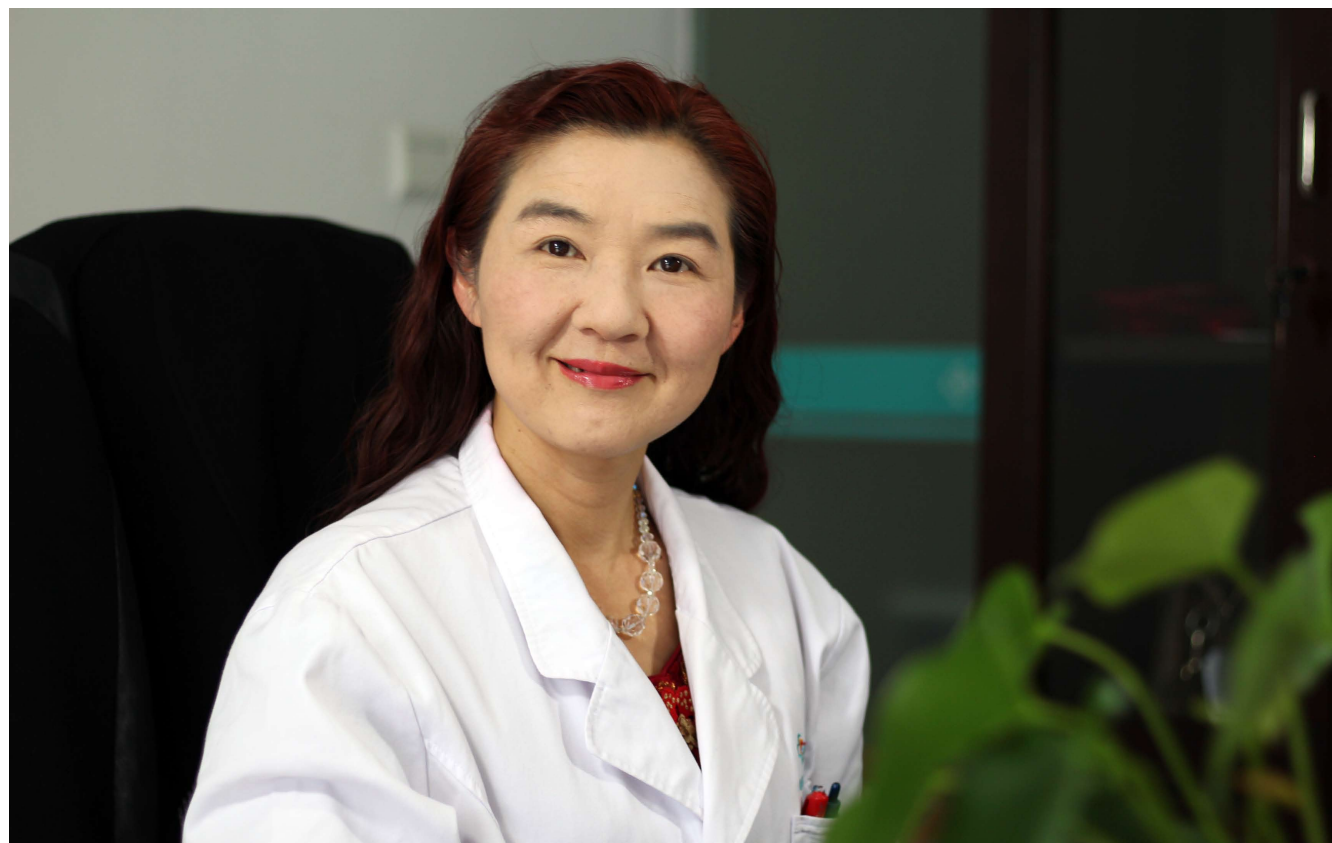


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主编

程英升, 教授, 200233, 上海市, 上海交通大学附属第六人民医院放射科

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制作

北京百世登生物医学科技有限公司
100025, 北京市朝阳区东四环中路62号, 远洋国际中心D座903室

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EDITOR-IN-CHIEF

Ying-Sheng Cheng, Professor, Department of Radiology, Sixth People's Hospital of Shanghai Jiaotong University, Shanghai 200233, China

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World Chinese Journal of Digestology

Baishideng Publishing Group Inc

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Fax: +1-925-223-8242

Telephone: +1-925-223-8243

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家族性腺瘤性息肉病的外科治疗进展

李凯钰, 刘刚

李凯钰, 刘刚, 天津医科大学总医院普通外科 天津市 300052

李凯钰, 住院医师, 主要从事结直肠肛门外科领域的临床及研究工作.

作者贡献分布: 本文综述由李凯钰构思完成; 刘刚审校.

通讯作者: 刘刚, 教授, 主任医师, 300052, 天津市和平区鞍山道154号, 天津医科大学总医院普通外科. landmark1503@163.com
电话: 022-60363901

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Progress in surgical treatment of familial adenomatous polyposis

Kai-Yu Li, Gang Liu

Kai-Yu Li, Gang Liu, Department of General Surgery, Tianjin Medical University General Hospital, Tianjin 300052, China

Corresponding author: Gang Liu, Professor, Chief Physician, Department of General Surgery, Tianjin Medical University General Hospital, 154 Anshan Road, Heping District, Tianjin 300052, China. landmark1503@163.com

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Abstract

Familial adenomatous polyposis (FAP) is an autosomal dominant genetic disease with a high tendency to develop colorectal cancer. The timing and choice of preventive surgical interventions should be based on the number, size and severity of adenomas, combined with a variety of considerations, in order to effectively prevent cancer and make patients easy to accept. Total proctocolectomy and ileal pouch-anal anastomosis (IPAA)

procedure, which could minimize the residual rectal mucosa and reduce the risk of adenoma recurrence, has become the first choice for patients with FAP. Besides, laparoscopic IPAA has obvious advantages such as cosmetic appearance, quick recovery, little adhesion and high pregnancy rate. Patients with FAP should be managed by experienced surgeons working in specialized medical centers in order to get the most reasonable treatment at the best time and achieve long-term effective outcomes.

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Key Words: Familial adenomatous polyposis; Ileal pouch-anal anastomosis; Ileorectal anastomosis; Surgical treatment; Laparoscopic techniques

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摘要

家族性腺瘤性息肉病(familial adenomatous polyposis, FAP)是一种癌变倾向较高的常染色体显性遗传病. 预防性外科干预的时机和手术方式的选择在以腺瘤的数量、大小和严重程度为主要决定因素的同时, 应结合多方面情况综合考虑, 在有效预防癌变的同时使患者易于接受. 全结直肠切除、回肠贮袋肛管吻合术(ileal pouch anal anastomosis, IPAA)已经成为FAP患者的首选治疗方案. IPAA能够最大限度减少直肠黏膜残留、降低腺瘤复发癌变风险, 而腹腔镜IPAA具有美观、恢复快、黏连少、妊娠率高等明显优势. FAP患者应由在专业的医疗中心工作的经验丰富的外科医生进行管理, 以便在最佳的时机得到最合理的治疗, 达到长期有效的治疗结果.

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关键词: 家族性腺瘤性息肉病; 回肠贮袋肛管吻合术; 回肠直肠吻合术; 外科治疗; 腹腔镜技术

核心提要: 本文是一篇关于家族性腺瘤性息肉病患者外科手术治疗时机、方案选择策略相关的文献综述, 总结了目前该疾病外科领域的治疗进展, 帮助读者深入认识该疾病的复杂性和外科治疗的有效性, 以便读者了解该疾病并作为参考。

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0 引言

家族性腺瘤性息肉病(familial adenomatous polyposis, FAP)又名腺瘤性结肠息肉病(adenomatous polyposis coli, APC), 是由5号染色体上的APC基因突变引起的常染色体显性遗传病^[1,2], 其经典表现以结肠和直肠中发生成百上千枚腺瘤性息肉为特征, 具有左半优势^[3,4]. FAP癌变倾向较高, 如不进行预防性干预, 在40岁以后几乎100%发生癌变^[5]. 临床症状、息肉数量和患者年龄是FAP癌变的主要高危因素, 而在低危个体中腺瘤癌变的可能性依然存在^[6]. 衰减型FAP(attenuated form, aFAP)在发病年龄、整体息肉负荷(通常为10-100)和癌症风险^[7]等方面表现都更为良性, 并且具有右半优势^[8]. 对FAP患者的临床管理的目的在于预防癌症死亡和保证生活质量. 迄今为止, 唯一合理的且具有良好预后的预防性手段仍是预防性手术切除^[9]. 由于FAP病变主要发生于结肠和直肠, 几乎很少发生于小肠, 这为外科手术根治提供了可能. FAP外科手术的发展近半个世纪发生着巨大变化, 本文就其外科治疗进展作如下综述.

1 FAP的外科手术时机

通过外科手术切除FAP患者部分肠段实际上是一种预防性治疗手段, 其手术时机在不同中心甚至不同外科医生间存在差异, 目前尚无明确指南. 在防止癌变发生的基础上, 还应充分考虑患者遗传背景、身体一般情况、教育水平、社会情感、财务状况等多方面综合因素以决定手术时机^[10]. 由于突变基因携带者从青春期开始就需要进行结肠镜检查, 故患者的教育、社交需求和财务状况等方面因素在决定手术时机时显得尤为突出, 应予以充分考虑合理规划手术^[11].

1.1 临床症状 临床症状作为FAP癌变的高危因素影响

着手术时机的决策. FAP的“特异性”症状包括血便、贫血、黏液便、腹泻、反复便秘腹泻交替等^[12]. 有症状患者的结直肠癌的发生率约为60%^[13], 当患者出现临床症状时往往表明癌变可能已经发生, 故即使是结直肠癌发病率较低的青少年FAP患者, 一旦出现症状也应尽早进行手术治疗^[14].

1.2 肠镜表现 特定的肠镜下和组织病理学特征可能给予预防性结直肠切除充分的理由. 研究表明^[6], 结肠息肉数量>1000枚的患者较<1000枚的患者癌症风险增加2.3倍. 且由于息肉较多的患者(>1000枚)内镜下检测和预防癌变存在困难, 故即使无症状的严重FAP患者(结肠息肉>1000枚和/或直肠息肉>20枚)一经发现也应尽早手术^[14]. 中等量息肉患者(100-1000枚)及少量息肉患者(<100枚)需每年复查结肠镜, 若腺瘤直径<9 mm且无高度不典型增生, 可逐年推迟手术. 若腺瘤数量迅速增多、存在高度不典型增生、或腺瘤直径超过10 mm, 应立即手术治疗.

1.3 年龄 年龄同样决定着手术时机的把握. 年龄低于20岁的患者中, 癌症患病风险约为1%^[15], 而在40岁以上的患者中, 65%被诊断为结直肠癌^[12]. 此外, 每增加10岁年龄组的癌症风险增加2.4倍, 故FAP患者最好在25岁前行手术治疗^[16]. 对于有明确家族史的儿童, 手术可推迟至十几岁^[17], 待身体和心智发育成熟后再考虑手术治疗^[18].

1.4 硬纤维瘤 硬纤维瘤是影响FAP患者生活质量的最具破坏性的因素, 也是FAP患者死亡的重要原因. 所有FAP患者必须被视为对于硬纤维瘤(肠系膜性纤维瘤病)具有潜在的敏感性. 由于手术创伤会触发硬纤维瘤的生长, 对于已发现硬纤维瘤家族史或个人病史的患者, 建议尽可能安全地推迟预防性结直肠手术^[19].

1.5 遗传信息 遗传信息是否能够指导手术时机的选择尚未达成共识. APC基因型可能与FAP的严重程度有关. 重度FAP患者基因突变多存在于密码子1250和1464之间, 尤其是密码子1309突变; 而轻度FAP患者的基因突变多发生于基因的末端和外显子9的可变剪接部分^[20]. 但由于疾病的发生发展过程相当多变, 即使在同一家系的不同个体间也存在着较大差异, 治疗时机的把握应该根据个体患者的结肠镜检查结果决定, 而非单纯基于基因突变位点^[21]. Lynch等^[22]人提出了一项以标准化FAP疾病进展为基础的评分系统以期明确阶段特异性干预措施. 该评分系统纳入了临床症状、组织病理学、年龄、职业、社会活动、硬纤维病史或家族史、既往手术、括约肌或骨盆功能障碍等诸多因素, 在标准化结直肠疾病进展的评估方面显示出了巨大的潜能, 但其能否在实际应用中实现标准化测量以及干预策略的有效性, 仍需

表 1 决定FAP手术时机的影响因素

影响因素	手术时机
出现明显临床症状者(具有高CRC风险)	尽快手术
少量息肉的无症状患者	可观察随访
息肉较大或伴高度不典型增生	立即手术
重度FAP肠镜表现/家族史/基因型	尽快手术
衰减型FAP肠镜表现/家族史/基因型	根据患者意愿(建议25岁前)
存在硬纤维瘤家族史或遗传易感性	延迟手术(需评估CRC风险)

FAP: 家族性腺瘤性息肉病; CRC: 结直肠癌。

大量研究评估(表1)。

2 FAP外科治疗的术式选择

FAP外科手术的目的在于通过切除已存在病变和可能发生病变的肠段预防结直肠癌的发生发展。最初, 在结直肠全部切除后直接在腹壁进行永久性末端回肠造口术, 这种方法虽然切除了全部病变肠段, 有效预防了息肉的复发及结直肠癌的发生, 但永久性回肠造口严重影响了患者术后的生活质量, 降低了其社交参与度与社会融入感, 由此引发的情感心理问题也随之而来。尤其对于年龄较小的患者及其家属, 永久性回肠造口多无法被接受。而作为一种预防性治疗措施, 永久性回肠造口也并不理想, 目前已很少应用于FAP的预防性治疗。

为了保留肛门功能, 全结直肠切除、回肠-肛管吻合术^[23], 部分结直肠切除、盲肠/升结肠-直肠吻合术等术式随后被引入FAP的治疗, 但由于术后便次较多严重降低患者生存质量、存在息肉复发及癌变高风险等原因, 在FAP的临床治疗上并未得到广泛应用。目前, FAP手术方式的选择主要是结直肠次全切除、回肠-直肠吻合术(ileorectal anastomosis, IRA)和全结直肠切除、回肠贮袋-肛管吻合术(ileal pouch anal anastomosis, IPAA)的选择^[24,25]。

2.1 结直肠次全切除、回肠-直肠吻合术 IRA手术切除了全部结肠, 只保留了部分直肠, 在有效预防了残余结直肠过多带来的FAP复发及癌变高风险的基础上, 保留了直肠的粪便存贮功能防止术后排便次数过多。它避免了直肠周围神经损伤带来的危险和后遗症, 且手术操作相对简单, 并发症较少, 术后肠功能恢复更接近正常^[26]。但残余直肠仍存在复发风险, 需终身进行结肠镜检查, 及时内镜下切除直肠残留息肉, 且最终可能仍需切除直肠。1996年, Vasen等人提出^[27]1250位点前基因突变的患者疾病发展更缓慢, 推荐此类患者行IRA手术治疗。IRA被推荐用于直肠腺瘤较少且有轻度表型家族

史的年轻患者和轻度FAP患者, 前提是需终身接受结肠镜检查。

2.2 全结直肠切除、回肠贮袋-肛管吻合术 对于重度FAP患者及直肠息肉较多的患者, 切除全部结直肠是十分必要的, 任何直肠黏膜的残留都会带来腺瘤癌变的风险, 而为了减少回肠内容物对肛门的直接刺激, IPAA应运而生(图1)。该术式去除了几乎所有结直肠黏膜, 直肠癌风险最小^[28], 既避免了永久性回肠造口, 又有效控制了便秘情况, 患者术后生存质量得到明显改善^[29]。IPAA在儿童FAP患者中应用的安全性也得到了证实^[30]。但其手术操作相对复杂, 直肠周围神经保护相当重要, 尤其对于年轻患者。且较低位的吻合往往需要预防性造口, 二次手术打击也应在决定手术方式时予以考虑。演变而来的还有回肠贮袋-直肠残端吻合术, 在一定程度上降低了手术难度, 但残留的直肠仍存在复发风险, 而手术操作较IRA复杂, 临床已很少使用(表2)。

3 相关问题的探讨

3.1 IPAA vs IRA 对于直肠中存在较大息肉的经典表型FAP患者, 推荐首选IPAA手术治疗。IPAA可以更彻底地清除肠黏膜, 最大限度地降低直肠癌的风险, 但由于技术的复杂性, 这一术式对外科医生手术技术要求较高^[31,32], 且存在较高的并发症发生率^[3,33], 如盆神经损伤, 可能导致泌尿功能和性功能障碍, 女性的生育能力下降^[34], 术后贮袋失败废弃风险^[35,36]等。外科医生的经验和技能可能会影响最终的术式选择及预后^[37]。

IRA作为保留直肠的预防性结肠切除术, 术后具有良好的功能结果, 但术后残余直肠腺瘤复发癌变风险较高, 需要终生进行肠镜检查, 监测直肠疾病进展。在IPAA出现以后, 术后直肠癌的发生率从15%-40%降低至不到10%^[38,39]。IRA通常推荐用于直肠息肉少的患者、aFAP、轻度表型家族史以及有怀孕需求的年轻女性, 其余患者均应接受IPAA^[39,40]。

IPAA和IRA的选择实际上是是否切除直肠的抉择。

表 2 IPAA与IRA的比较

术式	IPAA	IRA
适应证	直肠腺瘤数量较多(>20枚)或较大(>2 cm)或伴高度不典型增生者; 结直肠癌变者; 经典表型FAP; 重度表型家族史	直肠腺瘤 <20枚者; aFAP; 轻度表型家族史; 有生育需求的年轻女性
优势	癌变风险低, 生存质量较高	操作相对简单, 功能恢复良好; 并发症较少
劣势	操作复杂, 并发症风险较大; 多需预防性回肠造口, 行二期手术	终生直肠癌风险, 再次手术直肠切除可能较大
并发症	盆腔神经损伤, 远期贮袋炎等	肠梗阻、吻合口瘘等
随访	肠镜监测贮袋状况	肠镜监测直肠有无癌变

IPAA: 回肠贮袋肛管吻合术; IRA: 回肠-直肠吻合术.

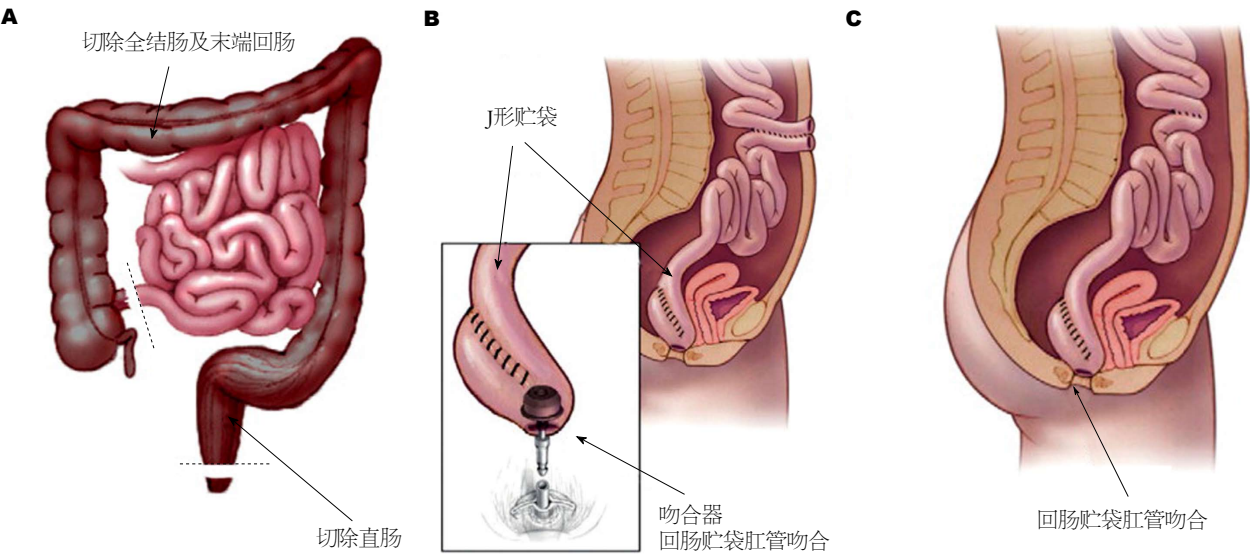


图 1 回肠贮袋肛管吻合术手术示意图^[3]. A: 全结直肠切除术; B: 回肠贮袋肛管吻合术和预防性回肠造口术; C: 回肠造口还纳术.

芬兰一项研究表明^[41], 结肠切除30年后, 二次行直肠切除术的累积风险为53%. 尽管长期监测, 仍有44%的人发生癌变. 这种风险与息肉的严重程度密切相关^[42], 20个直肠腺瘤的阈值是决定是否切除直肠的合理方法^[43]. 在经验丰富的FAP治疗中心推荐直肠息肉大于20枚的患者行IPAA术. 而手术治疗多年后腺瘤仍可能在回肠贮袋内发生^[44], 同时存在一定的恶变风险^[40,45].

2016年, Church等^[11]人提出存在硬纤维瘤高风险的患者应行腹腔镜IRA手术, 其术后硬纤维瘤发生风险可能较低, 应尽量避免使用IPAA术, 尤其是避免使用腹腔镜IPAA. 因为在13%的案例中硬纤维瘤很可能在全结直肠切除后影响贮袋下拉至盆腔行IPAA手术, 但还没有数据表明术后发生硬纤维瘤会影响IRA以后的直肠切除^[28]. 如果已患有硬纤维瘤的患者需要行全结直肠切除术, 肠切除后多采用末端回肠造口术.

3.2 开腹手术 vs 腹腔镜手术 微创技术的出现减轻了腹部结直肠切除术后患者的虚弱和痛苦程度, 腹腔镜手术的优势显而易见. 腹腔镜技术在直肠癌治疗中的应用价

值已得到证实^[46], 一些研究也验证了其在溃疡性结肠炎和FAP患者治疗中的有效性、可行性及安全性^[47]. 而这些疾病通常累及年轻、有活力、自身形象意识较强的患者, 是微创技术应用的理想领域. 因其较开腹手术后瘢痕小、更加美观而易被年轻人接受^[48]. 除了能减小体表瘢痕外, 腹腔镜技术还可能具有其他潜在优势.

回顾腹腔镜手术相关文献, 尽管手术时间可能相对较长, 但在生存率^[49]、并发症发生率、再次手术概率等方面与开腹手术组相比无明显差异^[50]. 腹腔镜对术野的放大作用使得解剖层面能够显现得更加清晰, 无血管平面的游离使手术失血更少^[51,52]. 此外, 由于腹腔镜手术创伤小, 感染风险更小^[53], 患者术后恢复较快, 能够更快地恢复肠道的连续性^[54]. 有大量证据表明^[55], 腹腔镜手术对组织骚扰小, 术后腹腔和盆腔粘连较少, 可降低术后肠梗阻风险^[56]、提高生育能力^[57]. 术后妊娠率较高^[57,58]使腹腔镜IPAA手术成为年轻女性FAP患者的最佳选择. 一项前瞻性随机对照研究表明^[59], 通过腹腔镜进行结直肠切除、回肠贮袋肛管吻合术似乎没有任何

缺点, 尽管这项研究因受试者多要求入腹腔镜手术组而被迫提前终止。

3.3 吻合器吻合 vs 手工缝合 1978年, Parks等^[60]首次描述了在黏膜切除术后, 于齿状线高度进行手工缝合的方法, 完成回肠贮袋-肛管吻合术。这种方法理论上可以去除所有具有肿瘤潜能的黏膜, 但仍可能残存部分黏膜岛的报道一出, 证明在溃疡性结肠炎和FAP患者中除去所有风险黏膜的假设优势证明并不充分。尽管黏膜切除可以降低腺瘤和癌症形成的风险, 但却会影响术后肛门功能^[61]。1986年, Heald^[62]提出了双吻合器吻合法, 除了技术上更容易、更快捷以外, 与手工缝合相比, 由于括约肌操作较少、吻合口上方保留了部分直肠袖带, 这一方法能达到较好的吻合效果且术后肛门功能恢复更好。但同时, 术后腺瘤复发风险可能更高, 也可能提高直肠癌的发病率^[63,64]。长久以来, 吻合器吻合和手工缝合利弊的比较一直受到学者们的关注。一项Meta分析显示^[61], 吻合器组的整体功能效果和可控性更好, 但吻合口愈合不良的发生率较高, 这在一项仅包含FAP患者的研究中得到证实^[59]。有研究表明^[65,66], 手缝组的脓毒性并发症发生率较高, 可能产生肛门刺激症状, 且存在一定的吻合口瘘和吻合口狭窄发生率。

总体来说, 吻合器IPAA的优点在于它比手工缝合更简单, 吻合更确切, 并发症少, 具有较高的安全性^[61]。而其缺点是残余直肠或肛管移行区(anal transition zone, ATZ)易导致腺瘤复发, 这种风险约为手缝IPAA的两倍^[67], 而不予干预复发腺瘤的ATZ最终可能导致癌变^[68]。但无论手缝还是吻合器吻合, 残余的直肠黏膜都可能导致腺瘤复发, 故每年进行结肠镜检查对所有回肠贮袋患者都是十分必要的^[68]。此外, 而由于目前研究随访时间较短, 且缺乏大规模的前瞻性研究, 残余直肠相关腺瘤形成的远期风险尚不清楚。但随着近期FAP患者腺瘤复发率较高的报道的出现, 一些学者可能改变其对于吻合器技术的偏好。

4 结论

FAP作为一种潜在恶变风险极高的癌前病变, 其预防性外科干预不容忽视。手术时机的把握需要根据临床表现、腺瘤负荷、患者年龄等癌变高危因素, 联合患者教育、社会、经济情况综合考虑。在有经验的中心, 全结肠切除、回肠贮袋肛管吻合术已经成为外科医生治疗FAP的首选而安全的治疗方案^[69]。在微创外科技术迅猛发展的今天, 腹腔镜系统的不断革新大大降低了结直肠手术的风险, 越来越多得到学者和大众认可, 但其是否能替代开腹手术还需要大量临床研究长期随访观察。随着机器人医疗技术的发展, FAP外科治疗又将迈入全

新的时代^[70]。

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• 消息 •

《世界华人消化杂志》外文字符标准

本刊讯 本刊论文出现的外文字符应注意大小写、正斜体与上下角标。静脉注射iv, 肌肉注射im, 腹腔注射ip, 皮下注射sc, 脑室注射icv, 动脉注射ia, 口服po, 灌胃ig. s(秒)不能写成S, kg不能写成Kg, mL不能写成ML, lcpm(应写为1/min)÷E%(仪器效率)÷60=Bq, pH不能写PH或P^H, *H. pylori*不能写成HP, T_{1/2}不能写成tl/2或T_{1/2}, V_{max}不能Vmax, μ不写为英文u. 需排斜体的外文字, 用斜体表示。如生物学中拉丁学名的属名与种名, 包括亚属、亚种、变种。如幽门螺杆菌(*Helicobacter pylori*, *H. pylori*), *Ilex pubescens* Hook, *et Arn. var. glaber* Chang(命名者勿划横线); 常数*K*; 一些统计学符号(如样本数*n*, 均数mean, 标准差SD, *F*检验, *t*检验和概率*P*, 相关系数*r*); 化学学中标明取代位的元素、旋光性和构型符号(如*N*, *O*, *P*, *S*, *d*, *l*)如*n*-(normal, 正), *N*-(nitrogen, 氮), *o*-(ortho, 邻), *O*-(oxygen, 氧, 习惯不译), *d*-(dextro, 右旋), *p*-(para, 对), 例如*n*-butyl acetate(醋酸正丁酯), *N*-methylaniline(*N*-甲基乙酰胺), *o*-cresol(邻甲酚), 3-*O*-methyl-adrenaline(3-*O*-甲基肾上腺素), *d*-amphetamine(右旋苯丙胺), *l*-dopa(左旋多巴), *p*-aminosalicylic acid(对氨基水杨酸)。拉丁字及缩写*in vitro*, *in vivo*, *in situ*; *Ibid*, *et al*, *po*, *vs*; 用外文字母代表的物理量, 如*m*(质量), *V*(体积), *F*(力), *p*(压力), *W*(功), *v*(速度), *Q*(热量), *E*(电场强度), *S*(面积), *t*(时间), *z*(酶活性, kat), *t*(摄氏温度, °C), *D*(吸收剂量, Gy), *A*(放射性活度, Bq), *ρ*(密度, 体积质量, g/L), *c*(浓度, mol/L), *φ*(体积分数, mL/L), *w*(质量分数, mg/g), *b*(质量摩尔浓度, mol/g), *l*(长度), *b*(宽度), *h*(高度), *d*(厚度), *R*(半径), *D*(直径), *T*_{max}, *C*_{max}, *V*_d, *T*_{1/2} *CI*等。基因符号通常用小写斜体, 如*ras*, *c-myc*; 基因产物用大写正体, 如P16蛋白。



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