

吲哚菁绿实时荧光显像技术在机器人结直肠癌手术中的应用与展望

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摘要

结直肠癌作为全球高发的恶性肿瘤之一, 其手术治疗的精准性直接影响患者预后。机器人手术系统凭借灵活的机械臂、高清三维显像及震颤过滤等优势, 已成为结直肠癌根治术的重要平台, 但其在触觉反馈, 肿瘤及淋巴结精准定位、血供评估等方面仍存在局限。吲哚菁绿(Indocyanine Green, ICG)实时荧光显像技术通过提供术中可视化导航, 在淋巴结示踪、血流灌注评估、肿瘤定位及神经与输尿管保护等方面展现出显著的视觉增强优势。近年来, 多项临床研究探索了ICG在机器人结直肠癌手术中的应用, 但在远期获益及标准化操作方面仍存争议。本文系统综述了ICG显像的基本原理及其在机器人结直肠癌手术中的应用现状, 分析其优势与局限性, 并探讨未来新型荧光剂型、自动化量化评估预警及多学科融合的发展方向, 以期为临床规范化应用提供参考。

关键词

结直肠癌, 机器人手术, 腹腔镜手术, 吲哚菁绿, 荧光显像, 术中导航, 精准手术

The Application and Prospects of Indocyanine Green Real-Time Fluorescence Imaging Technology in Robotic Colorectal Cancer Surgery

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Abstract

Colorectal cancer, as one of the globally prevalent malignant tumors, has its surgical treatment precision directly impacting patient prognosis. Robotic surgical systems, with advantages such as flexible robotic arms, high-definition three-dimensional imaging, and tremor filtering, have become an important platform for radical resection of colorectal cancer. However, they still have limitations in areas such as tactile feedback, precise localization of tumors and lymph nodes, and blood supply assessment. Indocyanine green (ICG) real-time fluorescence imaging technology, by providing intraoperative visual navigation, demonstrates significant visual enhancement advantages in lymph node tracing, blood flow perfusion assessment, tumor localization, and protection of nerves and ureters. In recent years, multiple clinical studies have explored the application of ICG in robotic colorectal cancer surgery, but controversies remain regarding long-term benefits and standardized procedures. This article systematically reviews the fundamental principles of ICG imaging and its current applications in robotic colorectal cancer surgery, analyzing its advantages and limitations, and discusses future development directions, including novel fluorescent agent formulations, automated quantitative assessment and early warning, and multidisciplinary integration, aiming to provide references for standardized clinical application.

Keywords

Colorectal Cancer, Robotic Surgery, Laparoscopic Surgery, Indocyanine Green (ICG), Fluorescence Imaging, Intraoperative Navigation, Precision Surgery

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1. 引言

结直肠癌是一种常见的消化道恶性肿瘤，全球死亡率排名第二，发病率排名第三[1]。2022年中国癌症统计数据显示，其发病率和病死率分别位居恶性肿瘤的第二位和第四位[2]。目前的治疗模式以手术为核心，结合新辅助治疗、辅助化疗及靶向免疫治疗等多学科综合治疗策略，但手术仍是结直肠癌治疗的最有效方案[3]，外科手术的精准程度直接决定了肿瘤根治效果及患者远期生存结局。

随着微创外科的发展，结直肠癌手术经历了从开腹、腹腔镜到机器人辅助手术的演进，如：机器人经自然腔道取标本手术(natural orifice specimen extraction surgery, NOSES)、机器人经肛全直肠系膜切除术(trans-anal total mesorectal excision, TaTME)等。机器人系统凭借其灵活的机械臂、高清三维显像及震颤过滤等优势在外科手术中崭露头角，但临床实践中仍面临诸多挑战：首先，淋巴结清扫的精准性直接影响病理分期及预后[4]，传统经验辨识存在漏检风险[5]；其次，吻合口漏仍是术后严重并发症，其发生与吻合部位的血液供应不足密切相关[6][7]，主观判断吻合口血供缺乏准确性[8]；此外，早期肿瘤、平坦型病变、经新辅助治疗后明显退缩的肿瘤、早期微小转移灶等在术中定位困难，影响安全切缘的获取，进而影响患者术后生活质量，比如：最大限度地保留肛门功能、减少性功能和泌尿功能障碍等并发症的发生

率。上述挑战提示,单纯依赖传统视觉及经验判断难以完全满足精准外科的发展需求。

针对这些挑战,手术技术、器械需要不断优化,术中实时荧光显像技术的赋能让其更有可能解决。既往常用的显色剂(如纳米碳、亚甲蓝、印度墨汁等)存在显像深度浅、易渗漏弥散、色素沉着等局限[9],甚至引发局部粘连、腹腔感染等问题。ICG作为一种近红外荧光染料,经静脉注射或局部注射等方式给药,可实现淋巴引流、肠管血运评估、肿瘤定位、输尿管及神经保护的实时可视化。ICG显像与机器人手术系统的整合,为应对上述挑战提供了重要工具,具有广阔的临床应用前景。

2. 机器人结直肠癌手术简介

自2000年达芬奇手术机器人通过FDA认证以来,该系统已广泛应用于众多手术科室,是目前全球使用最广泛的机器人手术系统[10],其作为一种新兴技术,正开启微创外科手术的新时代。机器人手术系统是由外科医师主导的机械臂操作系统,包括主控单元、床旁机械臂和影像处理系统。主控单元提供高清三维放大视野以识别精细结构,并具备震颤滤除功能[11]。机械臂采用EndoWrist®技术,实现七个自由度的精细操作,尤其适用于盆腔狭小空间,同时缩短培训周期[12]。影像处理系统支持三维高清成像和近红外荧光模式(Firefly®),用于血管造影和肿瘤探测等[13]。机器人手术与腹腔镜手术相比,在提高无病生存率,降低局部复发率、中转开腹率、术中出血量、手术并发症及改善术后功能恢复等方面可能更具优势[14]-[17]。

尽管机器人手术系统优势显著,但其固有局限性仍不容忽视。首先,该系统完全依赖术者在控制台对三维高清影像的实时解读;因此,视野清晰度、色彩还原度以及是否存在视觉盲区,直接决定了对解剖层级、血管路径及肿瘤浸润边界的辨识精度。一旦遭遇图像模糊、照明欠佳或镜头起雾等干扰,极易引发对组织层次或关键解剖结构的误判,从而增加医源性损伤风险;这一隐患在腹腔粘连、盆腔深部及肠系膜根部等解剖关系错综复杂的区域尤为突出。其次,由于缺乏触觉反馈,术者被迫高度依赖视觉线索来推断组织张力、质地、活动度及血管搏动状态。在执行粘连松解、血管骨骼化及肠管牵拉等操作时,仅能依据影像中组织的形变程度估算施力大小,这可能导致组织撕裂或意外出血。此外,对于早期肿瘤或经新辅助治疗后的患者,术中病灶及淋巴结的精确定位至关重要,而单一的视觉反馈模式往往难以满足此类高精度定位的临床需求。

3. ICG 荧光显像技术基本原理

1959年,ICG获得FDA批准用于医疗领域[18],是唯一被FDA和欧洲药品管理局批准的可用于临床的近红外荧光染料[19][20]。ICG的临床应用方案因显像目的不同而在给药途径及剂量上有所差异[21],在癌症病例中的中位剂量通常为0.2 mg/kg [22]。作为一种水溶性近红外荧光成像染料,ICG在近红外光(波长700~900 nm)激发下,在820 nm处发出荧光信号,可穿过5~10 mm的结缔组织[23]-[25],从而实现深层解剖结构的可视化与器官灌注的实时评估,指导手术有效开展。

静脉注射后,ICG迅速与血浆蛋白结合并停留在血管腔内,其血浆半衰期为150~180 s [26],最终经胆汁排泄,不经肠肝循环,体内清除迅速[27][28]。基于上述药代动力学特征,ICG在“血管期”可用于评估组织灌注情况,这在结直肠癌手术中对于判断吻合口血供尤为重要[28]。此外,在某些实体肿瘤中,ICG可通过增强的渗透和滞留效应(EPR效应)实现肿瘤显影[29][30]。

当黏膜下直接注射ICG时,染料可作为“荧光墨水”直接标记肿瘤,也可进入淋巴系统实现“淋巴期”示踪[31],这对精准淋巴结清扫及术后准确分期意义重大。

随着机器人手术系统集成近红外荧光模块(如达芬奇Xi及之后的手术系统),ICG荧光显像在结直肠癌外科的应用展现出固有优势:首先,荧光图像与手术操作视野完全同轴,无需额外调整或引入外部设

备,保证了手术流程的连续性;其次,术者可经操控台直接观察荧光信号,实现同步的实时显像,提高了人机交互的直观性;再者,系统支持多种模式成像(如灰度、伪彩色及荧光-白光融合模式),可根据临床需求提供个性化的视觉增强方案。

4. ICG 荧光显像在机器人结直肠癌手术中应用

4.1. 淋巴结示踪导航

淋巴结转移是造成结直肠癌术后复发和死亡的主要原因,彻底的淋巴结清扫是结直肠癌手术的关键环节,也是术后病理分期及制定后续治疗方案的基础。目前多项指南共识建议评估淋巴结数量应至少达到 12 枚[32] [33]。要实现精准清扫的重要途径是使淋巴结可视化显影,ICG 发挥的淋巴结示踪导航具有高检出率和高灵敏度[34]。多项研究探索了 ICG 在机器人结直肠癌手术中的淋巴示踪价值。在一项共 85 名行机器人右半结肠癌完整结肠系膜切除术(CME)及 D3 淋巴结清扫的研究中,对 50 名患者进行 ICG 黏膜下注射,术中均可观察到原发肿瘤部位及 D3 区域淋巴结显影,其中约 34%的患者发现了来自常规淋巴引流区域外的淋巴结[35]。另有一项涉及 129 例中低位直肠癌患者的前瞻性非随机对照研究报告,ICG 示踪可增加特定分组淋巴结的检出数量,改善了手术效果和患者预后[36]。此外,ICG 还能辅助识别转移的淋巴结,实现精准清扫[37]。前哨淋巴结作为肿瘤细胞转移的首站,其精准定位对术中实施淋巴结清扫至关重要。Daan J. Sikkenk 等研究显示:针对 cT₁₋₂N₀M₀ 的结肠癌患者,在 ICG 引导下的机器人前哨淋巴结的检测率达 100%,平均每位患者识别 2.3 个[38]。然而,ICG 示踪效果受肿瘤分期及新辅助治疗影响。研究发现,T₁₋₂ 期与 T₃₋₄ 期患者的 ICG 引导结直肠癌前哨淋巴结检出率虽无显著差异,但后者准确率(77% vs 98%)及灵敏度(30% vs 80%)显著下降,这可能与淋巴引流途径改变、局部淋巴液引流不畅有关[39]。

ICG 为结直肠癌手术中的淋巴结示踪导航提供新视角,但尚缺乏标准化的操作(如使用剂量、浓度、注射部位及荧光观察时间等);ICG 虽然增加了淋巴结的检出数量,但荧光淋巴结是否等同于肿瘤转移淋巴结仍需最终病理确认,荧光淋巴结的清扫对患者生存率、复发率及长期获益的影响仍有待研究进一步确认。

4.2. 血流灌注评估

吻合口漏是结直肠癌术后严重并发症之一,其发生率为 2%~19% [40],与吻合肠段的血液供应不足有关,直接导致患者死亡率增加、住院时间延长及引发一系列并发症。因此,术中精准评估肠管断端及吻合区域的血流灌注状态具有重要临床意义。

传统评估方法主要依赖术者对肠管色泽、切缘渗血情况及肠管边缘动脉搏动的主观观察,缺乏客观量化指标。在机器人手术中,由于缺乏触觉反馈,术者对血管搏动的判断更加依赖视觉信息,使客观灌注评估的需求更为迫切。新型术中荧光成像技术的引入,使术者能够在离断肠管血管前后及完成吻合前后,依据荧光显像情况及时调整手术决策,有助于术者选择最适宜的吻合或造口位置。与传统判断方式相比,该技术可实现实时、客观的血流灌注评估。

多项回顾性研究及荟萃分析提示,ICG 荧光评估可能降低吻合口漏发生率。一项纳入 4037 例患者的荟萃分析显示,ICG 组与对照组的吻合口漏发生率分别为 3.8%和 7.8% ($P < 0.00001$),总体并发症发生率分别为 15.6%和 21.2% ($P = 0.0008$) [41]。另一项涵盖 27 项研究、共 8786 例结直肠癌患者的荟萃分析进一步表明,与未使用 ICG 的对照组相比,采用 ICG 评估吻合口血供的患者其吻合口漏发生率显著降低 (OR 0.452; 95%CI 0.366~0.558)。该分析同时指出,基于 ICG 评估结果而更改手术方案的比例为 9.6%。然而,值得注意的是,在根据 ICG 提示调整手术方案后,吻合口漏的发生率却显著升高(OR 2.73; 95%CI

1.54~4.82)。研究者认为,这一现象可能与 ICG 的使用剂量、患者个体因素(如肥胖)及调整手术方案本身就是发生吻合口漏的高危因素等相关,即使调整后,新吻合区域的血供不足风险仍可能高于正常组织,且手术方案的改变可能导致肠道长度缩短、吻合口张力增加等问题的出现,从而进一步增加了吻合口漏的风险[42]。

尽管目前 ICG 荧光血管造影在降低术后吻合口漏发生率方面可能具有潜在的潜力,不同研究采取不同的评价体系导致结论不同,尚缺乏高质量的随机对照试验进一步证实。一项名为 FLUOCOL-1 的单盲、随机对照研究,计划纳入多中心的大量患者队列(共计 1010 例),有望填补这一证据空白[43]。值得关注的是,ICG 荧光信号的判读尚缺乏统一的定量标准。多种定量分析软件,如:Flow®800、ROIs Software、IC Calc、SPY-Q™和 the Quest Research Framework®等虽已出现,但尚未形成临床广泛认可的阈值体系。现有研究采用的评价指标包括荧光出现时间、最大荧光强度等,多达数十种不同指标,参数选择显著不同[44][45],导致最终判读的结果产生差异,从而影响手术方案的选择。因此,建立标准化给药方案及客观量化评价标准,是推动 ICG 灌注评估规范化应用的关键。ICG 荧光显像技术为血流灌注提供额外的参考信息,据此有相当比例的患者在术中调整了肠管的离断位置,但并非所有荧光显示不足区域均会最终发展为吻合口漏,可能存在“过度干预”的可能性,反而增加吻合口漏的风险。相反,即使荧光显像灌注良好,也仍会发生吻合口漏,因为除了血流灌注因素外,吻合的技术、张力以及患者全身状况等多种因素也在其中发挥重要作用,需要综合考虑并做出决策。

4.3. 肿瘤定位

在结直肠癌手术中,术中准确定位肿瘤对于实现肿瘤的根治性切除、制定个体化手术方案至关重要。尤其对于早期肿瘤、经新辅助治疗后病灶明显退缩或微小转移灶的情况,单纯依赖视觉判断及缺乏触觉反馈的机器人机械臂,术中肿瘤定位面临巨大挑战。

传统定位方法包括术前钛夹标记或内镜下染料注射。联合内镜虽可提高准确性,但会显著延长手术时间;运用如印度墨汁等传统染料虽可术前标记,但其为永久性色素,一旦渗出浆膜易污染手术视野,甚至诱发腹腔炎症、粘连或肠穿孔等并发症。

相比之下,ICG 与浆膜接触时不易引起炎症反应,且在白光模式下可见度低、仅在近红外模式下呈现高对比度荧光信号,对术者手术视野干扰更小[46]。Watanabe 等对 80 例结直肠癌患者行瘤周注射 1.25 mg ICG,结果显示 93.8% 的患者在术中发现病灶,且无明显不良反应[47]。一项纳入 165 例患者的研究显示,采用术前内镜黏膜下注射(中位剂量 0.5 mg),ICG 标记的检出率与注射时间密切相关:术前 6 天内注射检出率高达 100%,而术前 7~9 天至 10 天以上荧光信号明显减弱甚至无法识别,提示其存在特定的有效时间窗[46]。

肝脏是结直肠癌的主要远处转移器官,肝切除术是目前结直肠癌肝转移唯一可能治愈的选择[48]。对于术前 MR、CT 以及术中超声难以发现的微小病灶,高达 1/3 的患者术后会出现 R1 切除或病灶残留[49]。在一项针对 12 例结直肠癌肝转移患者的研究中,术前静脉注射 ICG 可辅助发现传统影像学漏诊的“边缘荧光”模式肝转移灶,有效提高病灶检出率[50]。

总体而言,ICG 在肿瘤定位中具有显著的临床辅助价值。但其最佳注射时间、给药剂量及标准化评价体系仍需大规模、多中心研究进一步明确。未来可探索术中联合超声,靶向荧光探针等技术的多模态应用,以实现更高精度的病灶识别。

4.4. 盆腔神经保护

盆腔自主神经在调节排尿、排便及性功能方面发挥重要作用[51][52]。结直肠癌手术,尤其是低位直

肠癌根治术中,因解剖空间狭窄及肿瘤侵犯等因素,盆腔神经极易受损,严重影响患者术后生活质量。因此,术中精准识别并保护盆腔自主神经是微创外科追求的重要目标。

盆腔自主神经及其周围分布的血管、脂肪组织会吸收或滞留 ICG,尽管神经组织本身不直接摄取 ICG,但在近红外光激发下,可通过周围组织(如脂肪、微血管)的荧光衬托,实现神经结构的间接识别[53]。Weng 等首次报道了在胸腔镜手术利用 ICG 荧光显像显示胸交感神经节[54]。在机器人辅助深部子宫内膜异位症手术中, Kanno 教授团队通过静脉注射 ICG (0.25 mg/kg),成功可视化下腹神经和下腹下神经丛,且术后未发生膀胱或直肠功能障碍等围手术期并发症[55]。针对结直肠癌手术, Jin 等证实术前 24 h 静脉注射高剂量 ICG (4.5 mg/kg),术中成功观察到内脏神经丛、肠系膜下动脉神经丛及骶神经丛,且术后所有患者均未出现神经丛损伤迹象[56]。

尽管 ICG 在盆腔自主神经识别机制上尚不完全明确,但其作为神经保护辅助工具的潜力已初显。目前,结直肠癌手术中的应用总体仍处于临床探索阶段其最佳给药剂量、给药时间窗、神经保护与功能之间关系的评价体系等均缺乏统一标准和方案,未来仍需更多高质量循证医学证据,以评估其在改善患者远期功能预后中的实际价值。

4.5. 输尿管保护

输尿管损伤是结直肠癌手术严重并发症之一,发生率为 0.15%~0.66% [57]。传统输尿管识别主要依赖术前影像学评估和术中解剖经验。虽然术中可通过观察输尿管蠕动或触摸、按压辨认其走行,但在机器人手术环境下,触觉反馈的缺失使术者更依赖视觉判断,尤其在粘连、炎症及解剖变异等复杂情况下,误伤风险进一步增加。

目前识别输尿管的技术可分为非荧光示踪和荧光示踪两类。非荧光法多为术前预防性置入输尿管支架,在术中通过触感识别,对于缺乏触觉反馈的机器人系统实用性有限,且存在泌尿系感染、血尿及输尿管损伤风险。荧光示踪法涉及临床应用的荧光试剂包括 ICG、荧光素钠及亚甲基蓝等[58]。其中,ICG 凭借极低的全身毒性(对肾功能不全者影响微乎其微)、卓越的显影效能及激发光深层穿透特性,成为目前临床应用最广泛的示踪剂[58]。

Soriano 等对 83 例患者行术中输尿管 ICG 注射,对比了“膀胱镜下导管尖端置入输尿管开口注射”与“导管完全植入输尿管后注射”两种入路,结果显示两组识别效果相当,但前者操作时间显著缩短(4 min vs 13.5 min, $P < 0.001$) [59]。

尽管 ICG 在提高输尿管可视化方面表现出色,但仍存在局限性:首先,通过膀胱镜注射 ICG 属于侵入性操作,增加了泌尿系损伤及感染风险;其次,ICG 的显影机制(可能与输尿管上皮蛋白质结合相关[60])及在病理组织中的对比度仍有待优化。因此,未来探索适配机器人系统的非侵入性、高靶向性荧光试剂,或研发经静脉注射后可直接经泌尿系统排泄并高度显影的示踪技术,将是该领域的重要发展方向。

5. 小结

ICG 近红外实时荧光显像技术联合机器人手术系统的有机结合,为结直肠癌的精准治疗提供了强有力的视觉增强支持。该技术在肠管血供评估、淋巴结示踪、肿瘤定位和输尿管、神经保护等方面展现出显著的术中导航优势。然而,目前 ICG 技术的临床应用仍面临诸多挑战:首先,循证医学证据尚不充分,尽管其短期临床疗效已获公认,但对患者远期获益的影响,仍亟需高质量、大样本的随机对照研究予以深层验证;其次,规范化标准的缺失限制了其精准应用,尽管 ICG 荧光显像已被纳入 2025 版的《机器人结直肠癌手术中国专家共识》和《国家卫生健康委员会中国结直肠癌诊疗规范》[61][62],但临床应用中的给药剂量、注射部位、观察时间窗及客观量化评价标准在学术界尚未达成高度共识;此外,机器人手

术系统及相关耗材的高昂成本也在一定程度上制约了该技术的广泛普及与推广。

展望未来, ICG 荧光成像技术将向智能化与多模态化深度演进。一方面, 科研重心应聚焦于克服 ICG 自身肿瘤特异性不足、荧光产率中等、易猝灭及物理稳定性欠佳等缺陷[63], 开发具有靶向性更强和光学性能更稳定的新型剂型。如靶向性荧光探针, 其通过将 ICG 与能够特异性识别肿瘤表面或肿瘤微环境中的特定分子(如受体、抗原)的配体(如抗体、多肽、纳米材料等)结合, 实现对病灶的主动靶向, 有效解决传统 ICG 在体内非特异性分布、代谢快及穿透深度有限的缺陷。另一方面, 依托人工智能与图像识别分析技术的发展, 算法升级有望辅助术者实时捕捉荧光信号的细微差异, 提供实时、自动化的量化评估与手术预警。如基于深度学习的自动化定量分析系统, 通过卷积神经网络, 对术中 ICG 荧光显像的实时视频流或静态图像进行量化分析, 识别肿瘤边界、淋巴管/淋巴结显影强度及吻合口血流灌注参数, 结合术前 CT/MRI 进行校准, 增强空间定位精度, 有望实现术中肿瘤切缘的毫米级精准评估, 减少主观判断误差, 降低阳性切缘率, 系统自动量化淋巴引流的方式, 辅助制定个体化淋巴结清扫范围, 提升手术根治性, 形成实时反馈, 有效缩短手术决策时间。再比如风险预测模型, 将 ICG 荧光信号与术前影像资料三维重建模型融合, 通过强化学习算法, 训练机械臂实时避让血管/神经/输尿管等, 规划最优手术路径, 提升微创手术精准度, 减少术者经验差异对预后的影响, 推动标准化手术流程的普及。未来, 机器人手术系统将演变为高度集成的智慧外科平台, 实现临床医学、分子生物学、影像学及数据科学等多学科成果的深度融合。ICG 近红外荧光成像作为该平台核心的可视化赋能技术, 将助力外科医生实现从术中解剖识别向器官功能评估与保护的跨越, 推动结直肠癌的精准外科治疗, 最终改善患者预后并使其最大程度获益。

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