

结直肠癌腹膜转移的诊治进展与挑战

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【摘要】 结直肠癌腹膜转移(peritoneal metastasis of colorectal cancer, PM-CRC)是结直肠癌远处转移中预后最差的亚型。近年来, 影像学、人工智能及成纤维细胞活化蛋白抑制剂(fibroblast activation protein inhibitor, FAPI)-正电子发射计算机断层显像(positron emission tomography-computed tomography, PET/CT)等新技术显著提升了隐匿病灶的检出率, 但其敏感性与特异性仍需提高。腹膜癌指数(peritoneal cancer index, PCI)作为肿瘤细胞减灭术(cytoreductive surgery, CRS)决策的核心量化工具, 因未对解剖区域加权而限制了其精准度。CRS联合腹腔热灌注化疗(hyperthermic intraperitoneal chemotherapy, HIPEC)是实现局部控制的标准组合, 关键在于通过精准分层筛选真正获益人群。此外, 加压腹腔气溶胶化疗和微小残留病变动态监测正在为个体化治疗和复发预警提供新手段。本文系统梳理了PM-CRC诊断评估、手术及局部治疗的最新证据, 剖析现存挑战, 旨在为临床科学决策与综合管理提供参考。

【关键词】 结直肠癌; 腹膜转移; 细胞减灭术; 腹腔热灌注化疗; 精准治疗

Advances and challenges in the management of peritoneal metastases from colorectal cancer

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【Abstract】 Peritoneal metastasis of colorectal cancer (PM-CRC) is the most aggressive and prognostically unfavorable form of distant dissemination in colorectal cancer. Recent advances in imaging, molecular diagnostics, systemic therapies and surgeries have improved early detection and stratified management of PM-CRC. Emerging modalities such as artificial intelligence, radiomics, and fibroblast activation protein inhibitor (FAPI)-positron emission tomography-computed tomography (PET/CT) outperform conventional CT in identifying peritoneal metastases, though further refinement in sensitivity and specificity is needed. The peritoneal cancer index (PCI) remains central to cytoreductive surgery (CRS) planning, yet its lack of regional weighting limits its application. CRS combined with hyperthermic intraperitoneal chemotherapy (HIPEC) is pivotal for locoregional control, with accurate patient selection being key to survival benefit. Novel techniques including pressurized intraperitoneal aerosol chemotherapy (PIPAC) and minimal residual disease (MRD) monitoring are paving the way for individualized therapy and early recurrence detection. This review summarizes recent advances in diagnosis and treatment of PM-CRC and discusses current challenges to guide evidence-based and personalized management strategies.

【Key words】 Colorectal cancer; Peritoneal metastasis; Cytoreductive surgery; Hyperthermic intraperitoneal chemotherapy; Precision therapy

结直肠癌(colorectal cancer, CRC)是消化道最常见的恶性肿瘤之一, 在中国人群中, 其发病率位

居第二, 死亡率位居第四^[1-2]。尽管早筛策略与综合治疗已显著改善整体预后, 结直肠癌腹膜转移(peritoneal metastasis of colorectal cancer, PM-CRC)仍是远处转移中预后最差的一种: 4%~10%的

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CRC 患者会出现腹膜受累,其中 2%~5%在初诊时即存在腹膜转移,而在复发或晚期患者中这一比例更攀升至 10%~25%^[3-4]。PM-CRC 缺乏特异症状,多因影像随访异常或肿瘤标志物“静默”升高而被发现,部分患者以腹水、腹胀或癌性肠梗阻为首发症状。

随着化学治疗(简称化疗)、分子靶向药物治疗及免疫治疗在转移性 CRC 中持续突破,“有效全身治疗联合以无疾病状态(no evidence of disease, NED)为目标的局部治疗”已成为改善晚期 CRC 整体预后的核心策略。据文献报道,PM-CRC 单纯药物治疗方案的中位总生存(overall survival, OS)期约 12 个月;经严格筛选并行细胞减灭术(cytoreductive surgery, CRS) + 腹腔热灌注化疗(hyperthermic intraperitoneal chemotherapy, HIPEC)者,中位 OS 期可跃升至 41 个月^[5]。2025 年中山大学肿瘤防治中心结直肠癌患者生存年鉴显示,2010—2021 年接受腹膜肿瘤减灭术的 CRC 患者,中位 OS 期达 29.8 个月,1、3、5 年 OS 率分别为 77.4%、44.8%、31.5%,再次验证了积极手术治疗的價值。本文围绕当前 PM-CRC 诊断与治疗中的新进展以及面临的挑战,对其诊治路径进行系统梳理,旨在助力临床精准决策,最大化患者获益。

1 腹膜转移诊断的挑战

1.1 影像学检查的局限性与革新

增强计算机断层扫描(computed tomography, CT)是 CRC 术后随访的标准影像手段,但对腹膜转移的敏感度有限;病灶直径<5 mm、位于肠系膜皱褶或合并腹水时,敏感度降至 50%以下^[6]。而盆腔磁共振成像(magnetic resonance imaging, MRI)并非常规项目,但当患者出现盆腔症状,或 CT 提示盆底可疑病灶时,高分辨率 T2WI 联合弥散加权成像(diffusion weighted imaging, DWI)可清晰显示直肠系膜筋膜、骶前及阴道后壁受累情况,能为是否需要盆腔脏器联合切除提供决策依据^[7]。

对于临床高度怀疑而影像阴性的隐匿性腹膜转移,建议行 ¹⁸F-氟代脱氧葡萄糖(¹⁸F-fluorodeoxyglucose, ¹⁸F-FDG)正电子发射计算机断层显像(positron emission tomography-computed tomography, PET/CT),以检测腹膜内高代谢结节并同步排除腹外转移。值得注意的是,道格拉斯陷窝是直立位腹膜腔最低点,最易早期受累,因此中国临床

肿瘤学会(Chinese Society of Clinical Oncology, CSCO)2025 版的结直肠癌诊疗指南将直肠指检列为直肠癌初诊及术后随访的常规项目,女性患者应同步行经阴道指检,以提高早期种植结节的检出率^[8]。

近年围绕腹膜转移的影像学评估迅速发展,既包括分子示踪剂的更新(提升肿瘤示踪的靶向性),也包括以人工智能为核心的图像信息挖掘。这些新兴技术与传统 CT/MRI 及 FDG-PET 互补,进一步提高了微小与隐匿病灶的检出率。当中的代表性进展如下。①成纤维细胞活化蛋白抑制剂(fibroblast activation protein inhibitor, FAPI)-PET/CT:以 ⁶⁸Ga-/¹⁸F-FAPI 为示踪剂,靶向肿瘤相关成纤维细胞活化蛋白(fibroblast activation protein, FAP),可弥补 FDG 在低代谢病灶中摄取不足的缺陷。多项对比研究显示,FAPI-PET/CT 对腹膜转移的总体检出率高于 FDG-PET,例如一项纳入 14 项研究共 527 例腹膜转移肿瘤的荟萃分析显示,FAPI 较 FDG 对腹膜转移肿瘤的总体诊断效能更优,合并敏感度为 0.84 比 0.46,特异度为 0.91 比 0.88,曲线下面积(area under the curve, AUC)为 0.92 比 0.52^[9]。在分区腹膜癌指数(peritoneal cancer index, PCI)评估中,FAPI 显像剂在右上腹、中上腹、左下腹及小肠系膜区的敏感度较 FDG 提升显著,其总体预测准确性约 80%;然而,小肠系膜区的敏感度仍仅为 47.6%,因此,准确的 PCI 仍需结合腹腔镜或开腹探查确认^[10-12]。②人工智能、深度学习与影像组学:利用含原发灶信息、临床特征、内脏脂肪参数等的影像学资料构建模型,可提升隐匿性微小腹膜转移病灶的检出率。此外,深度学习模型还可用于识别 CRS+HIPEC 的潜在获益人群,从而避免无效的探查手术。中国腹膜肿瘤协作组基于 186 例围手术期 PM-CRC 患者,构建了解耦特征对齐与融合(decoupled feature alignment and fusion, DeAF)深度学习模型,用于预测 CRS 可以达到的彻底性,协助术者进行决策^[13]。该模型内部验证队列预测 CRS 结局的 AUC 达 0.90(95%CI 0.793~1.000),在 3 个外部队列中 AUC 均超过 0.90,在指导 CRS 决策中显示出良好的预测性能与潜在的临床应用价值。

1.2 PCI 评分的局限与困境

PCI 仍是目前 PM-CRC 治疗决策中唯一获得广泛认可的肿瘤负荷量化工具^[14-15]。然而,随着临

床证据的积累,其固有缺陷日益凸显:①解剖覆盖不全。卵巢及大网膜是CRC腹膜种植的高发部位,却未被纳入13区PCI评分系统,导致这些区域的肿瘤负荷被系统性忽略。②区域权重无差别。现有PCI对各腹膜分区赋予同等分值,但多项研究已证实不同区域受累对CRS可切除性及长期预后的影响存在显著差异。其中,小肠系膜受累被反复验证为PM-CRC的独立不良预后因素,也是导致完全减灭[细胞减灭程度(completeness of cytoreduction, CC)-0]失败的最主要原因之一。因此,部分中心已将“小肠系膜PCI(small bowel PCI, sb-PCI)”单独列出,作为筛选CRS-HIPEC适应证的否决性参数^[16-18]。③影像与手术PCI一致性差。影像学PCI评估目前缺乏标准操作流程和报告规范。一项前瞻性研究显示,术前影像估算的PCI与术中实测一致率仅63.2%,32.0%病例的PCI被影像低估^[19]。因此,诊断性腹腔镜或剖腹探查仍是获取可靠PCI的金标准^[20-21]。综上,未来PM-CRC的个体化评估需从“总分”模式转向“功能-加权评分”模式;在量化肿瘤负荷的同时,引入区域权重系数,并建立影像-手术联合的标准化评估路径,方可更精准地指导治疗决策。

2 治疗挑战

2.1 PCI与CRS获益的相关性

多项回顾性及前瞻性研究一致证实,PCI是预测CRS-HIPEC生存获益的独立量化指标。当PCI<20分时,满意的减灭手术(CC-0/1)可显著延长中位OS期;反之,PCI≥20分者即使达成CC-0/1,生存获益仍极为有限,中位OS期延长通常不足3个月^[5, 22-24]。目前在前瞻性试验中,BEV-IP与PRODIGE 7研究将CRS的PCI上限设为25分^[5, 25],而CAIRO6和GECOP-MMC研究则设定为20分^[26-27],为临床决策提供了明确参考。

然而,PCI仅计算肿瘤负荷,未对不同解剖区域的手术难度和风险进行加权,导致相同分值下的实际获益存在显著差异:中腹部及大网膜病灶多可通过标准腹膜剥脱、网膜切除完成减灭;膈顶、肝十二指肠韧带、小肠系膜根部等部位因解剖复杂、血管密集,常需联合多脏器切除,手术难度与并发症风险显著增加;盆底病灶若侵犯直肠前壁或阴道后壁,需额外行低位前切除甚至盆腔脏器联合切除;小肠系膜广泛受累时,需谨慎评估因

切除范围过大而导致的短肠综合征。因此,对所有影像学评估为“潜在可切除”的患者,应常规行诊断性腹腔镜探查,必要时中转开腹,以获取真实PCI及受累部位,并重新评估满意减瘤的可行性,避免过度治疗。

2.2 关键部位的技术挑战与器官保护

CRS的可切除性与安全性取决于腹膜剥离范围及解剖复杂度。PM-CRC好发于膈顶、大网膜、小肠系膜、盆底及原手术瘢痕,各区域操作要点与并发症风险如下。①膈顶:需切断肝圆韧带,联合自动牵开器将肝脏向尾侧翻转,充分暴露并完整剥离膈肌腹膜。术中一旦损伤膈肌,必须以缝线行气密缝合,术后严密监测呼吸功能,警惕胸腔积液、肺不张或感染。②小肠:小肠受累范围直接决定CRS的可行性与术后生活质量。若小肠病灶无法清除,即使其他区域达CC-0/1减灭,仍可因术后肠梗阻或营养衰竭而丧失长期获益。因此,对小肠受累者需在彻底减灭与功能保全间进行权衡,术中应至少保留1.5~2.5 m空肠,防止短肠综合征^[28]。③盆底:单纯结节剔除易遗漏隐匿病灶。中山大学肿瘤防治中心的回顾性研究显示,与接受选择性盆腔腹膜剔除相比,接受盆底腹膜次全剥除的局限性盆底腹膜转移患者的3年无病生存(disease-free survival, DFS)率(65.9%比30.7%, $P<0.01$)及3年OS率(84.1%比68.5%, $P<0.01$)均提高^[29]。④卵巢:PM-CRC合并卵巢转移的发生率为34.3%~37.5%^[30]。Basingstoke系列报道显示,接受CRS-HIPEC的女性患者中,一侧卵巢肉眼可见受累时对侧镜下阳性率为45%;双侧肉眼观察为正常者镜下仍有17%阳性^[31]。因此,建议绝经后或无生育需求的女性患者常规行双侧附件预防性切除。

2.3 肿瘤生物学行为对治疗决策的影响

肿瘤在系统治疗过程中的动态生物学行为是决定是否施行CRS的另一核心要素。对于携带明确不良分子特征(如BRAF V600E突变)的患者,CRS往往难以带来长期生存获益,患者反而可能因围手术期肿瘤快速进展而缩短生存时间^[30-31]。因此,对此类PM-CRC病例,应下调可切除性阈值;PCI上限宜降至<10分,且须满足“经充分系统治疗后病灶稳定、全身负荷有限”的前提,经多学科团队严格评估后,方可考虑CRS。

2.4 HIPEC的优化与新技术

HIPEC是PM-CRC局部治疗的标准组成之

一,其应用场景与疗效证据可归纳为两类:①高危腹膜转移患者的辅助预防。COLOPEC的5年随访结果显示,T₄期或穿孔性结肠癌术后加用奥沙利铂 HIPEC 未降低18个月腹膜转移率,也未改善5年DFS/OS^[32];HIPECT4则证实,临床T₄期患者术中接受丝裂霉素C(mitomycin C, MMC)HIPEC可显著降低患者3年腹膜转移发生率(97.6%比87.6%, HR≈0.21),虽仍无DFS/OS获益,但MMC方案可作为辅助预防的可选策略^[33]。②满意CRS后的巩固治疗。PRODIGE 7研究的整体结果虽为阴性,但PCI 7~15分亚组可见OS获益,提示在中度肿瘤负荷,且能取得CC-0/1减灭的患者中,HIPEC仍可能延长疾病控制时间;疗效关键在于患者的实际PCI、CRS减灭程度及全身治疗的有效性^[5]。

此外,HIPEC的实施参数仍缺乏共识。其中,灌注温度相对明确,通常维持在(43±1)℃,可在最大化细胞毒效应的同时避免组织热损伤。灌注时间则差异显著,文献报道范围为30~90 min,且需结合药物剂量进行权衡;PRODIGE 7采用高剂量奥沙利铂(460 mg/m²)灌注30 min;CAIRO6则予MMC(35 mg/m²)灌注90 min^[5]。由于缺乏头对头临床试验,关于药物选择的争议最大。奥沙利铂与MMC仍为最常用的细胞毒性药物,雷替曲塞、洛铂等亦在探索阶段^[34-35]。未来应通过高质量的前瞻性研究,明确不同药物及剂量-时间组合的疗效与安全性,为HIPEC的个体化决策提供循证依据。

针对无法切除的PM-CRC,加压腹腔气溶胶化疗(pressurized intraperitoneal aerosol chemotherapy, PIPAC)成为新的探索方向。CRC-PIPAC II期单臂研究(*n*=20,奥沙利铂每6周1次)显示影像学缓解率为0,生化缓解率为50%,病理缓解率为56%,中位无进展生存(progression-free survival, PFS)期为3.5个月,中位OS期为8.0个月,毒性可控^[36];同一团队后续研究将PIPAC与一线系统治疗交替,中位PFS期升至10.0个月,中位OS期升至17.5个月,提示联合全身化疗策略可能进一步改善预后^[37]。未来,PIPAC还需要更多高质量循证医学证据来验证其治疗价值及应用规范。

3 新技术与未来展望

3.1 个体化治疗探索

多线耐药是PM-CRC治疗失败的首要原因。近期研究利用患者来源类器官体外药敏平台,对

缺乏循证依据的方案进行个体化筛选,为后续用药提供实验室级别证据^[38-39]。同时,靶向实体瘤的免疫细胞治疗,包括T细胞受体工程化T细胞(T cell receptor-engineered T cells, TCR-T)疗法与肿瘤浸润淋巴细胞(tumor-infiltrating lymphocyte, TIL)治疗等,已启动I/II期临床试验,旨在突破PM-CRC的免疫抑制微环境,拓展后线治疗选择^[40-41]。

3.2 腹膜转移的监测与随访

除常规影像及肿瘤标志物外,微小残留病变(minimal residual disease, MRD)检测正逐步用于PM-CRC的全程管理。以循环肿瘤DNA(circulating tumor DNA, ctDNA)为代表的MRD检测技术在消化道肿瘤诊治中日渐成熟^[42],基于肿瘤全外显子测序定制的个体化ctDNA动态检测可用于高危患者术后或在全身治疗联合局部治疗达到NED后的随访监测,辅助早期发现隐匿性腹膜转移并预测PFS期^[43-46]。但腹膜转移背景下的MRD阳性阈值、取样时间点及干预策略仍待前瞻性研究验证。

综上,PM-CRC的诊治范式正由“经验主导”转向“证据-分层”并重。诊断层面,PCI仍是唯一可量化的肿瘤负荷指标,但影像PCI的系统性低估及关键部位(小肠系膜、膈顶、盆底)信息缺失决定了“影像初评-腹腔镜/剖腹确诊”的组合仍是筛选可切除病例的关键;人工智能影像组学与FAPI-PET/CT可作为术前评估的增益工具,提高隐匿病灶的检出率。治疗层面,“有效全身治疗联合以NED为目标的局部治疗”是改善转移性CRC疗效的核心原则,同样适用于PM-CRC;满意的CRS、HIPEC及后续全身化疗构成多学科治疗的最佳组合。鉴于PM-CRC总体预后仍较差,临床决策须整合患者对生存获益、器官功能保全及生活质量的意愿,避免过度治疗。未来,更精准的围手术期预测模型、更有效的局部治疗手段、更个体化的分层治疗策略将会是PM-CRC诊治的发展目标与方向。

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