

综 述

HER-2阳性胃癌的影像学表现及研究进展*

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【摘要】胃癌是消化系统最常见的恶性肿瘤之一，早期症状不明显，一经发现常为晚期，预后极差，迫切需要新的治疗策略改善胃癌患者的预后。分子靶向药物曲妥珠单抗(针对人表皮生长因子受体2的单克隆抗体)联合化疗能显著改善胃癌患者的总体生存期及预后。传统的HER-2检测方法是对手术标本或活检标本进行免疫组织化学染色和荧光原位杂交，但胃癌具有高度异质性，活检标本仅显示肿瘤的一部分，这将会使测试结果不正确，假阴性的风险增高，患者失去靶向治疗的机会。随着医疗技术的日益成熟，越来越多的临床试验开始挖掘无创影像手段在甄别HER-2表达方面的价值。本文就无创影像手段在评估HER-2阳性胃癌方面的价值进行综述。

【关键词】胃癌；人表皮生长因子受体-2；电子计算机断层扫描；磁共振成像；影像学

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Imaging Manifestations and Research Progress of Human Epidermal Growth Factor Receptor2 Positive Gastric Cancer*

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ABSTRACT

Gastric cancer is one of the most common malignant tumors in the digestive system.The early symptoms are not obvious,and the prognosis is often very poor once found. New therapeutic strategies are urgently needed to improve the prognosis of patients with gastric cancer. Trastuzumab(Monoclonal antibody against human epidermal growth factor receptor 2)combined with chemotherapy can significantly improve the overall survival and prognosis of patients with gastric cancer. The traditional methods for the detection of human epidermal growth factor receptor2 are immunohistochemical staining and fluorescence in situ hybridization of surgical specimens or biopsy specimens,Gastric cancer is highly heterogeneous tumor,and biopsy specimens show only part of the tumor,which can lead to incorrect test results,an increased risk of false negative results,and patients losing the opportunity to target therapy. With the increasing maturity of medical technology,more and more clinical trials begin to explore the value of non-invasive imaging methods in identifying human epidermal growth factor receptor2 expression. This review documents the value of noninvasive imaging in evaluating human epidermal growth factor receptor2 positive gastric cancer.

Keywords: Gastric Cancer; Human Epidermal Growth Factor Receptor2; Computer Tomograph; Magnetic Resonance Imaging; Radiomics.

胃癌是消化系统最常见的恶性肿瘤，其死亡率和发病率均排世界癌症的第三位^[1]。人类表皮生长因子受体-2(human epidermal growth factor receptor 2, HER-2)是由ERBB2编码的原癌基因，位于17号染色体上，在正常情况下低表达或不表达，当外界环境发生某种变化时，可转变为癌基因，诱导细胞异常增殖。据统计，7%-36%的胃癌患者出现HER-2蛋白过表达^[2-5]。本文就HER-2阳性胃癌的影像学表现及研究进展进行综述。

1 HER-2阳性胃癌概述

HER-2是具有酪氨酸激酶活性的表皮生长因子家族受体中的一员。早在1986年就有文献报道称HER-2基因在胃癌细胞中过表达^[6]。自从Ⅲ期多中心随机对照临床试验(TOGA试验)^[7]和其他研究^[8-9]建议曲妥珠单抗(抗HER-2抗体)用于治疗HER-2阳性胃癌以来，HER-2检测已成为胃癌治疗策略中的一种常规手段，以达到指导胃癌个体化治疗的目的。目前，检测HER-2表达的主流方法是活检或手术标本的免疫组化(immunohistochemistry, IHC)分析加荧光原位杂交(fluorescent in situ hybridization, FISH)。然而，这种方法最明显的缺点是有侵入性、耗时长。且由于胃癌组织的瘤内异质性，活检标本并不能代表HER-2在整个肿瘤中的表达水平^[10-11]。因此，影像工具在评估HER-2状态中的研究价值逐渐成为人们关注的焦点。

2 HER-2阳性胃癌在CT中的影像学表现

MSCT(multi-slice spiral computer tomography, MSCT)检查是胃癌诊断和分期的首选方法，且较PET/CT和MRI经济、便捷^[12-14]。

据文献报道，HER-2阳性胃癌于贲门位置多见^[15-18]。多项研究认为HER-2表达与胃癌不良预后相关。潘等^[19]的和李等^[20]的研究纳入可接受胃癌根治术的患者，结果显示HER-2阳性胃癌患者多有淋巴结转移。但临床上胃癌患者一经发现即为晚期，且已有研究证明HER-2在胃癌不同阶段的作用不同，故仍需更多的研究将晚期胃癌患者纳入其中。之后Lee等^[21]的研究纳入无法接受根治术的晚期胃癌患者，主要对181例不可手术切除的胃癌患者的增强CT图像进行回顾性分析，发现HER-2阳性的患者T分期更高、更易伴有肝转移。郑等^[22]和Guan等^[23]的研究纳入包括可接受根治术或不可接受根治术的所有胃癌患者，发现HER-2阳性胃癌患者易发生肿瘤边界模糊，且具有较高的cT分期。目前HER-2表达与门静脉强化值之间的关系仍存在争议。潘等^[19]和刘等^[24]的研究认为HER-2阳性胃癌患者门脉期明显强化，这可能与血管内皮生长因子有关，有研究认为HER-2可促进血管内皮生长因子的表达，加快肿瘤新生血管的生成^[25]，而赵等^[26]的研究认为HER-2阳性患者具有相对小的门静脉强化值。

CT灌注成像主要用来评估肿瘤内血液动力学，是一种反映局部新生血管生成状态和检测肿瘤治疗反应的功能性成像方式。目前CT灌注成像参数与胃癌HER-2表达之间的相关性尚无定论，张敏等^[27]研究发现胃癌HER-2表达阳性组毛细血管表面通透性(permeability surface, PS)及血容量(blood volume, BV)数值均较HER-2阴性组高。而

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在Lee等^[28]的研究表明诸CT灌注参数与胃癌HER-2表达无相关性。

3 HER-2阳性胃癌在MRI中的影像学表现

磁共振成像(magnetic resonance imaging, MRI)具有软组织对比度高,多角度、多方位、多参数的成像能力,越来越多地应用于胃癌的临床诊疗,为进一步完善术前分期和评估治疗反应提供无创依据。研究发现在传统的弥散加权成像(diffusion-weighted imaging, DWI)中,表现扩散系数(apparent diffusion coefficient, ADC)与HER-2表达呈显著正相关^[29],但是通过传统DWI提取的ADC值,反映的是水分子扩散和微血管灌注的综合效应,并不能将两者解离开来,故引入了体素内非相干运动磁共振(incoherent intravoxel motion magnetic resonance, IVIMMR),它可以通过改变b值将扩散和灌注效应解离开来,生成独立的分子扩散图像与灌注图像,进行独立测量,在各种肿瘤的定性方面显示出巨大的潜力^[30-31]。Ji^[32]等通过胃癌患者术前常规序列图像和IVIM序列图像提取病灶的扩散和灌注效应参数,实验结果发现HER-2评分与扩散效应参数ADC值和纯扩散系数D值均呈显著正相关,这与先前对传统ADC值的研究一致。而HER-2评分与灌注效应参数血流灌注相关分数F值和伪扩散系数D*值之间没有显著相关性。该研究中IVIM成像对于b值的数目和设置是任意选择的,并没有优化,这可能会导致提取的参数值存在偏差,且该研究样本量小,仅纳入53例病人,未来仍需进行大样本、优化b值的实验来完善研究。最新的一项研究发现纳米氧化铁与抗HER-2片段抗体偶联可以作为一种新的针对HER-2的MRI造影剂,能够进行HER-2特异性肿瘤磁共振成像,在体内和体外都具有亲和力,使HER-2特异性肿瘤MRI成为可能^[33]。

4 HER-2阳性胃癌在PET-CT中的影像学表现

正电子发射计算机断层显像(positron emission tomography, PET-CT)是一项基于代谢显像和定量分析的影像学检查技术,广泛用于癌症患者的初始分期、评估治疗反应、检测疾病复发和预测预后。临床上常用的PET-CT参数包括最大标准化摄取值(maximum standard uptake value, SUV_{max})、肿瘤代谢体积(metabolic tumor volume, MTV)和总糖酵解量(total lesion glycolysis, TLG)。有研究表明胃腺癌患者HER-2的表达与MTV值相关^[34-35]。现有的研究关于HER-2表达与SUV_{max}和TLG之间的关系尚存争议。Park等^[36]对纳入的胃癌转移和复发患者的PET-CT图像进行分析,发现胃癌HER-2状态与SUV_{max}和TLG之间存在显著相关性,且HER-2的表达与SUV_{max}和TLG呈负相关,这与先前的研究结果一致^[37-39]。而有研究认为胃癌HER-2状态与SUV_{max}和TLG值之间无明显相关性^[35,40-42]。造成结果不同的原因可能是因为研究纳入的对象不同,有研究纳入局部进展期胃癌和晚期胃癌,但有的研究只纳入早期及局部进展期胃癌,由于胃癌组织中HER-2的表达与分期相关^[43-44],所以不同的纳入对象将会导致HER-2表达率不同。现阶段关于¹⁸F-FDG PET-CT影像图像参数在预测HER-2状态方面的价值仍存在争议。

5 HER-2阳性胃癌在放射组学中的研究进展

放射组学是一种新兴技术,使用自动数据表征算法,将从影像图像中标注的感兴趣区域转化为高通量的定量特征,采用统计学方法甄选出与目标结果高度相关的特征,在胃癌的术前无创检查中显示出优异的性能。Wang等^[45]通过对纳入的132例手术切除的晚期胃癌患者的动脉期(arterial phase, AP)和门静脉期(portal phase, PP)增强CT图像进行肿瘤分割和特征提取,发现AP放射组学模型在区分HER-2表达状态方面有很大的应用潜能,AUC为0.76。但该研究是基于单一的影像组学特征建立的模型,预测性能并不稳定。之后,有研究提出将临床特征和影像组学特征结合起来建立预测模型,Guan等^[23]研究通过对纳入的357名胃癌患者的增强CT动脉期图像进行病变分割,提取深度学习和影像特征,最终将与HER-2表达相关的独立因素包括辐射特征评分、CT报告的T分期和肿瘤标志物CA724水平结合起来构建的列线图在预测胃

癌HER-2表达方面的性能极好,AUC为0.921。Li等^[46]对纳入的胃癌患者增强CT门脉期图像进行影像组学特征提取,将与HER-2表达相关的影像组学特征和肿瘤标志物CEA结合起来构建的诺模图,训练组和验证组的放射组学特征AUC分别为0.782和0.736,校准曲线也表明列线图具有出色的预测性能,可以用于临床HER-2扩增的检测,对临床指导胃癌HER-2靶向治疗具有重大意义。

6 总结

本文回顾了与胃癌HER-2表达相关的影像学标志物的研究进展,HER-2阳性胃癌患者常见于贲门,且具有高CT分期、高ADC值和D值等,但目前临床试验中与胃癌HER-2过表达相关的部分影像资料参数(如SUV_{max}、TLG、CT门静脉强化值)之间的关系仍存在争议性,仍需进一步完善研究。其次由于胃癌组织中HER-2表达存在异质性,手术标本和匹配的活检标本不一致,在未来需进一步规范活检中HER-2的评估方法,以提高试验的准确性,为胃癌临床靶向治疗提供无创依据。综上,影像工具作为胃癌临床诊疗的常用辅助手段,在评估胃癌HER-2的表达中发挥着至关重要的作用,能够为临床筛选出适合抗HER-2治疗的胃癌患者,提高胃癌患者的生存率及改善预后,使每个患者都能得到合适的靶向治疗。

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