

· 综述 ·

## 纹理分析在结直肠癌诊治中的应用进展

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**【摘要】** 结直肠癌是常见恶性肿瘤,也是癌症相关死亡的第二大原因,其早期诊断和肿瘤分期对治疗方式的选择有重要意义。纹理分析是一种新型影像分析技术,通过纹理分析对影像学图像进行处理,能预测肿瘤侵袭程度、微小转移灶和治疗反应性等信息,有助于肿瘤的早期诊断、分期和预后评估。该文综述了纹理分析在结直肠癌中的应用进展。

**【关键词】** 结直肠癌;纹理分析;治疗反应

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**【Abstract】** Colorectal cancer is a common malignant tumor, and it is also the second leading cause of cancer-related death. Early diagnosis and tumor staging are of great importance for the choice of treatment. Texture analysis, as a new type of image analysis technique, can be used to predict the degree of tumor invasion, micrometastasis and therapeutic response thus contributing to the early diagnosis, staging and assessment of prognosis. This article summarizes the application of texture analysis in colorectal cancer.

**【Key words】** Colorectal cancer; Texture analysis; Therapeutic response

结直肠癌(colorectal cancer, CRC)居常见恶性肿瘤第3位、肿瘤相关死亡第2位<sup>[1]</sup>。其确诊依靠病理,影像学手段主要起提示诊断、进行治疗前评估及监测预后的作用。传统影像学检查在反映肿瘤形态、大小、部位、侵袭程度、远处转移等方面有一定价值,但对肿瘤的精确评估价值有限。近年来,越来越多的研究表明,纹理分析(texture analysis, TA)通过分析影像图像中像素或体素灰度的分布和联系,深度挖掘其细微结构和变化规律,能更精确地评估肿瘤异质性<sup>[2-4]</sup>、内在侵袭性和治疗抗性。因此,纹理分析有望成为更有效的肿瘤评估方式,指导临床选择合适治疗方案,有助于谋求患者效益最大化。

### 1 纹理分析

纹理分析是指通过对传统影像图像进行后处理,对图像像素的强度和空间分布特点进行数学分析与运算,从而量化纹理参数的一种方法<sup>[5]</sup>。

其图像来源主要为CT、MRI和一些后处理图像等:基于平扫CT的纹理分析主要反映肿瘤内部结构特点及坏死、出血、囊变等密度的改变;基于增强CT的纹理分析能进一步反映造影剂在血管内外分布的非均质性;基于MRI图像的纹理分析具有更高的对比度和分辨率,可减少图像噪声对纹理参数的影响<sup>[6]</sup>,从而更准确地反映纹理特征。

#### 1.1 纹理分析方法

常用的纹理分析方法主要分为四大类:统计分析法、结构分析法、模型分析法和频谱分析法<sup>[7]</sup>。统计分析法根据图像像素的强度和分布规律来反映图像纹理特征,常用的有灰度共生矩阵法和灰度-梯度共生矩阵法、长游程法等;结构分析法通过提取纹理内部空间排列和位置关系来获取结构信息,可反映组织空间结构及周期性规律;模型分析法将图像中的每一个像素都看作与

其相邻像素存在某种函数关系,进而从整体估算所有像素的空间位置关系;频谱分析法常采用Laplacian of Gaussian过滤技术来处理图像,将过滤条件调整至合适范围,然后经变换提取出纹理特征。

### 1.2 纹理参数的意义

纹理分析中,描述灰度变化规律的数字特征称为图像的纹理特征,用纹理参数来量化,常用的纹理参数主要有熵(entropy)、均匀性(uniformity)、对比度(contrast)、标准差(standard deviation, SD)、峰度(kurtosis)、偏度(skewness)等<sup>[8]</sup>。峰度和偏度是纹理的一阶统计参数,主要描述灰度直方图的分布特征;熵反映图像纹理的复杂度和混乱度,若纹理灰度分布随机则熵值较大;均匀性反映纹理的规则程度,纹理杂乱无章时均匀性较低;对比度反映图像的清晰度和纹理沟纹的深浅程度,纹理沟纹深,对比度大。

## 2 纹理分析在结直肠癌分期中的应用

### 2.1 评估肿瘤T分期

研究表明,与根治性手术相比,对局部晚期直肠癌(pT3-4期和(或)pN1-2期)患者行新辅助治疗(neoadjuvant therapy, NAT)后手术可降低50%~61%的局部复发风险<sup>[9]</sup>。然而,NAT也有骨髓抑制、药物性肝损伤等严重不良反应<sup>[10-11]</sup>。因此,准确的分期有助于患者选择正确的治疗方式,避免不必要的药物毒性反应。Liu等<sup>[10]</sup>研究表明,基于表观扩散系数(apparent diffusion coefficient, ADC)图的纹理分析可评估肿瘤T分期。该研究发现,与pT3-4期患者相比,pT1-2期患者图像的偏度、熵和对比度明显偏低,其中偏度和熵是肿瘤外侵的独立预测因子。理论上,偏度可反映感兴趣区(region of interest, ROI)像素灰度强度分布的不对称性,熵可反映像素的空间分布情况,较高的偏度和熵反映了ROI纹理的复杂性,提示病变区域异质性增加。因此,与pT1-2期相比,pT3-4期肿瘤具有更复杂的纹理特征。

### 2.2 诊断淋巴结转移

淋巴结转移对肿瘤分期及治疗方式的选择非常重要,同时也是判断预后的重要指标。影像学检查常基于淋巴结的形态学特征来鉴别其良恶性。但一项大样本研究指出,转移也可发生

于正常大小形态的淋巴结中,常规测量短轴直径不能作为淋巴结受累的可信指标<sup>[9]</sup>。Langman等<sup>[12]</sup>也认为,影像学检查对肿大的非转移性淋巴结的鉴别和小淋巴结中微转移灶的检出有很大局限性。纹理分析为淋巴结转移的确诊提供了新的方法。Liu等<sup>[10]</sup>应用结直肠癌原发灶的纹理特征来评估淋巴结状态,发现熵在无淋巴结累及(pN0)与淋巴结受累(pN1-2)的肿瘤之间差异有统计学意义。熵作为淋巴结转移的独立预测因子,其区分pN0期与pN1-2期患者受试者工作特征(receiver operating characteristic, ROC)曲线的曲线下面积(area under curve, AUC)为0.751,灵敏度和特异度分别为96.2%、45.3%。另一项针对220例淋巴结转移的结直肠癌患者的研究表明,良恶性淋巴结的CT纹理特征不同,恶性淋巴结的分数维度较良性淋巴结高,据此判断淋巴结转移的准确率达88%<sup>[13]</sup>。因此,对原发肿瘤及淋巴结纹理属性的评估有助于预测淋巴结转移情况。

### 2.3 检测肝脏微小转移灶

肝脏是结直肠癌患者最常发生转移的器官。有研究表明,结直肠癌患者同时性肝转移的发生率约20%<sup>[11]</sup>,随访1年后延迟性肝转移发生率为4.3%,而随访5年后发生率为14.5%<sup>[14]</sup>。有文献指出,58%~81%的结直肠癌肝转移患者在肝脏手术切除标本中可见微转移灶<sup>[15]</sup>,因此有学者认为延迟性肝转移可能是由肝内已存在的隐匿性转移发展而来<sup>[16]</sup>。相关研究表明,纹理分析有望发现形态学尚不可见的微转移灶,从而指导后续治疗。Rao等<sup>[17]</sup>对29例结直肠癌患者肝脏CT图像的非病灶区进行纹理分析,发现无转移灶、同时性肝转移和延迟性肝转移3组病例之间纹理参数存在差异,当微转移灶存在于无明显转移的肝组织中,会引起肝脏血流动力学发生改变,导致更高的空间异质性<sup>[18]</sup>,从而在纹理参数上与正常肝组织区分。但该结论尚需大样本研究的支持。

## 3 纹理分析在结直肠癌临床疗效和评估生存中的应用

### 3.1 预测原发肿瘤的治疗反应

NAT后行全直肠切除术是局部晚期直肠癌的首选治疗方法<sup>[19]</sup>,可有效减少复发率<sup>[20]</sup>,但也会导致对治疗部分反应(partial response,

PR)或无反应(non-response, NR)患者的过度治疗<sup>[23]</sup>,因此有必要对治疗反应进行准确和早期的评估。De等<sup>[22]</sup>研究表明, MRI图像的纹理参数可评估NAT治疗反应: NAT治疗前,病理完全反应(pathological complete response, pCR)组患者峰度比PR+NR组高, NAT治疗后pCR组峰度较PR+NR组低; pCR组患者NAT治疗后峰度下降程度明显较PR+NR组高。另一项研究<sup>[23]</sup>也发现,与其他参数相比,峰度是预测pCR的最有效参数,灵敏度和特异度分别为100%和67% (AUC=0.861, P=0.001)。这与理论结果一致,即具有较强治疗抗性和高侵袭性的肿瘤具有较高的异质性,因此纹理参数能有效量化肿瘤异质性,有望成为预测NAT治疗反应的生物成像标记。

### 3.2 预测肝转移灶的治疗反应

对于结直肠癌肝转移患者,手术切除是实现长期生存的最有效方法<sup>[24]</sup>。对暂时无法手术的患者可先行系统化疗,使转移灶体积缩小,分期下降后再行根治性手术<sup>[25]</sup>。临床研究表明,化疗反应良好者行根治性切除后可获得长期生存,但如果术前化疗不敏感,肝转移灶切除后患者预后也不理想<sup>[26]</sup>,因此有必要在术前正确预测治疗反应。以前对治疗反应的评估主要根据肿瘤退缩分级标准(tumor regression grading, TRG),有研究表明纹理分析可提供相关信息。Rao等<sup>[27]</sup>研究发现,熵和均匀性是区分化疗后良好反应(TRG 1~2)与不良反应(TRG 3~5)的重要预测因素; Ahn等<sup>[28]</sup>发现,较低的偏度和较小的标准差是治疗反应有效的独立预测因子,在验证队列中也显示出良好的预测价值(AUC=0.797)。理论上,对治疗反应良好的转移病灶常被坏死和纤维组织代替,具有更均质的内部结构;而不良反应病灶中仍有大量存活的肿瘤细胞,导致病灶仍有较大异质性。因此,纹理分析有望评估转移灶对化疗的敏感性,从而指导治疗方案的正确选择。

### 3.3 评估放化疗后总体生存

纹理分析还可被用于预测NAT治疗后患者的总体生存(overall survival, OS)。Ng等<sup>[29]</sup>发现,熵、均匀性、峰度、偏度和标准偏差均可作为总体生存率的独立预测因子。另一项基于MRI图像的纹理分析也发现了类似结果,该研究发现平均

阳性像素值、平均强度均可预测总体生存和无病生存(disease free survival, DFS),峰度可独立预测无复发生存(recurrence free survival, RFS)<sup>[30]</sup>。Miles等<sup>[31]</sup>的研究也表明,均匀性是长期生存的最佳预测参数。此外, Ganeshan等<sup>[32]</sup>研究发现,对结直肠癌肝转移患者,纹理分析也显示出预测生存的潜力,熵和均匀性与CRC肝转移患者的总体生存有关,在熵<2.0时准确鉴别了4例于36个月内死亡的患者,灵敏度和特异度分别为100%和65%。这些研究均表明,纹理参数有助于评估结直肠癌患者的预后和生存。

## 4 纹理分析的缺陷

目前,纹理分析处于发展阶段,其应用仍存在较多问题:①多种干扰因素对纹理参数的影响无法准确评估,如由胰岛素抵抗引起肝脏脂肪含量发生的微小变化<sup>[33]</sup>、放化疗导致肿瘤组织的纤维化和坏死程度<sup>[20]</sup>、原发病灶存在与否对血流动力学的改变等,因此需严格控制实验条件来获得准确的数据。②选择最大层面(2D)还是对肿瘤整体(3D)进行纹理分析仍值得探讨,有学者认为3D比2D分析更具代表性<sup>[34]</sup>,也有研究表明2D与3D分析的纹理参数并无统计学差异<sup>[35]</sup>。这可能是由于选取的ROI和所研究的类型不同所致,也提示不同肿瘤之间存在生物学差异,还需对不同器官的不同肿瘤类型进一步分析。③由于管电压和管电流均会对CT图像的采集产生不同程度的影响<sup>[39]</sup>,选取的过滤器不同也会使纹理参数的P值发生改变<sup>[22]</sup>,故有必要确定统一的采集参数和合适的过滤模式,从而使纹理分析更广泛地应用于临床实践。

## 5 展望

总之,越来越多的研究证据表明,纹理分析可用于判断结直肠癌患者的预后、评估远处转移、预测生存等,并有望作为治疗反应的新的生物成像标记来指导临床治疗。随着研究的进一步深入,纹理分析将在结直肠癌的应用中发挥更加积极的作用。

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