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论著·临床研究

转化区类型在评估阴道镜下未见宫颈病变者随机活检中的价值

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[摘要] **目的**·探讨宫颈转化区类型在评估阴道镜下未见病变者是否采用随机活检诊断宫颈高级别鳞状上皮内病变 (high-grade squamous intraepithelial lesion, HSIL) 中的价值。**方法**·选取因人乳头瘤状病毒 (human papillomavirus, HPV) 高危亚型感染或液基薄层细胞学检测 (thinprep cytologic test, TCT) 结果异常而行阴道镜检查且未见病变患者 517 例, 明确其宫颈转化区类型, 并行宫颈随机活检, 评估 I、II、III 型宫颈转化区对诊断宫颈 HSIL 的价值。**结果**·阴道镜下未见病变者 517 例, 其中 III 型转化区 396 例, 随机活检 HSIL 检出率为 3.8% (15/396); I、II 型转化区 121 例, HSIL 的检出率为 8.3% (10/121)。与 III 型转化区相比, I、II 型转化区 HSIL 的检出率显著升高 ($P=0.000$)。Logistics 回归结果提示, TCT 结果异常和转化区类型为 I、II 型是阴道镜下未见病变者检出 HSIL 的危险因素。**结论**·对于阴道镜下未见病变但转化区为 I、II 型及 TCT 异常的女性, 随机多点活检可提升其宫颈 HSIL 的检出率。

[关键词] 宫颈转化区; 宫颈高级别鳞状上皮内病变; 阴道镜; 随机活检

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Value of transformation zone type in the evaluation of random biopsy among patients without visible lesions under colposcopy

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[Abstract] **Objective**·To explore the value of cervical transformation zone (TZ) type in assessing whether a random biopsy should be used to diagnose high-grade squamous intraepithelial lesion (HSIL) among patients without visible lesions under colposcopy. **Methods**·A total of 517 patients who underwent colposcopy (without visible lesions) due to high risk subtype infection of human papillomavirus (HPV) or thinprep cytologic test (TCT) abnormality were enrolled. TZ types were identified, random biopsies were performed, and the value of TZ type I, II and III in the diagnosis of HSIL was evaluated. **Results**·There were 517 cases without visible lesions under colposcopy. Three hundred and ninety-six of them were TZ type III, and the detection rate of HSIL was 3.8% (15/396) by random biopsy, while one hundred and twenty one of them were TZ type I and II, and the detection rate of HSIL was 8.3% (10/121). Compared with the TZ type III, the detection rate of HSIL in the TZ type I and II was significantly increased ($P=0.000$). Logistic regression showed that TCT abnormality, TZ type I and II were the risk factors for HSIL detection in patients without visible lesions under colposcopy. **Conclusion**·Random multipoint biopsy can significantly increase detection rate of cervical HSIL when no visible lesion is visualized under colposcopy, particularly in women with abnormal TCT results or TZ type I and II.

[Key words] cervical transformation zone; cervical high-grade squamous intraepithelial lesion; colposcopy; random biopsy

在女性生殖系统恶性肿瘤中, 宫颈癌的发病率和死亡率均位列第一^[1]。近年来, 对宫颈癌前病变的早期诊断及有效治疗, 使得宫颈癌的发病率有了显著下降^[2-3]。阴道镜检查是辅助诊断宫颈癌前病变和早期宫颈浸润癌的有效手段之一, 但其结果受到多种因素的影响, 如宫颈转化区

(transformation zone, TZ) 类型^[4]。本研究对 517 例阴道镜下未见病变患者进行分析, 探讨 TZ 类型对阴道镜下未见病变者在诊断宫颈高级别鳞状上皮内病变 (high-grade squamous intraepithelial lesion, HSIL) 中的临床意义, 以期为阴道镜下未见病变患者进行随机活检提供指导意见。

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1 对象与方法

1.1 研究对象

选择2016年6月—2017年5月于上海交通大学医学院附属仁济医院宫颈疾病门诊就诊的患者。入组标准:①人乳头瘤状病毒(human papillomavirus, HPV)高危亚型16、18、31、33、35、39、45、51、52、56、58、59和68型感染;或宫颈液基薄层细胞学检测(thinprep cytologic test, TCT)结果异常,包括无明确诊断意义的不典型鳞状细胞(atypical squamous cell of undetermined significance, ASCUS)、不能排除高级别鳞状上皮内病变的非典型鳞状细胞(atypical squamous cells, cannot exclude high-grade squamous intraepithelial lesion, ASC-H)、低级别鳞状上皮内病变(low-grade squamous intraepithelial lesion, LSIL)以及HSIL。②行阴道镜检查且未见宫颈病变。排除标准:①合并严重慢性内科疾病。②合并急性生殖道感染。③有宫颈治疗史。④临床资料不完整。最终,本研究共计纳入517例患者,年龄为19~85岁,平均年龄(45 ± 13)岁。

本研究已通过上海交通大学医学院附属仁济医院伦理委员会审批(审批号:仁济伦审[2017]026号)。所有入组患者均签署了知情同意书。

1.2 研究方法

1.2.1 阴道镜检查及分组 采用阴道镜观察阴道及宫颈。2011年国际宫颈病理与阴道镜联盟公布的阴道镜术语将TZ分为3个类型,即I型为转化区在宫颈管口外且完整可见,II型为转化区部分在宫颈管内且完整可见,III型为转化区在宫颈管内且不能完整可见。依据2017年《中国宫颈癌筛查及异常管理相关问题专家共识》关于不同转化区的表述(即I、II型转化区相当于完全可见转化区,III型转化区相当于不完全可见转化区),本研究将纳入患者分为I、II型转化区和III型转化区共2组。

1.2.2 阴道镜下随机活检及分类 随机选取阴道镜下未见病变者宫颈的3、6、9、12点组织进行活检。同时,III型转化区者需行宫颈管搔刮术(endocervical curettage, ECC);而对于I、II型转化区者,如存在ECC指征,即TCT结果为ASC-H/HSIL、HPV16/18阳性、阴道镜检查图像不满意等,也需行ECC。随后,依据《WHO女性生殖器官肿瘤学分类(第4版)》,将2组患者的宫颈组织病理学结果分为慢性炎症、LSIL以及HSIL共3个类型。

1.3 统计学分析

采用SPSS 19.0软件对研究数据进行统计分析。定性

资料以频数和百分比表示,组间比较采用 χ^2 检验。采用Logistics回归模型对阴道镜下未见病变且组织学诊断为HSIL的患者的年龄、HPV分型、TCT结果进行相关性分析。 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 阴道镜检查结果

经阴道镜检查发现,本研究纳入的517例患者均未见病变发生,其中I、II型转化区者121例,III型转化区者396例。

2.2 组织病理学分析

517例阴道镜下未见病变者的随机活检结果显示,25例为HSIL(包含4例合并ECC提示HSIL),63例为LSIL,其余均为慢性炎症;其中,I、II型和III型转化区患者的组织病理学结果如表1。

表1 不同转化区患者的组织病理学类型分布(n)

Tab 1 Distribution of histopathological types in patients with different TZ types (n)

Histological classification	Type I, II (n=121)	Type III (n=396)
HSIL	10	15
LSIL	19	44
Chronic inflammation	92	337

2.3 不同转化区患者的年龄分布

采用 χ^2 检验对不同转化区患者的年龄分布进行分析,结果显示,III型转化区者平均年龄45岁,I、II型转化区者平均年龄36岁;且随着年龄的增加,III型转化区者在不同年龄分布中的占比逐渐升高(表2),其升高趋势亦具有统计学意义($P=0.000$)。

表2 不同转化区患者的年龄分布[n(%)]

Tab 2 Age distribution of patients in different TZ types [n(%)]

Age	Type I, II	Type III	P value
≥ 19 years and <30 years (n=68)	33 (48.5)	35 (51.5)	0.727
≥ 30 years and <40 years (n=138)	47 (34.1)	91 (65.9)	0.000
≥ 40 years and <50 years (n=112)	24 (21.4)	88 (78.6)	0.000
≥ 50 years and <60 years (n=118)	12 (10.2)	106 (89.8)	0.000
≥ 60 years (n=81)	5 (6.2)	76 (93.8)	0.000

2.4 不同转化区患者在不同年龄中的HSIL检出率

采用 χ^2 检验对患者经随机活检的HSIL检出率进行分析,组织病理学结果显示,有25例患者被检出HSIL,检出率为4.8%(25/517)。其中,15例为III型转化区患者,其检出率

为 3.8% (15/396); 10 例为 I、II 型转化区患者, 其检出率为 8.3% (10/121); 且后者的 HSIL 检出率高于前者 ($P=0.000$)。同时, 除 50 ~ 60 岁年龄段外, 不同类型转化区患者在同一年龄段内的 HSIL 检出率间差异均无统计学意义 (表 3)。

表 3 不同转化区患者在不同年龄中的 HSIL 检出率比较
Tab 3 Comparison of the detection rate of HSIL in patients with different TZ in different ages

Age	Total detection rate/%	Type I, II		Type III		P value
		n	Detection rate/%	n	Detection rate/%	
≥ 19 years and <30 years	5.9	2	6.1	2	5.7	0.953
≥ 30 years and <40 years	3.6	2	4.3	3	3.3	0.779
≥ 40 years and <50 years	6.3	3	12.5	4	4.5	0.167
≥ 50 years and <60 years	4.2	2	16.7	3	2.8	0.027
≥ 60 years	4.9	1	20.0	3	3.9	0.118

2.5 阴道镜下未见病变者 HSIL 检出率的相关性分析

本研究对阴道镜下未见病变且组织病理学诊断为 HSIL 的患者的检出率进行单因素 Logistic 回归分析, 包括年龄、HPV16/18 分型、TCT 结果及转化区类型等。结果显示, TCT 结果和转化区类型对该检出率的影响较大 ($P=0.003$, $P=0.049$)。随后, 对 TCT 结果和转化区类型进一步行多因素 Logistic 回归分析, 结果显示 TZ 为 I、II 型及 TCT 结果异常是阴道镜下未见病变者检出 HSIL 的危险因素。

表 4 患者 HSIL 检出率的相关性分析
Tab 4 Correlation analysis of HSIL detection rate in patients

Characteristics	n	Detection rate of HSIL/n (%)	Univariate Logistic regression analysis (P value)	Multivariate Logistic regression analysis	
				OR (95%CI)	P value
Age			0.210	/	
≥ 45 years	250	9 (3.6)			
<45 years	267	16 (6.0)			
HPV16/18 type			0.940	/	
HPV16/18+	80	4 (5.0)			
HPV16/18-	437	21 (4.8)			
TCT			0.003		
Abnormal	88	10 (11.4)		3.433 (1.438-7.881)	0.004
Normal	429	15 (3.5)		1	-
TZ type			0.049		
I, II	121	10 (8.3)		2.191 (1.004-5.013)	0.048
III	396	15 (3.8)		1	-

3 讨论

研究^[5]显示 HSIL 是一种可诱发宫颈浸润癌的癌前病变, 对其进行早期诊断将在宫颈癌的预防中发挥重要作用。阴道镜检查是评估 HSIL 的重要手段之一, 经验丰富的检查医师借助阴道镜可直接观察宫颈, 并对 TZ 进行分型, 发现可疑病灶^[6]。尽管阴道镜指导下的活检病理是诊断 HSIL 的金标准, 但阴道镜下所见的病理情况与实际

宫颈病变严重程度间仍存在一定的出入。有文献^[7]报道, 阴道镜指导下的点活检诊断 HSIL 的敏感度仅为 76.2%。大型宫颈癌筛查项目 ATHENA (Addressing the Need for Advanced HPV diagnosis) 研究^[8]对所有细胞学异常或 HPV 阳性者行阴道镜检查, 并对其中阴道镜检查充分且未见病变者随机取 1 点活检, 结果发现有 20.9% (81/388) 为宫颈上皮内瘤变 2 级 (cervical intraepithelial neoplasia 2, CIN2) 及以上病变 (CIN2+) 和 18.9% (45/238) 为 CIN3+。

另一项研究^[9]也发现,在阴道镜下未见病变的女性中随机取4点活检,共检出39%的患者为CIN2+。西班牙和荷兰两家临床中心进行的EVAH (Evaluating the Visual Appearance of cervical lesions in relation its histological diagnosis, Human papillomavirus genotype and other viral parameters)研究同样也认为,针对阴道镜下未见病变者,行随机活检同时行ECC可以显著提高检出宫颈CIN2+的敏感性^[10]。这些研究提示阴道镜下未见病变者仍存在一定的HSIL病变,不予活检会造成一定程度的HSIL漏诊。本研究显示,阴道镜下未见病变者经随机活检发现有4.8%发生HSIL病变,与上述结论相一致。

对于阴道镜下未见病变患者,如都予以活检则可能造成患者不必要的创伤以及医疗资源的浪费,因此把握在何种情况下对阴道镜检未见病变者行随机活检成为临床亟待解决的问题。既往研究^[8]认为,HPV16/18阳性是阴道镜下未见病变者检出HSIL的危险因素。Song等^[11]发现对于阴道镜检查未见明显病变而细胞学检查提示HSIL及以下的患者,随机活检可以发现25%的HSIL病变。Hu

等^[12]研究也认为,在阴道镜检查未见病变者中,CIN2+或CIN3+的风险随细胞学异常的严重程度的增加而增加。值得一提的是,上述研究均未对入组研究对象的转化区类型进行分析。而本研究发现,除了TCT结果异常这一危险因素外,转化区类型也可用于临床判断阴道镜下未见病变者是否有必要行随机活检;结果提示,阴道镜下未见病变者转化区类型不同,随机活检HSIL检出率存在显著差异,即转化区为I、II型者的检出率为8.3%,而转化区为III型者则为3.8%;多因素Logistic回归分析显示,转化区类型与阴道镜下未见病变者HSIL检出率有显著相关性,提示对阴道镜下未见病变者中转化区为I、II型者可通过随机多点活检提高其宫颈HSIL的检出率,而对于III型转化区者的作用则相对有限。继而强调,对于阴道镜下未见病变者,需重视转化区类型的区分。

综上所述,对于阴道镜下未见病变且有指征转诊阴道镜的患者,随机活检可以帮助诊断部分漏诊的HSIL,尤其是对于I、II型转化区类型患者。结合转化区类型及TCT结果对于避免漏诊阴道镜下未见宫颈病变患者中的HSIL具有一定的指导意义。

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