Advances in Clinical Medicine 临床医学进展, 2025, 15(8), 942-949
Published Online August 2025 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2025.1582319

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非小细胞肺癌免疫微环境的CT与PET/CT组学研究进展

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收稿日期：2025年7月12日；录用日期：2025年8月5日；发布日期：2025年8月14日

摘 要

免疫疗法已在非小细胞肺癌(NSCLC)治疗中发挥重要作用。肿瘤免疫微环境特征强烈影响NSCLC免疫治疗的潜在反应，准确评估NSCLC免疫微环境状态对制定免疫治疗策略和评估患者预后具有重要意义。CT影像组学利用定量分析纹理特征反映肿瘤异质性，已被应用于评估免疫微环境的研究。本文就影像组学在NSCLC免疫微环境研究中的应用现状进行综述，并对其应用前景进行展望。

关键词

非小细胞肺癌，免疫微环境，影像组学，肿瘤浸润淋巴细胞

Research Progress in CT and PET/CT Radiomics of the Tumor Immune Microenvironment in Non-Small Cell Lung Cancer

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Received: Jul. 12th, 2025; accepted: Aug. 5th, 2025; published: Aug. 14th, 2025

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文章引用: 黄晓舟, 钱丹飞, 杨建峰. 非小细胞肺癌免疫微环境的 CT 与 PET/CT 组学研究进展[J]. 临床医学进展, 2025, 15(8): 942-949. DOI: 10.12677/acm.2025.1582319

Abstract

Immunotherapy has played a pivotal role in the treatment of non-small cell lung cancer (NSCLC). The characteristics of the tumor immune microenvironment (TIME) significantly influence potential responses to immunotherapy in NSCLC, making accurate assessment of TIME status crucial for developing treatment strategies and evaluating patient prognosis. CT radiomics, through quantitative analysis of texture features that reflect tumor heterogeneity, has been increasingly applied in TIME evaluation research. This review summarizes current applications of radiomics in NSCLC TIME studies and discusses future perspectives.

Keywords

Non-Small Cell Lung Cancer, Tumor Immune Microenvironment, Radiomics, Tumor-Infiltrating Lymphocytes

1. 介绍

非小细胞肺癌(NSCLC)是最常见的肺癌类型，5 年生存率仅为 15% [1]。随着 NSCLC 免疫治疗的临床应用，肿瘤微环境(TME)研究越来越受到重视。肿瘤微环境(Tumor microenvironment, TME)包括网状纤维母细胞、血管内皮细胞、淋巴管上皮细胞、细胞外基质等间质细胞建立的微环境结构和不同亚型的 T、B 淋巴细胞、树突状细胞等免疫细胞浸润的免疫微环境[2]，在肿瘤发生、生长、侵袭、转移和治疗反应方面发挥重要影响[3] [4]。研究表明肿瘤免疫微环境(TIME)表型(例如被 $CD8^+$ T 细胞浸润的肿瘤)与免疫治疗的疗效和生存率呈正相关[5]-[8]。评估 TIME 各种成分的相互作用和免疫逃逸机制是进一步改善当前免疫疗法或开发新治疗方法的关键[9]。通过活检或手术取得病理标本是检测确定 TIME 表型的金标准，但存在肿瘤细胞播撒、术中出血、采样误差，可重复性差无法动态评估等缺陷[10]-[14]。

影像组学从 CT、MR、超声等图像中提取、整合特征，诊断并预测肿瘤组织学亚型、基因突变状态、基因表达水平以及临床预后[15]。CT 通过定量形态学及纹理特征揭示肿瘤异质性，间接反映微环境物理特性(如坏死、纤维化)及免疫浸润状态，但其功能信息局限，无法直接捕捉肿瘤的代谢活性或免疫细胞的动态分布。PET/CT 结合了 CT 的解剖信息和 PET 的功能代谢信息，尤其通过 18F-FDG 代谢参数(如 SUVmax、MTV)直接评估肿瘤葡萄糖代谢活性。研究表明，高 SUVmax 可能与“热”肿瘤(即高免疫细胞浸润)相关，而低 SUVmax 可能提示“冷”肿瘤(免疫排斥表型)。此外，PET/CT 可通过动态扫描评估肿瘤代谢的动态变化，为免疫治疗响应提供早期预测。但也存在辐射高、成本昂贵及免疫亚群特异性不足的缺点。CT 的纹理特征(如 GLNU)可量化肿瘤的结构异质性，而 PET 的代谢参数可反映肿瘤的生物学活性。两者结合可更全面地描绘肿瘤的“冷”“热”表型。PET/CT 的动态扫描可捕捉治疗前后代谢变化，而 CT 的稳定性特征可提供基线结构信息，两者结合有助于区分治疗引起的免疫激活与假性进展。

目前，对 NSCLC 的组学特征与 TIME 之间的相关性已得到证实。基于机器学习等放射组学模型已经得到广泛应用，影像组学评估 TIME 在临床实践中发挥重要的作用。本文就 CT 组学在 NSCLC 的 TIME 应用现状进行综述，并探讨其应用前景。

2. 程序性死亡 1/程序性死亡配体 1

在肿瘤免疫过程中，程序性死亡 1 (PD-1)/程序性死亡配体 1 (PD-L1)通路调节肿瘤浸润淋巴细胞(TIL)的活化。由于 T 细胞表面的 PD-1 受体与其配体(PD-L1)结合阻断 T 细胞活化及随后的免疫应答，使肿瘤细胞逃避免疫系统的攻击，导致预后较差[16]-[18]。因此，通过抗 PD-1 或抗 PD-L1 药物抑制 PD-1 和 PD-L1 结合恢复 T 细胞的免疫功能，从而提供良好的抗肿瘤效果[19] [20]。近年来的研究结果表明，抗 PD-1/PD-L1 单克隆抗体形式的免疫检查点抑制剂(ICI)已成为治疗 NSCLC 的基石，且在晚期转移性 NSCLC 患者的治疗中也显示出前景[21]-[23]。

PD-L1 的表达与 NSCLC 患者的预后相关，研究表明 PD-L1 表达阴性(肿瘤比例评分(TPS) < 1%)的患者不适合抗 PD-L1 抗体治疗，而 PD-L1 表达阳性(TPS ≥ 1%)的患者则可以从抗 PD-L1 抗体中获益[24] [25]。影像组学特征(如纹理特征、灰度共生矩阵特征)能够反映肿瘤内部的异质性，这种异质性可能与肿瘤微环境的病理生理学特征密切相关。例如，高熵值(Entropy)可能提示肿瘤内部坏死或纤维化区域的增加，而低对比度(Contrast)可能反映细胞密集区域的均质性[26] [27]。这些微环境特征可能通过影响免疫细胞的分布和功能，进一步调控 PD-L1 的表达。研究表明，肿瘤内部的坏死区域可能通过释放损伤相关分子模式(DAMPs)激活免疫应答，而纤维化区域则可能通过物理屏障限制 T 细胞浸润[28]。目前，NSCLC 患者 PD-L1 的放射组学研究主要集中于评估 PD-L1 表达和抗 PD-1/PD-L1 治疗反应的预测[29]-[38]。Weng 等研究者基于 CT 影像组学、临床病理学以及 CT 形态学特征参数建立放射组学模型，预测 120 例晚期 NSCLC 患者的 PD-L1 表达水平和肿瘤突变负荷(TMB)状态的受试者工作特征曲线下面积(AUC)分别为 0.839 和 0.818 [29]。Mu 等学者分析两家机构 210 例接受免疫检查点抑制剂(ICI)治疗的 NSCLC 患者 PET/CT 图像的放射组学特征和临床数据建立放射组学模型预测 NSCLC 患者患恶液质 AUC ≥ 0.74 [30]。此外，Li 等从 PET/CT 图像中提取影像组学特征和深度学习特征建立基于所选特征的融合模型，预测 136 例 NSCLC 患者的 PD-L1 表达，在训练和验证队列中 AUC 分别为 0.954 和 0.910 [31]。上述研究表明，影像组学预测模型可以个性化预测 NSCLC 患者 PD-L1 表达，筛选抗 PD-L1 免疫治疗获益的患者。

3. 肿瘤浸润淋巴细胞

肿瘤浸润淋巴细胞(TIL)，特别是 $CD8^+$ TIL 及其免疫调节细胞因子代表适应性免疫，在 NSCLC 免疫微环境中执行关键效应细胞毒性功能并介导 ICI 应答[39]。既往研究表明，通过显示 $CD8^+$ TIL 是否高浸润可评估抗肿瘤反应，并与 ICI 的临床应答相关，可作为判断患者预后的生物标志物[40]。由于 NSCLC 是一种高度时空异质性的疾病，且存在病理学采样偏差，在标本中评估的 TIL 可能无法代表整个肿瘤中的 TIL 水平[41]。

影像组学特征对肿瘤浸润淋巴细胞(TIL)的预测效能可能与其对肿瘤微环境物理特征的量化能力有关。例如，CT 图像中的高灰度值不均匀性(Gray-Level Non-Uniformity, GLNU)可能反映肿瘤内部的血管密度差异，而血管密度是影响 T 细胞浸润的关键因素之一[42]。此外，肿瘤内部的低密度区域(如囊变或坏死)可能通过减少 T 细胞的趋化和存活，降低 $CD8^+$ T 细胞的浸润水平[43]。目前，影像组学研究主要集中于 $CD8^+$ T 细胞并取得较满意的结果[38] [44]-[48]。Tong 等[44]分析 221 例 NSCLC 患者的 18F-FDG PET/CT 图像，并建立影像组学标记和临床特征联合预测模型，结果显示该模型在训练组和验证组中的 AUC 分别为 0.93 和 0.92，有效预测 NSCLC 患者 CD8 的表达。Chen 等[45]从 117 例 NSCLC 患者的 CT 图像中提取强 $CD8^+$ TIL 丰度的影像组学特征构建影像组学评分，研究证明基于 CT 的影像组学特征对 NSCLC 患者原发肿瘤病灶的 $CD8^+$ TIL 具有良好的预测效能，有望成为免疫治疗患者潜在生物标志物。此外，Mazzaschi 等[46] [47]建立基于 TIME 图谱的影像组学模型预测 NSCLC 患者的预后，并为晚期 NSCLC 病例提供可利用的预测策略。

近年的研究表明高 CD3 T 细胞计数是对 PD-1 阻断反应的独立预测因子[49]。总体 CD3 T 细胞计数较高与无进展生存期长具有相关性[50]。CD3 T 细胞具有抗肿瘤活性，对总生存期和复发率具有极大的预后意义，并且是重要的预后预测指标[51]-[53]。Chen 等[54]研究者基于 CT 组学特征和患者的临床病理信息建立放射组学模型，预测 105 例 NSCLC 患者的 CD3 T 细胞的表达的 AUC 为 0.94，在验证集中 AUC 为 0.73。

目前，对 NSCLC 中肿瘤浸润淋巴细胞的放射组学研究正持续推进，且大多数模型已取得良好的预测性能。研究主要包括两个方面：术前放射组学无创性预测 TIL 表达和放射组学特征结合 TIL 预测预后。总体上，NSCLC 肿瘤浸润淋巴细胞的放射组学研究已经启动，但是大多数研究集中在 $CD8^+$ T 细胞，需要对其他类型的 TIL 进行更多的研究。另外，TIL 研究以单中心以探索性、概念验证的方式进行，需要整合来自多个中心的数据提高这些预测模型临床可行性应用。

4. 影像组学在其他免疫微环境成分研究中的应用

影像组学还用于对自然杀伤(NK)细胞、接受放射治疗后的中性粒细胞与淋巴细胞比率(NLR)的预测进行建模。研究表明，抑制 IL6 可增强奥斯替尼耐药 EGFR 突变型 NSCLC 细胞中 NK 细胞介导的细胞毒性[55]。另一项研究表明，NSCLC 中 SERPINB 4 的上调抑制 NK 细胞介导的细胞毒性，是调节 NSCLC 的免疫应答的潜在治疗途径[56]。这些发现强调 NK 细胞在 NSCLC 中协调抗肿瘤反应的关键作用，并凸显以 NK 细胞为中心的治疗策略的新途径。Meng 等人开发了一种基于增强 CT 图像的放射组学模型，能够准确预测 NK 细胞在 NSCLC 中的浸润情况，具有良好的稳定性和诊断效能[57]。Hou 等人开发了一种基于三维(3D)剂量分布图、CT 图像以及临床特征的剂量组学&影像组学&临床融合模型，预测了 242 例局部晚期非小细胞肺癌(LA-NSCLC)患者放疗后 NLR，其 AUC 为 0.765。该模型可为放射治疗相关炎症反应的评价提供参考，对指导治疗方案的优化具有一定的应用价值[58]。

以上研究表明，影像组学在评估 NK 细胞、NLR 表达方面具有良好预测结果。证明影像组学具有评价其他 TIME 组分的潜力。在未来的研究中，同样需要扩大研究范围和样本量，以获得更准确和全面的 TIME 预测模型。

5. 问题和挑战

影像组学为 NSCLC 患者 TIME 的非侵入性评估提供了新思路，有助于治疗决策和预后判断，但其临床应用仍面临诸多挑战。

首先，影像组学模型建立需要预先在图像上手动分割病灶，复杂、耗时且主观，可靠性及可重复性难以保证，限制了其在临床上的推广。未来通过对尝试自动分割的研究可能会提高临床适用性，提高分割速度和准确性[59]。

再者，再现性仍然是现有影像组学模型的主要障碍[60]。对给定扫描仪内的稳定体模对象进行的重新测试研究估计，仅约 30%的 MRI 特征具有再现性，而多扫描仪体模研究显示特征再现性范围为 15%~85% [61]。多数影像组学特征缺乏明确的生物学解释，或仅反映技术差异及混杂因素。因此，有必要建立一致的方案，以避免数据采集的差异性。使用强度标准化，对感兴趣区进行异常值剔除，并采用固定的 bin 大小的灰度离散化，可以提高特征的可重复性[62]。

许多影像组学模型可能仅仅是基于训练数据集大小和可用特征数量之间的差异而过拟合其训练数据。因此，模型未能很好地推广到其他数据集。目前，基于影像组学对 NSCLC 的 TIME 评价多为单中心、小样本研究，结果尚未得到外部验证，这可能会对模型适应，优化和评估的过程产生负面影响[63]。因此，未来需开展多中心、标准化的大规模前瞻性研究，以系统性评估影像组学在 NSCLC 肿瘤微环境分析中的

实际效能。

尽管影像组学在预测免疫微环境状态方面显示出潜力，但其生物学解释仍需进一步明确。例如，某些纹理特征可能同时反映多种病理生理学过程(如坏死、纤维化或血管增生)，导致模型的可解释性降低。未来的研究应结合多组学数据，以明确影像组学特征与特定微环境特征(如免疫细胞空间分布或细胞外基质组成)的关联，从而提升模型的生物学合理性和临床适用性。

6. 结论

总之，精确成像已成为医学影像学的常态，影像组学的发展为非小细胞肺癌 TIME 的无创评价提供新的思路，同时也开创个性化 TIME 评价的新领域。目前，研究表明影像组学具有评估(上述的 PD-1/PD-L1，$CD8^+$ ，CD3 TIL，NK 细胞、NLR) TIME 的潜力，并且可以预期未来研究的突破。通过建立大型数据库和开展多中心合作，可以进一步推动影像组学的研究，更好地分析 TIME，并最终成为临床认可的无创评估方法。近年来，随着人工智能技术的快速发展，尤其是机器学习和深度学习领域的突破性进展，肺部疾病的影像诊断技术取得了显著进步。未来研究应整合影像组学与遗传学、分子生物学及病理学等多学科数据，以提升对恶性肿瘤预后评估的准确性。这种多学科融合的方法将为临床治疗方案的选择和优化提供科学依据，最终推动个体化精准医疗的实现。

基金项目

浙江省医药卫生科技计划一般项目(2023KY1236)；绍兴市科技计划基础公益类项目(2022A14010)。

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