

## 中低位直肠癌切缘微转移的研究进展

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### 背景资料

直肠癌是我国最常见的消化系统肿瘤之一, 采用规范化的全直肠系膜切除术后局部复发率仍较高, 其中直肠癌环周切缘及下切缘存在的微转移是局部复发和转移的重要因素, 并且在中低位直肠癌超低位保肛术中尤为重要。

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南京市医学科技发展基金资助项目, No. YKK12058

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收稿日期: 2015-03-22 修回日期: 2015-04-02

接受日期: 2015-04-08 在线出版日期: 2015-05-28

### Micrometastasis in resection margin of low rectal cancer

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Supported by: Medical Science and Technology Foundation of Nanjing, No. YKK12058

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Received: 2015-03-22 Revised: 2015-04-02

Accepted: 2015-04-08 Published online: 2015-05-28

### Abstract

Colorectal cancer is one of the most common digestive tumors in China. After normalized total mesorectal excision (TME), there is still a high rate of local recurrence. The presence of micrometastasis in the resection margin of low rectal cancer is an important factor predicting local recurrence and metastasis. In this paper, we discuss the recent progress in research of

micrometastasis in circumferential and distal resection margin of rectal cancer.

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Key Words: Rectal cancer; Circumferential resection margin; Distal resection margin; Micrometastasis

Jiang SS, Ge W, Zhang K, Zheng LM, Chen G. Micrometastasis in resection margin of low rectal cancer. *Shijie Huaren Xiaohua Zazhi* 2015; 23(15): 2410-2414  
URL: <http://www.wjgnet.com/1009-3079/23/2410.asp>  
DOI: <http://dx.doi.org/10.11569/wcjd.v23.i15.2410>

### 摘要

直肠癌是我国最常见的消化系统肿瘤之一, 采用规范化的全直肠系膜切除术(total mesorectal excision, TME)后局部复发率仍较高, 其中直肠癌环周切缘及下切缘存在的微转移是局部复发和转移的重要因素, 本文就直肠癌环周切缘及下切缘微转移的研究作一综述。

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关键词: 直肠癌; 环周切缘; 下切缘; 微转移

核心提示: 直肠癌环周切缘及下切缘的微转移是影响患者预后的重要指标之一, 低位超低位保肛手术已成为中低位直肠癌的首选术式, 在根治性手术的前提下, 直肠癌环周切缘及下切缘的微转移影响着合理的下切缘和环周切缘距离, 是手术的关键之一。

蒋松松, 戈伟, 张凯, 郑黎明, 陈刚. 中低位直肠癌切缘微转移的研究进展. 世界华人消化杂志 2015; 23(15): 2410-2414

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URL: <http://www.wjgnet.com/1009-3079/23/2410.asp>  
DOI: <http://dx.doi.org/10.11569/wjcd.v23.i15.2410>

## 0 引言

直肠癌是我国最常见的消化系肿瘤之一<sup>[1]</sup>, 采用规范化的全直肠系膜切除术(total mesorectal excision, TME)可以使局部复发率较传统手术显著降低, 但还是有5%-40%的患者发生癌肿局部复发或远处转移<sup>[2-4]</sup>, 特别是在中、低位直肠癌中局部复发或远处转移率居高不下, 残留于直肠切缘中的微转移灶可能为肿瘤局部复发的最重要原因; 直肠癌下切缘及环周切缘微转移将成为评价患者预后的重要因素。

## 1 直肠癌切缘微转移的意义

**1.1 微转移定义** 自从1868年Asworth在外周血中发现肿瘤细胞以来, 肿瘤微转移概念在临床实践中逐步建立并引起重视。1971年Huvos等在乳腺癌中首次正式提出“肿瘤微转移”的概念。其标准是直径 $\leq 2$  mm的肿瘤转移灶。肿瘤微转移是指用常规检查方法, 如影像学、常规病理学方法不能检出的非血液系统恶性肿瘤患者体内小簇或单个癌细胞的微小转移灶, 播散并存活于淋巴系统、血循环、骨髓、肝、肺等组织器官中间, 常无任何临床表现, 能够逃避免疫监视、侵犯血管并发展成肉眼可见的病变<sup>[5,6]</sup>。1993年, 国际抗癌联盟(Union for International Cancer Control, UICC)定义 $< 2$  mm的肿瘤转移灶为微转移。微转移灶无血供, 靠渗透作用获取氧和营养。癌巢生长至2-3 mm后, 癌细胞分裂和死亡处于一种动态平衡状态。这一平衡维持至癌细胞被免疫监视系统所识别、清除, 或获得血供生长, 成为显性转移。微转移是多种恶性肿瘤复发和转移的潜在因素<sup>[7]</sup>。

**1.2 直肠癌环周切缘及下切缘微转移意义** 规范的TME是中低位直肠癌的手术金标准, 可降低患者术后局部复发和转移, 但还是有5%-40%的患者发生癌肿局部复发或远处转移, TME术后组织病理评价的关键是系膜的完整性、下切缘和环周切缘状态。低位超低位保肛手术已成为中低位直肠癌的首选术式, 所以合理的下切缘距离是中低位直肠癌患者低位或超低位保肛手术的关键, 直肠癌下切缘的转移影响着患者的术后复发与转移<sup>[8]</sup>; 早在

1948年Black等<sup>[9]</sup>提出至少应切除2 cm, 1966年Grinnell<sup>[10]</sup>提出了5 cm, 1983年Williams等<sup>[11]</sup>提出了2.5 cm已足够, 后Madesan等<sup>[12]</sup>建议切除1 cm, 为了确保手术根治性建议对手术切缘做术中快速冰冻病理检, 但目前多数学者认为远端切除距离应为2 cm<sup>[13-17]</sup>。

环周切缘癌浸润(circumferential resection margin involvement, CRMi)同样是影响直肠癌预后的重要因素, Wibe等<sup>[18]</sup>研究发现, CRMi病例局部复发率为22%, 环周切缘(circumferential resection margin, CRM)阴性的病例局部复发率仅5%; 同时CRMi远处复发率为40%, CRM阴性的远处复发率仅12%, 同样Baik等<sup>[19]</sup>研究结果证实环周切缘癌浸润对术后局部复发有独立预测作用。微转移的概念提出以后, 自然引起医学界的关注, 成为目前结直肠癌研究领域的热点问题, 同时结直肠癌淋巴结微转移是否也具有等同于淋巴结转移的临床意义和预后判断价值已经渐渐得到很多学者的证实<sup>[20-26]</sup>。而直肠癌下切缘与环周切缘的微转移是否也具有等同于切缘转移的临床意义和预后判断价值已经成为新的研究热点, 需要得到进一步证实。

## 2 直肠癌切缘微转移的检测指标

**2.1 细胞角蛋白20(cytokeratin 20, CK20)** CK20具有严格的上皮组织特异性, 在癌变的上皮组织以及转移灶中均有较高的表达, CK20在以腺癌为常见的结直肠癌中高表达, 并且在正常血液、淋巴结及骨髓中均为阴性<sup>[27,28]</sup>; 在癌变的上皮组织以及转移灶中均有表达, 而且在肿瘤侵袭、转移扩散过程中能够保持相对稳定, 因此CK20作为直肠癌微转移的检测是可信的。Zhang等<sup>[29]</sup>检测CK20 mRNA作为结直肠癌患者外周血微转移指标, Ito等<sup>[30]</sup>检测CK20 mRNA作为腹腔冲洗液中微转移, 结果均显示CK20可以作为预后的独立危险因素。

**2.2 基质金属蛋白酶家族(matrix metalloproteinases, MMPs)** MMPs是一种重要的锌依赖蛋白酶, 是目前已知的能够降解胶原纤维的唯一酶类, 其中MMP-7最为重要, MMP-7由肿瘤细胞产生且能活化其他MMPs成员如MMP-2、MMP-9及灭活丝氨酸蛋白酶抑制剂<sup>[31]</sup>, 具有广泛的底物特异性和基质降解功能, 破坏机体防御肿瘤浸润转移的自然屏障, 研究证实MMP-7、MMP-9参

**□研究前沿** 肿瘤微转移是多种恶性肿瘤复发和转移的潜在因素, 直肠癌血液中肿瘤微转移已经被证实影响着患者的预后, 淋巴结的微转移已经渐渐被证实同样影响着患者的预后, 本文章将肿瘤微转移运用于环周切缘及下切缘, 这已经成为研究的新热点, 切缘的微转移是否也能影响患者预后, 还有待更多的临床及基础实验的证实。

**□相关报道** 李国胜等检测外周血CK20 mRNA表达与结直肠癌临床病理和预后的关系证实血液中结直肠癌的微转移影响患者的预后。

### 创新盘点

本文的研究重点是直肠肿瘤的微转移, 是目前研究的热点, 血液、淋巴结的肿瘤的微转移已经被证实影响着患者预后, 然而对于中低位直肠癌患者组织内的微转移, 环周切缘及下切缘的微转移, 是否也有同样影响患者的预后, 还有待进一步证实。

与了结直肠癌的发生、浸润和转移<sup>[32,33]</sup>。许多研究证实基质金属蛋白酶家族同样可以作为直肠癌微转移的检测指标。如国内孔祥瑞等<sup>[34]</sup>、冯俊伟等<sup>[35]</sup>及国外Ito等<sup>[36]</sup>、Gomes等<sup>[37]</sup>通过检测结直肠癌患者肿瘤的MMPs的表达, 研究显示MMPs可以作为患者预后的指标。

**2.3 癌胚抗原(carcinoembryonic antigen, CEA)** CEA是特异性癌胚抗原, 广泛运用于结直肠癌的诊断、治疗、预后, 是目前公认的最可信的与结直肠相关的肿瘤指标; 王金芝等<sup>[38]</sup>对50例大肠癌患者外周血中CEA mRNA检测, 发现对大肠癌诊断的敏感性为62.0%, 其阳性表达与患者的Dukes分期及有无远处转移有关, 该研究结果显示CEA可作为大肠癌病情发展和判断预后的指标, 同样Kanellos等<sup>[39]</sup>从1995-2000年对108例大肠癌患者外周血CEA进行检测, 证明了CEA mRNA的检测可以有效诊断大肠癌血液微转移。欧阳亮等<sup>[40]</sup>检测患者外周血和引流静脉血中CEA mRNA的表达, 来评估大肠癌血循环微转移, 并且得到相同的结果。目前, CEA已经作为大肠癌微转移检测的常用指标之一。

**2.4 其他指标** 随着检测技术的不断更新, 许多其他标志物也被用来检测微转移, 并取得了一定的成果, 如凋亡抑制蛋白家族中的生存素(Survivin)<sup>[41,42]</sup>、黏附分子蛋白中CD44<sup>[43-45]</sup>、CDX2<sup>[46-48]</sup>、Cadherin-17(CDH17)<sup>[49-51]</sup>等。

## 3 结论

直肠癌环周切缘及下切缘的微转移是影响患者预后的重要指标之一, 随着医疗技术的发展, 低位超低位保肛手术已成为中低位直肠癌的首选术式, 在根治性手术的前提下, 合理的下切缘和环周切缘距离是手术的关键之一, 对中低位直肠癌环周切缘及下切缘微转移的患者, 我们推荐需要行辅助性的放疗或化疗, 以降低术后的局部复发和转移。

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### 应用要点

低位超低位保肛手术已成为中低位直肠癌的首选术式, 在根治性手术的前提下, 直肠癌环周切缘及下切缘的微转移影响着合理的下切缘和环周切缘距离, 检测切缘是否存在微转移, 可以指导超低位保肛患者术后是否需要进一步预防性的治疗。



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**名词解释**  
**肿瘤微转移:** 是指用常规检查方法, 如影像学、常规病理学方法不能检出的非血液系统恶性肿瘤患者体内小簇或单个癌细胞的微小转移灶, 播散并存活于淋巴系统、血循环、骨髓、肝、肺等组织器官中间, 常无任何临床表现, 能够逃避免疫监视、侵犯血管并发展成肉眼可见的病变。

□ 符合评价  
研究的内容重要,  
具有新颖性, 而  
且研究提供了充  
足有意义的信息.

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编辑: 郭鹏 电编: 都珍珍

