·临床研究·

肝细胞癌患者肿瘤内脂肪含量与病理分级的相关性

徐　海[1]，梁晓韵[2]，王杨迪[3]，胡雪芳[3]，石思雅[3]，罗宴吉[3]
(1. 中山大学附属第一医院放射介入科，广东 广州 510080；2. 广州医科大学附属中医医院医学影像科，广东 广州 510130；3. 中山大学附属第一医院放射科，广东 广州 510080)

摘　要：【目的】比较不同病理分级 HCC 肿瘤内脂肪含量差异，并分析肿瘤脂肪含量在预测 HCC 病理分级中的潜在价值。【方法】回顾性分析行 MRI Dixon 检查且经病理证实的 96 例 HCC，按照 Edmondson-Steiner 病理分级法将其分为非低分化组和低分化组。2 名观察者分别测量两组病灶内的脂肪体积分数(FVF)，比较两组间 FVF 的差异，并分析肿瘤 FVF 在预测 HCC 病理分级中的潜在意义。【结果】2 名检测者测得病灶 FVF 结果一致性良好(ICC > 0.75)。非低分化组 HCC FVF 值[15.75(12.37~21.32)]高于低分化组[13.45(8.48~21.10)，Z=-1.972，P=0.049]，FVF 鉴别 HCC 病理分级的 AUC 值为 0.645，当 FVF 大于等于 15.4 时，其诊断为高分化的 HCC 的敏感性为 53%，特异性为 77%。【结论】MRI Dixon 能够全面准确评估 HCC 肿瘤内 FVF，HCC 肿瘤内 FVF 有助于术前评估 HCC 的病理分级。

关键词：肝细胞癌；磁共振成像；病理分化程度；化学移位；脂肪体积分数
中图分类号：R735.7　　**文献标志码：**A　　**文章编号：**1672-3554(2021)05-0778-05
DOI：10.13471/j.cnki.j.sun.yat-sen.univ(med.sci).2021.0517

Correlation between Intratumoral Fat Content and Pathological Grade of Hepatocellular Carcinoma

XU Hai[1], LIANG Xiao yun[2], WANG Yang-di[3], HU Xue-fang[3], SHI Si-ya[3], LUO Yan-ji[3]
(1. Department of Interventional Radiology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, China; 2. Department of Medical Imaging, Affiliated Hospital of Traditional Chinese Medicine, Guangzhou Medical University, Guangzhou 510130, China; 3. Department of Radiology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, China)
Correspondence to: LUO Yan-ji; E-mail: luoyj26@mail.sysu.edu.cn

Abstract:【Objective】To compare the difference of fat content in HCC tumors with different pathological grades, and to analyze the potential value of fat content in predicting the pathological grades of HCC.【Methods】Totally 96 patients with HCC who underwent MRI Dixon examination and were pathologically confirmed in the First Affiliated Hospital of Sun Yat-sen University between January 2009 and July 2017 were retrospectively analyzed. They were divided into non-poorly differentiated group and poorly differentiated group according to Edmondson-Steiner pathological grading. Two observers measured the fat volume fraction (FVF) in the lesions of the two groups. The difference of FVF between the two groups was compared. The potential value of tumor FVF in predicting the pathological grade of HCC was analyzed.【Results】The results of FVF between 2 observers were consistent (ICC >0.75). The FVF value in the non-poorly differentiated HCC group [15.75 (12.37~21.32)] was higher than that in the poorly differentiated HCC group[13.45, (8.48~21.10), Z=-1.972, P=0.049]. The AUC value of FVF in differentiating the pathological grade of HCC was 0.645. When the FVF was greater than or equal to 15.4, the sensitivity and specificity for the diagnosis of non-poorly differentiated HCC was 53% and 77%, respectively.【Conclusion】The examination of MRI Dixon can comprehensively and accurately evaluate the FVF in HCC

收稿日期：2021-06-18
基金项目：国家自然科学基金(81801761)
作者简介：徐海，医师，研究方向：影像技术应用，E-mail：xh_xz@163.com；罗宴吉，通信作者，E-mail：luoyj26@mail.sysu.edu.cn

tumors, and the FVF in HCC tumors is helpful for the preoperative evaluation of the pathological grade of HCC.

Key words: hepatocellular carcinoma; magnetic resonance imaging; degree of pathological differentiation; chemical shift; fat volume fraction

[J SUN Yat-sen Univ(Med Sci),2021,42(5):778-782]

肝细胞癌(hepatocellular carcinoma,HCC)是全球病死率排名第2的恶性肿瘤,我国是HCC高发地区[1]。HCC的病理按Edmondson-Steiner分级系统分为Ⅰ~Ⅳ级[2],其中非低分化组(高分化、中分化)病理学分级为Ⅰ、Ⅱ级,低分化组病理学分级为Ⅲ、Ⅳ级。病理分级是肝细胞癌最重要的独立预后预测因子,低分化HCC由于肿瘤侵袭性强、易早期远处转移等原因导致治疗效果及预后不佳[3]。有研究显示肝细胞癌肿瘤组织内的脂肪含量与其预后呈负相关,即含有脂肪的HCC的患者预后好于不含脂肪者[4]。然而,肝细胞癌病理分级与其脂肪含量的相关性鲜见报道。在本研究中,我们采用无创性磁共振成像(magnetic resonance imaging, MRI)Dixon技术定量测量HCC瘤内脂肪体积分数(fat volume fraction, FVF),比较非低分化及低分化HCC瘤内脂肪含量差异,并进一步分析肿瘤脂肪含量在预测其病理分级中的潜在价值。

1　材料与方法

1.1　病例资料

该研究已征得患者同意及签署知情同意书,并且取得医院伦理委员会的批准。回顾性分析2009年1月至2017年7月于中山大学附属第一医院进行上腹部MRI检查,并且经手术病理证实为HCC的患者资料。纳入标准:①术前1个月内进行上腹部MRI Dixon序列扫描;②肿瘤直径>1 cm;③接受部分肝脏切除手术,且术后病理证实为HCC。排除标准:①MRI扫描前进行过其他抗肿瘤治疗,包括经射频消融术、肝动脉化疗栓塞术、放疗及化疗;②无法获得明确的HCC Edmondson-Steiner病理分级;③MRI Dixon序列图像质量欠佳、难以分析。HCC的病理按照Edmondson-Steiner分级分为非低分化组(Ⅰ、Ⅱ级)和低分化组(Ⅲ、Ⅳ级)。

1.2　MRI检查

每个受试者仰卧时接受上腹部MRI检查,使用3.0 T MRI扫描仪(扫描机型:SIEMENS 3.0 T MAGNETOM Verio),使用体部8通道相控阵线圈。检查前嘱患者禁食、禁水4~8 h,行常规T1WI、T2WI和Dixon扫描序列,扫描前行初始定位图像,然后行常规T1WI、T2WI以及T1WI体积插值屏气检查(VIBE) Dixon扫描,覆盖所有上腹部器官。T1WI VIBE Dixon序列成像参数为:TE_1 2.5 ms;TE_2 3.7 ms;重复时间5.47 ms;角翻转5°;层厚3.0 mm。所有的受试者均被要求吸气后屏住呼吸,以确保图像采集的一致性。

1.3　图像阅片、后处理及观察指标

由2名分别具有7年和3年MRI诊断经验的放射科医师行双盲法独立数据测量并分别记录。

应用MATLAB平台(MATLAB r2011b, MathWorks, America)下创建的插件算法生成脂肪体积分数(FVF)灰度图及伪彩图,以伪彩图为测量图像,其他图像辅助病灶定位[5-6]。在病灶轴位面积最大层面及其相邻的上下两个层面分别放置感兴趣区(ROI),即总共测量病灶轴位图像的3个层面。ROI包含肿瘤最大截面,避开或挖除出血、坏死区。对于多发HCC,选取最大病灶进行测量。最终各病灶FVF值为2名测量者于3个层面ROI测量值的均值。

1.4　统计学分析

使用SPSS 25.0软件,使用组内相关系数(interclass correlation coefficient, ICC)检验。2名观察者测量FVF的一致性,取观察者测量结果的平均值进行分析,ICC ≥ 0.75为一致性良好。采用Shapiro-Wilk检验连续变量的正态性,符合正态分布的计量数据以均值±标准差表示,组间比较采用独立样本t检验;不符合正态分布的计量资料以中位数(四分位数)表示,组间比较采用Mann-Whitney U检验。使用受试者工作特征(Receiver operating characteristic curve, ROC)曲线分析肿瘤FVF用于鉴别非低分化和低分化HCC的诊断效能。P<0.05表示差异具有统计学意义。

2 结 果

2.1 病灶总体情况

最终纳入96例HCC,其中男86例,女10例;单发89例,多发7例。患者年龄符合正态分布,高分化组66例,年龄29~84(55±10)岁;低分化组30例,年龄25~75(53±11)岁。两组患者年龄差异无统计学意义(P=0.475)。2名观察者对病灶内FVF检测的一致性良好(ICC>0.75),正态性检验提示2名观察者所测得的FVF值不符合正态分布,因此以中位数(四分位数)表示(表1)。

表1 两名观察者测得各参数一致性的结果

Table 1 Consistency of parameters measured by two observers

Parameter	Non-poorly differentiated group			Poorly differentiated group		
	Observer 1	Observer 2	ICC	Observer 1	Observer 2	ICC
FVF	17.0 (12.0~21.3)	16.9 (13.3~22.7)	0.950	13.9 (9.8~17.1)	13.3 (8.7~17.2)	0.949

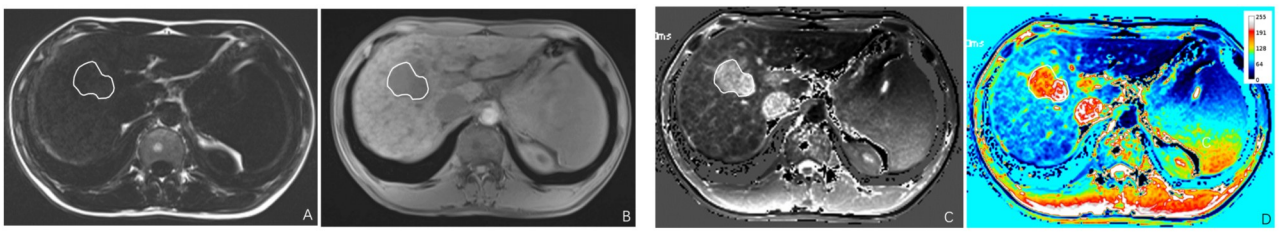
ICC: intraclass correlation efficient; FVF: fat volume fraction.

2.2 高分化和低分化HCC瘤内FVF的比较

正态分布检验提示FVF不符合正态分布,因此组间比较采用Mann-Whitney U检验。HCC病灶勾画见图1-2。高分化组HCC的FVF 15.8(12.4~21.3)显著大于低分化组[13.5(8.5~21.1);Z=-1.972,P=0.049]。

2.3 瘤内脂肪含量对HCC分化程度鉴别诊断效能的评估

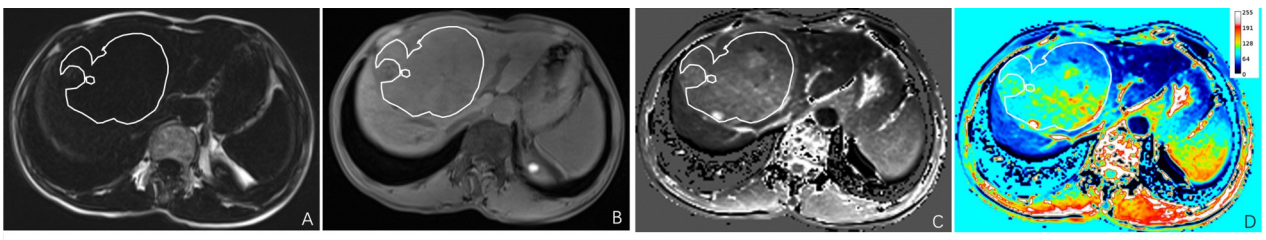
FVF鉴别HCC病理分级的AUC值95% CI为0.665(0.54, 0.79),当FVF大于等于16.0时,其诊断为非低分化的HCC的敏感性为53%,特异性为77%(图3)。



A 31-year-old male with non-poorly differentiated hepatic HCC within S8. The lipid phase (A) showed slightly high signal, while the aqueous phase (B) showed low signal. The FVF grayscale image (C) and pseudo-color image (D) showed high signal and orange-red, respectively. The intratumoral FVF was 31.9%.

图1 非低分化HCC瘤内FVF测量示意图

Fig. 1 FVF measurement in non-poorly differentiated HCC



A 70 years old male with poorly differentiated HCC within S4 and S8. The lipid phase (A) showed equal signal, the aqueous phase (B) showed slightly lower signal, FVF grayscale (C) and pseudo color (D) showed slightly higher signal and bluish blue, respectively. The intratumoral FVF was 7.2%.

图2 非低分化HCC瘤内FVF测量示意图

Fig. 2 FVF measurement in poorly differentiated HCC

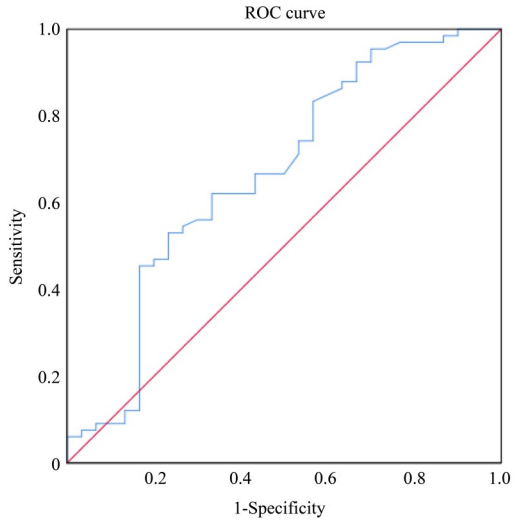


图3　FVF值诊断非低分化HCC的ROC曲线

Fig. 3　ROC curve of FVF value for diagnosis of non-poorly differentiated HCC

3　讨论

目前，无创性肝脏脂肪检测或定量的技术主要为MRI检查，优势在于其高分辨率、无辐射和高精度的成像特点。在以往研究中，磁共振波谱（MRS）成像被认为是准确定量内脏脂肪含量的金标准[7-8]。然而，MRS操作耗时且只能描述器官的一部分脂肪含量，体素的放置需要操作者的专业知识。此外，由于膈肌的呼吸运动引起腹部器官的移位，MRS的准确性易受到影响[9]。MRI Dixon技术是一种基于化学位移的两点脂肪-水分离方法，可用于内脏脂肪的定量测量，部分研究认为，与MRS相比，Dixon测量脂肪含量的准确性更高[10-11]。MRI Dixon技术基于脂肪组织的同反相位图像重建合成单纯的水相和脂相图像，与MRS相比其图像更容易获得[12-13]，同时，Dixon技术可以在一次呼吸中获得分离的水和脂肪相图像，将由呼吸引起的器官运动而造成伪影的误差降到最低。此外，Dixon技术可以提供内部器官脂肪沉积的整体视图，以评估整个肝脏的脂肪含量。

本研究结果提示低分化较非低分化HCC瘤内FVF显著减低，提示肿瘤灶内脂肪含量与预后可能相关，肿瘤内含脂肪含量越高，预示着肿瘤分化程度越高，预示着HCC病理分化更高，预后较低分化者好。本研究结果与熊瑜琦等的研究结果相仿[4]，该研究结果表明含脂肪成分的HCC患者肿瘤远处转移发生率显著低于不含脂肪成分的HCC患者，而且含脂肪成分的HCC患者中位TTP长于无脂肪成分者，但该研究仅对HCC瘤内脂肪成分进行了有或无的定性分析，未进行进一步的定量测量及相关性分析，本研究通过进一步精确定量测量HCC肿瘤内脂肪体积分数，分析了不同病理分级HCC脂肪体积分数的差异。瘤内FVF对HCC分化程度鉴别诊断效能的评估结果提示，当FVF大于等于15.4时，其诊断为非低分化的HCC的敏感性为56%，特异性为73%，提示HCC瘤内脂肪含量对HCC病理分级的预测具有一定准确性。瘤内脂肪含量升高预示肿瘤分化程度更高、预后更好，其内在机制与脂肪组织的代谢产物——脂联素有关，Manieri等提出，脂联素对肝细胞癌的生长具有抑制作用[14-15]，该研究提示脂联素水平的下降是肝细胞癌发生风险增加的原因。脂联素通过活化AMPK和p38α通路来抑制肝细胞癌的发生发展[16-17]，这项研究提供了对HCC发展过程中脂肪组织与肝脏的相互作用的深入了解，有可能指导新的肿瘤治疗策略。

本研究存在的局限性如下：首先是病例样本数量偏小，仅纳入病理分级诊断明确的病例导致的选择偏倚。此外，HCC肿瘤细胞病理分化存在时空异质性，ROI放置区域未能实现与病理分析取材区域完全一致，但多层面测量在一定程度上可减少该误差。全面精准评估肿瘤异质性，将在今后的研究中进行探讨。

总之，本研究提示，Dixon作为一种无创MRI技术，能够用于全面准确评估HCC肿瘤内脂肪含量，HCC肿瘤内脂肪含量的检测有助于术前评估HCC的病理分级，有望为患者预后预测及治疗策略提供一定参考价值。

参考文献

[1] 汪根树. 利用综合治疗措施进一步提高肝癌肝移植疗效[J]. 器官移植, 2021, 12(3): 249-256.
Wang GS. Improving efficacy of liver transplantation for hepatocellular carcinoma by comprehensive treatment [J]. Organ Transplant, 2021, 12(3): 249-256.

[2] 吴孟超, 汤钊猷, 刘彤华, 等. 原发性肝癌规范化病理诊断指南(2015年版)[J]. 临床肝胆病杂志, 2015, 31(6): 833-839.
Wu MC, Tang ZY, Liu TH, et al. Diagnostic guidelines for primary hepatocellular carcinoma (The 2015 edition)[J]. J Clin Hepatobiliary Dis, 2015, 31(6): 833-839.

[3] Yang JD, Heimbach JK. New advances in the diagnosis and management of hepatocellular carcinoma[J]. BMJ, 2020, 26: 371.

[4] 熊瑜琦,乔梁,李镝. 肝细胞癌患者肿瘤内脂肪成分有无与预后的关系[J]. 山东医药, 2014, 54(12): 42-43.
Xiong YQ, Qiao L, Li D. The relationship between lipid content and prognosis in patients with hepatocellular carcinoma [J]. Shandong Med, 2014, 54 (12): 42-43.

[5] Dong Z, Luo Y, Zhang Z, et al. MR quantification of total liver fat in patients with impaired glucose tolerance and healthy subjects [J]. PLoS One, 2014, 9 (10): e111283.

[6] Dong Z, Luo Y, Cai H, et al. Noninvasive fat quantification of the liver and pancreas may provide potential biomarkers of impaired glucose tolerance and type 2 diabetes [J]. Medicine (Baltimore), 2016, 95 (23): e3858.

[7] Yokoo T, Serai SD, Pirasteh A, et al. Linearity, bias, and precision of hepatic proton density fat fraction measurements by using MR imaging: A Meta-analysis[J]. Radiology, 2018, 286(2): 486-498.

[8] Gu J, Liu S, Du S, et al. Diagnostic value of MRI-PDFF for hepatic steatosis in patients with non-alcoholic fatty liver disease: a meta-analysis[J]. Eur Radiol, 2019, 29(7): 3564-3573.

[9] Corrias G, Erta M, Sini M, et al. Comparison of multi-material decomposition fat fraction with DECT and proton density fat fraction with IDEAL IQ MRI for quantification of liver steatosis in a population exposed to chemotherapy [J]. Dose Response, 2021, 19 (2): 1559325820984938.

[10] Koyuncu Sokmen B, Sahin T, Oral A, et al. The comparison of pancreatic and hepatic steatosis in healthy liver donor candidates[J]. Sci Rep, 2021, 11(1): 4507.

[11] Luo Y, Abiri P, Zhang S, et al. Non-invasive electrical impedance tomography for multi-scale detection of liver fat content [J]. Theranostics, 2018, 8 (6): 1636-1647.

[12] Alhulail AA, Patterson DA, Xia P, et al. Fat-water separation by fast metabolite cycling magnetic resonance spectroscopic imaging at 3 T: A method to generate separate quantitative distribution maps of musculoskeletal lipid components [J]. Magn Reson Med, 2020, 84(3): 1126-1139.

[13] Lins CF, Salmon CEG, Nogueira-Barbosa MH. Applications of the Dixon technique in the evaluation of the musculoskeletal system [J]. Radiol Bras, 2021, 54 (1): 33-42.

[14] Manieri E, Herrera-Melle L, Mora A, et al. Adiponectin accounts for gender differences in hepatocellular carcinoma incidence[J]. J Exp Med, 2019, 216 (5): 1108-1119.

[15] Geh D, Anstee QM, Reeves HL. NAFLD-associated HCC: Progress and opportunities [J]. J Hepatocell Carcinoma, 2021, 8(8): 223-239.

[16] Pasanta D, Htun KT, Pan J, et al. Magnetic resonance spectroscopy of hepatic fat from fundamental to clinical applications[J]. Diagnostics (Basel), 2021, 11(5): 842.

[17] Sigala DM, Widaman AM, Hieronimus B, et al. Effects of consuming sugar-sweetened beverages for 2 weeks on 24-h circulating leptin profiles, Ad libitum food intake and body weight in young adults[J]. Nutrients, 2020, 12(12): 3893.

(编辑 余 菁)