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新辅助放化疗间歇期巩固化疗对中低位局部进展期直肠癌的疗效及安全性

李素芳，钟声学，袁晓佳，吴庆珍

(广西科技大学第二附属医院放疗科，广西 柳州 545006)

[摘　要]　**目的：**探究新辅助放化疗间歇期巩固化疗对中低位局部进展期直肠癌的疗效及安全性。**方法：**回顾性分析2015年1月至2017年9月广西科技大学第二附属医院收治的64例中低位局部进展期直肠癌的临床资料。按新辅助治疗方案不同分为非巩固化疗组与巩固化疗组，每组32例。非巩固化疗组在行新辅助放化疗后6~8周进行手术治疗；巩固化疗组进行新辅助放化疗间歇期给予奥沙利铂及卡培他滨巩固化疗2~4个周期，2周后进行全直肠系膜切除(total mesorectal excision，TME)手术治疗。比较两组化疗疗效、根治性切除率、化疗不良反应发生情况，治疗前后血清肿瘤标志物癌胚抗原(carcinoembryonic antigen，CEA)、糖类抗原-199(CA199)、病灶内侵袭基因基质金属蛋白酶-9(matrix metalloproteinase-9，MMP-9)、MMP-11、锌指转录因子(Slug)表达水平，以及两组3年总体生存(overall survival，OS)率、无病生存(disease-free survival，DFS)率。**结果：**新辅助治疗后，非巩固化疗组中2例(6.25%)患者评估为临床完全缓解(clinical complete response，cCR)，巩固化疗组中有5例(15.62%)为cCR，术后病理证实均为病理完全缓解(pathologic complete response，pCR)，两组比较差异无统计学意义($P>0.05$)；巩固化疗组肿瘤消退分级(tumor regression grading，TRG)优于非巩固化疗组($P<0.05$)；巩固化疗组R0切除率高于非巩固化疗组($P<0.05$)；巩固化疗组CEA、CA199水平均低于非巩固化疗组(均$P<0.05$)；巩固化疗组手术切除病灶内MMP-9、MMP-11、Slug的mRNA水平均低于非巩固化疗组(均$P<0.05$)。巩固化疗组恶心呕吐、腹泻、血液系统毒性反应不良反应均高于非巩固化疗组(均$P<0.05$)；两组手术并发症发生情况比较，差异无统计学意义($P>0.05$)；巩固化疗组3年DFS率为46.88%，显著优于非巩固化疗组的34.38%($P<0.05$)，而两组3年OS率比较，差异无统计学意义(59.38% vs 53.13%，$P>0.05$)。**结论：**新辅助放化疗间歇期巩固化疗可提高中低位局部进展期直肠癌术前治疗效果，提高R0切除率，降低血清肿瘤标志物水平，抑制癌细胞侵袭，提高DFS率。

[关键词]　新辅助放化疗；巩固化疗；直肠癌；局部进展期；疗效

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通信作者 (Corresponding author)：李素芳，Email: gxkjdx_lisufang@163.com

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Efficacy of consolidation chemotherapy during neoadjuvant chemoradiation interval on mid-low locally advanced rectal cancer

LI Sufang, ZHONG Shengxue, YUAN Xiaojia, WU Qingzhen

(Department of Radiotherapy, Second Affiliated Hospital of Guangxi University of Science and Technology, Liuzhou Guangxi 545006, China)

Abstract **Objective:** To explore the efficacy and safety of consolidation chemotherapy during neoadjuvant chemoradiation interval in the treatment of mid-low locally advanced rectal cancer. **Methods:** The clinical data of 64 cases of locally advanced rectal cancer treated in the Second Affiliated Hospital of Guangxi University of Science and Technology from January 2015 to September 2017 were retrospectively analyzed. According to different neoadjuvant treatments, the patients were divided into a non-consolidation chemotherapy group and a consolidation chemotherapy group, with 32 cases in each group. The non-consolidation chemotherapy group received surgical treatment 6–8 weeks after neoadjuvant chemoradiotherapy. The consolidation chemotherapy group received oxaliplatin and capecitabine consolidation chemotherapy during neoadjuvant chemoradiation interval and total mesorectal excision (TME) surgery was performed after 2 weeks. The curative effect, radical resection rate and adverse reactions of chemotherapy were compared between the 2 groups. The expression levels of serum tumor markers [carcinoembryonic antigen (CEA), carbohydrate antigen-199 (CA199)], invasion genes [matrix metalloproteinase-9 (MMP-9), MMP-11 and zinc finger transcription factor (Slug)] before and after the treatment, and the overall survival (OS) rate and disease-free survival (DFS) rate at 3 years were detected and compared. **Results:** After neoadjuvant therapy, two patients (6.25%) in the non-consolidated chemotherapy group were evaluated as clinical complete remission (cCR), and five patients (15.62%) in the consolidated chemotherapy group were evaluated as cCR, and all were confirmed as pathological complete remission (pCR) by postoperative pathology, there was no significant difference between the 2 groups (P>0.05); the tumor regression classification (TRG) in the consolidation chemotherapy group was better than that in the non-consolidation chemotherapy group (P<0.05). R0 resection rate of the consolidation chemotherapy group was higher than that of the non-consolidation chemotherapy group (P<0.05); the levels of CEA and CA199 in the consolidation chemotherapy group were lower than those in the non-consolidation chemotherapy group (P<0.05). The mRNA levels of MMP-9, MMP-11 and Slug in the surgical resection lesions in the consolidation chemotherapy group were lower than those in the non-consolidation chemotherapy group (P<0.05); the adverse reactions of nausea, vomiting, diarrhea and hematological toxicity in the consolidation chemotherapy group were higher than those in the non-consolidation chemotherapy group (P<0.05). There was no significant difference in the incidence of surgical complications between the 2 groups (P>0.05). The 3-year DFS rate of the consolidation chemotherapy group was 46.88%, which was significantly better than that of the non-consolidation chemotherapy group (34.38%, P<0.05). There was no significant difference in 3-year OS rate between the 2 groups (59.38% vs 53.13%, P>0.05). **Conclusion:** Consolidated chemotherapy during the interval of neoadjuvant chemoradiotherapy in the treatment of mid-low locally advanced rectal cancer can improve the preoperative treatment effect, increase the resection rate of R0, reduce the level of serum tumor markers, inhibit the invasion of cancer cells, and improve DFS rate.

Keywords neoadjuvant chemoradiotherapy; consolidation chemotherapy; rectal cancer; locally advanced; curative effect

直肠癌是常见恶性肿瘤之一，好发于45岁左右的中年人群[1]。局部进展期直肠癌患者肿瘤与组织粘连严重，病灶面积较大，完整手术切除癌变组织难度较大，预后不良，且复发率较高[2]。针对局部进展期直肠癌预后不佳的问题，欧美国家多数肿瘤治疗中心已将新辅助放化疗联合手术切除作为标准治疗方案。新辅助放化疗可使直肠癌得到局部控制，可增加局部进展期直肠癌手术切除率和降期率[3-4]。但有研究[5-6]表明：新辅助放化疗后手术切除仍具有较高的远处转移率，且总生存率未得到明显获益。国内外专家提出在术前新辅助放化疗间歇期进行巩固化疗的策略，期望增加肿瘤降期率，提高直肠癌治疗效果，使患者生存获益。研究[7-8]显示：在术前新辅助放化疗后的间歇期进行巩固化疗的全程新辅助治疗方案，可获得较好的完全缓解率。但国内关于上述方案治疗局部中低位局部进展期直肠癌的报道较少，本研究回顾性分析64例中低位局部进展期直肠癌患者的临床资料，旨在探究新辅助放化疗间歇期巩固化疗方案的近期疗效及安全性。

1 对象与方法

1.1 对象

采用回顾性队列研究方法分析2015年1月至2017年9月广西科技大学第二附属医院收治的64例中低位局部进展期直肠癌患者的临床资料。纳入标准：1)治疗前经病理活检确诊为直肠腺癌；2)肿瘤距肛周距离小于10 cm；3)未发生远处转移；4)临床分期为cT3~4/N1~2、M0；5)既往未进行术前化疗、盆腔放疗。排除标准：1)无其他恶性肿瘤；2)既往进行直肠癌根治术；3)未完整完成新辅助治疗；4)临床资料不全。依据患者不同的治疗方案分为非巩固化疗组与巩固化疗组，每组32例。本研究经广西科技大学第二附属医院医学伦理委员会审核批准，患者均签署知情同意书。

1.2 方法

1.2.1 新辅助放化疗

非巩固化疗组进行新辅助放化疗。采用适形调强放疗：计划靶区总剂量45 Gy，放疗分割25次，1.8 Gy/次，5次/周。放疗期间口服1 000 mg/m^{2}卡培他滨(齐鲁制药有限公司，国药准字H20133361)进行化疗，2次/d，持续至放疗结束。新辅助放化疗后6~8周进行全直肠系膜切除(total mesorectal excision，TME)手术。

1.2.2 新辅助放化疗间歇期巩固化疗

巩固化疗组进行新辅助放化疗间歇期巩固化疗。新辅助放化疗同非巩固化疗组，间歇期给予CapeOX方案巩固化疗2~4个周期：第1天静脉注射130 mg/m^{2}奥沙利铂(齐鲁制药有限公司，国药准字H20203216)；第1天至第14天口服1 000 mg/m^{2}卡培他滨，2次/d；休息2周后进行TME手术。

1.2.3 手术治疗

两组手术均由同一个手术团队进行，均行经腹直肠癌切除术或腹会阴联合直肠癌根治术手术，手术均遵循TME术原则。

1.3 观察指标

1.3.1 疗效评估

于治疗后对患者进行肛门指检、结直肠镜、超声内镜、CT、MRI等检查，未发生病变残留则定义为临床完全缓解(complete clinical response，cCR)；经术后病理证实原发肿瘤获完全缓解且无肿瘤细胞残留为病理完全缓解(pathologic complete response，pCR)。采用Ryan等改良的评估肿瘤治疗反应分级系统对术后肿瘤标本进行肿瘤消退分级(tumor regression grade，TRG)评估：完全退缩为TRG 0级，接近完全退缩为TRG 1级，部分退缩为TRG 2级，退缩不良、无退缩为TRG 3级[9-10]。

1.3.2 手术评价

术后标本病理检查显示切缘远端、近端、径向边缘1 mm无肿瘤细胞残留为R0切除；显微镜下可见癌组织残留为R1切除；肉眼下可见癌组织残留为R2切除[11]。统计2组切除率。

1.3.3 肿瘤标志物

于治疗前1周内及手术前1周内抽取患者晨起空腹静脉血5 mL，用冷冻高速离心机以3 500 r/min离心15 min后取血清，采用酶联免疫分析法检测血清癌胚抗原(carcinoembryonic antigen，CEA)、糖类抗原199(cancer associated antigen，CA199)水平，试剂盒(ml038471、ml024075)均购自上海酶联生物科技有限公司。

1.3.4 肿瘤侵袭基因

使用PCR法检测治疗前活检直肠癌病灶(治疗前病灶)及手术切除病灶(治疗后病灶)标本中基质金属蛋白酶-9(matrix metalloproteinase-9，MMP-9)、MMP-11、锌指转录因子(Slug) mRNA水平。RNA提取试剂盒及反转录试剂盒(D9765、RR036A)均购置日本Takara公司。

1.3.5 化疗不良反应及术后并发症

观察并记录患者化疗后28 d内不良反应的发生情况，按美国国家癌症研究所的化疗药物不良反应评价标准(Common Terminology Criteria for Adverse Events，CTCAE)第4版对不良反应进行分级，并统计化疗后并发症发生率；观察并记录两组患者术后并发症发生情况。

1.3.6 随访

术后进行门诊随访，统计两组3年总体生存(overall survival，OS)率、无病生存(disease-free survival，DFS)率。

1.4 统计学处理

采用SPSS 21.0统计学软件进行数据分析，年龄、BMI、CEA、CA199、MMP-9、MMP-11、Slug等计量资料以均数±标准差($\bar{x}\pm s$)表示，组间对比采用独立样本t检验，组内对比采用配对t检验；性别、距肛门距离、病理分型、T分期、N分期、TNM分期、临床疗效、化疗不良反应、术后并发症等计数资料以例(%)表示，采用χ^2检验或Fisher确切概率法，TRG分级比较采用秩和检验；生存分析采用Kaplan-Meier法，组间比较用log-rank检验。P<0.05为差异有统计学意义。

2 结果

2.1 一般资料

两组患者一般资料比较，差异均无统计学意义(均P>0.05，表1)。

表1 两组一般资料比较(n=32)

Table 1 Comparison of general data between the 2 groups (n=32)

临床资料	非巩固化疗组	巩固化疗组	统计值	P
性别/例			0.254	0.614
男	19	17		
女	13	15		
年龄/岁	55.74 ± 8.46	55.49 ± 8.13	0.121	0.905
BMI/(kg·m^{-2})	23.14 ± 1.69	23.57 ± 1.42	1.102	0.275
距肛门距离/例			0.309	0.578
>6 cm	8	10		
≤6 cm	24	22		
病理分型/例			—	0.779*
G1	5	7		
G2	20	21		
G3	4	2		
G4	3	2		
T分期/例			—	0.857*
T2	2	3		
T3	20	22		
T4a	5	4		
T4b	5	3		
N分期/例			—	0.653*
N0	10	7		
N1	18	22		
N2	4	3		
TNM分期/例			0.262	0.614
II	12	14		
III	20	18		

*Fisher确切概率法。

*Fisher's exact probability method.

2.2 临床疗效

非巩固化疗组中2例(6.25%)患者在治疗后评估为cCR，巩固化疗组中有5例(15.62%)为cCR，术后病理证实均为pCR；新辅助治疗后，巩固化疗组TRG分级优于非巩固化疗组，差异有统计学意义(P<0.05，表2)。

2.3 手术评价

巩固化疗组R0切除率高于非巩固化疗组，差异有统计学意义(P<0.05，表3)。

2.4 肿瘤标志物

新辅助治疗前，两组CEA、CA199水平比较，差异均无统计学意义(均P>0.05)；新辅助治疗后，两组CEA、CA199水平均下降，且巩固化疗组低于非巩固化疗组，差异有统计学意义(均P<0.05，表4)。

2.5 肿瘤侵袭基因

两组术前活检病灶内肿瘤侵袭基因MMP-9、MMP-11、Slug的mRNA水平比较，差异均无统计学意义(均P>0.05)；新辅助化疗后，两组手术切除病灶内MMP-9、MMP-11、Slug的mRNA水平均降低，且巩固化疗组低于非巩固化疗组，差异有统计学意义(P<0.05，表5)。

2.6 化疗相关不良反应

患者均未因不良反应而终止治疗，经对症治疗后均可恢复正常。治疗过程中，巩固化疗组恶心呕吐、腹泻、血液系统毒性反应III级以上化疗不良反应发生率高于非巩固化疗组，差异有统计学意义(P<0.05，表6)。

2.7 手术相关并发症

两组手术相关并发症比较，差异无统计学意义(P>0.05，表7)。

2.8 远期疗效

非巩固化疗组与巩固化疗组3年OS率分别为53.13%、59.38%(χ^2=2.141，P=0.124)，DFS率分别为34.38%、46.88%(χ^2=4.158，P=0.037)，差异均有统计学意义。

表2 两组疗效比较(n=32)

Table 2 Comparison of curative effect between the 2 groups (n=32)

组别	TRG 0 (pCR)/[例(%)]	TRG 1/[例(%)]	TRG 2/[例(%)]	TRG 3/[例(%)]
非巩固化疗组	3 (9.38)	10 (31.25)	12 (37.50)	6 (18.75)
巩固化疗组	15 (46.88)	5 (15.63)	9 (28.13)	3 (9.38)
Z		6.520		
P		0.011		

表3 两组手术切除情况比较(n=32)

Table 3 Comparison of surgical resection between the 2 groups (n=32)

组别	R0/[例(%)]	R1/[例(%)]
非巩固化疗组	20 (62.50)	12 (37.50)
巩固化疗组	28 (87.50)	4 (12.50)
χ^2	5.333	
P	0.021	

表4 两组血清肿瘤标志物水平比较(n=32)

Table 4 Comparison of the levels of serum tumor markers between the 2 groups (n=32)

组别	CEA/(μg·L^{-1})		CA199/(U·mL^{-1})	
	新辅助治疗前	新辅助治疗后	新辅助治疗前	新辅助治疗后
非巩固化疗组	9.52 ± 3.23	7.09 ± 1.86*	30.47 ± 5.63	26.78 ± 3.23*
巩固化疗组	9.48 ± 3.35	4.18 ± 1.25*	30.36 ± 5.72	20.11 ± 2.50*
t	0.049	7.346	0.078	9.238
P	0.961	0.001	0.938	0.001

与同组治疗前相比，*P<0.05。

Compared with the same group before the treatment, *P<0.05.

表5 两组病灶内肿瘤侵袭基因mRNA水平比较(n=32)

Table 5 Comparison of mRNA levels of tumor invasion genes between the 2 groups (n=32)

组别	MMP-9		MMP-11		Slug	
	术前活检	手术切除	术前活检	手术切除	术前活检	手术切除
非巩固化疗组	1.21 ± 0.22	0.94 ± 0.18*	1.15 ± 0.28	0.86 ± 0.20*	1.18 ± 0.21	0.98 ± 0.26*
巩固化疗组	1.23 ± 0.25	0.59 ± 0.12*	1.16 ± 0.32	0.48 ± 0.15*	1.21 ± 0.23	0.73 ± 0.11*
t	0.340	9.152	0.133	8.598	0.545	5.009
P	0.735	0.001	0.895	0.001	0.588	0.001

与同组治疗前相比，*P<0.05。

Compared with the same group before the treatment, *P<0.05.

表6 两组化疗不良反应发生情况比较(n=32)

Table 6 Comparison of adverse reactions of chemotherapy between the 2 groups (n=32)

组别	恶心呕吐/[例(%)]	腹泻/[例(%)]	血液系统毒性反应/[例(%)]	周围神经病变/[例(%)]
非巩固化疗组	5 (15.63)	4 (12.50)	7 (21.88)	1 (3.13)
巩固化疗组	9 (28.13)	11 (34.38)	15 (46.88)	4 (12.50)
χ^2	3.925	4.267	4.433	1.953
P	0.048	0.039	0.035	0.162

表7 两组手术相关并发症发生情况比较(n=32)

Table 7 Comparison of surgical-related complications between the 2 groups (n=32)

组别	肠梗阻/[例(%)]	吻合口出血/[例(%)]	吻合口瘘/[例(%)]
非巩固化疗组	2 (6.25)	0 (0.00)	3 (9.38)
巩固化疗组	1 (3.13)	1 (3.13)	2 (6.25)
P	1.000	1.000	1.000

P值为Fisher精确概率所得。

P values are obtained by Fisher's exact probability.

3 讨论

局部进展期直肠癌是常见的消化道恶性肿瘤之一，由于中低位进展期直肠癌的解剖位置特殊、病灶体积较大，组织粘连及周围组织侵犯较为严重，单纯手术治疗效果不佳[12]。新辅助放化疗治疗局部进展期直肠癌具有缩小肿瘤体积、提高肿瘤降期率和根治性切除率的优点，但术前新辅助同步放化疗在降低远处转移率方面的效果欠佳[13]。为提高患者放化疗依从性及降期效果、降低可能存在的病灶转移风险，有专家[14]提出术前新辅助放化疗后的间歇期进行巩固化疗，这种全程新辅助治疗方式不仅增加了术前化疗强度，还可尽早治疗微转移病变，影响远处转移率。

pCR率是评价癌症化疗近期疗效的判断指标之一，同时也是观察及预测远期疗效的关键指标。本研究术后病理结果显示：在巩固化疗组中，15.62%的患者获得pCR，而非巩固化疗组仅有6.25%，提示采用新辅助放化疗间歇期巩固化疗方案有利于提高疗效。研究[15]显示：在经过新辅助放化疗间歇期巩固化疗的局部晚期直肠癌患者中，36%的患者获得了pCR，高于辅助治疗组的21%。本研究巩固化疗组pCR率较低的原因可能与患者入组时病理分期不同相关。2015年的一项大型回顾性分析研究[16]表明：TRG分级与淋巴管侵犯、淋巴结转移等预后因素呈正相关，而获得TRG 0级、TRG 1级的患者肿瘤治疗反应良好，其预期生存状况较好。本研究结果显示：同步放化疗后，巩固化疗组TRG分级优于非巩固化疗组，提示同步放化疗后进行巩固化疗有利于肿瘤退缩，原因可能为巩固化疗进一步使肿瘤病灶退缩，且放疗后肿瘤细胞需经过一定时间才能完全坏死，而新辅助放化疗间歇期巩固化疗方案为肿瘤组织退缩提供了充分的时间条件。本研究中巩固化疗组R0切除率高于非巩固化疗组，说明巩固化疗方案局部控制效果较好，可进一步缩小肿瘤，减少病灶及淋巴结对周围组织的侵袭，有利于病灶完整切除。

CEA与CA199为直肠癌常用肿瘤抗原标志物，对评判治疗疗效及病情进展具有重要意义[17-18]。在直肠癌发展过程中，癌细胞向周围组织侵袭，尤其是对内胚层细胞深度浸润，引起正常细胞糖基化修饰酶失活，进一步导致细胞表面糖类结构异常、糖链蛋白合成增加，最终引起CEA分泌增加；机体癌细胞发生侵袭和转移时可导致血中CA199水平升高，本研究结果显示巩固化疗组CEA、CA199水平低于非巩固化疗组，提示巩固化疗可有效抑制癌细胞侵袭和转移，增加正常细胞的自我调节能力，从而降低CEA、CA199水平。直肠癌病灶内癌细胞浸润生长与多个病理过程密切相关，其中细胞侵袭病理环节涉及到细胞外基质水解及细胞上皮-间充质转化[19]。MMP-9、MMP-11是具有蛋白水解功能的催化酶，有助于癌细胞的侵袭活动。Slug可通过与上皮标志基因结合而阻碍该基因表达，从而使细胞上皮表型减弱、细胞间质特征增强[20]。本研究结果显示：巩固化疗组手术切除病灶内MMP-9、MMP-11、Slug的mRNA水平均低于非巩固化疗组，从基因层面再次说明了巩固化疗有助于下调直肠癌病灶内促侵袭基因的表达，抑制癌细胞侵袭；巩固化疗组恶心呕吐、腹泻、血液系统毒性反应III级以上不良反应发生率高于非巩固化疗组，但两组手术并发症发生率比较无明显差异。这提示新辅助放化疗间歇期巩固化疗增加了患者急性不良反应的发生率，但并未增加术后并发症的发生风险。非巩固化疗组与巩固化疗组3年OS率(53.13%、59.38%)比较无差异，而DFS率(34.38%、46.88%)的差异有统计学意义，提示间歇期巩固化疗可使局部进展期直肠癌患者的生存获益，提高DFS率。Marco等[21]研究显示：全程新辅助治疗组3年DFS率高于未进行全程新辅助治疗组(85% vs 68%)，这与本研究结果存在差异，可能与所纳入研究对象病情不同相关。

综上，新辅助放化疗间歇期巩固化疗的治疗模式虽增加了放化疗不良反应，但提高中低位局部进展期直肠癌的TRG分级，提高R0切除率，同时能够降低血清肿瘤标志物水平，抑制癌细胞侵袭，提高DFS率。但本研究样本量较小，需进一步增加样本量，进行多中心对照研究，以验证间歇期巩固化疗对中低位局部进展期直肠癌的疗效。

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