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磁共振成像表观扩散系数与乳腺浸润性导管癌组织学分级及预后指标的相关性研究

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摘要 目的:探讨磁共振成像(MRI)表观扩散系数(ADC)与乳腺浸润性导管癌组织学分级及其预后指标的相关性。方法:收集2016年5月至2017年5月于我院就诊的并经手术病理确诊为乳腺浸润性导管癌的患者112例作为研究对象,选取患者乳腺癌组织样本作为病例组,同时选取患者对侧正常乳腺组织样本作为对照组,所有患者均行常规MRI和磁共振扩散加权成像(DW-MRI)检查,分别测量两组样本的ADC值,比较不同乳腺浸润性导管癌组织学分级与正常乳腺组织的ADC值,分析乳腺浸润性导管癌组织的ADC值与肿瘤直径大小、淋巴结转移状态、有无远处转移及雌激素受体(ER)、孕激素受体(PR)和Ki-67表达的关系,并分析ADC值与组织学分级及预后指标的相关性。结果:乳腺浸润性导管癌病理分级I级的ADC值低于对照组,病理分级II级的ADC值低于病理分级I级及对照组,病理分级III级的ADC值低于病理分级II级、I级及对照组,差异均具有统计学意义($P<0.05$)。乳腺浸润性导管癌患者中,肿块直径 <2 cm、无淋巴结转移、ER阴性、PR阴性、Ki-67阴性患者的平均ADC值均高于肿块直径 ≥ 2 cm、有淋巴结转移、ER阳性、PR阳性、Ki-67阳性患者,差异均具有统计学意义($P<0.05$);而有无远处转移患者之间比较差异无统计学意义($P>0.05$)。经Spearman秩相关分析结果显示,乳腺浸润性导管癌患者的ADC值与病理组织学分级呈现负相关关系($r_s=-0.716, P=0.000$);与肿块直径大小、有无淋巴结转移及ER、PR、Ki-67的表达均呈负相关($r_s=-0.316, -0.545, -0.667, -0.598, -0.443, P$ 均 <0.05),与有无远处转移无相关性($r_s=0.091, P=0.887$)。结论:乳腺浸润性导管癌的ADC值与癌组织学分级和预后相关指标存在一定相关性,可作为一种临床诊断和判断预后的重要指标,具有重要临床价值。

关键词: 磁共振成像;表观扩散系数;乳腺浸润性导管癌;组织学分级;预后

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Correlation Between Apparent Diffusion Coefficient of Magnetic Resonance Imaging and Histological Grade and Prognosis Index of Invasive Ductal Carcinoma of Breast

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ABSTRACT Objective: To investigate the correlation between the apparent diffusion coefficient (ADC) of magnetic resonance imaging (MRI) and histological grade and prognostic index of invasive ductal carcinoma of breast. **Methods:** 112 patients with invasive ductal carcinoma of breast who had been diagnosed by surgery and pathology in our hospital from May 2016 to May 2017 were collected as the subjects, the samples of patients with breast cancer were selected as the case group, the contralateral normal breast tissue samples were selected as the control group. All the patients underwent routine MRI and magnetic resonance diffusion weighted imaging (DW-MRI) examinations, the ADC value of the two groups were measured, the ADC value between different histological grading of invasive ductal carcinoma of breast and normal breast tissue were compared. The relationship between ADC value and tumor diameter, lymph node metastasis, distant metastasis, estrogen receptor (ER), progesterone receptor (PR) and Ki-67 expression in invasive ductal carcinoma of the breast were analyzed, and the correlation between ADC value and histological grade and prognostic index was analyzed. **Results:** The ADC value in the pathological grade I invasive ductal carcinoma of breast were lower than that in the control group, the ADC value in the pathological grade II were lower than that in the pathological grade I and the control group, the ADC value in the pathological grade III were lower than that in the pathological grade II, the pathological grade I and the control group, the differences were statistically significant ($P<0.05$). In patients with invasive ductal carcinoma of breast, the average ADC value of tumor diameter less than 2 cm, without lymph node metastasis, ER negative, PR negative, Ki-67 negative patients were higher than those of the mass diameter over 2 cm, lymph node metastasis, ER positive, PR positive, Ki-67 positive patients, the differences were statistically significant ($P<0.05$); while the difference of ADC value between patients with or without distant metastasis was not statistically significant ($P>0.05$). The Spearman rank correlation analysis results showed that the ADC value of invasive ductal carcinoma patients was negatively correlated with histological grade ($r_s=-0.716, P=0.000$); with tumor diameter, lymph node metastasis, ER, PR, Ki-67 expression were negatively correlated ($r_s=-0.316, -0.545, -0.667, -0.598, -0.443, P$ all <0.05), with distant metastasis was not correlated ($r_s=0.091, P=0.887$). **Conclusion:** The ADC value of invasive ductal carcinoma is correlated with histological grade and prognosis index, which can be used as an important index for clinical diagnosis and prognosis, and has important clinical value.

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05). There was no significant difference between the patients with or without distant metastasis ($P>0.05$). Spearman rank correlation analysis showed that there was negative correlation between ADC value and histopathological grading in invasive ductal carcinoma of the breast ($r_s=-0.716$, $P=0.000$), it was negatively correlated with tumor diameter, lymph node metastasis, and the expression of ER, PR and Ki-67 ($r_s=-0.316$, -0.545 , -0.667 , -0.598 , -0.443 , both $P<0.05$), there was no correlation between the patients with or without distant metastasis ($r_s=0.091$, $P=0.887$). **Conclusion:** The ADC value of invasive ductal carcinoma of breast is relate to the histological grade and prognostic index, it can be used as an important index to judge the clinical diagnosis and prognosis, which has important clinical value.

Key words: Magnetic resonance imaging; Apparent diffusion coefficient; Invasive ductal carcinoma of breast; Histological grade; Prognosis

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前言

乳腺癌是威胁女性健康的常见肿瘤,约占女性恶性肿瘤的1/4,其已经成为社会的重大公共卫生问题^[1,2]。在我国较多地区,乳腺癌的发病率已位居女性恶性肿瘤的首位,而且癌症发生人群呈年轻化的趋势^[3]。浸润性导管癌属于较为常见的乳腺癌,其肿瘤形态各异,且缺乏规律性的结构特征,表现为实性或者伴有合体细胞浸润,经常可见伴随有中央腔系的导管结构^[4,5]。影像学检查是诊断乳腺癌的重要手段,包括超声、CT、磁共振成像(Magnetic Resonance Imaging, MRI)等^[6]。近年来, MRI在诊断乳腺癌上进展迅速,尤其是对致密性的乳腺疾病诊断,而且对乳腺癌的检出率较高,已经成为乳腺方面疾病较为有效的检查方法^[7]。磁共振扩散加权成像(Diffusion Weighted Magnetic Resonance Imaging, DW-MRI)主要观测组织内水分子的布朗运动,不同病理生理状态下的组织密度不同,水分子扩散也不同,因此,利用 DW-MRI 能够直接反映乳腺浸润性导管癌的组织水分子的运动,从而可间接反应组织结构的变化^[8,9]。组织水分子的运动可用表观扩散系数(Apparent Diffusion Coefficient, ADC)来体现,可间接反应乳腺浸润性导管癌的病理分级状态^[10]。乳腺浸润性导管癌的预后因素包括雌激素受体(Estrogen Receptor, ER)、孕激素受体(Progesterone Receptor, PR)、Ki-67, 这些因素的表达水平与乳腺肿瘤的 MRI 表现密切相关^[11,12]。本研究旨在探讨乳腺浸润性导管癌的 ADC 值与其癌组织学分级及预后指标的关系。现报道如下:

1 资料与方法

1.1 一般资料

选取 2016 年 5 月~2017 年 5 月在我院就诊的 112 例经手术病理证实的乳腺浸润性导管癌患者作为研究对象,选取患者乳腺癌组织为病例组,同时选取患者对侧正常乳腺组织为对照组,所有样本穿刺后保存到 -80°C 的环境下。纳入标准:①临床症状、体征、病理活检、MRI 证实为乳腺浸润性导管癌;②病灶形态均为肿块型;③诊断前未实行任何放化疗治疗;④目前未服用任何可能影响研究结果的药物,如己烯雌酚、孕酮。排除标准:①处于妊娠期以及哺乳期的妇女;②心、肝、肾功能不全者;③合并其他良、恶性肿瘤者。112 例女性患者中,年龄 23~69 岁,平均年龄(53.5 ± 7.6)岁。乳腺浸润性导管癌分级采用乳腺癌 Nottingham 联合组织学分系统(SBR 分级系统)进行分级,其中 I 级为低度恶性(12 例),II 级为中度恶性(67 例),III

级为高度恶性(33 例);肿块直径 $\geq 2\text{ cm}$ 的 68 例,肿块直径 $<2\text{ cm}$ 的 44 例;有淋巴结转移 47 例,无淋巴结转移 65 例;有远处转移 55 例,无远处转移 57 例;ER 阳性 50 例,阴性 62 例;PR 阳性 70 例,阴性 42 例;Ki-67 阳性 73 例,阴性 39 例。所有患者均知情同意,本研究符合我院伦理委员会的相关规定,并已获得批准。

1.2 仪器与方法

1.2.1 MRI 扫描 MRI 扫描采用飞利浦公司生产的 Achieva 3.0T 超导型磁共振扫描仪,采用双穴 16 通道的乳腺表面线圈。患者取俯卧位,双乳悬垂于双孔内,行 MRI 扫描,之后行 TSE 序列 T1 加权像(T1WI)扫描以及横断面抑脂加权像(T2WI)扫描。T1WI 参数:回波时间(TR)/重复时间(TE)为 495 ms/10 ms,层厚=4 mm,层间距=0 mm,视野(FOV)=340 mm,矩阵=272×560,信号平均次数(NSA)=1;T2WI 参数:TR/TE 4213ms/120 ms,层厚=4 mm,层间距=0 mm,FOV=340mm,矩阵=272×512,NSA=1。继续动态增强扫描,采用增强 T1 高分辨率各向同性容积采集序列(THRIVE),经前臂静脉高压注射器以 2 ml/s 的速度注入钆喷酸葡胺注射液(0.1 mmol/kg),继续注入 0.9%氯化钠溶液约 20 mL,冲洗导管,扫描 8 次。采用平面回波成像(EPI)技术进行磁共振加权成像扫描,TR/TE 7099/51 ms,层厚=4 mm,层间距=0 mm,FOV=340 mm,矩阵=121×400,NSA=8,b 值分别为 0 和 800 s/mm²。

1.2.2 图像分析及 ADC 测定 使用 Philips Achieva 3.0T 超导型磁共振扫描仪的配套工具 Function Tool 进行图像和数据处理,综合 DW-MRI 图像、多期动态增强图像及 ADC 图,避开肉眼可见的病变,选取病灶最大层面,选取感兴趣区域面积为 30~45 mm²,由两名 5 年以上的放射科医师做质控,测量 3 次,平均值记为该样本的 ADC 值。

1.2.3 免疫组化法 手术病理切取切片组织与人体横轴方位方向一致,病理组织平铺于平片上,采用 10%甲醛溶液进行固定处理,脱水、石蜡包埋后进行连续切片(3 张),采用显微镜进行观察,评估病灶大小、形态、浸润以及病理组织学分级。采用免疫组化法对 ER、PR 和 Ki-67 的表达进行检测。ER、PR 阳性表达位于癌细胞核,呈现棕黄色颗粒为阳性。规定 8%及以上癌细胞核出现棕黄色颗粒记为染色阳性,小于 8%为染色阴性。Ki-67 阳性表达位于癌细胞核,呈现棕黄色颗粒为阳性,规定 10%及以上的癌细胞核出现棕黄色颗粒为染色阳性,小于 10%为染色阴性。

1.3 统计学处理

采用 SPSS 22.0 进行统计分析,ADC 值等计量资料采用均数 $\pm$ 标准差($\bar{x}\pm s$)表示,多组比较采用方差分析,两两比较采用 LSD-t 检验;采用 Spearman 进行相关性分析,以 $\alpha=0.05$ 为检验标准。

2 结果

2.1 不同乳腺浸润性导管癌组织学分级的 ADC 值与正常乳腺组织的比较

对照组的 ADC 值为 $(1.36\pm 0.09)\times 10^{-3}\text{ mm}^2/\text{s}$,病理分级 I 级的 ADC 值为 $(1.22\pm 0.21)\times 10^{-3}\text{ mm}^2/\text{s}$,病理分级 II 级的 ADC 值为 $(0.88\pm 0.14)\times 10^{-3}\text{ mm}^2/\text{s}$,病理分级 III 级的 ADC 值

为 $(0.77\pm 0.19)\times 10^{-3}\text{ mm}^2/\text{s}$,经方差分析,各组间整体比较差异有统计学意义($F=19.889, P=0.003$);经两两比较,病理分级 I 级的 ADC 值低于对照组,病理分级 II 级 ADC 值低于 I 级组及对照组,病理分级 III 级组的 ADC 值低于 II 级组、I 级组及对照组,差异均具有统计学意义($P<0.05$)。

2.2 ADC 值与肿瘤预后指标的关系

肿块直径 $<2\text{ cm}$ 、无淋巴结转移、ER 阴性、PR 阴性、Ki-67 阴性的平均 ADC 值均高于肿块直径 $\geq 2\text{ cm}$ 、有淋巴结转移、ER 阳性、PR 阳性、Ki-67 阳性,差异均具有统计学意义($P<0.05$)。而有无远处转移之间比较差异无统计学意义($P>0.05$)。见表 1。

表 1 不同乳腺浸润性导管癌预后指标 ADC 值的比较($\bar{x}\pm s$)
Table 1 Comparison of prognostic values of ADC for different invasive ductal carcinoma of breast($\bar{x}\pm s$)

	Groups	n	Average ADC value ($\times 10^{-3}\text{ mm}^2/\text{s}$)	t	P
Tumor diameter	$<2\text{ cm}$	44	1.25 ± 0.12	7.096	0.000
	$\geq 2\text{ cm}$	68	0.88 ± 0.13		
Lymph node metastasis	No	65	1.17 ± 0.16	6.440	0.000
	Yes	47	0.91 ± 0.22		
Distant metastasis	No	57	0.96 ± 0.13	1.365	0.175
	Yes	55	0.93 ± 0.10		
ER	Negative	62	1.02 ± 0.09	15.992	0.000
	Positive	50	0.90 ± 0.12		
PR	Negative	42	1.12 ± 0.10	9.417	0.000
	Positive	70	0.90 ± 0.13		
Ki-67	Negative	39	0.99 ± 0.11	3.876	0.000
	Positive	73	0.91 ± 0.12		

2.3 ADC 值与组织学分级和预后指标的相关性分析

乳腺浸润性导管癌患者 ADC 值与病理组织学分级呈现负相关关系($r_s=-0.716, P=0.000$);与预后指标包括肿块直径大小、有无淋巴结转移及 ER、PR、Ki-67 的表达均呈负相关($r_s=-0.316, -0.545, -0.667, -0.598, -0.443, P$ 均 <0.05),与有无远处转移无相关性($r_s=0.091, P=0.887$)。

3 讨论

乳腺癌是对女性健康构成巨大威胁的恶性肿瘤之一,其发病率不断上升,且趋于年轻化。目前乳腺癌的病因尚未阐明,临床防治策略主要依靠早发现、早诊断、早治疗的方式,以提升患者的预后生存质量^[13,14]。随着医学影像技术的不断发展,为早期发现和诊断乳腺癌带来了新的策略和方向。DW-MRI 技术是近年来应用于临床的影像技术,可通过微小分子水平反应人体组织在病理和生理状态下的结构变化,而且对于人体是无创性的^[15,16]。DW-MRI 技术的应用使得对人体成像的研究细化深入到微观世界,通过 DW-MRI 技术可测量施加的扩散敏感梯度场附近组织信号变化的强度,间接反映人体细胞水分子扩散运动的方向与程度,不同组织结构的水分子运动不同,进而通过水

分子运动变化,判断人体不同组织的微观结构变化以及生理病理状态^[17,18]。通常可根据 ADC 值来定量测量组织的水分子扩散,因此,其值的大小也可以反应组织的微观改变情况。在细胞膜较为完整、细胞密度大、细胞外间质少、组织液压力较高的组织内部,水分子运动较为局限,如肿瘤组织^[19]。DW-MRI 扫描肿瘤组织时,信号增高,造成 ADC 值降低,扫描时应当尽量避免坏死、液化区等区域,尽量降低组织的容积效应^[20]。其次,含有较高扩散加权因子的仪器,也能减弱组织内部对仪器的影响,如选择 3.0T 的 MRI 较 1.5T 的 MRI 效果更好,对肿瘤的早期鉴别也更为有利^[21,22]。最后,不同恶性程度的肿瘤组织,其细胞各种内外环境和细胞密度也存在差异,进而导致水分子扩散运动所有不同,其 ADC 也各异,可依此判断肿瘤不同的病理组织分级以及恶性程度^[23]。

本研究结果显示,肿瘤组织学分级越高的组织,其 ADC 值越低($P<0.05$)。由于在恶性程度越高的组织中,肿瘤数目多,细胞密度增大,细胞器增多,细胞核大分裂增多,导致水分子扩散运动较恶性程度低的组织弱,因此 ADC 值更低,这与于学娟等人^[24]的研究结论一致。而且本研究相关性分析提示,组织学分级与 ADC 值呈现负相关,与 Razek 等^[25]人的研究一致。本研究

结果还提示,肿块直径 <2 cm、无淋巴结转移、ER 阴性、PR 阴性、Ki-67 阴性的平均 ADC 值均高于肿块直径 ≥ 2 cm、有淋巴结转移、ER 阳性、PR 阳性、Ki-67 阳性($P < 0.05$),且进一步研究发现,ADC 值与肿块直径大小、有无淋巴结转移及 ER、PR、Ki-67 的表达均呈负相关($P < 0.05$),提示根据 ADC 的数值大小可对肿瘤预后进行评估。乳腺的生理变化受 ER、PR 调控,因此测量这两者的表达水平也可间接反映乳腺功能的变化,ER、PR 表达阳性者,细胞密度通常较高,ADC 值相对小^[26,27];Ki-67 属于增殖细胞相关核抗原,其表达水平与乳腺浸润癌导管癌的预后密切相关,表达水平越高,ADC 值越小,乳腺癌复发可能性大,扩散的可能性越大,患者生存期越短^[28,29]。谢宗玉等^[30]人研究发现乳腺浸润性导管癌患者的 ADC 值与病理组织分级、肿块直径大小、有无淋巴结转移、Ki-67 均无关,本研究结果与其结果不同。结果差异性可能是地区不同导致纳入的组织学样本不同,以及不同的 MRI 仪器导致测量的灵敏度不一样,又或是不同的试验测量方法导致免疫组化结果不一致所致。

综上所述,乳腺浸润性导管癌患者的组织学分级、肿瘤大小、淋巴结转移及 ER、PR、Ki-67 表达等变化可导致 ADC 值不同,通过定量测量乳腺浸润性导管癌患者早期 ADC 值,对于早期临床分型诊断以及判断患者的预后都有重要临床价值。

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