

• 综述 •

影像组学在前列腺癌中的研究进展

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[摘要] 前列腺癌(prostate cancer, PCa)是全世界第二大常见的男性恶性肿瘤, 对其早期筛查、辅助诊断、风险分层、治疗指导和疗效评估需要更加全面和一体化的方法。影像组学是一种以定量方式高通量提取和分析图像特征的技术, 目前已有大量研究表明它对PCa的无创诊断、侵袭性评估、疗效及预后评估均有重要的临床价值。随着当今成像方式的快速进步和人工智能技术的迅速发展, 影像组学技术拥有巨大潜力。文章回顾了基于多参数磁共振成像、正电子发射计算机断层扫描、计算机断层扫描、超声等不同成像方式的影像组学在PCa中的现有研究, 探讨其在未来应用中的潜力。

[关键词] 前列腺癌; 影像组学; 人工智能; 多参数磁共振成像; 正电子发射计算机断层扫描; 超声

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Advances of radiomics in prostate cancer

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[Abstract] Prostate cancer (PCa) is the second most common malignancy among men worldwide. A more comprehensive and integrated approach is needed for its early screening, auxiliary diagnosis, risk stratification, treatment guidance, and efficacy assessment. Radiomics, a technique that extracts and analyzes image features in a quantitative and high-throughput manner, has shown significant clinical value in the non-invasive diagnosis, aggressiveness assessment, treatment efficacy, and prognosis evaluation of PCa. With the rapid development of imaging modalities and artificial intelligence technologies, radiomics has tremendous potential. This article reviews the existing researches on radiomics based on multiparametric magnetic resonance imaging, positron emission tomography/computed tomography, computed tomography, ultrasound and other imaging modalities in PCa, emphasizing its potential in future applications.

[Key words] prostate cancer; radiomics; artificial intelligence; multi-parametric magnetic resonance imaging; positron emission tomography/computed tomography; ultrasound

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前列腺癌(prostate cancer, PCa)是男性泌尿生殖系统最常见的恶性肿瘤, 是全球男性第二大常见癌症, 也是男性癌症相关死亡的第五大原因^[1]。由于早期诊断的PCa患者生存率远高于晚期诊断患者, 及时发现PCa对降低病死率非常重要^[2]。随着成像方式的快速进步, 多参数磁共振成像(multi-parametric magnetic resonance imaging, mpMRI)已经成为

PCa检出和预测侵袭性的主要工具, 但mpMRI存在假阳性和假阴性情况^[3], 且观察者间一致性较差^[4], 很大程度依赖影像医师的经验和主观判断。前列腺特异性膜抗原(positron emission tomography/computed tomography, PET/CT)可用于PCa的分期和复发性PCa治疗后再分期, 比mpMRI灵敏度更高, 但特异度较低。计算机断层扫描(computed tomography, CT)和超声也可协助PCa的筛查, 但灵敏度和特异度较低。而影像组学技术通过分

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析医学图像中获得的数据, 转定性评估为定量评估, 为PCa的无创精准检出提供了新思路。人工智能(artificial intelligence, AI)技术是影像组学的重要方法学基础^[5], 影像组学和AI技术的有力结合使一些影像组学特征(radiomics features, RF)成为稳健可靠的标志物, 反映肿瘤内部的异质性和生物学表型^[6]。文章基于mpMRI、PET/CT、CT、超声等不同成像方式影像组学的最新研究进行综述, 并介绍AI技术如何改善影像组学并转化为临床实践。

1 影像组学概述

影像组学概念最早在2012年由Lambin等^[7]提出, 它是一种从标准医学图像中高容量挖掘定量图像特征的技术, 通过原始图像信息、算法、统计分析等工具的融合, 提供比传统影像学更加丰富的深层信息, 从而实现对疾病的精准诊疗。影像组学的基本步骤包括: 图像的采集和处理、感兴趣区域(region of interest, ROI)的分割、特征的提取和选择、模型的构建和验证。影像组学研究能够成立的最基本假设是, 肿瘤的宏观影像特征与基因、蛋白质、细胞、代谢等微观信息在时间和空间水平上的改变息息相关^[8-9]。

2 MRI影像组学在PCa中的应用

2.1 PCa的诊断

mpMRI目前是诊断PCa的首选影像学方法, 主要包含T2加权图像(T2 weighted imaging, T2WI)、弥散加权图像(diffusion weighted imaging, DWI)、表观弥散系数(apparent diffusion coefficient, ADC)图像和动态增强(dynamic contrast enhancement, DCE)图像, 在PCa早期筛查、辅助诊断、风险分层、指导治疗和疗效评估中发挥了重要作用^[10-12]。

Qi等^[13]评估整合了mpMRI的RF和临床-影像学危险因素联合模型在前列腺特异性抗原(prostate specific antigen, PSA)为4~10 ng/mL的可疑PCa患者中的诊断效能, 结果显示联合模型优于单纯的临床-影像学模型($P < 0.05$), 并识别出更多的阴性患者, 使18.4%的患者避免不必要的穿刺。李梦娟等^[14]基于双参数MRI(biparameter MRI, bpMRI)图像构建影像组学模型来预测临床显著性前列腺癌(clinically significant prostate cancer, csPCa), 发现灰度共生矩阵(gray-level co-occurrence matrix, GLCM)和形态特征在所有特征中占比较大, 但该研究样本量小, 未对病灶位置进行分类, 且缺乏组织病理分析。Chen等^[15]比较了影像组学与前列腺影像报告

和数据系统(prostate imaging reporting and data system, PI-RADS)评分在bpMRI与mpMRI检测csPCa中的表现, 最终显示bpMRI及mpMRI影像组学模型性能均优于PI-RADS评分系统(AUC: 0.953 vs. 0.853、0.968 vs. 0.863), 且两个影像组学模型间性能差异无统计学意义($P > 0.05$)。这符合目前的研究趋势, bpMRI省略DCE成像, 可以减少时间成本和检查费用, 同时获得近似mpMRI的诊断准确性^[16-18]。

随着AI技术与影像组学方法的结合, 研究者可以通过机器学习(machine learning, ML)甚至深度学习(deep learning, DL)方法评价医学图像, 有效减少了各种潜在偏差。Bleker等^[19]创建了一种自动固定ROI的方法, 使用ML算法基于mpMRI图像构建影像组学模型以识别外周带csPCa, 结果显示多变量特征选择和极致梯度提升算法的性能优于单变量特征选择和随机森林算法(AUC: 0.870 vs. 0.780), 且DCE特征并不能显著提高诊断性能, 这与先前得到的结论相同^[15]。但该模型仅适用于外周带病变, 移行带病变仍需要构建专用模型, 且需要在外部验证集中进一步评估该模型的普适性。Castillo等^[20]为了比较DL模型和影像组学模型对csPCa的诊断性能, 分别对3个不同机构的患者进行测试, 结果显示DL模型在训练集中表现更好, 但影像组学模型在所有验证集中均优于DL模型。这是第1个进行这种比较的研究, 但需要注意的是, DL模型识别整个前列腺图像中的csPCa, 而影像组学模型识别勾画的ROI中的csPCa。

2.2 PCa的Gleason评分(Gleason score, GS)及侵袭性预测

前列腺穿刺活检得到GS是目前最广泛采用的衡量PCa侵袭性水平的指标^[21]。研究表明, 低风险(GS<7)、中风险(GS=7)和高风险(GS>7)PCa的5年无生化复发(biochemical recurrence, BCR)率差异较大^[22], 治疗策略也差异较大^[23], 因此准确的风险分层对PCa治疗决策的制定和预后判断有至关重要的指导意义。但活检并不能反映整个病灶的异质性, 并且有出血、感染等风险^[24]。而mpMRI由于其阳性预测值较低^[25], 往往又会导致很多不必要的活检。因此, 影像组学的出现为PCa侵袭性的无创预测提供可能。

Gong等^[26]基于术前bpMRI图像分别构建T2WI模型、DWI模型和联合模型来无创预测高风险PCa, 结果表明联合模型预测能力最佳(AUC=0.788), 但较DWI模型并未显著提高($P > 0.05$)。众所周知病

变活检后的GS与相应根治性前列腺切除术(radical prostatectomy, RP)后的GS不一致仍然是一个未解决的问题^[27],而Zhang等^[28]研究表明,基于mpMRI的影像组学模型对PCa从活检到RP的GS升级有良好的预测性能,并开发了一种简单易用的诺莫图,帮助临床医生根据患者GS升级的风险决定继续实行主动监测或手术根治等。Ogbonnaya等^[29]全部使用RP标本作为参考标准,从bpMRI图像中提取GLCM特征,筛选能独立预测csPCa的RF并构建模型,该研究是第1个使用3D特异性模具将影像学和组织病理学信息整合在一起的前瞻性研究。

大量研究表明mpMRI的计算机辅助分析可以帮助进行PCa的分级及风险分层,Makowski等^[30]使用支持向量机(support vector machine, SVM)、随机梯度提升、随机森林和K-最近邻(K-nearest neighbor, KNN)这4种不同的ML算法训练模型对PCa进行风险分层,并评估T1 mapping特征的附加价值,结果显示SVM的准确率最高(AUC=0.92),且T1 mapping定量技术可提高影像组学模型的准确性,但该研究样本量小,无法充分确定T1 mapping定量技术的潜在价值。最近,Castillo等^[31]在一项多中心研究中使用ML算法构建区分高风险和低风险PCa的影像组学模型,并与影像医师的诊断进行比较,结果显示影像组学模型优于影像医师的诊断。这是第1个将影像组学模型的普适性作为主要关注点的研究,也提示要在多中心环境中训练验证影像组学模型后,才能将其应用于临床决策系统中。

2.3 PCa包膜外侵犯(extracapsular extension, ECE)的预测

ECE会导致PCa患者发生手术切缘阳性(positive surgical margins, PSM)和微转移的概率增加,也与不良预后和BCR相关^[32-33],对于这些患者需要考虑切除血管神经束或辅助治疗等^[34]。因此,术前准确识别ECE对于治疗方案的制定至关重要。一项Meta分析显示mpMRI术前预测ECE的灵敏度仅为57%^[35],而影像组学的出现提高了ECE检测的准确性^[36-38]。

Ma等^[39]基于T2WI图像构建影像组学模型,训练集和验证集的AUC分别为0.902和0.883,与影像医师的诊断灵敏度(46.88%~50.00%)相比,灵敏度(75.00%)显著提高,特异度差异无统计学意义,与先前的研究结果一致^[35],但该研究仅评估了T2WI图像的RF。Xu等^[40]基于mpMRI图像构建影像组学模型以术前预测ECE,结果显示其诊断效能明显优于

临床模型(0.865 vs. 0.658, $P=0.02$),决策曲线分析也证实该模型有良好的临床实用性。He等^[41]基于T2WI和ADC图像构建影像组学模型分别预测ECE和PSM,结果显示ADC模型性能最佳(AUC: 0.625、0.733),结合临床因素后的联合模型性能提高到0.728和0.766,也说明联合模型可提高对ECE和PSM的风险预测能力。另外该研究从原发灶中提取RF,说明ECE的发生与瘤内的异质性相关。而Bai等^[42]基于瘤周区域构建影像组学模型来预测ECE,结果显示瘤周区域的RF较瘤内区域能更好地预测ECE($P < 0.05$)。研究认为瘤周组织及微环境能够提供肿瘤诊断和预后相关的信息^[43],如瘤周血管和软组织、脂肪组织的变化可能与包膜受侵袭程度有关^[44-45]。

目前预测ECE的ML研究相对较少,Cuocolo等^[46]基于T2WI和ADC图像采用SVM算法构建ECE预测模型,并在多中心验证模型,结果显示模型在训练集中的准确率达83%,在两个外部验证集中的准确率达79%和74%,且与影像医师的诊断准确率差异无统计学意义,多中心验证的设计直接证明该模型具有良好的普适性,将其纳入ECE评分系统有望进一步提高诊断的准确性。Fan等^[47]基于mpMRI图像使用6种算法分别建立与PCa侵袭性相关的5种生物学特征(Ki-67、S100、ECE、PSM和神经周围侵犯)的影像组学模型并验证诊断效能,结果显示随机森林算法对Ki-67、S100、ECE、神经周围侵犯的预测性能最好(AUC: 0.87、0.80、0.85、0.82),SVM对PSM的预测性能最好(AUC: 0.77)。该研究证明了影像组学在预测PCa多种生物学特征方面的适用性,并提供ML参数为未来的标准化工作提供参考。

2.4 PCa BCR的预测

BCR是PCa患者治疗失败及死亡的主要原因,早期准确预测BCR有助于指导临床合理制定治疗方案,改善预后。

Zhong等^[48]使用基于卷积神经网络(convolutional neural network, CNN)的ML,构建mpMRI影像组学模型来预测局限性PCa患者放射治疗(radiation therapy, RT)后的BCR,结果表明该模型的总体准确率为74.1%,首次证明了mpMRI影像组学在评估局限性PCa患者RT后预后方面的潜力。在此基础上,Li等^[49]联合术前bpMRI的RF、GS分级分组和PSA水平建立RadClip诺莫图来预测RP术后的无BCR生存和不良病理,结果显示RadClip的模型C指数为0.77, AUC为0.71,其表现优于现有的预

测工具如前列腺癌风险评估评分和Decipher基因检测,有助于早期识别可以从新辅助治疗中获益的潜在患者。

2.5 PCa的疗效评估

对于局部进展性PCa,RP联合内分泌治疗、放化疗、免疫治疗、靶向治疗等是目前常用的治疗方法,可以术前降低肿瘤分期,术后消灭残留的病灶及微小转移灶,提高患者生存率^[23]。随着诸多新型治疗方法的问世,这些方法对PCa的疗效和不良反应评估成为了关键^[50-52]。

在RT方面,Abdollahi等^[53]根据RT前后ADC值的变化来评估33例接受调强RT的PCa患者的疗效,并基于RT前后的bpMRI图像开发影像组学模型,发现RT前后T2WI和ADC图像中提取的RF均可以预测早期RT反应。与以往研究不同的是,该研究结合RT后的图像特征,量化了肿瘤治疗后内部异质性的变化。尽管该研究样本较少,未设置验证组,但其先进的ML和影像组学方法,开拓了PCa个体化治疗的第1步。关于RT后的不良反应,尿道狭窄是PCa高剂量近距离RT的特异性晚期反应^[54],Tsang等^[55]探索非恶性尿道狭窄形成与沿尿道的剂量分布及RF的关系,发现剂量分布与尿道狭窄并无关联,而同质性和对比度特征能够识别RT后尿道狭窄。另外Abdollahi等^[56]还发现mpMRI的RF有早期预测RT后股骨骨折的潜力。

在内分泌治疗方面,鉴于接受雄激素剥夺疗法(androgen deprivation therapy, ADT)后的PCa患者PSA通常降至较低水平,限制了PSA在识别治疗反应梯度的作用。因此Tharmalingam等^[57]研究ADT前后MRI纹理特征的差异,发现能量及同质性特征在治疗后良性组织中显著增加,在恶性组织中显著降低,证实了RF可以作为预测PCa对ADT敏感性的标志物。

3 PSMA-PET/CT影像组学在PCa中的应用

PSMA-PET/CT是PCa最有前景的成像方式,多项研究证明PSMA-PET/CT在NM分期上比MRI、增强CT或Choline-PET/CT更准确,PSMA-PET/CT已成为复发性PCa治疗后再分期的金标准^[23]。但目前基于PSMA-PET/CT的影像组学研究仍然不多。

Zamboglou等^[58]探索了基于⁶⁸Ga-PSMA-11 PET/CT的RF检测CT无法检出的csPCa的可行性,最终研究发现两个RF(大小区域不均匀归一化和小区域强调)对漏诊的病灶有优秀的检测能力(AUC \geq 0.93)。

Feliciani等^[59]基于⁶⁸Ga-PSMA-11 PET/CT和ADC图像,筛选能够区分低级别(GS=3+3)和高级别(GS>3+3)PCa的RF,以减少对早期惰性PCa的过度诊疗,但该研究的局限性为PET/CT和ADC图像一致的病变数量较少。Erle等^[60]基于决策树分类器构建⁶⁸Ga-PSMA-11 PET/CT影像组学模型来鉴别晚期PCa患者的生理性和病理性摄取,证实了影像组学模型对晚期PCa患者M和N分期的准确性。Cysouw等^[61]在¹⁸F-DCFPyL PET/CT图像上评估影像组学模型能否预测PCa的淋巴结转移、远处转移、GS \geq 8和ECE,结果显示影像组学模型对PCa的GS评估和转移倾向有良好的预测能力(AUC:0.86),优于传统PET参数模型(AUC:0.81)。

4 CT影像组学在PCa中的应用

虽然CT成像在检测PCa病变方面缺乏特异度和灵敏度,但CT图像可以提供NM分期信息,特别是对有MRI禁忌证的患者,CT影像组学可以提供补充信息来完善PCa的诊疗方式。

Osman等^[62]对PCa风险分层进行了高精度分类,探索基于CT的RF对PCa侵袭性预测的价值,发现区分GS \leq 6与GS \geq 7、GS=3+4与GS=4+3、低风险组与高风险组、低风险组与中风险组的AUC分别为0.90、0.98、0.96、1.00,具有良好的灵敏度和特异度。Acar等^[63]使用基于ML的CT纹理特征来鉴别⁶⁸Ga-PSMA PET/CT图像上有PSMA表达的骨转移灶和无PSMA表达的硬化灶,研究结果显示短区域高灰度强调和峰值是最有意义的两个RF,且KNN模型预测性能最佳(AUC:0.76),证实CT影像组学在鉴别骨转移灶中的潜力。Peeken等^[64]开发了1个CT影像组学模型,以预测接受PSMA引导手术治疗(即在术中检测和切除PSMA-PET/CT阳性淋巴结的新型手术方法)后的复发性PCa患者的淋巴结转移状态,结果显示联合影像组学模型的性能最佳(AUC:0.95),优于传统CT参数如淋巴结短径为基础的模型(AUC:0.84)等。Mostafaei等^[65]在一项前瞻性研究中探索了CT的RF和临床-剂量学参数对RT引起的泌尿道和胃肠道不良反应(\geq 1级膀胱炎和直肠炎)的预测能力,结果显示CT影像组学模型对RT不良反应有较好的预测潜力(AUC:0.71、0.71),优于临床模型(AUC:0.67、0.66)。

5 超声影像组学在PCa中的应用

超声作为一种非侵入性、无辐射、经济实用的

成像方法,在前列腺活检中起着不可或缺的作用。近年来随着超声成像方式的增多,其影像组学研究也在逐渐增多。

Ou等^[66]开发了一个基于经直肠超声(transrectal ultrasound, TRUS)的影像组学模型,并联合临床危险因素构建诺莫图以在活检前预测PCa,研究结果显示部分RF是预测PCa的独立因素。Liang等^[67]通过TRUS和剪切波弹性成像(shear-wave elastography, SWE)构建多参数超声影像组学模型来鉴别前列腺良恶性病变,结果显示该模型的AUC为0.85,结合了临床参数的联合模型AUC为0.90,证实了多参数超声成像模型对PCa诊断的准确性。与之相似的,Wildeboer等^[68]通过ML将B超、SWE、动态对比增强超声造影(dynamic contrast-enhanced ultrasound, DCE-US)自身的定量参数与基于它们的RF结合构建多参数超声影像组学模型,评估其在PCa诊断中的潜力,研究结果显示该模型对PCa和csPCa的诊断性能良好(AUC:0.75、0.90),优于表现最佳的定量参数即灌注速度构建的模型(AUC:0.69、0.76),该模型性能的改善应归功于RF以及多参数联合。Zhang等^[69]构建了1个基于神经网络的DL技术,用于学习和融合从B超和实时弹性成像中提取的RF,在计算机辅助分析下诊断PCa,为疾病诊断提供较少的主观和人为干预,最终显示出良好的诊断能力(AUC:0.851)。

6 问题与展望

PCa的影像组学研究越来越受到重视,但在未来的研究和应用中仍存在许多挑战。第一,目前大多数研究是单中心、回顾性研究,样本量小,缺乏外部验证,限制了研究结果的准确性;第二,由于PCa的多灶性及异质性,穿刺活检作为金标准有可能导致漏诊或误诊,直接影响影像组学诊断的准确性;第三,虽然人工分割是目前描绘ROI最准确的方法,但观察者间和观察者内的变异性难以避免,未来需要进一步改进自动分割算法的可重复性以提高定位的准确性;第四,由于缺乏统一标准,不同的机器及采集方案等限制了影像组学模型的临床应用,但AI和ML技术的兴起可以限制这种偏差,未来仍需将这些技术与传统成像方式进行比较;第五,由于所选特征与临床结果之间的关系缺乏透明的解释,未来需要进一步了解影像组学背后的决策过程以提高可信度。随着影像组学应用潜力的证实,未来研究应侧重于影像组学与其他非成像生物标志物

的结合,比如基因组学,甚至可以综合基因组学、转录组学、蛋白质组学、代谢组学等,开发新的生物标志物,以加强对患者的临床管理。

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