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彩色能量多普勒超声阻力指数与宫颈癌患者 VEGF、MVD 以及临床病理特征的关系 *

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摘要 目的:研究彩色能量多普勒超声阻力指数与宫颈癌患者血管内皮生长因子(VEGF)、微血管密度(MVD)以及临床病理特征的关系。**方法:**以 2015 年 2 月-2018 年 2 月我院收治的宫颈癌患者 50 例为研究对象,记为宫颈癌组。另取同期于我院接受治疗的宫颈上皮内瘤变患者 50 例记为宫颈上皮内瘤变组,取同期于我院体检的健康志愿者 50 例记为对照组。采用经阴道彩色能量多普勒超声检测三组受试者阻力指数,采用免疫组织化学法检测三组受试者 VEGF 表达以及 MVD 值。分别比较三组受试者阻力指数、VEGF 表达及 MVD 值,并分析宫颈癌患者阻力指数与临床病理特征的关系,同时采用 Spearman 相关性分析宫颈癌患者阻力指数与 VEGF、MVD 的相关性。**结果:**宫颈癌组阻力指数低于宫颈上皮内瘤变组和对照组,且宫颈上皮内瘤变组低于对照组($P<0.05$);而宫颈癌组 VEGF 表达与 MVD 值高于宫颈上皮内瘤变组和对照组,且宫颈上皮内瘤变组高于对照组($P<0.05$)。病灶直径 <40 mm、临床分期 I-II 期、中高分化、无淋巴结转移宫颈癌患者阻力指数均高于病灶直径 ≥ 40 mm、临床分期 III-IV 期、低分化、有淋巴结转移宫颈癌患者($P<0.05$),而阻力指数与宫颈前后径、组织学类型无关($P>0.05$)。经 Spearman 相关性分析可得:宫颈癌患者阻力指数与 VEGF 以及 MVD 均呈负相关($P<0.05$)。**结论:**彩色能量多普勒超声可有效反映宫颈病变形态结构特征、血管生成状况以及浸润情况,临床工作中可联合彩色能量多普勒超声与 VEGF、MVD 的测定,有助于判断宫颈癌患者病情严重程度,为临床治疗方案的制定以及预后评估提供参考依据。

关键词:宫颈癌;彩色能量多普勒超声;阻力指数;临床病理特征;血管内皮生长因子;微血管密度

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Relationship between Resistance Index of Color Power Doppler Ultrasound and VEGF, MVD, Clinicopathological Features in Patients with Cervical Cancer*

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ABSTRACT Objective: To study the relationship between resistance index of color power Doppler ultrasound and vascular endothelial growth factor (VEGF), microvascular density (MVD), clinicopathological features in patients with cervical cancer. **Methods:** 50 patients with cervical cancer who were treated in our hospital from February 2015 to February 2018 selected as research object and recorded as a cervical cancer group. Another 50 patients with cervical intraepithelial neoplasia who were treated in our hospital in the same period were recorded as cervical intraepithelial neoplasia group, and 50 healthy volunteers who were received physical examination in our hospital in the same period were recorded as control group. Transvaginal color power Doppler ultrasound was used to detect the resistance index of the three groups. Immunohistochemistry was used to detect the expression of VEGF and MVD value in three groups. The resistance index, VEGF expression and MVD value of the three groups were compared. The relationship between resistance index and clinicopathological features of patients with cervical cancer was analyzed. At the same time, Spearman correlation was used to analyze the correlation between resistance index and VEGF, MVD in patients with cervical cancer. **Results:** The resistance index of the cervical cancer group was lower than that of the cervical intraepithelial neoplasia group and the control group, and the cervical intraepithelial neoplasia group was lower than that of the control group, the expression of VEGF and MVD value in cervical cancer group were higher than those in cervical intraepithelial neoplasia group and control group, and the cervical intraepithelial neoplasia group were higher than those in control group ($P<0.05$). The resistance index in patients with lesion diameter <40 mm, clinical stage with I-II stages, middle and high differentiation, no lymph node metastasis were higher than that of the lesion diameter ≥ 40 mm, clinical stage with III-IV stages, low differentiation, lymph node metastasis ($P<0.05$), and the resistance index was not related to the anteroposterior diameter of the cervix and histological type ($P>0.05$). Spearman correlation analysis showed that the resistance index of patients with cervical cancer was negatively correlated with VEGF and MVD ($P<0.05$). **Conclusion:** Color power Doppler ultrasound can effectively reflect the

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morphological features, angiogenesis and infiltration of cervical lesions. In clinical work, it is possible combined with color power Doppler ultrasound and VEGF, MVD to effectively judge the severity of patients with cervical cancer, and it can provide a basis for formulating clinical treatment protocols and evaluating prognosis.

Key words: Cervical cancer; Color power Doppler ultrasound; Resistance index; Clinicopathological features; Vascular endothelial growth factor; Microvessel density

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前言

宫颈癌属于临床上常见的女性生殖系统恶性肿瘤之一,其发病率在发展中国家仅次于乳腺癌,且具有年轻化趋势,对女性的生命健康安全造成了严重影响^[1,2]。由于该病发病早期具有较强的隐匿性,临床上大部分患者一经确诊便已是中晚期,彻底丧失了手术根治的时机^[3,4],因此,寻找一种早期诊断宫颈癌的有效手段显得尤为重要。彩色能量多普勒超声主要是以能量的方式显示肿瘤内部血流情况,是一种观察机体内肿瘤血流情况的无创性技术,临床上在多种疾病中均有较好的应用效果^[5,6]。阻力指数可有效反映肿瘤血管的生成状况^[7],血管内皮生长因子(vascular endothelial growth factor, VEGF)、微血管密度(microvessel density, MVD)均是临床用以评价血管活性强度的指标,而肿瘤血管生成在肿瘤的生长、转移过程中起着至关重要的作用^[8,9]。鉴于此,本研究通过探讨彩色能量多普勒超声阻力指数与宫颈癌患者 VEGF、MVD 以及临床病理特征的关系,旨在为临床诊治宫颈癌提供数据支持,现作以下报道。

1 资料与方法

1.1 一般资料

以 2015 年 2 月-2018 年 2 月我院收治的宫颈癌患者 50 例为研究对象,记为宫颈癌组,年龄 22-59 岁,平均(40.38±5.32)岁;宫颈前后径<30 mm 者 14 例,≥30 mm 者 36 例;病灶直径<40 mm 者 37 例,≥40 mm 者 13 例;临床分期:I-II 期 40 例,III-IV 期 10 例;组织学类型:鳞癌 42 例,腺癌 8 例;分化程度:低分化 9 例,中高分化 41 例;有淋巴结转移 17 例,无淋巴结转移 33 例。另取同期于我院接受治疗的宫颈上皮内瘤变患者 50 例记为宫颈上皮内瘤变组,年龄 23-56 岁,平均(41.51±4.68)岁;极轻度与轻度不典型增生 20 例,中度不典型增生 16 例,重度不典型增生或原位癌 14 例。宫颈癌组与宫颈上皮内瘤变组纳入标准:(1)宫颈癌与宫颈上皮内瘤变均参照《妇产科学》^[10]中所制定的相关诊断标准;(2)均经手术病理检查确诊;(3)入院前均未接受任何相关治疗者;(4)临床病历资料完整者。排除标准:(1)合并其他恶性肿瘤疾病者;(2)既往有宫颈严重疾病或手术史者;(3)妊娠期或哺乳期妇女;(4)伴有精神疾病或交流沟通障碍者;(5)正参与其他研究者。取同期于我院进行体检的健康志愿者 50 例记为对照组,年龄 22-60 岁,平均(40.97±5.41)岁。三组年龄比较差异无统计学意义($P>0.05$),说明组间存在可比性。三组受试者及其家属均签署了知情同意书,我院伦理委员会已批准。

1.2 研究方法

所有受试者均行阴道彩色能量多普勒超声检查;超声探头

频率为 5.5-7.5MHz,告知受试者排空膀胱,取截石位,在探头上涂抹耦合剂并套上避孕套,随后将探头缓慢置入阴道内直至阴道穹窿部或宫颈表面,然后向横向和纵向等多方位转动探头进行探测。采用二维超声扫查,扫查时记录病灶大小、位置、形态、内部回声等情况,待二维声像图清晰显示后转换成彩色能量多普勒血流显像模式,以观察病灶内部以及周边的血流情况,同时采用脉冲多普勒检查肿瘤内部血流,待血流显像稳定后进行血流各指标(包括收缩期峰流速、舒张期末流速、舒张期末流速)的测量,连续测量 3 个周期,结果取 3 次的平均值,其中阻力指数=(收缩期峰流速-舒张期末流速)/舒张期末流速。采用免疫组织化学法检测三组受试者 VEGF、MVD 表达,具体方式如下:采用链霉素抗生物素蛋白-过氧化酶免疫组化法对所有受试者的组织切片进行染色,一抗为鼠抗人 CD34 单克隆抗体与 VEGF 单克隆抗体,试剂盒购自上海酶联生物科技有限公司。

1.3 判断标准

VEGF 阳性表达的判定标准^[11]:①细胞质中含有棕黄色颗粒的肿瘤细胞即为阳性细胞,选择 10 个高倍的视野,阳性细胞数占比小于 5%为 0 分,5%-25%为 1 分,26%-50%为 2 分,51%-75%为 3 分,大于 75%为 4 分;②染色强度判断:0 分为无染色,1 分为黄色,2 分为棕黄色,3 分为棕褐色;阳性细胞数占比评分与染色评分乘积为总得分。阴性表达:总得分为 0-1 分;阳性表达:总得分为 2-12 分。MVD 评估标准如下^[12]:于低倍镜下检查微血管染色情况,取癌巢间质血管最多的 3 个视野,并在通过高倍镜观察 3 个视野,记录每个视野中的 MVD 值,将 3 次的平均值记为最后结果。

1.4 统计学方法

本研究数据均录入 SPSS20.0 软件进行统计分析,采用($\bar{x} \pm s$)表示计量资料,实施 t 检验,多组间对比采用单因素方差予以分析,采用[n(%)]表示计数资料,实施 χ^2 检验,宫颈癌患者阻力指数与 VEGF 以及 MVD 的关系采用 Spearman 相关性分析,检验水准 $\alpha=0.05$ 。

2 结果

2.1 三组受试者阻力指数、VEGF 表达以及 MVD 值对比

宫颈癌组阻力指数低于宫颈上皮内瘤变组和对照组,且宫颈上皮内瘤变组低于对照组;而宫颈癌组 VEGF 表达与 MVD 值高于宫颈上皮内瘤变组和对照组,且宫颈上皮内瘤变组高于对照组($P<0.05$)。见表 1。

2.2 宫颈癌患者阻力指数与临床病理特征关系分析

病灶直径<40 mm、临床分期 I-II 期、中高分化、无淋巴结转移宫颈癌患者的阻力指数高于病灶直径≥40 mm、临床分期

III-IV 期、低分化、有淋巴结转移宫颈癌患者 ($P<0.05$), 而阻力指数与宫颈前后径、组织学类型无关 ($P>0.05$), 见表 2。

表 1 三组受试者阻力指数、VEGF 表达以及 MVD 值对比

Table 1 Comparison of resistance index, VEGF expression and MVD value of subjects between three groups

Groups	n	Resistance index	Positive expression of VEGF[n(%)]	MVD value
Cervical cancer group	50	0.45± 0.09 ^{#*}	41(82.00) ^{#*}	27.01± 8.25 ^{#*}
Cervical intraepithelial neoplasia group	50	0.55± 0.12 [#]	20(40.00) [#]	11.12± 3.51 [#]
Control group	50	0.80± 0.15	3(6.00)	6.49± 4.15
F	-	11.068	15.392	20.536
P	-	0.000	0.000	0.000

Note: compared with the control group, [#] $P<0.05$; compared with cervical intraepithelial neoplasia group, * $P<0.05$.

表 2 宫颈癌患者阻力指数与临床病理特征关系分析($\bar{x}\pm s$)

Table 2 Relationship between resistance index and clinicopathologic features of patients with cervical cancer($\bar{x}\pm s$)

Clinicopathologic feature	n	Resistance index	t	P
Anteroposterior diameter of the cervix(mm)	<30	0.48± 0.08	1.671	0.101
	≥ 30	0.43± 0.10		
Lesion diamete(mm)	<40	0.51± 0.10	2.601	0.012
	≥ 40	0.42± 0.08		
Clinical stage	I-II stages	0.48± 0.09	5.313	0.000
	III-IV stages	0.32± 0.06		
Histological type	Squamous cell carcinoma	0.46± 0.10	0.799	0.428
	Adenocarcinoma	0.43± 0.03		
Differentiation degree	Low differentiation	0.37± 0.07	4.157	0.000
	Middle and high differentiation	0.49± 0.08		
Lymphatic metastasis	Yes	0.41± 0.07	3.309	0.002
	No	0.50± 0.10		

2.3 宫颈癌患者阻力指数与 VEGF 以及 MVD 的相关性分析 VEGF 以及 MVD 均呈负相关 ($P<0.05$), 见表 3。
经 Spearman 相关性分析可得: 宫颈癌患者阻力指数与

表 3 宫颈癌患者阻力指数与 VEGF 以及 MVD 的相关性分析

Table 3 Correlation analysis of resistance index and VEGF and MVD in patients with cervical cancer

Indexes	Resistance index	
	r	P
VEGF	-0.374	0.000
MVD	-0.485	0.000

3 讨论

近年来,随着人们生活方式以及饮食结构的改变,宫颈癌患者越来越多,已成为严重影响女性生命安全的重要疾病之一^[13,14]。有研究报道显示,在肿瘤生长以及转移的过程中血管形成发挥了重要的作用,并且在其血管前期以及血管期两个阶段中不受任何因素控制^[15,16]。早期有效的治疗对宫颈癌患者的预后具有极其重要的意义,因此寻找一种有效的宫颈癌早期诊断手段成为了目前临床上研究的热点。VEGF 是目前发现的功能最强的促进血管内皮细胞分裂增殖的生长因子,具有诱导血管生

成的作用^[17,18]。而 MVD 是评价肿瘤血管生成的重要指标,亦是判断肿瘤进展以及转移能力的指标^[19,20]。

本研究结果显示,从健康人群到宫颈上皮内瘤变患者再到宫颈癌患者,阻力指数逐渐降低,而 VEGF 表达与 MVD 值逐渐升高,提示了上述三项指标可能与宫颈癌的发生、发展存在密切相关。阻力指数是用以反映血管周围阻力变化的有效指标,且其水平与血流阻力成正比,因此,肿瘤组织血管丰富的区域血流大,血流阻力就小,其阻力指数也相应的处于较低水平^[21,22]。VEGF 是调控实体瘤血管发生以及新生血管形成的因子之一,其合成与分泌主要在肿瘤细胞中,以自身分泌以及旁分

泌途径发挥作用,从而促进新血管的生成,而新血管作用于癌细胞,导致更多数量的癌细胞增殖,并形成恶性循环^[23-25]。已有研究报道表明^[26],在人类多种肿瘤细胞中存在高表达,且其表达与宫颈癌的发生、发展存在密切相关,是独立预测宫颈癌预后的指标之一。MVD 则是用以直接检测肿瘤血管数量的指标,亦是目前临床上用以评估肿瘤血管生成状况的金标准,其表达水平的升高反映了肿瘤进展、转移性较高以及病情更加严重等情况^[27-29]。此外,病灶直径 <40 mm、临床分期 I - II 期、中高分化、无淋巴结转移宫颈癌患者阻力指数均高于病灶直径 ≥ 40 mm、临床分期 III - IV 期、低分化、有淋巴结转移宫颈癌患者,这提示了阻力指数与宫颈癌患者临床病理特征存在密切相关。原因主要与患者的病情进展等因素有关,其中阻力指数反映了肿瘤内血管阻力,因此其可有效反映宫颈癌的血栓生成特征,并且阻力指数属于彩色能量多普勒超声检测血流动力学参数之一,因此在临床上其可能对宫颈癌的诊断、临床分期以及预后评估起着一定的辅助作用^[30]。此外,本研究经 Spearman 相关性分析可得:宫颈癌患者阻力指数与 VEGF 以及 MVD 均呈负相关 ($P < 0.05$)。这提示了在临床工作中,可通过彩色能量多普勒超声检查联合检测 VEGF 表达及 MVD 值,从而有利于宫颈癌的早期诊断,进而为临床治疗方案的制定提供参考依据,以达到改善预后的目的。

综上所述,在彩色能量多普勒超声检查的基础上联合检测 VEGF、MVD 表达,有利于早期诊断宫颈癌,并有助于评估判断患者的病情严重程度。

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