·专题论坛·

# 局部进展期直肠癌新辅助放化疗后病理完全缓解的复发模式

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**【摘要】** 中低位局部进展期直肠癌接受新辅助同步放化疗后，部分患者可实现病理完全缓解（pCR），pCR后出现复发的概率较小，其术后治疗及随访策略尚未统一。本文总结pCR患者的复发模式，包括远处转移率、远处转移时间与转移的部位特点、局部复发率及局部复发时间特点等，以期对pCR患者的术后治疗及随访提供参考。pCR患者的总体复发比例低，局部复发少见，以远处转移为主，最多见的转移部位是肺脏，其次是区域外的淋巴结转移，复发时间推迟，故应该适当调整复查和随访方案，延长随访时间，并对易复发部位重点监测。

**【关键词】** 直肠肿瘤，局部进展期；　新辅助放化疗；　病理完全缓解；　复发模式

**基金项目：**国家自然科学基金（81972317）；中国医学科学院医学与健康科技创新工程（2021-I2M-1-021、2021-I2M-C&T-A-013）

**Recurrence pattern of pathological complete response after neoadjuvant chemoradiotherapy in locally advanced rectal cancer**

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**【Abstract】** Patients with locally advanced rectal cancer who undergo neoadjuvant chemoradiotherapy may achieve pathological complete response (pCR). The incidence of recurrence is low among patients with pCR, there is still a lack of consensus on postoperative treatment and follow-up strategy. This review summarizes the recurrence patterns of patients with pCR, including distant metastasis rate, characteristics of distant metastasis time and location, local recurrence rate, and local recurrence time. The aim is to provide reference for the postoperative treatment and follow-up strategy of patients with pCR. Patients with pCR have a low recurrence rate, with infrequent local recurrence. Distant metastasis is the most common recurrence pattern, primarily in the lung and secondly in the regional lymph node. The time of recurrence is delayed which suggests the need for appropriate adjustments to follow-up strategy, extending the follow-up period, and placing emphasis on monitoring sites prone to recurrence.

**【Key words】** Rectal neoplasms, locally advanced;　Neoadjuvant chemoradiotherapy;　Pathological complete response;　Recurrence pattern

**DOI：**10.3760/cma.j.cn441530-20240125-00042

**收稿日期**　2024-01-25　　**本文编辑**　万晓梅

**引用本文：**孙志刚，张海增. 局部进展期直肠癌新辅助放化疗后病理完全缓解的复发模式[J]. 中华胃肠外科杂志，2024，27(4)：365-371. DOI：10.3760/cma.j.cn441530-20240125-00042.

**Fund programs:** National Natural Science Foundation of China (81972317); Chinese Academy of Medical Sciences (CAMS) Initiative for Innovative Medicine (2021-I2M-1-021, 2021-I2M-C&T-A-013)

随着研究证据的增多，美国国立综合癌症网络（National Comprehensive Cancer Network，NCCN）指南推荐临床 TNM 分期为Ⅱ、Ⅲ期的中低位局部进展期直肠癌患者（locally advanced rectal cancer，LARC）进行新辅助放化疗（neoadjuvant chemoradiotherapy，NCRT）[1]。接受 NCRT 后行全直肠系膜切除术（total mesorectal excision，TME）已成为 LARC 的标准治疗。

2004 年发表的随机对照研究结果显示，NCRT 与术后放化疗（postoperative chemoradiotherapy，PCRT）相比，可显著提高患者 5 年局部无复发生存率（recurrence-free survival，RFS）（94% 比 87%，$P<0.01$），从而一举奠定了 NCRT 在 LARC 治疗中的地位，但是两组患者 5 年无远处转移生存率（distant metastases free survival，DMFS）及总生存率（overall survival，OS）差异无统计学意义[2]。长期随访数据显示，NCRT 组的 10 年 RFS 仍显著高于 PCRT 组，但两组 10 年 DMFS 及 10 年 OS 仍无差异[3]。这说明 NCRT 能够明显提高直肠癌的局部控制率、减少局部复发率[4]；但并没有降低直肠癌术后的远处转移率，也没有提高患者的远期生存率[5]。最新的研究显示，接受 NCRT 的患者术后局部复发率为 5.7%，远处转移率为 30.5%[6]。

大量研究表明，直肠癌 NCRT 后的治疗反应与患者的预后密切相关[7-8]。治疗反应中肿瘤退缩程度最好的是达到病理完全缓解（pathological complete response，pCR），即切除肿瘤标本（包含所有切除的淋巴结）在显微镜下检查未见任何肿瘤细胞残存，在 ypTNM 分期中标记为 ypT0N0M0。pCR 患者具有较好的预后，较少出现复发转移，但 pCR 后患者仍有一定的复发率，不能忽视，而且人们对 pCR 后的复发模式认识不足，故本文对 LARC 患者 pCR 后的复发模式进行综述，以加深理解，并为 pCR 患者的术后治疗及随访提供参考。NCRT 有多种形式，但本文主要是针对最常用的术前长程同步放化疗。

一、LARC 患者接受 NCRT 后的 pCR 率

NCRT 术后的病理学检查可观察到肿瘤病灶呈现不同程度的退缩与缓解，这说明肿瘤存在不同的治疗反应。NCRT 后实现 pCR 提示患者预后好，这也是我们在肿瘤综合治疗中努力追求的结果[7]。文献报道，NCRT 后接受 TME 手术的 pCR 率为 8%~25%[8-19]。pCR 率与病例的入组标准、新辅助治疗的方案等密切相关。近年来，随着全程新辅助治疗、术前放疗+免疫治疗等的逐步开展，pCR 率也在逐步升高[20-21]。实际上，NCRT 后部分患者因达到临床完全缓解（clinical complete response，cCR）后没有进行手术治疗，或者仅接受了经肛局部切除等治疗，这些都影响了研究者对 pCR 患者比例的估算。巴西学者 Habr-Gama 在对 71 例新辅助治疗后实现 cCR 的患者仅进行了严密随访观察，而未进行手术治疗，结果发现，其局部复发率（2.8%）和远处转移率（4.2%）都控制在很低的水平，故他率先提出对新辅助治疗后达 cCR 的患者可采取“等待观察”（watch and wait）策略[22]。此后，“等待观察”策略被其他医生逐步应用于 cCR 患者中[23-27]。但目前对 cCR 的评估主要依赖影像学检查和肠镜（超声内镜）检查，其准确程度与医生的经验及设备的性能密切相关。目前这些评价手段尚不够理想，甚至有文献报道，cCR 判断的准确率仅为 25%[28]。总之，cCR 不等于 pCR，所以目前有观点认为，只有低风险肿瘤才适合上述“等待观察”策略[29]。随着诊疗技术的进步，有越来越多的新手段被用来预测患者是否实现 pCR，这些都有助于 pCR 的准确评价和“等待观察”的精准开展，如循环肿瘤 DNA（circulating tumor DNA，ctDNA）就被用来预测肿瘤在病理学上的退缩反应，同时可以用于 pCR 患者的随访复查等[30-34]。

二、pCR 患者的生存率和复发率

pCR 的患者术后 5 年 OS 为 87.0%~92.9%[10-12]；总体复发率在 6%~17% 之间[9-11,14,16-19]。Park 等[9]的研究发现，pCR 患者 5 年 RFS 为 90.5%，5 年远处转移发生率为 7.0%，5 年内仅出现局部复发的比率为 0%。可见 pCR 患者术后的复发形式主要为远处转移，而非局部复发。Fokas 等[14]针对 pCR 患者进行中位时间长达 132 个月的随访，发现其远处转移的 10 年累计发生率为 10.5%。Wasmuth 等[10]的研究中共有 147 例 pCR 患者，其中有 12 例（8%）发生远

处转移。Zorcolo 等[11]针对 12 项研究共 1 913 例患者进行分析发现，其中 300 例（15.6%）实现了术后 pCR，该部分患者的 OS 和 DFS 分别为 92.9% 和 86.9%，但纳入的研究中位随访时间均不足 5 年（23~46 个月）。也有研究纳入 242 例 pCR 患者，依据复发高危因素，把所有患者分成两组，DMFS 分别为 94.2% 与 81.8%[35]。Maas 等[7]进行的较大样本量的 Meta 分析，3 105 例 pCR 患者的 5 年远处转移率为 11.2%。Capirci 等[36]对 566 例获得 pCR 的患者进行 46 个月随访后，发现远处转移率为 8.9%。

肿瘤退缩分级（tumor regression grade，TRG）是针对原发肿瘤的治疗效果进行的病理评估，TRG 退缩良好的患者，远处转移的风险也低，两者关联显著。局部肿瘤退缩效果不明显可能反映了肿瘤具有较强的侵袭性，说明肿瘤在对 NCRT 的治疗反应差的同时，也表现出了较高的转移倾向。有研究认为，导致 NCRT 耐药和治疗抵抗的生物学机制与导致远处转移的生物学机制密切相关，甚至可能重叠[14]。肿瘤消退程度和远处转移的风险之间的联系可能与其他几种生物学机制有关：如实现 pCR 后，肿瘤总负荷的减少可能会将循环肿瘤细胞的含量及其播散种植限制在较低水平[37]；NCRT 后 pCR 或近似 pCR 的肿瘤消退可能逆转了肿瘤的免疫抑制并激发全身免疫监测反应[38]。

三、pCR 患者远处转移的部位特点

NCRT 后实现 pCR 的 LARC 患者具有较好的预后，复发转移的比例一般低于 15%[9-11,14,16-19]。最终可纳入 pCR 患者预后分析的阳性事件数少，所以也少有研究针对 pCR 患者的术后复发转移部位和特点进行研究。

在没有接受新辅助治疗的结直肠癌患者中，肝脏是最常见和最先转移的部位[39]。而对于没有接受新辅助治疗的直肠癌来说，肺是最常见的转移部位[40-41]。有研究发现，直肠癌 NCRT 后患者的肺转移发生率甚至达到肝转移发生率的两倍，认为可能是 NCRT 改变了肿瘤细胞的生物学行为和肿瘤转移的好发部位，从而导致了肺转移发生率的上升[42]。NCRT 后直肠癌患者最常见的远处转移部位是肺已被诸多研究所证实，发生比例在 10%~25% 不等[43-49]。但是，因为基线特征不同，所以直接比较 NCRT 对直肠癌转移部位的影响，往往会导致错误的结果。因此，我们对接受 NCRT 和 PCRT 的直肠癌患者进行严格的倾向性评分匹配，以平衡两组患者的基线特征，结果发现，无论是接受 NCRT 还是 PCRT 的直肠癌患者，其最常见的转移部位都是肺，两组的肺转移率相当，其次是肝，这说明 NCRT 并没有改变肿瘤转移的好发部位，肺转移的高发与肿瘤的位置有关[50]。中低位直肠癌肿瘤细胞可通过髂血管直接进入体循环，所以更容易发生肺部转移[51-52]。接受 NCRT 的 pCR 患者多数为中低位直肠癌，受此影响，pCR 患者最常见转移部位是肺。

肝脏的转移发生率较低[50,52-53]。Fan 等[53]报道了 195 例 pCR 患者中 1.5%（3/195）的患者发生局部复发；远处转移患者包括肺转移 7 例（7/195，3.6%）、侧方淋巴结转移 3 例（3/195，1.5%），其他部位区域外淋巴结 3 例（3/195，1.5%，包括 2 例腹膜后淋巴结，1 例主动脉旁淋巴结），1 例肝转移（1/195，0.5%），同时有骨转移、脑转移各 1 例[52-53]。

我们总结本中心 108 例 pCR 患者发现，远处转移 11 例（10.2%），其中肺转移 3 例（2.8%），髂血管淋巴结 3 例（2.8%），腹膜后淋巴结转移 4 例（3.7%），肝转移 1 例（0.9%），其他部位包括脑转移、腹壁转移和输尿管转移和背部皮下转移各 1 例；在所有转移患者中，单发转移患者有 7 例，多发转移患者有 4 例[19]。所以，肺、侧方淋巴结和区域外淋巴结是相对常见的转移部位。因此，在定期复查中，要格外密切关注这些部位。

四、pCR 患者局部复发的特点

接受 NCRT 的直肠癌患者局部复发比例低[50,54]；pCR 患者的局部复发率更低，一般在 0~2.6% 之间[11,14,36,53,55]。甚至很多研究中没有出现局部复发事件[8-10,15,56-57]。Capirci 等[36]的研究纳入 556 例 pCR 患者，局部复发率为 1.2%（7/556），中位复发时间为 26 个月，且多数复发患者为男性（6/7）。Smith 等[55]的研究中 pCR 患者的局部复发率为 1%（1/100）。笔者既往的研究中，108 例 pCR 患者出现局部复发的也仅有 1 例[19]。

五、pCR 患者复发的时间特点

因为对于未接受新辅助治疗的直肠癌患者，大部分的术后局部复发和远处转移发生在术后两年内，所以目前的随访方案为术后两年内每 3 个月复查 1 次，术后 2~5 年内每半年复查 1 次，5 年后每年复查 1 次[1]。在 NCRT 广泛应用后，局部复发和远处转移的时间明显推迟。我们经过倾向评分匹配研究发现，NCRT 组与 PCRT 组的术后复发高峰时

间均是术后两年内，但NCRT组患者的复发时间较PCRT组患者复发时间明显延迟，中位远处转移时间分别为21.2个月与16.4个月，中位局部复发时间分别为29.2个月与18.7个月[50]。NCRT组患者术后两年内复发比例为51.9%（41/79），3~5年内占比为41.8%（33/79），5年后占比为6.4%（5/79）[50]。PCRT组的直肠癌患者，术后两年内的复发比例为66.2%（100/151），3~5年内的复发占比为29.8%（45/151），5年后占比仅为4.0%（6/151）[50]。肺转移通常发生在术后36个月内，所以术后前3年应对患者严密监测和密集随访，进行胸部、腹部和盆腔的CT扫描[47]。

笔者既往针对单中心的数据分析发现，108例pCR患者中有12例患者出现复发，术后两年内复发4例（4/12，33.3%），多数患者（8/12，66.7%）的复发时间在手术两年后，其中术后5年后复发的有3例（3/12）；12例患者中位复发时间为39.08个月[19]。可见，pCR的直肠癌患者发生局部复发与远处转移的时间明显推迟，所以应该考虑延长术后密切复查的时间由两年变为3年（每3个月复查1次），其后每半年复查1次至术后7~8年，然后再改为每年1次[58-59]。

六、影响pCR患者复发的临床病理因素

Fan等[53]报道，在195例获得pCR的LARC患者中，有10例患者在治疗前影像学评估认为存在可疑盆腔外淋巴结转移，其中3例（30%）在术后随访中出现盆腔外淋巴结复发，这说明患者盆腔外淋巴结可能并没有因为NCRT而得到完全缓解，而手术有可能遗漏了转移盆腔外淋巴结的切除。有研究发现，生存结果与治疗前的年龄和临床分期有关，术后辅助化疗的价值具有争议[36]。NCRT后术后病理残存肿块或瘢痕体现了原始肿瘤的负荷，具有预后价值[54,60]。我们研究发现，术后病理残存肿块或瘢痕最大直径以及治疗前肿瘤距肛缘距离是影响pCR患者术后复发的因素，当术后病理残存肿块或瘢痕最大直径≥2 cm、治疗前肿瘤距肛缘距离<4 cm时，pCR患者术后复发的比例升高，且该部分患者可能从术后化疗中获益[19]。

另外，中性粒细胞与淋巴细胞比率（neutrophil-to-lymphocyte ratio，NLR）被认为是LARC患者预后的独立危险因素，低NLR组与高NLR组的5年DFS分别为90.6%和71.3%（$P$=0.031）[61]。另有研究发现，高分子量糖蛋白（Mucin 1，MUC1）的高表达是pCR患者DMFS的独立预测因子[57]。

七、pCR患者术后治疗

Collette等[62]研究显示，给予pCR患者辅助化疗可显著提高其OS。荟萃分析表明，辅助化疗与pCR患者OS的改善有关[63]。也有回顾性研究发现，术后辅助化疗能改善pCR患者的5年OS[64]。所以NCCN指南建议对pCR患者进行术后辅助化疗[1]。但也有研究发现，pCR的患者不接受辅助化疗是安全的[65-67]。因此，辅助化疗的额外获益目前尚不确定[9]。我们的研究发现，pCR患者术后是否需要化疗不应一概而论，存在复发高危因素如术后病理残存肿块或瘢痕最大直径≥2 cm、治疗前肿瘤距肛缘距离<4 cm的患者，可能可以从术后规范化疗中获益[19]。

**总结** LARC患者pCR后复发比例低，局部复发少见，以远处转移为主。远处转移中最多见的转移部位是肺，其次是侧方淋巴结转移和其他部位的区域外的淋巴结转移。pCR患者的复发时间推迟，应该适当调整随访方案，延长随访时间。

**利益冲突** 所有作者均声明不存在利益冲突

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