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放免联合治疗驱动基因阴性NSCLC脑转移的研究进展

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摘　要

非小细胞肺癌(NSCLC)是脑转移发生率最高的实体瘤之一，在驱动基因阴性患者中，约28.8%在初诊时已存在脑转移，既往传统治疗后中位总生存期仅10~12个月。放疗作为局部控制的主要手段，整体疗效有限。免疫检查点抑制剂的出现为此类患者提供了新的系统治疗选择。研究发现，放疗通过多种途径，与免疫治疗协同增强抗肿瘤免疫。多项最新临床研究进一步证实，放疗联合免疫治疗能显著提高驱动基因阴性NSCLC脑转移患者的颅内控制率、延长生存期，且安全性总体可控。本文旨在综述该联合治疗方案在此类患者中的最新研究进展，以期为临床实践及未来治疗策略优化提供参考。

关键词

非小细胞肺癌，脑转移，免疫治疗，放射治疗，驱动基因阴性

Research Advances in Radiotherapy Combined with Immunotherapy for Driver Gene-Negative NSCLC with Brain Metastases

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Abstract

Non-Small Cell Lung Cancer (NSCLC) is one of the solid tumors with the highest incidence of brain

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metastases. Among patients with driver gene-negative NSCLC, approximately 28.8% present with brain metastases at initial diagnosis, and the median overall survival with traditional treatments has historically been only 10~12 months. Radiotherapy, as the primary local control modality, shows limited efficacy. The advent of immune checkpoint inhibitors has provided a novel systemic treatment option for these patients. Research indicates that radiotherapy can synergize with immunotherapy to enhance anti-tumor immunity through multiple mechanisms. Recent clinical studies further confirm that the combination of radiotherapy and immunotherapy significantly improves intracranial control rates and prolongs survival in patients with driver gene-negative NSCLC brain metastases, with an overall manageable safety profile. This review aims to summarize the latest research progress regarding this combination therapy for such patients, in order to provide references for clinical practice and the optimization of future treatment strategies.

Keywords

Non-Small Cell Lung Cancer, Brain Metastases, Immunotherapy, Radiotherapy, Driver Gene-Negative

1. 引言

肺癌是全球范围内发病率与死亡率最高的恶性肿瘤[1]，其中非小细胞肺癌(Non-Small Cell Lung Cancer, NSCLC)占约 85% [2]。脑转移是 NSCLC 常见且预后不良的转移事件，在晚期驱动基因阴性患者中，约 28.8%在初诊时即已发生[3]。随着全身治疗进步与影像技术发展，NSCLC 脑转移的临床诊断数量持续攀升，使其成为日益突出的临床挑战。然而，该人群传统治疗(如手术、放化疗等)后中位总生存期多仅为 10~12 个月，预后亟待改善[4] [5]。近年来，免疫检查点抑制剂(尤其是抗 PD-1/PD-L1 药物)在晚期 NSCLC 治疗中取得突破。另外，研究发现，放疗不仅能局部杀伤肿瘤，还可通过诱导免疫原性细胞死亡、改变肿瘤微环境、调节血脑屏障等多重机制，与免疫治疗产生协同作用，增强全身抗肿瘤免疫[6] [7]。放免联合在驱动基因阴性 NSCLC 脑转移患者治疗中展现巨大潜力，但其最佳联合模式、时机及安全性仍在探索中。本文旨在系统综述该领域的最新研究进展，以期为临床实践与治疗策略的优化提供依据。

2. 放免联合的分子机制

驱动基因阴性 NSCLC 脑转移的分子特征为放免联合治疗提供了多层次的生物学基础。首先在基因组层面，高肿瘤突变负荷与基因组不稳定性为免疫治疗提供新抗原基础[8]-[10]，但表观遗传重塑可介导耐药[11]，提示需联合干预。放疗可作为“原位疫苗”[12]，激活抗肿瘤免疫应答，协同克服耐药。继而，在肿瘤微环境层面，“相对免疫活化”的表型(如更高的细胞毒性 T 细胞浸润)为免疫治疗创造有利条件[13]。放疗则可重塑免疫抑制性微环境，上调抗原提呈和共刺激分子表达，促使“冷”肿瘤向“热”肿瘤转化[12]，增强抗肿瘤免疫。最后在代谢层面，脑转移瘤通过重编程以适应颅内特殊的营养与氧合微环境，这对放疗与免疫治疗均产生影响[14]。一方面，肿瘤细胞的代谢状态(如氧化还原平衡、DNA 损伤修复能力)直接决定放疗敏感性；另一方面，肿瘤微环境中的代谢物如乳酸可建立免疫抑制生态，削弱免疫细胞的杀伤功能[15]。因此，未来治疗策略有望在放免联合基础上，进一步整合代谢通路调节剂，以期同时增

敏放疗并逆转免疫抑制，克服代谢相关的联合治疗抵抗。

综上，驱动基因阴性NSCLC脑转移的分子特征不仅揭示了放疗联合免疫治疗的必要性，也为个体化治疗策略的制定提供了科学依据。从分子机制到临床实践的转化研究，将推动该联合模式不断完善，最终改善患者的生存与生活质量。

3. 放疗

随着免疫联合化疗成为驱动基因阴性NSCLC脑转移的一线标准治疗，脑部放疗的角色正从传统的姑息减症向追求长期病灶控制转变，其应用策略需基于病灶数量、症状负荷及患者全身状况进行个体化决策。对于无症状患者，通常优先全身治疗，并对后续残留病灶考虑立体定向放射外科(Stereotactic Radiosurgery, SRS)或全脑放疗(Whole Brain Radiotherapy, WBRT)；若有症状，则需积极联合局部放疗，其中SRS适用于直径 ≤4 cm、数目有限的病灶，而WBRT多用于挽救治疗、多发病灶或术后辅助，并可结合海马保护技术与美金刚以降低神经认知损伤风险。

脑部放疗热点已从比较不同放疗模式的优劣，转向以“颅内肿瘤总体积”等更具预测价值的指标作为决策依据[16]，旨在实现SRS与WBRT的精准抉择，平衡病灶控制与神经功能保护。研究表明，SRS的适应症已不再局限于病灶数目，即使对超过20个转移灶的NSCLC患者，其生存与局部控制亦可与单发转移者相当[17]。同时，SRS技术亦持续优化：在计划方面，海马回避技术被证实能在多发性脑转移SRS中提升适形度、降低脑组织受照剂量[18]；在实施方面，磁共振引导的分次SRS (如GASTO-1075研究)可实现更高精度照射[19]，而其与贝伐珠单抗联用(如GASTO-1053研究)有望在延长控制时间的同时保护认知功能[20]，为替代WBRT提供新思路。此外，全球前瞻性多中心研究表明SRS联合电场治疗可以显著延长NSCLC脑转移患者无进展生存期，而不会降低生活质量或认知功能[21]。总之，NSCLC脑转移的放疗已进入以精准技术为基础、兼顾长期疗效与神经认知功能保护的新阶段。未来，SRS相关结合剂量–反应关系前瞻性研究(如SAFER研究) [22]及多种治疗模式的整合，将进一步推动脑转移放疗的个体化发展。

4. 免疫治疗

中枢神经系统功能性淋巴引流的存在[23]，以及肿瘤脑转移导致血脑屏障破坏和特殊的颅内免疫微环境[24]，为免疫治疗应用于NSCLC脑转移奠定了理论基础。抗血管生成药物可抑制肿瘤血管生成，增强药物在病灶的递送，协同免疫治疗发挥抗肿瘤效应[25]。

前瞻性临床研究证实了免疫治疗在NSCLC脑转移中的疗效。帕博利珠单抗单药在PD-L1阳性患者中的颅内客观缓解率(intracranial Objective Response Rate, iORR)为29.7% [26]。KEYNOTE系列研究的汇总分析进一步表明，帕博利珠单抗联合化疗能改善伴稳定脑转移的NSCLC患者的预后[27]。全球首个针对NSCLC脑转移人群的免疫联合化疗前瞻性研究(CAP-BRAIN)显示，卡瑞利珠单抗联合化疗一线治疗非鳞状NSCLC伴无症状脑转移患者，iORR达57.5%，中位颅内无进展生存期(intracranial Progression-Free Survival, iPFS)为8.4个月[28]；长期随访中位总生存期达18.4个月[29]。另一项II期研究(Atezo-Brain)中，阿替利珠单抗联合化疗在同类人群中亦取得较好颅内疗效(iORR 42.7%，iPFS 6.9月) [30]。ASTRUM-002研究在预设脑转移分层分析中，显示斯鲁利单抗联合化疗较对照组显著延长中位PFS (8.1 vs 4.1) [31]。在此基础上的联合方案也在不断探索。然而双免联合短疗程化疗II期研究(NIVIPI-BRAIN)未达到预期的颅内疗效(iPFS 4.9月) [32]。而另一项前瞻性II期四药联合研究(SUPER BRAIN)，发现斯鲁利单抗 + 贝伐珠单抗 + 含铂双药化疗在驱动基因阴性非鳞状NSCLC伴脑转移患者中取得了13.1个月的iPFS [33]，提示联合抗血管治疗可能进一步改善疗效。

5. 放疗联合免疫治疗

放免联合治疗在驱动基因阴性 NSCLC 脑转移中展现出明确的临床转化前景。目前相关临床研究主要集中在有症状脑转移人群。回顾性证据提示，放疗与免疫治疗的时序安排可能影响疗效：同步或短间隔联合(如 SRS 后 30 天内)相比序贯治疗，可显著提高颅内完全缓解率、持续控制率及总生存期[34]-[36]。在此基础上，多项前瞻性研究进一步验证了该策略的潜力。

C-Brain 研究作为全球首个前瞻性探索 WBRT/SRS 同步联合卡瑞利珠单抗与化疗(放疗 7 天内)的临床试验，创新性纳入 71%有症状脑转移患者，结果显示该方案疗效卓越(iORR 82.5%，中位 iPFS16.1 个月，中位总生存期 20.9 个月)且安全性可控[37]。MD 安德森癌症中心开展的 I/II 期研究也证实，在 SRS 前后 7 天内联用纳武利尤单抗和伊匹木单抗安全可行，且颅内疾病控制优于单纯放疗历史数据(中位 iPFS 19.2 个月) [38]。吴一龙教授团队开展的 CTONG 2003 随机对照研究进一步证实，对比单纯放化疗，卡瑞利珠单抗 + 化疗联合放疗可显著改善包括活动性脑转移患者的 PFS (11.2 vs 6.7 个月)与 iPFS (19.1 vs 9.9 个月)，且不增加放疗相关毒性，不影响生活质量，反而一定程度改善患者认知功能[39]。该研究采用的个体化精准放疗模式，在首次全身治疗 42 天内，根据病灶特征(大小、位置等)分别选择 WBRT (30 Gy/10 次)或分层剂量 SRS/分次 SRS (针对≤4 cm 病灶给予 15~24 Gy 单次处方，>4 cm 病灶给予分次 SRS；而脑干等关键功能区附近病灶，≤2 cm 病灶给予 16 Gy 单次处方，>2 cm 病灶给予分次 SRS)。

上述证据支持放免联合在有症状脑转移中具有良好的应用价值，提示在稳定性脑转移患者中提前引入放疗联合免疫治疗，可能带来更优的生存获益。两项 Impower 系列前瞻性研究荟萃分析表明，在阿替利珠单抗背景下对稳定性脑转移灶进行放疗具有协同效应，甚至可使该人群预后优于无脑转移者[40] [41]。然而，这些研究未深入探讨放疗介入时机、模式、剂量与分次等关键参数，未来仍需更多高质量研究以明确放免联合在稳定性脑转移中的疗效与安全性。

随着患者生存延长，认知功能障碍与放射性脑损伤等不良事件的管理日益重要。目前证据显示，单药免疫检查点抑制剂与 SRS 同步使用并未显著增加坏死风险[37] [39]，其主要风险仍取决于放疗剂量学参数。临床实践中，评估放射性坏死风险的最佳参数是受照 ≥12 Gy 剂量的正常脑组织体积(V12 Gy) [42]，肿瘤大体积(如直径 >2 cm) [43]亦是独立风险预测因子；最新研究表明对于单次 SRS 照射小的脑转移瘤，更有临床意义的参数是肿瘤体积小于 2.5~5 立方厘米且接受 15 Gy 的照射剂量[44]。另外，采用双重免疫检查点抑制剂(如伊匹木单抗联合纳武利尤单抗)是明确的独立高风险因素[45]。此外脑放疗后病灶反应的评估在临床和放射影像学上仍然是一个挑战。目前颅内疗效评估遵循 RANO-BM 标准，依据靶病灶直径总和的动态变化进行客观判断。即使先进的技术提示肿瘤复发，对放疗后出现突然和指数增长也应谨慎分析，因为这可能与炎症变化相对应[46]。对“假性进展”(或治疗相关效应)与真实肿瘤进展的正确区分，可以避免不必要的治疗中断。此外，这种影像学上的“进展”可能被视为一个与良好预后相关的潜在积极信号[47]。在临床实践中，鉴别放射性坏死与肿瘤复发推荐采用循序渐进的多模态影像技术组合：首选动态磁敏感对比增强灌注加权成像(DSC-PWI)，若放射性坏死区域表现为相对脑血容量(rCBV)显著降低，而肿瘤复发区域 rCBV 明显升高；当灌注结果不明确时，可进一步联合磁共振波谱(MRS)检测胆碱/肌酸比值(复发者显著升高)或进行氨基酸 PET 成像(复发呈高代谢摄取)，通过这种多参数影像交叉验证策略，能够为临床决策提供客观依据，有效区分两类病变。总之，临床医生必须对接受联合治疗(尤其是双重免疫治疗)的患者进行个体化的风险评估，并通过优化放疗计划、审慎选择免疫治疗方案以及加强治疗后的影像学监测，以平衡疗效与安全性。

对于脑转移引起的水肿或放疗相关炎症需要使用糖皮质激素缓解症状。然而回顾性分析表明，基线期(首次免疫治疗前后 28 天)大剂量使用糖皮质激素(累积剂量 ≥100 mg)，会缩短接受免疫联合颅内放疗

非小细胞肺癌脑转移患者的生存期[48]。因此，在放免联合治疗期间需权衡激素的获益与风险：对于无症状或轻度水肿患者，应避免预防性使用或采用最低有效剂量。对于已使用激素的症状型患者，应在神经系统症状稳定后尽早开始递减，目标是在免疫治疗启动后 2 至 4 周内将地塞米松剂量降至每日≤2 mg。针对放疗后急性期水肿，建议采用短期方案(如地塞米松 4~8 mg/天，疗程不超过 1 周)并快速减量，或联用甘露醇等非激素脱水药物以减少糖皮质激素的累积剂量。整个治疗过程中，需密切结合神经症状与影像学随访，实现症状控制与免疫疗效保护之间的最优化管理。

6. 小结

综上所述，驱动基因阴性 NSCLC 脑转移的治疗已进入以“放疗联合免疫治疗”为核心的新阶段。临床与临床前研究表明，该联合策略具有协同增效作用，可激活系统性抗肿瘤免疫，为患者带来持续生存获益。目前临床实践仍需更多 III 期研究明确放疗模式、免疫方案的最佳组合与时序安排，并建立放射性脑坏死等不良事件的规范化防治体系。随着对 NSCLC 脑转移生物学行为理解的深入和前瞻性证据的积累，放免联合治疗将朝着更精准、个体化的方向演进，从而为患者争取更优的长期生存。

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