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液基细胞学和 DNA 倍体检测筛查宫颈病变的临床研究

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摘要 目的:研究液基细胞学和 DNA 倍体检测筛查宫颈病变的价值,为临床应用提供理论依据。**方法:**选择 2011 年 6 月-2013 年 5 月在我院门诊就诊或体检中心体检,行宫颈癌筛查的 2034 名受试者,同时行宫颈液基细胞学检查和细胞 DNA 倍体分析,其中 71 人有组织病理学结果。**结果:**71 例组织病理学结果中,组织学诊断慢性宫颈炎 33 例,CIN I 21 例,CIN II 11 例,CIN III 6 例;液基细胞学 TBS 分级 26 例 WNL,24 例 ASCUS,4 例 ASC-H,14 例 LSIL,3 例 HSIL;DNA 定量细胞学异倍体细胞数 0 个 24 例,1~2 个 35 例,3~14 个 11 例,15~个 1 例。ROC 曲线液基细胞学曲线下面积为 0.921(95%CI 为 0.859~0.983),DNA 倍体检测曲线下面积为 0.836(95%CI 为 0.743~0.929)。**结论:**液基细胞学与 DNA 倍体检测对筛查宫颈病变有较高的预测价值,值得在临床上推广应用。

关键词:液基细胞学;DNA 倍体检测;宫颈病变;筛查

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The Study of Liquid-based Cytology and DNA Ploidy Screening to Detect Cervical Lesions

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ABSTRACT Objective: To study the value of liquid-based cytology and DNA ploidy screening on detecting cervical lesions, so as to provide a theoretical basis for clinical applications. **Methods:** 2034 cervical cancer screening subjects were selected in our hospital from June 2011 to May 2013. All of them received liquid-based cervical cytology and cell DNA ploidy analysis, and 71 cases turned out with histopathology results. **Results:** Among the 71 cases with histopathology results, there were 33 cases of chronic cervicitis, 21 cases of CIN I, 11 cases of CIN II, and 6 cases of CIN III, by histological diagnosis; considering the liquid-based cytology TBS grade, there were 26 cases of WNL, 24 cases of ASCUS, 4 cases of ASC-H, 14 cases of LSIL, and 3 cases of HSIL; As for DNA quantitative cytology several different ploidy, none was detected in 24 cases, 1 to 2 in 35 cases, 11 cases of 3 to 14, 1 case with more than 15. The area under the ROC curve of liquid-based cytology was 0.921 (95% CI: 0.859 - 0.983), while the area under the curve of DNA ploidy detection was 0.836 (95% CI: 0.743 - 0.929). **Conclusion:** Liquid-based cytology and detection of DNA ploidy screening for cervical lesions have a high predictive value, and are worthy of clinical application.

Key words: Liquid-based cytology; DNA ploidy detection; Cervical lesions; Screening

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前言

宫颈癌是最常见的妇科恶性肿瘤之一,发病率排女性恶性肿瘤第二位,仅低于乳腺癌,且在发展中国家为第一位^[1-3]。原位癌的高发年龄约为 30~35 岁,浸润癌约为 45~55 岁,近年来宫颈癌发病有年轻化的趋势^[4]。因此宫颈癌对发展中国家妇女带来的危害越来越大,也因此受到了人们越来越多的关注^[5]。伴随着近些年来宫颈细胞学筛查的普遍使用,宫颈癌和癌前病变

的二级预防早发现、早治疗落实得越来越好,宫颈癌的发病率和死亡率已经明显降低^[6]。为探讨液基细胞学和 DNA 倍体检测筛查宫颈病变的价值,本研究选择 2034 名行宫颈癌筛查的受试者,同时行宫颈液基细胞学检查和细胞 DNA 倍体分析,计算宫颈液基细胞学检查和细胞 DNA 倍体分析的敏感度和特异度,为临床应用提供理论依据。现将结果报告如下。

1 对象与方法

1.1 对象

选择 2011 年 6 月-2013 年 5 月在我院门诊就诊或体检中心体检,行宫颈癌筛查的 2034 名受试者,年龄 27~58 岁,均为无症状但要求进行宫颈防癌检查者。剔除标本不满意及二次送检者,共 1985 例,同时行宫颈液基细胞学检查和细胞 DNA 倍体分析,其中 71 人有组织病理学结果。

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1.2 方法

1.2.1 液基细胞学诊断 每张涂片经 2 位细胞学病理医师读片,诊断不一致的涂片进行复核。采用 TBS 系统进行分级:①未见癌前病变及癌细胞,正常范围(WNL);②无明确诊断意义的不典型鳞状细胞(ASCUS);③不典型鳞状细胞,不排除高度病变(ASC-H);④鳞状上皮内低级别病变(LSIL);⑤鳞状上皮内高级别病变(HSIL);⑥不典型腺细胞(AGC);⑦原位腺癌(AIS)。

1.2.2 细胞 DNA 定量诊断及倍体分析 细胞 DNA 定量诊断由广州华银医学检验中心处理,根据扫描结果 DNA 定量为 5C 的细胞数量(N)给出下列临床建议:N=0,未见异常 DNA 倍体细胞:建议 1 年后复查; $0 < N < 3$,见少量异常 DNA 倍体细胞:嘱受检者 3-6 月复查; $3 \leq N < 15$,可见异常 DNA 倍体细胞:建议受检者进一步检查; $N \geq 15$,可见大量异常 DNA 倍体细胞:建议受检者进一步检查。扫描约 8000 个细胞,上皮细胞 > 5000 为合格,以同一标本上淋巴细胞作为对照,正常分类细胞背景必须干净无杂质,且细胞规则,没有重叠,如不能确定可在显微镜下仔细分辨。DNA 含量 $> 5C$ 细胞的玻片,技术人员在显微镜下均进一步核实,以防止细胞图像分析系统把垃圾和重叠的

细胞核误作为癌细胞或异常细胞。

1.2.3 阴道镜检查及组织学诊断 凡是宫颈液基细胞学检查结果高于 ASCUS (包括 ASC-H、LSIL、HSIL、AGC、AIS),或者 DNA 倍体检测发现异常 DNA 倍体细胞 ≥ 3 个,或者 ASCUS+DNA 倍体检测发现 DNA 倍体异常细胞 ≥ 1 个以上的受检者,或者临床怀疑受检者宫颈病变,均建议其行阴道镜检查并对可疑部位进行活检。病理诊断分为正常或宫颈炎、CIN I、CIN II、CIN III。以病理结果 CIN I 作为评估阳性病变阈值。

1.3 统计学分析

采用 SPSS 20.0 统计软件建立数据库并进行统计分析,采用受试者特征工作曲线(ROC)分析液基细胞学及 DNA 倍体检测切点判断宫颈病变的敏感性和特异性。检验水准 $\alpha=0.05$ 。

2 结果

2.1 TCT 结果与宫颈活检组织病理学诊断的关系

71 例组织病理学结果中,组织学诊断慢性宫颈炎 33 例,CIN I 21 例,CIN II 11 例,CIN III 6 例,液基细胞学 TBS 分级 26 例 WNL,24 例 ASCUS,4 例 ASC-H,14 例 LSIL,3 例 HSIL。见表 1。

表 1 TCT 结果与宫颈活检组织病理学结果的比较

Table 1 Comparison of the TCT results and cervical biopsy results

组织学诊断 Histodiagnosis	TBS 分级 TBS classification					合计 Total
	WNL	ASCUS	ASC-H	LSIL	HSIL	
慢性宫颈炎 Chronic cervicitis	25	7	1	0	0	33
CIN I	1	14	2	4	0	21
CIN II	0	2	0	9	0	11
CIN III	0	1	1	1	3	6
合计 Total	26	24	4	14	3	71

2.2 DNA 定量细胞学结果与宫颈活检组织病理学诊断的关系

71 例组织病理学结果中,组织学诊断慢性宫颈炎 33 例,CIN I 21 例,CIN II 11 例,CIN III 6 例,DNA 定量细胞学异倍体

细胞数 0 个 24 例,1~2 个 35 例,3~14 个 11 例,15~ 个 1 例。见表 2。

表 2 DNA 定量细胞学结果与宫颈组织病理学结果的比较

Table 2 Comparison of DNA quantitative cytology results and cervical pathology results

组织学诊断 Histodiagnosis	DNA 异倍体细胞数(N) Number of DNA heteroploid cell(N)				合计 Total
	0	1~2	3~14	15~	
慢性宫颈炎 Chronic cervicitis	21	12	0	0	33
CIN I	2	18	1	0	21
CIN II	1	2	8	0	11
CIN III	0	3	2	1	6
合计 Total	24	35	11	1	71

2.3 液基细胞学、DNA 倍体检测 ROC 曲线

以组织学诊断作为金标准,CIN I 或以上判断为阳性病变。ROC 曲线显示液基细胞学有较高的预测价值,液基细胞学曲线下面积为 0.921 (95%CI 为 0.859~0.983),DNA 倍体检测

曲线下面积为 0.836(95%CI 为 0.743~0.929),两者之间的差异无统计学意义($P>0.05$)。

通过绘制 ROC 曲线(图 1),液基细胞学与诊断为宫颈阳性病变相关的临界点为 ASCUS 及以上,敏感度为 97.4%,特异度

为 75.8% ;DNA 倍体检测与诊断为宫颈阳性病变相关的临界点为 DNA 异倍体细胞数 1~2 及以上,敏感度为 92.1% ,特异度为 63.6% 。

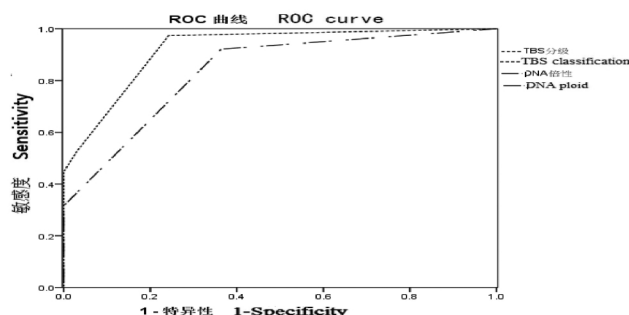


图 1 液基细胞学、DNA 倍体检测判断宫颈病变的 ROC 曲线

Fig. 1 ROC curve of liquid based cytology, DNA ploidy in the detection of cervical lesions

3 讨论

宫颈癌是最常见的妇科恶性肿瘤之一,且近年来宫颈癌发病有年轻化的趋势,给人们带来的危害和负担越来越大^[7,9]。随着社会的发展,人们二级预防的意识不断增强,自行宫颈癌筛查的受试者日益增多^[10]。细胞学检查是宫颈癌与 CIN 筛查的主要方法之一,自巴氏涂片在宫颈癌筛查开始应用以来,加上系统性细胞学检查的应用,使宫颈癌的总体发病率已下降 2/3 左右,但该方法仍受限于取材技术、制作涂片、染色、阅片水平等因素,造成巴氏细胞学方法假阴性率在 15%~40%左右^[11,12]。近年来,随着液基薄层细胞学技术的飞速发展,弥补了巴氏涂片的缺点,较传统涂片法涂片质量和敏感度更高,但是因为形态学检查所具有的局限性,和长时间阅片导致的视觉疲劳问题,造成敏感性相对较低,重复性较差以及较多意义不明的判片结果^[13,14]。

细胞 DNA 倍体分析系统进行宫颈病变诊断已经在临床上得到了越来越多的应用,细胞 DNA 定量分析已经成为一种常规的临床检测技术^[15]。细胞 DNA 倍体分析相对更客观、快速、准确,可以有效防止人为的疏漏或经验不足,以及仅从单一的细胞形态改变给出诊断造成的缺陷,出现非整倍染色体是肿瘤发生发展的一项重要指标^[16]。正常细胞(即二倍体 DNA 细胞,2C 细胞)和肿瘤细胞生长增殖时,细胞核内 DNA 结构和含量都会发生改变,5cERa(5c exceeding rate)是指 DNA 含量高于正常二倍体 G0/G1 期细胞 2.5 倍的细胞数,5C 细胞在二倍体肿瘤中出现时,则说明肿瘤细胞的遗传学不稳定性,DNA 异倍体定量分析可用于评估肿瘤预后^[17,18]。相对于液基细胞学,细胞图像分析系统价廉、操作直观简便,DNA 倍体分析,所需人员和实验室条件相对简单,经短期培训后,有较好的可实施性,防癌普查报告结果简明易懂,可弥补需要专业细胞诊断人员的缺陷^[19,20]。

本研究发现,液基细胞学与诊断为宫颈阳性病变相关的临界点为 ASCUS 及以上,敏感度为 97.4% ,特异度为 75.8% ;DNA 倍体检测与诊断为宫颈阳性病变相关的临界点为 DNA 异倍体细胞数 1~2 及以上,敏感度为 92.1% ,特异度为 63.6% 。该结果为临床上单独应用液基细胞学或 DNA 倍体检测,或者

联合应用液基细胞学和 DNA 倍体检测筛查宫颈病变提供了理论依据。

综上所述,液基细胞学与 DNA 倍体检测对筛查宫颈病变有较高的预测价值,值得在临床上推广应用。

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