type of radiotherapy administered, and minimally invasive surgery did not significantly affect survival ($P > .05$ for each) (Table 4). Analysis of multiple factors revealed that the number of PLNMs was independently associated with prognosis. The mortality risk was 2.75-fold higher in patients with stage IIIC1pN>2 than in patients with stage IIIC1pN1-2 (HR 2.753, 95% CI 1.527-4.965, $P = .001$) (Table 4).

Discussion

This study highlights that stage IIIC1 cervical cancer comprises a heterogeneous patient population with variable prognoses, which significantly differed on the basis of the T stage and the extent of PLNMs.

Evidence-based research has implicated metastatic lymph nodes as a high-risk factor that negatively affects prognosis in patients with cervical cancer.[15,16] Stage IIIC only includes metastatic lymph nodes, which may overlap or contradict the prognosis of earlier stages. For example, a retrospective study of 11 733 patients with stage III cervical cancer that included information from the Surveillance, Epidemiology, and End Results database reported longer survival in patients with stage IIIC1 than in patients with stage IIIA or IIIB cancer.[17] Unfortunately, the prognostic outcomes of stage IIIC2 are unknown. We observed that the 5-year OS rate was significantly lower (23.1%) and the mortality risk was 3-fold higher in patients with stage IIIC2 than in patients with stage IIIA cancer.

Although the 2018 FIGO staging system resulted in upward migration of most stages, survival rates varied among the stage III substages.[18] We observed that tumor size and local invasion may affect prognosis and therefore analyzed the data of patients with stage IIIC1 cancer based on the T stage and observed that survival significantly differed across the T1, T2, and T3 disease stages. All patients with stage IIIC1 (T1) cancer underwent radical surgery, and the 5-year OS rates were higher in these patients than in those with stage IIIA. Patients with stage IIIC1 (T3) did not undergo radical surgery, and the 5-year OS

Table 2. Univariate and multivariable analysis for survival in stage III cohort.

CHARACTERISTIC	NO.	SURVIVAL RATE (%)		MULTIVARIABLE (VS STAGE IIIA)		MULTIVARIABLE (VS STAGE IIIB)		MULTIVARIABLE (VS STAGE IIIC1)	
		5YEAR	*P* VALUE	HR (95% CI)	*P* VALUE	HR (95% CI)	*P* VALUE	HR (95% CI)	*P* VALUE
Age, y			.806						
<65	358	46.4							
⩾65	60	39.6							
Histology			.402						
Squamous	326	45.8							
Adenocarcinoma	51	42.9							
Adenosquamous	41	34.6							
Grade			.481						
3	81	47.4							
2	266	46.0							
1	20	48.0							
Unknown	51	44.4							
FIGO stage			<.001						
IIIA	42	43.3		1.000					
IIIB	120	40.6		1.135 (0.710-1.814)	.596	1.000			
IIIC1	190	54.1		1.432 (0.867-2.366)	.161	1.261 (0.871-1.827)	.219	1.000	
IIIC2	66	23.1		2.958 (1.757-4.983)	<.001	2.606 (1.752-3.877)	<.001	2.066 (1.438-2.969)	<.001
Tumor size, cm			<.001						
<4	187	69.4		1	.001				
⩾4	231	36.5		1.554 (1.191-2.029)					
Neoadjuvant chemotherapy			.271						
Yes	72	62.3							
No	346	53.9							
Radical hysterectomy			<.001						
Yes	168	72.1		1	<.001				
No	250	48.3		2.22 (1.57-3.13)					
Minimally invasive surgery			.752						
Yes	32	70.9							
No	136	73.5							
Radiotherapy			.083						
3- DCRT	180	46.5		1	.654				
IMRT	238	54.1		1.071 (0.793-1.447)					
Consolidation chemotherapy			.852						
Yes	314	45.9							
No	104	45.0							

Abbreviations: 3-DCRT, 3-dimensional conformal radiotherapy; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; IMRT, intensity-modulated radiotherapy.

Table 3. Univariate and multivariable analysis for survival in stage IIIC1 cohort.

CHARACTERISTIC		SURVIVAL RATE (%)		MULTIVARIABLE	
	NO.	5-YEAR	*P* VALUE	HR (95% CI)	*P* VALUE
Age, y			.311		
<65	174	52.9			
⩾65	16	64.3			
Histology			.228		
Squamous	152	58.6			
Adenocarcinoma	23	55.2			
Adenosquamous	15	33.3			
Grade			.745		
3	37	48.9			
2	126	54.7			
1	6	55.9			
Unknown	21	52.4			
T stage			<.001		<.001
T1	87	72.2		1	
T2	58	54.1		2.189 (1.197-4.005)	.011
T3	45	18.6		5.085 (2.827-9.147)	<.001
Tumor size (cm)			.003		.015
<4	87	65.9		1	
⩾4	103	44.1		1.735 (1.112-2.70)	
Neoadjuvant chemotherapy					
Yes	51	61.3			
No	139	54.2			
Radical hysterectomy			<.001		.054
No	62	34.9		1	
Yes	128	63.5		0.353 (0.122-1.018)	
Minimally invasive surgery			.159		
Yes	23	67.2			
No	167	52.4			
Radiotherapy			.084		.216
3-DCRT	88	47.8		1	
IMRT	102	56.2		0.751 (0.478-1.182)	
Consolidation chemotherapy			.469		
Yes	147	54.9			
No	43	51.5			

Abbreviations: 3-DCRT, 3-dimensional conformal radiotherapy; CI, confidence interval; HR, hazard ratio; IMRT, intensity-modulated radiotherapy.

rates were lower in these patients than in those with stage IIIA or IIIB disease. These findings suggest that the extent of local tumor invasion is as important as lymph node metastasis. In our study, patients who underwent radical hysterectomy were not balanced across the groups comprising patients with different stages of the disease. In fact, the management of patients with stage IIIC1 cancer remains controversial. The ABRAX trial is a multicenter, retrospective cohort study that investigated whether a radical uterine procedure was associated with improved oncological outcomes in this patient population. The results showed that radical hysterectomy did not improve survival, regardless of tumor size or histopathological type, and that definitive chemoradiation was necessary.[19] Recent National Comprehensive Cancer Network guidelines recommend primary chemoradiation as a category 1 recommendation for patients with stage III cervical cancer.[20] Based on previous studies, favorable prognosis in patients with stage IIIC1 (T1) may be attributable to the local earlier stage (2019 FIGO staging) in contrast to radical surgery. The 5-year OS rate in patients with stages IIIA/IIIB cervical cancer was only

Table 4. Univariate and multivariable analysis for survival in stage IIIC1p (T1/T2a) cohort.

CHARACTERISTIC		SURVIVAL RATE (%)		MULTIVARIABLE	
	NO.	5YEAR	*P* VALUE	HR (95% CI)	*P* VALUE
Age, y			.266		
<65	116	62.7			
⩾65	12	79.1			
Histology			.665		
Squamous	109	65.8			
Other	19	63.2			
Grade			.827		
G1-2	94	65.2			
G3	23	60.9			
Unknown	11	71.4			
T stage			<.001		.001
T1	87	75.1		1	
T2a	41	46.5		2.659 (1.487-4.755)	
Lymph node metastasis			<.001		.001
N1-2	80	76		1	
N>2	48	47.9		2.753 (1.527-4.965)	
Bilateral lymph node metastasis			.825		
Yes	27	69.6			
No	101	64.4			
Tumor size, cm			.012		.059
<4	66	77.4		1	
⩾4	62	54.1		1.804 (0.979-3.323)	
Neoadjuvant chemotherapy			.218		
Yes	51	59.5			
No	77	66.5			
Minimally invasive surgery			.364		
Yes	23	63.6			
No	105	73.9			
Radiotherapy			.937		
3-DCRT	23	65.2			
IMRT	105	65.5			
Consolidation chemotherapy			.027		.071
Yes	111	68.3		0.507 (0.242-1.060)	
No	17	47.1		1	

Abbreviations: 3-DCRT, 3-dimensional conformal radiotherapy; CI, confidence interval; FIGO, International Federation of Gynecology and Obstetrics; HR, hazard ratio; IMRT, intensity-modulated radiotherapy.

45.0%. Concurrent chemoradiation therapy is the standard treatment for locally advanced cervical cancer. Optimization of external beam radiation therapy and brachytherapy in patients with involvement of the lower thirds of the vagina and/or extension to the pelvic wall is important for favorable outcomes.[21] A study has reported that metastatic lymph nodes negatively affected prognosis based on T stage; the effect of stage IIIC2 was most pronounced in patients with T1B cancer, and the effect of stage IIIC2 cancer was significantly lesser in those with T3 disease. Within the T1B group, we observed no difference in survival rates associated with stage IIIC1 in patients with the lower T stages (IB1-2).[22] Nomograms developed in a study achieved significant prognostic power and more comprehensively predicted survival outcomes compared with existing staging criteria, including tumor size, lymph node metastasis, and pelvic wall involvement.[23] Patients with stage IIIC1 have varying prognoses based on tumor size and local invasion. In clinical practice, 2018 FIGO stage IIIC1 requires

inclusion of T staging to effectively guide clinical management and predict prognosis.

In contrast, patients with cervical cancer with PLNMs show diverse risk profiles, which is mainly attributable to additional variables such as bilateral presentation and the number of lymph nodes affected in such cases.[24,25] Comparison of the prognostic accuracies of lymph node staging systems (2018 FIGO, metastatic lymph node ratio, number, and the log-odds of lymph nodes metastasis) shows that the number of metastatic lymph nodes system most accurately predicts prognosis in patients with lymph node metastasis after radical operations.[26] This study highlights that the number of positive pelvic lymph nodes is an accurate predictor of prognosis in patients with stage IIIC1p (T1/T2a) cervical cancer. Prognosis in these patients with >2 lymph node metastases was significantly poor, which is consistent with the findings of previous retrospective studies.[27] The researchers observed that the prognostic value of PLNMs in patients with cervical cancer who underwent radical surgery and chemoradiotherapy was associated with PLNMs >3, nonsquamous cell carcinoma, and lymphovascular invasion.[28] These findings suggest that the number of metastatic lymph nodes system may be useful to stratify risk groups of recurrence associated with surgically resected cervical cancer showing high-risk factors.

The limitations of this study include the retrospective design and small sample size of some of the patient groups, which may introduce bias. Furthermore, some patients did not undergo PET-CT, which may affect accurate diagnosis of lymph node metastasis. Therefore, large multicenter trials are warranted to validate our findings that support revision of the 2018 FIGO staging system.

Conclusion

Our present model facilitates better prognostic stratification of patients and emphasizes the independent roles of primary and locoregional disease, which suggests that the extent of local tumor invasion is as important as lymph node metastasis as contributors to prognosis and that T and N independently affect prognosis. Furthermore, our present results serve as a potentially important guideline for optimal clinical management of patients with stage IIIC1 cervical cancer. The existing 2018 FIGO staging system may limit its clinical utility, and the available tools require optimization. We are hopeful that stage IIIC1 cervical cancer will be restaged based on the T stage considering tumor size, local tumor invasion, and metastatic lymph nodes.

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Author Contributions

Conceptualization: Xingtao Long, Misi He, Qi Zhou; data curation: Xingtao Long, Lingling Yang; formal analysis: Dongling Zou; writing—original draft: Xingtao Long; writing—review & editing: Misi He, Lingling Yang; investigation: all authors; methodology: Xingtao Long; formal analysis: Dongling Zou; project administration: Qi Zhou; software: Dong Wang; language editor: Misi He, Yuemei Chen.

Ethical Approval

The study was approved by the ethics committee of Chongqing University Cancer Hospital, Chongqing, China (project number: 2019[177]).

Consent to Participate

Informed consent for using medical information for scientific purposes was obtained from all subjects.

ORCID iDs

Xingtao Long https://orcid.org/0000-0002-3294-1265
Misi He https://orcid.org/0000-0001-8469-7690
Qi Zhou https://orcid.org/0000-0001-5673-4263

Availability of Data and Materials

In accordance with the journal's guidelines, we will provide our data for the reproducibility of this study in other centers if such is requested.

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