Advances in Clinical Medicine 临床医学进展, 2023, 13(4), 6176-6181
Published Online April 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.134870

Hans汉斯

细胞外体积分数在肿瘤相关领域中的应用进展

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收稿日期：2023年3月19日；录用日期：2023年4月15日；发布日期：2023年4月23日

摘　要

恶性肿瘤(癌症)是威胁人类健康的重要原因之一，全面的了解肿瘤生物学行为，明确肿瘤的发生发展机制，有利于我们制定全面的战略和措施应对癌症带来的日益增长的死亡威胁。细胞外基质(extracellular matrix, ECM)在肿瘤的生物化学、生物力学、结构组成和分布上发生改变，它参与促进肿瘤细胞的生长、侵袭、转移和血管生成，而且抵抗细胞死亡和药物扩散。细胞外体积分数(Extracellular volume fraction, ECV)可以量化ECM，基于影像学检查的ECV分数与组织病理上的ECV具有较高的一致性，具有无创、定量、可重复等优点，在肿瘤相关预测因子、组织病理分级分化、复发转移及疗效评估等方面广泛应用，本文对ECV在肿瘤相关领域的应用进行了阐述和总结。

关键词

细胞外体积分数，肿瘤，细胞外基质，影像学检查

Advances in the Application of Extracellular Volume Fraction in Tumor-Related Fields

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Received: Mar. 19th, 2023; accepted: Apr. 15th, 2023; published: Apr. 23rd, 2023

Abstract

Malignant tumors (cancer) are one of the most important causes of threats to human health. A comprehensive understanding of tumor biological behavior and clarification of the mechanisms of tumor development are beneficial for us to develop comprehensive strategies and measures to

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文章引用: 徐阳, 郭大静. 细胞外体积分数在肿瘤相关领域中的应用进展[J]. 临床医学进展, 2023, 13(4): 6176-6181.
DOI: 10.12677/acm.2023.134870

deal with the increasing threat of death from cancer. Extracellular matrix (ECM) is altered in the biochemistry, biomechanics, structural composition and distribution of tumors, and it is involved in promoting tumor cell growth, invasion, metastasis and angiogenesis, and it resists cell death and drug diffusion. Extracellular volume fraction (ECV) can quantify ECM, and ECV fraction based on imaging examination has high consistency with ECV on histopathology, which has the advantages of non-invasive, quantitative and reproducible, and is widely used in tumor-related predictors, histopathological grading and differentiation, recurrence and metastasis, and efficacy assessment, etc. In this paper, the application of ECV in tumor-related fields is described and summarized.

Keywords

Extracellular Volume Fraction, Tumor, Extracellular Matrix, Radiographic Examination

1. 引言

恶性肿瘤(癌症)是全球主要的死亡原因之一，距世界卫生组织(the World Health Organization, WHO) 2019 年的估计，癌症是 183 个国家中 112 个国家 70 岁前死亡的第一或第二大死因。近年来，中国的恶性肿瘤发生率和死亡率日益增加。据相关统计[1] [2]，2016 到 2020 年间，我国癌症新发病例从 406.4 万增长到 457 万，死亡病例从 241.4 万增长到 300 万，对个人健康、社会经济带来了巨大威胁和负担。因此，深入了解肿瘤的发生发展机制并制定全面的战略是当今社会急需解决的公共卫生问题之一。

细胞外基质(extracellular matrix, ECM)是所有组织和器官的基本和核心组成部分，是多细胞生物存在的必要条件。而在癌症中，细胞外基质在生物化学、生物力学、结构组成和分布上发生改变[3]。有证据显示 ECM 参与促进肿瘤细胞的生长、侵袭、转移和血管生成，而且抵抗细胞死亡和药物扩散[4]。因此，深入了解 ECM 与肿瘤生物学行为及免疫反应之间的关系，有助于临床优化诊疗方案，延长患者的总体生存期[5]。在目前的临床实践中，组织病理学检查仍然是评估 ECM 的唯一金标准，但它是一种有创检查，存在操作过程中可能引起肿瘤细胞扩散、并发症等风险，并且其观察结果因抽取的样本和观察者不同存在差异。因此，开发一种无创、准确且高效的 ECM 评估方法具有临床实际意义。细胞外体积分数(Extracellular volume fraction, ECV)是血管外细胞外体积分数和血管内空间分数之和，代表总的间质空间。ECV 可以将 ECM 进行量化，并且以前的研究表明在不同的肿瘤中 ECV 均有所增加[6] [7] [8]。基于影像学检查计算的 ECV 分数评价 ECM 与组织病理诊断的 ECM 结果具有较高的一致性[9] [10]。本文阐述并总结了对基于影像学检查的 ECV 分数在肿瘤相关领域中的应用进展。

2. ECV 测量方式

临床上影像学检查使用的常规造影剂是一种细胞外示踪剂，它经静脉注射后能在细胞外组织间隙(包括血管内、血管及细胞之间的间隙)随意流动直到细胞内外达到平衡状态(即平衡时相)。在肿瘤区域以及同层面的主动脉区域放置感兴趣区(Region of interests, ROIs)，其中，在主动脉区域选择 ROI 时避开血管壁，在肿瘤区选择 ROI 时避开肿瘤内部坏死区和出血区，并收集扫描前后 1 周内的血细胞比容(Hematocrit, HCT)，就可以根据以下公式计算出 ECV：ECV (%) = (1 − HCT) × ($\Delta HU_{肿瘤}/\Delta HU_{动脉}$) × 100%，其中 ΔHU

$_{肿瘤}$和ΔHU $_{动脉}$分别是处于平衡时相的肿瘤ROI和同层面主动脉ROI的CT值减去平扫期CT值的差值[11]。

目前，用于可靠估计ECV的最小扫描平衡时相还没有很好地标准化，有研究者认为在对比剂注射后3分钟进行扫描可较好地显示病变及测量ECV，且易于临床推广，但是也有研究者选择在对比剂注射后4分钟，10分钟甚至更久的时间进行平衡时相的扫描来计算ECV分数[12] [13] [14]。

3. ECV与肿瘤预测因子相关的应用

Nishimuta等人[12]的研究结果表明，基于平衡时相的增强CT扫描计算出的ECV可能是一种替代胃癌的肿瘤侵袭方式(pattern of tumor infiltration, INF)的体内生物标志物，这种基于图像的生物标志物具有对整个肿瘤进行非侵入性评估的优势，并且与内窥镜活检标本相比具有极好的重复性，可为临床优化治疗方案提供参考。肝硬化是慢性肝脏疾病纤维化的终末期，也是肝细胞癌(hepatocellular carcinoma, HCC)的重要危险因素，Bak等[15]发现通过平衡时相扫描获得的双能CT (Derived from dual-energy CT, DECT)碘图的fECV评分独立地与基线时肝脏失代偿的存在相关，并且是肝硬化患者随后LRE (Liver-related evente，LRE，即肝功能失代偿事件和HCC)的独立预测因素，它能够较为准确地预测个体的LRE的风险，以便协助临床实施最具临床相关性和成本效益的策略。

4. ECV在预测肿瘤组织病理分级、分化方面的应用

平衡时相的动态增强CT扫描或磁共振(MRI)成像测定的ECV与病理纤维化体积相关，肝细胞癌多数是在伴有肝脏纤维化大的慢性疾病上发展而来的，崔凤娇等人通过CT平扫及平衡时相(注射对比剂140 s后)的图像计算出细胞外体积分数(extracellular volume fraction, fECV)来评估肝细胞癌分化程度，其结果显示高分化HCC的ECV显著高于低分化HCC，高分化组与低分化组诊断界值为28.56%，灵敏度为71%，特异度为90%，的AUC为0.869 (95% CI: 0.759~0.979)。肾透明细胞癌是肾细胞癌中最常见的类型，它的分期和分级是预测肿瘤特异性生存的重要预后因素，Adams等人[16]基于MR-based T1 mapping对ECV进行非侵入性量化，其结果显示低级别肿瘤(ISUP 1级，414.8 ms ± 151.2 ms；ISUP 2级，668.5 ms ± 127.0 ms)相比，高级别鳞癌(ISUP 3级，829.5 ms ± 42.0 ms；ISUP 4级，966 ms ± 34.6 ms)的T1弥散值明显增高，并且通过Spearman相关分析得出MR来源的ECV与组织学ECV之间有很强的相关性($p < 0.01$，r = 0.88)，T1弥散值也与组织学ECV密切相关(r = 0.81)，证实了T1 mapping可以非侵入性的区分高级别和低级别肾细胞癌。DECT能够对表现出不同能量依赖性X射线吸收行为的物质进行材料表征应用，由它生成的碘浓度(Iodine concentration, IC)图可以提供血管生成的信息，被证明在评估不同器官的病变方面是有用的[17]，Takumi等人[18]利用平衡时相的双能CT计算ECV和IC，来评估诊断胸腺上皮肿瘤WHO亚型分类的可能性，结果显示高危胸腺上皮肿瘤(high-risk thymic epithelial tumor, HRTET)的ECV分数显著高于低危胸腺上皮肿瘤(low-risk thymic epithelial tumor, LRTET组(32.8% vs. 24.5%, $p = 0.021$)。

5. ECV在预测肿瘤复发、转移等方面的应用

颈部淋巴结(Cervical lymph node, LN)转移在乳头状甲状腺癌(Papillary thyroid cancer, PTC)的危险分层中起着关键作用，这与个别治疗方案的确定有关，肿瘤细胞的扩散可能破坏其内部结构，从而导致PTC转移淋巴结中ECV分数的变化[19] [20] [21] [22]，Zhou等人招募了54名患者，收集了157个颈部淋巴结样本(81个非转移淋巴结和76个转移淋巴结)，用于评估DECT来源的ECV分数诊断乳头状甲状腺癌淋巴结转移的性能，并将其与传统单能量CT (Conventional single-energy CT, SECT)来源的ECV分数进行了比较，结果显示PTC患者颈部转移淋巴结组的ECV_D和ECV_S均显著高于非颈部转移淋巴结组，并且即使是在动脉期的CT图像上存在伪影干扰的情况下，ECV_D仍然表现出优于ECV_S的可比性。

6. ECV 在肿瘤疗效评估方面的应用

动态增强 MRI 成像定量的胰腺恶性实体病变的血管外细胞外体积分数与纤维硬化间质显著相关，而后者导致化疗药物抗药性并促进恶性生长和转移[23] [24]，Fukukura 等[11]报道称通过平衡期的增强 CT 扫描测定的肿瘤 ECV 是预测胰腺导管腺癌患者化疗后生存期的有用的影像生物标志物。Luo 等人[25]通过测定平衡时相的 CT 增强扫描的 ECV，用于预测局部晚期直肠癌新辅助放化疗(neoadjuvant chemoradiotherapy, NCRT)的病理完全缓解(pathological complete response, pCR)，结果显示 NCRT 之前的 ECV 分数(ECV fraction before NCRT, ECV_{pre})不能用于预测 NCRT 的有效性，而 NCRT 之后的 ECV 分数(ECV after NCRT, ECV_{post})和 ECVΔ 都能有效的区分出接受 NCRT 的 pCR 和非 pCR 患者，其中 ECV_{post} 结合 ECV_{Δ} 表现最好，AUC 为 0.92。

7. 小结与展望

基于影像学检查获得的 ECV 分数是一种非侵入性的定量分析 ECM 的策略，具有比拟组织病理学 ECV 的准确性，还具有可重复性、易于获取等优势，不仅在肿瘤诊疗相关领域广泛应用，还常用于肝脏、胰腺及心脏等器官纤维化的评估[26] [27] [28]。目前，基于影像学检查的 ECV 相关研究才处于起步阶段，其准确性受限于平衡时相的扫描时间、ROI 勾画层面校准、 红细胞压积等[9] [29] [30]各种因素，并且目前大多数研究是在较小的、单一的数据集中进行评估，其可行性受限。在未来，随着成像及计算机技术的不断发展，联合多中心的研究开展，我们相信上述问题均会得到解决，并且我们也期待未来的研究为 ECV 的应用开拓新的领域。

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