

吲哚菁绿辅助微创手术在直肠癌侧方淋巴结转移治疗中的疗效与预后影响：系统评价与分析

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摘要: 聚焦直肠癌侧方淋巴结转移, 评估其诊断方法与治疗策略, 着重吲哚菁绿 (Indocyanine green, ICG) 辅助侧方淋巴结清扫 (Lateral Lymph Node Dissection, LLND) 的应用效果, 同时探讨淋巴结转移 (Metastatic Lymph Node, MLN) 与癌结节 (Tumor Deposits, TD) 的病理交互作用。方法: 通过文献回顾与综合分析, 评估高分辨率MRI、光谱CT及ICG荧光显影技术的诊断效能, 比较新辅助放化疗 (Neoadjuvant Chemoradiotherapy, NCRT)、LLND及ICG辅助LLND等治疗手段的疗效与安全性。结果: ICG在前哨淋巴结 (Sentinel Lymph Nodes, SNs) 检测中灵敏度及阴性预测值高, 辅助LLND可显著提高淋巴结检出率, 减少术后并发症, 优化手术效果, 尤其在预防吻合口瘘方面优势显著。TD作为直肠癌的重要病理特征, 与区域淋巴结转移密切相关, 提示肿瘤侵袭性高, 需更广泛的手术切除和更积极的术前放化疗。结论: ICG辅助LLND在直肠癌侧方淋巴结转移治疗中前景广阔, 但仍需严谨临床试验验证其长期疗效与安全性, 确保患者得到最佳治疗方案。

关键词: 吲哚菁绿, 全直肠系膜切除术, 辅助侧方淋巴结清扫, 新辅助放化疗, 侧方淋巴结, 直肠癌

Effect and prognosis of indocyanine green assisted minimally invasive surgery in the treatment of lateral lymph node metastases in rectal cancer: a systematic review and analysis

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Abstract: Objective: Focusing on lateral lymph node metastases of rectal cancer, evaluating diagnostic methods and treatment strategies, focusing on the application effect of Indoline green (ICG) as an aid to lateral lymph node dissection (LLND), and exploring the pathological interactions between lymph node metastases (MLN) and Tumor Deposits (TD).Methods: Through literature review and comprehensive analysis, the diagnostic efficacy of high-resolution MRI, spectral CT and ICG fluorescence imaging was evaluated, and the efficacy and safety of neoadjuvant chemoradiotherapy (NCRT), LLND and ICG-assisted LLND were compared. Results: ICG has high sensitivity and negative predictive value in sentinel lymph nodes (SNs) detection, and assisting LLND can significantly improve the lymph node detection rate, reduce postoperative complications, and optimize the surgical effect, especially in the prevention of anastomotic fistula. As an important pathological feature of rectal cancer, TD are closely related to regional lymph node metastasis, suggesting that the tumor is highly aggressive and requires more extensive surgical resection and more aggressive preoperative chemoradiotherapy. Conclusion: ICG-assisted LLND has broad prospects in the treatment of lateral lymph node metastasis of rectal cancer, but rigorous clinical trials are still needed to verify its long-term efficacy and safety to ensure that patients get the best treatment plan.

Keywords: ICG; TME; LLND; NRCT; Lateral lymph nodes; Rectal cancer

1. 引言

直肠癌作为我国常见恶性肿瘤, 其发病率逐年攀升⁽¹⁾。西方国家常用新辅助放化疗 (Neoadjuvant Chemoradiotherapy, NCRT) 缩小肿瘤、提高R0切除率和保肛率, 但并发症风险与局部复发率仍较高⁽²⁾。鉴于此, 亚洲尤其是日本学者倡导: 对特定分期的低位直肠

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癌实施预防性辅助侧方淋巴结清扫 (Lateral Lymph Node Dissection, LLND) 进一步提升疗效⁽³⁾。然而, 侧方淋巴结区域解剖复杂, 手术操作空间有限, 存在技术挑战和并发症风险⁽⁴⁾。因此, 迫切需要探索新的治疗策略以提高疗效。吲哚菁绿 (Indocyanine green, ICG) 荧光导航技术在直肠癌侧方淋巴结转移治疗中优势显著, 可提高淋巴结检出率, 减少血管损伤及术后并发症, 优化手术效果并缩短手术时间⁽⁵⁾。

直肠癌侧方淋巴结清扫, 中国和日本的研究重点与临床应用存在显著差异。中国聚焦直肠癌LLND控制局部复发的有效性, 但发现对系统性转移控制作用有限; 认为术前放化疗联合LLND可提高患者的生存率和无复发生存率, 但需谨慎选患者以防并发症^(6,7)。相比之下, 日本关注侧方淋巴结转移患者预后, 虽发现这类患者总体预后差, 但在特定群体中实施LLND可提高生存率⁽⁸⁾。ICG辅助微创手术的临床应用, 日本学者在直肠癌的治疗中广泛应用, 尤其擅长淋巴结清扫和血管成像, 注重精细操作, 手术时间长但并发症少⁽⁹⁾。而中国, ICG技术在直肠癌手术中逐渐推广, 专家通过共识和研究推动规范化应用, 但成熟度仍低于日本⁽¹⁰⁾。

2. 直肠癌侧方淋巴结转移的诊断: 技术与方法的改进

淋巴结转移 (Metastatic Lymph Node, MLN) 是直肠癌的重要转移方式, 癌结节 (Tumor Deposits, TD) 是直肠癌淋巴引流区域内的一种特殊病理特征⁽¹¹⁾。无论有无区域淋巴结转移, TD均影响N分期 (N0→N1c) 及预后, 并与病理性壁外静脉浸润 (Extramural Vascular Invasion, EMVI) 相关⁽¹²⁾。影像学检查是评估TD和淋巴结状态的重要手段, 可明确肿瘤分期、TD特征及淋巴结转移情况⁽¹³⁾。

2.1. 传统影像学方法在直肠癌侧方淋巴结转移中的诊断

内镜超声 (Endoscopic Ultrasound, EUS) 能清晰显示直肠壁层次, 对T分期准确性高, 但在评估侧方淋巴结 (尤其是盆腔深部淋巴结) 时受限, 其N分期灵敏度和特异性仅为0.95和0.78⁽¹⁴⁾。普通CT通过测量淋巴结大小 (短径≥5mm) 初步判断转移风险, 但易假阳性, 且对深部侧方淋巴结评估不足⁽¹⁵⁾。PET-CT能提供全身代谢信息, 但空间分辨率低, 对小淋巴结检测能力有限, 且假阳性率较高⁽¹¹⁾。

2.2. 高分辨率MRI

在直肠癌诊断中, 高分辨率MRI虽是评估淋巴结转移的关键工具, 但其N分期的敏感性和特异性仅分别为58–77%和62–74%, 存在局限性⁽¹¹⁾。EMVI是重要预后因素, 出现在约1/3的直肠癌患者中, 与远处复发和预后不良密切相关^(16,17)。将淋巴结短径阈值 (Lateral Lymph Node, LLN) 设为5mm时, MRI的阳性预测值和阳性似然比最高, 且MRI-EMVI阳性时行短期术前放疗可减少复发⁽¹⁶⁾。因此, 结合MRI-EMVI检查可提高淋巴结阳性检测的准确性, 并预防侧方淋巴结复发。

此外, MRI通过高分辨率T2WI和CET1WI能精准识

别直肠癌中的TD和MRI检测到的MLN, MRI检测到的TD (MRI-detected TDs, mTDs) 与术后病理证实的TD (pathology-proven TDs, pTDs) 高度一致, 且与远处转移 (postoperative distant metastasis, PDM) 和淋巴结转移 (pathology-proven lymph node involvement, pLN) 密切相关⁽¹⁸⁾。多变量分析显示, mTDs和腹膜反折侵犯是PDM的独立风险因素, 而mTDs和mLN是pLN的独立风险因素⁽¹⁸⁾。基于这些因素构建的列线图在预测PDM和pLN方面表现出色, C指数分别为0.837和0.817⁽¹⁸⁾。因此, 准确区分TD和MLN对制定治疗方案至关重要, TD的存在提示肿瘤侵袭性高, 可能需更广泛的手术切除和更积极的术前放化疗⁽¹⁹⁾。

2.3. 光谱CT

光谱CT利用双层探测器技术, 可在淋巴结形态改变前检测肿瘤细胞早期浸润, 并通过碘含量 (Iodine Content, IC) 参数反映肿瘤血管生成和血流情况⁽²⁰⁾。研究显示, 光谱CT凭借双层探测器及定量参数分析, 可精准识别结肠癌外转移和转移性淋巴结, 具有较高的准确率和优越的诊断性能⁽²¹⁾。IC定量参数可有效区分结直肠癌区域淋巴结的性质, 多参数联合分析构建的回归模型展现出高效的鉴别诊断能力, 为结直肠癌淋巴结定性诊断提供了新方法。

2.4. ICG荧光显影技术

ICG在SNs检测中灵敏度为91.3%, 且阴性预测值达100%, 结合全直肠系膜切除术 (Total Mesorectal Excision, TME) +LLND可进一步提升治疗效果⁽⁵⁾。然而, 出现假阳性淋巴结可能与注射位置不当、剂量不足或肿瘤阻塞淋巴管有关⁽²²⁾。但多部位注射ICG可显著提高前哨淋巴结示踪成功率 (从不足40%提升至75%)⁽²³⁾。因此, ICG辅助LLND在直肠癌侧方淋巴结远处转移的治疗中更安全有效, 但掌握ICG显影技术需要长时间训练。

3. 直肠癌侧方淋巴结转移的治疗策略

3.1. NCRT

在欧美, NCRT已被广泛认可为一种有效控制直肠癌侧方淋巴结转移的治疗手段, 可减少手术时间和术后并发症, 但对于高危患者 (如LLN短轴直径≥7mm), NCRT联合TME不足以预防侧方淋巴结复发 (Lateral Lymph Node Recurrence, LLR)^(3,24)。研究显示, LLN≥7mm的患者LLR率可达19.5%, 而实施LLND可将其降至5.7%⁽²⁵⁾。国际直肠癌侧方淋巴结协助小组建议, NCRT前LLN短径≥7mm作为转移判断标准, NCRT后闭孔淋巴结短径>6mm、髂内淋巴结短径>4mm作为残留阳性淋巴结标准, 退缩不佳者需考虑LLND⁽³⁾。此外, 有文献提出, NCRT+TME+LLND的治疗效果相对较好, 术后侧方淋巴结转移的发生率显著低于NCRT+TME治疗的患者, 而通过NCRT后的残余阳性LLN可以通过LLND解决⁽²⁴⁾。

短程放疗 (Short-Course Radiotherapy, SCRT) 在局部晚期直肠癌 (Locally Advanced Rectal Cancer,

LARC)治疗中表现出优于长程放化疗 (Long-Course Chemoradiotherapy, CRT) 的无病生存期 (Disease-Free Survival, DFS) 和总生存期 (Overall Survival, OS)，且有助于保留括约肌功能⁽²⁶⁾。尽管长程和短程放化疗能有效控制局部复发，但与LLND在控制侧方复发方面的比较研究仍不足。对于不愿手术的患者，全新辅助治疗 (Total Neoadjuvant Therapy, TNT) 通过术前全身化疗和放疗，可提高DFS和OS，降低远处转移风险，并提高病理完全缓解率 (Pathological Complete Response, PCR)⁽²⁷⁾。

3.2. LLND

国际多中心研究发现，NCRT后侧方淋巴结短轴直径 <7mm的患者复发率为4.9%，且小淋巴结 (<7mm) 导致的侧方复发占比达44%⁽²⁸⁾。这提示小淋巴结在治疗后仍可能带来较高的复发风险。既往研究表明，侧方淋巴结肿大 ($\geq 5\text{mm}$)，即使接受 $\geq 95\%$ 的计划放疗剂量，4年侧方型复发率仍高达12.5%⁽²⁹⁾。此外，侧方淋巴结短径 $\geq 7\text{mm}$ 是NCRT后侧方型局部复发的独立危险因素，行LLND可显著降低患者的5年侧方复发率 (5.7% vs 19.5%， $P=0.042$)、局部复发率 (5.7% vs 25.6%， $P=0.005$) 和远处转移率 (13.5% vs 30.8%， $P=0.028$)⁽²⁵⁾。JCOG0212研究显示，侧方淋巴结短径<5mm时，阳性率为5.2%⁽³⁰⁾。韩国研究也指出，即使侧方淋巴结退缩至<5mm，LLND仍能显著降低局部复发率，强调了LLND的重要性⁽³¹⁾。日本学者提出，髂内和闭孔淋巴结清扫被视为预防性LLND的一部分，应用预防性LLND可显著提升患者3年生存率，但手术复杂性和术后并发症仍是挑战⁽⁴⁾。中国则推荐局部进展期直肠癌患者接受NCRT+TME，并根据影像学评估选择性LLND，旨在降低肿瘤负荷、提高手术切除率并处理侧方转移⁽⁴⁾。

3.3. ICG辅助LLND

ICG辅助LLND在直肠癌治疗中优势显著。2006年，Nagata⁽³²⁾等首次报道其在术中识别SNs的效率是传统手术的五倍，但在T3期及以上直肠癌中存在假阴性，可能与肿瘤阻塞淋巴回流有关⁽³³⁾。2010年，Noura⁽³⁴⁾等对25例pT3期低位直肠癌患者进行SNs活检，23例成功检测到SNs，其中6例接受侧方淋巴结清扫。结果显示，侧位SNs的检测在预测侧方淋巴结状态方面具有高度准确性。在2022年的GREENLIGHT试验中，Ribero⁽³⁵⁾等人研究了ICG荧光淋巴标记在D3淋巴结清扫术中的应用。发现内窥镜下肿瘤周围注射ICG能清晰显示所有患者的淋巴路径，D3区淋巴结的检出率达到92.8%，导致50%的病例调整了淋巴结清扫范围，并确定手术前24小时为ICG注射的最佳时间点。此外，Wan⁽¹⁰⁾等研究表明，获取更多D3淋巴结样本能更精确地进行N分期，指导辅助治疗，且不增加手术并发症风险，从而改善患者预后。

ICG荧光显影技术还可提高手术精确度和安全性，尤其在评估肠吻合口血流灌注方面。使用ICG荧光血管造影技术可降低术后吻合口瘘 (Anastomotic Leak, AL) 发生率⁽³⁶⁾。Watanabe⁽³⁷⁾等人的研究证实，ICG可有效降低AL风险。在Safiejko等⁽³⁸⁾人的荟萃分析纳入32项研究 (共

11,047例结直肠癌患者)，发现ICG组AL发生率为3.7%，显著低于非ICG组的7.6%，表明其在降低AL发生率方面具有显著价值。因此，ICG-FI (ICG荧光成像) 在结直肠癌手术中，尤其是预防AL方面，是一种有益的辅助工具。

4. 讨论

4.1. 直肠癌侧方淋巴结转移的诊断与治疗进展

直肠癌侧方淋巴结转移是影响患者预后的关键因素。传统影像学方法 (EUS、普通CT、PET-CT) 虽常用，但存在局限性，如EUS评估受限、普通CT易假阳性、PET-CT对小淋巴结检测能力有限且假阳性率高^(11,15)。新型影像学技术 (高分辨率MRI、光谱CT、ICG荧光显影) 显著提升诊断准确性，其中高分辨率MRI结合MRI-EMVI检查、光谱CT的高准确率以及ICG荧光显影技术的高灵敏度和阴性预测值，结合TME+LLND可进一步提升治疗效果^(5,16)。在治疗方面，NCRT可有效控制侧方淋巴结转移，但高危患者需结合LLND；虽然LLND在治疗中具有重要意义，但其手术操作复杂且并发症风险较高；而ICG辅助LLND可提高手术精确度和安全性，尤其在预防吻合口瘘方面效果显著^(3,36)。TD与MLN均对患者的预后有重要影响。TD提示肿瘤具有较高的侵袭性，并独立于MLN，是不良预后的关键指标⁽¹⁹⁾。在临床实践中，需高度重视TD和MLN，并在治疗方案中加以考虑。

4.2. ICG的吸收机制与EPR效应：肿瘤治疗的新视角与应用潜力

目前，尚无直接证据表明肿瘤细胞具有特异性吸收ICG的能力。在肿瘤异种移植物中观察到的ICG优先吸收现象，可能与肿瘤细胞内吞活性增强和细胞间连接破坏有关⁽³⁹⁾。1986，Hiroshi Maeda博士及其研究团队⁽⁴⁰⁾首次提出实体瘤中的“增强通透性和保留效应” (Enhanced Permeability and Retention Effect, EPR效应)，该效应指出间质液压力和实体应力会导致大分子药物向肿瘤内部渗透受阻，并影响药物在肿瘤内的分布。然而，这些压力会使功能性淋巴管塌陷⁽⁴¹⁾，这可能是ICG在转移淋巴结中显影效果不佳的原因。由于间质液压力和实体应力主要影响药物向肿瘤中心的渗透，而对外围区域影响较小⁽⁴²⁾，因此扩大切除显影区域可能是一种有效策略。但实施这一策略时，需综合考虑肿瘤的生物学特性、患者的具体情况以及治疗的安全性和有效性。

4.3. ICG与白蛋白的结合：增强肿瘤成像的关键与临床应用前景

目前，相关文献提出肿瘤对单独注射的ICG的靶向性可由EPR效应解释，其机制为ICG在给药时能与血清中的白蛋白结合⁽⁴³⁾。研究表明，ICG与白蛋白的结合可改善水解稳定性，提高光致发光量子产率 (Photoluminescence Quantum Yield, PLQY)，对肿瘤成像和光热疗法具有重要意义⁽⁴⁴⁾。在白蛋白环境中，ICG荧光强度可显著增强⁽⁴⁵⁾。然而，肿瘤能通过吸收白蛋白作为能量来源，减少

淋巴结中的白蛋白含量，进而影响ICG的显影⁽⁴⁶⁾。因此，肿瘤侵犯导致淋巴结中白蛋白减少，将会减少ICG与白蛋白的结合，进而影响ICG在淋巴结中的显影效果。

5. 总结

ICG荧光显影技术在直肠癌侧方淋巴结转移治疗中的应用正逐渐成熟，未来将有望成为关键治疗的手段。且ICG可精确定位前哨淋巴结，为患者定制个性化治疗方案，并用于术后监测复发或转移，指导治疗调整。并随着技术进步，ICG注射将更精准，显影效果优化，并发症风险降低，且标准化手术流程可提高手术一致性和成功率。

本文系统回顾了ICG辅助微创手术在直肠癌侧方淋巴结转移治疗中的应用效果，展示ICG可提高淋巴结检出率和减少术后并发症的优势。然而，由于本研究仅基于已发表的文献进行分析，可能存在一定的局限性。未来需要更多高质量的随机对照试验和长期随访数据，以验证ICG辅助LLND的长期疗效和安全性，并优化其临床应用。

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