

# 基于深度学习的影像组学在结直肠癌中的研究进展

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**[摘要]** 传统的影像学检查方法对结直肠癌的早期诊断、预后判断及放化疗效果的预测意义有限, 近年来, 随着图像处理与计算机技术的不断发展, 应用影像组学的分析方法对结直肠癌患者进行准确的术前评估, 疗效预测, 制定精准的个体化治疗方案是该领域新的研究热点。作者将影像组学技术在结直肠癌术前分期、疗效评价及预后评估等不同诊疗阶段的研究成果进行总结并探讨其应用价值。

**[关键词]** 影像组学; 结直肠癌; 磁共振成像; 深度学习

## Advances in application of radiomics in colorectal cancer

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**Abstract** In recent years, with the continuous development of image processing and computer technology, the use of imaging histological analysis methods for accurate preoperative evaluation of patients with colorectal cancer, efficacy prediction, the development of accurate individual treatment is a new research hotspot in this field. In this article, we summarize the research results of imaging techniques in the different stages of colorectal cancer diagnosis and treatment, such as preoperative staging, curative effect evaluation and prognosis evaluation.

**Key words** radiomics; colorectal cancer; magnetic resonance imaging; deep learning

结直肠癌(colorectal cancer, CRC)是全世界常见的恶性肿瘤之一, 在中国的发病率位列所有癌症的第五位(在男性中排第五位, 在女性中排第四位), 且发病率和死亡率逐年上升<sup>[1]</sup>。因此, 结直肠癌的诊断、治疗及预后的研究在我国具有重要意义。传统的影像学检查方法能反映CRC的部位、大小、形态、周围侵犯及远处转移等情况, 但对CRC的早期诊断、预后判断及放化疗效果的预测意义有限。目前, 如何对CRC患者进行准确的术前评估, 疗效预测, 制定精准的个体化治疗方案是当前CRC的研究热点。随着计算机水平的不断发展, 影像学的医生和学者们也在寻找新的方法来分析诊断图像, 因此, 影像组学的发展成为医学影像学的新领域。

影像组学(radiomics)的概念最早是由荷兰学者Lambin教授于2012年提出<sup>[2]</sup>, 是一种通过提取医学图像中的细微定量特征, 并分析特征与临床及基因数据之间的关系来建立预测模型的新兴技术。利用这种技术, 不仅可以自动进行肿瘤分期, 还可以对患者的生存期进行预测。近年来, 影像组学在结直肠癌的诊疗过程的各个阶段均涌现出阶段性的研究成果<sup>[3-5]</sup>, 因此, 笔者将这些研究成果进行总结并探讨其应用价值。

### 1 影像组学

影像组学定义为从传统的影像学图像中提取和分析许多与若干临床终点相关的定量影像特征, 进行特征分析和模型建立, 对病理、基因突变状态、治疗反应和临床结果进行预测

并验证<sup>[6]</sup>。影像组学工作流程包括以下步骤: (1) 图像采集; (2) 创建具有临床和影像资料的数据集; (3) 将DICOM图像从图像储存和传输系统(picture archiving and communication system, PACS)导出到将用于进行图像分析的计算机软件; (4) 在图像中进行感兴趣区域(region of interest, ROI)或感兴趣体积(volume of interest, VOI)的分割, 分割对象是图像的某一层面或特定区域的体积; (5) 特征提取; (6) 选择最相关的特征, 以构建适当的模型来预测临床终点; (7) 利用内部和(或)外部数据对模型进行验证<sup>[6]</sup>。

### 2 基于深度学习的影像组学

基于深度学习的影像组学方法不同于传统的影像组学, 构建的模型可以自动学习提取和选择图像特征并进行预测, 从而更全面、深入地挖掘图像中的信息。深度学习是一类算法的总称, 并不是某种特定的模型, 只要采用较深的神经网络结构, 就可以称为深度学习。目前, 影像组学最常用的是卷积神经网络(convolutional neural network, CNN)、稀疏自编码器(sparse auto-encoder, SAE)等。相较于传统影像组学, 深度学习具有如下优点: 第一, 传统影像组学的特征具有通用性, 而缺乏针对性, 例如结直肠癌这类有变形的肿瘤, 有些特征就很难应用; 第二, 传统影像组学需要明确的计算公式, 因此只能有限地定义这些特征, 而深度学习则是利用卷积神经网络提取特征, 通过不断地数据学习获得特征, 因此具有较强的针对性<sup>[7]</sup>。

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### 3 影像组学在结直肠癌中的应用

目前,有一些研究已经在探索影像组学在CRC中的潜在应用。这些应用可分为以下几类:(1)预测局部晚期直肠癌(locally advanced rectal cancer, LARC)在新辅助放化疗(neoadjuvant chemoradiotherapy, nCRT)后的病理完全缓解(pathologic complete response, pCR);(2)术前预测肿瘤的TNM分期;(3)预测患者的生存期;(4)预测肿瘤的KRAS基因突变。

#### 3.1 预测LARC患者nCRT后的病理完全缓解

目前LARC患者的标准治疗方法是nCRT后全直肠系膜切除术(total mesorect excision, TME)<sup>[8]</sup>。大约20%的患者在放化疗后可以达到pCR,这些对放化疗反应良好的患者,可以考虑保留器官,如观察等待或局部切除策略<sup>[9-10]</sup>。因此,确定可靠的肿瘤反应预测因子为患者提供个体化治疗方案至关重要。医学成像方面,磁共振成像(magnetic resonance imaging, MRI)是预测nCRT治疗效果的最有价值的工具。有研究表明,从T2WI中提取的若干一阶纹理特征与pCR具有相关性,利用这些纹理特征判别pCR的ROC(receiver operating characteristic curve)曲线下的面积(area under curve, AUC)值为0.67至0.91<sup>[11-14]</sup>。但这些研究均未建立先进的预测模型。另一些学者评价了更复杂的纹理性特征,并建立了较好的预测模型<sup>[5, 15-17]</sup>,这些模型将影像组学特征与临床风险因素(如年龄,性别,治疗前后的CEA, CA19-9水平,肿瘤治疗前后的大小等)相联合,在测试组中预测pCR的AUC在0.72至0.93<sup>[5, 15-18]</sup>之间。T2WI是分割肿瘤ROI或VOI的主要序列;然而,一些研究也使用了其他序列,包括T1WI、表观弥散系数(apparent diffusion coefficient, ADC)和动态增强MRI(dynamic contrast enhanced MRI, DCE-MRI)等序列。Cui等<sup>[16]</sup>开发了一个包含T2WI、T1WI增强和ADC图的列线图,同时结合了纹理特征和pT分期,在训练集和验证集中该列线图在区分pCR时都显示出良好的鉴别能力,ROC曲线下面积分别为0.948和0.966。有些研究在开发预测模型时应用深度学习等新技术,利用数据“学习”能力来改进预测结果,Ferrari等<sup>[19]</sup>基于高分辨率T2WI的纹理分析,建立两种不同的人工智能(artificial intelligence, AI)模型:一种模型区分病理完全应答(complete response, CR)与部分应答(partial response, PR)、无应答(non-response, NR),另一种模型区分NR与CR、PR,在验证队列中,CR分类的AI模型显示出良好的辨别力,ROC曲线下面积为0.86, NR分类的AI模型辨别力显示ROC曲线下面积为0.83。深度学习的自动分类技术可同时分析大量具有潜在相关性的影像特征,利用其相关性做出判别,因此其执行效果明显优于临床医生的视觉分析。

#### 3.2 术前预测肿瘤的TNM分期

##### 3.2.1 预测肿瘤的T分期

术前分期为T1~2期的直肠癌患者,可直接选择TME手术切除,而分期为T3~4期的患者,先行nCRT降期后再行手术治疗可以有效地减少复发和转移的风险,并有效地延长患者的生存期<sup>[20]</sup>。但nCRT也有明显的不良反应,如药物性肝损伤、骨髓抑制等<sup>[21]</sup>。准确的术前分期有利于选择合适的治疗方法,减少或避免药物引起的毒性反应。Liang等<sup>[22]</sup>对CRC的CT图像进行纹理分析,发现16个纹理特征是区分T1~2期和T3~4期肿瘤的独立预测因子。Lu等<sup>[23]</sup>通过提取直肠癌患者ADC图像的纹理特征并分析,发现pT1~2分期的均匀性和能量均显著高于pT3~4分期,而pT1~2分期的熵显著低于pT3~4分期。此外,通过逻辑回归分析得出的预测概率在区分pT3~4期肿瘤时产生更大AUC<sup>[23]</sup>。均匀性和能量均反映的是图像灰度分布的均匀程度,较高的均匀性和能量表明图像的均匀性较低,熵表示ADC灰度分布的空间无序性,熵值越高,反映出病变的异质性越大。Ma等<sup>[24]</sup>基于高分辨率T2WI图像的放射组学建立了多个预测模型并进行比较,对于T分期,多层感知器(multilayer perceptron, MLP)分类器的判别能力最好,AUC值为0.809。以上研究结果均提示从影像图像中提

取的部分特征对于术前预测直肠癌的病理T分期具有重要价值,可以帮助临床医生选择合适的治疗策略。

##### 3.2.2 预测肿瘤的N分期

准确评估CRC患者的淋巴结(lymph node, LN)状态对治疗计划、预测局部复发和总生存率至关重要<sup>[25]</sup>。MRI基于大小和形态学特征来评估转移性LN的准确性较差,其敏感度为77%,特异度为71%<sup>[26]</sup>。Liu等<sup>[21]</sup>分析ADC图像的纹理特征,发现与pN1~2肿瘤相比,pN0期肿瘤的ADC mean和ADC max显著更高,且熵值更低。并通过多因素逻辑回归分析发现,ADC max和熵是预测LN状态的独立预测因子<sup>[21]</sup>。Chen等<sup>[27]</sup>使用计算机断层扫描(computed tomography, CT)直肠内超声和超声剪切波弹性成像建立多个列线图来预测直肠癌患者淋巴结转移情况,多参数列线图与常规影像学图像相比,具有更高的诊断性能(训练集和验证集的AUC值分别为0.87和0.86)。因此,对原发肿瘤和淋巴结进行影像组学分析有助于预测CRC患者的淋巴结状态。

##### 3.2.3 预测肿瘤的M分期

肝脏是CRC最常见的转移部位,约26.5%的患者在确诊CRC后5年内会发生肝转移(liver metastases, LM)<sup>[28]</sup>。异时性肝转移(metachronous liver metastases, MLM)是指在原发性阶段没有肿瘤转移的证据,但在基线分期和治疗后发展为LM,它被认为是从隐匿性转移和微转移发展而来<sup>[29-30]</sup>。识有研究发现基于CT门静脉期图像的纹理特征和临床数据建立的逻辑回归模型显示出最大的净收益,训练集、验证集的AUC值分别为0.90±0.02、0.86±0.11<sup>[31]</sup>。Liang等<sup>[32]</sup>研究基于直肠癌患者T2WI和动态增强静脉期图像的纹理分析,建立支持向量机和Logistic回归预测模型,发现Logistic回归模型的预测性能最好,AUC值为0.74。运用基于影像组学和临床风险特征的机器学习模型来预测结直肠癌患者发生肝转移的可能性,对高危患者采用新辅助放化疗和(或)更严格的随访方案均有助于降低发生MLM的风险。

#### 3.3 预测患者的生存期

基于<sup>18</sup>F-FDG PET-CT<sup>[33]</sup>和MRI<sup>[34-35]</sup>的影像组学分析也被用来预测CRC患者的生存预期。一些研究发现几个影像组学特征与无进展生存期(progression free survival, PFS)和总生存期(overall survival, OS)<sup>[33-35]</sup>相关。Meng等<sup>[34]</sup>发现,将纹理特征和临床数据相结合建立的模型可显著提高预测LARC患者的DFS,ROC曲线下面积在训练集和验证集中分别为0.804和0.788,这提示我们在研究患者的生存预期时,除了纳入临床因素外,影像组学特征也应作为生物学标记物考虑在内。

#### 3.4 预测患者KRAS基因状态

随着基因检测技术的不断应用,将诊断成像与不同癌症的基因表达相匹配的需求已经成为一个关键的研究领域。研究较多的是KRAS基因状态,大约40% CRC患者存在KRAS基因突变,且对表皮生长因子受体(epidermal growth factor receptor, EGFR)的药物具有低反应性的特点<sup>[36]</sup>。有研究结果显示,野生型KRAS基因的患者可从西妥昔单抗治疗中获益,而突变型患者不但没有受益,反而会增加发生不良反应的风险<sup>[22]</sup>。所以CRC患者在接受分子靶向药物治疗之前进行KRAS基因检测显得尤为重要。一项针对直肠癌CT图像的纹理分析研究发现,野生型KRAS基因组的熵值显著高于突变型组<sup>[23]</sup>。Xu等<sup>[37]</sup>研究T2WI的纹理分析在区分直肠癌KRAS基因状态时发现,KRAS突变组的六个纹理参数(均值,方差,偏度,熵,灰度不均匀,游程长度不均匀)显著高于野生组( $P < 0.0001$ )。除MRI外,许多学者还研究了<sup>18</sup>F-FDG PET在影像基因组学中评估结直肠癌KRAS突变的作用。Lovinfosse等<sup>[4]</sup>研究发现一些标准摄取值(standard uptake value, SUV),例如SUVmax和SUVmeans,以及偏斜度与直肠癌的KRAS突变状态之间存在关联。这些研究说明,影像图像的纹理分析可为预测CRC患者是否存在KRAS基因突变提供参考。

综上所述,影像组学经过近几年的研究与发展,已形成一



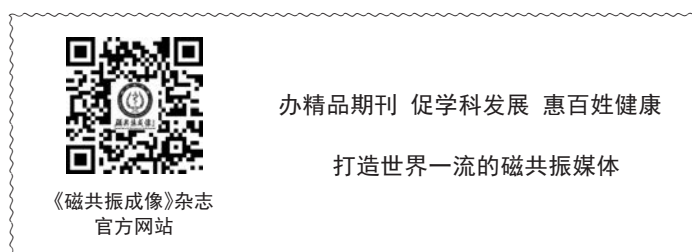
套较为完整的理论体系和技术流程,并在较多疾病领域均取得了进展性的成果。笔者介绍了影像组学在结直肠癌患者诊疗过程中的应用及研究成果。然而,在常规实施该技术之前,仍有一些挑战,例如建立大数据库和实现数据共享、进行大规模多中心的测试和验证、预测模型的设计优化和对结果的解释能力等。随着人工智能技术的不断发展,基于大数据的影像组学技术,不仅能在结直肠癌诊断和治疗的各个阶段发挥作用,而且能在其他肿瘤甚至非肿瘤性疾病的诊断和治疗方面取得进展,从而促进个性化精准治疗的发展。

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