【评论】局部进展期直肠癌全程新辅助治疗短程放疗后序贯卡培他滨加奥沙利铂联合信迪利单抗对比短程放疗后序贯卡培他滨加奥沙利铂（SPRING-01）：一项单中心、开放标签、2期随机对照试验临床研究

李佑
上海交通大学医学院附属瑞金医院普外科 上海 201801
E-mail：jefflee1026@hotmail.com

［Article］TIAN F, DAI H, SHA D, et al. Total neoadjuvant treatment with short-course radiotherapy followed by sintilimab plus capecitabine-oxaliplatin versus short-course radiotherapy followed by capecitabine-oxaliplatin in patients with locally advanced rectal cancer (SPRING-01): a single-centre, open-label, phase 2, randomised controlled trial[J]. The Lancet. Oncology, 2025, 26(8): 1043-1054.

［Abstract］**Background** Neoadjuvant short-course radiotherapy combined with chemotherapy as total neoadjuvant therapy increases the pathological complete response rate for patients with locally advanced rectal cancer. The potential synergistic effects of combining radiotherapy and immunotherapy might benefit patients with locally advanced rectal cancer. We aimed to compare the efficacy and safety of short-course radiotherapy followed by capecitabine-oxaliplatin chemotherapy with or without immunotherapy as total neoadjuvant therapy in patients with locally advanced rectal cancer. **Methods** SPRING-01 was a single-centre, open-label, phase 2, randomised controlled trial done at the Shandong Provincial Hospital, China. Patients were aged 18-85 years with an Eastern Cooperative Oncology Group performance status of 0-1 and had biopsy-confirmed, newly diagnosed, treatment-naive, primary, locally advanced rectal adenocarcinoma with at least one of the following features: clinical tumour stage T_{3-4} or greater, clinical nodal stage N_1 or higher, extramural vascular invasion, mesorectal fascia involvement, or lateral lymph node metastasis. Participants were randomly assigned (1∶1) to receive either sintilimab plus capecitabine-oxaliplatin or capecitabine-oxaliplatin alone. The randomisation sequence was generated using computer-generated random numbers with SAS software version 9.4, using a simple randomisation method without stratification or blocking, and allocation was concealed using opaque, sealed envelopes. Neither patients nor clinical staff were masked to treatment allocation; however, pathological assessments and data analyses were conducted in a blinded manner. Patients received short-course radiotherapy (5 × 5 Gy over 5 days) followed by six cycles of intravenous capecitabine-oxaliplatin chemotherapy (intravenous oxaliplatin 130 mg/m^2 over 2 h on day 1, and oral capecitabine 1 000 mg/m^2 twice daily on days 1-14 of each 3-week cycle) with or without intravenous sintilimab (200 mg/m^2 on day 1 of each 3-week cycle), starting 1 week after completion of radiotherapy. Total mesorectal excision surgery, was done 2-3 weeks after the completion of total neoadjuvant therapy. The primary endpoint was the pathological complete response rate in the intention-to-treat population. The trial was registered with the Chinese Clinical Trial Registry (ChiCTR2100052288). **Findings** Between Oct 8, 2021, and Sept 26, 2023, 116 patients with locally advanced rectal cancer were screened, of whom 98 eligible patients were randomly assigned to the sintilimab plus capecitabine-oxaliplatin group (n=49) or the capecitabine-oxaliplatin group (n=49). 68 (69%) of 98 patients were male and 30 (31%) were female; all patients were Asian. Median follow-up was 25 months (IQR 20-32). The pathological complete response rate was significantly higher in the sintilimab plus capecitabine-oxaliplatin group than in the capecitabine-oxaliplatin group (29 [59.2%, 95%*CI* 45.4-72.9] *vs.* 16 [32.7%, 19.5-45.8]; P=0.015). Postoperative complications occurred in 11 (24% [95%*CI* 12-37]) of 45 patients in the sintilimab plus capecitabine-oxaliplatin group and in five (11% [2-21]) of 44 in the capecitabine-oxaliplatin group. Treatment-related adverse events during neoadjuvant therapy occurred in 45 (92%) of 49 patients in the sintilimab plus capecitabine-oxaliplatin group and in 44 (90%) of 49 patients in the capecitabine-oxaliplatin group. The most common treatment-related adverse events in the sintilimab plus capecitabine-oxaliplatin group and the capecitabine-oxaliplatin group were thrombocytopenia (18 [37%] *vs.* 26 [53%]), leukopenia (19 [39%] *vs.* 26 [53%]), anaemia (27 [55%] *vs.* 33 [67%]), nausea or vomiting (25 [51%] *vs.* 27 [55%]), and diarrhoea (21 [43%] *vs.* 24 [49%]). Grade 3-4 treatment-related adverse

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events were observed in 16 (33%) patients in the sintilimab plus capecitabine-oxaliplatin group and 17 (35%) patients in the capecitabine-oxaliplatin group. The most common grade 3-4 adverse event was thrombocytopenia, reported in six (12%) patients in the sintilimab plus capecitabine-oxaliplatin group and in 11 (22%) patients in the capecitabine-oxaliplatin group. Serious adverse events occurred in 15 (31%) of 49 patients in the sintilimab plus capecitabine-oxaliplatin group and in nine (18%) of 49 patients in the capecitabine-oxaliplatin group. The most common serious adverse event in both treatment groups was thrombocytopenia. One (2%) patient in the capecitabine-oxaliplatin group died from septic shock due to acute ileus. No treatment-related deaths occurred in the sintilimab plus capecitabine-oxaliplatin group. **Interpretation** In patients with locally advanced rectal cancer, short-course radiotherapy combined with sintilimab and capecitabine-oxaliplatin as a total neoadjuvant treatment significantly increased the pathological complete response rate while maintaining manageable safety profile. These findings suggest that this regimen might be a promising neoadjuvant treatment approach for locally advanced rectal cancer.
[Keywords] locally advanced rectal cancer, total neoadjuvant therapy, short-course radiotherapy, immunotherapy

[中文提要] **背景** 短程放疗联合化疗作为全程新辅助治疗可提高局部进展期直肠癌患者的病理完全缓解率。放疗与免疫治疗联合的潜在协同效应可能使局部进展期直肠癌患者获益。本研究旨在比较短程放疗后序贯卡培他滨加奥沙利铂联合或不联合免疫治疗作为全程新辅助治疗在局部进展期直肠癌患者中的疗效与安全性。**方法** SPRING-01是一项在中国山东省立医院开展的单中心、开放标签、2期随机对照试验。入组患者年龄18~85岁，东部肿瘤协作组体能状态评分为0~1分，经活检确诊为初治、原发局部进展期直肠腺癌，且至少满足以下一项特征：临床肿瘤分期为T_{3-4}期或更高分期、临床淋巴结分期为N_1期或更高分期、血管外侵犯、直肠系膜筋膜受累或侧方淋巴结转移。患者按1∶1比例随机分配至信迪利单抗联合卡培他滨加奥沙利铂组（联合组）或单用卡培他滨加奥沙利铂组。随机序列是采用SAS软件（9.4版）生成的简单随机数字序列，无分层或分组限制，分配方案通过不透明密封信封进行隐匿。患者和临床医护人员均知晓治疗分组，但病理评估和数据分析采用盲法进行。患者在完成短程放疗（5天内每天5 Gy，共5次）后1周开始接受6周期静脉化疗【第1天静脉注射奥沙利铂130 mg/m²（2 h输注）；第1~14天口服卡培他滨1 000 mg/m²，每日2次；每3周为一个周期】，联合或不联合信迪利单抗（每3周周期的第1天静脉注射200 mg/m²）。全程新辅助治疗结束后2~3周行全直肠系膜切除术。主要终点为意向治疗人群的病理完全缓解率。本研究已在中国临床试验注册中心注册（ChiCTR2100052288）。**结果** 2021年10月8日至2023年9月26日期间，共有116例局部进展期直肠癌患者接受筛查，其中98例符合条件的患者被随机分配至联合组（n=49）或单用卡培他滨加奥沙利铂组（n=49）。98例患者中，男性68例（69%），女性30例（31%）；所有患者均为亚洲人。中位随访时间为25个月（四分位间距20~32）。联合组的病理完全缓解率显著高于单用卡培他滨加奥沙利铂组【29例（59.2%，95%*CI*：45.4~72.9） *vs*. 16例（32.7%，95%*CI*：19.5~45.8），P=0.015】。术后并发症方面，联合组45例患者中有11例（24%，95%*CI*：12~37）发生并发症，而单用卡培他滨加奥沙利铂组44例患者中有5例（11%，95%*CI*：2~21）发生并发症。新辅助治疗期间，联合组49例患者中有45例（92%）出现治疗相关不良事件，单用卡培他滨加奥沙利铂组49例患者中有44例（90%）出现治疗相关不良事件。两组最常见的治疗相关不良事件为血小板减少【联合组18例（37%） *vs*. 单用卡培他滨加奥沙利铂组26例（53%）】、白细胞减少【联合组19例（39%） *vs*. 单用卡培他滨加奥沙利铂组26例（53%）】、贫血【联合组27例（55%） *vs*. 单用卡培他滨加奥沙利铂组33例（67%）】和恶心或呕吐【联合组25例（51%） *vs*. 单用卡培他滨加奥沙利铂组27例（55%）】。联合组16例（33%）患者和单用卡培他滨加奥沙利铂组17例（35%）患者出现3~4级治疗相关不良事件。最常见的3~4级不良事件为血小板减少，联合组6例（12%）患者和单用卡培他滨加奥沙利铂组11例（22%）患者报告该事件。严重不良事件方面，联合组49例患者中有15例（31%）发生严重不良事件，单用卡培他滨加奥沙利铂组49例患者中有9例（18%）发生严重不良事件。两组最常见的严重不良事件均为血小板减少。单用卡培他滨加奥沙利铂组1例（2%）患者因急性肠梗阻导致感染性休克死亡，联合组未发生治疗相关死亡。**解释** 在局部进展期直肠癌患者中，短程放疗后序贯卡培他滨加奥沙利铂联合信迪利单抗作为全程新辅助治疗，显著提高了病理完全缓解率，同时保持了可控的安全性。这些发现表明，该方案可能成为局部进展期直肠癌的一种有前景的新辅助治疗选择。
[关键词] 局部进展期直肠癌；全程新辅助治疗；短程放疗；免疫治疗

【评论】局部进展期直肠癌（locally advanced rectal cancer，LARC）的标准治疗从最初以手术为主，发展到新辅助放化疗（neoadjuvant chemoradiotherapy，nCRT）联合全直肠系膜切除术（total mesorectal excision，TME）及后续辅助化疗的综合治疗策略[1]，这些综合治疗策略显著降低了局部复发率，提高了保肛率。但远处转移仍然是影响患者长期生存的主要因素[2]。为了进一步改善患者预后，全程新辅助治疗（total neoadjuvant therapy，TNT）旨在提高肿瘤降期率、降低远处转移风险，并为部分患者实现器官保留（如“观察与等待”策略）提供可能[1]。TNT已成为高风险LARC患者的推荐方案之一[3]。

近年来，免疫检查点抑制剂（immune checkpoint inhibitors，ICIs）的出现彻底改变了肿瘤治疗格局。ICIs对错配修复功能缺陷（deficient mismatch repair，dMMR）或微卫星高度不稳定（microsatellite instability-high，MSI-H）的结直肠癌患者显示出突破性的疗效[4]。2024年中国临床肿瘤学会结直肠癌诊疗

指南提出，对于dMMR/MSI-H型局部晚期的结直肠癌，可考虑一线使用免疫治疗，并根据疗效决定后续治疗方案[5]。然而，错配修复功能正常（proficient mismatch repair，pMMR）或微卫星稳定（microsatellite stability，MSS）的结直肠癌占大多数，pMMR的直肠癌患者比例更高，达到85%~95%，而pMMR的患者通常对ICIs治疗反应不佳[6]。如何提高pMMR/MSS型LARC患者对免疫治疗的敏感性，成为当前研究的热点。有研究者将ICIs与放化疗等传统新辅助治疗手段相结合，即新辅助免疫治疗，期望通过放化疗改变肿瘤微环境，调节T细胞的活性，增强ICIs的抗肿瘤活性，从而改善pMMR/MSS型LARC患者的治疗结局[7]。

与传统新辅助放化疗20%~30%的病理完全缓解（pathological complete response，pCR）率相比，多项研究证实，在TNT框架下联合PD-1/PD-L1抑制剂能够显著提升pMMR/MSS型LARC患者的pCR率和完全缓解（complete remission，CR）率[8]。一项2025年的回顾性研究纳入了211例LARC患者，结果显示，接受免疫治疗联合TNT（ICIs+TNT）的患者pCR率达到49.4%，显著高于接受免疫治疗联合标准nCRT（ICIs+nCRT）患者的35.3%（$P=0.039$）[9]。另一项2025年发表的荟萃分析纳入了19项研究（1 324例患者），结果表明，新辅助ICIs联合放化疗将pMMR型LARC患者的总体CR率从24%提高到42%（$P<0.001$），pCR率从24%提高到37%（$P=0.008$）[10]。该研究将新辅助放化疗联合免疫检查点抑制剂的治疗周期增加，旨在最大化肿瘤退缩率，研究主要终点为意向治疗人群的病理完全缓解率。从研究结果看，联合免疫检查点抑制剂的全程新辅助放化疗方案取得了令人欣喜的结果，即pCR高达59.2%。在取得如此里程碑式的结果之下，外科医师可以进一步探讨局部切除甚至观察等待作为后续方案的可能性。尽管多项研究显示新辅助免疫治疗的潜力，但关于最佳的联合方案（如放疗模式、化疗方案、免疫药物选择）以及各治疗手段的最佳时机和顺序（如同步、序贯、诱导、巩固）尚未形成共识[10]。

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