



在线全文

脑胶质瘤MRI参数、微血管密度与预后的相关性研究*

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【摘要】目的 分析多模态MRI检查参数[表观弥散系数(ADC)、脑血流量(CBF)、胆碱(Cho)/肌酸(Cr)]与脑胶质瘤患者微血管密度(MVD)的相关性及其对预后的评估价值。**方法** 回顾性分析2019年1月–2024年1月间在我院确诊为脑胶质瘤的200例患者病历资料,以WHO为分级基础,Ⅰ~Ⅱ级为低级别组($n=122$);Ⅲ~Ⅳ级为高级别组($n=78$);以预后情况为依据,分为预后良好组($n=114$)和预后不良组($n=86$)。Pearson相关性检验多模态MRI检查参数与脑胶质瘤MVD之间的关系,受试者工作特征曲线(ROC)的曲线下面积(AUC)评价多模态MRI检查参数以及MVD对高级别脑胶质瘤患者的诊断价值及其预后不良的预测价值,最后Hosmer-Lemeshow检查评估模型的拟合度。**结果** 低级别患者ADC值高于高级别组,CBF、Cho/Cr以及MVD均低于高级别组($P<0.05$)。预后良好组患者ADC值高于预后不良组,CBF以及Cho/Cr值均低于预后不良组($P<0.05$)。脑胶质瘤患者ADC与MVD呈负相关($r=-0.226, P=0.001$);CBF和Cho/Cr与MVD均呈正相关($r=0.235, 0.396, P<0.001$)。ADC、CBF、Cho/Cr、MVD诊断高级别脑胶质瘤患者的AUC分别为0.870、0.696、0.926、0.950,四者联合的AUC为0.997。多模态MRI检查参数对脑胶质瘤患者预后的ROC曲线中,DC+CBF+Cho/Cr联合预测的AUC为0.876,ADC、CBF、Cho/Cr单独诊断的AUC分别为0.718、0.688、0.808。Hosmer-Lemeshow检验显示ADC+CBF+Cho/Cr联合预测模型拟合度良好($\chi^2=8.570, P=0.380$),即ADC+CBF+Cho/Cr联合预测模型具有较高的精确度。**结论** ADC、CBF、Cho/Cr与脑胶质瘤患者MVD具有弱相关性,四者联合诊断高级别脑胶质瘤患者的价值较高,前三者联合对患者预后的预测价值较高。

【关键词】 多模态MRI 脑胶质瘤 微血管密度 预后

Study of the Correlation Between MRI Parameters, Microvascular Density, and Prognosis in Glioma

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[Abstract] Objective To analyze the correlations between multimodal MRI examination parameters – apparent diffusion coefficient (ADC), cerebral blood flow (CBF), and choline (Cho)/creatinine (Cr)—and microvessel density (MVD) in patients with glioma, as well as the prognostic value of these parameters. **Methods** The medical records of 200 patients diagnosed with glioma at our hospital from January 2019 to January 2024 were retrospectively analyzed. According to the WHO classification, patients were divided into a low-grade group ($n=122$) and a high-grade group ($n=78$). Patients were further divided into a good prognosis group ($n=114$) and a poor prognosis group ($n=86$). The Pearson correlation test was used to analyze the relationship between multimodal MRI parameters and MVD in glioma patients. The area under the curve (AUC) of receiver operating characteristic (ROC) curve was used to evaluate the diagnostic value of multimodal MRI parameters and MVD for high-grade glioma and their predictive value for poor prognosis. The Hosmer-Lemeshow test was used to assess the goodness of fit of the model. **Results** The ADC value in the low-grade group was higher than in the high-grade group, while CBF, Cho/Cr, and MVD were lower in the low-grade group ($P<0.05$). The ADC value in the good prognosis group was higher than in the poor prognosis group, while CBF and Cho/Cr values were lower in the poor prognosis group ($P<0.05$). ADC was negatively correlated with MVD in glioma patients ($r=-0.226, P=0.001$); CBF and Cho/Cr were positively correlated with MVD ($r=0.235$ and $0.396, P=0.001$ and <0.001 , respectively). The AUCs of ADC, CBF, Cho/Cr, and MVD for diagnosing high-grade glioma were 0.870, 0.696, 0.926, and 0.950, respectively. The combined AUC of these four parameters was 0.997. For prognosis prediction based on multimodal MRI parameters, the combined AUC of ADC+CBF+Cho/Cr was 0.876, while the AUCs of ADC, CBF, and Cho/Cr alone were 0.718, 0.688, and 0.808, respectively. The Hosmer-Lemeshow test showed that the

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combined model (ADC + CBF + Cho/Cr) fit was good ($\chi^2 = 8.570$, $P = 0.380$), indicating that the combined prediction model had high accuracy. **Conclusion** ADC, CBF, and Cho/Cr have a weak correlation with MVD in glioma patients. The combination of these four parameters has high value in diagnosing high-grade glioma, and the combination of the first three parameters has higher predictive value for patient prognosis.

[Key words] Multimodal MRI Brain glioma Microvascular density Prognosis

脑胶质瘤作为中枢神经系统常见的原发性恶性肿瘤,具有病程进展快、预后差等特点,原癌基因和抑癌基因结构以及功能异常是该病发病的主要原因,在中枢神经系统原发性肿瘤中约占45%,大多呈浸润性生长,和周围脑组织之间界限不清晰,其治疗与预后评估一直是临床研究的重点和难点^[1-3]。近年来,磁共振成像技术在脑胶质瘤异质性评估中展现出显著潜力,其临床应用范围持续扩大。多模态MRI检查不仅包含常规序列,还整合了多种先进的成像技术,能够全面反映肿瘤的多种生物学特征,为疾病的分期和治疗方案的制定提供重要依据^[4-5]。微血管密度(micro-vessel density, MVD)在脑胶质瘤的生长、侵袭和转移过程中起着关键作用,能够反映病灶部位的血管生成情况,对肿瘤的恶性程度进行评估,与患者的预后密切相关^[6]。目前,已陆续有学者将多模态MRI检查用于脑胶质瘤患者的术前分级,但其是否能用于预测脑胶质瘤患者的术后疗效尚存争议^[7-8]。因此,深入探究多模态MRI检查参数与脑胶质瘤患者MVD的相关性,明确其在预后评估中的价值,对于优化脑胶质瘤的治疗方案、改善患者预后具有重要的临床意义。

1 资料与方法

1.1 一般资料

回顾性分析2019年1月–2024年1月间在我院确诊为脑胶质瘤的200例患者病历资料。纳入标准:(1)符合临床相关诊断标准^[9],且经外科手术病理活检证实为脑胶质瘤;(2)术前行MRI检查且检查前无相关治疗史;(3)存在完整的影像和临床资料;(4)均为初次发作,未曾接受过放化疗。排除标准:(1)序列缺失或者图像质量差;(2)存在颅脑手术史;(3)脏器功能不全;(4)失访者。脑胶质瘤参考WHO分级,Ⅰ~Ⅱ级为低级别($n=122$);Ⅲ~Ⅳ级为高级别($n=78$)。

随访1年,将患者分为预后不良组($n=86$),其余为预后良好组($n=114$)。预后不良包括复发、恶化、死亡。复发定义为肿瘤生长范围相比术前扩大或在不同部位出现。本研究经石河子大学第一附属医院科技伦理委员会审批通过(批准号KJ2025-316-01),批件有效期13个月。

1.2 扫描方法

采用多模态MRI扫描,GE3.0T磁共振,头颅8通道相控

阵线圈。常规扫描:(1)T1加权成像(T1WI),回波时间(TE)与重复时间(TR)分别为20 ms和1 780 ms,扫描层厚为6 mm,层间距为1 mm,矩阵为320×224,视野(FOV)为24 cm×24 cm;(2)T2加权成像(T2WI):TE与TR分别为145 ms和5 000 ms;扫描层厚为6 mm,层间距为1 mm,成像矩阵设置为320×224;FOV为24 cm×24 cm;(3)T2-Flair:TE为112 ms,TR为5 800 ms,扫描层厚是6 mm,层间距为1 mm,矩阵为320×224,FOV为24 cm×24 cm。增强扫描:T1三维快速扰相梯度回(T1-3D-FSPGR):利用高压注射器,通过肘静脉以团注的方式注入对比剂Gd-DTPA,注射剂量为0.1 mmol/kg,注射速率为2 mL/s。扩散张量成像(DTI)及扩散加权成像(DWI)扫描采用自旋回波平面回波成像(SE-EPI)序列,梯度扩散因子(b)取值为1 000 s/mm²。其中,DTI的TR为5 900 ms,TE为85 ms,成像矩阵为160×192,扫描的层厚和层间距与常规扫描一致;DWI的TR为6 200 ms,TE为90 ms,成像矩阵为160×160,扫描的层厚和层间距同样与常规扫描保持一致。PWI扫描总共进行100期,先进行10期预扫描,之后通过肘正中静脉以4 mL/s的速度快速灌注30 mL对比剂来开展灌注成像。MRS扫描的TE为144 ms,TR为1 000 ms;扫描层厚是1 mm,层间距为1 mm,成像矩阵为16×16;FOV为24 cm×24 cm。

1.3 数据测量

将扫描所得的原始数据传至GE3.0T磁共振系统,在病灶的最大层面放置感兴趣区(region of interest, ROI),约占最大层面的75%以上,选择避开血管、空洞及坏死区域,尽量包含整个病灶,需要测量的数据包括:表观弥散系数(apparent diffusion coefficient, ADC)、脑血流量(cerebral blood flow, CBF)以及胆碱(choline, Cho)/肌酸(creatine, Cr),各参数取3次测量平均值,由2名经验丰富的放射科医师,以双盲法进行阅片。使用kappa值评价两名医生测量结果的一致性,本研究中kappa值均大于0.7,一致性较高。

1.4 肿瘤MVD分析

取患者石蜡切片,常规HE染色,一抗(人CD34,货号:M7165,供应商:Agilent DAKO,浓度:1:100稀释),由两名病理医师分别对患者的MVD水平进行独立分析。CD105可作为识别血管内皮细胞的特异性标志物,经染色处理后,该标志物可呈现棕色或棕黄色。在本研究中,

当细胞胞质中棕黄色占比达到10%及以上时,判定该细胞为表达阳性。阳性计数标准以EICHTEN等^[10]的研究为依据,通过观察5个不同视野内的微血管数量,求其平均值即为MVD的数值。

1.5 统计学方法

采用SPSS 26.0对数据进行统计分析。计量资料经正态性检验,符合正态分布的数据均采用 $\bar{x} \pm s$ 表示,组间比较采用独立样本 t 检验。Pearson相关分析多模态MRI检查参数与脑胶质瘤患者MVD的相关性。绘制受试者工作特征(receiver operator characteristic, ROC)曲线,以曲线下面积(area under the curve, AUC)评价多模态MRI检查参数及MVD对高级别脑胶质瘤患者的诊断

价值及其预后预测价值,最后Hosmer-Lemeshow检查评估模型的拟合度。对数据集中的缺失值问题,通过全数据集随机森林插补法进行处理。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 不同病理分级的患者检查参数值对比

低级别患者ADC值高于高级别组,CBF、Cho/Cr以及MVD均低于高级别组,差异有统计学意义。见表1。

2.2 不同预后的患者检查参数值对比

良好组患者ADC值高于不良组,CBF以及Cho/Cr值均低于不良组。见表2。

表 1 不同病理分级的患者检查参数值对比

Table 1 Comparison of patient examination parameters by pathological grade					
Group	<i>n</i>	ADC/($\times 10^{-3}$ mm ² /s), $\bar{x} \pm s$	CBF/(mL/[100 g·min]), $\bar{x} \pm s$	Cho/Cr ($\bar{x} \pm s$)	MVD ($\bar{x} \pm s$)
Low-level	122	2.15 ± 0.46	1.16 ± 0.30	1.81 ± 0.37	29.98 ± 9.32
High-level	78	1.47 ± 0.39	1.32 ± 0.31	2.60 ± 0.41	63.41 ± 18.59
<i>t</i>	—	10.805	3.631	14.116	16.841
<i>P</i>	—	< 0.001	< 0.001	< 0.001	< 0.001

Multimodal MRI examination parameters include apparent diffusion coefficient (ADC), cerebral blood flow (CBF), and choline (Cho) to creatine (Cr) ratio (Cho/Cr). MVD: micro-vessel density.

表 2 不同预后的患者多模态MRI检查参数对比

Table 2 Comparison of multimodal MRI examination parameters in patients with different prognoses				
Group	<i>n</i>	ADC/($\times 10^{-3}$ mm ² /s), $\bar{x} \pm s$	CBF/(mL/[100 g·min]), $\bar{x} \pm s$	Cho/Cr ($\bar{x} \pm s$)
Good prognosis	114	1.89 ± 0.37	1.18 ± 0.36	2.09 ± 0.30
Poor prognosis	86	1.59 ± 0.34	1.41 ± 0.32	2.53 ± 0.38
<i>t</i>	—	5.877	4.689	9.150
<i>P</i>	—	< 0.001	< 0.001	< 0.001

All abbreviations are given in the footnote to Table 1.

2.3 多模态MRI检查参数与脑胶质瘤患者MVD的相关性分析

Pearson相关性分析结果显示,脑胶质瘤患者多模态MRI检查参数中的ADC与MVD呈负相关关系($r = -0.226$, $P = 0.001$); CBF和Cho/Cr与MVD均呈正相关关系($r = 0.235$, 0.396 , $P = 0.001$, < 0.001)。

2.4 多模态MRI检查参数及MVD对高级别脑胶质瘤患者的诊断价值

ROC曲线分析结果显示: ADC、CBF、Cho/Cr、MVD的AUC分别为0.870(95%CI: 0.821 ~ 0.918)、0.696(95%CI: 0.620 ~ 0.772)、0.926(95%CI: 0.888 ~ 0.981)、0.950(95%CI: 0.919 ~ 0.981); ADC+CBF+Cho/Cr+MVD四项联合的AUC为0.997(95%CI: 0.993 ~ 1.000)。见图1。

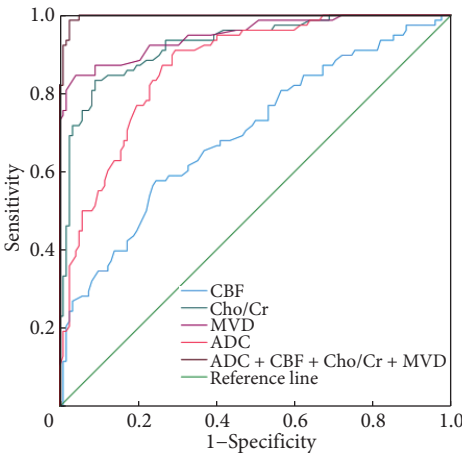


图 1 多模态MRI检查参数及MVD对高级别脑胶质瘤患者的ROC诊断曲线
Fig 1 Parameters of multimodal MRI and the ROC diagnostic curve of MVD in patients with high-grade glioma

All abbreviations are given in the footnote to Table 1.

2.5 多模态MRI检查参数对脑胶质瘤患者预后的预测价值

ADC+CBF+Cho/Cr联合预测的AUC为0.876(95%CI: 0.826 ~ 0.927), 高于ADC(AUC: 0.718, 95%CI: 0.646 ~ 0.789)、CBF(AUC: 0.688, 95%CI: 0.614 ~ 0.761)、Cho/Cr(AUC: 0.808, 95%CI: 0.744 ~ 0.872)的单独诊断。见图2所示。Hosmer-Lemeshow检验示联合预测模型拟合度良好 $\chi^2=8.570$, $P=0.380$, 说明ADC+CBF+Cho/Cr联合预测模型具有较高的精确度。

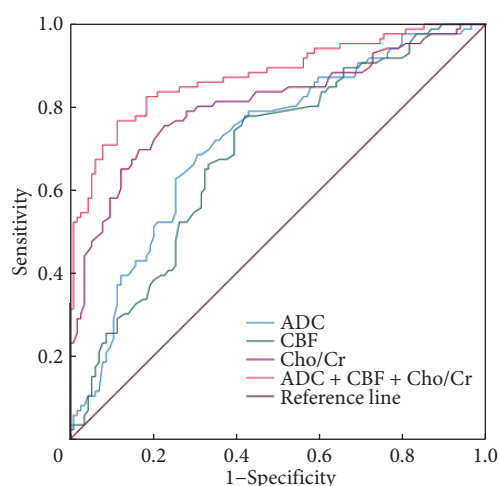


图2 多模态MRI检查参数对脑胶质瘤患者预后的ROC曲线

Fig 2 The ROC curve of multimodal MRI examination parameters for predicting the prognosis of patients with glioma

All abbreviations are given in the footnote to Table 1.

3 讨论

脑胶质瘤作为中枢神经系统最常见的原发性恶性肿瘤,其侵袭性强、预后差的特点对临床精准诊疗提出严峻挑战^[11]。近年来研究表明^[12],MVD作为反映血管生成活性的关键病理指标,与胶质瘤的恶性程度、侵袭性及预后存在显著相关性。然而,传统病理学评估依赖于术后标本,难以实现术前无创性评价及动态监测,促使多模态MRI技术在微循环特征可视化领域展现出重要价值。多模态MRI整合了结构成像与功能成像技术,能够从分子运动、血流灌注及血管通透性等多维度解析肿瘤微环境,不仅兼具脑胶质瘤形态成像与功能分析功能,还反映其异质性特征,辅助病理分级评估^[13-14]。本次研究整合了多模态MRI参数(包括DWI的ADC值、PWI的CBF值、MRS的Cho/Cr比值),从分子扩散、血流灌注及代谢活性三个维度全面解析肿瘤微环境。相比以往单一模态研究,能提供更立体的生物学信息,更全面地反映脑胶质瘤的病理特征。

在患者组织内,细胞结构与密度的变化与其体内水

分子的分布密切相关。随着疾病进展,细胞内外空间布局及细胞膜结构发生改变,进而影响水分子的分布状态,通过细胞膜两侧渗透压的波动,导致细胞含水量出现显著变化。既往研究表明^[15],多模态MRI影像参数与脑胶质瘤的病理分级具有显著相关性。本次研究结果显示,低级别患者ADC值高于高级别组,CBF和Cho/Cr以及MVD值均低于高级别组,与刘天笑等^[16]的研究结果相似。在肿瘤患者的病变进程中,大量微血管出现无序增殖,同时在肿瘤细胞与免疫细胞的协同作用下,新生血管的细胞畸形率显著上升,细胞形态与含水量均发生明显改变^[17]。在高级别脑胶质瘤的进展中,细胞有丝分裂活跃,血管内皮细胞受损明显;而随着病理分期的加重,细胞畸形率进一步升高,细胞密度增大,细胞间隙显著减小,导致水分子扩散受限加剧,ADC值随之降低^[18-19]。高级别胶质瘤的异常血管生成能力更强,低级别胶质瘤血管生成活性较弱,微血管结构相对完整,血流灌注水平较低,使得CBF值较低^[20]。此外,当脑组织发生病变时,神经元细胞会受到不同程度的损伤或被病变组织取代,导致Cr、Cho的代谢谱峰形及波峰高度发生相应改变,在本次研究中,高级别脑胶质瘤患者的Cho/Cr比值高于低级别患者,提示高级别胶质瘤的细胞增殖活性更强、膜磷脂代谢紊乱,对神经元的破坏程度更严重^[21]。深入研究结果显示,联合诊断的AUC为0.997,表明多模态MRI检查应用于脑胶质瘤的分级诊断具有较高的可行性。当前,放化疗、靶向以及外科手术等是临床常用的脑胶质瘤治疗手段,但关于该病的预后仍是临床的重点和难点^[22]。临床相关研究表明^[23],在正常脑组织中微血管数量较少,形态呈现规则状态,而脑胶质瘤患者的血管增生显著增加,并且随着病理级别的升高,血管增生愈发明显,显象的血管数量也随之增多。本次研究结果显示,预后良好组患者的ADC值高于不良组,CBF、Cho/Cr以及MVD值均低于不良组,说明肿瘤细胞的密度相对较低、细胞外间隙相对较大,水分子扩散受限程度较轻,且肿瘤组织的血流供应相对较少,血管生成能力较弱,限制了脑胶质瘤的发展,对患者预后产生积极影响。Pearson相关性分析结果显示,脑胶质瘤患者多模态MRI检查参数中的ADC与MVD呈负相关;CBF和Cho/Cr与MVD均呈正相关,三者相关系数绝对值均处于0.2~0.4区间,属于弱相关,提示上述影像学参数虽可在一定程度上反映肿瘤微血管生成的活跃程度,但其单独作为MVD的替代评估指标效能有限,仅可作为临床与研究中评估肿瘤血管生成特征的辅助参考,其与MVD的弱关联本质上既反映了ADC、CBF、Cho/Cr等参数本身受细胞密度、水肿、代谢活性等多因素共同影响

的特性,也体现了脑胶质瘤异质性强、微血管生成调控机制复杂的生物学特点,后续可通过构建多参数联合模型、结合分子亚型分层分析进一步提升影像指标对MVD的评估价值。进一步深入探究结果显示,三者联合的AUC高于ADC、CBF、Cho/Cr的单独诊断,且该联合预测模型具有较高的精确度。由此观之,多模态MRI检查参数对脑胶质瘤预后的预测具有重要的意义,可进一步提升胶质瘤预后评估的准确性。传统病理学评估依赖于术后标本,难以实现术前无创性评价及动态监测,而本研究利用多模态MRI技术,可在术前对脑胶质瘤患者进行无创性评估,为临床医生制定治疗方案提供重要依据。

综上所述,本研究证实了多模态MRI参数(ADC、CBF、Cho/Cr)与脑胶质瘤MVD具有一定的相关性,并验证了联合参数在预后评估中的高价值。然而,研究存在测量主观性、随访时间较短等局限性,因此,未来需通过多中心验证、影像组学与人工智能融合、动态监测及多组学整合,进一步提升多模态MRI在胶质瘤精准诊疗中的应用效能。

* * *

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