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酰胺质子转移加权成像对肿瘤的研究进展

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摘 要

酰胺质子转移加权成像(Amide Proton Transfer Weighted, APTw)是一致化学交换饱和技术(Chemical Exchange Saturation Transfer, CEST)的亚型，它是一种新型的分子磁共振成像技术。该技术主要基于细胞蛋白和组织中内源性多肽生成图像对比度，间接反映细胞的代谢及生理病理变化。目前APTw成像已经在多种肿瘤成像方面表现出良好的发展前景，特别在脑肿瘤和肿瘤治疗方面的应用显示出较大的优势。本文旨在描述APTw成像的基本原理及APTw成像在肿瘤中的研究现状、缺陷及前景。

关键词

酰胺质子转移，化学交换饱和转移，肿瘤，磁共振成像

Research Progress on Tumor by Weighted Imaging of Amide Proton Transfer

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Abstract

Amide proton transfer weighted imaging (APTw) is a subtype of chemical exchange saturation transfer (CEST) and a novel molecular magnetic resonance imaging technique. This technology is mainly based on the contrast of images generated by endogenous peptides in cell proteins and tissues, indirectly reflecting the metabolic and physiological pathological changes of cells. At

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present, APTw imaging has shown good development prospects in the imaging of various tumors, especially in the application of brain tumor and tumor treatment. This article aims to describe the basic principles of APTw imaging and the current research status, shortcomings, and prospects of APTw imaging in tumors.

Keywords

Amide Proton Transfer, Chemical Exchange Saturation Transfer, Tumor, Magnetic Resonance Imaging

1. 引言

磁共振成像技术在我国已经发展了数十年，在临床上许多方面都展现了科技的先进性，是一种高度通用的成像技术。目前磁共振成像是诊断疾病、指导治疗和评估疗效的关键方式。在众多机构的数据表明，APTw 技术为肿瘤的诊断中增加了重要价值，如肿瘤的检测于分级[1]-[6]，治疗效果于肿瘤复发的评估[7] [8] [9]，于肿瘤进展和生存相关的预后[10] [11]和基因标志物的鉴别[12] [13] [14]，已经得到了临床的广泛关注和认可[6]。APTw 主要基于细胞蛋白和组织中内源性多肽生成图像对比度，间接反映细胞的代谢及生理病理变化，为临床诊断和治疗提供帮助[15] [16] [17] [18] [19]。

2. APTw 成像技术原理

APTw 属于 CEST 成像的一种亚型，其技术原理也和 CEST 大致相同，但也有自己的技术特点。CEST 增强灵敏度的原理是低浓度溶质分子通过射频(RF)使特定的可交换质子饱和来标记[20]。溶质质子具有不同于水的共振频率，但是由于溶质浓度很低(μM 至 mM 范围)，单次饱和度转移不足以对水质子产生任何影响(100M 范围)，因此在常规 MR 成像中是看不见的。鉴于水池相对于饱和溶质质子池来说更大，每个交换发生时，饱和的溶质质子都会被非饱和水质子所取代，然后再次被饱和。这种饱和传输可以将饱和能量转移到自由水中，降低水的磁化强度和信号。在饱和脉冲的持续作用下，饱和传输会在扫描区域不断积累水的饱和。这种放大机制使得间接观察低浓度溶质成为可能，从而获得关于受检测目标物质含量和环境信息的数据。该技术最初应用于健康成人的膀胱尿素显像[21]，并且目前常用的可交换质子的体内代谢产物包括酰胺键(-NH)、胺键(-NH2)、羟基(-OH)等[22]。由于酰胺质子在体内游离蛋白质和多肽中广泛存在，因此基于 CEST 的 APTw 成像可以成为一种有效的无创分子检测工具[23]。

APTw 磁共振成像是周进元教授[24]等人在 2003 年提出的一种基于化学交换饱和转移的分子磁共振成像的方法，用于检测体内蛋白质含量和 PH 值，进而达到诊断疾病的一种新型的成像技术。APTw 成像的基础是 CEST 双池(溶质池和溶液池)交换模型，在 APTw 成像中，通过预先使用特定频率的偏振射频脉冲来选择饱和移动蛋白质骨架中可交换的氨基质子(溶质池)。被饱和的可交换质子通过化学交换转移到水分子(溶液池)，导致水分子的饱和度不断增加，从而引起水信号的逐渐下降。通过监测质子的转移速率，我们可以得到氨基质子的浓度信息[24]。通过记录自由水在不同饱和频率脉冲下的信号，可以得到 Z 谱图像。通过计算在±3.5 ppm 处的非对称磁化转移率(MTRasym)，可以反映 APTw 的信号强度。MTRasym (3.5 ppm)的计算公式为 MTR (+3.5 ppm) − MTR (−3.5 ppm) = APTR + MTR'_{asym} (3.5 ppm) [25]。其中，Ssat

(±3.5 ppm)代表在±3.5 ppm 处的饱和脉冲下的水信号强度，S_0代表没有施加饱和脉冲时的水信号强度，MTR'_{asym} (3.5 ppm)代表除了蛋白质酰胺质子转移率(APTR)之外，在低饱和率下的其他贡献部分[26]。MTR'_{asym}来源于脂肪族氨基酸、半固态池及脂肪族、烯类、芳香族等组织内酰胺质子产生的磁化传递效应[27]。当组织环境中的 PH 值较低时，酰胺质子电负性增大，交换的速率加快，组织环境中饱和自由水的信号越高，MTR_{asym}值就越高，APT 效应越显著[28]。因此利用 Z 谱可以计算出特定频率下的非对称磁化转移率 MTR_{asym} (3.5 ppm)，去反映 APT 信号强度。

3. APTw 在肿瘤的研究进展

周进元[29]教授在动物肿瘤模型的试验中发现在肿瘤区域 APT 呈现高信号。3 年后第一次用于人类的 APT 数据证实相对于正常实质和肿瘤水肿区，高级别的肿瘤 APT 呈现高信号[30]。由此，APTw 成像能够提供诊断价值信息且不需要外源性对比剂。

3.1. 胶质瘤

胶质瘤是成人最常见的脑肿瘤，不同级别的胶质瘤的组织病理学改变不一样，其治疗和预后也差别极大。区分胶质瘤分级的金标准为有创性的病理活检，并且存在进一步转移的风险，因此磁共振无创的重要性就突显出来。近年来，因为 APTw 成像能够观察到内源性分子的变化，所以 APTw 成像能否对胶质瘤进行准确分型、分级得到了广泛的关注。研究结果显示，Togao [31]等人发现 APTw 成像在非强化胶质瘤中，高级别胶质瘤(HGG)的 APTw 信号强度(2.70% ± 0.58%)明显高于低级别胶质瘤(LGG)的 APTw 信号强度(1.87% ± 0.49%)，并且两者之间存在统计学差异($P = 0.0001$)。Choi [32]等人的研究发现随着胶质瘤分级的增高，APT 信号强度也增加，且 II 级(0.84% ± 0.60%)、III 级(1.55% ± 0.87%)、IV 级(2.53% ± 0.70%)脑胶质瘤分级之间有统计学差异($P < 0.001$)，这些结果与 Su [33]和 Song [34]等人的研究结果基本一致。出现这个现象主要归因于脑肿瘤中有较高的内源性游离蛋白及多肽浓度，随着胶质瘤的分级的增加，内源性游离蛋白及多肽也随着增加，所以 APT 信号强度增加。此外，Chen [35]等人研究发现 APT 信号强度和 Ki-67 成正相关。一般来说 Ki-67 抗原能够反映肿瘤细胞的增殖速度和侵袭能力，对胶质瘤预后意义重大[36]。Park [37]等研究表明 APTw 成像也能够区分复发性肿瘤和治疗引起的变化，是一种有效的生物标志物成像。Jiang、Chen、Onishi [38] [39] [40]等人的最新研究也是赞同这个观点的。但是由于 APTw 成像空间分辨率较低，需要 3D-T1W1 或者 T1W1 增强扫描结合才能更好的评估肿瘤疗效。最近有研究发现异柠檬酸脱氢酶基因(IDH)野生型胶质瘤的 APT 信号比 IDH 突变型胶质瘤的 APT 信号显著增高[15] [41]，这意味着 APTw 成像有助于术前评估脑胶质瘤 IDH 的突变状态，能够提供胶质瘤基因型诊断方面的价值。

3.2. 转移瘤

对于脑肿瘤而言，转移瘤和高级别胶质瘤之间是影像上的难点和重点，脑转移瘤、胶质瘤是常见的脑恶性肿瘤，两者的发病率在近十几年不断增加。多项研究表明[42] [43]，肿瘤周围水肿区的 APT 信号可以作为两者的鉴别，两者均为恶性肿瘤，肿瘤的生长速度快，异质性很高，瘤内的细胞密度大，血脑屏障通透性增高，蛋白质等大分子物质渗出明显，积聚在肿瘤周围形成水肿。转移瘤的瘤周水肿主要是因为毛细血管异常渗漏相关的血管源性水肿，而胶质瘤的瘤周水肿常常由肿瘤细胞的浸润引起，所以解释了胶质瘤的瘤周水肿信号会比转移瘤的瘤周水肿高。Yu [44]等研究者发现 APTw 成像鉴别孤立性脑转移瘤(Solitary Brain Metastases, SBMs)和胶质母细胞瘤(Gliobastomas, GBMs)与上述结果相似，SBM 组的肿瘤周围脑区(Peritumoral Brain Zone, PBZ)的各个 APT 信号明显低于 GBM 组($P < 0.001$)。

3.3. 肺癌

目前临床上对肺癌的病理类型的诊断主要靠病理活检这个金标准，但侵袭性、取样误差和并发症限制了其应用。近些年，利用 APTw 成像直接对肺癌进行的研究也越来越多。Togao [45]等人运用 A549 人肺癌细胞和 Lewis 鼠源性细胞进行体外研究，发现 Lewis 肺癌(Lewis Lung Carcinoma, LLC)的 MTR_{asym} (3.5 ppm)大于 A549，而病理结果证实，LLC 的细胞密度更大且增殖更活跃，为 APTw 成像鉴别肺癌类型提供了可靠的理论基础。Ohno [46]等研究者首次将 APTw 成像用于胸部肿瘤的前瞻性临床研究，包括 13 例恶性胸部病变和 8 例良性胸部病变，结果发现恶性肿瘤的磁化非对称转移率(3.5 ppm)明显高于良性病变($P = 0.008$)，其他胸部恶性肿瘤明显高于肺癌($P = 0.005$)，肺癌中的腺癌也显著高于肺癌中的鳞状细胞癌($P = 0.02$)，表明 APTw 成像在胸部肿瘤良恶性及肺癌不同病理类型的鉴别中具有潜在的临床价值。Ohno [47]等人的另一项研究，在 82 名肺结节患者中发现 APTw 成像与 DWI 联合 FDG-PET/CT 成像在良恶性肺结节的鉴别诊断中效能相似，并且其特异性和准确性是高于单独应用 DWI 诊断。这也为 APTw 成像在研究肺癌脑转移瘤病理类型提供了潜在研究价值。部分研究[48] [49] [50]证明 APTw 成像是具有区分复发性肿瘤和治疗效果的能力，这些结果都证明了 APTw 成像在肿瘤学中的潜力，为区分活动性肿瘤和放射性坏死提供了一种无创成像的生物标志物。

3.4. 直肠癌

MRI 是直肠癌诊断、疗效评估和随访的重要检查。近年来，APTw 成像联合其他 MRI 序列有望成为一种全新的多模态成像方式应用于直肠癌的诊疗中。Nishi [51]等人发现中分化的直肠腺癌 APT 信号(2.85% ± 1.51%)高于高分化的直肠腺癌(1.24% ± 0.57%)，并且低分化腺癌的 APT 信号与肿瘤分级显著相关($P = 0.019$)。Chen 和 Li [52] [53]的研究也发现 APT 信号与直肠癌 WHO 分级成正相关。同时 Li 也发现 APT 信号在进展期的肿瘤和有淋巴转移的肿瘤中明显增加，P53 阳性组和 KI-67 高增殖组 APT 信号显著升高，因此 APTw 成像适合直肠腺癌，并且 Wei [54]等人发现 T2WI 联合 APT 可以准确预测直肠腺癌患者的淋巴结转移，这为 APTw 成像评估直肠腺癌转移提供诊断价值。在治疗方面，Nishie [55]等的研究表明治疗前 APT 成像可以预测晚期直肠癌(LARC)患者对新辅助化疗(NAC)的反应。Chen 等评估了 APTw 成像联合 DWI 预测 LARC 患者对 NAC 的疗效，结果显示 NAC 后所有的直肠癌患者 APT 信号降低，肿瘤体积缩小，癌胚抗原水平下降，这可能是因为化疗导致的细胞增殖减慢或停止，减少了肿瘤细胞和蛋白质合成。所以 APTw 成像可以非侵入性的定量评估直肠癌的化疗效果，为直肠癌个体化治疗提供预后价值。

3.5. 乳腺癌

乳腺癌在女性的癌症死亡率中位居榜首[56]。对文献的调查显示，APT 研究涉及乳腺癌主要集中在两个临床方面，第一个方面是乳腺癌良恶性比较以及恶性程度的比较，其次是评估疗效反应。文洁[57]等人的研究发现乳腺癌平均 APT 信号强度与乳腺良性病变平均 APT 信号强度差异无统计学意义($P = 0.917$)。Meng [58]等人的结果显示乳腺癌恶性肿瘤 APT 信号强度显著低于良性病变，Liu [59]等人发现恶性乳腺癌的 APT 信号要显著高于乳腺良性病变。这可能与研究的样本量、病理类型多样化有关。所以 APT 在评估乳腺癌良恶性之间的价值仍未确定。在恶性程度的比较方面，文洁和 Liu 的研究结果却相似，III 级病变的 APT 信号要显著高于 II 级和 I 级，且 APT 信号强度与 ki-67 显著相关，这说明侵润程度越高的乳腺癌肿瘤其肿瘤细胞增殖越活跃，肿瘤细胞聚集区的蛋白质和多肽含量也就越多，APT 信号强度也就越高。为了评估对 NAC 的反应，Krikken 等人测试了 APT 对 NAC 早期反应的能力，发现 APT 在评估 NAC 早期阶段的效果是可行的。Zhang [60]等人发现 APTw 成像能够检测治疗效果，但是对于三阴性乳

腺癌的患者，病理缓解并没有得到完全的区分。

4. 局限性

和其他 MRI 序列相同，APTw 成像容易产生一些混淆的信号，这可能会造成结果的误导。从技术的角度来说，B_0 的不均匀性是 APTw 成像的中一个关键问题，虽然大部分可以通过水的共振频率重新排列并去除，但有时大脑周围和颅骨会发现一些低信号或者高信号，不应将其于 APTw 效果混淆。APT 成像还依赖于体内的 pH 值及蛋白质浓度[61]。有研究表明，交换速率会随着 pH 值的变化而变化，因次 APT 信号减低可以被 pH 值降低所解释[62]。然而，pH 值并不认为是恶性肿瘤中 APT 信号的主要来源。对于肿瘤这中很难探测到其微小 pH 值改变的疾病中，APT 信号强度的高低近似取决于细胞内蛋白质的含量。除了上述的 PH 值影响以外，还有其他因素也可以增加 APT 信号的强度如囊肿和空腔病变、颅内出血和脑组织水肿等[63] [64] [65]。因此，在解释 APT 成像结果时，应将这些因素认为可能的影响因素。

APTw 成像可能成为在肿瘤术前分级、预测、鉴别以及治疗相关的方面的生物影像标志物，这使我们从分子学角度对肿瘤的进行研究，去了解肿瘤的分子学特征，对肿瘤分子学理解的增加也将推动新型免疫疗法和靶向疗法的持续发展，这些疗法和靶向疗法在血液肿瘤屏障之外具有更高的生物利用度，并推动放射治疗和微创手术技术的进步，使患者的预后在未来肯定会得到改善。

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向绪洋起草和撰写稿件，获取、分析或解释本研究的数据/文献；李孝忠对稿件重要内容进行了修改；林慧婷获取、分析或解释本研究的数据/文献。全体作者都同意发表最后的修改稿，同意对本研究的所有方面负责，确保本研究的准确性和诚信。

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