Analysis on high-risk factors of lesion residual after undergoing conization of cervix

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Abstract: To prevent cervical intraepithelial neoplasia (CIN) and relapse of cervical cancer, we have to analyze the high-risk factors of lesion residual after undergoing conization of cervix. Regression analysis upon data of clinical case of 267 patients after undergoingcold knife conization of cervix of two times will be carried out, in order to analyze the high-risk factors of lesion residual after operation. There are 74 patients with lesion residual after undergoing cold knife conization among the 267 patients. Result of single-factor analysis shows that involved gland (P=0.003), involved number of quadrant of cervix uteri >2 (P=0.006) and incisal margin involvement (P=0.002) are all relevant factors of lesion residual after undergoing conization of cervix. The result shows that positive incisal margin after operation is the independent risk factor (P=0.022) for lesion residual after Logistic regression analysis upon relevant factor has been implemented. Involved gland, involved number of quadrant >2 and incisal margin involvement are high-risk factors of lesion residual after undergoing conization of cervix, among which the incisal margin involvement has to be paid much attention.

1. Introduction

The death rate of cervical cancer has ranked 7th [1] among all kinds malignancies, which is also the top three malignancy that lead to death of woman. There are 500,000 emerging patients across the world, among which there are 80% of patients from developing countries, and the patients are tend to be younger and younger [2-3]. There are 130,000 emerging patients per year in China, accounting for 1/3 [4] of the number of the whole world. Cervical intraepithelial neoplasia (CIN) is a series of precancerous lesions that are related to cervical cancer, and ASCCP has pointed out that the patient with CINⅡ-Ⅲ grade and being satisfied with colposcopic biopsy can be operate dconization of cervix with preserving fertility [5]. Micro-invasive carcinoma of uterine cervix (MIC) includes cervical cancer I A1 and I A2, with cervical tissue pathology colposcopic invasive depth no more than 5 mm of epithelial basement membrane and with its horizontal diffusion no more than 7 mm. For patient required forfertility with MIC, especially for cervical cancer I A1, can be operated conization of cervix, and cervical cytology with follow-up visit of HPV DNA testing will be carried out after the operation above has been finished 3 months and 6 months later. If the results of follow-time of two times are both showing in negative, after that the test has to be implementedeach year once [6]. Regression analysis upon data of clinical case of 267 patients after under-going cold knife conization of cervix of two times will be carried out, and the related high-risk factors of lesion residual after operation has to analyze as well, in order to guide the noticed factors of cold knife conization and to prevent relapse of CIN and cervical cancer.

2. Data and method

2.1. General Data

We had selected 267 patients after under-going cold knife conization of two times as object of study, which are patients with CIN being treated in the affiliated hospital of Qingdao university medical college from Jan. 2011 to Dec. 2015, among which there are 6 patients with cervical cancer Ⅰ A2being operated radical hysterectomy, bilateral salping-oophenrectomy and pelvic lymph node dissection, there are 89 patients with cervical cancer Ⅰ A1 being operated epifacial panhysterectomyor bilateral salping-oophenrectomy; there are 21 patients with positive incisal margin after undergoing conization of cervix, which have been operated panhysterectomy or cold knife conization; there are 150 patients with uterine benign lesion have been operated panhysterectomy.

2.2. Methods

2.2.1. Clinical data

Clinical data of 267 patients had been sorted in order to analyze the relationship between age, menstruation and fertility status, result of cervical cytology, copy number of HPV, result of cervical pathology, condition of incisal margin, involved number of quadrant, condition of involved gland of patient and lesion residual after operation.

2.2.2. Statistical method

Multiple-factor analysis and single-factor analysis upon materials will be carried out by adopting statistics software SPSS 22.0. χ^2 testing shall be adopted to test

the difference of enumeration data, and t testing shall be adopted to test the difference of measurement data. Logistic regression analysis shall be used for multiple-factor analysis, with regarding difference P<0.05 as having statistical significance.

3. Result

3.1. Lesion residual condition after undergoing conization of cervix

The age scope of the 267 patients in this study is from 28-75 years old, with average age 46.84 ± 7.11 years old. The basic clinical data of patient includes age, menopause (Yes/No), gravidity, parity, LCT,

pathologic biopsy vaginoscopy and pathology after undergoing cold knife conization, among which the pathology after undergoing cold knife conization includes pathological grading, involved gland (Yes/No), involved number of quadrant and positive incisal (Yes/No). There are 74 patients with lesion residual among the 267 patients, the pathological diagnosis after operation and condition of lesion residual after second operation see table 1. The pathological diagnosis after operation is the highest grade lesion in pathologic diagnosis of cervical biopsy and pathologic diagnosis of conizationspecimen.

Table 1 Pathological diagnosis and conditionof lesion residual after operation of patient.

	Total(n)	Lesion Residual			Lesion without residual
		CIN II and below	CINⅢ	Cancer	
CIN II and below	44	3	2	0	39
CINⅢ	128	23	9	0	96
ⅠA1	89	23	7	2	57
ⅠA2	6	3	0	2	1

3.2. Single-factor analysis
3.2.1. χ^2 testing of enumeration factor

Influential factors of lesion residual after undergoing conization of cervix include age, menopause (Yes/No), gravidity, parity, LCT, pathologic biopsy vaginoscopy, pathology after undergoing cold knife conization and condition of positive Incisal margin after undergoing χ2 testing, related results see table 2. Moreover, in line with testing result, LCT includes low grade lesion group (includes ASC-US and LSIL) and high grade lesion group (includes HSIL and ASC-H). For the result of pathologic biopsy vaginoscopy, we will diagnose the patient with early infiltration and with early companion infiltration as ⅠA1.

The age scope of the 267 patients in this study is from 28-75 years old, with average age 46.84 ± 7.11 years old, and the median age is 46 years old. Let 50-year-old be the boundary, age ≥50-year-old (76 cases) and <50-year-old (191 cases)with lesion residual after operation is 17 (22.4%) cases and 57 (29.8%) cases respectively, and we can conclude χ^2=1.516, P=0.230 by comparing the two groups, which is no statistical significance. There are 52 patients of post-menopause, among which there are 15 (28.8%) patients with lesion residual, and there are 215 patients of pre-menopause, among which there are 59 (27.4%) patients with lesion residual, and we can conclude χ^2=0.041, P=0.864 by comparing the two groups, which is no statistical significance. The gravidity scope is from 1-8 times, with 3 times as median, and let 3 times be the boundary. Gravidity≥3 times (169 cases) and <3 times (98 cases)with lesion residual after operation is 52 (30.8%) cases and 22 (22.4%) cases respectively, and we can conclude χ^2=2.143, P=0.158by comparing the two groups, which

is no statistical significance. The parity scope is from 0-7 times, with 2 times as median. Parity≥2 times (78 cases) and <2 times (189 cases)with lesion residual after operation is 27 (34.6%) cases and 47 (24.9%) cases respectively, and we can conclude χ^2=2.619, P=0.132 by comparing the two groups, which is no statistical significance. There are 105 cases with low grade lesion in LCT, among which there are 35 caseswith lesion residual after operation, and there are 162 cases with high grade lesion, among which there are 39 caseswith lesion residual after operation, and we can conclude χ^2=2.726, P=0.123 by comparing the two groups, which is no statistical significance. The pathologic biopsy vaginoscopy includes lesion of CIN Ⅱ and below(29 cases), CIN Ⅲ (216 cases) and MIC(22 cases), among which MIC includes cervical cancer ⅠA1 and suspicious early infiltration, and we can conclude χ^2=2.439, P=0.295 by comparing the three groups, which is no statistical significance. In pathologic biopsy vaginoscopy, the patients with uninvolved gland are 107 cases, and the patients with involved gland are 160 cases, and we can conclude χ^2=0.173, P=0.780 by comparing the three groups, which is no statistical significance.

In line with lesion grade after operation, it includes lesion of CINⅡ(44 cases) and below, CINⅢ(128 cases) and MIC (95 cases), and we can conclude χ^2=12.326, P=0.002 by comparing the three groups, which is having statistical significance, and we can also conclude P>0.017 by comparing the each two groups, which is no statistical significance. There are 61 cases with uninvolved gland after operation, among which there are 8 cases with residual; and there are 206 cases with involved gland after operation, among which there are 66 cases with residual, and we can

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conclude χ^2=8.413, P=0.003，which is having statistical significance. In accordance with the involved number of quadrant, quadrant ≤2 (190 cases) and >2 times (77 cases) with lesion residual after operation is 43 cases and 31 cases respectively, and we can conclude χ^2=8.499, P=0.006 by comparing the two groups,

which is having statistical significance. There are 40 cases with positive incisal margin, among which there are 20 cases with residual; and there are 227 cases withnegative incisal margin, among which there are 54 cases with residual, and we can conclude χ^2=11.662, P=0.002，which is having statistical significance.

Table 2 Single factor analysis result of lesion residual after operation (n).

factor		residual	without	χ^2	P
age	≥50	17	76	1.516	0.230
	<50	57	191		
menopause	yes	15	37	0.041	0.864
	no	59	156		
gravidity	≥3times	52	117	2.143	0.158
	<3times	22	76		
parity	≥2times	27	51	2.619	0.132
	<2times	47	142		
lct	low grade cervical lesions	35	70	2.726	0.123
	high grade cervical lesions	39	123		
pathologic biopsy vaginoscopy	CIN II grade and below	5	24	2.439	0.295
	CIN Ⅲ	61	155		
	Ⅰ A1	8	14		
gland of pathological biopsy	yes	46	114	0.173	0.780
	no	28	79		
pathology after operation	CIN II grade and below	5	39	12.326	0.002
	CIN Ⅲ	32	96		
	mic	37	58		
gland of lesion after operation	yes	66	140	8.413	0.003
	no	8	53		
number of quadrant	>2	31	46	8.499	0.006
	≤2	43	147		
positive incisal margin	yes	20	20	11.662	0.002
	no	54	173		

3.2.2. t-testing of measurement factor

There are 110 patients having HPV-DNA before operation, among which there are 39 patients with lesion residual (35.4%), with testing range of HPV –DNA as 2.37~2710.3RLU/PC and average value as 582.92RLU/PC, and t testing result see table 3. The t testing result of residual group and without residual group is t=0.882, P=0.381 respectively, which is no statistical significance.

Table 3 Single factor analysis ofhpv-dna copy number and lesion residual.

	n	average value	p
Without residual	71	760.184±675.539	0.381
residual	39	880.997±650.162	

3.3. Logistic regression analysis

In line with single factor analysis, the related factors of lesion residual after operation include pathological grading, involved gland of lesion after operation, involved number of quadrant and positive incisal margin. Logistic analysis of related factor of lesion residual after operation see table 4. The result shows that positive incisal margin after operation is the independent risk factor (P=0.022<0.05) for lesion residual after Logistic regression analysis upon relevant factor has been implemented.

4. Discussion

Conization of cervix is an important method to treat and diagnose cervical lesions, especially for high-grade intraepithelial neoplasia and MIC, and it also has exerted significant effect upon screening of cervical cancer. Conization of cervix has advantage of easy operation, time-saving, small-wound, less-bleeding, recover-soon, cost saving and preserving uterus and fertility. However, it has existed risk of lesion residual because of limitation of the operation. There are 74 cases with lesion residual among the total 267 cases, with residual rate as 27.7%.

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Table 4 Logistic analysis of related factor of lesion residual after operation (n).

Factor		residual	without	P
pathological grading after operation	CIN II and below	5	39	
	CINⅢ	32	96	0.062
	MIC	37	58	
involved gland of lesion after operation	Yes	66	140	0.524
	No	8	53	
involved number of quadrant	>2	31	46	0.227
	≤2	43	147	
positive incisal margin	Yes	20	20	0.022
	No	54	173	

4.1. Age and menopause

Tan Xianjie [7] thought that there is correlation between age ≤45-year-old and lesion residual. Park [8] thought that age >50-year-old can be used for group research analysis upon high-risk factor of lesion residual, and it was concluded that P>0.05, which is no statistical significance. The median age is 46 years old among the age scope of the 267 patients in this study and let 50-year-old be the boundary, with the result showing that there is no correlation with age and lesion residual. Nungrutai [9] thought that menopause is the high-risk factor of lesion residual, while it is showed in this study that there is no correlation with menopause and lesion residual.Since menopause or elderly patients suffer cervical canals atrophy, making the cervix transition belt closer to cervical canal, while CIN has mulifocality and presents the characteristics of multipoint distribution. It is much easier for atrophy cervix to hide in the cervical canal, after the operation of cervix conization, the risk of tumor residue increases. However, the research believes there is no correlation among age, menopause, and lesion residue. Perhaps the elderly or menopause patients do not desire fertility, and the patients don't have the concerns that conization influences cervical function, thus inadvertently the conization scope is expanded. Or one can directly conduct the entire panhysterectomy after excluding cervical minimal infiltration, which may reduce the risk of lesion residue.

4.2. Pathological result

The result in this study shows that grading of pathologic biopsy vaginoscopy, involved gland of pathologic biopsy and grading of pathology have no correlation with lesion residual after operation, which is consistent with the researching result of Park [8]. The analysis on pathologic involved gland after operation shows that involved gland of uterine neck is the high-risk factor of lesion residual, which is consistent with the researching result of Dong [10]. In accordance with the classification method of WHO, the grading of CIN shall be based on the proportion of atypicalproliferation degree of cell and anomalous cell accounting for epithelial cell on uterine neck. With the

grading of CIN lesion and malignancy degree of tumor tissue becoming higher and higher, the occurrence rate of cervical cancer will become higher and higher as well. After gland has been involved, atypical cell will remain in cervical canals, which will be covered by epithelial cell, by which it is available to develop into cervical cancer. Moreover, involved number of quadrant >2 is the relevant factor of lesion residual, which is consistent with the researching results of Nungrutai [9] and Lu. Bycombin thought that the effective method of preventing lesion residual after operation of patients with CIN is enlarging the scope of conization to some extent, by combining with trait of lesion of various grades and multicenter of uterine neck.

4.3. Positive incisal margin

The result in this study shows that positive incisal margin after undergoing conization of cervixis the relevant factor of lesion residual, while positive incisal margin after operation is the independent risk factor for lesion residual after Logistic regression analysis upon relevant factor has been implemented. The scope of conization of cervix is the determinant of if incisal margin will be involved. To date the common scope of cold knife conization is cutting 0.5cm of vaginoscopylesion, and the top of conization shall reach to cervical canalsof 2～2.5cm, and border area of cervical canals [12] shall also be cut. Enlarging scope of conization to some extents is apt to reduce positive rate of incisal margin. However, study shows that the high-risk age scope of CIN is from 25-35-year-old, and enlarging operation scope is accessible to increase the occurrence of complication and having bad effect upon function of neck of uterus, by which it can lead to increase occurrence rate of premature birth and second trimester abortion. Because this kind of patients are always requesting for fertility, most of them with positive incisal margin after undergoing conization of cervix will not undertake the operation again. Kietpeerakool [13] has carried out follow-up visit upon 85 cases with positive incisal margin after undergoing conization of cervix, and found out that there are only 44 cases with residual or

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relapse. Hence, positive incisal margin is high-risk factor of lesion residual, and it can be observed by follow-up visit, and one can find out if it is necessary to undertake the operation again in line with the condition of visit. However, the patient of MIC with incisal margin after undergoing conization of cervix has to undertake the operation again.

4.4. HPV DNA testing

The testing result of HPV DNA in this study shows that it has no relationship with lesion residual after operation. However, the research carried out by Park et al. [9] shows that HPV-DNA≥300RLU/PC, which is the high-risk residual factor of lesion residual. The research carried out by Jiang Xuefeng [14] upon relapse factor of 44 cases with CIN after operation shows that RLU/PC≥500 tested by HPV is the high-risk relapse factor (P=0.025). Alonso [15] have untaken follw-up visist for 203 cases after LEEP operation, and there are 36 cases (17.7%) with residual and relapse, with lesion residual and relapse rate of HR-HPVcapacity (>1000 RLU) as 31.8%, with relapse rate of its corresponding capacity as 9.4% (P=0.005). Jeong-Yeo [16] claimed that the method by combining the HPV testing before undergoing conization of cervix and incisal margin status to predict lesion residual is in better predictive effect. Therefore, there is correlation between HPV-DNA testing result of high capacity and lesion residual and relapse after operation. However, there are only 110 cases with HPV DNA testing results among all the 267 cases. Hence the difference of correlation might have something to do with insufficient number of cases, for which we have to enlarge the number of case for further research.

5. Conclusion

Above all, the result in this study shows thatinvolved gland, involved number of quadrant >2 and incisal margin involvement of conization specimen are high-risk factors of lesion residual after undergoing conization of cervix, among which the incisal margin involvement of conization specimen is the independent risk factor for lesion residual. Hence, close follow-up visit has to be carried out up the patient after undergoing conization of cervix, in order to find out lesion residual in time and undertake intervention treatment as soon as possible, and to prevent relapse of CIN and cervical cancer.

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