妇科肿瘤专题 • 临床研究 •

宫颈锥切术后病变残留的危险因素分析*

王明宇,程广艳,张雯雯,田静,曲芃芃△
300100 天津,天津市中心妇产科医院 妇瘤科

[摘要] **目的:** 探讨宫颈高级别鳞状上皮内病变(high grade squamous intraepithelial lesions,HSIL)行宫颈锥切术后切缘阳性患者,出现病变残留的预测因素。**方法:**对我院 2018 年 6 月至 2018 年 12 月因 HSIL 锥切手术,因切缘阳性接受二次手术的 80 例患者进行横断面研究,采用单因素及多因素 Logistic 回归模型,分析患者年龄、生育情况、绝经状态、吸烟与否、高危型人乳头瘤病毒(high-risk human papillomavirus,HR-HPV)感染型别、宫颈液基细胞学检查结果、颈管搔刮结果、转化区类型、病变是否累及腺体、病变范围(累及象限)、圆锥周长、圆锥长度、阳性切缘位置等因素与宫颈锥切术后病变残留的相关性。**结果:**单因素分析显示宫颈 HSIL 患者锥切术后病变残留与绝经状态($P=0.025$)、HR-HPV感染型别($P=0.011$)、转化区类型($P=0.005$)、圆锥长度($P<0.001$)相关;多因素回归分析提示圆锥长度($OR=0.21$, CI 0.071 ~ 0.633)和转化区类型($OR=2.394$ CI 3.198 ~ 4.100)是病变残留的独立危险因素。**结论:**转化区类型和锥长是锥切术后病变残留的独立危险因素。

[关键词] 宫颈鳞状上皮内病变;宫颈锥切术;切缘阳性;病变残留;危险因素
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Risk Factors for the Incidence of Residual Lesions after Cervical Conization

Wang Mingyu, Cheng Guangyan, Zhang Wenwen, Tian Jing, Qu Pengpeng
Department of Gynecologic Oncology, Tianjin Central Hospital of Gynecology and Obstetrics, Tianjin 300100, *China*
Corresponding author: Qu Pengpeng, E-mail: qu.pengpeng@hotmail.com
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[**Abstract**] **Objective**: To explore factors predicting the incidence of residual lesions in high grade squamous intraepithelial lesions (HSIL) patients with positive margin after cervical conization. **Methods**: A cross-sectional study was conducted on 80 HSIL patients who got positive margin after conization and underwent the second surgery in our hospital from June 2018 to December 2018. Logistic regression models were used to analyze the correlation between the incidence of residual lesions and factors including age, parity, postmenopausal status, history of smoking, types of high-risk human papillomavirus (HR-HPV), results of liquid based cytology, results of endocervical curettage (ECC), types of transformation zone, the extent of lesions (involved quadrants), glandular involvement, the location of the positive margin, the perimeter of cone and the length of cone. **Results**: Monofactor analysis showed that the incidence of residual lesions were correlated with postmenopausal status ($P=0.025$), the type of HR-HPV ($P=0.011$), the type of transformation zone ($P=0.005$) and the length of cone ($P=0.000$). Multivariate regression analysis suggested that the length of cone ($OR=0.21$, $CI=0.071-0.633$) and the type of transformation zone ($OR=2.394$, $CI=3.198-4.100$) were independent risk factors for the incidence of residual lesions. **Conclusion**: The type of transformation zone and cone length are independent risk factors for the incidence of residual lesions after conization.

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[通讯作者] △曲芃芃,E-mail: qu.pengpeng@hotmail.com

[**Key words**] Cervical squamous intraepithelial lesion; Cervical conization; Positive margin; Residual lesion; Risk factor

宫颈癌是全世界妇女中第二常见的恶性肿瘤[1]。高级别鳞状上皮内病变(high grade squamous intraepithelial lesions, HSIL)与子宫颈癌密切相关,通常采用宫颈冷刀切除术或环形电切除术治疗,可达到在获得组织样本的同时兼顾诊断与治疗的双重目的[2]。锥切术后切缘状态与本病持续/复发风险相关[3-4]。据估计,切缘阴性患者治疗后两年的复发率约为 4% ~18%,平均为 8%,然而,在切缘阳性的患者中,复发的风险可达到切缘阴性患者的 5 倍[5],有研究报告称,这一风险约为 38.8%[6]。

对于锥切术后切缘阳性的患者,处理方法是存在争议的。一些专家建议对切缘阳性的患者进行临床随访,进行包括宫颈液基细胞学检查(liquid based cytology, TCT)、高危性人乳头瘤病毒(high-risk human papillomavirus, HR-HPV)分型及阴道镜在内的检查;而另一些专家则建议进行再次手术治疗,如二次锥切或子宫切除术。而最终决定的依据往往是患者年龄、生育要求、是否有适当的随访,或是否存在其他妇科疾患包括子宫肌瘤、腺肌症等,这些疾患本身可能就是子宫切除的指征。

事实上,部分女性是没有必要接受二次手术的,因为并没有病变残留,也有研究认为一些锥切术后的病变残留可以自然消退,二次手术可能给患者带来不良影响,二次锥切可能影响有生育要求者的妊娠结局,导致出现早产、胎膜早破甚至失去妊娠机会,并且增加了手术并发症。如果不进行手术,就会出现另一种风险,那就是有 HSIL 甚至恶性肿瘤残留风险的患者没有得到充分的治疗,有研究认为锥切术后切缘阳性的患者估计病变残留的可能性大于 30%[7-8],因此,许多研究人员都在寻找可能与 HSIL 病变残留相关的危险因素,而这些危险因素的识别可以指导我们做好术前评估,对于切缘阳性的患者选择适当的治疗方法。本研究旨在探讨 HSIL 合并宫颈锥切术后切缘阳性患者,出现病变残留的高危因素。

1　资料与方法

1.1　临床资料

这一横断面研究是在宫颈 HSIL 患者中进行的。符合条件的患者是我院 2018 年 6 月至 2018 年 12 月因宫颈 HSIL 行锥切手术,切缘阳性(共计 226 例)接受二次手术(共 80 例)作为治疗选择的女性。80 例初治宫颈 HSIL 锥切术后切缘阳性患者,年龄 30 ~67 岁,平均(49.32 ±9.34)岁,孕次 0 ~8 次,产次 0 ~3 次,吸烟者 4 例,不吸烟者 76 例,共有 8 例接受二次锥切,72 例接受全子宫切除术。

1.2　研究方法

根据二次手术后的标本中是否存在病变残留,将患者分为两组:残病组和无残病组。两组患者均收集了人口学、临床和组织学信息。将人口统计学、临床和锥切标本特征作为残留病变的可能危险因素进行分析。

1.3　统计学方法

采用 SPSS 20.0 统计分析软件对数据进行分析。计量资料经正态性检验符合正态分布者,以 $\bar{\chi} \pm s$ 表示,采用 t 检验;计数资料以例数和百分率表示,采用卡方检验或 Fisher 精确概率法。在多因素分析中,采用 Logistic 回归模型,确定患者的各种特征与病变残留的关系。$P<0.05$ 为差异有统计学意义。

2　结　果

2.1　锥切术后病变残留的单因素分析

对 80 例宫颈锥切术后行二次手术的患者标本进行分析,残病组 32 例(40%),无残病组 48 例(60%)。对病变残留可能存在的危险因素(年龄、产次、绝经与否、吸烟与否、HR-HPV 分型、TCT、颈管搔刮(endocervical curettage, ECC)、转化区类型、圆锥周长、圆锥长度、病变范围、累腺与否、阳性切缘位置等)进行了分析。宫颈 HSIL 患者术后病变残留与绝经状态、HR-HPV 分型、转化区类型、锥切长度密切相关(表 1)。

2.2　宫颈锥切术后病变残留危险因素的多因素分析

二次手术中残留病灶的 Logistic 回归分析(因变量:残留病变;自变量:绝经状态、术前 HR-HPV 分型、TCT、转化区类型、锥切长度)。多因素回归分析提示锥切长度及转化区类型与病变残留有关($P<0.05$)(表 2)。

表 1 宫颈锥切术后病变残留危险因素单因素分析

Table 1. Monofactor Analysis of Risk Factors of the Incidence of Residual Lesions after Cervical Conization

Variable	Residue group (n = 32)	Non-residue group (n = 48)	t/x^2	P
Age (y)			1.701	0.075
≤45	10	22		
>45	22	26		
Parity			0.175	0.675
≤2	30	46		
>2	2	2		
Postmenopausal status			5.000	0.025
Yes	24	24		
No	8	24		
History of smoking			0.089	0.911
Yes	1	3		
No	31	45		
HR-HPV type[a]			6.486	0.011
HPV high risk 16/18 (+)	25	20		
HPV high risk others (+)	6	19		
TCT[b]			2.220	0.695
Negative	2	1		
ASC-US	8	15		
ASC-H	5	4		
LSIL	6	11		
HSIL	11	17		
ECC[c]			1.651	0.229
+	26	37		
−	2	8		
Type of transformation zone			8.028	0.005
Ⅰ − Ⅱ	9 (28.125%)	29 (60.42%)		
Ⅲ	23 (71.875%)	19 (39.58%)		
Extent of lesions			0.008	0.927
≥2 quadrant	15 (46.875%)	22 (45.83%)		
<2 quadrant	17 (53.125%)	26 (54.17%)		
Glandular involvement			0.130	0.719
Yes	27 (84.375%)	42 (87.50%)		
No	5 (15.625%)	6 (12.50%)		
Positive cone margin[d]			0.359	0.382
Positive endocervical margin	27 (84.375%)	33 (68.75%)		
Positive ectocervical margin	10 (31.25%)	20 (41.67%)		
Positive basal margin	9 (28.125%)	8 (16.67%)		
Cone perimeter (cm)	4.63 ± 1.05	4.64 ± 0.76	0.015	0.988
Cone length e (cm)	1.48 ± 0.35	1.82 ± 0.38	4.173	0.000

[a] In the residue group, 1 case did not underwent hybrid capture based human papillomavirus detection, 1 case was not typed, HPV high risk 16/18 (+) and HPV high risk others (+) were positive in 1 case; in the non-residue group, 5 cases underwent hybrid capture based human papillomavirus detection, 8 cases were not typed, HPV high risk 16/18 (+) and HPV high risk others (+) were positive in 4 cases. HC2: Hyrid capture 2; HR-HPV: High-risk human papillomavirus; HPV: Human papillomavirus.

[b] TCT: Liquid based cytology; ASC-US: Atypical squamous cells of unknown significance; ASC-H: Atypical squamous cells cannot exclude high grade squamous intraepithelial lesion on cytologic smear; LSIL: Low-grade squamous intraepithelial lesions; HSIL: High-grade squamous intraepithelial lesions.

[c] 4 and 3 cases did not underwent ECC in the residue group and the non-residue group, respectively. ECC: Endocervical curettage.

[d] In the residue group, endocervical, ectocervical and basal margins were positive in 3 cases; ectocervical and basal margins were positive in 1 case; endocervical and ectocervical margins were positive in 2 cases; endocervical and basal margins were positive in 5 cases. In the non-residue group, endocervical, ectocervical and basal margins were positive in 4 cases; ectocervical and basal margins were positive in 2 cases; endocervical and ectocervical margins were positive in 6 cases; endocervical and basal margins were positive in 3 cases.

[e] Cone length was defined as the length between the ectocervical margin and the endocervical margin according to the International Federation for Cervical Pathology and Colposcopy (IFCPC) in 2011 (as is shown in Figure 1).

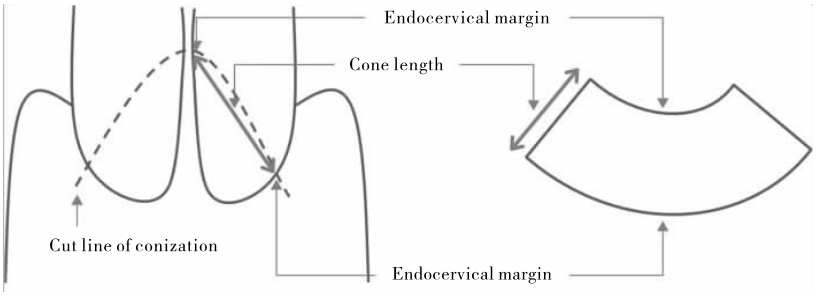

图 1　锥切标本横截面及展开图

Figure 1. Cross Section and Expansion of Conization Specimen

Cone length was defined as the length between ectocervical margin and the endocervical margin as defined by the International Federation for Cervical Pathology and Colposcopy in 2011.

表 2　宫颈锥切术后病变残留危险因素多因素 logistics 分析

Table 2. Multivariate Logistic Regression Analysis of Risk Factors for Residual Lesions after Cervical Conization

Variable	*B*	*SE*	*Wald*	*df*	*P*	*OR*	95% *CI*	
							Lower	Upper
Postmenopausal status	1.327	1.505	0.778	1	0.378	3.769	0.197	23.025
Transformation zone	0.873	0.275	10.107	1	0.001	2.394	1.398	4.100
Cone length	−1.551	0.558	7.721	1	0.005	0.210	0.071	0.633

3　讨　论

在本研究中，约 40% 接受二次手术的患者存在病变残留，这一结果与国内一些学者报道的宫颈 HSIL 锥切术后切缘阳性行二次手术后发现病灶残留率为 41.12% 的研究结果保持一致[8]。

对于锥切术后病变残留的相关因素，文献报道也存在很大分歧。但一般认为，切缘阳性是锥切术后病变残留的独立危险因素[7-12]。但并非所有切缘阳性患者都有残留，故本研究选取的研究对象为切缘阳性进行二次手术患者。

在我们研究中，转化区类型是病变残留的独立影响因素，Ⅰ～Ⅱ型转化区病例共计有 38 例，其中 9 例出现病变残留，Ⅲ型转化区病例共计 42 例，其中 23 例出现病变残留。Ⅲ型的病变残留率明显高于Ⅰ～Ⅱ型。其他研究也已证实转化区类型与病变残留的高风险密切相关[13]。究其原因考虑主要为，阴道镜检查及术中复方碘溶液染色只能评估宫颈表面病变范围，但对于阴道镜检查不满意的Ⅲ型转化区患者，与Ⅰ型和Ⅱ型相比，随着转化区逐渐延伸到子宫颈深部，手术难度增加，易出现切除范围不够，而引起病变残留。

到目前为止，各种研究对锥长的定义不同。2011 年，国际宫颈病理和阴道镜联合会（International Federation for Cervical Pathology and Colposcopy，IFCPC）定义的锥长为从切除标本的远端或外部边缘到近端或内缘的距离[9]。但现在大多数研究分析的是锥深，而不是锥长，本研究是依据的 IFCPC 定义测量的锥长（图 1），发现影响病变残留的另一个独立因素是圆锥标本的长度，浅锥可导致病变切除不完全，这与 Kawano 等[14]的研究一致。有研究显示，圆锥深度小于 10 mm 会显著增加病变残留的发生率，而圆锥深度大于 18 mm 则排除了这种可能性[15-16]。根据患者年龄和宫颈鳞状上皮内病变类型，Bae 等[17]发现了 3 个理想的圆锥深度临界点：40～50 岁的 CIN Ⅲ患者圆锥深度截断值（AUC 0.64，敏感度 0.86）为 1.8 cm；小于 50 岁的 CIN Ⅱ患者的截断值为 1.2 cm（AUC 0.75，敏感度 0.90）；小于 40 岁的 CIN Ⅲ患者截断值为 1.8 cm（AUC 0.60，灵敏度 0.88）；小于 40 岁的 CIN Ⅱ女性，截断值为 0.9 cm（AUC 0.87，灵敏度 0.83）。Papoutsis 等[18]的研究显示，当锥深小于 10 mm 时，在大环切除转化区后，患者有可能出现阳性边缘。将这些研究结果与我们的研究结果进行比较，我们可以得出结论，圆锥标本的长度与病变残留是相关的。

国外一些学者认为更年期状态与病变残留的高风险密切相关。有研究认为主要是与绝经后女性雌激素水平低下有关，低雌激素水平减少了分泌干扰素-γ 和肿瘤坏死因子-α 的细胞数量，从而降低了免疫反应性，并且对促炎细胞因子的释放有加速作用，从而促进病变进展[19]。另有报道认为与生殖道萎缩和绝经女性宫颈鳞柱交界区内移增加手术难度有

关[20]。而在我们此次研究中,并未证实更年期状态是病变残留的独立危险因素,考虑可能与绝经年限不同,所导致身体激素水平及生殖道形态差异很大有关。

综上所述,转化区类型和锥切长度是宫颈锥切术后病变残留的独立危险因素。应加强对患者术前的评估,设计手术切除圆锥的形状,术中注意锥切范围,特别是Ⅲ型转化区患者,以期降低病变残留发生率。

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