直肠癌患者新辅助同步放化疗后病理完全缓解的影响因素分析

陶金华,王贵玉,马德宁,张 骞,王 猛,李 波,罗 军,蒋 来,刘 卓
(中国科学院大学附属肿瘤医院(浙江省肿瘤医院),中国科学院基础医学与肿瘤研究所,浙江 杭州 310022)

摘 要:[目的]探讨直肠癌新辅助放化疗(nCRT)后 pCR 的预测因素,并分析 pCR 对术后并发症的影响。[方法]回顾性分析中国科学院大学附属肿瘤医院 2008—2016 年收治的接受新辅助治疗并进行根治性手术切除直肠癌患者 456 例。依据术后病理将患者分为 pCR 组和非 pCR 组。单因素和多因素分析 pCR 的影响因素,并分析两组术后并发症情况。[结果]456 例患者中,98 例(21.4%)达到 pCR,pCR 组和非 pCR 组患者在年龄、性别、肿瘤分化、临床 T 和 N 期、手术类型、放疗剂量和术后并发症方面无明显差异,与 pCR 相关的因素包括肿瘤大小、治疗前 CEA 水平、放疗剂量以及手术间隔时间超过 8 周;多因素分析结果显示,治疗前 CEA 水平(OR=0.440,95%CI:0.254~0.837,*P*=0.017)和手术间隔时间(OR=2.641,95%CI:1.385~5.104,*P*=0.003)是 pCR 的独立预测因素。[结论]治疗前 CEA 水平和手术间隔时间与 nCRT 后 pCR 率有关,pCR 不增加术后并发症的发生风险。

主题词:直肠肿瘤;新辅助同步放化疗;病理完全缓解;预后
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Analysis of Influencing Factors of Pathological Complete Remission After Neoadjuvant Concurrent Chemoradiotherapy in Rectal Cancer Patients

TAO Jin-hua, WANG Gui-yu, MA De-ning, ZHANG Qian, WANG Meng, LI Bo, LUO Jun, JIANG Lai, LIU Zhuo
(*The Cancer Hospital of the University of Chinese Academy of Sciences(Zhejiang Cancer Hospital), Institute of Basic Medicine and Cancer (IBMC), Chinese Academy of Sciences, Hangzhou* 310022, *China*)

Abstract: [Objective] To investigate the predictive factors of pathologic complete response(pCR) after neoadjuvant chemoradiotherapy(nCRT) for patients with rectal cancer, and to analyze the effect of pCR on postoperative complications. [Methods] A total of 456 patients from The Cancer Hospital of the University of Chinese Academy of Sciences(Zhejiang Cancer Hospital) who had clinical stage Ⅱ/Ⅲ rectal cancer and underwent a long-course neoadjuvant CRT, followed by curative surgery from 2008 to 2016 were included. Patients were divided into two groups according to their responses to neoadjuvant therapy: the pCR and non-pCR groups. The clinical parameters were analyzed by univariate and multivariate analyses, with pCR as the dependent variable. And the postoperative complications were analyzed between the two groups. [Results] Of the 456 patients, 98(21.4%) achieved pCR. There was no significant difference in age, gender, tumor differentiation, clinical T and N stages, surgery type, radiotherapy dose and postoperative complications between pCR group and non pCR group. The factors related to pCR included tumor size, pretreatment CEA level, radiotherapy dose and the operation interval was more than 8 weeks. Multivariate analysis showed that CEA level before treatment (OR=0.440, 95%CI:0.254~0.837, *P*=0.017) and operation interval (OR=2.641, 95%CI:1.385~5.104, *P*=0.003) were independent predictors of pCR. [Conclusion] CEA level before treatment and operation interval are related to pCR rate after nCRT, pCR is not associated with an increased risk of major postoperative complications.

Subject words: rectal neoplasms; neoadjuvant chemoradiotherapy; pathologic complete response; prognosis

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通信作者:刘卓,主治医师,硕士;中国科学院大学附属肿瘤医院结直肠外科,浙江省杭州市拱墅区半山东路 1 号(310022);E-mail:zhuoliu1985@126.com
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新辅助同步放化疗(neoadjuvant chemoradiotherapy,nCRT)是当前局部进展期直肠癌的标准治疗。接受nCRT的直肠癌患者达到病理学完全缓解(pathologic complete response,pCR)与部分肿瘤残留的患者相比,长期预后效果更好[1]。直肠癌根治性手术对肠道功能、排尿/排便功能以及性功能有显著影响,必要时直肠癌患者需行临时或永久性造口。在过去十多年中,“等待与观察”这种策略越来越得到行内专家的认可,有望成为根治性放化疗患者的替代方案[2-3]。这种策略建议接受新辅助治疗后出现临床完全缓解的患者(clinical complete response,cCR)无需行手术治疗,建议密切监测,只有在复发的情况下才行补救手术[4]。最新研究数据表明,低风险肿瘤更加适合上述策略[5]。然而,cCR不等同于pCR,大约75%的cCR患者术后证实存在肿瘤残留[6]。此外,即使pCR的患者,仍然有15%有淋巴结部分肿瘤残留[7],是预后不良的独立影响因子[8]。因此,确定可预测pCR的临床因素具有重要意义,既可以提高pCR率,又可以选择患者,避免不必要的手术。本研究的目的是探讨直肠癌nCRT后预测pCR的临床病理和治疗相关因素,并分析pCR对术后并发症的影响。

1 资料与方法

1.1 一般资料

纳入标准:①经病理证实为原发性直肠癌,根据影像学判断为局部晚期(Ⅱ~Ⅲ期),且无肝肺等远处转移;②接受新辅助放化疗;③新辅助放化疗后行根治性手术。

排除标准:①短程放化疗;②放化疗期间出现远处转移需改变治疗方案者;③因肿瘤梗阻、穿孔等并发症急诊手术者;④影响手术切除范围的,经肛局部切除、内镜下切除或扩大切除者。

回顾性分析2008—2016年中国科学院大学附属肿瘤医院结直肠外科接受治疗的患者,共有456例患者符合入组标准。根据患者病案号以及医院信息系统(Hospital Information System,HIS)收集患者完整的临床数据。患者人口统计学因素包括年龄,性别,肿瘤分化程度,肿瘤大小,病理TNM分期,手术清扫淋巴结数目,术前癌胚抗原(CEA),肿瘤种植,肿瘤退缩分级(tumor regression grade,TRG),脉管瘤栓(lymphovascular invasion,LVI),周围神经侵犯(perineural invasion,PNI),环周切缘(circumferential resection margin,CRM),手术类型,手术间隔时间,放疗剂量和术后并发症。

入组456例Ⅱ~Ⅲ直肠癌患者,中位年龄54岁,男性306例(67.1%),女性150例(32.9%);肿瘤分化程度中分化占66.9%(305/456);术前临床分期Ⅱ期患者92例(27.4%),Ⅲ期患者364例(72.6%);所有患者都接受了长程放射治疗,放疗剂量50 Gy(50 Gy/25 f)。近2/3患者保留了肛门括约肌功能。nCRT结束至手术开始时间定义为手术间隔时间,手术间隔中位时间56 d(25~105 d);456例患者中,98例(21.5%)患者获得pCR,358例(78.5%)患者未获得pCR,两组患者在年龄、性别、肿瘤分化程度、临床分期、手术类型、放疗剂量以及术后并发症方面无显著性差异,两组在治疗前肿瘤大小、肿瘤CEA水平、肿瘤种植、LVI、PNI、CRM、清扫淋巴结数目以及手术间隔时间有显著性差异(Table 1)。研究经过中国科学院大学附属肿瘤医院伦理委员会批准。

1.2 观察指标

主要指标是pCR的预测因素,定义最终病理标本中不存在肿瘤(ypT_0N_0)。次要指标是术后并发症与pCR的相关性。使用术后住院时间(postoperative hospital stay,POHS)、30 d死亡率和非计划二次入院作为术后并发症的替代指标。

1.3 统计学处理

应用SPSS 23.0进行统计分析。对于连续变量使用平均数和标准差,对于分类变量使用频数和百分数来描述。对连续变量和分类变量分别使用Mann-Whitney U检验和Fisher精确检验,使用多因素Logistic回归分析与nCRT疗效独立相关的因素。使用t检验分析POHS和nCRT疗效之间的相关性。所有统计检验均为双侧,P<0.05为差异有统计学意义。

2 结 果

2.1 影响pCR因素分析

单因素分析显示,治疗前肿瘤大小(OR=0.33,95%CI:2.27~4.14,P=0.008),治疗前CEA水平(OR=0.46,95%CI:0.25~0.84,P=0.007),放疗剂量

Table 1　Comparison of clinicopathological features between two groups

Clinicopathological factors	Total (n=456)	pCR group (n=98)	Non-pCRgroup (n=358)	*P*
Age(years)	54.0±3.4	54.0±2.9	54.0±5.6	0.763
Gender				0.931
Male	306(67.1%)	67(68.4%)	239(66.8%)	
Female	150(32.9%)	31(31.6%)	119(33.2%)	
Differentiation				0.733
Well	85(18.6%)	22(22.4%)	63(17.6%)	
Middle	305(66.9%)	63(64.2%)	242(67.6%)	
Poor	61(13.4%)	11(11.2%)	50(14.0%)	
Undifferentiated	5(1.1%)	2(2.2%)	3(0.8%)	
Tumor size(cm)	4.0±1.8	3.8±1.3	5.2±1.9	<0.001
cTNM				0.693
Ⅱ	92(20.2%)	25(25.5%)	67(18.7%)	
Ⅲ	364(79.8%)	73(74.5%)	291(81.3%)	
cT classification				0.324
2	36(7.9%)	5(5.1%)	31(8.7%)	
3	331(72.6%)	75(76.6%)	256(71.5%)	
4	89(19.5%)	18(18.3%)	71(19.8%)	
cN classification				0.768
0	92(20.2%)	21(21.4%)	71(19.8%)	
1	252(55.3%)	54(55.1%)	198(55.3%)	
2	112(24.6%)	23(23.5%)	89(24.9%)	
CEA level before treatment (ng/ml)	3.8±1.9	2.9±1.4	4.2±2.1	0.001
Tumor deposition				<0.001
Positive	29(6.4%)	4(4.1%)	25(7.0%)	
Negative	427(93.6%)	94(95.9%)	356(93.0%)	
Before treatment LVI				<0.001
Positive	20(4.4%)	2(2.0%)	18(5.0%)	
Negative	436(95.3%)	96(98.0%)	340(95.0%)	
Before treatment PNI				<0.001
Positive	47(10.3%)	2(2.0%)	45(12.6%)	
Negative	409(89.7%)	96(98.0%)	313(87.4%)	
Before treatment CRM				<0.001
Positive	25(5.5%)	0(0)	25(7.0%)	
Negative	431(94.5%)	98(100%)	333(93.0%)	
Number of lymph nodes dissected	16.6±3.2	14.8±4.1	19±2.8	<0.001
Type of surgery				0.543
LAR	268(58.8%)	52(53.1%)	216(60.3%)	
APR	172(37.7%)	42(42.8%)	130(36.3%)	
Hartmann	16(3.5%)	4(4.1%)	12(3.4%)	
Radiotherapy dose(Gy)	50(40~60)	50(46~60)	50(40~60)	0.224
Interval between operations(d)	56±4.7	58±5.3	52±4.6	<0.001
Classification of postoperative complications				0.316
0	249(54.6%)	61(62.2%)	188(52.5%)	
1	115(25.2%)	21(21.4%)	94(26.3%)	
2	74(16.2%)	13(13.3%)	61(17.0%)	
≥3	18(4.0%)	3(3.1%)	15(4.2%)	
Postoperative hospital stay(d)	7.4±4.9	7.2±3.8	7.49±5.5	0.476

(OR=1.63,95% CI:1.16~2.28,*P*=0.007) 以及手术间隔时间 (OR=1.25,95% CI:1.03~1.51,*P*=0.001) 与 pCR 相关(Table 2)。

多因素分析显示,治疗前 CEA 水平≥5 ng/ml (OR=0.440,95%CI:0.254~0.837,*P*=0.017), 并且从 nCRT 完成到手术间隔时间≥8 周 (OR=2641,95% CI:1385~5.104,*P*=0.003) 为 pCR 的独立预测因素 (Table 3)。

2.2　术后并发症

在倾向调整后的分析中,pCR 组平均 POHS 为 7.26 d,非 pCR 组平均 POHS 为 7.49 d,平均缩短 0.23 d (*P*= 0.045)(Table 4)。30 天术后并发症以及非计划二次入院两组未见统计学差异 (Table 4)。

3　讨　论

文献报道直肠癌新辅助治疗后 pCR 发生率 0~30%,甚至更高[9-10],与所研究的人群密切相关。相关回顾性队列研究分析了 pCR 的影响因素, 并且已经将各种与疾病相关的因素确定为 pCR 的潜在预测因素,包括治疗前低 CEA 水平[11],nCRT 后低 CEA 水平,治疗前肿瘤大小和治疗后肿瘤大小,治疗前肿瘤转移侵袭能力,较低的 N 分期,高分化肿瘤,低位肿瘤[12],较低的 T 分期, 中性粒细胞与淋巴细胞低比例[13]。明确和检测这些因素有助于选择患者提高新辅助治疗 pCR 率,并可用于更准确地为患者提供有关其预后和治疗方案的建议。其中有几个因素也是直肠肿瘤无法保留肛门手术的必要因素; 因此, 具有这些特征

Table 2 Univariate analysis of related factors affecting pCR

Clinicopathological factors	pCR group (n=98)	Non-pCR group(n=358)	OR	95%CI	*P*
Differentiation					
Well	22(22.4%)	63(17.6%)	1.00	–	
Middle	63(64.2%)	242(67.6%)	1.01	0.86~1.19	0.823
Poor	11(11.2%)	50(14.0%)	0.98	0.63~1.06	0.348
Undifferentiated	2(2.2%)	3(0.8%)	0.73	0.46~1.17	0.342
Tumor size(cm)					
≥4	45(45.9%)	208(58.1%)	1.00	–	
<4	53(54.1%)	150(41.9%)	0.33	2.27~4.14	0.008
cT classification					
2	5(5.1%)	31(8.7%)	1.00	–	
3	75(76.6%)	256(71.5%)	0.95	0.93~1.18	0.948
4	18(18.3%)	71(19.8%)	0.68	0.67~1.07	0.813
cN classification					
0	21(21.4%)	71(19.8%)	1.00	–	
1	54(55.1%)	198(55.3%)	0.97	0.88~1.07	0.872
2	23(23.5%)	89(24.9%)	0.91	0.86~1.09	0.715
CEA level before treatment(ng/ml)					
≤5	74(75.5%)	209(58.4%)	1.00	–	
>5	24(24.5%)	149(41.6%)	0.46	0.25~0.84	0.007
Radiotherapy dose(Gy)					
<50	5(5.1%)	20(5.6%)	1.00	–	
≥50	93(94.9%)	338(94.4%)	1.63	1.16~2.28	0.017
Interval between operations (weeks)					
<8	22(22.4%)	79(22.0%)	1.00	–	
≥8	9(77.6%)	26(78.0%)	1.25	1.03~1.51	0.001

Table 3 Multivariate analysis of pCR predictors

Clinicopathological factors	OR	95%CI	*P*
CEA level before treatment(ng/ml)			
<5	1		
≥5	0.440	0.254~0.837	0.017
Interval between operations (weeks)			
<8	1		
≥8	2.641	1.385~5.104	0.003

Table 4 Postoperative complications of pCR group and non-pCR group

Clinicopathological factors	OR	95%CI	*P*
Complications after 30 days			
pCR group	1.00		
Non-pCR group	0.61	0.33~1.14	0.119
Unplanned second admission			
pCR group	1.00		
Non-pCR group	0.90	0.75~1.08	0.271

90%以上甚至全部的肿瘤患者可能是新辅助治疗后无需行根治性手术的推荐患者。研究还发现一些治疗相关因素与 pCR 可能相关,包括手术间隔时间[14-16]、同步化疗方案以及放疗剂量[17-18]。手术间隔时间一直是关注重点,虽然没有明确 pCR 的最佳手术时间间隔,但是这些研究的总体结论是,在 nCRT 结束后手术间隔时间超过 8 周,pCR 率逐渐提高。最近大量关于手术间隔时间的研究,结论一致认为手术间隔时间超过 8 周可以提高 pCR 率。

放疗剂量与 pCR 率[19-20]之间存在着确定的关系,本研究发现放疗剂量越高,pCR 率越高。目前国家综合癌症网络(NCCN)指南建议标准剂量为 45 Gy,考虑到瘤床,最高剂量为 50.4 Gy。本研究中 100%的患者接受了该范围内的剂量治疗。随着放疗剂量增加,必然也会引起毒副反应加重;然而,最近对 14 项研究包括 487 例局部进展期直肠癌患者的 meta 分析显示,全部使用 60 Gy 剂量治疗,均表现出可接受的早期毒性,pCR 率为 20.4%,3 级或更高的毒副反应仅占 10.3%。适形调强放疗(IMRT)虽然还不是标准治疗,但有助于进一步降低毒副反应,且不会影响 pCR 率[21-22]。

在本研究期间,pCR 率有所下降。可能的解释是,在研究期间,一定比例的 cCR 患者选择经肛门局部切除或非手术治疗,从研究人群中剔除这些可能最终达 pCR 的患者将导致样本偏倚,从而减少了 pCR 的患者,pCR 率下降。其次,由于选择偏倚,患者样本的偏差可能也解释了我们分析

的另一个结果，即肿瘤大小与 pCR 率相关，较大的肿瘤其 pCR 率可能较高，这一发现与其他的研究结果矛盾[23]。可能原因是，在 nCRT 后直径较小的肿瘤患者更加倾向于选择经肛门局部切除，如果他们是 pCR，则被排除在研究样本中，而非 pCR 患者则选择根治性切除术，因此包含在研究样本中，从而得出了肿瘤大小与 pCR 率相关，事实是较小的肿瘤其 pCR 率可能较高。

nCRT 后，pCR 与术后并发症相关性存在争议。Hardimanr 等[24]通过比较 nCRT 联合卡培他滨或伊立替康化疗方案直肠癌患者的病理反应类型（主要与次要应答者/非应答者），发现 nCRT 和吻合口瘘发生率之间的关联。Eisar 等[25]发现，最终病理标本中的肿瘤降期与术后并发症的风险增加明显相关。相反，Zaborowsk 等[26]发现在接受腹腔镜全直肠系膜切除术的患者中，pCR 患者术后并发症较少，伤口感染率较低，吻合口瘘发生率较低，POHS 较短。另一方面，Okuyama 等[27]发现 pCR 患者与非 pCR 患者术后并发症差异无统计学意义。

使用 POHS、术后 30 d 死亡率和非计划二次入院作为术后并发症的指标，本研究中 pCR 患者和非 pCR 患者之间没有统计学差异。倾向调整分析显示，非 pCR 患者相比于 pCR 患者的 POHS 稍长，但是否有临床意义仍不明确。

本研究的局限性包括：①与 pCR 潜在相关的因素的缺失或无法测量；②选择偏倚，排除经肛门局部切除或非手术治疗的患者；③缺乏患者详细的淋巴结分期信息，在分析中可能存在误差。

综上所述，nCRT 后直肠癌患者接受根治性切除术，超过 1/5 的患者获得了 pCR。pCR 不增加术后并发症发生风险，手术间隔时间超过 6~8 周与 pCR 率较低相关。

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