

Review

A Review of Neoadjuvant Chemoradiotherapy for Locally Advanced Rectal Cancer

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Abstract

Neoadjuvant chemoradiotherapy has become the standard treatment for locally advanced rectal cancer. Neoadjuvant chemoradiotherapy not only can reduce tumor size and recurrence, but also increase the tumor resection rate and anus retention rate with very slight side effect. Comparing with preoperative chemotherapy, preoperative chemoradiotherapy can further reduce the local recurrence rate and downstage. Middle and low rectal cancers can benefit more from neoadjuvant chemoradiotherapy than high rectal cancer. It needs to refine the selection of appropriate patients and irradiation modes for neoadjuvant chemoradiotherapy. Different therapeutic reactions to neoadjuvant chemoradiotherapy affect the type of surgical techniques, hence calling for the need of much attention. Furthermore, many problems such as accurate staging before surgery, selection of suitable neoadjuvant chemoradiotherapy method, and sensitivity prediction to preoperative radiotherapy need to be well settled.

Key words: Rectal cancer, preoperative concurrent chemoradiotherapy

Introduction

Colorectal cancer is the fourth most common cancer worldwide, with rectal cancer estimated to be 39670. The etiology of colorectal cancer involves multiple genes and three possible pathways: chromosomal instability, mismatch repair (MMR) and the hypermethylation of the promoter of the MLH1 gene. Mutations in genes such as APC, k-ras, and p53 are associated with chromosomal instability. Microsatellite instability (MSI) is a genetic hypermutability which is present in about 90% of HNPCCs that carry germline inactivation in DNA mismatch repair genes (transform growth factor- β receptor II, the proapoptotic BAX gene and β -catenin). About 12-15% of sporadic cancer shows MSI.

Careful consideration of primary tumor, regional lymph node and distance metastasis will improve the

survival of rectal cancer with the selection of appropriate treatment. Three major treatments including surgery, radiotherapy, and chemotherapy, must be well integrated. Combined treatment reduces loco-regional recurrences but the overall survival rate has not been remarkably improved. With better staging, better surgery technique, and incorporation of radiotherapy, slightly better 5-year survival rate has been reported in several large randomized trials [1,2].

The most important prognostic factor for overall survival rate is the pathologic extent of disease (TNM stage), lymphatic invasion, vascular invasion, pathologic type, circumferential resection margin and the type of surgical technique (the length of the cutting edge and degree of lymph node dissection). Downstage effect of neoadjuvant radiochemotherapy

(nCRT) is also considered as a risk factor.

The loco-regional recurrence rate of resectable stage II ~ III rectal cancer patients was 15% to 65%. Even with the total mesorectal excision (TME), local regional recurrence rate of stage III patients is up to about 20% ~ 30%. To improve the local control rate and long-term survival rate, it is necessary for resectable stage II ~ III patients to receive neoadjuvant therapy before surgery. Preoperative concurrent radiochemotherapy (nCRT) have become the standard treatment for resectable stage II ~ III patients. For unresectable locally advanced rectal cancer, preoperative concurrent chemoradiotherapy is the only standard treatment, and most of these patients become resectable after the nCRT.

Preoperative chemoradiotherapy has been recommended as the standard treatment for locally advanced middle and low rectal cancer. Preoperative chemoradiotherapy can reduce the tumor mass, block the tumor invasion, increase the tumor resection rate, and anus retention rate, reduce iatrogenic dissemination during operation, and reduce the local recurrence rate. This article summarized the progress of the preoperative chemoradiotherapy for rectal cancer.

1 Concurrent preoperative chemoradiotherapy

National Comprehensive Cancer Network

(NCCN) guidelines recommend preoperative concurrent chemoradiotherapy as a priority standard treatment for II/III rectal cancer. Clinical Trials FFCD 92-03 and EORTC 22921 studied preoperative radiotherapy and concurrent preoperative chemoradiotherapy from 1993 to 2003. The results showed that for patients with resectable rectal cancer, concurrent preoperative chemoradiotherapy significantly further improved the pathologic complete response (pCR) and local control rate, it decreased the pathological staging compared with preoperative radiotherapy, but failed to improve the long-term survival and retention rate of anal sphincter. Besides this, a recent report from Hwang showed that pathologic stage can predict prognosis in patients who gets preoperative chemoradiotherapy [3]. Comprehensive treatment is the only way to ensure the treatment efficacy for resectable stage II-III rectal cancer [4-9] (Table 1).

Concurrent preoperative chemoradiotherapy followed with total mesorectal excision (TME) surgery plus systemic chemotherapy is the firstly recommended standard treatment method [10].

Phase III randomized study in Netherlands showed that tumor location was a prognostic factor for treatment efficacy. Middle and lower rectal cancer benefited more from neoadjuvant chemradiotherapy compared with high rectal cancer [4-9] (Table 1).

Table 1. Randomize studies of preoperative concurrent chemoradiotherapy for rectal cancer.

Studies (time)	Eligible criteria	Groups (cases)	5 year local recurrence rate (%)	5 year disease-free survival rate (%)	5 year survival rate (%)	pCR (%)
Sweden Brandengen (2008) [4]	unresectable locally advanced rectal cancer	preoperative concurrent chemoradiotherapy(n=98)		63 (p= 0.003)	66 (p=0.09)	16 (p=0.04)
		preoperative radiotherapy alone (n=109)		44	53	7
CAO/ARO-094(2004) [5]	T ₃₋₄ / N+	preoperative concurrent chemoradiotherapy(n=399)	6 (p =0.006)	68 (p > 0.05)	76 (p>0.05)	
		postoperative concurrent chemoradiotherapy(n=237)	13	65	74	
NSABP-R03(2009) [6]	T ₃₋₄ / N+	preoperative concurrent chemoradiotherapy(n=123)	23.9 (p=0.0115)	64.7 (p= 0.065)	74.5 (p=0.01)	
		postoperative concurrent chemoradiotherapy(n=131)	27.5	53.4	65.6	
Poland study (2004) [7]	stage II ~ III resectable rectal cancer	preoperative concurrent chemoradiotherapy(n=157)		68 (p >0.05)	76 (p > 0.05)	15 (p<0.001)
		Preoperative radiotherapy alone (5Gy × 5f) (n=155)		65	74	1
FFCD9203(2006) [8]	stage II ~ III resectable rectal cancer	preoperative concurrent chemoradiotherapy(n=375)	8.1 (p = 0.004)		67.4 (p = 0.684)	11.4 (p =0.001)
		Preoperative radiotherapy alone (n=367)	16.5		66.9	3.6
EORTC22921 (2006) [9]	stage II ~ III resectable rectal cancer	preoperative concurrent chemoradiotherapy(n=505)	7.6 (p = 0.002)	58.2 (p = 12)	65.8 (p = 0.84)	14 (p =0.005)
		Preoperative radiotherapy alone (n=506)	17.1	52.2	64.8	5.3

It is a current consensus that [11] patients with T3N0 and T1~3N1~2 rectal cancer judged by imaging should receive preoperative chemoradiotherapy. Only for those patients with contraindications, surgical resection is firstly considered. Neoadjuvant chemoradiotherapy of rectal cancer includes long-term preoperative radiotherapy, long-term preoperative concurrent chemoradiotherapy (concurrent radiotherapy, CRT) and short-term preoperative radiotherapy [12-15] (Table 2).

There are minor differences between National Comprehensive Cancer Network (NCCN) guideline and European Society for Medical Oncology (ESMO) guidelines regarding the neoadjuvant chemoradiotherapy for locally advanced rectal cancer.

NCCN guidelines suggest that, neoadjuvant and adjuvant therapy are recommended for those patients with high risk of local recurrence, including stage II (T3-4, lymph node negative, tumor invaded through the intestinal muscle layer) and stage III (positive lymph node, no distant metastasis). The recommended radiation dose is 45~50Gy in 25~28 fractions using multiple radiation fields (generally 3~4 fields technique). Positioning and other techniques to minimize the volume of small bowel in the fields are encouraged. The treatment period for neoadjuvant chemoradiotherapy is about 5.5~6 weeks followed with 5~10 weeks interval, after which surgery is given.

European Society for Medical Oncology (ESMO) guidelines recommended for the first time in 2013, that the treatment for rectal cancer should be stratified based on the recurrence risk. The recurrence risk is mainly evaluated by the pretreatment MRI including

the tumor invasion depth (T staging), number of metastatic lymph nodes (N staging [16], the distance to anus, invasion situation of mesorectal fascia (MRF) and extramural vascular (EMVI), etc. Patients should be divided into ultra-low-risk group, low-risk group, medium-risk group and high-risk group according to the recurrence risk. The manner of treatment after the stratification differs a lot from the traditional single treatment.

For ultra-low-risk group, surgery can be directly conducted without neoadjuvant chemoradiotherapy regardless of the tumor location. For patients with low-risk rectal cancer, which include T1~2, early T3N0, tumor invasion depth less than 5 mm assessed by MRI, unaffected mesorectal fascia (MRF) and extramural vascular (EMVI), if the tumor is located above the muscoli levator ani and it is middle and low rectal cancer, surgery can be delivered directly. If pathology indicates the adverse prognostic factors including the metastatic lymph nodes or positive circumferential resection margin, chemoradiotherapy or chemotherapy should be added [17].

Medium-risk group include patients with T2~3, part of T4a (only part of peritoneum invaded), tumor invasion depth more than 5 mm assessed by MRI, un-affected mesorectal fascia (MRF), or/and metastatic lymph nodes. For medium-risk group patients, neoadjuvant chemoradiotherapy can significantly reduce the local recurrence rate. There is controversy in the selection of long course or short course of treatment, but long course chemoradiotherapy can bring higher pCR rate, and it is currently the first choice of most radiotherapy center.

Table 2. Randomize studies of preoperative short course radiotherapy (5Gy×5f) for rectal cancer.

Studies	Time	Eligible criteria	short course radiotherapy	Drug of concurrent chemotherapy	Interval to Surgery	Cases	pCR (%)
TROG 0104 [12]	2012	stage II ~ III resectable rectal cancer	Short course, 5Gy×5f			163	3-year local relapse rate 7.5%
			Long course concurrent chemoradiotherapy			163	3-year local relapse rate 4.4% (p = 0.24)
RAPIDO [13]	2013	stage II ~ III resectable rectal cancer	short course radiotherapy, 5Gy×5f, following chemotherapy	Following Capecitabine +Oxaliplatin 6 cycles		Recruiting	
			long course concurrent chemoradiotherapy, 50.4Gy/28f,	Concurrent chemotherapy Capecitabine		Recruiting	
Bujko [14]	2013	stage II ~ III unresectable rectal cancer	short course radiotherapy, 5Gy×5f, following chemotherapy	Following 5-FU+Oxaliplatin 3 cycles	49		21
			long course concurrent chemoradiotherapy, 50.4Gy/28f,	5-FU+Oxaliplatin	48		9
Stockholm III [15]	2010	stage II ~ III resectable rectal cancer	short course radiotherapy, 5Gy×5f,		120	4~8 weeks	12.5
			short course radiotherapy, 5Gy×5f,		118	2~3 days	0.8
			long course radiotherapy alone, 50Gy/25f,		65	4~8 weeks	5

High-risk group include patients with T3~T4b with mesorectal fascia (MRF) invasion, or/and metastatic iliac lymph nodes. Long course chemoradiotherapy followed with TME surgery after 6 to 8 weeks is the first choice and accepted treatment modalities for high-risk group patients. For elderly patients or patients who can not tolerate long-term course of chemotherapy, 5×5Gy short course of radiotherapy can be considered.

ESMO guide recommended short course radiotherapy (1 week, 25 Gy/5f) or long course radiotherapy (45-50.4 Gy/1.8-2 Gy), combined with 5-fluorouracil (5-FU).

The advantages of neoadjuvant chemoradiotherapy include: (1) Preoperative tumor is susceptible to radiotherapy and the treatment effect is better than that of postoperative radiotherapy, as local blood supply is not damaged and tumor oxygenation is important for radiation sensitivity; (2) Preoperative neoadjuvant chemoradiotherapy can downstage tumors, which is illustrated through the decreased thickness of invaded intestinal wall and decreased numbers of metastatic lymph nodes, even to pCR. Thus preoperative chemoradiotherapy can decrease positive rate of surgical margin and increase R0 resection rate and anal sphincter preservation rate for low rectal cancer; (3) After neoadjuvant chemoradiotherapy, tumor tissue appears necrosis and fibrosis with different degrees, active tumor cells are greatly reduced, the probability of tumor cells falling off, spreading and planting during the operation are greatly reduced, thus the local recurrence reduces; (4) As the structure of abdomen organs are with no damage and adhesion before the neoadjuvant radiotherapy, the radiation reaction and acute toxicity reaction are minimum. Majority of patients can complete the therapeutic doses of radiotherapy with well tolerance; (5) Neoadjuvant radiotherapy can improve the local control rate.

The disadvantages of preoperative chemoradiotherapy include: (1) Patients can not obtain accurate preoperative pathologic staging in two cases including early rectal cancer (T1-T2N0) and over estimation of staging by preoperative clinical imaging [18], which will lead to certain blindness in selecting the treatment model. The other case is, if there is undiscovered distant metastasis before the surgery, the main factor affecting the prognosis is distant metastasis lesion rather than local recurrence. Thus, it is important to accurately select the patients for preoperative radiochemotherapy through improving the accuracy of preoperative imaging (including transrectal ultrasound, CT or MRI); (2) For those tumors which are insensitive to radiotherapy and chemotherapy, neoadjuvant chemoradiotherapy

may delay the opportunity of surgical resection, which leads to tumor development during this period; (3) Preoperative radiotherapy increases the difficulties of surgery, especially for short-term hypofractionated radiotherapy. In the time of surgery, tumors and surrounding tissue are still in inflammatory represented as congestion and edema which can increase intraoperative bleeding. After long-term preoperative radiotherapy, tissue becomes fibrotic and tumor closely adhere to surrounding structures, which accordingly increases the difficulties of surgical separation and postoperative complications including anastomotic leakage (LAR surgery) and perineal wound dehiscence (APR surgery).

Preoperative radiotherapy is effective in downstage, increasing resection rate and local control rate, especially for patients with low rectal cancer, and increase overall survival rate for a certain part of patients. Postoperative radiotherapy is helpful to improve the local control rate.

Multivariate analysis showed the distance from tumor to anal verge, T stage and the response of tumor to preoperative chemoradiotherapy are independent factors affecting the sphincter preserving rate [19]. Infiltration beyond serosa, lymph node metastasis and positive circumferential margin are significant predictors for local recurrence, distant metastasis and overall survival rate [20, 21].

For T3 patients with infiltration beyond serosa more than 5mm who receive only surgery, their recurrence rate and prognosis are significantly worse. Thus for those T3 patients with tumor located in the middle of rectum, infiltration depth beyond serosa less than 5 mm and with negative lymph node, short-term preoperative radiotherapy or TME surgery alone may be enough; But for those T3 patients with infiltration beyond serosa more than 5 mm, or with positive lymph node, or circumferential resection margin (CRM) >1 mm, or need Mile's surgery, long-term preoperative radiochemotherapy plus TME surgery followed by postoperative intensified chemotherapy are necessary and important. If CRM < 1 mm, the radiation dose need to be increased and more effective combined chemotherapy need to be explored besides every other treatment are same as above [22].

2 Preoperative radiotherapy

2.1 Patients selection for neoadjuvant radiotherapy

Overtreatment in preoperative radiotherapy needs to be noted and prevented. The choice and strategy of neoadjuvant therapy is based on the

clinical diagnosis. Because the clinical diagnosis induces 10% to 20% possibility of overestimate or underestimate, so how to select appropriate patients for neoadjuvant therapy is a study hotspot. Due to the error of preoperative staging, a small portion of T1-T2, N0 patients can be misdiagnosed into middle-risk and high-risk group, resulting in unnecessary treatment. Preoperative evaluation system needs to contain at least MRI or endo-luminal ultrasound. Even though, comparative study of preoperative therapy *vs* postoperative therapy published in New England Journal of Medicine in 2004 by Germany Rectal Cancer Research Group showed that there were still 18% of T1-T2N0 stage patients who have been misdiagnosed as high-risk patients (T3 or N1) by endosonography [5]. In addition, a small part of poorly differentiated rectal cancer may resist neoadjuvant treatment and tumor continues developing in the process of neoadjuvant treatment, these patients should be examined and evaluated in time. Neoadjuvant treatment can be replaced by surgery when necessary [23].

2.2 Dispute of the indication of preoperative chemoradiotherapy

2.2.1 The majority of patients with T1~2N0M0 rectal cancer can be cured by surgery.

The treatment dispute mainly exists in the mid-risk group. The data of disease-free survival rate and local failure rate showed that the survival rate of mid-risk patients has the potential to be further improved. Because preoperative radiotherapy or concurrent chemoradiotherapy can reduce the local failure of patients in stage II and III, the mid-risk group needs neoadjuvant chemoradiotherapy. There exist controversies toward selecting short-term or long-term conventional fractionated chemoradiotherapy. It showed that patients with mid-low rectal cancer and high-risk benefit from the conventional fractionated long term chemoradiotherapy [24]. Current researches have confirmed that both preoperative short-term and long-term chemoradiotherapy can contribute to the local control of T3 rectal cancer. If T3 patients can be downstaged (pT0-2) followed by neoadjuvant radiotherapy, then the adjuvant chemotherapy will contribute more.

2.2.2 The main dispute of the indication of preoperative chemoradiotherapy is T3N0 patients.

Researchers have studied the relations between local recurrence and different clinical features of T3 patients, including the tumor location, with or without neural invasion, and the distance from tumor to anus.

Peng *et al.* studied the T3N0 patients without nerve invasion and found that the 5-year local recurrence rate of these patients is only 7.9% comparing with 22.7% ($p=0.017$) of patients with neural invasion. This suggests that for this part of T3N0 patients, the role of neoadjuvant chemoradiotherapy may be limited.

2.2.3 Tumor invasion depth in the intestinal wall in T3N0 patients related to the prognosis and treatment choice.

Shin analyzed 291 cases patients with T3 rectal cancer and divided patients into 4 subgroups according to the depth of invasion, T3a, < 1mm; T3b, 1.5mm; T3c, 5~15 mm; T3d > 15mm. Five-year Disease free of survival rates of these four subgroups were for 86.5%, 74.2%, 58.3% and 29% respectively ($p<0.001$).

Merkel *et al.* study showed that regardless of metastasis status of lymph node, 5-year cancer specific survival rate of patients with T3 tumor and the infiltration depth < 5mm was 85%, whereas that of T3 patients with tumor infiltration depth ≥ 5 mm was 54%. In Mercury's study, the recurrence rate of patients who were T3 tumor infiltration depth < 5mm and without mesorectal clearance invasion, without vascular tumor thrombus, and without high risk factors evaluated by MRI, was only 1.7% when they only received surgery. So for this part of T3N0 patients, the role of neoadjuvant chemoradiotherapy may be limited.

Classification of T3 subgroup has currently been carried out in the preoperative evaluation of rectal cancer by MRI, but has not yet been formally incorporated into the TNM staging criteria. The two classification systems for assessing the depth of invasion by MRI are ESMO and RSNA standards.

ESMO standard is described as T3a, <1mm; T3b, 1.5mm; T3c, 5~15mm; T3d > 15mm. RSNA standard is described as T3a, <5mm; T3b, 5-10mm; T3c, >15mm. ESMO standard is more accurate, but increased the difficulties of measuring, and with low repeatability. RSNA standard has more clinical application value.

The possibility of local recurrence varies with the tumors locations in rectum. The risk of recurrence is significantly reduced when the tumor is located more than 10cm far from the anal margin, even if the patients received only surgery. Thus, neoadjuvant treatment has limited role for this part of patients. But this needs to be confirmed by large-scale randomized clinical studies.

2.3 Radiotherapy with sphincter preservation

A study showed when 35 patients received pelvic irradiation 55 Gy in 4~6 weeks, there were 45% and 23% of patients respectively had the urgency of

defecation and fecal incontinence. And internal anal sphincter or external anus sphincter were all damaged proved through resting (no-load) anal pressure and full load (squeeze) anal pressure compared with baseline [25]. The damage mechanism was not fully understood and electromyography of anal sphincter did not show abnormal nerve conduction signal, so it probably related to damage of muscle itself. Therefore, appropriate radiotherapy manner and dosage should be carefully considered [26].

Both three-dimensional conformal radiotherapy and intensity-modulated radiotherapy can reduce the actual received dose of anal sphincter without affecting the radiotherapy effect. The key point is to clearly contour the anal sphincter continuously in each slides of CT images (MRI is preferable), and restrict the dose of anal sphincter through lead blocking technology. It can reduce the received dose from original 33 Gy to 6 Gy [27]. For a certain portion of irradiation fields which include the anal sphincter and distal rectum, the dose should also be limited to 40~45 Gy [28].

2.4 The benefits and impact of IMRT in the neoadjuvant radiotherapy for local advanced rectal cancer

For neoadjuvant radiotherapy, Intensity modulated radiotherapy (IMRT) was used to reduce the radiation-associated toxicities by decreasing the volume of high irradiation dose of surrounding normal tissues, especially the small bowel, compared with conventional radiotherapy or three dimensional conformal radiotherapy (3DCRT) [29-31].

IMRT allows higher radiation doses to be focused on tumor while minimizing the dose to surrounding normal critical structures. Compared to conventional 2D or 3D radiation therapy, IMRT showed similar target coverage with reduced dose to the small bowel, bladder, pelvic bone and femoral heads Hartley's meta-analysis reviewed a total of 3157 rectal cancer patients and found that IMRT may provide a potential to increase treatment dose aiming to improving tumor response and decrease the dose delivered to normal structures [16, 21, 23, 29, 32-39].

Studies also compared volumetric modulated arc therapy (VMAT) and IMRT in patients with locally advanced rectal cancer (LARC) when treated with neoadjuvant chemoradiotherapy. Wen's study found that VMAT showed similar target coverage as IMRT does but with superior normal tissue sparing [40]. This indicates VMAT may be better in neoadjuvant radiotherapy, but this need more studies and evidence.

3 Selection of concurrent preoperative chemoradiotherapy scheme

Capecitabine vs 5-FU

Multiple phase I studies of concurrent chemoradiotherapy have proved the safety of capecitabine in 1600 mg/(m²·d) and 1650 mg/(m²·d) combined with preoperative radiotherapy [12, 36, 37, 41-43]. Phase II studies have indicated that the downstage rate and pathologic complete response rate (9.2%~31%) of preoperative capecitabine are similar with that of preoperative 5-FU [35, 39, 44-48]. In 2009, NCCN also recommended capecitabine as a radiotherapy sensitizer for the concurrent preoperative chemoradiotherapy of rectal cancer [49].

In 2011 ASCO, NASBP R-04 firstly randomly compared the effect of capecitabine and 5-FU in preoperative concurrent chemoradiotherapy of rectal cancer. Their results proved that there was no significant difference in pCR rate and third-degree and fourth-degree of adverse reactions rate between capecitabine and 5-FU, which confirmed capecitabine was suitable for preoperative chemoradiotherapy for rectal cancer [50].

A phase III clinical multicenter, randomized, non-inferiority study published recently also confirmed the position of capecitabine in adjuvant and neoadjuvant radiotherapy/chemotherapy of locally advanced rectal cancer. Their results showed that there was no statistical difference of 3 years' DFS and local recurrence rate between capecitabine and 5-FU. It suggested capecitabine can replace 5-FU as adjuvant or neoadjuvant chemotherapy for locally advanced rectal cancer [38].

Oxaliplatin

In the concurrent preoperative chemoradiotherapy of locally advanced rectal cancer, will the effect of combination of oxaliplatin with capecitabine or 5-FU be better than that of single drug of capecitabine or 5-FU [51]? There are 4 prospective phase III randomized studies focus on this issue including STAR-01, ACCORD12/0405, NSABPR-04 and PETACC 6 [50, 52-55] (Table 3).

Studies showed that combination oxaliplatin with capecitabine or 5-FU failed to increase the pCR rate or downstage rate comparing to single drug, while dramatically increased the third-degree and fourth-degree of adverse effects. ACCORD 12/0405 reported that there was no significant difference in 3-year local recurrence rate (4% vs. 6%), disease-free survival rate (74% vs 69%) and overall survival rate (both 88%) between combined two drugs and single drug. Therefore, NCCN recommends the standard drug of preoperative concurrent chemoradiotherapy

for rectal cancer is still single capecitabine or 5-FU [50, 53-55] (Table 3).

4 Evaluation criteria for the efficacy of neoadjuvant therapy for rectal cancer

How to evaluate the efficacy of preoperative concurrent chemoradiotherapy for local advanced rectal cancer? The criteria are very important. Evaluation methods include clinical symptoms, serum biomarkers and imagings including transrectal ultrasound (ERUs), computer tomography (CT), magnetic resonance imaging (MRI), and positron emission tomography (PET) [56, 57]. Furthermore, the following two issues are worth of attention [58, 9].

Molecular markers

The relativity between microsatellite instability (MSI) and prognosis and efficacy of chemotherapy for rectal cancer is a hotspot of molecular marker research at present [60, 61]. Ribic's study showed that MSI may indicate the good prognosis of rectal cancer patients [62]. Sargent reported the lack of mismatch repair protein (dMMR) was associated with MSI, and dMMR might be an independent predictor of good prognosis [63].

Evaluation criterion of efficacy of neoadjuvant therapy for rectal cancer

RECIST criterion (2000, version 1.0, 2009, version 1.1): considering the defects of WHO criterion, European Association of Cancer Research and Treatment, the U.S. National Cancer Institute and Canadian National Cancer Institute published a new

evaluation RECIST criterion in solid tumors in 2000 [64,65]. New criteria clearly define the size of minimum tumor focus, total numbers of target lesions and viscera restrictions in details, and avoid over evaluation of progression as WHO criterion does. RECIST criterion clearly classifies tumors into measurable lesions and immeasurable lesions.

Measurable lesions refers to tumor lesions with diameter ≥ 20 mm by routine examination method or diameter ≥ 10 mm by spiral CT. Immeasurable lesions are all other lesions except measurable lesions, including lesions with diameter less than specified size, bone lesions, meningeal lesions, peritoneal effusion, pleural effusion, pericardial effusion, abdominal mass and cystic lesions which can not be confirmed and evaluated by imaging. However, RECIST criteria still have its limitations including the followings: single diameter measurement is not suitable for tumor with non-peripheral growing manner; changes in tumor size can not fully reflect the tumor biological characteristics after treatment; anatomical changes come more slowly than functional changes; the evaluation for tumor in cavity organ is not accurate enough [56].

5 Effect of preoperative chemoradiotherapy affecting the choice of surgery

Habr-Gama *et al.* found that 5-year overall survival (OS) rate and disease free survival (DFS) rate of those patients who obtained clinical complete remission (CCR) through preoperative chemoradiotherapy can reached 83% and 92% respectively, and the local recurrence rate of patients who undergo waiting for observation after CCR was 31% [66]. Therefore caution needs to be taken in waiting and observing strategy and non-operative treatment on the patients with CCR after preoperative chemoradiotherapy. In Belluco's retrospective analysis of 139 cases of T3N0~1 patients with rectal cancer, there were no statistical significant difference of overall survival rate between patients received TME resection and patients received partial resection who all obtained pCR after neoadjuvant chemoradiotherapy [67]. The evidence suggested that the intensity of the following treatment can be reduced if patients with CCR have achieved neoadjuvant chemoradiotherapy. Suitable population must be paid attention. It also needs to judge and consider the balance between the higher recurrence rate and the higher sphincter preserving rate. In addition,

Table 3. Randomize studies of preoperative concurrent chemoradiotherapy with Oxaliplatin for rectal cancer.

Studies	Time	Concurrent chemotherapy Groups	Dose of concurrent radiotherapy	Cases	pCR (%)
ACCORD [54]	2010	Capecitabine	45 Gy/25f	299	13.9 ($p = 0.09$)
		Capecitabine combined with oxaliplatin	50 Gy/25f	299	19.2
STAR-01 [53]	2011	5-FU	50.4 Gy/28f	379	16 ($p = 0.904$)
		5-FU combined with oxaliplatin		368	16
NSABP R04 [50]	2011	5-FU / Capecitabine	50.4~55.8 Gy/25f	1608	19.1 ($p = 0.46$)
		5-FU / Capecitabine combined with oxaliplatin			20.9
CAO/AR0-04 [55]	2012	5-FU(W1,2,4,5)	50.4 Gy/28f	624	12.3 ($p = 0.045$)
		5-FU combined with oxaliplatin (W1,2,4,5)		613	16.5

the evaluation of the efficacy of neoadjuvant radiochemotherapy should be as enough as possible. It needs to maximally improve the accuracy of evaluation [24].

6 Interval time between neoadjuvant therapy and surgery

Up to now, it is hard to recommend specific interval time between the neoadjuvant therapy and followed surgery. There are two famous researches which studied the suitable interval time between the neoadjuvant therapy and followed surgery. First study is Lyon trial which was from 1990 to 2001 [68]. The neoadjuvant radiotherapy dose is 39 Gy/13 times. Group 1 took the short interval time and Group 2 took longer interval time, 6-8 weeks. The effective rate of radiotherapy of group 1 and group 2 were 53.1% and 71.7% respectively. The pathologic downstage rate of group 1 and group 2 were 10.3% and 26% respectively. The anus preservation rate of group 1 and group 2 were 68% and 76% respectively. This result suggested that long interval time is better than short interval time.

The second research is a prospective analysis of 397 patients with locally advanced rectal cancer who underwent surgical resection 4~8 weeks (interval time) after the neoadjuvant chemoradiotherapy. They studied the difference between group A (4W~6W interval time) and group B (6W~8W interval time) [69]. They found that the efficiency of chemoradiotherapy of group B can not be further improved, and the rate of complications and local recurrence rate of group B can not be further reduced compared with group A.

So, the interval time of 4~6 weeks after the neoadjuvant chemoradiotherapy before surgery is recommended.

7 Use of metformin during neoadjuvant therapy

Studies suggest that metformin may be an effective chemopreventive agent in neoadjuvant chemoradiotherapy of locally advanced rectal cancer [70]. Some study examined the effect of metformin use on pathologic complete response (pCR) rates and outcomes in rectal cancer. Metformin users have significantly higher pCR rates than either nondiabetics or diabetics not using metformin. Metformin use was significantly associated with pCR rate on univariate and multivariate analyses.

Furthermore, patients taking metformin had significantly increased disease-free and overall survival compared with other diabetic patients. Metformin use is associated with significantly higher

pCR rates as well as improved survival. Thus, metformin may be helpful in the neoadjuvant chemoradiotherapy of locally advanced rectal cancer.

8 Preoperative chemotherapy

There is new direction of preoperative chemotherapy study, introducing sequential concurrent chemoradiotherapy before the surgery.

Sequential concurrent neoadjuvant chemoradiotherapy

There have been some phase II clinical studies in this area, and got some encouraging results, pCR of 14%-36% observed. A Spanish study compared group 1 (4 cycles of XELOX, followed by concurrent neoadjuvant chemoradiotherapy with XELOX, followed by surgery) and group 2 (concurrent neoadjuvant chemoradiotherapy with XELOX, followed by surgery, followed by 4 cycles of XELOX adjuvant chemotherapy). The conclusion is inducing chemotherapy and sequential concurrent neoadjuvant chemoradiotherapy can be implemented; Preoperative chemotherapy was better tolerated than postoperative chemotherapy; Inducing chemotherapy did not increase the toxicity of concurrent chemoradiotherapy; The R0 resection rate and pCR rate of inducing chemotherapy followed by concurrent chemoradiotherapy were same as those of preoperative chemotherapy alone. These phase II studies give us a lot of inspiration. At present, phase III study, RAPIDO research, has been carried out in Europe. NCCN guidelines have recommended inducing chemotherapy combined with sequential synchronous chemoradiotherapy as a 2A grade suggestion.

9 Some questions of neoadjuvant chemoradiation for locally advanced rectal cancer need further study

Although some clinical trials have currently revealed the standard of neoadjuvant chemoradiotherapy for locally advanced rectal cancer, there are still some questions need further study[71]: (1) Whether treatment effect can be improved by increasing the radiation dose or not? (2) In the study of ASAR-01, the combination of drugs, oxaliplatin, reduced the intraperitoneal metastasis during the operation, whether it can also increase overall survival rate or not? (3) How to accurately recognize the insensitive patients in order to avoid over-treatment on insensitive patients? (4) The necessity of stratified treatment? Is it good to apply single chemotherapy drug for low-risk patients and combined chemotherapy drug for high-risk-patients?

Hope there would be more clinical trials to answer these questions.

In summary, neoadjuvant chemoradiotherapy is still the standard treatment mode for locally advanced rectal cancer. Taking a more personalized treatment scheme is a trend for patients with mid-risk rectal cancer; for mid-risk and high-risk patients, more effective combined therapeutic means is the future direction.

Competing Interests

The authors have declared that no competing interest exists.

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