·专家述评·

童彤，副主任医师，复旦大学附属肿瘤医院放射诊断科主任助理。2003年毕业于复旦大学临床医学系，2008年获复旦大学影像医学与核医学博士学位，2014年在美国斯隆-凯特琳癌症中心胃肠影像组做访问学者。以第一责任人承担多项省部级及局级科研基金项目研究。在国内外核心期刊发表学术论文20余篇，其中SCI收录期刊发表学术论文7篇。目前担任上海市医学会放射学专科分会青年学组委员，并兼任《放射学实践》杂志审稿专家。

MRI新技术在评估结直肠癌肝转移中的应用

张　换，童　彤
复旦大学附属肿瘤医院放射科，复旦大学上海医学院肿瘤学系，上海 200032

【摘要】 多层螺旋CT是评估结直肠癌肝转移最常用的影像学技术。与CT相比，MRI具有较高的软组织对比度，特别是引入扩散加权成像、动态增强、肝胆特异性对比剂等成像新技术后，MRI在肝转移灶评价中的优势愈加明显。该文综述了MRI新技术的基本原理、主要功能学参数及其在结直肠癌肝转移评价中的应用。

【关键词】 结直肠癌肝转移；磁共振成像；扩散加权成像；动态增强；肝胆特异性对比剂

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Application of new magnetic resonance technologies in assessment of colorectal liver metastases

ZHANG Huan, TONG Tong (Department of Radiology, Fudan University Shanghai Cancer Center; Department of Oncology, Shanghai Medical College, Fudan University, Shanghai 200032, China)
Correspondence to: TONG Tong E-mail: t983352@126.com

【Abstract】 Multidetector CT is used to be the most common imaging technology in the evaluation of colorectal liver metastases. The heightened soft-tissue resolution provided by magnetic resonance (MR) imaging makes it a potential problem-solving tool in the assessment of colorectal liver metastases, particularly with the introduction of new imaging technologies, such as diffusion weighted imaging (DWI), hepatocyte-specific contrast-enhanced MR imaging, dynamic contrast-enhanced MRI (DCE-MRI), and so on. In this paper, their basic principles, main function parameters, and applications in the evaluation of colorectal liver metastases are reviewed.

【Key words】 Colorectal liver metastasis; Magnetic resonance imaging; Diffusion weighted imaging; Dynamic contrast-enhanced magnetic resonance imaging; Hepatocyte-specific contrast agent

结直肠癌是常见恶性肿瘤之一。2015年中国癌症数据调查显示，结直肠癌发生率在男性、女性中分别居第5和第4位，死亡率在所有癌症相关死亡中居第5位[1]。Siegel等[2]预测2016年结直肠癌以男女人群中各8%的发生率位列第三大常见肿瘤。转移是影响患者预后的不良因素，肝脏则是结直肠癌最常发生转移的器官，超过一半的患者发生同时或异时性肝转移[3]。肝转移灶的手术切除可显著提高患者的生存率，但目前只有少数结直肠癌肝转移患者可实现根治性手术切

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通信作者：童彤　E-mail：t983352@126.com

除[4-5]。对于不可切除和广泛扩散的患者来说，其主要治疗方式是姑息性化疗。影像学技术可帮助评价病灶数量、大小及位置分布，从而判断可切除性，评估治疗反应及监测复发，在结直肠癌肝转移患者病情评估中起着十分重要的作用。

多层螺旋CT是最常用于结直肠癌肝转移灶检出和评估的影像学方法[6]。在肝脏脂肪浸润情况下，CT对转移灶的检出很困难，而患者化疗后并发脂肪肝及脂肪性肝炎是其常见不良反应[7-8]。CT平扫和增强图像上肝实质背景密度取决于脂肪浸润程度而相应降低，使少血管肝转移灶的检出大打折扣[9]。不仅如此，CT所应用的传统实体瘤评价标准主要是基于肿瘤形态学变化，并不能良好反映病灶的病理学反应[10]，而治疗后与患者预后息息相关的正是转移灶中残活肿瘤细胞的存在[11]。

MRI技术可多参数、多序列、多方位成像，具有较高的软组织对比度和良好的空间分辨率。研究表明，对于新辅助化疗后并发肝脂肪变时结直肠癌肝转移灶的检出，MRI以明显的统计学差异优于多层螺旋CT，特别是对小病灶(≤1 cm)的检出[9, 12]。尤其在引入动态增强MRI (dynamic contrast-enhanced MRI，DCE-MRI)和扩散加权成像(diffusion weighted imaging，DWI)等功能学成像方式后，MRI在结直肠癌肝转移影像学评估中的优势更加明显[13-15]。

1 DWI在评价结直肠癌肝转移中的应用

DWI的显像原理是基于水分子的自由扩散，亦即布朗运动。但在活体生物组织中，由于细胞外微体系结构、主动运输机制及微血管循环等因素，水分子扩散得以缓慢进行。这种水分子自由扩散的限制性合成效应在DWI中以表观扩散系数(apparent diffusion coefficient，ADC)来定量显示。研究发现，结直肠癌肝转移灶的早期ADC值变化可预测治疗效果[16-17]。其中，治疗无效组较治疗有效组有更高的ADC均值，且有效组的治疗后ADC值较治疗前明显升高，最早出现于化疗3~7 d后，早于瘤体的大小变化。Wagner等[18]进一步以结直肠癌肝转移患者治疗后的病理学结果作为参照，发现转移灶外周部位(残活肿瘤细胞主要存在部位)的ADC值随着病理学反应不同而差异很大，绝大部分病理缓解组的均值为1.749，显著高于局部性病理缓解组(1.346；P=0.013)及病理无缓解组(1.398；P=0.013)。

组织DWI信号衰减除取决于水分子扩散外，还受微循环血流灌注的影响，基于随b值呈线性衰减的DWI模型(即单指数模型)会导致组织ADC值偏高[19-21]。因此，DWI单指数模型过于简单，不能真实反映生物组织的复杂结构及其分子的运动情况。体素内不相干运动(intravoxel incoherent motion，IVIM)双指数模型是描述DWI信号非单指数衰减最常用的模型。IVIM双指数模型基于非高斯扩散理论，可描述组织非高斯扩散特性，反映扩散的两种成分，即单纯水分子扩散和灌注相关扩散，较普通单指数模型能更好地拟合DWI上影像信号衰减，量化相关参数，揭示组织异质性，反映组织病理生理学的微观变化。IVIM-DWI通过较大范围内的多b值相结合，包括低b值(<200 s/mm^2)和高b值(≥200 s/mm^2)，不仅限于计算ADC值，更可真实衡量水分子扩散和微循环灌注的各自影响，并由此衍生出自由水分子扩散参数(D)、灌注参数(D*)及灌注分数(f)。ADC值较其他参数更利于对肝脏病灶进行定性[22]。Chiaradia等[23]研究发现，结直肠癌肝转移灶的f值明显小于周围正常肝组织(P<0.001)，以病理学作为参照标准发现病灶坏死比例与ADC、D值正相关。Granata等[24]发现，灌注参数f与病灶的血管靶向药物治疗反应具有统计学相关性，提出f值治疗前后下降54%可作为评价结直肠癌肝转移治疗有效的生物学指标，灵敏度和特异度分别为62%和93%。

2 MRI肝胆特异性造影剂在评价结直肠癌肝转移中的应用

MRI对比剂有钆类、铁类、锰类等，大多通过肾脏排泄，极少数可被肝细胞摄取并通过肝胆系统排泄。传统的非特异性细胞外钆对比剂如钆喷酸葡胺(gadolinium-diethylenetriamine pentaacetic，Gd-DTPA)在肝脏分布无特异性，静脉注射后迅速分布于全身血管系统，随后弥漫至细胞外间隙，主要反映组织血液供应状态，通过多时相扫描动态观察肝内病灶强化方式的演变过程。结直肠癌肝转移灶是典型的少血供病灶，在

动脉期呈等信号或稍低信号，门静脉期病灶显示最明显，呈环状强化，平衡期对比剂退出显示低信号或中心等信号[1]。

能通过肝胆系统代谢的对比剂即肝胆特异性对比剂，正在逐步取代传统性对比剂，在肝脏肿瘤对比剂中占主要地位[25]。其一方面具有与Gd-DTPA相似的细胞外代谢过程，能提供与前者类似的多期动态增强扫描图像，另一方面则优先被有功能的肝细胞摄取并随后分泌入胆管，在延迟一定时期后出现肝实质和胆管系统的特异性强化。静脉注射后，这些对比剂有双相增强模式，第一相随注射立即发生，延迟相则发生在10~120 min内[26]。病灶对对比剂的吸收程度间接反映病灶内细胞学特性，特别是对于肝转移患者来说，其肝功能多数是正常的，鉴于肝转移灶对肝特异性对比剂的较少摄取，其肝胆特异性增强相的信号强度会明显低于正常肝实质背景信号，十分有利于转移灶的检出[28]。目前，常用的两种肝胆特异性对比剂分别是钆塞酸(gadolinium-ethoxybenzyl-diethylenetriamine pentaacetic acid，Gd-EOB-DTPA)和钆贝葡胺(gadobenate dimeglumine，Gd-BOPTA)，均为非特异性对比剂Gd-DTPA的衍生物[27]。

相比于CT，利用肝胆特异性对比剂的增强MRI检测结直肠癌肝转移灶具有更高的灵敏度和特异度[28]，尤其是在脂肪肝背景下对小病灶(≤1 cm)的检出[29-30]。肝胆特异性对比剂增强联合DWI可显著提高肝转移患者术前化疗的诊断准确性[31]。Hosseini-Nik等[32]提出肝胆特异性对比剂增强联合DWI很有希望能检测出结直肠癌肝转移术前化疗完全缓解，这对决定术前化疗后患者的后续手术方案有重要意义。因此，虽然肝胆特异性对比剂价格较贵，但其对病灶的高检出率可一定程度上弥补这种缺点，准确的检出定性可相对避免后续更多的放射学检查、活检，甚至手术切除[26]。

3 DCE–MRI在评价结直肠癌肝转移中的应用

DCE-MRI可反映肝脏组织和肿瘤的肝动脉、门静脉供血情况及对比剂到达时间，量化病灶的血流情况和毛细血管渗出性，这些直接决定了化疗药物向转移灶的运送情况[33-34]。其定量参数主要包括: ① 传输参数(Ktrans)：对比剂从血管内到血管外的速率常数，反映微血管流量及微血管通透性；② 流出速率常数(Kep)：组织间隙对比剂重吸收回血管的速率常数；③ 血管外细胞外间隙空间体积比(Ve)：血管外细胞外间隙空间体积比越接近0，表明血管化程度越强；④ 血浆体积比(Vp)：血浆空间体积比越接近0，表明血管化程度越差[35]。

DCE-MRI通过描述病灶的微血管灌注情况可用于评估抗血管药物治疗效果，其血流动力学参数较DCE-CT有更好的再现性，更利于实现标准化及保证质量可靠[36]。研究发现，基线Ktrans值高的转移灶药物治疗效果较好，治疗后Ktrans下降>40%与结直肠癌肝转移患者更好的无进展生存期密切相关[37-38]。Coenegrachts等[39]发现，结直肠癌肝转移灶整体Kep值治疗有效组明显高于治疗无效组(Kep=0.098 52、0.078 29)，有效组治疗6周后Kep值明显下降，由此提出Kep值可用于治疗疗效预测及早期疗效评价。Hirashima等[40]通过多因素分析同样证实，治疗7 d后Ktrans及Kep比例下降(△Ktrans及△Kep)与肿瘤缩小显著性相关(△Ktrans：P=0.009；△Kep：P=0.043)，△Ktrans还与较长的疾病进展期相关(P=0.001)，从而提出△Ktrans可作为预测较好治疗效果及疾病进展期的一种药效动力学指标。

4 功能MRI的优势及局限

MRI具有较高的软组织对比度，脂肪肝背景下较CT能更好地检出结直肠癌肝转移灶，且不接受电离辐射，可短期多次重复。MRI功能学成像方式不仅提供结直肠癌肝转移灶的形态学和功能学特征，有利于患者治疗方案选择；治疗后功能学参数变化还与病理反应密切相关，可用于早期治疗效果评估，及时调整治疗方案，从而影响个体化治疗发展。

虽然MRI是一种评价结直肠癌肝转移的高敏感方法，但其检查时间较长，价格相对昂贵，并不适用于所有患者。患者必须能配合呼吸指令，必须严格筛选不兼容的植入设备，以及幽闭恐怖症和严重肾脏疾病等禁忌证。

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