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磁共振功能成像在监测乳腺癌新辅助化疗中的应用和进展*

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摘要:近年来,新辅助化疗在原发乳腺癌治疗中运用越来越广泛。影像学手段在评价新辅助化疗疗效、指导临床治疗方案的制定中发挥重要作用。磁共振功能成像的引入,可以加深对恶性乳腺肿瘤的病理生理活动及分子生物学特性的了解,监测化疗疗效,提高早期预测的准确性。本文总结功能学 MRI(磁共振成像)探测乳腺癌患者生物标志物的研究现状及发展情况,描述各种生物学标志物特性,评价其潜在的临床应用价值和局限性。以下将对动态增强磁共振成像、弥散加权成像、血氧水平依赖成像以及波谱成像等几种磁共振功能学成像方法的原理进行描述,重点对其在监测乳腺癌新辅助化疗中的应用进行综述。

关键词:乳腺癌;磁共振功能成像;新辅助化疗

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Function Magnetic Resonance: Monitoring Response to Chemotherapy in Breast Cancer*

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ABSTRACT: Recently, neoadjuvant chemotherapy is used in women with primary breast malignancies increasingly. The effects of imaging techniques on evaluating response to NAC and establishing clinical dosage plans are important. Functional MR techniques can provide new sight to detect pathophysiological and biomolecular processes in breast malignance lesions. We describe the characteristics of various biomarkers detected by function MR and evaluate their potential clinical application value and limitations. This article summarizes principle of several function magnetic resonance techniques (DCE-MRI, DWI-MRI, BOLD, MRS) and focuses on the application of these techniques in monitoring the response to chemotherapy.

Key words: Breast cancer; MRI; NAC

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前言

新辅助化疗(neoadjuvant chemotherapy, NAC)由于其术前降低肿瘤级别、提高保乳手术成功率、早期治疗微小肿瘤等优势,现已成为治疗乳腺癌的一种常规手段。如何精准、早期、无创伤的评价乳腺癌新辅助化疗的疗效,是临床中亟需解决的问题。常规临床检查无法满足临床日益精准化、个体化的需求,而不断发展的影像学技术则为乳腺癌新辅助化疗提供新的监测手段。与钼靶、超声等其它影像手段相比, MRI 在评价新辅助化疗疗效,监测缓解率方面担当者更重要的角色,对于非肿块及散在多发型乳腺肿瘤优势更加明显^[1]。早期确定其疗效对于连续性治疗方案的制定来说非常重要。磁共振功能成像从评价分析肿瘤微环境的变化角度,得到细胞密度、组织缺氧程度、代谢水平、癌细胞稳定性等信息,可以提高早期预测能力,并能提供替代性生物学标志物。为提高监测乳腺癌新辅助化疗的效

率,磁共振功能成像在评价化疗疗效的相关研究已经越来越受到研究者的重视。本文将对几种磁共振功能成像方法的工作原理及其相关生物学标志物评价疗效的有效率方面进行综述。

1 动态增强磁共振成像(DCE-MRI)

乳腺 DCE-MRI 检查,静脉注射低分子量对比剂含钆化合物,对比剂为顺磁性,有缩短 T1 效应^[2]。不同组织对比剂摄取和流出有差别,使 T1 加权图像上信号有增强的效果。DCE-MRI 通过时间信号强度曲线(TIC)进行半定量分析;通过引入药代动力学模型定量分析评价肿瘤内对比剂的变化情况。定量参数包括:(1)转移系数 K_{trans},描述对比剂由血管内扩散到肿瘤间隙中的跨膜运输活动,反应血管壁的渗透性;(2)速率常数 k_{ep},反应随时间推移对比剂扩散回血管内的活动;(3)血管外细胞外的空间 V_e^[3]。

DCE-MRI 在诊断及鉴别良恶性乳腺癌中有一定应用价

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值。半定量分析 TIC 曲线可发现:良性病灶多呈 I 型曲线(流入型);恶性病灶中,II 型曲线(平台型)与 III 型曲线(流出型)约占 90 %^[4]。许多研究已证明定量参数 K^{trans} 、 k_{ep} 在乳腺癌中普遍为高水平^[56]。DCE-MRI 可以显著提高诊断敏感性(89~100 %)^[7],但在大多研究中其特异性并不高^[8],表现为与钼靶基本相同,略高于超声^[9]。结合平扫图像形态学特征,可以提高乳腺 MR 诊断特异性。

将 DCE-MRI 应用于监测 NAC,发现在 1/3 行 NAC 并有效的局部晚期乳腺癌患者中, K^{trans} 、 k_{ep} 显著降低^[10];接近 1/3 的无缓解患者,其 V_e 值增高。化疗的抗血管生成作用会对微环境产生影响,这些参数的变化可能与微血管的密度和微结构的功能变化有关。相关研究表明:一期化疗和二期化疗过程中, K^{trans} 值都可以成为一种预测性的生物学标记物,拥有指示抗血管生成药物及血管破坏性因子作用的功能^[10,11]。有研究者提出当 K^{trans} 值变化超过 40 %时,认为是对治疗有效^[12]。然而也有一些矛盾的文献显示:NAC 后 K^{trans} 、 k_{ep} 没有降低^[13]。对于这些研究中得到不同的结果,原因可能包括入组患者数量、肿瘤类型、化疗的药物以及治疗后扫描的时间点的不同。治疗有效的判定标准也不一致也会造成不同结果,这需要大量研究确定有效的标准。

2 弥散加权成像(DWI-MRI)

磁共振脉冲序列下,水分子的微观运动会引起信号缺失,DWI-MRI 通过探测这种微观运动来反应组织间的固有差异^[14]。乳腺癌中由于癌细胞增殖导致细胞间隙变小,水分子弥散活动受到限制,而布朗运动导致的信号丢失也将降低,反应水分子弥散活动的参数 ADC(表现弥散系数)值下降,在 DWI 图像上乳腺癌病灶区域表现为高信号^[15]。DWI-MRI 检查提供组织细胞密度、细胞膜间隙以及组织微环境的相关信息,可为 DCE-MRI 诊断提供该方面的补充信息^[16]。

DWI 参数可以作为监测新辅助化疗的一项早期生物学指标^[17]。细胞凋亡会导致细胞膜完整性破坏,使阻碍水分子弥散的膜性成分减少,同时细胞的皱缩会扩大细胞间隙,因此水分子弥散活动会增强。这种变化在 DWI 检查中表现为 ADC 值增加约 35 %,而该参数的变化要明显早于局部肿瘤大小发生改变之前^[18]。张静等研究中,乳腺癌患者行新辅助化疗,有效组 ADC 值升高,化疗第 2~8 个疗程与化疗前肿瘤 ADC 值 $((0.98 \pm 0.18) \times 10^{-3} \text{ mm}^2/\text{s})$ 相比,均有统计学意义;而无效组化疗前后,肿瘤 ADC 值无统计学差异^[19]。而在形态学发生变化前,DWI 还能探测到 ADC 值的短暂降低,原因可能是化疗导致细胞膨胀,血运及细胞外间隙也发生了变化。汪晓红等的研究中,ADC 值也可以预测 NAC 疗效,有效组患者行 NAC 前的 ADC 值要显著低于无效组,表明 ADC 值低的乳腺癌病灶 NAC 疗效更佳^[20]。DWI 从分子水平的角度来反应组织功能、评价 NAC 疗效,目前由于图像分辨率低等因素,单独应用较少。另外,各研究中也存在标准不一致导致结果不尽相同的情况,未来需要大样本的进一步研究。

3 磁共振波谱成像(MRS)

MRS 利用的是 ^1H 与其他 ^{31}P 、 ^{23}Na 、 ^{19}F 等不成对质子的原

子核自旋现象,探测该原子在磁场中吸收并释放的射频^[21]。如获得含有特定原子化合物的波谱分布情况,则可以提供癌细胞代谢变化的信息。 ^1H MRS 可以探测到乳腺癌组织中,磷脂代谢过程中含胆碱的代谢物水平很高,由游离胆碱、甘油磷酸胆碱、胆碱磷酸等共同形成波谱 3.22 ppm 处的高峰。而在正常乳腺组织中没有此峰,良性乳腺病灶中可以在 3.25 ppm 处发现高峰^[22,23]。

许多研究已证明,总胆碱(tcho)浓聚水平可以成为恶性肿瘤的一个生物学标记物^[24],联合 DCE-MRI 及 T2 加权像可以显著提高诊断乳腺癌特异性(88 %~100 %)^[25]。 ^1H -MRS 活体监测乳腺癌新辅助化疗的代谢变化已被许多研究证明具有良好的应用价值,恶性组织或残余恶性病灶中 tcho 水平及水脂比率增加。相关研究中表明,新辅助化疗两周期后,判断是否病理缓解时,探测胆碱信号降低的敏感性要高于探测肿瘤大小变化^[26]。活体 ^1H MRS 是一种独立的、大体素的检查技术,它涵盖全部水以及脂肪成分的变化信息,因此在异质性较大的肿瘤中,定量分析胆碱水平的敏感性会降低,例如浸润性小叶癌及导管原位癌。另外,部分容积效应在大体素中会对量化胆碱产生影响,这成为新辅助化疗后进行波谱分析需要解决的问题。

(^{23}Na) MRI 也已经被证明可以反应细胞完整性及细胞代谢活动,并具有良好的敏感性,表现为肿瘤组织中 ^{23}Na 浓聚显著提高^[27]。 ^{23}Na 图像可以结合高分辨率 ^1H 图像从而进一步精确诊断,且不需要额外的扫描。目前已有一些研究指出(^{23}Na)MRI 在新辅助化疗后可以探测到钠浓聚的显著降低,通过未来的大量研究论证,(^{23}Na)MRI 有望提供新的替代性生物标记物^[28]。

4 血氧水平依赖磁共振成像(BOLD)

BOLD(Blood oxygen level-dependent)依赖于脱氧血红蛋白的顺磁性。脱氧血红蛋白的浓聚会增快弛豫速率 $R2^*$ ($=1/T2^*$),而 $T2^*$ 图像信号强度降低。氧化作用则产生相反的效果。因此,脱氧血红蛋白成为 BOLD 标记组织缺氧的生物学标志物^[29]。

在关于乳腺癌患者的研究中已经证明:接受化疗前的肿瘤中 $R2^*$ 值要比在正常乳腺基质中低很多,且具有统计学意义^[30]。这表明乳腺肿瘤比正常乳腺组织氧含量多,可能是因为肿瘤组织血管分布更多。正常乳腺组织中的 $R2^*$ 值较肿瘤高,与 Cooper 韧带胶原纤维接近,Cooper 韧带维持正常乳腺结构完整并可以使 $R2^*$ 值增高。有研究表明,NAC 有效的瘤内纤维化也可能增加 $R2^*$ 水平,但这一结论需要更多研究来论证^[31]。在部分 NAC 治疗后有疗效的病灶中, $R2^*$ 值增加,有研究者认为可能是病灶供血血管减少造成的。在已发表的文献中,BOLD 运用于乳腺癌诊断中时并不能与 DCE-MRI 参数的有效率相媲美,例如 K^{trans} 、rBV(血容量)、rBF(血流量),甚至是一些形态学参数^[30]。然而乳腺肿瘤类型不同,微血管的复杂性和异质性也不尽相同,BOLD 方法从氧化水平角度评价肿瘤 NAC 治疗后变化,可以为 DCE-MRI 提供良好辅助。

5 小结与展望

传统的乳腺癌影像诊断中,形态学变化并不能完全反应 NAC 的疗效,无法提供肿瘤微环境变化的信息。面对临床治疗方案日渐呈个体化、精准化的趋势,磁共振功能成像的发展打

破了传统方法的局限性。磁共振功能成像能够早期提供较为可靠的信息,评价高度恶性、预后差的乳腺肿瘤化疗疗效、监测其功能变化,从而为治疗方案更精准的制定提供帮助。本文总结几种磁共振功能成像方法在监测乳腺癌 NAC 中的应用,拓宽了传统影像方法的思路及视角。随着物理、计算机技术及磁共振理论不断丰富和发展,其参数也会从更多角度反应生物体微环境的变化。在未来的研究中,功能学 MRI 的参数需要更多大量本研究来论证其准确性,标准化诊断阈值及应用方法,使之早日常规应用于临床,对乳腺癌的诊断治疗提供更有效的帮助。

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