



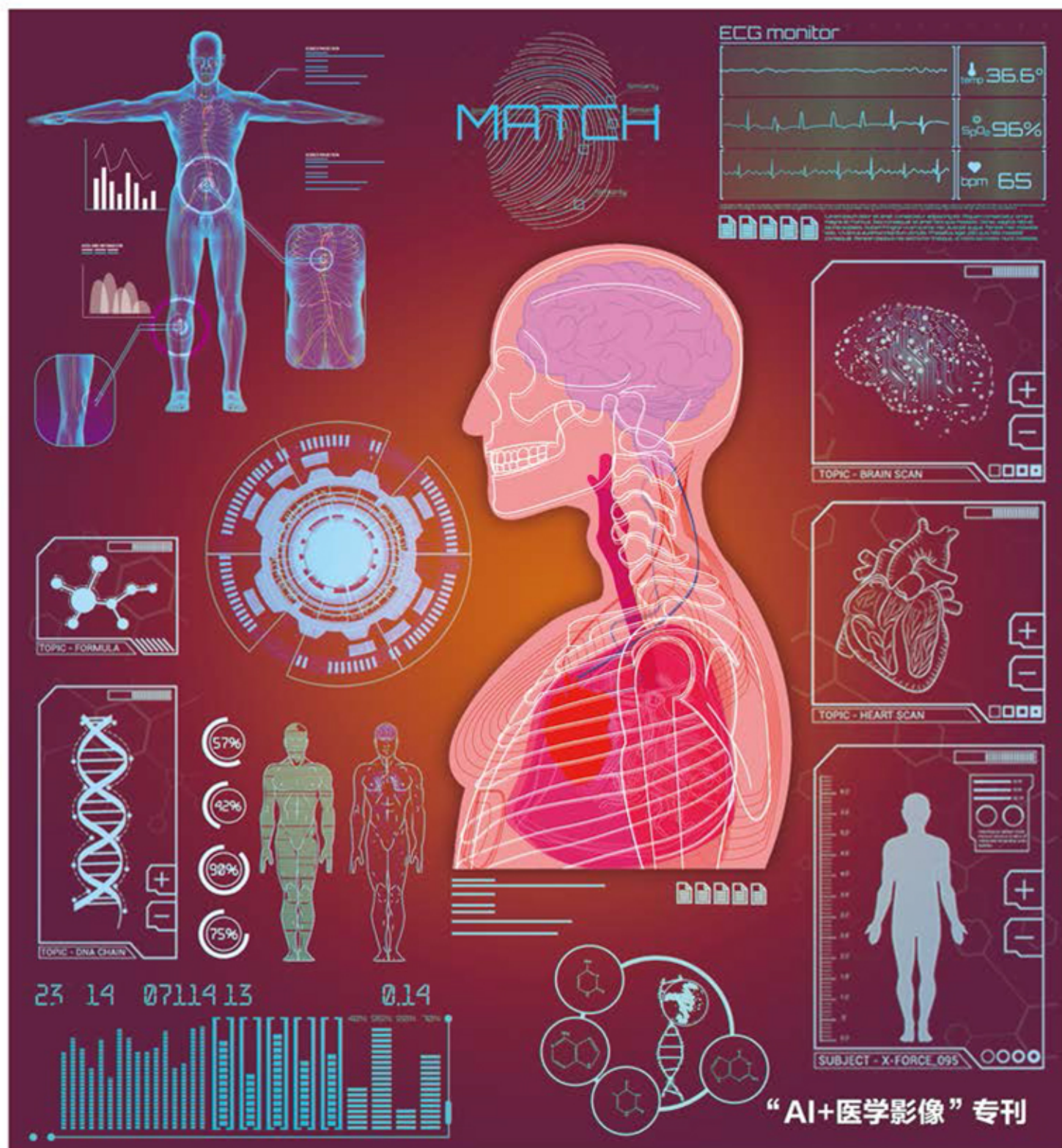
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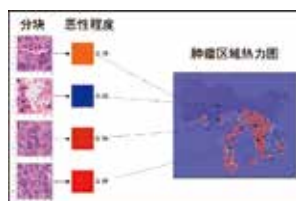
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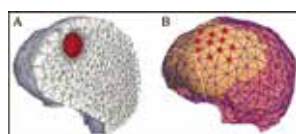
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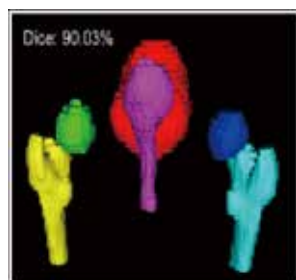
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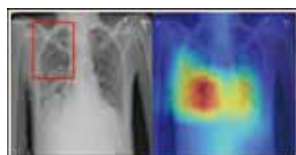
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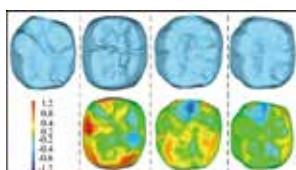
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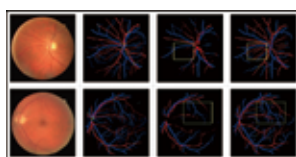
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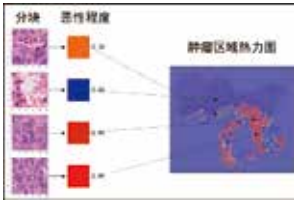
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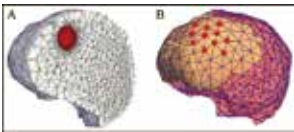
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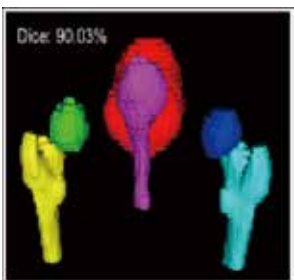
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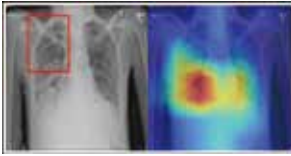
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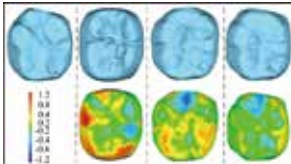
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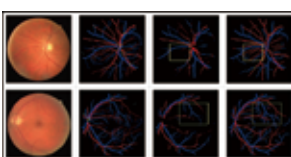
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## IVIM 及纹理分析在术前预测宫颈癌类型 和淋巴结转移研究进展

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**摘要:** 本文综述了体素内不相干运动扩散加权成像(intravoxel incoherent motion diffusion-weighted imaging, IVIM-DWI)及纹理分析技术在术前鉴别宫颈癌组织学亚型及淋巴结转移的临床应用进展。MRI(magnetic resonance imaging)是宫颈癌临床术前最常用的影像学诊断和分期方法。宫颈癌的组织学类型及有无淋巴结转移与患者的生存及预后紧密相关。IVIM-DWI 为 MRI 新型功能成像技术,其 D 值反映组织内单纯水分子的布朗运动信息、间接反映恶性肿瘤组织细胞密集度;其 D\* 值和 f 值能提供肿瘤组织内血流灌注的信息。影像组学的纹理分析技术(texture analysis, TA)通过提取肿瘤组织的纹理特征进行客观、定量分析,能检测人眼不能识别的肿瘤组织的微观改变,揭示更多肿瘤组织的灰度分布与定量数据特征,为临床术前预测宫颈癌不同组织学类型及转移淋巴结提供了可能。

**关键词:** 宫颈癌;体素内不相干运动扩散加权成像(IVIM-DWI);纹理分析;淋巴结;转移

### Advances in preoperative identification of subtypes and lymph node metastasis of cervical cancer by IVIM and texture analysis

Li Cuiping<sup>1</sup>, Dong Jiangning<sup>1,2</sup>

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**Abstract:** Cervical cancer is an important public health problem worldwide, and its high incidence and trends in younger generation also attract increasing attention. The biological behavior and prognosis of cervical cancer are closely related to its histological type and lymph node metastasis. Cervical cancer has many histological types; the most common type is squamous cell carcinoma, accounting for about 80%; the second most common type is adenocarcinoma, accounting for about 15%~20%, whose incidence is increasing in recent years because of the prevalence of cervical cancer screening. The rare types are adenosquamous carcinoma and neuroendocrine tumors (small cell carcinoma). Their incidence is about 5% and is increasing in recent years because of the cervical cancer screening. Cervical squamous cell carcinoma is more sensitive to radiotherapy and has a better prognosis, whereas cervical adenocarcinoma is less sensitive to radiotherapy and prone to lymph node and hematogenous metastasis. Small cell carcinomas are sensitive to chemotherapies due to their particular origin, prone to early lymph node metastasis, and have poor prognosis. Determining lymphatic metastasis based on magnet-

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ic resonance imaging (MRI) is the main factor to evaluate the prognosis of cervical cancer and formulate treatment plan. In the early diagnosis of cervical cancer, 10% ~ 30% of patients have lymph node metastasis. Thus, the evaluation of pelvic and retroperitoneal lymph node metastasis of cervical cancer before treatment will be directly related to the choice of treatment options and prognosis of patients. Although cervical conization and lymph node biopsy are the gold standard for the diagnosis of cervical cancer histopathology and metastatic lymph nodes, the limitations of sampling and the heterogeneity of tumors do not fully reflect the histological information of primary lesions and metastatic lymph nodes of cervical cancer, and biopsy can increase the risk of tumor dissemination. MRI is the commonly used imaging diagnosis and staging method for cervical cancer before surgery. Intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI), a new functional imaging technique for MRI, is a multi-b-value and bi-exponential model diffusion-weighted technique, which can separate the random diffusion motion of water molecules from the microvascular perfusion effect and reflect the diffusion information of biological tissues. The main parameters are as follows: ADC, D,  $D^*$ , and f value. The  $ADC_{stand}$  value is similar to the ADC (apparent diffusion coefficient) value in a single-value DWI (diffusion weighted imaging) model, which reflects the combined effect of tissue diffusion and perfusion but can simply reflect the diffusion movement of water molecules in tissues. Given the influence of the elevation of microcirculation blood perfusion, the measured values tend to be high. The D value reflects Brownian motion information of pure water molecules in tissues and indirectly reflects cell density in tumors. The  $D^*$  value and f value provide information of microcirculatory blood flow perfusion in tumors. Moreover, the  $D^*$  value primarily reflects the blood velocity of microcirculation, whereas the f value primarily reflects the blood volume of microcirculation. Therefore, IVIM-DWI based on multiple parameters can play an important role in tumor characterization, staging, typing, and prediction of lymph node metastasis. At present, artificial intelligence (AI) plays a role in all aspects of people's life. Texture analysis (TA) technology is an important branch of AI research. Medically, TA has become a new research hotspot in Radiomics. TA uses corresponding computer software to extract texture features of lesion tissues from images for objective and quantitative analysis based on imaging images, which can detect microscopic changes of tumor tissues that cannot be recognized by the human eyes, and reveal gray distribution and quantitative data features in tumor tissues. To date, TA is based on images such as computed tomography (CT), MRI, or positron emission tomography (PET) /CT. Three methods are identified to obtain texture features: statistics based, transformation based, and structure based. Among the methods, the most commonly used method is statistics based. Texture features include first-order features, second-order features, and high-order features. First-order features, also known as histogram analysis, describe the gray distribution of individual pixel values in the region of interest, including mean, variance, skewness, kurtosis, and entropy. Second-order features represent local texture features on the basis of the relationship between adjacent 2 pixels. Common methods include gray-level co-occurrence matrix, gray-level run-length matrix, and gray-level area-size matrix. In addition, high-order features analyze local image information by applying gray-level difference matrix of adjacent pixels to reflect the change of local intensity or the distribution of homogeneous regions. TA can quantify the distribution of texture features, such as signal intensity distribution, morphology, and heterogeneity at the lesion site, to reflect the lesion features objectively and comprehensively. Therefore, TA plays an important role in the qualitative, definitive, and differential diagnosis of diseases. Researchers interpret texture information in images on the basis of imaging images, combined with imaging technology and computer AI technology, through the analysis of quantitative data, which provides a possibility for clinical preoperative prediction of different histological types of cervical cancer and metastatic lymph nodes. This article reviews the recent research progress in the clinical application of IVIM-DWI and TA in the preoperative identification of histological subtypes and lymph node metastasis of cervical cancer.

**Key words:** cervical cancer; intravoxel incoherent motion diffusion-weighted imaging (IVIM-DWI); texture analysis (TA); lymph node; metastasis

## 0 引言

宫颈癌 (cervical cancer) 是全球范围内重要的

公共卫生问题,其高发病率和低龄化发病趋势亦越来越引起人们的重视 (Burzawa 等, 2015)。根据 2018 年国际妇产科联合会 (International Federation of Gynecology and Obstetrics, FIGO) 对宫颈癌的分期

方法,首次将淋巴结转移纳入分期,且明确提出目前最好的方法是用影像学来评估(Lee和Atri,2019)。常规磁共振序列不仅显示宫颈癌侵犯深度和播散范围等解剖学信息,还可以显示淋巴结的大小、形态及信号特征,但其特异性较低(Zhang等,2017)。虽然宫颈锥切及淋巴结穿刺活检是诊断宫颈癌病理组织学及转移淋巴结的金标准,但是,受取材的局限性及肿瘤的异质性影响并不能全面反映宫颈癌组织学信息,且增加肿瘤播散的风险。

宫颈癌在组织学上有多种分型,最常见类型为鳞状细胞癌,占比约为80%;其次常见类型为腺癌,占比约15%~20%,且随着宫颈癌筛查的普及,其发病率呈上升趋势;少见类型为腺鳞癌及神经内分泌肿瘤(小细胞癌)。宫颈鳞癌较适用于放射治疗,敏感性较高,其预后相对较好;宫颈腺癌对放射治疗的敏感性较鳞癌差,易发生淋巴结及血行转移(Jonska-Gmyrek等,2019)。小细胞癌由于其特殊来源对于化学治疗比较敏感,易早期淋巴结转移,预后较差。依据影像学判断有无淋巴结转移是评价宫颈癌预后及制定治疗计划的主要因素(Lee和Atri,2019)。在宫颈癌早期确诊时,10%~30%的患者存在淋巴结转移,因此宫颈癌术前评估宫颈癌盆腔与腹膜后有无淋巴结转移将直接关系到治疗方案的选择与患者的预后(Lee和Atri,2019)。

## 1 IVIM-DWI 术前预测宫颈癌组织学类型的研究进展

扩散加权成像(diffusion weighted imaging, DWI)是一种依赖于细胞内、外和血管内水的微观流动性的成像技术(Le Bihan等,1986),可早于病理学及形态学检测出组织含水量的变化。表观扩散系数(apparent diffusion coefficient, ADC)为DWI定量描述指标,人体中不同组织的水分子扩散性差异较大,扩散性还通过与不同细胞膜、细胞器、分子以及组织灌注等的相互作用而改变,ADC值受到血流灌注的抬升影响,故单指数模型扩散加权序列并不能准确反映肿瘤组织水分子扩散的特性。鉴于此,Le Bihan等人(1986)首先提出多**b**值双指数DWI模型,即体素内不相干运动扩散加权成像(intravoxel incoherent motion diffusion weighted imaging, IVIM-DWI)技术,该理论将单个体素内水分子的纯扩散运动和毛细血

管网内血液微循环区分开,应用从低到高的多个**b**值( $\geq 4$ 个)(李志伟等,2013),依据双指数模型计算而得到相关参数,计算为

$$S(b)/S(0) = f \exp(-D^*b) + (1-f) \exp(-Db)$$

式中, $S(b)$ 为相应**b**值的DWI信号强度, $S(0)$ 为**b**值为0时的DWI信号强度, $D$ 为组织内水分子纯扩散系数, $D^*$ 为微循环灌注相关系数, $f$ 为微循环灌注在DWI衰减中所占比例(Tamura等,2012; Chandarana等,2011)。

基于以上原理,IVIM-DWI的相关参数在宫颈癌术前诊断、分级、分期和疗效评估中的应用逐渐推广,而在术前评估宫颈癌组织学类型的临床应用研究也逐步开展。

IVIM-DWI在宫颈癌诊断、病理分级、临床分期及放化疗疗效的评估中应用越来越广,赵晓艳等人(2018)及何志兵等人(2019)研究发现IVIM-DWI相应参数可反映组织血供及肿瘤血管生成情况,在宫颈癌的诊断及病理分级、分期中辅助临床。程楠等人(2017)及李志森等人(2019)发现IVIM-DWI的定量参数可将宫颈癌与正常宫颈组织区分开来。叶晓华等人(2016)及孟楠等人(2018)的研究指出IVIM-DWI的相关参数可定量反映宫颈癌的组织学特征,有助于鉴别宫颈癌组织学亚型。

IVIM-DWI技术在术前无创性评估宫颈癌及其他器官肿瘤组织学亚型的应用也逐渐增多,张利祥(2018)术前鉴别宫颈鳞癌和腺癌时发现**D**值较其他参数具有较高的诊断效能,原因是腺癌的肿瘤细胞常见为排列成高柱状或腺管状,肿瘤细胞分泌较多粘液成分,组织结构较疏松;而鳞癌的肿瘤细胞多排列成实体癌巢状、组织结构较紧密。因此鳞癌**D**值较腺癌低,IVIM-DWI参数与临床病理学具有较高的一致性,其具有潜在的应用价值逐渐显现,该技术可以弥补组织学活检时取材的局限性,提高术前诊断宫颈癌组织学类型的准确性。

## 2 纹理分析术前预测宫颈癌组织学亚型的研究进展

纹理分析(texture analysis, TA)逐渐成为肿瘤影像组学领域的研究热点,无创性地通过从影像学图像中提取肉眼无法识别的纹理特征,来揭示肿瘤的异质性和某些基因组织学特征,并利用这些定量信

息研究疾病的鉴别诊断、分级、分型及疗效评价等 (Gillies 等, 2016; Cai 等, 2016; Li 等, 2018; 张利文等, 2017; 刘士远和萧毅, 2017)。目前, 纹理分析技术已经在脑、肺、乳腺、肝及盆腔等部位肿瘤的诊断、疗效评估及预后预测中广泛应用 (McLaren 等, 2009; Ganeshan 等, 2012; Xie 等, 2018; Brenet 等, 2019; Vignati 等, 2015; Zhu 等, 2018; 王敏红和冯湛, 2018)。

目前, 纹理分析技术主要基于影像学图像, 应用相应计算机软件, 通过量化具有不同灰度强度的像素 (2D 图像) 或体素 (3D 图像) 的空间分布, 并统计其变量 (例如相关性、均匀性、对比度和熵等) 之后, 再自动提取信息的后处理方法, 所提取的纹理特征包括: 一阶特征, 又称直方图分析, 描述感兴趣区 (region of interest, ROI) 内单个像素值的灰度分布, 包括平均值 (mean value)、方差 (variance)、偏度 (skewness)、峰度 (kurtosis) 和熵 (entropy); 二阶特征计算相邻 2 个像素而表现局部的纹理特征, 常用方法包括灰度共生矩阵 (gray-level co-occurrence matrix, GLCM) 和游程矩阵 (run length matrix, RLM) 等; 高阶特征则利用统计方法分析局部的图像信息 (岳茜 等, 2019; 施奕倩, 2017)。

纹理分析在医学图像中的应用最早基于 MRI (magnetic resonance imaging), 基于 MRI 图像纹理分析 (MR texture analysis, MRTA) 常见为基于 T<sub>2</sub>-weighted imaging (T<sub>2</sub> WI)、IVIM-DWI 及 dynamic contrast enhanced MRI (DCE-MRI), 已在头颈部、胸部、腹盆部及四肢中均有应用, 既有助于病变的定量及定性分析, 又能对病变进展程度和病灶成分进行区分评估, 寻找预后判断指标来早期评估患者的复发分险。Jakola 等人 (2018) 发现纹理特征均匀性可以区分低级别胶质瘤 (low-grade gliomas, LGG) 患者的异柠檬酸脱氢酶 (isocitrate dehydrogenase, IDH) 分型 (野生型或突变型), MRTA 对术前分子分析起到重要补充作用。Sun 等人 (2018) 基于增强后的高分辨率 T<sub>1</sub> 加权图像和扩散加权图像所提取的纹理特征证实有助于鉴别乳腺癌的分子亚型, MRTA 为乳腺癌分子亚型的预测提供了一条新的途径。周智等人 (2019) 和王绎忱等人 (2018) 发现通过 DCE-MRI 和 T<sub>2</sub> WI 压脂序列提取病灶的纹理特征有助于鉴别透明细胞肾细胞癌、乳头状肾细胞癌及嫌色肾细胞癌, 并具有较高的诊断效能。

在宫颈癌分型方面的研究中, 谢元亮等人 (2019) 应用 DCE-MRI 的纹理分析技术通过对病灶手动分割后提取一阶灰度直方图及二阶纹理特征, 在鉴别宫颈鳞癌与宫颈腺癌, 即预测宫颈癌组织分化时具有较高的诊断效能。Ciolina 等人 (2019) 应用 T<sub>2</sub> 加权图像发现 MRTA 在预测肿瘤对化疗反应方面超过了传统预后因素的作用, 而且在鉴别宫颈癌组织学类型方面显示了潜在的作用。因此, MRTA 有助于术前预测宫颈癌的分化和组织学分型。

### 3 常规影像学方法结合 IVIM-DWI 和纹理分析技术术前预测宫颈癌淋巴结转移风险的研究进展

2018 版子宫颈癌 FIGO 分期系统将盆腹腔淋巴结转移影像学表现正式纳入分期信息来源, 并作为临床活组织检查的补充。正电子发射断层显像/X 线计算机断层成像仪 (positron emission tomography / computed tomography, PET/CT) 被认为是评价盆腔和腹膜后淋巴结转移及远处转移的最佳方法 (Lee 和 Atri, 2019)。如果 PET/CT 不可用, MRI 是第 2 选择 (Atri 等, 2016)。目前已有研究发现了宫颈癌原发灶的 ADC 值与淋巴结转移之间具有相关性, 其中平均 ADC 对 ROI 依赖性最小, 可以作为预测宫颈癌淋巴结转移的一个独立预测参数应用 (Mongula 等, 2019)。IVIM-DWI 及纹理分析技术在术前预测与评估淋巴结转移的研究是目前影像学研究的热点之一, 在头颈部、肺部、乳腺及直肠等部位恶性肿瘤的研究中已取得可靠结果, 说明这 2 种方法在技术层面诊断和预测宫颈癌淋巴结转移方面具有可行性。

目前, 国内外已有学者研究基于磁共振 T<sub>2</sub> WI、IVIM-DWI 及 DCE-MRI 的纹理分析技术在早期预测淋巴结转移、鉴别正常淋巴结与转移淋巴结, 并得出该研究具有较高的预测价值, 但尚无关于短径小于 10 mm 的转移淋巴结与正常或炎性增生的淋巴结鉴别诊断的研究。现行常规 CT 和 MRI 主要是依据淋巴结的大小 (短径 > 10 mm)、边界 (光滑或毛糙)、有无环形强化及扩散受限与否来评估淋巴结转移 (牛微和罗娅红, 2017)。对于短径较小的转移性淋巴结往往漏诊, 对于短径较大的炎性增生性淋巴结容易误诊。IVIM-DWI 结合纹理分析技术则可以更为客观地评估微小腹盆腔转移淋巴结内肿瘤细胞

密度和微循环的定量信息,从而更早地较传统MRI技术判断鉴别诊断淋巴结病变的性质,为宫颈癌临床诊疗工作提供更加客观准确的影像学依据。

## 4 结 语

IVIM-DWI技术可以从分子水平反映宫颈癌肿瘤组织水分子扩散和微循环的定量信息,间接地反映宫颈鳞癌、腺癌及小细胞癌细胞内外间隙水分子扩散系数、细胞密度和微循环的微观信息,通过测定 $D$ 值、 $D^*$ 值和 $f$ 值可以在治疗前一定程度上鉴别宫颈癌的组织学亚型,弥补穿刺、锥切活检等诊断方法的不足。MRTA是影像组学的重要组成部分。尽管MRTA应用于宫颈癌的组织学亚型的研究仍处于初级阶段,但因其能发现人眼不能识别的量化灰阶和数据特征,在宫颈癌亚型的鉴别诊断方面也将发挥一定作用。

IVIM-DWI技术和基于MRI的纹理分析技术的结合,将会在治疗前鉴别评估宫颈癌组织学亚型及盆腔和腹膜后淋巴结转移等临床应用方面发挥积极作用;二者联合应用有可能进一步提高宫颈癌术前组织学亚型及盆腹腔良恶性淋巴结鉴别诊断的准确性,弥补术前取材活检的局限性及肿瘤组织异质性所导致的诊断不准确的不足,提高宫颈癌的疗效与患者生存率,具有较好的应用前景。

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