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· 文献综述 ·

新辅助化疗方案在可切除结肠癌中的应用进展

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摘要

新辅助化疗(NACT)是指针对潜在可根治切除的肿瘤患者,以消除微转移、降低肿瘤分期和手术难度、改善术后局部复发和远处转移等为目的,在肿瘤手术切除或放疗之前,先予以全身化疗,待手术或放疗之后继续完成全程化疗的综合方案。结肠癌是最常见的癌症之一,肿瘤根治性切除联合术后辅助化疗是临床潜在可根治切除结肠癌的主要治疗方式。虽然这种治疗模式较前显著改善了患者的预后,但术后局部复发和远处转移仍是患者最主要的致死因素。近年来NACT方案开始被引入局部进展期结肠癌和原发灶可切除的肝转移患者等潜在可根治切除结肠癌患者的治疗。然而,结肠癌患者是否适合NACT及其方案的选择还存在较大的争议。笔者就局部进展期结肠癌、可切除结肠癌肝转移等在NACT中的进展与争议,以及影像学检查对NACT的作用作一综述。

关键词

结肠肿瘤; 肿瘤辅助疗法; 诊断显像; 综述

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Progress of application of neoadjuvant chemotherapy in resectable colon cancer

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Abstract

Neoadjuvant chemotherapy (NACT) refers to a comprehensive treatment plan for patients with potentially resectable tumors by performing systemic chemotherapy before tumor resection or radiotherapy, and then continuing to complete the whole course of chemotherapy after surgery or radiotherapy, with the aim of eliminating micrometastases, tumor downstaging and reducing surgical difficulty. Colon cancer is one of the most common cancers, and radical tumor resection combined with postoperative adjuvant chemotherapy is the main treatment for potentially curable colon cancer. Although this treatment mode has significantly improved the prognosis of patients, postoperative local recurrence and distant metastasis are still the main causes of death. In recent years, NACT has been introduced as a treatment option for potentially curable colon cancer patients such as those with locally advanced colon cancer or with liver metastases and resectable primary tumor. However, there is still a

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significant controversy regarding whether colon cancer patients are suitable for NACT and the choice of NACT regimens. Here, the authors address the progress and controversies of NACT in locally advanced colon cancer and resectable colon cancer liver metastasis, as well as the role of imaging examinations in NACT.

Key words

Colonic Neoplasms; Neoadjuvant Therapy; Diagnostic Imaging; Review

CLC number: R735.3

结直肠癌是世界上发病率和病死率最高的恶性肿瘤之一^[1]。在我国,结直肠癌同样是最常见的消化道恶性肿瘤,其中结肠癌约占40%,临床上结直肠外科医生最常面对的是可切除的结肠癌^[2]。在过去的几十年,根治性手术联合术后辅助化疗的综合治疗模式将可根治切除结肠癌患者的5年总体生存(overall survival, OS)率提高了约20%,然而术后局部复发和远处转移仍是其最主要的致死原因^[3-4]。研究^[5]表明尽管术后辅助化疗可提高II~III期结肠癌患者的无瘤生存(disease free survival, DFS)率,但其术后的5年复发率可能超过25%。因此,已有的辅助化疗策略的疗效并没有达到一个非常满意的水平,仍需不断优化。

新辅助化疗(neoadjuvant chemotherapy, NACT)概念是1982年由Frei首次提出的,是指针对潜在可根治切除的肿瘤患者,为降低肿瘤分期、降低手术难度或改善生存等目的,在肿瘤切除或放疗之前,先应用化疗药物予以全身化疗,待手术或放疗之后继续完成全程化疗的综合治疗方案。NACT最先应用于乳腺癌、胃癌和食管癌等恶性肿瘤中,并获得良好疗效^[6-9]。此后的研究也发现,对进展期直肠癌行新辅助放化疗后,常可获得满意的肿瘤降期,并可显著降低局部复发率、提高保肛率及改善术后的器官功能,甚至部分患者可以达到完全病理缓解^[10-11]。这些研究结果极大地启发了结肠癌治疗方案的改善,由此研究者开始探索NACT在不同分期结肠癌中的应用效果。

相比于传统的手术及术后化疗,NACT具有一定的理论优势:(1)术前缩小原发肿瘤,提高根治性手术的切除率;(2)减少术中肿瘤细胞种植播散,避免转移扩散;(3)有效消灭微小转移灶和亚临床病灶,降低术后转移风险及术后复发率。虽然NACT的优势已被证实,但仍存在以下潜在问题:(1)肿瘤早期进展,错过最佳手术窗口期;(2)治疗期间病灶出现梗阻、穿孔、出血等需急诊手术;

(3)肿瘤病理完全缓解导致切除范围不确定性;(4)化疗诱导的肝损伤有可能增加手术难度及术后并发症等;(5)如何选择恰当的病例开展NACT并进行疗效评估仍有一定困难。基于NACT在结肠癌治疗应用中的这些争议点,本综述探讨了NACT在局部晚期结肠癌、可切除结肠癌肝转移中的应用及进展以及影像学评估在NACT中的作用。

1 局部晚期结肠癌NACT的应用

局部晚期结肠癌定义为T3期且肿瘤浸润固有肌层深度 ≥ 5 mm或T4期的结肠癌^[12-13]。对局部晚期结肠癌患者进行NACT,理论上可以清除循环中微转移病灶和降低分期,达到提高根治性切除率和延长术后DFS时间及OS时间的目标。目前局部晚期结肠癌的标准治疗方案是根治性手术加术后以氟尿嘧啶类为基础的辅助化疗。然而术后辅助化疗对局部晚期结肠癌患者降低复发转移风险的作用相对有限,因此多项针对局部晚期结肠癌行NACT的II期和III期临床试验^[14-18]已展开,研究结果已初步证实NACT的可行性及有效性。如2012年FQxTROT试验^[14]招募了150例局部晚期结肠癌患者,以2:1的比例随机分为NACT组和对照组,NACT组治疗方案为:术前奥沙利铂+亚叶酸+氟尿嘧啶(OxMdG方案)3周期+手术+术后9个周期辅助化疗,对照组进行手术+术后12个周期的辅助化疗(OxMdG方案)。结果显示NACT组的R₀切除率更高,肿瘤缓解率更高,而围手术期并发症发生率和病死率无明显差别,提示NACT是安全有效的。2019年FQxTROT试验^[19]发布了部分结果,尽管结果显示NACT组的2年失败率(定义为复发或持续进展)与直接手术组(14% vs. 18%, $P=0.11$)无明显差异,但该研究证实了NACT并没有增加手术并发症,证实其安全可行,并能诱导肿瘤分期下降,降低不完全切除率。类似的,在

2015年PRODIGE 22试验^[12]中, 120例局部晚期结肠癌患者被随机分为NACT组和对照组。NACT术前接受4个周期的FOLFOX4, 术后继续接受8个周期的相同方案化疗, 而对照组接受手术加术后12个周期的FOLFOX4辅助化疗。与对照组相比, 尽管NACT组的3年OS时间、DFS时间、无复发生存期没有显示出统计学的优势, 但NACT组的并发症发生率与对照组相比没有显著差异, 而主要缓解率更高, 提示局部晚期结肠癌患者NACT安全可行^[20]。2021年一篇Meta分析^[21]比较了NACT后手术与直接手术治疗局部晚期结肠癌患者, 研究发现NACT在局部晚期结肠癌的治疗中是安全的, 其副作用可接受。目前的数据支持NACT提高肿瘤降期和使R₀切除率增加。随后, 2022年一项Meta分析^[22]纳入了8篇高质量的临床研究, 尽管该分析承认NACT治疗局部晚期结肠癌的可行性, 具有可接受的毒性和围手术期发生率。但该研究否认了NACT能给局部晚期结肠癌患者带来生存获益, NACT对局部晚期结肠癌的治疗仍需谨慎。

T4期肿瘤是局部晚期结肠癌中的代表类型, 越来越多的研究^[23-28]聚焦于T4期结肠癌NACT的疗效分析。目前研究认为NACT是一种有望改善T4期结肠癌肿瘤预后的治疗策略。2016年美国国立综合癌症网络指南(National Comprehensive Cancer Network, NCCN)将NACT作为T4b期结肠癌患者的治疗方案^[29]。我国一项回顾性研究^[24]分析40例接受NACT后手术治疗的cT4N+结肠癌患者, 发现NACT后手术对于cT4N+结肠癌患者是安全有效的。但该研究的样本量较少且为回顾性研究, 其研究结果还需进一步前瞻性随机对照研究验证。Dehal等^[23]对27 575例局部晚期非转移性结肠癌患者回顾性分析发现, 接受NACT的pT4b期结肠癌患者相比只接受辅助化疗的患者, 3年死亡风险降低23% ($P=0.04$)。倾向评分匹配后, T4b患者NACT组的3年OS率为74%, 而辅助化疗组的3年OS率为66%, NACT组的OS时间明显优于辅助化疗组($HR=0.7, P=0.0002$); 然而, 在T3期和T4a期分层研究中没有发现NACT组具有类似的生存优势。2021年一篇Meta分析^[27]比较T4期结肠癌直接手术治疗和NACT+手术治疗之间的肿瘤结局, 结果发现相比于直接手术治疗, NACT提高了切缘阴性切除率和OS率。因此, NACT在T4期结肠癌患者的疗效已被证实, 2021年NCCN指南^[30]推荐FOLFOX或

CAPEOX作为T4b期结肠癌NACT的治疗方案。

基于上述研究数据, 表明局部晚期结肠癌特别是T4期结肠癌中行NACT可带来肿瘤分期降低、病理缓解和切缘阴性等优势, 且不增加术后并发症的发生率, 证实NACT在局部晚期结肠癌治疗中具有安全性和可行性^[31-33]。然而, 目前已有研究均存在一定局限性, 例如病例选择偏差、样本数量过少、缺少对照组等。因此目前除T4b期结肠癌外, 尚没有临床指南将NACT应用在所有局部晚期结肠癌治疗中, 需要进一步大样本量、多中心和更多分层的前瞻性临床试验来提供更高级别的证据。

2 梗阻性结肠癌NACT的应用

接近20%的结直肠癌被诊断时发现合并肠梗阻, 其中70%的肠梗阻发生在左半结肠, 此类患者的生存率极低, 给临床治疗带来严峻的挑战^[34-35]。目前几项研究已经证实放置可扩张金属支架(self-expanding metallic stent, SEMS)治疗左半结肠癌梗阻患者的疗效。然而有研究表明置入支架后会造成肠壁水肿, 手术时间间隔较短会增加手术难度。因此有研究提出, 在将支架置入后和手术之间的时间间隔适当延长至9~10周, 并在此期间实施NACT, 利于患者肠道功能恢复同时也有助于改善患者的生存结局。

一项回顾性研究^[36]分析了11例接受SEMS后行NACT的梗阻性左半结肠癌患者, 该研究结果发现SEMS联合NACT后手术治疗梗阻性左半结肠癌是安全可行的, 且不增加术后发病率。该研究有一定的局限性, 需要大规模的临床随机对照实验进一步研究。2021年一项前瞻性研究^[37]对照分析了70例梗阻性左半结肠癌患者支架置入术+NACT+择期手术和支架置入术+择期手术, 该研究发现在支架置入和手术之间纳入适度的NACT, 药物的不良反应可控, 方案安全可行, 且具有缩短手术时间、减少术中出血量、降低造口率, 提高腔镜手术率等优势, 同时可降低患者肿瘤标志物和肿瘤活力指标水平的表达, 加速患者术后康复, 是一种可推广的新型治疗方案。2022年一项前瞻性、单臂、多中心试验^[38]使用mFOLFOX6 6个周期的NACT方案治疗梗阻性结肠癌, 证实了使用mFOLFOX6的NACT是可行的, 可能是梗阻性结肠癌患者的一种

治疗选择。但该结论仍需要进一步的大规模研究来证实。综上所述,大量的研究证实对梗阻性结肠癌患者放置支架后行NACT治疗是一种安全可行的方案,然而在临床实际应用中我们更应该根据患者特性谨慎NACT方案的应用,化疗周期的选择等,否则可能会增加化疗方案的不良反应导致患者更差的预后。

3 可切除结肠癌肝转移患者NACT的应用

转移是结肠癌患者死亡的主要原因,而高达20%~25%的结肠癌患者临床首诊时即伴有远处脏器转移,其中15%~25%的患者为同时性肝转移^[39-43]。手术是可切除结肠癌肝转移患者目前唯一可能治愈的治疗方法,切除后20%~50%的患者可达到5年生存期^[44-46]。对于可切除结肠癌肝转移患者,NACT能够治疗其微转移、评估化疗反应性和提高阴性切缘等优势^[47-48]。然而有研究^[49-52]显示对于可切除的肝转移患者,部分患者在NACT治疗过程中会发生疾病进展,导致NACT并没有显示出对OS时间的益处。因此,NACT治疗可切除结肠癌肝转移患者的有效性和安全性仍存在争议。

有史以来规模最大的一项针对可切除肝转移结肠癌患者的临床前瞻性III期随机对照试验—EORTC 40983研究^[53],共纳入364例分别接受NACT和单纯手术治疗的患者,结果显示:在实际完成切除的303例患者中,接受NACT患者的3年无进展生存(progression-free survival, PFS)率与单纯手术组相比增加了9.2% (42.4% vs. 33.2%, $P=0.025$)。然而,在后续长达8.5年的随访研究结果中却未能证实NACT对OS时间的影响^[54]。随后,NCCN指南以及CSCO结直肠癌诊疗指南^[29, 55]在内的多项结直肠癌诊疗指南均将NACT加入至可切除结肠癌肝转移患者的推荐治疗中,推荐奥沙利铂作为NACT首选基础方案(FOLFOX/CapeOX)。与直接手术相比,通过NACT可以达到更好的手术切除率,使患者更大程度的获益。一项纳入32项NACT联合手术治疗可切除结肠癌肝转移患者临床研究^[56]分析显示,NACT可以改善可切除的结肠癌肝转移患者的长期预后,NACT联合手术比单纯手术在DFS时间和PFS时间中更具优势,且NACT组并没有增加任何并发症的风险。一项国际多中心倾向评分匹配分析^[57],研究显示相比于仅接受NACT,围手术期策

略增加了患者的OS时间和无复发生存期。但是上述大多数研究并没有将结肠癌与直肠癌行NACT的结果分开讨论。尽管如此,在大多数研究中NACT组中结肠癌患者占比50%以上,因此研究的结果同样可以反映结肠癌肝转移患者NACT的益处。

也有研究结果并不完全支持NACT用于可切除结肠癌肝转移患者^[58-62]。一项多中心队列研究^[59],通过纳入1471例结直肠癌肝转移患者,发现接受NACT的患者发生术后并发症的风险明显增高,而且NACT并没有明显改善OS率和DFS率,此研究中接受NACT与不接受NACT的结肠癌患者比例分别为65.3%、64.2%。Reddy等^[60]也发现可切除同时性结肠癌肝转移患者行NACT组患者的OS时间更短。Lehmann等^[61]对已有研究进行了系统回顾,认为NACT对可切除结肠癌肝转移患者的DFS率以及OS率缺乏益处,因此不推荐常规使用NACT。2022年一项多中心倾向评分匹配队列研究^[62]NACT可切除结直肠癌肝转移患者中的价值,研究发现前期手术组患者的5、7、10年OS率明显优于NACT组(分别为64%、51%、44%和50%、31%、18%, $P=0.004$),相比于直接手术,NACT并没有改善患者的OS率。

NACT在结肠癌肝转移患者中并没有发现OS率获益,研究者开始思考其真实获益人群。研究^[63-64]根据临床风险评分(clinical risk score, CRS)中原发肿瘤淋巴结阳性、无病间隔时间<12个月、肝转移灶数量>1个、肿瘤最大直径>5 cm、癌胚抗原(carcino embryonic antigen, CEA)>200 ng/mL 5个风险因素将患者分为高复发风险组(3~5分)和低复发风险组(0~2分),发现NACT对低复发风险组的OS率没有明显影响,但可显著延长高复发风险组的OS率。这些发现促使越来越多的研究尝试对可切除结肠癌肝转移患者进行风险分层。Zhu等^[65]研究虽然也未能证实NACT联合手术可改善可切除的结直肠癌肝转移患者的OS时间,但发现原发肿瘤为T4期、肝转移灶个数>4,最大肝转移灶直径>5 cm以及血清CEA水平高于25 ng/mL是影响OS率的危险因素。我国最近一项针对初始可切除结肠癌肝转移患者是否使用NACT的Meta分析^[66]表明,初始可切除的结肠癌肝转移患者接受NACT的长期获益并不明显。可使用临床风险评分的策略对于高复发风险的结肠癌肝转移患者行NACT,可能延长患者OS时间。因此,或许应根据评估可切除结

肠癌肝转移患者的复发风险来决定是否需要NACT，对低危患者可选择直接手术治疗，但对于高复发风险患者应先进行NACT后再行手术治疗。正在进行的CHARISMA研究^[67]将高危患者（CRS为3~5分）随机分为单纯手术组和NACT组（基于奥沙利铂的6个周期NACT），两组患者均未进行术后辅助化疗，该研究的完成或可解释结肠癌肝转移高危患者采取NACT后手术治疗是否能改善OS时间这一问题。

目前研究发现对于可切除结肠癌肝转移患者使用NACT可带来PFS时间或DFS时间的优势，但OS时间似乎并不受益。这一差异很有可能是因为目前已有OS时间研究存在异质性所致，如入组患者的数量、化疗方案和手术技术的一致性以及复发情况下的后续治疗差异等。为降低这些异质性，未来我们需要对患者进行更精确的分层研究，以得到更准确的研究结论。鉴于此，有研究^[63, 68]推荐以CRS来指导是否选择NACT，CRS越高，术后复发风险越大，则NACT可能越能带来生存获益。2019年《CSCO结直肠癌诊疗指南》^[55]推荐对于CRS低危患者（0~2分），建议直接手术后行辅助化疗；而对于CRS高危患者（3~5分），则建议先行NACT后手术，再进行其他局部治疗或术后辅助化疗。ESMO共识^[69]也做出了类似推荐。以往的CRS系统包括无病间隔、肝转移的大小和数量、肿瘤和淋巴结的分期、CEA水平、肿瘤分级、切缘状况和年龄等，然而越来越多的研究发现，仅靠已有的CRS仍不足以达到精确分层^[68, 70-71]。未来的评分系统若结合遗传因素和基因检测，如RAS和BRAF突变状态以及肝外疾病等，将更有利于个体化的NACT治疗决策。因此，对于临床评分高复发风险的可切除结肠癌肝转移患者，应建立一个多学科治疗团队（MDT），根据患者特征（身体状态、合并症、年龄、既往辅助治疗等），肿瘤特征（肿瘤负担、转移部位、原发肿瘤部位等）以及分子特征（RAS/BRAF转态、微卫星不稳定、HER-2过表达等）等综合选择个体化的因素，决定是否应用NACT治疗方案。

4 不同解剖部位结肠癌NACT的探索

左、右半结肠癌在胚胎起源、解剖结构、生理功能以及分子生物学特征等方面存在明显差

异^[72-73]。如左半结肠癌与抑癌基因的失活和KRAS基因突变等相关；而右半结肠癌则与癌基因的激活、BRAF基因突变、CpG岛甲基化表型和MSI阳性表达等相关^[74]。生物特征差异性表达在一定程度上可以解释治疗效果的差异，因此需要根据不同肿瘤部位的分子生物学差异，从而选择更恰当的治疗方式。多数研究^[75-76]表明，在辅助化疗或靶向治疗中，左侧结肠癌的预后明显优于右侧。Benedix等^[75]研究报道发现，尽管左半结肠癌中远处转移更常见，但在调整肿瘤分期后，其OS率明显优于右半结肠癌。由于右半结肠多表现为基因突变型，治疗时多用化疗联合贝伐单抗，而非抗EGFR靶向药，如西妥昔单抗等；而左半结肠癌基因常表现为野生型，推荐化疗联合西妥昔单抗或贝伐单抗^[76]。但是右半结肠癌错配修复基因突变（高微卫星不稳定）常见，对免疫治疗具有更好的应答。然而关于左右半结肠癌的NACT方案差异目前还没有临床研究，或许可以借鉴术后辅助化疗方案，对不同肿瘤部位结肠癌NACT的效果及方案开展相应的临床实验。

5 影像学检查对NACT决策和疗效评估的影响

结肠癌患者能否恰当使用NACT的一个关键因素是治疗前对患者肿瘤进行准确的临床分期，“过度分期”可能导致患者被过度治疗，而“低估分期”可能让患者失去NACT的机会^[16, 77-78]。因此精确的治疗前肿瘤临床分期是正确施行NACT的重要前提，而影像学检查是术前评估肿瘤分期最重要的检测方法。腹部增强CT是目前结肠癌中应用最广泛的影像学分期工具，但其用于预测是否适合NACT的准确性还存在争议。早期利用CT进行局部晚期结肠癌分期的研究发现，CT对结肠癌T分期和N分期的预测准确率分别仅为60%和62%^[79]。FOXTR0T研究^[14]也显示CT对判断T分期的准确性仅为47%，N分期为44%。复旦大学一项尚未发表的针对术前CT诊断cT4期结肠癌的初步结果研究发现，49%的术前CT诊断为cT4期的患者术后病理诊断为pT3期^[80]。同样，Dam等^[81]观察25例术前CT诊断为cT4期的患者，仅有9例（36%）术后病理诊断为pT4期，而14例（56%）术后病理诊断为pT3期。相反地，有研究^[82]显示高达35%的术后

pN+的病例被术前影像学评估为淋巴结阴性。磁共振成像(MRI)是目前直肠癌术前分期的标准检查手段之一,也被用来作为结肠癌术前T分期和N分期的一种新兴工具^[31, 83]。多项研究比较了MRI和CT对局部晚期结肠癌的诊断性能,一致认为MRI在确定有浆膜受累的T3/4期肿瘤方面优于CT^[84-87],且T3/4期肿瘤假阳性分类率较低^[88-89]。MRI在将来可能成为评估局部晚期结肠癌患者临床分期的标准检测方式。目前常用的影像学评估往往对结肠癌术前T分期明显高估,而淋巴结阳性率往往在术前影像学诊断中被低估。因此,NACT治疗前T分期以及N分期不准确的问题亟需解决。MDT被认为是提高术前肿瘤分期评估准确率的重要手段,但开发敏感度和特异度更高的新型诊断方法或策略将更为重要。

6 总结与展望

NACT逐渐成为局部晚期结肠癌患者的重要治疗措施。近年来多项研究证实了NACT治疗的安全性,采用NACT可能对高风险的T4b期患者带来生存获益,NACT也为转移性结肠癌肝转移患者带来了DFS时间获益。但目前NACT的应用仍具备较多的局限性:包括化疗药物的潜在脏器功能损害、传统影像学技术分期的不准确性以及缺乏前瞻性大样本的临床试验数据提供更高级别的生存获益证据。尽管如此,NACT仍是结肠癌治疗中一种不断发展的新的治疗模式。近几年不断有研究报告免疫治疗药物如PD-1/PD-L1抑制剂在结肠癌治疗中取得了满意的临床疗效,甚至有的研究中报道临床缓解率达到100%。因此,随着结肠癌分子靶向药物和免疫制剂等的不断发展,在MDT的基础上,NACT与免疫治疗、靶向治疗等合理结合,将使结肠癌的治疗走向更加精准和个性化的时代,以提供更优的生活质量和更显著的长期生存获益。

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作者贡献声明:肖帅负责论文的选题、整体框架设计及修订;吴晓凤负责论文的资料收集、撰写、修改;许云华、付广协助指导论文撰写、修改;黄秋林协助指导论文选题,修订。

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