Advances in Clinical Medicine 临床医学进展, 2026, 16(5), 2273-2285
Published Online May 2026 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2026.1652038

结直肠癌新辅助治疗进展

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收稿日期：2026年4月21日；录用日期：2026年5月15日；发布日期：2026年5月26日

摘　要

结直肠癌(Colorectal Cancer, CRC)新辅助治疗(Neoadjuvant Therapy)是局部进展期结直肠癌(Local Advanced Colorectal Cancer, LACRC)多学科综合治疗的核心手段，具有肿瘤降期、提升肿瘤R0切除率、降低复发转移风险、保留器官功能等多种优势，可有效改善患者生存预后与生活质量。文章总结了CRC新辅助治疗的研究及临床应用进展，重点分析了直肠癌与结肠癌的治疗策略、新辅助免疫治疗的应用突破及现存不足，为LACRC个体化诊疗方案的优化提供参考。

关键词

结直肠癌，局部进展期结直肠癌，新辅助治疗，全程新辅助治疗，新辅助化疗，新辅助免疫治疗

Advances in Neoadjuvant Therapy for Colorectal Cancer

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Received: April 21, 2026; accepted: May 15, 2026; published: May 26, 2026

Abstract

Neoadjuvant therapy for colorectal cancer (CRC) serves as a core modality of multidisciplinary comprehensive treatment for local advanced colorectal cancer (LACRC). It confers multiple advantages including tumor downstaging, elevated R0 resection rate, reduced risk of recurrence and metastasis,

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文章引用: 练达, 刘鲲鹏, 崔欣, 孟子钰, 侯代鑫, 姜昊, 谢鹏宇. 结直肠癌新辅助治疗进展[J]. 临床医学进展, 2026, 16(5): 2273-2285. DOI: 10.12677/acm.2026.1652038

and preserved organ function, thereby effectively improving patients' survival prognosis and quality of life. This article summarizes the research and clinical application progress of neoadjuvant therapy for CRC, with focuses on the therapeutic strategies for rectal cancer and colon cancer, the application breakthroughs and existing limitations of neoadjuvant immunotherapy, so as to provide references for the optimization of individualized diagnosis and treatment regimens for local advanced colorectal cancer.

Keywords

Colorectal Cancer, Local Advanced Colorectal Cancer, Neoadjuvant Therapy, Total Neoadjuvant Therapy, Neoadjuvant Chemotherapy, Neoadjuvant Immunotherapy

1. 引言

CRC 是世界上第三常见的癌症，也是癌症相关死亡的第二大原因[1]-[3]。CRC 现已成为 50 岁以下成年人癌症死亡的主要原因，原因至今仍大多未知[4]。LACRC 指 II 期(cT3~4, N0)/III 期(cT1~4, N+)的 CRC，占初诊患者比例较高，目前根治性手术切除仍然是最佳的治疗手段[5]，然而单纯手术治疗局部复发率与远处转移率高，预后不佳[6]。目前迫切需要改进现有的治疗方法，并开发新的治疗策略以改善这类患者的预后[7]。

新辅助治疗是指在可能实现根治性局部治疗(Definitive Local Treatment)之前给予的癌症治疗手段[8]，包括化疗[9]、放疗[10] [11]、免疫治疗[12]-[14]等，核心目标为肿瘤降期、提高 R0 切除率、清除微小转移灶、降低术后复发风险其，其被视为降低手术复杂性和改善局部疾病控制的手段。所使用的治疗方法及其适应症因多种因素而异，包括肿瘤位置、肿瘤生物学及预期的最终治疗方案。新辅助疗法在 CRC 患者治疗中已有明确作用[15]。随着现有治疗方式的进步以及新辅助治疗及后续手术适应症的改进，其作用仍在不断扩大。

2. CRC 治疗方法的发展

2.1. 直肠癌(Rectal Cancer, RC)

RC 常见表现为直肠出血、肠道习惯改变和狭窄[16]。RC 指为位于肛缘 15 厘米范围内的肿瘤，通过刚性乙状结肠镜检查或磁共振成像(MRI)测量。根据距肛缘的距离，RC 被划分为低、中、高位三种，分别为距肛缘 0 至 5 厘米、5 至 10 厘米、10 至 15 厘米[17]。

2.1.1. RC 治疗方法的发展

目前 RC 的治疗是过去 40 年来手术技术及其与化疗和/或放疗结合的改进结果。这些改进的主要目的是降低手术后局部复发的风险。在 20 世纪 80 年代之前，手术后局部复发十分常见，有报道显示其发生率在 30%至 40%之间[18]。局部复发患者常发生盆腔脏器侵犯，伴难治疼痛和严重的泌尿生殖功能障碍，这些症状难以得到缓解。

全直肠系膜切除术(Total Mesorectal Excision, TME)是推动 RC 治疗技术进步最重要的贡献之一[19]。TME 的适应症是对直肠中部和下三分之一直肠肿瘤进行治愈性切除，TME 技术的发明立即大幅降低了

局部复发率，5 年局部复发率从高达 40%降至 3.7% [20]。对于中低位 RC，低位前切除术(LAR)配合 TME 已被证明能最大限度地减少局部区域复发[21] [22]。Heald 等[23]后来对大批量患者进行随访发现 TME 不仅降低了整体复发率，还提升了生存率，TME 后 5 年生存率从 38%提升到了 68%。TME 被越来越多的指南及专家共识列为 RC 外科切除的标准方法[24] [25]。

然而，在 TME 技术推广之前，已有其他学者探究术前进行放疗对于 RC 的好处。Påhlman 等的一项随机试验显示，术前放疗优于术后放疗[26]，5 年局部复发率显著降低。后来的多项研究也证明了这点[27] [28]。但这些研究均有局限性，他们研究的对象均为无法实施手术的 RC 患者，并且研究发现术前实施放疗的患者仅降低了局部的复发率，但对于总体生存期无明显差异[29]-[31]。

2.1.2. RC 的新辅助治疗

上述研究对于新辅助治疗奠定了基础。研究显示新辅助治疗能降低手术后局部复发率，但总体生存率仍无明显改善[11] [26] [30] [31]，主要被用来降低手术复杂性和改善局部疾病控制的手段，对于低位 RC 保肛手术能更好的保护肛门括约肌的功能[32]。

RC 的新辅助疗法主要有两种，短程放疗(SCRT)、长程化疗(CRT)。研究显示其在局部复发率及生存率等方面无明显差异[33] [34]。

近年来，SCRT、CRT 的替代方案，全程新辅助治疗(Total Neoadjuvant Therapy, TNT)出现。TNT 通过术前予以足剂量化疗来提升治疗依从性与远期疗效。该化疗方案可联合 SCR 或 CRT 实施；根据给药时机在放疗前或放疗后，其分别称为诱导化疗或巩固化疗[35]。研究显示对比 CRT，TNT 能显著提高 R0 切除率、局部复发率、远处转移率，从而提高无病生存率[36]-[38]。

新辅助化疗(Neoadjuvant Chemotherapy, NAC)即化疗作为单一药物的治疗方式，一些证据表明 NAC 在部分直肠癌患者中不劣于 CRT，但对比 CRT 多数研究显示其在肿瘤 R0 切除率方面无明显差异[39]-[41]，需要更多临床研究进行验证。

随着新辅助治疗技术的发展，对于是否需要在治疗后进行手术治疗产生了大量研究。其被称为非手术管理(Non-Operative Management, NOM) [42]，指完全缓解的患者不会按原计划进行 TME 术，而是接受严格监测以在早期发现癌症复发，即“观察等待策略”[43]。NOM 的主要优势是避免了直肠切除术的手术并发症及手术对功能和生活质量的长期影响。Habr-Gama A 等[44]于 2004 年首次报道，他们将 71 名 CRT 后临床完全缓解(Clinical Complete Response, cCR)的患者被纳入监测，而非进行手术。在近 5 年的中位随访中，仅有 2 名患者出现局部肿瘤复发，只有 3 名患者出现了远处转移。并且多项研究显示 NOM 和 CRT 后接受 TME 术的患者在复发率、远处转移、生存率方面无显著差异[45]-[49]。Garcia-Aguilar 等[50]的一项随机对照试验采用 TNT 作为 NOM 方案，患者先进行 CRT 后对于 cCR 者进行 NOM 治疗而其余患者进行 TME，两者在 3 年及 5 年随访中生存率及复发率无显著差异，且由于器官得以保存，NOM 组有更高的生活质量。

在 NOM 的基础上，另一种治疗策略诞生，将新辅助治疗结合原发肿瘤局部切除(Local Excision, LE)。在多项临床研究中，对比 LE 和 TME，两者在局部复发率、生存率方面无显著差异[51]-[53]，甚至 TME 组的复发率较高。对大多数 pT1 的 RC 患者提供治愈方法[54]，临床反应良好的 cT2-3 的 RC 患者，LE 有更好的预后，对生活质量影响最小[55]。

2.2. 结肠癌(Colon Cancer)

与 RC 相比，新辅助疗法在结肠癌患者治疗中的作用尚未被充分证明。目前结肠癌患者的标准治疗是外科切除，对 III 期患者以及伴不良预后因素的 II 期患者术后行化疗[56]-[58]。预防术后复发在结肠癌患者术后管理中仍尤为重要，多达 25%的化疗患者术后复发，且在有不良预后因素的患者中发生率更高[59]。

2.2.1. 结肠癌的 NAC

多项研究显示 NAC 既可降低手术复杂性，也可降低患者术后复发风险[60]-[62]。

目前结肠癌的 NAC 主要有两项临床试验，PRODIGE 22 [63] [64]及 FOxTROT [65]-[67]，均表现出病理肿瘤退缩率更高(Pathological Tumour Regression)、肿瘤降期更明显、R0 切除率也更高。在 FOxTROT 的临床研究还发现了 NAC 对不同 MMR (Mismatch Repair)疗效的影响[68]，对比 dMMR (Deficient MMR)患者，pMMR (Proficient MMR)的无病生存期提高更明显，显著改善了疾病预后[69]。

2.2.2. 特殊治疗策略：腹腔热灌注化疗(Hyperthermic Intraperitoneal Chemotherapy, HIPEC)

在结肠癌局部进展与高复发风险人群中，预防腹膜转移是临床难点。腹腔热灌注化疗(HIPEC)作为区域强化治疗手段，被视为结肠癌治疗的另一种策略[70]。其被用于降低腹膜种植风险，成为结肠癌综合治疗的重要补充。

对于多项腹膜转移的高危因素，如 pT4 期结肠癌、肿瘤穿孔、黏液性及印戒细胞组织学类型的结肠癌、肿瘤位于右半结肠、以及肿瘤非完整切除(R1、R2 切除)等[71]-[74]，HIPEC 具有多项优势，如高热与多种化疗药物之间的协同效应；高剂量化疗药物灌注腹腔，可杀死游离癌细胞(Free Cancer Cell, FCC)并防止其定植在腹膜引起种植转移；同时与传统化疗相比，还能减少全身毒性反应；对于结肠癌合并恶性腹腔积液，可明显改善腹水症状，提高患者生活质量[75]-[79]。

但 HIPEC 在临床推广中仍存在显著争议与局限：其一，生存获益证据不一致，多项III期随机对照研究证实其可降低腹膜复发风险，但尚未转化为明确的总生存获益；其二，适用人群界定不清，对低危患者过度使用会额外增加并发症风险与医疗经济负担；其三，技术标准尚未全球统一，灌注温度、时长、化疗药物选择及实施时机(术中/术后)等关键参数缺乏共识；其四，并发症风险偏高，腹腔感染、肠瘘、邻近器官损伤等不良事件发生率高于单纯手术，一定程度上限制了该技术的广泛应用[80]-[84]。

3. CRC 的新辅助免疫治疗(Neoadjuvant Immunotherapy, NAIT)

21 世纪是免疫治疗的时代，在多种癌症中免疫检查点抑制剂(Immune Checkpoint Inhibitor, ICI)显示出令人瞩目的疗效[85]。

CRC 传统上被认为是“冷肿瘤”[86]，其特征是免疫原性低且对 ICI 反应有限，尤其是错配修复完整/微卫星稳定(Mismatch Repair Proficient/Microsatellite Stable, pMMR/MSS)肿瘤[87]-[89]。直至错配修复缺陷/高度微卫星不稳定(Mismatch Repair Deficient/Microsatellite Instability-High, dMMR/MSI-H)这一 CRC 亚型的发现[90]，免疫治疗在 CRC 领域的应用终于迎来了转折。CRC 中 dMMR/MSI-H 亚型最早由 Thibodeau 等[91]于 1993 年报道，发现微卫星序列不稳定性与错配修复功能障碍有关。研究显示 dMMR/MSI-H 状态在 CRC 中多见于右半结肠癌，其具有肿瘤分期较早、分化较低、肿瘤浸润淋巴细胞显著等临床病理学特征[92] [93]。I~III 期 dMMR 亚型的 CRC 有更好的预后(尤其 II 期)，这可能与肿瘤中更有效的免疫监视和更高的肿瘤内 T 细胞密度相关。由于 dMMR 积聚的增多，产生了大量肿瘤新抗原，使免疫识别提高，具备免疫治疗的能力[94]，使其成为对程序性死亡蛋白-1 (Programmed Death-1, PD-1)阻断敏感的基础[95] [96]。Le DT 等[97]于 2015 年首次证明了 PD-1 的抑制剂帕博利珠单抗在 dMMR/MSI-H 转移性 CRC 患者中显示出高效抗肿瘤活性，而 pMMR/MSS 患者无一应答。这一研究明确了 dMMR/MSI-H 状态为免疫治疗效果有力的生物标志物，明确其免疫治疗的效果[98] [99]。

3.1. dMMR/MSI-H 状态的 NAIT

目前国内外临床指南[25] [100] [101]推荐对于 dMMR/MSI-H 的非转移性结肠癌患者，若符合 cT4b 期、伴巨块型淋巴结转移(长径 > 2 cm)、局部不可切除 3 个条件中任意 1 个，推荐行新辅助免疫治疗，

然后行根治性手术。在 NICHE-3 和 PICC [96]试验中，NAIT 表现出显著的高反应率，局部晚期 dMMR/MSI-H 状态的 CRC 的病理完全反应(pCR)率均在 65%以上[102]-[104]。对比直接手术方案，NAIT 治疗后患者疗效获益更明显。部分缓解(PR)患者往往需要手术切除以实现 pCR，进一步若能准确区分 pCR 的患者与 PR 患者，通过精确评估能有效地避免手术[105] [106]。

一项 Meta 分析[87]显示 dMMR/MSI-H 状态的 CRC 中，单靠影像学评估无法可靠评估 NAIT 的疗效。选择最佳治疗方案并追求非手术管理，放射学评估应与内镜和肿瘤标志物分析等其他方式相结合，以确保治疗效果的准确评估[107]-[109]。

对于 RC，NAIT 已经很好的运用于局部晚期直肠癌(Locally Advanced Rectal Cancer, LARC)。多项临床研究显示[110]-[112] dMMR/MSI 患者对于 NAIT 的疗效获益，极高的 CR 率也让低位直肠器官保留的“观察等待策略”[43]成为可能。

3.2. pMMR/MSS 状态的 NAIT

在临床上 dMMR/MSI-H 状态患者仅占 4%~5%，绝大多数 CRC 患者具有 pMMR/MSS 状态，肿瘤缺乏诱导 T 细胞起始的抗原，且肿瘤微环境缺乏 T 细胞浸润，通常对 ICI 的单一免疫疗法不敏感[113]-[115]，缺乏抗肿瘤效果。目前大多数治疗策略采用联合疗法，结合免疫治疗与放化疗，将“冷肿瘤”逆转为对免疫治疗敏感的“热肿瘤”，以提升 pMMR/MSS 状态 CRC 免疫疗法的疗效[10] [81] [116]-[119]。

3.2.1. 短程放疗序贯化疗 + 免疫联合治疗

“短程放疗序贯化疗 + 免疫”是 pMMR/MSS 型 LACRC 新辅助治疗证据最充分的方案，获国内专家共识优先推荐[10]。短程放疗(5 × 5 Gy)通过诱导肿瘤免疫原性细胞死亡、促进血管正常化、下调免疫抑制微环境发挥免疫协同效应，且骨髓毒性更轻，可最大化放免协同作用[120]。III 期 UNION 研究显示，该方案 pCR 率达 39.8%，显著优于传统长程放化疗(16.3%)，3 年无病生存率提升 12.5%，安全性良好[117]；TORCH-C、STELLAR 研究也证实其在结直肠癌中优异的病理退缩率与 100% R0 切除率[37] [118]。

3.2.2. 化疗 + 抗血管生成靶向治疗 + 免疫三联联合治疗

“化疗 + 抗血管生成靶向 + 免疫三联”是无放疗指征患者的核心方案，形成“化疗杀伤 + 抗血管重塑微环境 + 免疫激活”的协同闭环，逆转“冷肿瘤”表型[121]-[123]。多项 II 期研究显示，该方案 pCR 率 28.9%~31.2%，显著病理退缩率超 57%，R0 切除率 100%；FOxTROT 亚组分析证实，其可使结肠癌患者病理退缩率提升 3.2 倍，3 年无病生存率提升 18.7% [66]。

3.2.3. 新型免疫制剂联合免疫检查点抑制剂(Immune Checkpoint Inhibitor, ICI)治疗

双特异性抗体、ADC、新型免疫检查点抑制剂为核心，分别通过募集 T 细胞、靶向杀伤诱导免疫原性死亡、协同解除免疫抑制发挥作用。早期研究显示，双抗、ADC 联合 ICI 的 pCR 率达 24.5%~33.3%，PD-1 联合 LAG-3 抑制剂病理退缩率达 42.1%，显著优于单药免疫[124]。

4. 多学科综合治疗(MDT)在结直肠癌新辅助治疗中的核心地位与工作模式

结直肠癌新辅助治疗贯穿分期评估、方案制定、疗效监测、手术决策、术后辅助治疗及全程随访全流程，MDT 模式已被 CSCO、NCCN、ESMO 等国内外权威指南列为局部进展期结直肠癌新辅助治疗决策的金标准[25] [100] [125] [126]，是保障诊疗规范性、改善患者生存预后与生活质量的核心基石。其核心价值体现在四方面：一是整合多学科专业意见，避免单一学科诊疗偏差，多项大样本研究证实，经 MDT 评估的患者，新辅助治疗方案指南符合率、R0 切除率与 3 年无病生存率显著提升，术后并发症发生率明显降低[127]；二是综合肿瘤特征、患者意愿与身体状态，平衡肿瘤根治性与器官功能保护，制定个体化

保肛、非手术管理策略，避免过度治疗[128]；三是实现治疗全流程动态监测与多学科评估，及时调整方案，提升患者治疗耐受性与依从性；四是促进学科协作与临床研究转化，推动区域诊疗规范化。规范的MDT团队以胃肠外科、肿瘤内科、放疗科、影像科、病理科、内镜科医师为核心固定成员，按需纳入造口、营养、心理等扩展成员，MDT工作需覆盖治疗前、中、后全流程，同时通过固定会议制度、决策复盘机制、团队培训体系与数字化平台建设实现质量控制，保障诊疗决策的精准性与同质化。

5. 总结与展望

过去四十年来，CRC的治疗模式发生了巨大转变，从以单纯手术为主的单一治疗模式，发展为手术、化疗、放疗、免疫治疗相结合的多学科综合治疗体系。新辅助治疗作为其中的核心组成部分，其应用范围不断扩大，对肿瘤降期作用明显，显著提高了肿瘤R0切除率，保留器官功能，降低局部复发和远处转移风险，极大改善了患者的生存质量及预后。

在直肠癌领域，TME仍然为外科治疗的金标准，而短程放疗、长程放化疗以及全程新辅助治疗的应用进一步优化了肿瘤学疗效。非手术管理和新辅助治疗联合局部切除策略的提出，更是在保证肿瘤根治性的前提下，最大限度地保留了肛门括约肌功能，显著提升了患者的长期生活质量。

NAIT的出现使肿瘤治疗提升到了基因层面。对于dMMR/MSI-H亚型的LACRC，新辅助免疫治疗展现出了极高的pCR率，为器官保留和非手术管理提供了重要的临床证据。并且还需要进一步提高影像学检查的准确性以提高pCR患者的识别率。但对于占绝大多数的pMMR/MSS亚型患者，单一免疫治疗效果有限，且目前对于此类的研究相对缺乏，有待进一步的临床研究。

未来随着临床应用范围的进一步扩大，需要聚焦四个方面：首先，需要进一步探索和验证更可靠的疗效预测生物标志物，结合影像学、内镜、活检和分子生物学等多维度评估手段，实现对治疗反应的精准预测和动态监测，从而筛选出最适合非手术管理的患者，避免不必要的手术创伤和过度治疗。其次，针对pMMR/MSS亚型结直肠癌，需要开展更多大样本、多中心、随机对照临床试验，系统探索免疫治疗与化疗、放疗、靶向治疗等不同联合方案的最佳剂量、时序和组合，以提高其免疫原性和治疗效果。此外，新型免疫治疗药物如双特异性抗体、抗体药物偶联物、CAR-T细胞疗法等在新辅助治疗中的应用也值得期待，它们可能为难治性结直肠癌患者带来新的希望。同时，还需要进一步明确结肠癌新辅助治疗的最佳适应症、疗程和方案，以及腹腔热灌注化疗在不同高危人群中的应用价值和时机，不断完善治疗指南。

基金项目

黑龙江省大学生创新创业训练计划项目(编号 S202510222084)；黑龙江省省属高等学校基本科研业务费(编号 23KYYWF0596)。

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