专家述评

肝内胆管细胞癌的影像学研究新进展

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【摘　要】肝内胆管细胞癌（intrahepatic cholangiocarcinoma，ICC）是原发于肝内的第二大常见恶性肿瘤。根治性手术切除仍是ICC的主要治疗手段，但术后复发率高。靶向治疗已成为不可切除ICC的主要替代治疗方案，但其疗效仍待进一步证实。肿瘤组织病理及微环境与ICC预后密切相关。基于典型组织结构改变的表征影像特征是ICC诊断、治疗后疗效评估、预后判定的基础，对ICC患者临床精准化管理具有重要价值。本文就肝内胆管细胞癌的组织病理、肿瘤微环境、无创影像学诊断、生物学行为、疗效预测和预后评估等新进展深入评述基于微观结构病理改变的宏观影像学基础，提高ICC的影像学认识，助力ICC的早诊精治。

【关键词】肝内胆管细胞癌，影像诊断，预后评估
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Recent advances in radiological imaging studies of intrahepatic cholangiocarcinoma

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【**Abstract**】Intrahepatic cholangiocarcinoma (ICC) is the second most common malignant tumor originating in the liver. Radical surgical resection remains the main treatment for ICC, but the postoperative recurrence rate is high. Targeted therapy has become the main alternative treatment for unresectable ICC, but its efficacy needs further confirmation. Tumor histopathology and microenvironment are closely related to the prognosis of ICC. Imaging features based on typical tissue structure changes are the imaging basis for ICC diagnosis, post-treatment efficacy evaluation, and prognostic prediction, and are of great value for precise clinical management of ICC patients. This article intends to focus on the histopathology, tumor microenvironment, non-invasive imaging diagnosis, biological behavior, curative effect prediction and prognosis evaluation of intrahepatic cholangiocarcinoma, in-depth explanation of the macro imaging basis based on microstructural pathological changes, improve the imaging understanding of ICC, and help early diagnosis and intensive treatment of ICC.

【**Key words**】Intrahepatic cholangiocarcinoma; Imaging diagnosis; Prognostic evaluation



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肝内胆管细胞癌（intrahepatic cholangiocarcinoma，ICC）是原发于肝内的第二大常见恶性肿瘤，约占所有原发肝脏恶性肿瘤的10%～15%。由于其常缺乏特异临床症状，大多数ICC患者就诊时处于疾病进展期或已发生转移[1]。目前，根治性手术切除仍是ICC的主要治疗手段，但术后复发率高，术后5年生存率仅为14%～40%[2-3]。近年来，靶向治疗已成为不可切除ICC主要替代治疗方案，但其疗效仍待进一步证实[4]。

肿瘤微环境（tumor microenvironment，TME）中肿瘤相关成纤维细胞增殖驱动相关特异性反应所致“促纤维增生间质（desmoplastic stroma）”，是肝内胆管细胞癌肿瘤微环境中的典型组织学结构[5-7]。TME中多种细胞可同时影响肿瘤的增殖与侵袭，导致不良的预后结局[5,8-9]。结构即影像，基于典型组织结构改变的表征影

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像特征是ICC诊断、治疗后疗效评估、预后判定的影像基础，对ICC患者临床精准化管理具有重要价值。

本文拟围绕肝内胆管细胞癌的组织病理、肿瘤微环境、无创影像诊断、生物学行为、疗效预测和预后评估等深入评述基于微观结构病理改变的宏观影像基础，提高ICC的影像学认识，助力ICC的早诊精治。

1 ICC的组织病理及肿瘤微环境

组织病理学上，ICC是一种起源于胆管的乏血供腺癌[10]。根据宏观生长模式，ICC可分为肿块型、管周浸润型和管内生长型[11]。同时，根据受累导管类型，可进一步分为小胆管型和大胆管型[12-13]。不同组织学亚型的癌前病变类型、起源细胞和分子改变不同。小胆管型多发生在慢性肝病背景上[14]，胆管内乳头状肿瘤是其典型的癌前病变；大胆管型常以慢性炎症为基础，癌前病变多为胆道上皮内肿瘤[15-16]。尽管ICC细胞起源仍存在争议[17]，但目前研究认为小胆管型主要源于肝干/祖细胞和成熟肝细胞[18]，而大胆管型主要源于胆道干/祖细胞[19]。在分子水平上，小胆管型多表现为异柠檬酸脱氢酶（IDH1,IDH2）突变或成纤维细胞生长因子受体2融合[20-21]，而大胆管型肝内胆管细胞癌多以KRAS或TP53（10%～40%）突变为主[22]。

TME主要由细胞外基质（extracellular matrix，ECM）、肿瘤相关的成纤维细胞（cancer-associated fibroblasts，CAFs）和肿瘤相关的巨噬细胞（tumor-associated macrophage，TAMs）组成，通过肿瘤细胞与肿瘤微环境中不同成分之间交互作用而影响肿瘤的发生发展。首先，慢性肝损伤所致成纤维细胞活化、炎症细胞侵袭和肿瘤细胞过度表达基质细胞蛋白（如骨膜蛋白、腱糖蛋白-C和骨桥蛋白），以及过度分泌蛋白水解酶，导致肿瘤体积增大、淋巴结转移、肿瘤细胞增殖和侵袭[23-24]。此外，骨膜蛋白（periostin）、腱糖蛋白-C和骨桥蛋白的合成以及基质金属蛋白酶的分泌也导致了细胞外基质的重构[25-26]。肿瘤细胞分泌的炎性细胞因子，如转化生长因子-β（TGF-β）和血小板衍生生长因子-D（PDGF-D），会触发肿瘤相关的成纤维细胞招募和积聚[5]，而肿瘤相关的成纤维细胞释放许多旁分泌介质，包括肝素结合表皮生长因子（HB-EGF）[27]、基质细胞衍生因子-1（SDF-1）[28]、血管内皮生长因子（VEGF）-A/C[29]和血小板衍生生长因子B（PDGF-B）[30]，可导致肿瘤细胞增殖、微血管浸润及不良预后结局。同时，较高水平的肿瘤相关成纤维细胞可能表达较多的α-平滑肌肌动蛋白（α-SMA），这有助于促结缔组织间质的存在和积累。最后，肿瘤细胞分泌的细胞因子和趋化因子也将血液中单核细胞来源的肿瘤相关巨噬细胞（TAMs）招募到促结缔组织基质中[31-32]，进一步增强Wnt信号通路和缺氧诱导因子-1α（HIF-1α）的表达，促进肿瘤细胞增殖和与转移、侵袭和药物耐药性相关的基因突变[33-34]。

2 ICC的影像学诊断

早期发现和精准诊断是提高ICC临床治愈、改善预后的前提。ICC不同宏观生长模式的影像表现不一。管周浸润型ICC常表现为管壁增厚、近端导管扩张[35]；管内生长型表现为节段性或弥漫性胆管扩张[35-36]；肿块型常表现为肝内肿块或结节。影像学检查可清晰地显示肿块的大小、范围、周围组织侵犯、血管侵犯、淋巴结以及肝内、外转移[37]。典型ICC影像表现为动脉期周围环状高信号（APHE）、癌周廓清和延迟性中心强化[38-39]，与其大体组织病理学解剖结构相对应，即ICC周围包绕致密肿瘤细胞，中心区域以丰富的促纤维增生的间质为主。静脉注射造影剂后，富含肿瘤细胞的周边区域表现为周围环状强化及廓清，但由于造影剂渗透较慢，滞留时间较长，表现为中心纤维延迟强化[40]。同理，磁共振扩散张量成像（DWI）“靶征”、肝胆期“类靶征”均与其病理组织结构相关。目前，CT诊断ICC的敏感度为67.5%～91.9%，特异度为63.5%～90.6%，MR的敏感度为66%，特异度93%[41-42]。

3 ICC治疗后疗效的影像学评估

目前广泛应用的治疗反应评价标准包括实体瘤疗效评价标准（RECIST）、改进的RECIST标准、容积法RECIST（vRECIST）、欧洲肝脏研究协会（EASL）、定量EASL（qEASL）、Choi标准和实体瘤正电子发射断层扫描（PET）疗效评价标准（PERCIST 1.0）。RECIST、改良的RECIST和容积法RECIST分别将肿瘤大小、动脉期强化的最大的肿瘤直径、动脉期强化的最大的肿瘤体积的变化作为肿瘤反应评估的客观指标[43-45]。EASL和qEASL标准则指出，可通过动脉期增强肿瘤面积的减少和动脉期增强肿瘤体积或百分比的减少来评估肿瘤反应[46-47]。Choi标准建议评估病变的大小和密度变化[48]。PERCIST 1.0基于18F-FDG PET-CT或PET-MRI，将吸收18F-FDG的病变定义为存活肿瘤，将目标病变中SUVpeak的降低定义为目标病变的肿瘤反应，非目标病变的不进展加上目标病变的肿瘤反应是整体肿瘤反应[49]。与RECIST相比，改良的RECIST和EASL标准评估治疗后反应更为可靠[50-51]。同时，无论肿瘤大小如何，PERCIST 1.0与存活的肿瘤细胞数量有相关性[52]。然而，改进后的RECIST、EASL、Choi标准和PERCIST 1.0也有其自身的局限性，在应用二维测量方法时，如mRECIST和EASL标准，由于促纤维增生的间质增多和血管基质减少，导致不规则或边缘环状增强，可能导致观察者间和观察者内的一致性较低[53-54]。此外，由于ICC密度较低，绝对密度的微小下降可能导致

较高的相对变异，Choi标准的评估结果可靠性有所降低[55]。

与EASL或改进的RECIST标准相比，肿瘤坏死引起的ADC值变化评估肿瘤治疗后疗效更为可靠，且不受肿瘤强化程度影响[56]。无法手术切除的ICC患者在接受TACE治疗时，存活肿瘤体积的变化是其预后的潜在影像标志物[57]。然而，ICC可表现出多种强化模式，亦会导致肝动脉期和门静脉期的强化容积明显降低[58]。未来多参数融合的体积变化，如肿瘤体积、ADC值变化联合体积强化变化相结合有助于进一步提高治疗反应评估的准确性。此外，基于TACE治疗前增强CT的相关影像组学高维特征，包括较高的平均直方图值和较低的峰度值的ICC患者的预后结局明显优于无相关特征的患者[59]，其可能与致密的促纤维增生的间质和坏死区域所导致癌症进展和治疗耐药性相关[60-61]。

4 ICC预后的影像学评估

ICC肿瘤内促纤维增生的间质比例与影响预后的生物标志物（如HIF-1α和Ki-67）的表达，具有相关性。同时，与影响预后的危险因素如微血管侵袭[62]和淋巴结转移显著相关[60,63-65]。影像学检查可对ICC肿瘤内促纤维间质进行评估，与小胆管型ICC相比，大胆管型肝内胆管细胞癌促纤维增生的间质比例更高，预后更差[14,66]。促纤维增生间质的比例与强化程度明显相关，如伴有致密的促纤维增生间质的ICC在动脉期多表现为弥漫性低信号和环状强化，而非弥漫性高信号[47]；肝胆期高信号或等信号则表明肿瘤内伴有较高比例的促纤维增生的间质[63]。然而，目前ADC值与促纤维增生间质的关系仍有争议，YAMADA等[66]发现ADC_{Low}组（不小于1/3弥散限制）促纤维增生间质的比例明显高于对照组，而LEE等[67]则得出了相反的结果。因此，仍需要大规模、前瞻性的多中心研究进一步评估ADC值与促纤维增生间质比例的关系。

此外，影像学征象也与一些影响预后的生物标志物相关。血管内皮生长因子的高表达会导致预后不良。基于增强CT[68]的定量放射组学特征可预测血管内皮生长因子的表达。PD-1和PD-L1位于T淋巴细胞、抗原提呈细胞和肿瘤细胞的膜表面，是免疫逃逸的重要生物标志物，与不良预后相关[69-70]。ZHANG等[71]发现基于MRI的动脉期放射组学特征对PD-1/PD-L1表达具有较高的预测精度。异柠檬酸脱氢酶（IDH）突变是人类癌症的代谢酶基因中心[72]，在肝内胆管细胞癌的癌变过程、治疗选择和预后评估方面起着至关重要的作用。ZHU等人[73]证实门静脉期癌灶的CT值在区分有无IDH突变的肝内胆管细胞癌方面表现良好，而IDH突变的肝内胆管细胞癌CT值升高是否与VEGF水平升高有关，还有待进一步研究。

近年来，结合影像学征象和免疫组化标记物的综合预测模型已被开发用于预测肝内胆管细胞癌的预后。ZHAO等[74]研究了54例肝内胆管细胞癌患者的常规影像学征象（增强模式）、预后生物标志物血管内皮生长因子受体（VEGFR）和放射组学征象，并构建了一个诊断准确性较高的肝内胆管细胞癌早期复发预测模型。然而，单中心小样本的回顾性研究限制了该预测模型的泛化性。因此，进一步进行具有外部验证的大规模多中心前瞻性数据研究对预后评估是十分必要的。

5 小结与展望

ICC组织亚型和肿瘤微环境与肿瘤的诊断、预后评价和治疗反应评估密切相关。利用功能、定量影像学成像技术可对其多种微观病理环境进行精准量化和可视化分析，是ICC精准诊断、个性化治疗的前提。建立基于“影像-病理”的ICC诊断和评价体系，可从根本上提高ICC的早诊精治能力，助力ICC精准化、个性化临床路径的开展。

展望未来，要持续关注ICC发生发展过程中关键病理、分子及基因层面的改变，利用多种功能影像技术和数据后处理方法，实现ICC发展的全程可视化和定量化研究。要更重视研究反应肿瘤预后的微观标志物其宏观影像学基础，构架阐述微观病理与宏观影像的研究桥梁，借助最先进的分子生物学及表观遗传学技术，丰富ICC影像学理论的发展前沿。要更加积极地构建标准化的ICC影像数据库，运用智能影像技术深入挖掘肿瘤微观病理异质，同时构建更为稳定、高效、可靠的ICC影像分析平台，为基于病理的影像诊断效能、辅助临床治疗决策、改善患者生存预后及推动肿瘤个性化精准治疗提供有力支撑。

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