

Analysis of the risk factors of residual lesions after conization and prognosis of multifocal micro-invasive squamous cell cervical carcinoma treated with different types of surgery

CHENGYAN LUO^{1*}, JIANGNAN QIU^{1*}, JIE ZHANG^{1*}, LIN YUAN^{1*}, CHANG LIU^{2*},
CONG WANG³, YANG LI³, LIYA ZHANG⁴ and WENJUN CHENG¹

¹Department of Gynecology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029;

²Department of Gynecology, The First Hospital of Lanzhou University, Lanzhou, Gansu 730000; ³Department of Pathology, The First Affiliated Hospital of Nanjing Medical University, Nanjing, Jiangsu 210029; ⁴Research Center of Biostatistics and Computational Pharmacy, China Pharmaceutical University, Nanjing, Jiangsu 211198, P.R. China

Received February 19, 2019; Accepted July 5, 2019

DOI: 10.3892/mco.2019.1904

Abstract. The aim of the present study was to evaluate the residual lesions after conization and the clinical outcome of patients with multifocal micro-invasive squamous cell cervical carcinomas (MMSCCs) treated with different surgical strategies. A retrospective study was carried out in 98 patients with MMSCCs diagnosed by conization and treated between January 2010 and December 2016 in 2 institutions. The patients underwent further different surgeries as therapeutic conization, extrafascial hysterectomy (ES), modified radical hysterectomy (MRH), radical hysterectomy (RH) with or without pelvic lymph node dissection (PLND) and regular follow-up. The clinicopathological characteristics of all of the patients were recorded. The risk factors of residual lesions and that of the recurrence were also analyzed in the present study. The logistic regression analysis revealed that cone margins ($P=0.001$) were correlated with residual disease after conization whereas parameters including age, gravidity, parity, menopause, stage, LVSI and the number of lesions were not predictors of residual lesions. The cone margin status also indicated the incidence of residual disease as follows: The risk of residual disease was lower with a negative margin when compared with the margin with micro-invasive carcinoma [MIC; odds ratio (OR)=0.064, $P=0.012$] and was lower in margin with a high-grade intraepithelial lesion than the margin with MIC (OR=0.297, $P=0.287$). The Cox regression analysis

revealed that there were no significant correlations between the following surgery scales and postoperative recurrences, nor were any significant correlations found between the recurrences and the gravidity and parity, postmenopausal state, stage, residual disease after conization, margin status, LVSI and number of lesions ($P>0.05$). Positive cone margin was the only predictive factor for residual disease in patients with MMSCCs. There were no significant correlations between the surgical scales and postoperative recurrences. This result may be due to the excellent prognosis of MICs despite multiple lesions, regardless the treatment.

Introduction

Cervical cancer is ranked fourth in regard to incidence and mortality in women worldwide and ranked second in incidence and mortality behind breast cancer among females in less developed countries in 2018 (1). Cervical cancer was one of the two most common causes of cancer-associated deaths in females aged 15-59 years in China (2). The mortality rates of cervical cancer in females are increasing with an annual percent change of 5.7% in China. Due to the widespread uptake of screening programs for cervical cancer, an increasing number of younger women are being diagnosed at earlier stages (3).

Micro-invasive squamous cell carcinomas of the cervix (MSCCs) refer to International Federation of Gynecology and Obstetrics (FIGO) stage IA cervical carcinoma including IA1 and IA2 according to pathological assessments with cone specimen (4). It is totally different with treatment and prognosis between stage IA1 and IA2 for single lesion cervix cancer, but there has been very few cases reported for multiple lesions. Multifocal MSCCs (MMSCCs) were first presented by Reich and Pickel (5) when there was more than one invasive focus of MSCCs with cone specimen. There are very few cases reported in the literature and no definitive consensus on the treatment policy of MMSCCs. Management of these cases is controversial. Regardless of multifocal lesions, some doctors have recommended that the same conservative surgical

Correspondence to: Professor Wenjun Cheng, Department of Gynecology, The First Affiliated Hospital of Nanjing Medical University, 368 North Jiangdong Road, Nanjing, Jiangsu 210029, P.R. China
E-mail: chengwenjundoc@163.com

*Contributed equally

Key words: multifocal micro-invasive squamous cell cervical carcinomas, residual disease, surgery, recurrence

approaches could be considered with a single focus due to the excellent prognosis of MSCCs. Bean *et al* (6) reported that the 5-year survival rates for 5,749 patients were 96.7% with stage IA1 SCCs and 95.6% with stage IA2, respectively. By contrast, other doctors hold the view that the same surgical scales for stage IB1 should be considered, as the total horizontal spread exceeds 7 mm when there are ≥ 3 foci (5).

Different approaches for patients with MMSCCs vary from conization to radical hysterectomy (RH) with or without lymphadenectomy. The aim of the present study was to explore appropriate treatments for MMSCCs and to analyze the prognosis of different surgical strategies.

Materials and methods

Patient recruitment. In the present retrospective study, a total of 98 patients were included and the records of patients who were diagnosed with MMSCCs at stages IA1 and IA2 according to the 2009 FIGO classification and were treated at Gynecologic Department in The First Affiliated Hospital of Nanjing Medical University (Nanjing, China) and The First Hospital of Lanzhou University (Lanzhou, China) between January 2010 and December 2016 were reviewed. Preoperative diagnosis was made after analysis of the serial sections from cone specimens performed with loop electrosurgical excision procedures (LEEP) or cold knife conization (CKC) by two experienced gynecological pathologists. Patients were excluded from the study if they had other histological subtypes such as adenocarcinoma or adenosquamous carcinoma, or if they had previous therapy such as chemotherapy and radiation history. The present research was approved by the Ethical Committees of The First Affiliated Hospital of Nanjing Medical University (Nanjing, China) and The First Hospital of Lanzhou University (Lanzhou, China). Written informed consent was obtained from each patient prior to study initiation.

The data collected included age, parity, gravidity, menopause status, conization method and the corresponding surgical procedure. The histopathological characteristics of the cone specimens and the further surgical specimens were reviewed by two independent pathologists for depth of invasion, horizontal spread, number of micro-invasive lesions, lymphovascular space involvement (LVSI), margin status, residual disease, parametrium condition and lymph nodal metastasis. Reich and Pickel (5) proposed that depth should be measured perpendicularly from the epithelial-stromal junction to the deepest point of the tumor, the horizontal spread of the unifocal lesion being measured in a straightforward manner, but the appropriate method is unclear in regard to multifocal lesions, which can be located close together or far apart. For MMSCCs, the width and depth of every focus should be measured separately without accumulation and that of the largest focus should be used for analysis (7). The ectocervical and endocervical margins of cone specimens were recorded separately as follows: Negative, low-grade intraepithelial lesion (LSIL), high-grade intraepithelial lesion (HSIL), micro-invasive carcinoma (MIC), and invasive carcinoma (IC). LVSI was considered to be present when tumor cell clusters were found within endothelial cell-lined spaces adjacent to the cervical stroma and immunohistochemical examination was

utilized if necessary. After initial diagnostic conization, the patients underwent further treatment including therapeutic conization, EH, MRH, or RH with or without PLND, which was defined according to NCCN Guideline (8). The final surgical specimens were evaluated for the following factors: i) Presence or absence of residual disease; ii) parametrial or nodal involvement; iii) and the section margin status of the vagina and parametrium. Residual disease is well defined in case of negative margin for single lesion, while it is quite difficult for multiple lesions, which was described as negative, LSIL, HSIL, MIC and IC.

Follow-up. All of the patients were followed-up at 3-6 months intervals for 2 years, then every 6 months for 3 years, and then annually until November 2018, which was the date of the last follow-up. During the follow-up period, the patients underwent pelvic examination, vault or cervical thinprep cytologic test, human papillomavirus (HPV) DNA test and squamous cell carcinoma antigen (SCC-Ag), colposcopy and imaging examination via magnetic resonance imaging if necessary. Treatment outcomes, recurrent status, complications of surgery, and adjuvant radiation therapy were recorded.

Statistical analysis. Descriptive statistics included the means and standard deviation for continuous variables, the median and quartiles for nonparametric variables, and numbers and percentages for categorical variables. The independent sample t-test or ANOVA analysis were used to compare the differences between the groups of continuous variables. The rank sum test was used to compare the differences between the groups of the nonparametric variables. The Pearson Chi-square/Fisher's exact tests were used to compare categorical data. The logistic regression model was used to analyze the association between risk factors and residual lesions. The Cox regression model was used to analyze the risk factors of recurrence. All analyses were performed with SPSS software version 22.0 (SPSS Inc.). $P < 0.05$ was considered to indicate a statistically significant difference.

Results

Patient and treatment demographics. A total of 98 women with MMSCCs were included in the present study. The mean age at diagnosis was 48.1 ± 5.9 years (range, 36-61 years). In total, 2 women (0.2%) were nulliparous, and 32 (32.7%) patients were postmenopausal. All of the patients underwent cone biopsy through LEEP, 74 (75.5%) cases showing MMSCCs at FIGO stage IA1 and 24 (24.5%) cases at stage IA2. Of all of the patients, 35 (35.7%) patients had margin involvement in the cone specimen, 28 (28.6%) with HSIL, 7 (7.1%) with IA1 and 63 (64.3%) with a negative margin. LVSI was detected in 9 (9.2%) cases with the cone specimen.

Risk factors of residual lesions after conization. All of the patients had multiple foci of micro-invasive lesions in the cone specimens, of whom 36 (36.7%) cases had 2 foci, 31 (31.6%) had 3 foci, and 31 (31.6%) had >3 foci. The exact number of lesions was not recorded when >3 foci were found. In the final pathology of the following surgical specimens, residual disease was found in 48 (49.0%) patients, 3 (3.1%) cases had

Table I. Clinicopathological characteristics of the 98 micro-invasive squamous cell cervical carcinoma patients comparing those with and without residual diseases and the risk factors associated with residual diseases.

Variables	Residual disease		$\chi^2/Z/t$	P-value
	Absent	Present		
Age, years	48.2±5.9	47.3±6.0	-0.926	0.357
Gravidity	3.0 (3.0-4.0)	3.0 (2.5-4.0)	0.438	0.508
Parity				
0	1 (2.0)	1 (2.1)	2.040	0.747
1	33 (66.0)	31 (64.6)		
2	16 (32.0)	14 (29.2)		
3	0 (0.0)	2 (4.2)		
Menopause				
No	36 (72.0)	30 (62.5)	1.005	0.390
Yes	14 (28.0)	18 (37.5)		
FIGO stage				
IA1	37 (74.0)	37 (77.1)	0.126	0.816
IA2	13 (26.0)	11 (22.9)		
Cone margin status				
Negative	42 (84.0)	21 (43.8)	19.423	<0.001
HSIL	8 (16.0)	20 (41.7)		
MIC	0 (0.0)	7 (14.6)		
LVSI				
No	46 (92.0)	43 (89.6)	0.171	0.738
Yes	4 (8.0)	5 (10.4)		
Number of lesions				
2	20 (40.0)	16 (33.3)	2.040	0.747
3	17 (34.0)	14 (29.2)		
>3	13 (26.0)	18 (37.5)		
Surgical procedures				
Conization	11 (22.0)	6 (12.5)	4.057	0.410
EH	12 (24.0)	11 (22.9)		
MRH	8 (16.0)	7 (14.6)		
RH	7 (14.0)	14 (29.2)		
RH and PLND	12 (24.0)	10 (20.8)		

HSIL, high grade squamous intraepithelial lesion; MIC, microinvasive cervical cancer; EH, extrafascial hysterectomy; MRH, modified radical hysterectomy; RH, radical hysterectomy; RH and PLND, radical hysterectomy and pelvic lymph node dissection; LVSI, lymphovascular space involvement. $\chi^2/Z/t$ include three values: Age was analyzed by t-test, expressed by mean ± SD and the statistic was t value; number of pregnancies was not normally distributed, nonparametric test method was used to analyze the variable, expressed by median and quartile and the statistic was Z value; the Chi-square test were used to analyze birth, menopause or not, cone margin status, LVSI, Number of lesions and surgical approach, expressed by the number of use cases and the percentage and the statistic was χ^2 .

IA2 lesions, 13 (13.3%) cases had IA1 lesions, 29 (29.6%) cases had HSIL, 3 (3.1%) cases had LSIL, and 50 patients (51.0%) had no residual disease in the final specimen. A total of 7 cases showed 'upstaged' conditions: 2 cases with IA1 changed to IA2 stage in the cone specimen, and 5 cases with IA2 changed to microscopic stage IB1 with residual disease exceeding micro-invasive parameters. Of these 5 cases, 2 with LVSI had pelvic lymph nodes metastasis and accepted postoperative radiation therapy: One with right iliac nodes metastasis, another with left obturator nodes metastasis. No one had para-

metrial involvement. All of the final pathologies showed clear resection margins including parametrial and vaginal margins. The clinicopathological characteristics between those with and without residual diseases, and the risk factors associated with residual disease in the final surgery specimen were presented in Table I. The logistic regression analysis showed the cone margins ($P<0.001$) were correlated with residual disease after conization whereas parameters including age, gravidity, parity, menopause, stage, LVSI and the number of lesions were not predictors of residual lesions. It was also revealed that the cone

Table II. Effect of cone margin status on the residual diseases in micro-invasive squamous cell cervical carcinomas.

Variable	B	S.E.	Wald	df	Sig.	Exp (B)	95% CI for Exp (B)	
							Lower	Upper
Margin (MIC)			13.948	2	.001			
Margin (negative)	-2.748	1.094	6.311	1	.012	.064	.008	.547
Margin (HSIL)	-1.214	1.141	1.132	1	.287	.297	.032	2.780
Constant	2.079	1.061	3.844	1	.050	8.000		

Logistic regression analysis including binary and multivariate variables, was performed to test the risk factors of residual disease after conization, including: Age, parity, gravidity, menopause, number of micro-invasive lesions, lymphovascular space involvement and margin status. The model was constructed using the conditional backward stepwise method, only variables with $P < 0.05$ were retained. HSIL, high grade squamous intraepithelial lesion; MIC, microinvasive cervical cancer. S.E., standard error of mean; df, degrees of freedom; Sig., significance; Exp (B), the exponent of B; CI, confidence interval.

margin status indicated the incidence of residual disease as follows: The risk of residual disease was lower with negative margins than in margins with MIC (OR=0.064, $P=0.012$) and lower in margin with HSIL than in margin with MIC (OR=0.297, $P=0.287$; Table II). The residual lesions in the final surgical specimen were categorized as LSIL, HSIL, IA1 and IA2. Beyond the presence of residual disease, the association between the factors and the extent of residual disease were analyzed. Multinomial logistic regression analysis showed that there was a significant difference in positive margin distribution among the groups when the residual disease presented as LSIL ($P < 0.001$), IA1 ($P=0.006$), and no lesions, with different numbers of foci between HSIL and no lesions ($P=0.031$), which meant the margin status and the number of lesions were associated with the extent of residual disease (data not shown).

Outcomes. The patients underwent different subsequent surgeries between 4 and 8 weeks after conization. No intraoperative complications occurred as intestinal, ureter and bladder injuries. Constipation and urodynamic dysfunction such as dysuria and urinary incontinence were observed in the clinic after RH, and RH and PLND, and lymphocyst and lymphedema presented more after RH and PLND; all had resumed after 6-24 months. The clinicopathological and patient characteristics among the different surgical groups were displayed in Table III. All of the patients were followed up and the mean duration was 67 ± 21 months. There was no distant metastasis or death due to cervical cancer during the follow-up period. Disease recurrence was defined as the histology-confirmed diagnosis of HSIL [or intraepithelial vaginal neoplasia grade 3 (VAIN3) in the vaginal vault, if hysterectomy], MIC or IC. The recurrence rate among the 5 types of surgical scales were presented in Table IV. No significant differences for the recurrence rate among the five surgical approaches were observed. There were 12 cases (12.2%) of HSIL (or VAIN3) recurrence in the present study and the mean recurrence time was 39 ± 14 months: 3 cases after second conization, 3 after hysterectomy, 1 after MRH, 2 after RH, and 3 after RH and PLND. The Cox regression model was used to analyze the relative factors of recurrence such as age, gravidity and parity, postmenopausal state, residual disease after conization, margin status, LVSI, number of lesions and different surgical

scales; however, no risk factors were significantly different ($P > 0.05$; data not shown).

Discussion

A total of 98 cases of MMSCCs were retrospectively analyzed in the present study and the positive cone margin was the only predictive factor for residual disease after conization. There were no significant correlations between the followed surgical scales and postoperative recurrences. When MSCCs were found at the first cone specimen with positive margin, the sequential procedures as conization are needed not only for the definitive diagnosis but also the therapy. Repeat cone biopsy to better evaluate depth of invasion or EH or MRH and PLND should be considered if margins are positive for carcinoma or dysplasia (category 2B for node dissection) according to the National Comprehensive Cancer Network Guidelines Version 2 2019 on cervical cancer (8). However, MMSCCs have rarely been reported in the literature. The present study made efforts to identify the risk factors and extent of residual disease in the remaining cervix after conization and to explore the proper surgical scale for MMSCCs and prognosis after different surgical scales, avoiding overtreatment without compromising oncological outcome.

The results revealed that the positive cone margin was the only independent risk factor of residual disease after conization in patients with MMSCCs ($P < 0.001$), whereas other parameters including age, parity, postmenopausal status, number of lesions, LVSI and surgical scale were not significantly correlated with the presence of residual disease ($P > 0.05$). The association between conization margins and the presence of residual disease in MMSCCs were consistent with the characters of mono-focus MIC described, including IA1 and IA2 stages in several previous studies (9-11). Diaz *et al* (12) revealed that positive endocervical curettage (ECC), the combination of ECC and positive margin on conization, and a tumor volume of $\geq 50\%$ of the total conization specimen were predictors of residual disease in SCC. In a study by Won *et al* (13), positive cone margin (combined ectocervical and endocervical) and the depth of invasion were identified as independent risk factors for residual disease after conization in early-stage cervical cancer, whereas multifocal lesions

Table III. Clinicopathological characteristics of the 98 micro-invasive squamous cell cervical carcinoma patients who underwent 5 types of surgical scales.

Variables	Conization	EH	MRH	RH	RH and PLND	χ^2/Z	P-value
Age, years	41.0 (39.0-44.0)	50.0 (45.0-54.0)	48.0 (45.0-55.0)	48.0 (46.0-50.0)	49.0 (48.0-53.0)	28.975	<0.001
Gravidity	3.0 (3.0-3.0)	3.0 (2.0-4.0)	3.0 (2.0-4.0)	3.0 (3.0-4.0)	4.0 (3.0-4.0)	7.523	0.111
Parity							
0	2 (11.8)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	10.319	0.477
1	10 (58.8)	17 (73.9)	11 (73.3)	13 (61.9)	13 (59.1)		
2	5 (29.4)	6 (26.1)	4 (26.7)	8 (38.1)	7 (31.8)		
3	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	2 (9.1)		
Menopause							
No	17 (100.0)	14 (60.9)	9 (60.0)	14 (66.7)	12 (54.5)	13.027	0.010
Yes	0 (0.0)	9 (39.1)	6 (40.0)	7 (33.3)	10 (45.5)		
FIGO stage							
IA1	17 (100.0)	23 (100.0)	13 (86.7)	14 (66.7)	7 (31.8)	36.806	<0.001
IA2	0 (0.0)	0 (0.0)	2 (13.3)	7 (33.3)	15 (68.2)		
Margin status							
Negative	14 (82.4)	17 (73.9)	9 (60.0)	10 (47.6)	13 (59.1)	10.538	0.172
HSIL	2 (11.8)	6 (26.1)	6 (40.0)	7 (33.3)	7 (31.8)		
MIC	1 (5.9)	0 (0.0)	0 (0.0)	4 (19.0)	2 (9.1)		
LVI							
Negative	17 (100.0)	23 (100.0)	15 (100.0)	21 (100.0)	13 (59.1)	22.292	<0.001
Positive	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	9 (40.9)		
Number of lesions							
2	10 (58.8)	17 (73.9)	5 (33.3)	3 (14.3)	1 (4.5)	39.306	<0.001
3	2 (11.8)	3 (13.0)	7 (46.7)	12 (57.1)	7 (31.8)		
>3	5 (29.4)	3 (13.0)	3 (20.0)	6 (28.6)	14 (63.6)		

Age and number of pregnancies were not normally distributed, the nonparametric test method was used to analyze the two variables, expressed as the median and quartile and the statistic was Z value. The χ^2 test was used to analyze birth, menopause or not, Cone margin status, lympho-vascular space involvement and number of lesions, expressed as the number of use cases and the percentage, and the statistic was χ^2 . HSIL, high grade squamous intraepithelial lesion; MIC, microinvasive cervical cancer; EH, extrafascial hysterectomy; MRH, modified radical hysterectomy; RH, radical hysterectomy; RH and PLND, radical hysterectomy and pelvic lymph node dissection.

Table IV. Association analysis between the recurrence and the 5 types of surgical scales.

Recurrence	Conization (%)	EH (%)	MRH (%)	RH (%)	RH and PLND (%)	χ^2	P-value
No	14 (82.4)	20 (87.0)	14 (93.3)	19 (90.5)	19 (86.4)	1.214	0.939
Yes	3 (17.6)	3 (13.0)	1 (6.7)	2 (9.5)	3 (13.6)		

The χ^2 test were used to analyze the association between the recurrence and the 5 types of surgical scales, expressed as the number of cases and the percentage, and the statistical analysis was conducted with the χ^2 test. EH, extrafascial hysterectomy; MRH indicates modified radical hysterectomy; RH, radical hysterectomy; RH and PLND, radical hysterectomy and pelvic lymph node dissection.

were not related to these. The literature rarely discusses the predictors of residual disease for MMSCCs after conization. The results of the present study also demonstrated that the cone margin status indicated the incidence of residual disease as follows: The risk was lower with a negative margin than a margin with MIC (OR=0.064, P=0.012) and with a lower margin with HSIL than in a margin with MIC (OR=0.297,

P=0.287). Although the P-value of the latter was greater than 0.05, the OR of residual disease was decreased to 0.297 with the HSIL margin compared with the MIC margin. This indicated that residual lesions most likely existed when the margin was MIC, whereas it was not likely with a negative margin, which need to be further certified due to the limited numbers of cases with MMSCCs and retrospective nature of the design

in our study. Beyond the presence of residual disease, the association between the factors and the extent of residual disease was further analyzed and it was revealed to be significantly different with positive margin distribution among the groups when the residual disease presented as LSIL, IA1 and no lesions, with different numbers of foci between HSIL and no lesions, which indicated that margin status and the number of lesions were associated with the extent of residual disease. A multicenter retrospective study of 153 women with MICCs over 10 years by Sopracordevole *et al* (14) demonstrated that residual disease was significantly related to positive margins in the primary cone specimens. They identified 4 cases with cancer in the post-surgical specimens, with multifocal disease on the primary cone specimens, despite having unaffected surgical margins and a lack of LVSI. The results indicated that multifocal disease might affect the residual lesions besides positive margins. The accurate stage for MSCCs could be reached after an evaluation of conization specimen with negative margin of microinvasion. However, when the margin is positive with HSIL and the subsequent conization is quite difficult especially for those elder patients with distinct atrophic cervix or those with 'small size' cervix after the first conization. The diagnosis get more complicated with the multiple lesions and 'up-staged' conditions occur occasionally. 5 cases with IA2 upstaged to microscopic stage IB1 with residual disease exceeding microinvasive parameters in our study. It demonstrated the association between the cone margin status and the extent of residual disease with MMSCCs.

Given that multifocal disease is diffusely distributed in the cervix and vagina with 'skip characters', the diagnosis of MMSCCs in cone specimen depends on careful and standardized pathological assessment by skilled pathologists. Other notable difficulties arise from the definition of multifocality, how to measure the precise depth and width of MICs, how to combine the data observed in the different foci and the appropriate surgical scale for MMSCCs, avoiding overtreatment without compromising oncological outcomes. According to the National Comprehensive Cancer Network Guidelines version 2 2019 on cervical cancer, repeat cone biopsy to better evaluate depth of invasion or EH or MRH and PLND should be considered if margins are positive for carcinoma or dysplasia (category 2B for node dissection) (8). One can infer that for cone margin status, the involvement of LVSI should be considered for the further surgical treatment of MICCs. There has been no definitive consensus on the treatment for MMSCCs. Amongst the 98 MMSCC patients in the present study, the definitive surgeries were performed depending on: Tumor stage, cone margin status, involvement of LVSI, fertility-sparing desire and clinicians' experience. Some doctors hold the view that the sum-up width is above 7 mm and the surgery scale should be referred to stage IB1 even if a LEEP/Cone (first procedure) was with negative margins, while others insist that the same conservative surgical approaches could be considered with a single focus due to the excellent prognosis of MSCCs, regardless of multifocal lesions. During the follow-up in our study, there were no micro-invasive or invasive cancer recurrence, no distant metastasis and no cervical carcinoma-related deaths. There were 12 cases (12.2%) of recurrence with HSIL (or VAIN3)

and the mean recurrence time was 39±14 months: 3 cases after second conization, 3 cases after hysterectomy, 1 case after MRH, 2 cases after RH, and 3 cases after RH and PLND. The recurrence rate in the present study differed with that reported in other studies, which was attributed to the definition of relapse as HSIL (VAIN3) or worse in the present study, whereas only micro-invasive or invasive cancer were applied in other studies. The Cox regression analysis showed there were no significant correlations between the surgical scales and postoperative recurrences, nor were there significant correlations found between the postoperative recurrences and parameters such as age, gravidity and parity, postmenopausal state, stage, residual disease after conization, margin status, LVSI and number of lesions ($P>0.05$). This result may be due to the excellent prognosis of MSCCs despite multi-focal lesions, regardless of the treatment. There were no reports regarding the risk factors for MMSCC recurrence. A study of 3,987 women with MIC reported that the 5 year survival was similar for conization and hysterectomy in both SCCs (stage IA1: 95.1 and 95.6%; stage IA2: 90.2 and 96.3%) and adenocarcinomas (stage IA1: 98.8 and 96.9%; stage IA2: 97.8 and 98.2%) (15). Hartman *et al* (16) reported that 88% of recurrences occurred in the first 36 months after treatment for MIC. Qian *et al* (9) identified LVSI as an independent risk factor for recurrence in stage IA1 cervical cancer. Papakonstantinou *et al* (17) found that positive endocervical and ectocervical conization margins were risk factors for residual disease and recurrence. The risk of recurrence is higher in patients with a positive endocervical margin than those with a positive ectocervical margin (17). In Won's report, 2 recurrences occurred within 12 months after CKC with free margins (13). In the present study, 1 case relapsed in the 12th month after surgery, whereas the other 11 cases happened after 12 months. The recurrences within 12 months may be attributed to multifocal disease with discontinuities in the cervix and vagina, whereas after 12 months it may be related to persistent HPV infection. No significant risk factors related to relapse were concluded from the present data, this may be due to the limited number of cases with MMSCCs.

In conclusion, positive cone margin was the only predictive factor for residual disease in patients with MMSCCs. There were no significant correlations between the surgical scales and postoperative recurrences. This may be due to the excellent prognosis of MMSCCs despite multi-focal lesions, regardless of the treatment. To the best of our knowledge, this is the first study to investigate residual lesions after conization and the clinical outcome of patients with MMSCCs. The results may be useful to support the treatment policy for MMSCCs to reduce surgical morbidity without compromising oncological outcomes. The limitations of the present study include the retrospective nature of the design and the limited number of MMSCC cases. However, the results warrant further prospective and randomized control study, and long-term follow-up periods would be required in future studies.

Acknowledgements

The authors would like to thank Yi Jiang, MD from Department of Gynecology, for statistical analysis.

Funding

The present study was supported by the Project of Science and Technology of Nanjing, Jiangsu, P.R. China (grant no. 201605002).

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Authors' contributions

CLu researched the literature, analyzed the results and wrote the paper. JQ, JZ, LY and CLi reviewed the medical records, collected the clinical data and conducted the follow-up for all patients. CW and YL reviewed the histopathological characteristics of cone specimens and the post-surgery specimens. LZ performed the statistical analysis. WC conceived and designed the study, and reviewed the paper. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The research was approved by the ethical committee of the first affiliated hospital of Nanjing Medical University (Nanjing, China) and of the first hospital of Lanzhou University (Lanzhou, China). Informed consent for participation in the study was obtained from all participants.

Patient consent for publication

Informed patient consent for the publication in the study was obtained from all participants.

Competing interests

The authors declare that they have no competing interests.

References

1. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 68: 394-424, 2018.
2. Chen W, Sun K, Zheng R, Zeng H, Zhang S, Xia C, Yang Z, Li H, Zou X and He J: Cancer incidence and mortality in China, 2014. *Chin J Cancer Res* 30: 1-12, 2018.
3. Chen W, Zheng R, Zhang S, Zeng H, Xia C, Zuo T, Yang Z, Zou X and He J: Cancer incidence and mortality in China, 2013. *Cancer Lett* 401: 63-71, 2017.

4. Pecorelli S, Zigliani L and Odicino F: Revised FIGO staging for carcinoma of the cervix. *Int J Gynecol Obstet* 105: 107-108, 2009.
5. Reich O and Pickel H: Multifocal stromal invasion in microinvasive squamous cell carcinoma of the cervix: How to measure and stage these lesions. *Int J Gynecol Pathol* 21: 416-417, 2002.
6. Bean LM, Ward KK, Plaxe SC and McHale MT: Survival of women with microinvasive adenocarcinoma of the cervix is not improved by radical surgery. *Am J Obstet Gynecol* 217: 332.e1-332.e6, 2017.
7. Kurman RJ, Carcangiu ML, Herrington CS and Young RH (eds.): Tumors of the uterine cervix. In: WHO Classification of Tumors of Female Reproductive Organs. 4th edition. International Agency for Research on Cancer, Lyon, pp171, 2014.
8. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines[®]) Cervical Cancer. Version 2.2019-October 12, 2018. https://www.nccn.org/professionals/physician_gls/pdf/cervical.pdf. Accessed November 19, 2018.
9. Qian Q, Yang J, Cao D, You Y, Chen J and Shen K: Analysis of treatment modalities and prognosis on microinvasive cervical cancer: A 10-year cohort study in China. *J Gynecol Oncol* 25: 293-300, 2014.
10. Yoneda JY, Braganca JF, Sarian LO, Borba PP, Conceição JC and Zeferino LC: Surgical treatment of microinvasive cervical cancer analysis of pathologic features with implications on radicality. *Int J Gynecol Cancer* 25: 694-698, 2015.
11. Suri A, Frumovitz M, Milam MR, dos Reis R and Ramirez PT: Preoperative pathologic findings associated with residual disease at radical hysterectomy in women with stage IA2 cervical cancer. *Gynecol Oncol* 112: 110-113, 2009.
12. Diaz ES, Aoyama C, Baquing MA, Beavis A, Silva E, Holschneider C and Cass I: Predictors of residual carcinoma or carcinoma-in-situ at hysterectomy following cervical conization with positive margins. *Gynecol Oncol* 132: 76-80, 2014.
13. Won AS, Li WH and Cheung TH: Predictive factors for residual disease in hysterectomy specimens after conization in early-stage cervical cancer. *Eur J Obstet Gynecol Reprod Biol* 199: 21-26, 2016.
14. Sopracordevole F, Chiossi G, Barbero M, Cristoforoni P, Ghiringhello B, Frega A, Tortolani F, Boselli F, Clemente N, Ciavattini A and Italian Society of Colposcopy and Cervico-Vaginal Pathology: Surgical approach and long-term clinical outcome in women with microinvasive cervical cancer. *Anticancer Res* 34: 4345-4349, 2014.
15. Spoozak L, Lewin SN, Burke WM, Deutsch I, Sun X, Herzog TJ and Wright JD: Microinvasive adenocarcinoma of the cervix. *Am J Obstet Gynecol* 206: 80.e1-e6, 2012.
16. Hartman CA, Teixeira JC, Barbosa SB, Figueiredo SM, Andrade LA and Bastos JF: Analysis of conservative surgical treatment and prognosis of microinvasive squamous cell carcinoma of the cervix stage IA1: Results of follow-up to 20 years. *Int J Gynecol Cancer* 27: 357-363, 2017.
17. Papakonstantinou K, Kyrgiou M, Lyons D, Soutter WP and Ghaem-Maghami S: Management of stage Ia1 squamous cervical cancer and the importance of excision margins: A retrospective study of long-term outcome after 25 years of follow-up. *Am J Obstet Gynecol* 211: 625.e1.e6, 2014.



This work is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International (CC BY-NC-ND 4.0) License.