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述评 EDITORIAL

早发性与晚发性结直肠癌临床特征比较及预后的分析

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Comparison of clinical features and prognosis of early- and late-onset colorectal cancer

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Abstract

Colorectal cancer is a common digestive system tumor, ranking third in incidence and second in fatality rate in the world. In recent years, the total incidence and fatality rate of colorectal cancer decrease, but early-onset colorectal cancer (EOCRC) shows an overall rising trend. Colorectal cancer diagnosed at less than 50 years of age is generally defined as EOCRC, which has unique clinical features and a poorer prognosis than late-onset colorectal cancer. This article reviews the clinical features and prognosis of EOCRC.

Key Words: Early-onset colorectal cancer; Clinical feature; Prognosis

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摘要

结直肠癌(colorectal cancer, CRC)是全球常见的消化系肿瘤, 发病率位于世界第3, 病死率位居世界第2, 近年来结直肠癌总的发病率及病死率有所下降, 但早发性结直肠癌(early-onset colorectal cancer, EOCRC)呈整体增长趋势. 通常把<50岁诊断的结直肠癌定义为EOCRC, 与晚发性结直肠癌(late-onset colorectal cancer, LOCRC)相比, 其具有独特的临床特征, 且预后较差. 本文就EOCRC的临床特征及预后进行简要述评.

关键词: 早发性结直肠癌; 临床特征; 预后

核心提要: 与晚发性结直肠癌相比, 早发性结直肠癌(early-onset colorectal cancer, EOCRC)有其独特的临床特征及预后, 甚至有研究者认为EOCRC是一个独立的疾病

而并非结直肠癌的一个亚组.

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0 引言

结直肠癌(colorectal cancer, CRC)是全球第三大常见癌症, 也是全球癌症相关死亡的第二大原因[1]. 近年来, 随着诊治水平提高及一级预防的重视, CRC发病率较前有所下降, 但早发性结直肠癌(early-onset colorectal cancer, EOCRC)的发生率和病死率却呈现增长趋势[2,3], 尤其是在35岁以下年轻人中表现得更为明显[4], 而对于这种上升趋势的原因目前尚不清楚. EOCRC是美国50岁以下人群中第二大常见癌症, 也是导致美国50岁以下人群癌症死亡的第三大原因[5]. 研究预测, 到2030年, 美国早发性结肠癌和直肠癌发病率将分别占到10.9%和23%[6]. 我国关于此方面的流行病学数据尚未公布, 仅在部分文献中有所提及. 但很明确的是, EOCRC相比晚发性结直肠癌(late-onset colorectal cancer, LOCRC)来说, 有其独特的临床特征, 本文将对两者的临床特征比较及对EOCRC的预后作简要分析.

1 流行病学特点

自20世纪90年代以来, 澳大利亚、加拿大、丹麦等9个国家的EOCRC发病率呈持续上升趋势[3,7], 欧洲的一项研究也得出了相同结论, 显示20-49岁成年人的CRC发病率是增加的[8]. 格陵兰、冰岛、斯洛文尼亚、加泰罗尼亚、拉脱维亚和瑞士的发病率没有明显变化. 意大利是唯一一个从1998年起以每年1.8%的速度显著降低20-39岁人群CRC发病率的国家[7-9]. 同样, 在亚洲国家EOCRC发生率也是呈上升趋势的, 日本除外, 年龄<50岁的人群呈下降趋势, 可能与其筛查年龄放宽至较年轻有关. 日本自1992年开始使用粪便免疫化学试验进行CRC筛查, 也说明早期开展CRC筛查一定程度上有助于解决CRC发病率上升的难题[10]. 关于EOCRC发病率逐年增加的原因, 目前尚未明确, 但有相关研究认为与以下因素相关, 例如个体因素(男性、25岁以后、白色人种)、家族史(一级亲属有CRC家族史、Lynch综合征)、生活方式(包括饮酒、久坐、压力、高脂、高热量低纤维饮食和含硫微生物饮食等)、不恰当抗生素使用、肠道微生态以及代谢综合征, 其中高脂血症是一般危险因素, 而肥胖是高危险因素; Kim等[1,11-15]还研究了EOCRC与糖尿病的关系, 风险<50岁且患有2型糖尿病的患者CRC和晚期腺瘤的风险增加有关.

2 早发性结直肠癌与晚发性结直肠癌的临床特征比较

目前各国的研究表明, EOCRC与LOCRC在临床表现、肿瘤部位、组织学特征、分子学特征等方面都存在差异, 这些证据更加表明EOCRC是一种独立的疾病, 应引起临床重视. 大多数研究都认为EOCRC主要表现为以下症状和体征: 腹痛、便血、体重减轻、贫血、食欲减退、排便习惯改变、肠梗阻等表现[16-18]. 在一项1025例患者研究中[19], 886例(86.4%)在诊断时有症状: 直肠癌患者比结肠癌患者更容易出现症状[499人中有449人(90.0%) *vs* 524人中有435人(83.0%); P<0.001]; 在139例无症状患者中, 19例(13.7%)因贫血, 10例(7.2%)因粪便隐血阳性, 3例(2.2%)因腹部肿块, 3例(2.2%)因直肠指检发现肿块, 110例(79.1%)因其他原因进行相关检查发现. 另外, EOCRC发病较隐匿, 早期多无症状, 且年轻人群因为经济及就诊意识等原因, 出现症状就诊时已发生远处转移, 处于晚期病程. 几项大型研究统计显示[20-23], 3期和4期CRC占54%-61.8%. 有相关文章提出, 由于临床医生对年轻患者相关症状(如便血、腹痛等)不重视, 认为是常见的良性病变或功能性疾病(如肠易激综合征、内痔等), 对诊断造成延后, 从而导致在年轻人中观察到的疾病阶段较晚[24]. 国外有研究总结, EOCRC患者从出现症状至诊断的平均时间是6个月, 长于LOCRC患者[25], 因此提高临床医师对年轻患者EOCRC评估及识别意识十分重要. 与LOCRC相比, EOCRC的发生部位更倾向于远端结肠和直肠, 准确说是乙状结肠和直肠, 也正因此EOCRC患者比LOCRC更容易出现上述临床表现[26]. 在Chang等[27]的一项研究中, 80%早发性肿瘤(定义为年龄≤40岁)出现在左侧结肠和直肠, 而在晚发组中, 只有58%肿瘤出现在左侧结肠和直肠. 甚至有研究表明, 左半结肠和直肠肿瘤的百分比随着年龄的增长而下降[28]. 因此有专家建议, 用乙状结肠镜作为筛查方法, 早期识别左半结肠和直肠肿瘤. 组织病理学特征方面, 与LOCRC相比, EOCRC多表现为不良组织病理学特征, 分化差、周围神经侵犯、静脉侵犯、粘液细胞和(或)印戒细胞形态等[27]. 一项分析64068例EOCRC患者的综合研究显示, 与LOCRC患者相比, 年轻患者更常表现出低分化(18% *vs* 20.4%)和粘液样及印戒样形态(10.8% *vs* 12.6%)[20]. 在EOCRC中, 粘液组织学占10.0%-14.5%, 印戒组织学占2.0%, 低分化或未分化癌高达27.9%. 国家癌症数据库的数据显示, 与LOCRC相比, EOCRC更有可能有粘液或印戒组织学特征(12.6% *vs* 10.8%, P<0.01), 分化较差或无分化(20.4% *vs* 18%, P<0.01)[27,29-31]. 需要注意的是, 有炎症性肠病(inflammatory bowel disease, IBD)的EOCRC患

者更加容易出现粘液或印戒组织学特征. 所以不能排除, EOCRC患者诊断时常为晚期可能与这些不良的组织病理学特征及其潜在的遗传基础相关, 加速肿瘤进展, 从而导致较差的预后. 另外, EOCRC患者的肿瘤瘤体与LOCRC相比, 体积更大, 最大径>5 cm多见[32]. 最近的研究表明, 1/5的EOCRC归因于遗传性癌症综合征, 其中一半归因于林奇综合征(lynch syndrome, LS)[33]. 虽然20% EOCRC可能涉及种系遗传改变, 但遗传综合征仍然只占少数, 并且大多数EOCRC是散发性的, 没有相关家族史[34,35]. 在分子学特征方面的研究, 目前存在矛盾性, 部分研究表明EOCRC更常表现为微卫星不稳定MSI(MSI-H)[36,37], 且这些MSI肿瘤大多与LS有关, 很少与MLH1失活有关, 而是与MSH2失活有关[38]. 然而有研究认为大多数EOCRC表现为微卫星稳定MSS. EOCRC MSS肿瘤通常位于左侧结肠, 很少与其他原发性肿瘤相关, 并且具有很强的家族性, 与LOCRC MSS相区别[39]. CpG岛甲基化表型较少出现在EOCRC中, 另LINE-1低甲基化是EO-CRC隐含的另一个特征, 是全基因组低甲基化的替代标记[40]. 有证据表明[41], LINE-1低甲基化程度是CRC癌症相关死亡率和总死亡率增加的独立因素. 关于基因突变, 目前大部分研究认为EOCRC较少含有K-RAS(KRAS)、B-Raf(BRAF)V600E和腺瘤性结肠息肉病基因序列变异[27,28,42,43].

3 早发性结直肠癌与晚发性结直肠癌的预后比较

尽管EOCRC不同于LOCRC, 但目前还没有针对EOCRC的治疗方案, 因此关于EOCRC的预后仍是人们较关心且存在较大争议的热点问题. 虽然EOCRC在组织病理学上表现较差且易转移, 但其预后是否更差尚未有定论.

Burnett-Hartman等[44]提出, 在调整某些临床特征因素后, EOCRC患者的CRC特异性死亡风险低于晚发性CRC患者. Abdelsattar等[45]在1999-2011年基于SEER数据库的回顾性队列研究中发现, EOCRC患者比LOCRC患者获得了更有利的CRC特异性生存. 一项基于1991-1999年SEER数据库的比较研究[21]显示, EOCRC患者的5年CRC特异性生存率与晚发性CRC患者是相似的. 有文章指出, 虽然EOCRC被诊断时常处于晚期, 但经过积极治疗, 可以提高疾病特异性生存率[23]. 一项包含辅助化疗临床试验中Ⅱ期或Ⅲ期CRC患者的大规模研究显示, EOCRC患者和LOCRC患者的癌症特异性死亡率相似. 在该研究中, EOCRC患者更易出现区域转移性淋巴结, 但比LOCRC患者更有可能完成计划的治疗时间和接受更高强度的治疗. 但同时, 高风险Ⅲ期EOCRC患者尽管治疗强度更高, 但复发率更高, 因此还是不能否认其更具侵袭性[46]. 在Zaborowski的研究中[47], 手术切除后早发组的5年(overall survival, OS)有所提高, 而年轻组和老年组的5年无病生存率均为81%. 对于晚期和转移性CRC, 研究发现EOCRC患者的无进展生存期较短, 但这并不影响与LOCRC患者相比的死亡相对风险或总生存OS[48]. 死亡率方面, 虽然CRC死亡率总体呈下降趋势, 2000-2014, LOCRC死亡率下降了34%, 但EOCRC死亡率上升了13%[49]. 这些研究存在一个明显局限性, 常常把遗传性结直肠癌纳入分析, 导致EOCRC生存结果产生偏倚.

Chen等[50]提出, 与一般人群相比, EOCRC人群在诊断后3年内的非癌症死亡风险较高, 但随着时间推移, 这种差异逐渐缩小. 诊断年龄、种族、性别、诊断年份、分级、分期和手术是OS独立预后因素. 另一项研究中, 在65岁以上CRC患者中, 诊断后3年内和9年内结直肠癌死亡比例分别超过70%和60%[51]. 而Chen等[50]研究结果为大约90%和75%EOCRC患者的结直肠癌死亡在随访的3年和10年内. 这可能是由于老年患者合并症的患病率相对较高, 而且更有可能死于其他疾病. 美国临床肿瘤学会临床指南强调右侧结肠癌确诊后2-4年内复发风险较高, 而对EOCR而言, 其复发和转移情况的关注应该定在一个更长的时间(10年)[52]. 随着癌症检测和治疗的进步, EOCRC患者OS在近40年有了显著改善. 肿瘤分期或级别较高的患者预后较差, 手术仍是有效的治疗方法. 上述的独立预后因素有助于识别高危患者. 国内有相关研究对EOCRC的疾病负担进行了分析, 结果显示2019年中国EOCRC相关伤残调整寿命年(disability-adjusted life years, DALYs)占所有结直肠癌相关DALYs的20.40%, 占全球EOCRC相关DALYs的30.63%[53]. 早识别高危患者并积极治疗, 是目前最好解决沉重疾病负担的方法. 一项网络荟萃分析[54]根据年龄提出了不同预后: 对5年OS和5年癌症特殊生存(cancer special survival, CSS)的分析表明, <30岁的患者预后最差, 尽管后者没有表现出统计学差异, 但<30岁仍是一个值得注意的年龄组. 此项分析中, EOCRC的5年OS好于LOCRC, 提示其远期预后较好. 然而, 两组患者在5年CSS、5年无病生存(disease free survival, DFS)和短期OS方面的预后并无差异. 除此之外, 有研究对遗传性和IBD相关的EOCRC进行了分析, 与散发性的CRC比较, IBD相关的CRC患者的5年OS无明显差异, 但按年龄对患者进行分类时, IBD相关的CRC在<50岁的年轻患者中存活率较低. 与散发性EOCRC相比, IBD相关的EOCRC可能是独特的, 预后更差, 而平均年龄发病的IBD-CRC在预后方面可能类似于平均年龄发病的散发性CRC. 该研究中[55], LS患者占遗传性组的大多数, 并且其存活率高于散发性EOCRC. 之所以众多研究结果出现矛盾, 可能是生存数据有限的原因, 未来还需要更多的真实生存数据进行进一步的深入研究.

4 启示与预防措施

近年来, CRC流行病学在变化, EOCRC发病率呈上升趋势, 尤其是20-49岁年龄段, 且预后较差, 基于人群筛查策略应该有所改进, 结合暴露因素及家族史的风险分层将是制定最佳筛查策略的关键. CRC筛查方法有多种, 包括粪便免疫化学检测、多靶点粪便DNA检测、结肠镜检查、乙状结肠镜检查或上述方法组合[56]. 美国癌症协会于2018年发布了一项建议, 45岁开始进行CRC筛查[57]. 此外, 美国预防服务工作组的指南于2021年进行了更新, 美国结直肠癌多社会工作组于2022年更新了指南, 两者都建议在45岁开始对平均风险个体进行筛查[58,59]. 然而, 亚太指南仍保留广泛开展结直肠癌筛查的起始年龄为50岁的建议[60]. 但许多模拟模型都显示出在45岁时开始CRC筛查可能具有成本效益[61,62]. 因为目前大多数国家的初筛年龄仍为50岁, 所以能用于评估筛查年龄定为45岁带来的收益的数据有限. 然而, 日本已经实施了基于人口的CRC筛查, 它的一项研究显示, 在<50岁的患者中, 筛查发现的CRC与未筛查的CRC相比, 死亡风险降低50%[63]. 该研究中还发现, 与50-75岁组相比, 40-44岁组的癌症特异性存活率更差. 与50-75岁组相比, 45-49岁组的癌症特异性生存率没有差异. 也就是说, CRC筛查为45-49岁的患者提供了有意义的生存优势. 一些指南建议在40岁前或最年轻的一级亲属被诊断为CRC的年龄-10岁开始CRC筛查, 特别是对于有CRC家族史的个体, 例如有一级亲属在60岁之前被诊断为CRC的个体, 或有两个或两个以上一级亲属在任何年龄被诊断为CRC的个体[57-59]. 在40-49岁的EOCRC中, 25%符合早期筛查的家族史标准, 如果早期筛查, 几乎所有符合标准的病例都能更早诊断出CRC[64]. 因此获得家族史信息对于识别高危患者, 实施个体化筛查指南非常重要[65]. 此外, 有学者建议对所有EOCRC患者进行肿瘤MSI检测或MLH1、MSH2、MSH6和PMS2的免疫组织化学检测[66]. 优化筛查策略, 要结合遗传风险因素、生活方式因素、环境危险因素, 优先无创、便捷方式, 同时还要考虑社会经济效应. 同时也有学者提出, 目前EOCRC的生物分子机制尚未清晰[67], 目前的筛查及预防策略也许并不适合EOCRC, 还需要足够证据来支撑. 针对肿瘤的生物分子特征量身定做的治疗方案是改善EOCRC患者预后所必需的.

此外, EOCRC患者由于治疗需要, 可能有长期后遗症, 例如性功能障碍、焦虑、身体形象较差、排便尴尬和大便失禁等, 影响生活质量, 甚至出现焦虑、抑郁等心理障碍[68,69]. 因此诊治过程中, 应对患者的心理健康多加关注, 及早心理咨询、心理健康指导介入.

5 结论

EOCRC是不同于LOCRC的一种独立疾病, 近年来随着CRC发病率在下降, EOCRC反而呈现逐年上升趋势, 这种趋势变化的原因尚不明确, 且具有其独特的临床特征及较差的预后. 作为年轻群体, 为个人、家庭及社会带来较大的疾病负担, 因此优化EOCRC筛查策略迫在眉睫. 加强对年轻群体的健康宣教及临床诊治中需要对年轻人群的相关可疑症状加以重视, 早期识别、早期积极治疗.

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