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· 临床研究 ·

DTI 定量参数对脑胶质瘤的诊断价值及其与血管内皮生长因子、
细胞核增殖相关抗原的关系*徐慧琳 蔡元卿[△] 龚明福 张 曦 谷卓玉

(中国人民解放军陆军军医大学第二附属医院放射科 重庆 400037)

摘要 目的:探讨扩散张量成像(DTI)定量参数对脑胶质瘤的诊断价值及其与血管内皮生长因子(VEGF)、细胞核增殖相关抗原(Ki-67)的关系。**方法:**选取2014年6月到2017年6月期间在我院接受治疗的90例脑胶质瘤患者,根据病理分级的不同分为中低级别组($n=46$)和高级别组($n=44$),比较两组患者表观扩散系数(ADC)值、各向异性分数(FA)值、相对表观扩散系数(rADC)值、相对各向异性分数(rFA)值、VEGF和Ki-67的阳性率,分析ADC值、FA值、rADC值、rFA值与VEGF、Ki-67表达的相关性。**结果:**高级别组的ADC值、FA值、rADC值和rFA值低于中低级别组($P<0.05$)。高级别组病理组织中VEGF、Ki-67的阳性表达率高于中低级别组($P<0.05$)。经Spearman相关分析显示,ADC值、FA值、rADC值和rFA值与VEGF、Ki-67的表达水平均呈负相关($P<0.05$)。**结论:**DTI定量参数与脑胶质瘤病理分级和VEGF、Ki-67的表达水平密切相关。

关键词:脑胶质瘤;扩散张量成像;参数;诊断价值;血管内皮生长因子;Ki-67;关系

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The Value of DTI Quantitative Parameters in the Diagnosis of Glioma and Its
Relationship with Vascular Endothelial Growth Factor and Cell Nuclear
Proliferation Related Antigen*XU Hui-lin, CAI Yuan-qing[△], GONG Ming-fu, ZHANG Xi, GU Zhuo-yu

(Department of Radiology, The Second Affiliated Hospital of PLA Army Medical University, Chongqing, 400037, China)

ABSTRACT Objective: To investigate the diagnostic value of diffusion tensor imaging (DTI) quantitative parameters for glioma and its relationship with vascular endothelial growth factor (VEGF) and proliferating cell nuclear antigen (Ki-67). **Methods:** 90 patients with glioma who were treated in our hospital from June 2014 to June 2017 were selected. According to the pathological grade, the patients were divided into the middle and low grade group ($n=46$) and the high grade group ($n=44$). The apparent diffusion coefficient (ADC) value, the anisotropy fraction (FA) value, the relative apparent diffusion coefficient (rADC) value, the relative anisotropy fraction (rFA) value, the positive rate of VEGF and Ki-67 were compared between the two groups. The correlation between ADC value, FA value, rADC value, rFA value and VEGF, Ki-67 expression was analyzed. **Results:** The ADC value, the FA value, the rADC value, and the rFA value of the high grade group are lower than the middle and low grade group ($P<0.05$). The positive expression rate of VEGF and Ki-67 in the pathological tissue of the high grade group was significantly higher than that in the middle and low grade group, and the difference was statistically significant ($P<0.05$). Spearman correlation analysis showed that ADC value, FA value, rADC value and rFA value were negatively correlated with the expression levels of VEGF and Ki-67 ($P<0.05$). **Conclusion:** The quantitative parameters of DTI are closely related to the pathological grade of brain glioma and the expression levels of VEGF and Ki-67.

Key words: Glioma; Diffusion tensor imaging; Parameters; Diagnostic value; Vascular endothelial growth factor; Ki-67; Relationship

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前言

脑胶质瘤是最常见的原发性颅内肿瘤,其主要产生于患者的大脑或者由脊髓胶质细胞癌发生进一步癌变而来,患者主要

表现出头痛、癫痫、恶心、呕吐、偏身感觉障碍、视物模糊等症状,并且可以对局部脑组织功能造成严重影响^[1,2]。脑胶质瘤多呈恶性,且易发生局部扩散,临床治疗难度大,患者预后通常较差,由于不同恶性程度的脑胶质瘤的治疗方案不一样,因此在

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作者简介:徐慧琳(1987-),本科,住院医师,从事DTI定量参数对脑胶质瘤的诊断价值方面的研究,E-mail: vuvcu@163.com

[△] 通讯作者:蔡元卿(1982-),男,本科,主治医师,从事DTI定量参数对脑胶质瘤的诊断价值方面的研究,E-mail: mnhgqif@163.com

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治疗前对其恶性程度进行准确的判断具有重要的临床意义^[3-5]。扩散张量成像(Diffusion tensor imaging, DTI)技术是基于扩散加权成像技术发展而来一种较新的成像技术,其相关参数可用来反映脑组织水分子的扩散情况,对脑胶质瘤分级、神经纤维束的完整性以及肿瘤周边水肿情况具有重要的评估价值^[6,7]。血管内皮生长因子(Vascular endothelial growth factor, VEGF)可促进新生血管的生成,在多种恶性肿瘤的发生、发展中起到重要的作用^[8,9]。Ki-67是一种细胞核增殖相关抗原,其表达水平与肿瘤细胞的增殖情况密切相关^[10]。目前关于DTI定量参数与脑胶质瘤患者的VEGF、Ki-67表达的关系的相关研究较少。本研究旨在探讨DTI定量参数对脑胶质瘤分级的诊断价值,并进一步分析其与VEGF、Ki-67表达的关系,以期临床诊治脑胶质瘤提供参考,现报道如下。

1 资料与方法

1.1 一般资料

选取2014年6月到2017年6月期间在我院接受治疗的90例脑胶质瘤患者,纳入标准:①所有患者均表现出脑胶质瘤的相关临床症状,且经临床病理确诊^[11];②所有患者均进行了DTI检查;③术前均未进行放化疗治疗,并于检查一周内接受手术治疗;④患者及其家属对本研究内容知情同意,并签署知情同意书。排除标准:①合并其他恶性肿瘤者;②临床资料不全者;③合并血液疾病、免疫系统疾病者;④存在精神疾病者;⑤合并其他严重脑部疾病者。根据世界卫生组织(World Health Organization, WHO)分级标准进行肿瘤病理分级,其中I级10例(5例毛细胞星形细胞瘤,3例室管膜下巨细胞星形细胞瘤,2例节细胞胶质瘤),II级36例(20例弥漫性星形细胞瘤,7例少突星形细胞瘤,6例少突胶质细胞瘤,3例多形性黄色星形细胞瘤),III级26例(17例间变性星形细胞瘤,5例间变性少突胶质细胞瘤,2例间变性多形性黄色星形细胞瘤,2例间变性少突星形细胞瘤),IV级18例(均为胶质母细胞瘤),其中I-II级为中低级别组,共46例,男性22例,女性24例,年龄24-73岁,平均 (48.36 ± 7.21) 岁,III-IV级为高级别组,共44例,男性25例,女性21例,年龄26-71岁,平均 (47.59 ± 6.78) 岁。两组患者年龄、性别等一般资料比较差异无统计学意义($P > 0.05$),均衡可比。本研究已通过我院伦理委员会的批准。

1.2 检测方法

1.2.1 影像学检查 所有患者均进行磁共振成像(Magnetic resonance imaging, MRI)检查(GE Signa HDxt1.5T),定位后,对患者行轴面SE-T1WI序列扫描,扫描参数:重复时间(Repetition time, TR)为1400 ms,恢复时间(Recovery time, TE)为14 ms,采用轴位FSE-T2WI序列、FLAIR-T2WI序列对患者进行扫描,扫描参数分别为:TR为3600 ms,TE为102 ms;TR为8500 ms,TE为145 ms,反转时间(Inversion time, TI)为2100 ms。DTI采用自旋回波-平面成像序列对患者进行横断面扫描,扫描参数:TR为8000 ms,TE为98.3 ms,b值去0和1000 s/mm²,激励次数为1次,弥散梯度场取25个不同的方向。将自旋回波-平面成像序列图像传至服务器,用软件(FuncTool 4.5)进行后处理,图像校正减少其他因素的影响,设定阈值,计算相关参数数值。

1.2.2 病理组织中 VEGF、Ki-67 检测 收集所有患者手术切除的病理组织,常规固定、包埋、切片,二甲苯溶液脱蜡后采用梯度酒精水化,滴加3%过氧化氢降低内源性过氧化酶活性,乙二胺四乙酸(Ethylenediamine tetra acetic acid, EDTA)高压热修复,滴加VEGF抗体(鼠抗人,北京中杉金桥生物技术有限公司)、Ki-67抗体(鼠抗人,北京中杉金桥生物技术有限公司),4℃过夜处理,DAB显色,苏木素复染,梯度酒精脱水,二甲苯溶液透明,中性树胶封片。在高倍镜(400×)下随机选取5个视野,VEGF阳性染色为细胞质呈棕黄色,Ki-67阳性染色为细胞核呈棕黄色。VEGF采用半定量计分法,阳性细胞占比得分:阳性细胞占比为0-10%的0分,阳性细胞占比为11-25%得1分,阳性细胞占比为26-50%得2分,阳性细胞占比为51-75%得3分,阳性细胞占比为76-100%得4分。染色强度得分:若无阳性着色得0分,淡黄色染色得1分,黄色染色得2分,棕黄色染色得3分。阳性细胞占比得分与染色强度得分的乘积为最终得分,最终得分 ≥ 4 分为阳性,最终得分 < 4 分为阴性。Ki-67直接通过阳性细胞占比判定是否为阳性表达,阳性细胞占比不小于10%为阳性,阳性细胞占比小于10%为阴性。

1.3 观察指标

比较中低级别组和高级别组的表观扩散系数(Apparent diffusion coefficient, ADC)值、各向异性分数(Fractional anisotropy, FA)值、相对表观扩散系数(Relative apparent diffusion coefficient, rADC)值、相对各向异性分数(Relative fractional anisotropy, rFA)值。比较中低级别组和高级别组病理组织中VEGF、Ki-67的阳性表达率,采用Spearman分析ADC值、FA值、rADC值、rFA值与VEGF、Ki-67表达的相关性。

1.4 统计学方法

所有数据均用SPSS19.0进行统计分析,VEGF、Ki-67阳性率、性别比例等计数资料以率(%)的形式表示,采用 χ^2 检验,ADC值、FA值、rADC值和rFA值等计量资料以 $(\bar{x} \pm s)$ 的形式表示,采用t检验,采用Spearman分析ADC值、FA值、rADC值和rFA值与VEGF、Ki-67表达之间的相关性。检验标准设置为 $\alpha = 0.05$ 。

2 结果

2.1 中低级别组和高级别组 DTI 定量参数比较

高级别组的ADC值、FA值、rADC值和rFA值低于中低级别组($P < 0.05$),具体数据如表1所示。

2.2 中低级别组和高级别组病理组织中 VEGF、Ki-67 表达比较

高级别组病理组织中VEGF、Ki-67的阳性表达率高于中低级别组($P < 0.05$),具体数据如表2所示。

2.3 脑胶质瘤患者 DTI 定量参数与 VEGF、Ki-67 表达的相关性

经Spearman相关分析显示,ADC值、FA值、rADC值和rFA值与VEGF、Ki-67的表达水平均呈负相关($P < 0.05$),具体数据如表3所示。

3 讨论

WHO将脑胶质瘤分为I-IV级,高级别脑胶质瘤恶性程度高,常出现囊变坏死及出血,周围脑组织伴有水肿,且形态不规则、边界不清,而中低级别的脑胶质瘤中I级为良性肿瘤,II级

表 1 中低级别组和高级别组 DTI 定量参数比较($\bar{x} \pm s$)Table 1 Comparison of DTI quantitative parameters between middle low grade group and high grade group ($\bar{x} \pm s$)

Groups	n	ADC value($\times 10^{-3} \text{ mm}^2/\text{s}$)	FA value	rADC value	rFA value
Middle and low grade group	46	1.41 $\pm$ 0.31	0.16 $\pm$ 0.07	1.91 $\pm$ 0.45	0.33 $\pm$ 0.12
High grade group	44	1.16 $\pm$ 0.33	0.07 $\pm$ 0.02	1.66 $\pm$ 0.42	0.16 $\pm$ 0.07
t		3.706	8.212	2.722	8.161
P		0.000	0.000	0.008	0.000

表 2 中低级别组和高级别组病理组织中 VEGF、Ki-67 表达比较[n(%)]

Table 2 Comparison of the expression of VEGF and Ki-67 in pathological tissues of middle low grade group and high grade group[n(%)]

Groups	n	VEGF		Ki-67	
		Positive	Negative	Positive	Negative
Middle and low grade group	46	18(39.13)	28(60.87)	15(32.61)	31(67.39)
High grade group	44	42(95.45)	2(4.55)	30(68.18)	14(31.82)
χ^2		32.105		11.383	
P		0.000		0.001	

表 3 脑胶质瘤患者 DTI 定量参数与 VEGF、Ki-67 表达的相关性

Table 3 Correlation between DTI quantitative parameters and expression of VEGF and Ki-67 in patients with glioma

Indexes	ADC value		FA value		rADC value		rFA value	
	r	P	r	P	r	P	r	P
VEGF	-0.392	0.012	-0.536	0.000	-0.331	0.034	-0.584	0.000
Ki-67	-0.459	0.001	-0.518	0.000	-0.452	0.004	-0.543	0.000

则是介于良性与恶性之间的肿瘤^[12-14]。通常情况下,I级和II级的脑胶质瘤患者通过手术切除并辅以放化疗后可获得较好的预后,而III-IV级脑胶质瘤患者需要切除的范围较大,治疗方案通常是手术切除、放疗和化疗为主的综合治疗^[15,16]。由此可见,脑胶质瘤的分级与治疗方案的选择和患者的预后密切相关,因此术前准确的评估脑胶质瘤病理分级具有重要的意义。DTI是一种无创、便捷的检查手段,且不需要注射对比剂,对肾功能不全患者尤为适用^[17]。DTI的产生把影像诊断技术的应用扩大到了分子层面,可通过三维角度定量检测到水分子扩散的情况,ADC值和FA值是DTI最常用的定量参数,其中ADC值主要反映细胞外间隙的大小,可用于评估细胞内外间隙水分子的扩散情况,FA值是扩散各向异性成分与扩散张量总值的比值,可反映扩散的方向和大脑白质纤维的完整性^[18]。相关研究显示^[19],不同级别的脑胶质瘤的ADC值和FA值具有一定的差异,可用两参数来评估脑胶质瘤的级别。

本研究结果显示,高级别组的ADC值、FA值、rADC值和rFA值低于中低级别组($P<0.05$)。在活体组织内,组织细胞结构、密度和微循环等因素均会对水分子的扩散程度造成一定影响,肿瘤组织内的肿瘤细胞构成、胶质组织、肿瘤基质等都可以水分子扩散,进而影响ADC值^[20,21]。通常情况下中低分级脑胶质的肿瘤细胞增殖程度低于高级别脑胶质瘤,因此瘤体肿瘤细胞成分较少,细胞外间隙较大,利于水分子扩散,因此ADC值、rADC值升高^[22,23]。而FA值受到组织细胞紧密程度的影响,中低分级脑胶质的肿瘤细胞紧密程度较低,且随着胶质瘤浸润的

加深,正常细胞的结构也将遭到破坏,从而细胞内水分子弥散的各向异性也相应的降低,进而导致FA值、rFA值降低^[24,25]。VEGF在血管生成中具有重要的作用,直接参与了肿瘤新生血管的生成,而新生血管是肿瘤获取氧气和营养物质的主要途径,其在肿瘤的浸润和转移中扮演重要角色,因此VEGF的表达与恶性肿瘤的发展密切相关^[26-28]。Ki-67可反映肿瘤细胞的增殖情况,其在G0期无明显表达,在G1期、S期、G2期、M期均可检测到Ki-67表达,而在M期后期则很快消失,且Ki-67的半衰期短,因此可通过检测其水平来判定细胞增殖的情况^[29,30]。本研究结果显示,高级别组病理组织中VEGF、Ki-67的阳性表达率高于中低级别组($P<0.05$),这主要是因为高级别的脑胶质瘤其新生血管更多,且肿瘤细胞增殖更加旺盛,因此VEGF、Ki-67的阳性表达率更高。经Spearman相关分析显示,ADC值、FA值、rADC值和rFA值与VEGF、Ki-67的表达水平均呈负相关($P<0.05$),由此可见DTI定量参数与VEGF、Ki-67的表达水平具有明显的相关性,因此可以通过检测DTI定量参数来评估脑胶质瘤的恶性程度。

综上所述,DTI定量参数ADC值、FA值、rADC值和rFA值与肿瘤分级存在一定的相关性,且与肿瘤组织中的VEGF、Ki-67的表达水平密切相关,临床上可通过DTI检查来预测脑胶质瘤患者的分级情况,为治疗方案的制定和患者预后的评估提供参考。

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