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·文献综述·

肝细胞癌肿瘤包膜与治疗决策及预后关系的研究进展

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摘　要　肝细胞癌（HCC）是全球癌症相关死亡的重要原因之一。近年来研究表明，肿瘤包膜作为HCC的经典病理特征，在疾病侵袭性评估、治疗策略制定及预后分层中具有重要临床价值。术前主要依赖影像学评估包膜状态，组织病理学仍为诊断金标准。根据完整性可分为完整、不完整及缺失三类。完整包膜可作为物理屏障限制肿瘤浸润，显著降低微血管侵犯风险，是术前预测侵袭性的重要影像学标志。在外科治疗中，包膜完整者在保证切缘阴性的前提下可考虑窄切缘策略以保留功能性肝实质，而包膜不完整或缺失者则需扩大切缘。在非手术治疗方面，包膜完整与经肝动脉化疗栓塞疗效、放疗局部控制及系统治疗预后密切相关，可能涉及肿瘤微环境、血流动力学及分子信号通路等机制。作为连接肿瘤生物学特征与治疗决策的重要桥梁，肿瘤包膜在HCC精准分层治疗中仍具有广阔的研究前景。

关键词　癌，肝细胞；肿瘤包膜；切缘；预后；综述
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Tumor capsule in hepatocellular carcinoma: implications for treatment decision-making and prognostic stratification

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Abstract　Hepatocellular carcinoma (HCC), a leading cause of cancer-related mortality worldwide, demonstrates marked heterogeneity in biological behavior and therapeutic response. Emerging evidence indicates that tumor capsule integrity, a classical histopathological feature, plays a pivotal role in risk stratification and treatment decision-making. Preoperative assessment primarily relies on imaging modalities, whereas histopathology remains the gold standard. According to structural integrity, the capsule can be categorized as complete, incomplete, or absent. An intact capsule functions as a physical barrier that limits tumor invasion and is closely associated with a lower incidence of microvascular invasion. In surgical management, narrow-margin resection may be considered in capsule-intact tumors when negative margins are secured, whereas wider margins are recommended for tumors with incomplete or

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absent capsules. Beyond surgery, capsule integrity has been correlated with therapeutic response to transarterial chemoembolization, radiotherapy, and systemic therapies, potentially through mechanisms involving tumor hemodynamics, microenvironmental modulation, and oncogenic signaling pathways as a bridge linking tumor biology with therapeutic strategies. Tumor capsule status warrants further investigation in the era of precision medicine.

Key words Carcinoma, Hepatocellular; Tumor Capsule; Margins of Excision; Prognosis; Review

CLC number: R735.7

肝细胞癌（hepatocellular carcinoma，HCC）是全球癌症相关死亡的主要病因之一。根据2022年全球癌症统计报告，HCC当年导致超过75万死亡，其中亚洲地区（尤其是中国）的疾病负担最为突出[1]。手术切除、经肝动脉化疗栓塞（transcatheter arterial chemoembolization，TACE）、分子靶向治疗和消融治疗等是HCC的主要治疗手段，研究显示HCC肿瘤包膜与HCC治疗的预后相关。作为HCC的重要组织学标志，肿瘤包膜通过双重路径影响治疗预后：在宏观层面，包膜完整性直接关系到手术切缘的确定以及局部治疗（如TACE和消融）的病灶控制效果；在微观层面，完整包膜可限制肿瘤细胞扩散，而包膜不完整或缺失则与微血管侵犯（microvascular invasion，MVI）及早期复发显著相关[2]。值得注意的是，近年来研究还发现肿瘤包膜特征可能影响靶向药物的治疗反应，这为个体化治疗提供了潜在依据。本文系统综述HCC肿瘤包膜的病理学意义、临床检测方法及其对HCC治疗效果影响的机制，旨在为优化治疗策略提供理论支撑，并展望未来研究方向。

1　HCC肿瘤包膜的由来

正常肝脏天生具有包膜，是由内层的Laennec包膜和外层腹膜组成的双层结构，包绕正常的肝脏组织。而HCC的肿瘤包膜是紧密环绕在肿瘤的周围纤维结构，由肿瘤与正常肝脏细胞相互作用形成。组织学上，肿瘤包膜由I/IV型胶原蛋白及α-平滑肌肌动蛋白（α-smooth muscle actin，α-SMA）阳性的肌成纤维样细胞构成，典型厚度为0.5~2.5 mm[3-4]。HCC包膜形成通常经历三个阶段，即无包膜期、包膜形成期和包膜突破期。研究表明肝硬化患者更容易产生包膜[5]，肿瘤包膜的形成过程与肝硬化结节中的纤维条索相似，二者具有相同的构成[3]，这从侧面提示肝硬化与HCC之间的联系。

影像学是术前诊断包膜的重要手段[6]，肝脏影像报告和数据系统（Liver Imaging Reporting and Data System，LI-RADS）[7]将CT/MRI门静脉期至延迟期的环形强化定义为典型包膜征象；也有学者指出钆塞酸二钠增强MRI肝胆期显示的低信号环状边缘可以用于诊断包膜和HCC[8]（图1为组织学证实伴肿瘤包膜的HCC患者MRI图像）。目前影像学评估主要将包膜分为完整、不完整及缺失三类，其环形强化的机制涉及包膜内新生血管及包埋肝实质的血供[9]。然而影像学所显示的肿瘤包膜并非都是真包膜。真包膜是指在组织学上是包绕在肿瘤周围的纤维结构，可以通过肉眼观察到，并通常由病理医生在镜下确认，而假包膜是组织学上未观察到有纤维结构，仅在影像学上具有包膜外观，其表现可能因为肿瘤生长对周围肝窦、纤维组织和肝实质的机械性压迫，在影像上形似包膜。肿瘤包膜的病理学检查始终是诊断的“金标准”。组织学显示，肿瘤包膜由排列紧密的I型胶原蛋白和α-SMA阳性的肌成纤维样细胞构成，这些细胞呈现特征性的梭形形态，可通过常规HE染色和免疫组化技术明确识别[3]。而假包膜则缺乏这些组织学特征。约15%的HCC切除后经病理检查证实为假包膜[5]。影像学上真假包膜难以区分[10-12]，尽管有研究尝试应用深度学习模型自动识别MRI图像中的包膜结构，但其检测效能仍需通过多中心研究验证[13]。对于术前影像检测到包膜的病例，建议结合术后病理检查验证包膜性质。

HCC的包膜作为物理屏障，可以有效阻止癌细胞向周围组织浸润，从而降低MVI及远处转移的风险[14]，突破包膜的HCC往往恶性程度大大增加，可能需要扩大切缘以保证生存。从病理分型角度观察，肿瘤包膜的完整性呈现显著异质性。

根据世界卫生组织大体分型标准，弥漫型HCC多表现为包膜缺失，而巨块型及结节型HCC更易形成完整包膜[15]。临床研究进一步发现，直径≥10 cm的肿瘤出现包膜缺损的概率显著升高[16]，提示包膜状态可作为评估肿瘤侵袭性的生物学指标[17]。

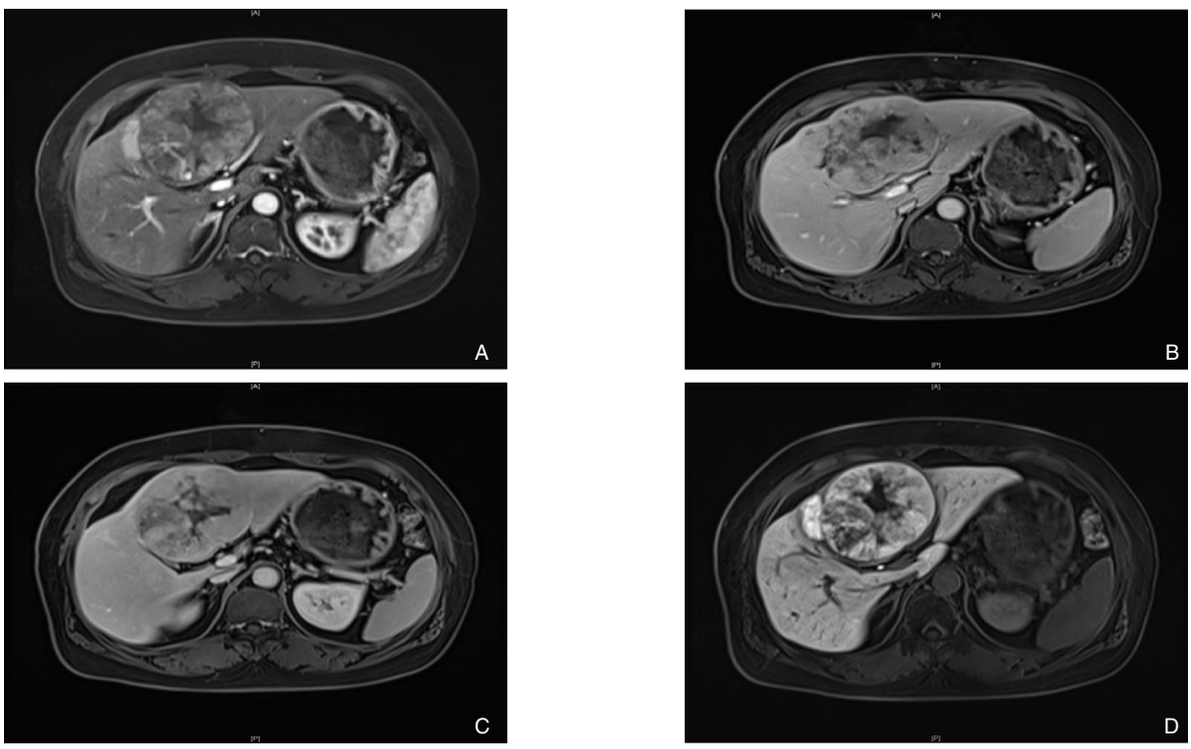

图1 伴有组织学纤维包膜的HCC患者影像特征 A：动脉期MRI图像显示高血管性占位性病变；B–C：门脉期和延迟期MRI图像显示肿瘤周围有高信号边缘；D：肝胆期MRI图像显示肿瘤周围低信号边缘

Figure 1 Imaging features of HCC with a histologically confirmed fibrous capsule A: Arterial-phase MRI image showing a hypervascular mass lesion; B–C: Portal venous-phase and delayed-phase MRI images demonstrating a hyperintense rim surrounding the tumor; D: Hepatobiliary-phase MRI image showing a hypointense rim around the tumor

2 HCC肿瘤包膜与手术切缘及预后的关系

在精准医疗时代，外科手术在HCC治疗中仍占主导地位[18]。包膜完整的患者手术是否需要宽切缘，目前仍有待研究，多项研究显示使用较窄的切缘并不会影响其预后。

完整的肿瘤包膜作为天然解剖屏障可有效降低切缘阳性风险：有研究[19]显示，包膜完整组术中镜下切缘阳性率显著低于不完整组（8% *vs.* 15%，*P*=0.012），在保证切缘阴性的情况下，窄切缘（沿包膜切除）与宽切缘（≥1 cm）的5年总生存（overall survival，OS）率无显著差异（66.1% *vs.* 75.9%，*P*=0.259），这为保留功能性肝实质手术方式提供了依据。

相反，包膜不完整或缺失病例需采取积极切缘策略，研究[20]显示，宽切缘（≥7 mm）可使5年OS率提升至82.3%（*vs.* 53.5%，*P*=0.029），无复发生存率达47.1%（*vs.* 33.8%，*P*=0.015），另有研究[21]显示在直径>3 cm肿瘤中，宽切缘（≥5 mm）较窄切缘（<5 mm）显著降低复发率（7.1% *vs.* 41.0%，*P*=0.046）并延长OS（*P*=0.018）。

此外，包膜完整性与MVI存在显著关联，完整的包膜可以预防MVI的发生，因而包膜完整性可作为术前预测MVI的重要指标。综合评估包膜特征有助于识别MVI高风险病例，进而指导术中选择解剖性肝切除或扩大切缘等保护性策略[2,22–25]。

包膜状态是影响HCC患者预后的重要因素[26]。包膜完整患者的无复发生存期[5年累计无进展生存（progression free survival，PFS）率：6.7% *vs.* 0%，*P*=0.025]及OS（中位OS：39个月 *vs.* 27个月，*P*=0.036）显著优于不完整组，在肿瘤体积大、位置不佳或紧邻重要血管的复杂性HCC中差异更为显

著（3 年 OS 率：38.89% *vs.* 4.76%，*P*<0.001）[16,27]。门静脉癌栓的晚期 HCC 患者进行手术治疗，肿瘤包膜仍然是影响其预后的因素[28]。

3　HCC 肿瘤包膜对其他治疗方式的影响

3.1　TACE

肿瘤包膜完整性显著影响 TACE 的治疗应答与远期预后。多项临床研究证实，包膜完整患者的客观缓解率（*OR*=3.168，95% *CI*=1.360~7.377，*P*=0.008）及 OS（*P*=0.001）均显著优于包膜不完整者，这一规律在传统 TACE（conventional transcatheter arterial chemoembolization，cTACE）和载药微球 TACE（drug-eluting beads transcatheter arterial chemoembolization，DEB-TACE）中具有普适性[29-31]。该现象的潜在机制可能与包膜在栓塞过程中的屏障作用密切相关。完整包膜可限制栓塞剂向周围组织扩散，从而提高肿瘤内压，促进血管湖现象（vascular lake phenomenon，VLP）的形成。VLP 不仅有助于增强局部药物浓度，还能延长药物在肿瘤内的滞留时间，从而提升抗肿瘤效应[31]。相反，包膜不完整或缺失被认为是 TACE 疗效不佳及早期复发的独立危险因素[32-33]。

不仅如此，包膜完整性也在 TACE 序贯治疗中具有动态预测价值。Zhang 等[34]报道了包括肿瘤包膜完整性、甲胎蛋白水平、肿瘤数量和受累肝叶的预测模型，预测多次 TACE 获益可能性。Chen 等[35]研究显示，前 3 次 TACE 均无应答的患者继续 TACE 治疗无明显获益，因此预测第 3 次 TACE 的疗效至关重要，其构建的预测模型中肿瘤包膜是重要的预测因素之一。

3.2　消融治疗

HCC 肿瘤包膜的影像学清晰边界可为消融范围规划提供解剖参考，可根据肿瘤包膜判断消融范围是否足够[36-37]。肿瘤包膜与消融治疗预后的关联性目前尚无定论。部分研究显示包膜状态与消融术后 OS 无显著关联[38]，部分研究认为不完整的包膜是早期复发的危险因素[37]，而另一些研究则发现包膜完整患者的 PFS（13.0 个月）相较于包膜不完整（17.0 个月）以及无包膜的患者（24.0 个月）反而缩短（*P*=0.012）[39]，这可能受研究人群的异质性（如肿瘤大小、解剖位置的差异）和样本量的影响，肿瘤包膜对 HCC 消融预后的影响仍有待于进一步研究[40]。

3.3　靶向与免疫治疗

多个预测模型显示肿瘤包膜完整性是影响 HCC 靶向与免疫治疗预后的重要指标。GRAPHS-CRAFITY 评分系统整合包膜完整性、肿瘤生长模式等参数，依据评分将接受免疫治疗的患者分为不同预后亚组，各组中位 OS 存在显著差异（中位 OS：低分组未达到；中分组 15.5 个月；高分组 4.7 个月，*P*<0.001）[41]。Sheng 等[42]开发的列线图模型通过结合包膜状态、影像异质性及血流动力学指标，可有效预测仑伐替尼联合 PD-1 抑制剂的治疗反应。

肿瘤包膜状态和靶向与免疫治疗应答关联的机制研究越来越多。研究表明，包膜不完整或无包膜的肝细胞癌中 BRAF、RAF1 基因表达显著上调[43]，这可能增强对索拉非尼（靶向 VEGFR/BRAF/MAPK 通路）及仑伐替尼（抑制 PDGFR/RET 信号）的治疗敏感性[44]。临床观察[45]发现，接受转化治疗后肿瘤包膜边界趋于清晰化，可考虑“沿包膜切除”策略以保留肝实质功能，但其预后价值仍需更多证据支持。

在肿瘤微环境层面，包膜完整性受多因素调控，巨噬细胞在肿瘤包膜破损区域的高度浸润可能促进肿瘤进展，而仑伐替尼通过减少肿瘤相关巨噬细胞数量，可能间接影响包膜稳定性[46-47]；$CD13^+$癌症干细胞沿肿瘤包膜分布，其耐药特性可通过 CD13 抑制剂联合化疗部分逆转，临床前研究已证实该策略的协同抗肿瘤效应[48-49]。同样值得关注巨噬细胞上的异常表达的 CD200R 以及癌细胞中的 lnc-ATG9B-4、CDK5 等分子，可能成为新型靶向治疗的突破口[50-51]。

3.4　放射治疗

放射治疗在肝细胞癌治疗中多作为晚期患者的补充选择，其应用受限于肝脏辐射耐受剂量与肿瘤根治性剂量之间的矛盾。近年来，立体定向放射治疗（stereotactic radiotherapy，SBRT）因精准剂量分布及局部控制优势受到关注[52]。临床观察显示，包膜完整的 HCC 对 SBRT 具有更优的放射敏感性：其客观缓解率显著提升，且 2 年局部控制率与 OS 表现更佳。其原因可能是完整包膜通过限制肿瘤细胞外溢，降低肝内照射野外复发风险[53]。此外，包膜在增强 CT 上的清晰边界可为 SBRT 靶区勾画提供解剖参考，有助于缩小计划靶体积，从

而减少周围正常肝组织受照剂量。

4 小结与展望

肿瘤包膜作为HCC的重要病理学特征，显著地影响了HCC患者的治疗与预后。包膜的存在与完整性可以指导手术决策，完整肿瘤包膜者即使采取更窄的切缘，术后生存表现仍然良好。同时，完整肿瘤包膜的HCC患者具有更好的TACE及靶向与免疫治疗效果，还可以作为消融治疗与SBRT范围的标志。作为经典病理特征，肿瘤包膜仍存在巨大的研究潜力，需要更多的高质量研究探索有关治疗策略。

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