MRI 纹理特征定量分析用于 $T_{2,3}$ 期直肠癌精准分期的初步研究

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摘　要:[目的] 探讨磁共振成像(magnetic resonance imaging,MRI)纹理特征定量分析用于鉴别 $T_{2,3}$ 期直肠癌异质性及精准分期的价值。[方法] 回顾性分析 15 例经手术病理证实 T_2 及 T_3 期病例,且在术前两周内行直肠 MRI 高分辨率平扫,每个病例选取显示病变较为满意 T_2WI 轴位图像的若干层面,其中 T_2 期 8 例选取 41 层,T_3 期 7 例选取 40 层,在 MaZda 软件中勾画病变感兴趣区 (region of interest,ROI)提取病变纹理特征,用该软件提供的纹理特征选择方法中的交互信息(mutual information,MI)、Fisher 系数(Fisher coefficient,Fisher)、分类错误概率联合平均相关系数(classification error probability combined with average correlation coefficients,POE+ACC)3 种方法联合(Fisher+POE+ACC+MI,FPM)对提取纹理进行降维处理得到 30 个纹理特征,然后用该软件提供的纹理特征分类分析方法非线性分类分析(nonlinear discriminant analysis,NDA)对 81 个样本进行分类分析。采用组间与组内的平方和比例(between-category to within-category sums of squares,BW)和决策曲线分析法(decision curve analysis,DCA)筛选出 3 个最优特征,并比较两者差异。利用二元 Logistic 回归及 ROC 曲线计算三者独立及联合的诊断效能。[结果] 81 层图像分类的准确性为 92.6%,以 T_2 期图像作为阴性组、T_3 期图像作为阳性组计算敏感性为 93.0%,特异性为 93.2%,漏诊率为 7.0%,误诊率为 6.8%。以 BW 及 DCA 方法筛选出两组最优特征相同,前 3 个最优特征为 S(4,0) 平方和(sum of squares,SumOfSqs)、S(5,0)SumOfSqs、S(3,0)SumOfSqs,效能排序有差异,三者联合的敏感性和特异性分别为 85.0% 和 70.4%,独立的敏感性和特异性分别为 80.0%和 62.9%,80.0%和 62.9%,72.5%和 60.3%。三者联合及独立的敏感性和特异性均低于 30 个纹理 NDA 分类结果。[结论] $T_{2,3}$ 期直肠癌异质性有明显差异,MRI 纹理特征定量分析能为 $T_{2,3}$ 期直肠癌的术前精准分期提供可靠客观依据。

关键词:直肠癌;纹理特征分析;T 分期;精准分期;磁共振成像
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Preliminary Study on Precise Staging of Rectal Cancer Stage $T_{2,3}$ Based on Quantitative Analysis of MRI Texture Features

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Abstract:[Purpose] To investigate the quantitative analysis of MRI texture features in differentiating heterogeneity and precisely staging for rectal cancer stage $T_{2,3}$. [Methods] Clinical and imaging data of 15 patients with stage $T_{2,3}$ rectal cancer confirmed by postoperative pathology,who underwent rectal high-resolution MRI scan two weeks before operation,were retrospectively analyzed. The images which were more satisfied with the axial T_2WI were selected,and 41 images were selected in 8 stage T_2 cases and 40 images were selected in 7 stage T_3 cases. By MaZda software,the region of interest(ROI) of the lesion was delineated for extracting the texture features. The mutual information (MI),Fisher coefficient(Fisher),and classification error probability combined with average correlation coefficients (POE+ACC) were provided by the software. The Fisher,POE+ACC and MI,and FPM(combination of Fisher,POE+ACC and MI) were used for screening texture features,then 30 texture features were obtained. Nonlinear classification analysis(NDA) was used for classifying 81 samples. Three optimal features were screened by the methods of BW (between-category to within-with-the-sums,BW) and DCA (decision curve analysis,DCA),then comparing the differences of the result. The diagnostic efficacy of three single features,and their combination was analyzed by using binary Logistic regression and ROC curve. [Results] The accuracy of image classification in 81 samples was 92.6%. The sensitivity of T_2 image as negative group and T_3 image as posi-

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tive group was 93.0%, the specificity was 93.2%, the missed rate was 7.0%, and the misdiagnosis rate was 6.8%. The two sets of optimal characteristics were selected by BW and DCA methods, the first three optimal features were S(4,0) sum of squares(SumOfSqs), S(5,0)SumOfSqs, S(3,0)SumOfSqs, and the efficiency order was different. The sensitivity and specificity of the combination of three optimal features were 85.0% and 70.4%, and the sensitivity and specificity of three single features were 80.0% and 62.9%, 80.0% and 62.9%, 72.5% and 60.3%, respectively. The sensitivity and specificity of the three single features or their combination were lower than the results of 30 texture features NDA classifications. [Conclusion] There are significant differences in the heterogeneity of rectal cancer stage $T_{2,3}$, and the quantitative analysis of MRI texture feature may provide a reliable and objective basis for precise staging of preoperative rectal cancer stage $T_{2,3}$.
Key words: rectal cancer; texture analysis; T stage; precise staging; magnetic resonance imaging

随着医学成像技术的改进及诊疗水平的提高，直肠癌的早期诊断率已得到了明显提升，目前直肠癌的治疗是以手术为主，放疗、化疗为辅的综合治疗。中国临床肿瘤学会(CSCO)结直肠癌诊疗指南提出磁共振成像（magnetic resonance imaging，MRI）应被列为所有直肠癌患者分期检查手段，但在MRI图像上对直肠癌T_2与T_{3a}期及T_3期是否累及直肠周围系膜筋膜的判断有时较为困难，且受诊断医生的经验与主观因素影响较大[1]。图像纹理特征可以一定程度揭示肿瘤的异质性，本文探讨常规MRI纹理特征分析用于直肠癌$T_{2,3}$期异质性鉴别的价值及对精准分期的意义。

1 资料与方法

1.1 临床资料

选取2018年4月至2019年3月期间在河南大学淮河医院行直肠磁共振高分辨扫描的直肠癌患者，纳入标准：①经病理证实的直肠腺癌$T_{2,3}$期患者；②高分辨T_2WI扫描，图像质量良好，病变显示清晰；③磁共振扫描前无放化疗及相关手术。排除标准：①术后病理结果为黏液腺癌或非直肠腺癌如：肛管鳞癌、黑色素瘤等；②伪影较多、图像信噪比较差的患者；③病灶实性成分少，囊变坏死成分多。

15例符合条件的术后病理为T_2、T_3期患者被纳入本研究，且手术后均有病理作为肿瘤浸润周围深度及组织学类型的诊断依据。年龄50~81岁，平均年龄(65.0±10.4)岁。T_2期8例选取41层图像，T_3期7例选取40层图像，共81个样本。

1.2 MRI检查方法

在磁共振进行扫描前，要求患者排便清空肠道。采用德国西门子公司Verio 3.0T磁共振扫描仪，盆腔覆盖表面线圈，头先进仰卧位。扫描序列及参数：T_2WI盆腔冠状位：TR3500ms，TE101ms，矩阵288×320，FOV230mm×230mm，层厚5mm，层间距6mm；T_2WI直肠矢状位：TR3500ms，TE84ms，矩阵403×448，FOV200mm×200mm，层厚3mm，层间距3.9mm；T_2WI直肠横轴位：TR4500ms，TE101ms，矩阵322×448，FOV160mm×200mm，层厚3.5mm，层间距4.6mm；T_1WI直肠横轴位：TR634ms，TE12ms，矩阵336×448，FOV160mm×200mm，层厚3.5mm，层间距4.6mm；DWI直肠横轴位：TR5400ms，TE93ms，矩阵120×160，FOV221mm×260mm，层厚4.5mm，层间距5.9mm；T_2WI盆腔横轴位：频率选择脂肪抑制序列，TR4330ms，TE105ms，矩阵260×320，FOV192mm×240mm，层厚4.5mm，层间距5.9mm。

1.3 图像选择

从我院的影像归档与通信系统(Picture Archiving and Communication System，PACS）中选取T_2WI轴位序列中病灶显示较为满意，同时容积效应及伪影较小的层面，将所有数据图像从PACS导出为DICOM格式，将T_2WI周围图像导入MaZda软件中，为了减少对比度及亮度等参数变化对纹理结果的影响，需对图像的灰度进行统一化处理。由3位高年资有盆腔诊断经验的放射科医师进行感兴趣区域(region of interest，ROI)评阅及描绘，可结合T_1WI、DWI序列及增强T_1WI图像以确保ROI区域覆盖整个肿瘤区域及所在肠管，ROI区域应超过病灶边缘距离至少为1mm。

1.4 图像纹理分析

①纹理特征提取：选定ROI区域后MaZda除外

几何特征共有279个纹理特征提取如下：直方图[均值(mean)，方差(variance)，偏度(skewness)，峰度(kurtosis)，百分位数(perc. 1%，10%，50%，90%，99%)]，灰度共生矩阵[角度二阶矩(angular second moment，AngScMom)，对比度(contrast)，相关性(correlation，Correlat)，熵(entropy)，和熵(sum entropy，SumEntrp)，平方和(sum of squares，SumOfSqs)，和平均(sum average，SumAverg)，和方差(sum variance，SumVarnc)，逆差分矩(inverse difference moment，InvDfMom)，差熵(difference entropy，DifEntrp)，差异方差(difference variance，DifVarnc)(对于4个方向(0、45、90、135度)和5个像素间距离(偏移；n=1到5)]，游程矩阵[游程长度非均匀性(run length nonuniformity，RLNonUni)，灰度非均匀性(grey level nonuniformity，GLevNonU)，长游程权重(long run emphasis，LngREmph)，短游程权重(short run emphasis，ShrtREmp)，游程中的图像分数(fraction of image in runs，Fraction)]，绝对梯度(absolute gradient)(梯度均值GrMean，方差GrVariance，偏度GrSkewness，峰度GrKurtosis，非零GrNonZeros)，自回归模型[Teta1–4(parameter θ1–4)，Sigma(parameter σ)和小波变换(Wavelet)(小波变换系数的能量分解为LL、LH、HL、HH 4个分量，L和H分别表示低通和高通滤波输出，在5个尺度计算哈尔小波，例如WavEnLL_s-1)。

②纹理特征筛选方法：提取纹理特征值后，需选择最具有鉴别意义的纹理特征。MaZda软件有3种纹理特征降维选择可供选择，包括Fisher系数(Fisher coefficient)、分类错误概率联合平均相关系数(classification error probability combined with average correlation coefficients，POE+ACC)以及交互信息(mutual information，MI)，上述每个方法均可选择出10个最具有鉴别诊断意义的纹理特征值，或者将3个方式联合(Fisher+POE+ACC+MI，FPM)，可选择出的纹理特征参数有30个。本次研究中采用FPM来筛选出有鉴别和诊断价值的纹理参数。

③纹理特征分析方法：MaZda的统计分析程序模块B11，用于选择纹理参数预处理，探索性分析和纹理数据分类。用于磁共振图像的定量分析，包含4种用于数据分类纹理分析的方法：原始数据分析(raw data analysis，RDA)、线性分类分析(linear discriminant analysis，LDA)、主要成分分析(principal component analysis，PCA)以及非线性分类分析(nonlinear discriminant analysis，NDA)。利用这些纹理分析分类方式可对磁共振序列的多种纹理参数进行处理分类，本研究采用NDA方法对81个样本进行分类。得到综合纹理参数对81个样本分类的准确性、敏感性、特异性、漏诊率、误诊率。从30个纹理特征中筛选出3个最优纹理，评价独立及联合纹理的诊断效能。

1.5 统计学处理

以SPSS23.0进行统计分析，独立样本 t 检验对两组纹理参数进行统计学差异检验($P<0.05$)，样本是否符合正态分布，去除无统计学差异的纹理参数。采用组间与组内的平方和比例(between-category to within-category sums of squares，BW)和决策曲线分析法(decision curve analysis，DCA)筛选出3个最优特征，并比较两者差异。利用二元Logistic回归及ROC曲线计算三者独立及联合的诊断效能。

2 结 果

2.1 $T_{2,3}$期直肠癌T_2WI图像纹理特征NDA分类结果

以FPM来筛选出30个纹理，独立样本 t 检验显示两组纹理具有显著统计学差异($P<0.05$)，样本符合正态分布。用NDA方法对81个样本30个T_2WI纹理特征进行分类，30个纹理特征 t 检验结果见表1(Table 1)，其中3个T_2期样本分类为T_3期，3个T_3期样本分类为T_2期，以T_3期为阳性组，T_2期为阴性对照组，计算准确性为92.6%，敏感性93.0%，特异性93.2%，漏诊率7.0%，误诊率6.8%。

2.2 T_2WI最优纹理筛选及诊断效能

以BW方法筛选出前3个最优特征，分别为S(4，0)SumOfSqs、S(5，0)SumOfSqs、S(3，0)SumOfSqs，如图1(Figure 1)。以DCA方法筛选出前3个最优特征分别为S(5，0)SumOfSqs、S(4，0)SumOfSqs、S(3，0)SumOfSqs，如图2(Figure 2)。BW及DCA方法筛选出两组最优特征相同，效能排序有差异。以本研究中纳入的直肠癌患者T分期为因变量，3个最优特征为自变量，进行二元Logistic回归分析以输入方式计算联合概率，并得到三者联合及独立ROC曲线，如图3及表2(Table 2；Figure 3)。三者联合的敏感性和

特异性分别为 85.0%和 70.4%；S(4,0)SumOfSqs 纹理的敏感性和特异性分别为 80.0%和 62.9%，cutoff 值为 1576.828；S(5,0)SumOfSqs 纹理的敏感性和特异性分别为 80.0%和 62.9%，cutoff 值为 1541.797；S(3,0)SumOfSqs 纹理的敏感性和特异性分别为 72.5%和 60.3%，cutoff 值为 1643.555。三者联合及独立的敏感性和特异性均低于 30 个纹理 NDA 分类结果。

Table 1　Results of 30 T_2WI texture features of $T_{2,3}$ stage rectal cancer

Texture features	Texture vaules of T_2 stage lesions(N=41)	Texture vaules of T_3 stage lesions(N=40)	*t*	*P*
S(3,0)SumOfSqs	1569.1±71.5	1666.8±90.2	−5.409	<0.001
S(4,0)SumOfSqs	1521.4±74.8	1632.9±100.4	−5.675	<0.001
S(5,0)SumOfSqs	1487.5±79.1	1602.8±110.2	−5.423	<0.001
S(2,−2)SumOfSqs	1599.0±72.5	1683.4±96.1	−4.467	<0.001
S(5,−5)SumOfSqs	1466.7±89.9	1578.9±122.3	−4.717	<0.001
S(2,0)SumOfSqs	1629.5±66.2	1701.2±81.2	−4.358	<0.001
S(3,−3)SumOfSqs	1533.5±81.4	1641.3±108.5	−5.066	<0.001
S(0,5)SumOfSqs	1540.8±80.8	1649.5±115.3	−4.924	<0.001
S(3,3)SumOfSqs	1532.0±75.2	1635.0±105.3	−5.078	<0.001
S(4,4)SumOfSqs	1492.0±80.2	1598.1±110.6	−4.955	<0.001
Horzl_RLNonUni	3364.3±723.0	4132.7±986.0	−4.007	<0.001
Perc.10%	214.4±62.0	269.4±53.5	−4.265	<0.001
S(0,5)DifEntrp	1.9±0.0	1.9±0.1	1.877	0.064
WavEnHL_s−4	61114.7±30146.8	45515.8±11600.9	3.059	0.003
S(1,0)SumOfSqs	1692.0±63.2	1734.9±73.9	−2.811	0.006
Teta1	0.7±0.1	0.6±0.0	3.056	0.003
Skewness	1.0±0.3	0.7±0.5	3.731	<0.001
135dr_RLNonUni	3427.8±742.7	4201.5±1007.9	−3.94	<0.001
Perc.1%	119.7±65.2	155.9±54	−2.713	0.008
S(1,−1)SumOfSqs	1679.4±63.4	1726.5±82.7	−2.884	0.005
Mean	402.8±73.3	495.2±89.0	−5.104	<0.001
S(4,−4)SumOfSqs	1492±85.9	1605.1±118.4	−4.93	<0.001
Perc.50%	355.4±57.9	445.2±102.8	−4.859	<0.001
S(5,5)SumOfSqs	1467.3±81.9	1572.0±114.1	−4.752	<0.001
S(4,0)SumVarnc	4469.6±463.3	4975.7±518.6	−4.635	<0.001
S(0,5)SumVarnc	4445.0±514.1	5043.9±651.4	−4.599	<0.001
S(5,0)SumVarnc	4064.5±428.9	4564.5±552.2	−4.558	<0.001
S(0,4)SumVarnc	4801.9±509.4	5372.7±619.5	−4.534	<0.001
S(3,−3)SumVarnc	4512.9±519.3	5057.7±570.4	−4.498	<0.001
S(0,4)SumOfSqs	1576.0±76.0	1668.7±110.3	−4.416	<0.001

Notes：SumOfSqs：sum of squares；RLNonUni：run length nonuniformity；DifEntrp：difference entropy；RLNonUni：run length nonuniformity；Teta1：parameter θ1；SumVarnc：sum variance

3　讨　论

直肠癌的精准分期有助于临床医生制定合适的治疗方案，直肠 MRI 检查对直肠癌的诊断、术前分期的评估及观察预后有很重要的作用[2]，传统 MRI 检查可得到直肠癌形态学上的信息，尚无法进行定量评价，导致 TNM 分期出现偏倚。近年来，随着影像组学、精准医学的逐渐发展，影像诊断进入了大数据时代[3]，由传统的灰阶图像的诊断提升到基于影像图像的影像组学分析，也即从病变位置形态的研究进阶为病变内部自身性质的探索[4-6]。直肠癌 T_3 期具有较高的转移及复发风险，但 T_2 期和 T_3 期的诊断准确率很低，长期以来，众多学者致力于如何提高 T_2 期与 T_3 期的诊断率及鉴别诊断[7]。现有研究证明纹理分析可为影像诊断提供新的诊断工具[8-9]。纹理分析以图像的特征为基础，通过一些图像处理技术来提取纹理特征参数，然后运用数学计算区域内的灰度级的

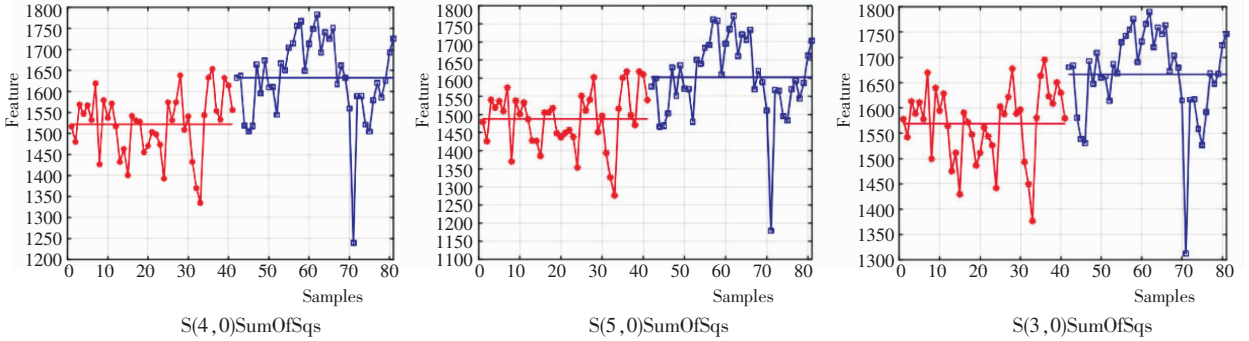

Figure 1　The top three optimal features selected by BW method

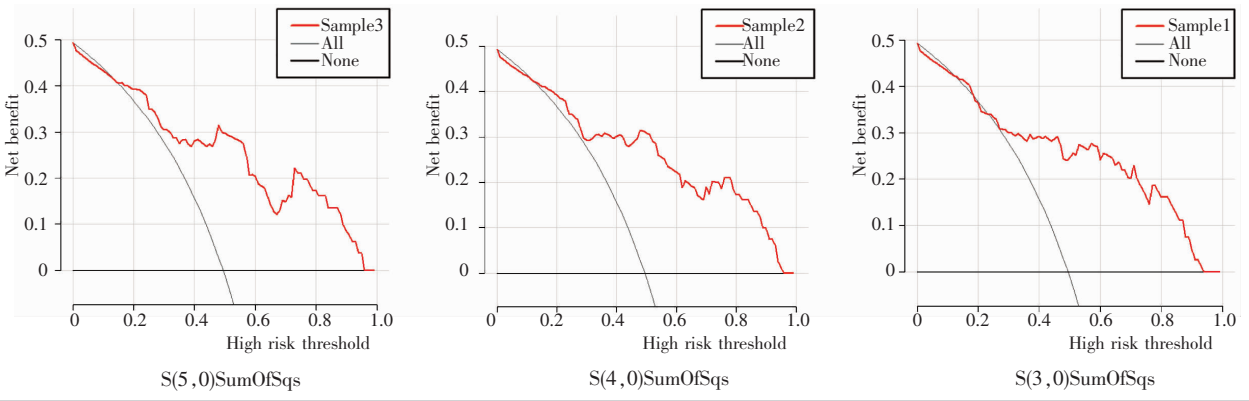

Figure 2　The top three optimal features selected by DCA method

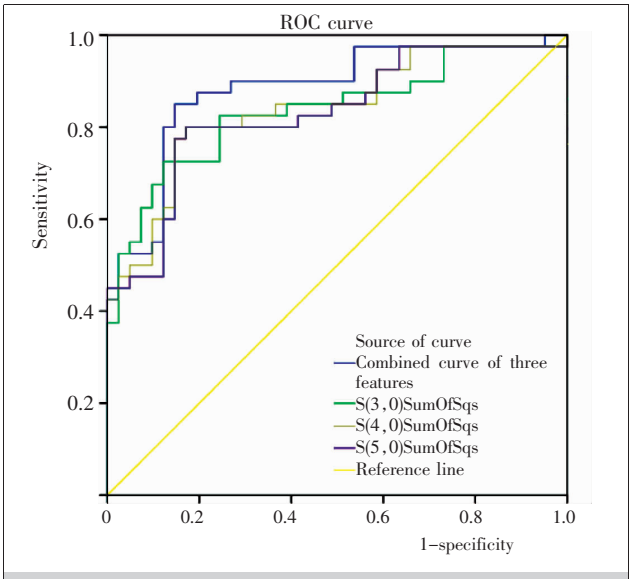

Figure 3　Three optimal textures combined and independent ROC curves

Table 2　Three optimal textures combined and independent areas under ROC curves

Test result variable	Area	Standard error	*P*	95% confidence interval
Combined curve	0.882	0.039	<0.001	0.806~0.958
S(3,0)SumOfSqs	0.835	0.046	<0.001	0.744~0.926
S(4,0)SumOfSqs	0.840	0.045	<0.001	0.752~0.929
S(5,0)SumOfSqs	0.831	0.046	<0.001	0.741~0.921

Note:SumOfSqs:sum of squares

空间分布特点，即将医学图像的灰度表示成纹理信息，进而对肿瘤进行定量或定性的分析，以对肿瘤进行更准确的分期，对临床疾病的诊断提供新的参考思路[10-11]。近年来更多研究显示，基于 MRI 的纹理参数分析在结直肠癌的治疗评估也具有一定的应用价值[12-15]。

目前图像纹理分析已广泛应用于肿瘤的诊断、鉴别诊断及疗效评估中[16-18]。对于直肠癌，Liang 等[19]对 494 例患者的 CT 纹理特征进行分析研究，探索了影像组学特征与直肠癌分期间的关系，其使用 LASSO 算法筛选出的 16 个特征可作为独立危险因子对直肠癌进行准确分期($T_{1,2}$ *vs* $T_{3,4}$)，表明影像组学相关纹理特征可能成为直肠癌术前分期的辅助工具。本次研究将图像纹理分析方法应用于直肠癌 T_2 期和 T_3 期的鉴别，首先提取 T_2 期和 T_3 期直肠癌 81 个(T_2WI)图像样本 279 个纹理特征值，研究发现直肠癌 T_2 期与 T_3 期间纹理特征存在显著差异，将提取的纹理特征经过 FPM 来降维筛选出 30 个有统计学意义(P<0.05)的纹理参数，再用 NDA 方法对 81 个样本 30 个 T_2WI 纹理特征进行分类分析，然后以 T_3 期为阳性组，T_2 期为阴性对照组，计算准确性为 92.6%，特异性 93.2%，准确性高于以 BW 及 DCA 方法筛选出的 3 个最优特征的联合和独立准确性，AI-Sukhni 等[1]的一项 Meta 分析显示，直肠 MRI 对直肠癌 T 分期（$T_{1,2}$/$T_{3,4}$）诊断的敏感性与特异性分别为 87%与 75%，其准确性亦低于本研究中 30 个纹理的准确性，表明选用的纹理参数越多，用于图像判读的准确性越高，由于纹理参数越多，其用于诊断所包含的信息亦越多。钟红霞[20]针对 $T_{1,2}$/$T_{3,4}$ 的直肠癌鉴别诊断研究显示，T_2WI 纹理特征参数中 sd0/4、entropy 存在显著差异，仅在早期($T_{1,2}$ 期)和进展期($T_{3,4}$ 期)两组间做了纹理差异分析，未对 T_2、T_3 期精准分期做量化研究。本研究利用 ROC 曲线对该联合参数及其单变量的诊断价值进行分析评估，曲线下面积越接近 1.0 说明诊断价值越大，接近 0.5 时一般认为无

诊断价值,结果显示,该联合参数预测的曲线下面积为 0.882,其敏感性为 85.0%,特异性为 70.4%,其单变量参数曲线下面积介于 0.831~0.840,表明多参数联合预测的准确性较高，其诊断的准确性优于单变量。每个纹理特征参数反映了区域内的灰度级变化,单独每个纹理特征参数在鉴别中有一定的准确性,为综合考虑每个纹理特征参数在直肠癌分期鉴别中的意义，通过多参数联合分析诊断效能较单因素分析显著提高，在直肠癌 T_2 期和 T_3 期的鉴别上取得更好的效果,故在临床实践中有一定的实用性。

筛选出的优势纹理特征主要集中在 SumOfSqs,该纹理特征属于灰度共生矩阵。灰度共生矩阵基于对相邻强度值的相对频率进行编码，反映不同像素强度的空间关系[21]。SumOfSqs 是影像纹理灰度变化均一的度量，反映了图像灰度分布的均匀程度和纹理粗细程度，值越大则纹理越粗糙，越小则纹理细致，较高的纹理值提示病变的异质性越高。直肠癌 T_3 相对于 T_2 期有更高的侵袭性,T_3 期直肠癌穿透固有肌层,并且有可能侵犯壁外血管,细胞核浆比、肿瘤血管、细胞外基质的变化以及肿瘤内坏死都会引起肿瘤异质性的变化[22],我们猜测直肠癌在 T_2 期的基础上外侵演变为 T_3 期,其病变的异质性也发生变化,反映在纹理特征上的相应改变。Liu 等[23]通过 ADC 图像的直方图和灰度共生矩阵的比较研究显示,灰度共生矩阵对比度、相关性、熵的值升高时,肿瘤向外浸润的风险显著上升,与我们研究结果相似。本文的研究结果显示直肠癌 T_2WI 图像灰度共生矩阵 SumOfSqs 的值升高时,肿瘤的异质性增高,向外浸润风险上升,T_3 期概率增高，可作为肿瘤壁外浸润的独立预测因素。

本研究的主要不足：第一，影像组学特征是从 MRI 轴位截面图上手动勾画的 ROI 中提取,ROI 区域不能准确地描绘肿瘤的形态、体积,可能会影响纹理特征的准确性,需继续改进纹理特征的提取方式;第二,本研究属于回顾性分析,可能存在选择偏倚,且纳入的样本量不够大,需进一步扩大样本量,减少数据量对结果准确性的影响，同时本研究可以通过对其他序列如 T_1WI、ADC 等提取纹理特征，多序列联合诊断直肠癌;第三,本研究是利用纹理特征对直肠癌术前 T 分期精准诊断进行初步探索,样本较小未能建立分类模型，还需今后在大样本基础上进一步研究。

综上所述,MRI 纹理定量分析能为 $T_{2,3}$ 期直肠癌的术前诊断提供可靠客观依据，有助于后期临床制定个性化治疗方案,达到精准诊疗的目的。

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