直肠癌术前放化疗的临床研究进展

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摘　要：术前放化疗是局部晚期直肠癌的标准治疗。随着术前放化疗的广泛开展，相关研究日趋深入细化，文章就直肠癌术前放化疗的同步化疗方案、局部放疗加量、同步放化疗联合新辅助化疗等临床研究进展作一综述。
主题词：直肠肿瘤；放射疗法；化学药物疗法；外科手术
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Progress in Clinical Studies of Preoperative Chemoradiotherapy for Rectal Cancer

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Abstract：Preoperative chemoradiotherapy has become standard therapy for locally advanced rectal cancer. Based on extensively used preoperative chemoradiotherapy and some studies in-depth on relevant issues. Progress in preoperative chemoradiation，primary region radiation boost and combination modality of preoperative chemoradiation with neoadjuvant chemotherapy for rectal cancer are reviewed.
Subject words：rectal neoplasms；radiotherapy；chemotherapy；surgery

基于CAO/ARO 094等Ⅲ期临床研究证据[1-3]，直肠癌术前较术后同步放化疗可提高局部控制率和减少毒性，治疗指南推荐术前放化疗作为局部晚期直肠癌的标准治疗。随着术前放化疗的广泛开展，相关研究日趋深入细化，本文将简述直肠癌术前放化疗的临床研究进展。

1　术前同步化疗方案研究

直肠癌术前同步化疗卡培他滨可以替代静脉5-Fu已进入临床指南。2012年德国研究[4]入组392例Ⅱ/Ⅲ期直肠癌患者，随机分为5-Fu组和卡培他滨组，并因计划修正，分层为术前和术后放化疗。两组的5年总生存率(overall survival，OS)分别为76%和67%(P=0.0004)，达到非劣性研究终点；卡培他滨更显示出降低远处转移的优势（19% *vs* 28%，P=0.04）。2014年NSABP R-04研究[5]采用静脉5-Fu或卡培他滨方案术前放化疗的5年OS分别为79.9%和80.8%，支持卡培他滨替代5-Fu。

奥沙利铂加入术前同步放化疗的意义不显著(Table 1)。STAR-01[6]、ACCORD[7]、NSABP R-04[8]和PETACC 6[9]等研究提示氟尿嘧啶加奥沙利铂组的病理完全缓解（pathologic complete remission，pCR）率无获益，仅CAO/ARO 04研究[10]提示奥沙利铂组的pCR率占优。后续的生存结果[5,11,12]显示氟尿嘧啶加奥沙利铂组的3年无病生存率(disease free survival，DFS)无获益，CAO/ARO 04研究[13]仍继续提示奥沙利铂组3年DFS获益。伊立替康加入术前同步放化疗的随机研究有限。RTOG 0012研究[14]结果示5-Fu联合伊立替康的pCR率为28%。RTOG 0247研究[15]将104例局部晚期直肠癌随机分为伊立替康组和奥沙利铂组，4~8周后根治切除。初步结果显示，伊立替康和奥沙利铂组的毒性类似，伊立替康组

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Table 1 Randomize studies of preoperative concurrent chemoradiation for rectal cancer

Studies	Concurrent chemotherapy	Concurrent radiotherapy dose	N	pCR(%)	3-year DFS
German Study [4]	5-Fu	50.4Gy/28f	195		67%(5-year OS)
	Cap		197		76%
RTOG 0247[15,16]	5-Fu+Iri	50.4Gy/28f	52	10	85% (4-year OS)
	5-Fu+Ox	50.4Gy/28f	52	21	75%
STAR-01[6]	5-Fu	50.4Gy/28f	379	16(*P*=0.904)	
	5-Fu+Ox		368	16	
NSABP R04[5,8]	5-Fu/Cap	50.4~55.8Gy/25f	1608	19.1(*P*=0.46)	80.0%(5-year OS)(No difference)
	5-Fu/Cap+Ox			20.9	79.9%
1D[7,11]	Cap	45Gy/25f	299	13.9(P=0.09)	69.3%(*P*=0.574)
	Cap+Ox	50Gy/25f	299	19.2	70.9%
CAO/ARO-04[10,13]	5-Fu	50.4Gy/28f	624	12.3(*P*=0.045)	71.2%(*P*=0.03)
	5-Fu+Ox		613	16.5	75.9%
PETCC 6[9,12]	Cap	50.4/28f	547	11.3(*P*=0.37)	74.5%(*P*=0.781)
	Cap+Ox	50.4/28f	547	13.3	73.9%

Note:Cape:Capecitabine,Ox:Oxaliplatin,Iri:Irinotecan.

的 pCR 率仅 10%,低于奥沙利铂组的 21%。但 2011 年该研究长期结果[16]令人惊讶,伊立替康组 4 年DFS 和 OS 为 66%和 85%，反比奥沙利铂组 (56%和 75%)高 10%,联合伊立替康方案的研究有望重启。

西妥昔单抗或贝伐单抗是Ⅳ期结、直肠癌的主要靶向药物。西妥昔单抗是针对 EGFR 的单克隆抗体,直肠癌术前西妥昔单抗联合放化疗研究[17]显示 pCR 率为 0~23.1%，未能提示近期疗效提高(Table 2),EXPET-C 随机Ⅱ期临床研究[18]也提示卡培他滨联合奥沙利铂方案加西妥昔单抗不提高 pCR 率。贝伐单抗是针对 VEGF 的人源化单克隆抗体，放化疗联合贝伐单抗的直肠癌术前研究 pCR 率为 16%~32%[17]，缺乏随机研究。根据上述结果,直肠癌术前靶向药物同步放化疗尚不能进入Ⅲ期临床研究。

2 术前放疗加量研究

术前放化疗基础上局部放疗加量尚无明确证据，应用同步加量调强放疗(SIB-IMRT)技术的研究逐渐增多。序贯局部放疗加量研究中，RTOG 0012 随机Ⅱ期研究[14]最受关注。该研究显示 5-Fu 联合超分割放疗 45.6Gy 并局部加量至 55.2~60Gy 组的 3/4 级毒性略低于 5-Fu+CPT-11 同步 50~54Gy 组,两组 pCR 率均为 28%。RTOG 0012 研究 5 年结果[19]显示,两组局部复发率 16%和 17%,5 年 OS 分别为 61.5%和 75.3%，联合方案化疗同期局部加量放疗的模式值得研究。同步放疗加量方面,多项 SIB-IMRT 技术用于直肠癌术前同步放化疗的Ⅱ期研究[20~23]显示毒性可耐受,pCR 率为 23%~38%,但缺乏随机研究。与前

Table 2 Phase Ⅱ study of target therapy combined with preoperative concurrent chemoradiation[17]

Authors	Study type	N	Target therapy combined with concurrent chemoradiation	pCR(%)
Cetuximab				
Rodel,2008	Ⅰ/Ⅱ	58	C225,Cap,Ox,50.4Gy	9
Velenik,2009	Ⅱ	37	C225,Cap,45Gy	8
Horisberger,2009	Ⅱ	50	C225,Cap,Iri,50.4Gy	8
Bertolini,2009	Ⅱ	35	C225,5-Fu,50.4Gy	8
Mc Collum,2010	Ⅱ	67	C225,5-Fu,50.4~54Gy	31
Dewdney,2012	Ⅱ	163	C225,Cap,50.4Gy	18
Kim,2013	Ⅱ	39	C225,Cap,Iri,50.4Gy	23.1
Bevacizumab				
Wilett,2010	Ⅰ~Ⅱ	32	Bev,5-Fu,50.4Gy	16
Crane,2010	Ⅱ	25	Bev,Cap,50.4Gy	32
Velinik,2011	Ⅱ	61	Bev,Cap,50.4Gy	13
Nogue,2011	Ⅱ	47	Bev,Cap,OX,50.4Gy	34
Resch,2012	Ⅱ	8	Bev,Cap,50.4Gy	25
Kenecke,2012	Ⅱ	42	Bev,Cap,Ox,50.4Gy	17
Landry,2013	Ⅱ	54	Bev,Cap,Ox,50.4Gy	17
Dellas,2013	Ⅱ	70	Bev,Cap,Ox,50.4Gy	17

Note:C225:Cetuximab,Bev:Bevacizumab,Cape:Capecitabine,Ox:Oxaliplatin,Iri:Irinotecan.

述研究方向不同，2014 年 Engels 等[24]报告了针对术前单纯放疗同步加量的随机Ⅱ期临床研究，盆腔 46Gy 并局部加量至 55.2Gy 组(55 例)和卡培他滨同步 46Gy 组(59 例)的 pCR 率为 16%和 21%(*P*=0.33)；3 级毒性分别为 4%和 7%，无 4 级毒性。单纯放疗同步加量可推荐用于不耐受化疗的直肠癌的术前治疗，但能否替代标准同步放化疗，需要Ⅲ期临床研究证实。

直肠癌术前单纯放疗加量研究主要基于中等分割(3Gy/次)模式。Lyon R96-02 关注术前放疗剂量对保留肛门的影响[25]。T_{2-3}(腔内超声)、距离肛门≤6cm 直肠癌随机分为序贯高剂量组(D_T39Gy/13 次+腔内照射)和中等分割剂量组(D_T39Gy/13 次)。两组 pCR 率(24%:2%，*P*=0.004)和保肛率(76%:40%，*P*=0.004)，高剂量组均高于中等剂量组，但 2 年无局部复发生存率相当(92% *vs* 88%)。高剂量组腔内加量放疗提高了 pCR 率、增加保肛率，但未提高生存。Lyon R96-02 长期研究结果[26]显示，两组 10 年局部复发率相当，高剂量腔内加量组 10 年无造瘘率更高(71% *vs* 37%，*P*=0.001)。2014 年波兰Ⅲ期临床研究[27]将 T_{3-4}/T_2N^+患者（338 例）随机分为超分割高剂量组(D_T42Gy/1.5Gy，Bid）和中等分割剂量组(D_T39Gy/13 次)，放疗后 1~2 周手术。两组的 5 年无局部复发生存率(81.4%:79.8%)和 5 年 OS(61%:61%)无差别，术后并发症比例(25%:32%，*P*=0.17)相当，超分割组生活质量评估更佳。直肠癌术前中等分割(3Gy/次)单纯放疗值得研究。

3 术前大分割放疗的研究

大分割(5Gy×5 次)放疗是欧洲可切除直肠癌术前标准治疗之一，也有新的进展(Table 3)。既往研究[28]中，短程放疗 OS 和 DFS 与长程同步放化疗相当，但 pCR 率和降期率低。TROG 0104 研究提示[29]，可切除的 T_3 期直肠癌术前短程放疗与长程同步放化疗的 OS、DFS 和局部复发率均无差别。经典的术前大分割(5Gy×5 次)放疗到手术的间歇期短(5 次放疗)可尽快手术，但肿瘤降期不足；近期研究[30,31]提示延长间歇期及间歇期给予化疗可提高 pCR 率。直肠癌术前大分割(5Gy×5 次)放疗联合术前化疗对比长程同步放化疗Ⅲ期临床研究正在进行[31,32]。

4 术前放化疗联合术前化疗(靶向)的研究

局部晚期直肠癌术前同步放化疗和化疗的结合包括术前同步放化疗先于术前化疗模式和术前化疗先于术前同步放化疗模式。前者仅在少量Ⅱ期临床研究中尝试，pCR 率为 15%~23%，有待观察。术前化疗先于术前同步放化模式更受关注，随机Ⅱ期临床研究结果 pCR 率为 14%~18%，Ⅲ期临床研究相应

Table 3 Random studies of preoperative short course radiotherapy(5×5)for rectal cancer

Studies	Eligible criteria	Groups	N	pCR(%)
Stockholm Ⅲ[30],2010	Stage Ⅱ/Ⅲ resectable rectal cancer	Short course 5×5, delay 4~8 weeks	120	12.5
		Short course 5×5, delay 2~3 days	118	0.8
		Long course radiotherapy alone 2×25, delay 4~8 weeks	65	5
TROG 0104[29],2012	Stage Ⅱ/Ⅲ resectable rectal cancer	Long course concurrent chemoradiation	163	3-year local relapse rate 4.4%(*P*=0.24)
		short course 5×5	163	3-year local relapse rate 7.5%
Bujko[31] ,2013	Stage Ⅱ/Ⅲ unresectable Rectal cancer (estimated 540 cases)	Short course 5×5, following 5-Fu+Ox 3 cycles	49	21
		Long course concurrent chemoradiaiton (50.4Gy/28f，5-Fu+Ox)	48	9
RAPIDO[32],2013	Stage Ⅱ/Ⅲ rectal cancer (estimated 885 cases)	Short course 5×5,following Cap+OX 6 cycles	Recruiting	
		Long course concurrent chemoradiaiton (50.4Gy/28f，Cap)	Recruiting	

Note：Cap：Capecitabine，Ox：Oxaliplatin.

Table 4 Random studies of preoperative chemotherapy followed by concurrent chemoradiation for rectal cancer

Authors	Study type	N	New adjuvant chemotherpy	Preoperative concurrent chemoradiation	pCR(%)
Roh,2009[33]	Ⅲ	123	5-Fu+Lv 6 cycles	5-Fu+Lv,50.4Gy	13.8
		131	No	Postoperative treatment	N/A
Fernandez-Martos,2010[35]	Ⅱ	54	Cap+Ox 4 cycles	Cap+Ox,50.4Gy	14
		46	No	Cap+Ox,50.4Gy	13
Dewdney,2012[34]	Ⅱ	44	Cap+Ox 4 cycles	Cap,50.4Gy	15
		46	Cap+Ox+C225 4 cycles	Cap + C225,50.4Gy	18
Borg,2014[39]	Ⅱ	46	Bev+5-Fu+Ox 12 weeks	Bev+5-Fu,RT	23.8
		45	–	Bev+5-Fu,RT	11.4

Note:C225:Cetuximab,Bev: Bevacizumab,Cape:Capecitabine,Ox:Oxaliplatin.

队列的 pCR 率为 14%,近期疗效未见提高[33~35](Table 4)。在依据不足的情况下[35,36],NCCN 指南(2015 版)仓促将该模式列入局部晚期直肠癌术前治疗推荐,合理性有待商榷。

术前化疗+靶向治疗联合术前放化疗是直肠癌的研究热点。2013 年欧洲针对Ⅳ期直肠癌的Ⅱ期临床研究[37],采用 5×5 短程放疗序贯 6 个周期贝伐单抗联合 CAPOX 方案,结果 49 例Ⅳ期直肠癌中 43 例接受了直肠癌根治性手术,pCR 率为 26%,并据此启动 RAPIDO 研究。2014 年有研究[38]针对 T_3、距离肛缘≥5cm 直肠癌,给予贝伐单抗联合 FOLFOX 方案 4 个周期后序贯 FOLFOX 方案 2 个周期,评价进展的患者予同步放化疗+手术、未进展患者直接手术。结果 32 例患者中 2 例需同步放化疗,全组 pCR 率 25%,未见局部区域复发,4 年 OS 达 91%,该方案进入 PROSPECT 研究。2014 年,针对 T_3 期直肠癌的随机Ⅱ期临床研究[39]显示,术前贝伐单抗诱导化疗联合同步放化组的 pCR 率为 23.8%,单纯术前同步放化组 pCR 率仅 11.4%,初步肯定该研究方向。

5 术前放化疗后的手术选择

直肠癌放化疗后接受 TME 手术是目前的标准治疗,已有研究尝试按放化疗疗效决定肛门保留。2013 年 Pucciarelli 等[40]报告依据局切术后病理选择治疗的Ⅱ期临床研究,63 例 $T_{2\text{-}3}$ 期直肠癌同步放化疗后接受局部切除,术后病理 $ypT_{0\text{-}1}$ 者 43 例密切观察,其余 20 例接受 TME 手术。结果全组 3 年 OS 和 DFS 分别为 91.5%和 91.0%。GRECCAR 2 研究[41]是在 $T_{2\text{-}3}$ 期中低位直肠癌经同步放化疗后残存肿瘤≤2cm 的患者中对比局部切除或 TME 手术的Ⅲ期临床研究,局切组患者术后病理 $ypT_{0\text{-}1}$ 者观察,其余接受 TME 手术,与 Pucciarelli 研究策略相同。2014 年初步结果显示 145 例患者完成入组,35%局切患者接受 TME 手术。TME 术后病理 $ypT_{0\text{-}1}$ 患者伴 ypN_1 比例低于 $ypT_{2\text{-}3}$ 患者(0∶15%,P=0.012)。依据同步放化疗后局部切除的病理决定肛门保留的模式值得探索,生存结果有待随诊。

术前放化疗后临床 CR 者,等待观察策略受到关注。Maas 等[42]报道 192 例局部晚期直肠癌患者经术前放化疗,21 例(10.9%)达 cCR,因故拒绝手术,中位随访 25 个月,仅 1 例复发且经挽救性手术治愈。全组 2 年 DFS 和 OS 分别为 89%和 100%;与术后 pCR 者疗效相似(2 年 DFS 和 OS 为 91%和 93%),提示 cCR 患者可尝试等待观察。与之相似,2014 年巴西研究长期结果显示[43],183 例局部晚期直肠癌患者经术前放化疗,90 例达 cCR 未行手术治疗。随诊 60 个月,28 例(31%)局部区域复发,其中 26 例经手术挽救切除。全组 5 年 LRFS(包括挽救手术)94%,5 年 DFS 和肿瘤相关生存率分别为 68%和 91%,78%的患者保留肛门。

6 术前放化疗后的术后辅助化疗

现有指南推荐直肠癌术前放化疗和 TME 术后接受 5-Fu 辅助化疗,两项随机研究[44,45]挑战了该推荐(Table 5)。EORTC22921 研究[44]关于是否辅助化疗,其 2×2 设计的Ⅲ期临床研究中是否辅助化疗的两组匹配情况和样本量合理性并不确定;Adore 研究[45]关于术后化疗是否加入奥沙利铂,其仅为Ⅱ期随机研究,且单药辅助化疗组 3 年 DFS 低,存在争

Table 5 Random studies of adjuvant chemotherapy following preoperative chemoradiation and TME surgery

	Study type	N	Adjuvant chemotherapy	DFS(%)	OS(%)
EORTC 22921,2014[44]	Phase Ⅲ		–	43.7(10 year)	48.4(10 year)
		1011	5-Fu	47.0,*P*=0.29	51.8,*P*=0.32
ADORE,2014[45]	Phase Ⅱ	161	5-Fu	62.9(3 year)	
		160	5-Fu+oxaliplatin	71.6,*P*=0.047	

议。由于两项研究角度不同且存在不足,辅助化疗结论未定。直肠癌术前同步放化疗和TME术后是否辅助化疗、化疗方案和适应人群等问题有待研究。

综上，直肠癌术前放化疗临床研究的部分进展已进入指南,更多问题还在探索。同步放化疗(包括大分割放疗）联合新辅助化疗或靶向治疗成为研究热点,相关Ⅲ期临床研究正在进行。同步放化疗后的术后辅助化疗需要更多Ⅲ期临床研究证实。术前单纯放疗中等分割(3Gy/次)模式显示了长期生存结果,该模式与化疗结合有相当研究空间。同步放化疗后保留肛门的尝试受到关注,随机研究正在进行。而术前化疗方案及放疗剂量的探索还有待疗效突破。直肠癌术前放化疗的研究已经和影像诊断、分子病理、分子生物学的进展相互结合，这种结合正成为临床研究的新方向。

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