局部中晚期直肠癌术前多模式放化疗的最新进展

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摘要：我国直肠癌患者确诊时多已进展至中晚期，局部复发率及远处转移率均较高。术前放化疗能使肿瘤降期，提高手术R0切除率和肿瘤局部控制，但远处转移率仍居高不下。加强术前化疗及肿瘤局部照射剂量等多种方案的优化探索，有望进一步降低局部复发，减少远处转移，使患者达到长期生存获益，是目前局部中晚期直肠癌研究的热点。

关键词：中晚期直肠癌；术前放化疗；远处转移率
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Scheme optimization for preoperative chemoradiotherapy to locally advanced rectal cancer

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Abstract: In China, most of patients with rectal cancer have been diagnosed in advanced stage, with a higher rate of local recurrence and distant metastasis. Preoperative chemoradiotherapy can improve tumor downstaging, surgical R0 resection rate and local control. However, it has not reduced the rate of distant metastatic relapse. Enhancing preoperative chemotherapy and increasing radiation doses have been reported to further reduce the local recurrence, distant metastasis rate, even to achieve a long-term survival benefit, and becomes the hotspot of research to locally advanced rectal cancer.

Keywords: locally advanced rectal cancer; preoperative chemoradiotherapy; distant metastatic

术前新辅助放化疗联合全直肠系膜切除手术(total mesorectal excision，TME)联合术后辅助化疗是目前国际上局部中晚期直肠癌推荐治疗模式[1-2]，虽然肿瘤局部复发率(local recurrence，LR)控制较好(5% ~ 10%)，但远处转移率仍在30%左右，总生存期(overall survival，OS)未见明显提高。如何进一步提高肿瘤局部控制、降低远处转移率已成为中晚期直肠癌领域的研究热点。本文就目前国内外关于局部中晚期直肠癌术前放化疗多种模式的最新探索进展进行综述。

1 术前放疗标准方案

直肠癌术前放疗包括短程放疗(short-course radiotherapy，SCRT)和长程同期放化疗(long-course chemoradiotherapy，LCCRT)两种方案[2]。LCCRT指术前给予患者常规分割放疗DT 45.0 ~ 50.4 Gy(1.8 ~ 2.0 Gy/次，5次/周，共25 ~ 28次)，同步5-FU或卡培他滨化疗，放化疗后6 ~ 8周手术；而SCRT给予患者大分割放疗，总剂量DT 25 Gy(5 Gy/次，5次/周，共5次)，放疗结束后1周手术。多项Ⅲ期临床研究对比了术前SCRT与LCCRT，结果显示两者LR、OS相似，但LCCRT较SCRT提高了肿瘤的退缩，降低了手术风险[3-6]。波兰一项研究纳入312例可手术切除的Ⅱ、Ⅲ期直肠癌患者随机分组，155例术前行SCRT，放疗结束1周手术，157例术前行LCCRT，放化疗结束4 ~ 6周手术，结果显示LCCRT组较SCRT组提高了病理完全缓解率(pathologic complete response，pCR)(16.1% *vs* 0.7%)，切缘阳性率降低(4.4% *vs* 12.9%)，但保肛率、4年LR、无病生存期(disease-free survival，DFS)及OS方面均无统计学差异，3、4级急性不良反应发生率明显增加(18.2% *vs* 3.2%)，两组依从性分别为97.9%和69.2%[3]。目前，临床上仍然以术前LCCRT为局部中晚期直肠癌的标准治疗方案，美国国家综合癌症网(National Comprehensive Cancer Network，NCCN)2016版指南指出，对于相对早期(T3分期)直肠癌患者可以考虑行术前SCRT。

关于术前同步化疗方案，NCCN指南推荐口服卡培他滨或静滴5-FU作为首选，卡培他滨在病理缓解率、降期率、局部控制率方面与5-FU相似，由于其避免了静脉穿刺、减少静脉血栓形成、无需住院、不良反应程度轻等优点在临床被广泛使用[7]。其他药物如奥沙利铂、替吉奥、伊立替康、靶向药物西妥昔单抗和贝伐单抗等在局部中晚期直肠癌术前同步放化疗中的报道目前来看并没有使患者明显获益，同时增加了不良反应的发生风险，其应用仅限于临床试验[8-11]。

2 诱导化疗+术前放(化)疗

有学者认为术前未行足量的化疗以及术后辅助化疗依从性较差是导致目前治疗模式总生存未获益的主要原因，

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因此主张将术后辅助化疗提至术前，期望化疗后肿瘤局部缩小，控制和清除微转移灶，达到降低远处转移的目的[12]。美国纪念斯隆-凯特琳癌症中心(Memorial Sloan-Kettering Cancer Center，MSKCC)单中心回顾研究显示，61例患者先行FOLFOX4诱导化疗，然后行同步放化疗和手术，术后病理缓解率达到27%[13]。西班牙GCR-3Ⅱ期研究入组108例患者，结果显示先行4周期CAPOX诱导化疗后再行同步放化疗组与标准同步放化疗组，患者pCR、R0切除率、DFS、OS均无明显差异，但诱导化疗组Ⅲ度以上不良反应率明显降低(19% *vs* 54%)[14]。

3 术前放化疗+诱导化疗+TME手术

将术后化疗提早至放化疗与手术间的“窗口期”，以加强术前化疗强度，尽可能消灭微小转移灶，同时延长术前放化疗与手术时间间隔，提高肿瘤降期率。Glynne-Jones等[15]认为，术前放化疗+诱导化疗模式有望在提高ypCR、R0切除率和DFS方面取得突破。国外一项Ⅱ期临床研究，在术前放化疗结束至TME术前的“窗口期”内分别加入0、2、4、6个疗程mFOLFOX6方案巩固化疗，结果显示ypCR率分别为18%、25%、30%、38%，同时巩固化疗的增加和放疗至手术时间的延长，虽然增加了盆腔纤维化的发生，但并未增加手术难度和术后并发症的发生率，长期生存结果值得期待[16]。

4 短程放疗+延迟手术时间 ± 诱导化疗

短程放疗由于放疗时间短，患者依从性好，能有效节约医疗资源，在北欧应用较广泛；其缺点在于无法行同步化疗，间歇期短，肿瘤未得到足够退缩。延迟放疗后手术时间，可以使肿瘤充分降期。Bujko等[17]认为，短程放疗后延迟手术时间减少了严重的放疗并发症，pCR率约提高10%。随着手术时间的延迟，切缘阳性率和手术难度有所增加，同时对于放射抵抗的患者无疑增加了“窗口期”远处转移的风险。一些学者尝试短程放疗后延迟手术的同时添加多周期巩固化疗，期望降期并提高肿瘤控制[16,18-19]。波兰一项Ⅲ期临床研究纳入515例患者，随机分为LCCRT和SCRT两组，LCCRT组放疗剂量为50.4 Gy/28次，FOLFOX4方案同步化疗；SCRT组5×5 Gy放疗后接受3周期FOLFOX4方案巩固化疗，两组均在放疗后12周接受手术。结果表明，SCRT延迟手术组较LCCRT组急性不良反应降低($P<0.006$)，R0切除率及3年DFS相似(77% *vs* 71%，$P=0.081$；53% *vs* 52%，$P=0.74$)，局部治疗失败及远处转移率无统计学差异(22% *vs* 21%，$P=0.82$；30% *vs* 27%，$P=0.26$)，3年OS方面SCRT组稍获益(73% *vs* 65%，$P=0.046$)[20]。瑞典PAPIDO Ⅲ期研究将局部晚期直肠癌患者随机分两组，一组患者行常规术前放化疗(45～50 Gy/25次+卡培他滨)联合手术治疗，术后加(或不加)辅助化疗；另一组接受术前短程放疗(25 Gy/5次)后给予6周期CapOX方案巩固化疗后手术治疗，术后不给予辅助化疗[21]，该研究假设短程放疗联合新辅助化疗在不减少局部控制的情况下增加无病生存和总生存，结果尚未报道。

5 放疗局部加量

直肠癌复发模式以骶前及直肠系膜区复发为主，提高直肠病灶局部照射剂量，可使肿瘤最大可能退缩，提高肿瘤降期及局部控制率[22-23]。Ballonoff等[24]的Ⅱ期临床研究，直肠肿瘤及阳性淋巴结局部同期补量至55 Gy/25次，同期卡培他滨化疗，术后ypCR率达到38%，急性4级腹泻发生率为13%。西班牙Hernando-Requejo等[25]入组74例患者，盆腔照射46 Gy/23次，肿瘤局部及阳性淋巴结同期补量至57.5 Gy/23次，同期卡培他滨化疗，ypCR率达到30.6%，3年OS达到95.45%，急性3级不良反应率为17.6%，未见4级急性不良反应。荷兰Burbach等[26]认为局部进展期直肠癌局部加量至60 Gy以上可以提高患者pCR率，且不良反应可以接受。

解放军总医院放疗科在局部中晚期直肠癌术前新辅助同期加量调强放疗方面开展了一些研究，第一阶段肿瘤病灶局部同期加量至56.25 Gy/25次，结果显示，在正常器官保护剂量上加量组(simultaneous integrated boost-IMRT，SIB-IMRT$_{56.25Gy}$)相较于非加量组IMRT$_{50Gy}$安全可行；在临床疗效上，加量组ypCR率达到23%，同时未见3、4级急性不良反应，3年OS达97%[27]。第二阶段将剂量分割模式提升至58.75 Gy/25次，BED达72.6 Gy(EQD2≈60 Gy；$\alpha/\beta=10$)，目前入组40例患者，初步显示3、4级急性不良反应在10%以下，术后并发症未见明显增加，ypCR率达到30%以上，远期生存是否获益正在研究中。

6 单纯新辅助化疗

美国MSKCC中心纳入32例cT2/3中位直肠癌患者，术前行6周期FOLFOX6联合贝伐单抗化疗，未行术前放疗，结果显示R0切除率100%，pCR为25%，4年内未见局部复发，结果令人鼓舞[12]。日本一项研究入组41例高危中晚期直肠癌患者，术前单纯行4周期Xelox化疗，术后ypCR仅为12.2%[28]。对于一些局部复发风险较低的患者，是否术前单纯多周期化疗能够替代标准术前放化疗，美国大型Ⅲ期随机临床研究(PROSPECT，NCT01515787)正在探索中，研究目的在于确定非高危直肠癌患者术前应用6个疗程FOLFOX及选择性放化疗方案的有效性。国内中山大学牵头大型FORWARC随机临床研究，纳入495例Ⅱ～Ⅲ期直肠癌患者，随机分成5-FU单药化疗联合放疗组、FOLFOX6化疗联合放疗组及单纯mFOLFOX6化疗组。结果显示3组pCR率依次为14%、28%、7%，肿瘤降期率为37%、56%、36%，R0切除率为90%、88%、91%，单纯化疗组急性不良反应和术后并发症明显低于另外两组[29]，疗效及远期结果尚待进一步报道。

7 结语

关于进展期直肠癌术前放化疗模式国内外进行了许多探索，提高直肠病灶照射剂量及加强窗口期化疗有望提高远期生存，术前同步放化疗后6～8周内接受TME术仍是目前推荐的治疗模式。年龄较大、体质虚弱或有全身合并症而不能耐受同期化疗的患者可选择术前SCRT，更多新的突

破乃至新规范的建立尚需更多长期随访数据及Ⅲ期研究的证实。

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