

钆塞酸二钠磁共振成像表观弥散系数值联合最大强化率鉴别肝硬化背景下不典型增生结节与小肝癌

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摘要: 目的 探讨钆塞酸二钠磁共振成像(magnetic resonance imaging, MRI)表观弥散系数(apparent diffusion coefficient, ADC)联合增强血管期病灶最大强化率(maximum enhancement rate, ER_{max})鉴别诊断肝硬化背景下不典型增生结节(dysplastic nodule, DN)与小肝癌(small hepatocellular carcinoma, sHCC)的价值。方法 回顾性分析2016年1月至2019年9月在南京市第二医院就诊、具有肝硬化背景并经术后病理或肝组织活检确诊的33例sHCC和24例DN患者的MRI平扫+扩散加权成像(diffusion weighted imaging, DWI)+钆塞酸二钠增强图像。对患者图像进行编号,采用两种方法盲法阅片。首先使用方法一(MRI平扫+DWI+增强血管期)进行诊断,打乱顺序后相隔2周再使用方法二(方法一+增强肝胆期)进行诊断,计算两种方法的敏感性、特异度和正确率。测量两组患者病灶ADC值和ER_{max},采用受试者工作特征(receiver operator characteristic, ROC)曲线分析ADC值、ER_{max}及ADC+ER_{max}的鉴别诊断效能。结果 方法二的敏感性(90.9% vs 69.7%)和正确率(89.5% vs 71.9%)均显著高于方法一($\chi^2 = 4.694$, $P = 0.030$; $\chi^2 = 5.632$, $P = 0.018$),特异度(87.5% vs 75.0%)差异无统计学意义($\chi^2 = 1.231$, $P = 0.267$)。sHCC患者病灶ADC值显著低于DN患者[(1.24 ± 0.21) × 10⁻³ mm²/s vs (1.54 ± 0.19) × 10⁻³ mm²/s], ER_{max}显著高于DN患者[(79.03 ± 18.22)% vs (49.52 ± 15.16)%],差异均有统计学意义($t = -5.835$, $P < 0.001$; $t = 6.620$, $P < 0.001$)。病灶ADC值、ER_{max}及ADC+ER_{max}鉴别sHCC和DN的曲线下面积分别为0.851、0.895和0.950,约登指数分别为0.543、0.657和0.771。ADC+ER_{max}联合鉴别诊断sHCC的特异度(97.1% vs 75.0%)显著高于方法一($\chi^2 = 13.917$, $P < 0.001$),敏感性(80.0% vs 69.7%)差异无统计学意义($\chi^2 = 1.508$, $P = 0.219$);与方法二相比,敏感性(80.0% vs 90.9%)和特异度(97.1% vs 87.5%)差异均无统计学意义($\chi^2 = 2.065$, $P = 0.151$; $\chi^2 = 3.794$, $P = 0.051$)。结论 MRI钆塞酸二钠增强肝胆期图像有利于提高sHCC的诊断效能。对于无肝细胞特异性对比剂的医疗单位,采用ADC值联合血管期强化的ER_{max}可达到与之相近的鉴别诊断效能。

关键词: 磁共振; 钆塞酸二钠; 表观弥散系数; 小肝癌; 不典型增生结节

Apparent diffusion coefficient values combined with maximum enhancement rate in gadoxetate disodium magnetic resonance imaging to identify dysplastic nodule and small hepatocellular carcinoma in the context of liver cirrhosis

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Abstract: Objective To evaluate the value of apparent diffusion coefficient (ADC) values combined with maximum enhancement rate (ER_{max}) in gadoxetate disodium magnetic resonance imaging (MRI) on identifying dysplastic nodule (DN) and small hepatocellular carcinoma (sHCC) in the context of liver cirrhosis. **Methods** The MRI + diffusion weighted imaging (DWI) + gadoxetate disodium enhanced images of patients with sHCC (33 cases) and patients with DN (24 cases) who were confirmed by pathology or biopsy in the Second Hospital of Nanjing from January 2016 to September 2019 were retrospectively analyzed. The

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patients were all in the context of liver cirrhosis. The images of patients were numbered and read blindly by two methods. Firstly, method 1 (non-enhanced MRI + DWI + enhanced vascular phases images) was used to diagnose, secondly, the order of the images were shuffled and after two weeks method 2 (method 1 + enhanced hepatobiliary phase images) was used to diagnose. The sensitivity, specificity and accuracy of the two methods were calculated. ADC value and ER_{max} of lesions in the two groups were measured. The receiver operating characteristic (ROC) curve was used to analyze the differential diagnostic efficacy of ADC value, ER_{max} and ADC + ER_{max} . **Results** The sensitivity (90.9% vs 69.7%) and accuracy (89.5% vs 71.9%) of method 2 were significantly higher than those of method 1 ($\chi^2 = 4.694, P = 0.030$; $\chi^2 = 5.632, P = 0.018$), the differences of specificity (87.5% vs 75.0%) was not statistically significant ($\chi^2 = 1.231, P = 0.267$). ADC value $[(1.24 \pm 0.21) \times 10^{-3} \text{ mm}^2/\text{s}$ vs $(1.54 \pm 0.19) \times 10^{-3} \text{ mm}^2/\text{s}]$ of lesions in patients with sHCC was lower and ER_{max} $[(79.03 \pm 18.22)\%$ vs $(49.52 \pm 15.16)\%]$ was higher than those with DN, and the differences were statistically significant ($t = -5.835, P < 0.001$; $t = 6.620, P < 0.001$). The area under the curve of ADC value, ER_{max} and ADC + ER_{max} in the identification of sHCC and DN were 0.851, 0.895 and 0.950, and the Youden index were 0.543, 0.657 and 0.771, respectively. The specificity of ADC + ER_{max} in the identification of sHCC was significantly higher than that of method 1 (97.1% vs 75.0%, $\chi^2 = 13.917, P < 0.001$), and the difference of sensitivity was not statistically significant (80.0% vs 69.7%, $\chi^2 = 1.508, P = 0.219$). There were no significant differences in sensitivity (80.0% vs 90.9%) and specificity (97.1% vs 87.5%) compared with method 2 ($\chi^2 = 2.065, P = 0.151$; $\chi^2 = 3.794, P = 0.051$). **Conclusions** The gadoxetate disodium hepatobiliary phase images of enhanced MRI is beneficial to increase the diagnostic efficiency of sHCC. ADC combined ER_{max} of enhanced vascular phases MRI can achieve the similar diagnostic efficacy for hospitals without hepatocellular specific contrast agents.

Key words: Magnetic resonance; Gadaxetate disodium; Apparent diffusion coefficient; Small hepatocellular carcinoma; Dysplastic nodule

肝细胞癌 (hepatocellular carcinoma, HCC) 是最常见的肝脏原发肿瘤, 病死率高, 早期诊断和治疗对改善预后至关重要^[1-3]。直径较大的HCC常具有典型的影像学表现, 诊断较为明确。但直径 ≤ 2 cm的小肝细胞癌 (small hepatocellular carcinoma, sHCC) 影像学表现常不典型, 且多数继发于肝硬化, 常与不典型增生结节 (dysplastic nodule, DN) 表现相混淆, 进一步增加了诊断难度^[4-8]。钆塞酸二钠是肝细胞特异性对比剂, 用于肝脏占位性疾病, 具有常规对比剂的血管期强化和特异性肝胆期表现^[9-12]。钆塞酸二钠增强有利于提高sHCC的诊断效能^[13-15]。目前钆塞酸二钠在部分大型医院已用于临床, 但因其成本较高, 尚未在全国多数医院中普及。本研究对确诊的DN和sHCC患者磁共振成像 (magnetic resonance imaging, MRI) 结果进行回顾性分析, 通过对病灶表观弥散系数 (apparent diffusion coefficient, ADC) 和增强血管期最大强化率 (maximum enhancement rate, ER_{max}) 的联合分析探讨其鉴别诊断效能。

1 资料与方法

1.1 研究对象 回顾性分析2016年1月至2019年9月在南京市第二医院就诊、具有肝硬化背景并经术后病理或肝组织活检确诊的33例sHCC和24例DN患

者的MRI平扫+扩散加权成像 (diffusion weighted imaging, DWI) + 钆塞酸二钠增强图像。所有患者磁共振检查前均签署知情同意书, 该研究获本院伦理委员会批准 (批准文号: 2015120531)。

1.2 纳入和排除标准 纳入标准: ①具有肝硬化背景, 单个病灶直径 ≤ 2.0 cm, 同一患者两病灶直径之和 ≤ 3.0 cm; ②MRI检查前尚未针对病灶进行药物或介入治疗; ③MRI检查后, 病灶均有术后病理或肝组织活检的明确诊断; ④患者或授权家属签署知情同意书。排除标准: 患者配合不佳, 图像伪影重。

1.3 检查方法 采用GE Signa Pioneer 3.0 T MRI (美国) 扫描仪, 8通道腹部线圈和呼吸门控技术。检查前患者均禁食6 h以上, 扫描前对患者进行呼吸配合训练, 取仰卧体位, 扫描范围包括全部肝组织。MRI平扫包括横断位 T_2 WI压脂 (TR 4000 ms, TE 72 ms)、横断位 T_1 WI (TR 128 ms, TE 5 ms)、冠状位 T_2 WI (TR 2800 ms, TE 80.1 ms)。DWI序列采用横断位扫描, b 值= $0.800 \text{ s}/\text{mm}^2$, TR 7244 ms, TE 100 ms, 矩阵 128×128 , 层厚5 mm, 层间距1 mm, 扫描时间131 s。增强扫描采用横断位或冠状位扫描, 参数如下: TR 4.7~5.1 ms, TE 1.9~2.3 ms, 层厚4.5 mm, 无间隔扫描, 矩阵 288×192 ; 使用

专用双通高压注射器经患者肘前静脉以2.5 ml/s注射0.025 mmol/kg钆塞酸二钠(德国拜耳医疗保健有限公司),注射完毕后再以相同流率注射生理盐水15 ml冲洗。注入对比剂后15~20 s进行动脉期扫描,50~60 s时门静脉期扫描,90~120 s时平衡期扫描,20 min时行肝胆期扫描。

1.4 图像分析处理 图像数据导入PACS阅片系统及MRI自带后处理工作站。对患者图像进行编号(隐藏患者姓名和病理活检结果),采用以下2种方法盲法阅片,首先使用方法一(MRI平扫+DWI+增强血管期)阅片并记录诊断结果,相隔2周将图像顺序打乱后再使用方法二(方法一+增强肝胆期)阅片并记录诊断结果,计算两种诊断方法的敏感性、特异度和正确率。阅片由两位高年资主治医师分别进行,对同一编号图像诊断不一致时,由另一位副主任医师判定。ADC图由DWI序列自动重建。感兴趣区(region of interest, ROI)在病灶最大层面图像选取,保持圆形或椭圆形,根据病灶大小尽量包全病灶,ROI为0.5~2 cm²,尽量避开胆管、血管、出血、坏死、囊变、脂肪和各种伪影,测量sHCC和DN病灶的ADC值和钆塞酸二钠增强血管期的ER_{max}。同一患者ROI保持一致,并测量2次取均值。两位医师分别按照上述方案测量后取均值用于最终的数据分析。根据病灶不同时期MRI图像信号强度(signal intensity, SI)计算ER_{max}。公式如下:

$$ER_{\max} = (SI_{\text{增强}} - SI_{\text{平扫}}) / SI_{\text{平扫}} \times 100\%$$
, SI_{增强}取增强血管期中最高的SI。

1.5 统计学处理 使用SPSS 20.0软件进行数据分析,年龄、ADC和ER_{max}为计量资料,符合正态分布,以 $\bar{x} \pm s$ 表示,两组间比较采用独立样本 t 检验。性别、敏感性、特异度及正确率等计数资料以例数和百分数表示,采用 χ^2 检验。采用受试者工作特征(receiver operating characteristic, ROC)曲线分析ADC值、ER_{max}及ADC + ER_{max}的鉴别诊断效能。采用MedCalc 18.9软件对组间ROC曲线下面积(area under the curve, AUC)进行 z 检验。以 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 一般资料 33例sHCC患者中男性19例,女性14例,年龄(59.76 ± 10.91)岁(37~75岁),其中2例患者有2个病灶,共计35个病灶;24例DN患者中男性11例,女性13例;年龄(62.96 ± 10.14)岁(41~79岁),其中1例患者有2个病灶,共计25个病灶。两组患者性别构成比和年龄差异无统计学意义($\chi^2 = 0.768$, $P = 0.381$; $t = -1.126$, $P = 0.265$)。57例患者中48例患者有乙型肝炎肝硬化病史,6例患者有乙型肝炎合并丙型肝炎肝硬化病史,3例患者有酒精性肝硬化病史。

2.2 2种方法盲法阅片的诊断效能 sHCC典型MRI表现见图1。两种方法盲法阅片的诊断结果表1。方

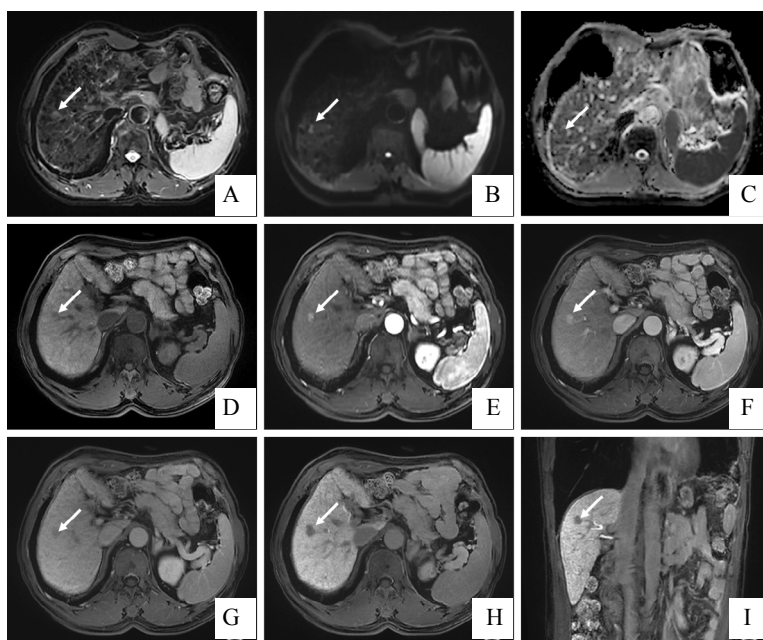


图1 某伴肝硬化病史sHCC男性患者(62岁)的MRI图像

注:肝右前叶上段小结节样异常信号,病灶长径约1.3 cm,边界欠规整。T₂压脂(A)序列病灶呈高信号,DWI(B)序列呈病灶高信号,相应ADC图(C)呈低信号,T1压脂(D)序列病灶呈低信号,增强动脉期(E)病灶明显强化,增强门脉期(F)病灶明显强化,增强平衡期(G)病灶强化信号明显减低(低信号),增强肝胆期(H和I)病灶呈明显低信号

法一(MRI平扫+DWI+增强血管期)诊断sHCC的敏感性、特异度和正确率分别为69.7%(23/33)、75.0%(18/24)和71.9%(41/57);方法二(MRI平扫+DWI+增强血管期和肝胆期)诊断sHCC的敏感性、特异度和正确率分别为90.9%(30/33)、87.5%(21/24)和89.5%(51/57)。方法二的敏感性和正确率均显著高于方法一($\chi^2 = 4.694$, $P = 0.030$; $\chi^2 = 5.632$, $P = 0.018$), 特异度差异无统计学意义($\chi^2 = 1.231$, $P = 0.267$)。

2.3 两组患者病灶ADC值和ER_{max} sHCC患者病灶ADC值显著低于DN患者, ER_{max}显著高于DN患者, 差异均有统计学意义($t = -5.835$, $P < 0.001$; $t = 6.620$, $P < 0.001$), 见表2。

2.4 病灶ADC值和ER_{max}的鉴别诊断效能 病灶ADC值、ER_{max}及二者联合(ADC + ER_{max})鉴别诊断sHCC和DN效能见表3, ROC曲线见图2。病灶ADC值和ER_{max}联合鉴别sHCC和DN的约登指数为0.771, 高于ADC值和ER_{max}单独诊断的约登指数(0.543、0.657)。病灶ADC值和ER_{max}鉴别sHCC和DN的AUC差异无统计学意义($z = 0.732$, $P = 0.464$); 病灶ADC值+ ER_{max}的AUC显著高于ADC值和ER_{max}, 差异有统计学意义($z = 2.515$,

$P = 0.012$; $z = 2.212$, $P = 0.046$)。ADC + ER_{max}联合鉴别诊断sHCC的特异度显著高于方法一($\chi^2 = 13.917$, $P < 0.001$), 敏感性差异无统计学意义($\chi^2 = 1.508$, $P = 0.219$); 与方法二相比, 敏感性和特异度差异均无统计学意义($\chi^2 = 2.065$, $P = 0.151$; $\chi^2 = 3.794$, $P = 0.051$)。

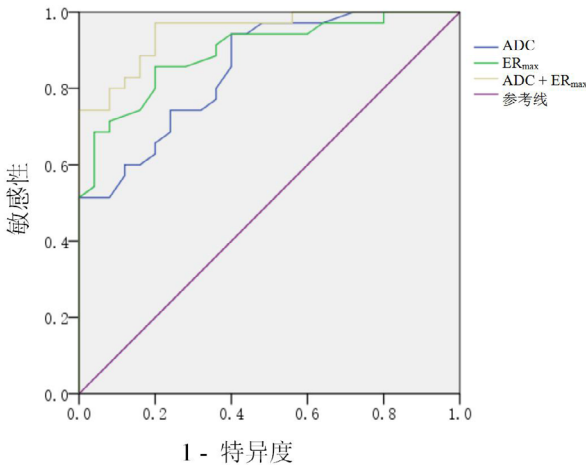


图2 病灶ADC值、ER_{max}及两者联合鉴别诊断sHCC和DN的ROC曲线

表1 两种方法盲法阅片的诊断结果(例)

项目	病理结果		合计		项目	病理结果		合计
	sHCC	DN				sHCC	DN	
方法一					方法二			
sHCC	23	6	29		sHCC	30	3	33
DN	10	18	28		DN	3	21	24
合计	33	24	57		合计	33	24	57

注: 方法一为MRI平扫+DWI+增强血管期, 方法二为方法一+增强肝胆期; sHCC为小肝细胞癌, DN为不典型增生结节

表2 sHCC患者和DN患者病灶ADC值和ER_{max}($\bar{x} \pm s$)

组别	例数	ADC ($\times 10^{-3} \text{ mm}^2/\text{s}$)	ER _{max} (%)
sHCC组	33	1.24 ± 0.21	79.03 ± 18.22
DN组	24	1.54 ± 0.19	49.52 ± 15.16
t值		-5.835	6.620
P值		< 0.001	< 0.001

注: sHCC为小肝细胞癌; DN为不典型增生结节; ADC为表观弥散系数, ER_{max}为最大强化率

表3 ADC值、ER_{max}及二者联合(ADC + ER_{max})鉴别诊断sHCC和DN的效能

指标	AUC	95%CI	诊断阈值	敏感性(%)	特异性(%)	约登指数	P值
ADC ($\times 10^{-3} \text{ mm}^2/\text{s}$)	0.851	0.758~0.945	1.52	60.0	94.3	0.543	< 0.001
ER _{max} (%)	0.895	0.817~0.973	63.50	80.0	85.7	0.657	< 0.001
ADC + ER _{max}	0.950	0.900~0.999	-	80.0	97.1	0.771	< 0.001

注: ADC为表观弥散系数, ER_{max}为最大强化率

3 讨论

70%~90%的HCC发生于慢性肝病及由此发展而来的不同程度的肝脏纤维化或肝硬化背景下,往往是从再生结节逐渐转变为低级别DN、高级别DN,再形成sHCC后最终发展而来^[16-19]。HCC的早期诊断及治疗对延长患者生存期和提高患者生活质量至关重要。较大的HCC常具有较为典型的“快进快出”影像学表现,MRI平扫序列具有高组织分辨率,结合DWI序列的弥散受限和对比剂增强序列显示出病灶特征性的血管期强化表现,通常可明确诊断。然而有研究表明,对于肝硬化背景下直径 ≤ 2 cm的sHCC,仅30%~40%的病灶具有典型的血管期强化表现,诊断较困难^[20]。本研究中方法一阅片采用了MRI平扫+DWI+增强血管期图像,诊断sHCC的敏感性、特异度和正确率均欠佳,提示通过常规血管期强化表现诊断直径 ≤ 2 cm的sHCC较困难,与上述研究结论基本符合^[5,8,20]。

肝细胞特异性对比剂钆塞酸二钠可提高肝硬化背景下直径 ≤ 2 cm的具有不典型影像学表现sHCC的诊断效能^[9,12,21-23]。本研究中方法二在方法一的基础上增加了增强肝胆期图像的阅片,与方法一相比,诊断sHCC的敏感性、特异度和正确率均有所提高,提示钆塞酸二钠肝胆期可提高sHCC诊断效能,但诊断敏感性、特异度及正确率均不能达100%,这与兰红琳等^[24]报道的并非所有sHCC在肝胆期都能表现为典型的低信号,同样并非肝胆期低信号小结节就一定是sHCC的结论一致。Golfieri等^[25]研究表明,在DN发展为低分化HCC的过程中,对钆塞酸二钠的摄取能力逐渐下降,亦有5%~10%的HCC会出现异常摄取,在肝胆期表现为等信号或高信号,同样也有DN表现为低信号,该结论与本文结果相符。

钆塞酸二钠价格较高,在一定程度上限制了其使用,仅在某些较大型三甲医院内可常规使用,未能在全国所有医院普及。MRI钆塞酸二钠增强不仅具有常规对比剂的血管期强化图像,还可得到特异性肝胆期图像。本研究通过比较增强血管期病灶 ER_{max} 和ADC值与方法一和方法二诊断sHCC的效能发现,ADC+ ER_{max} 可达到常规MRI平扫+DWI+增强血管期联合肝胆期图像的诊断效能,为不能普及钆塞酸二钠对比剂的医疗单位提供了一个可能,通过测定病灶ADC值和增强血管期图像 ER_{max} 可实现类似于常规MRI平扫+DWI+钆塞酸二钠增强血管期和肝胆期的诊断效果。

本文不足之处在于:①病灶ROI选取时不可避免参杂部分主观性,测量结果可能受影响,在研究

过程中已通过两位影像科医师分别放置ROI,且同一患者测2次取均值,两位阅片者结果再取均值用于最终的数据分析,以尽可能减小误差;②钆塞酸二钠对比剂使用剂量低于常规对比剂,可能对病灶增强信号和量化的 ER_{max} 有一定影响,可在未来研究中进一步探讨,但钆塞酸二钠与常规对比剂对于病灶在血管期的强化规律和特征是一致的,因此研究结果具有一定的推广应用潜力;③本文只针对sHCC和DN两种病变的鉴别诊断,对于其他种类小病变的鉴别诊断价值需进一步研究。

综上,MRI钆塞酸二钠增强肝胆期图像有利于提高sHCC的诊断效能。对于无肝细胞特异性对比剂的医疗单位,通过ADC值联合血管期强化的 ER_{max} 可达到与之相近的鉴别诊断效能。

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