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REVIEW

Adjuvant chemotherapy for rectal cancer: Is it needed?

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Abstract

Adjuvant chemotherapy has become a standard treatment of advanced rectal cancer in the West. The benefits of adjuvant chemotherapy after surgery alone have been well established. However, controversy surrounds the use adjuvant chemotherapy in patients who received preoperative chemoradiotherapy, despite it being recommended by a number of international guidelines. Results of recent multicentre randomised control trials showed no benefit of adjuvant chemotherapy in terms of survival and rates of distant metastases. However, concerns exist regarding the quality of the studies including inadequate staging modalities, out-dated chemotherapeutic regimens and surgical approaches and small sample sizes. It has become evident that not all the patients respond to adjuvant chemotherapy and more personalised approach should be employed when considering the benefits of adjuvant chemotherapy. The present review discusses the strengths and weaknesses of the current evidence-base and suggests improvements for future studies.

Key words: Rectal cancer; Adjuvant chemotherapy

Core tip: Adjuvant chemotherapy for rectal cancer is a contentious issue despite its widespread use. Recent randomised controlled trials have shown no benefit in survival of adjuvant chemotherapy in patients treated with preoperative chemoradiotherapy. It is becoming evident that not all patients benefit from adjuvant chemotherapy and identification of these patients should be the focus of future studies. The present review discusses the current evidence-base for adjuvant chemotherapy in rectal cancer and provides directions for future research.

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INTRODUCTION

The role of adjuvant chemotherapy in advanced rectal cancer in combination with preoperative chemoradiotherapy is controversial. Colorectal cancer is a major cause of morbidity and mortality worldwide. It is the third most common cancer worldwide and the fourth most common cause of cancer-related death[1]. Rectal cancer is defined as carcinoma arising in the distal 15 cm from the anal verge. It is estimated that approximately 40000 new cases of rectal cancer were diagnosed in the United States and 14226 in the United Kingdom in 2014[2,3]. Surgical treatment is the cornerstone of curative therapy for rectal cancer. Indeed, patients with early disease (stage Ⅰ, T1/2, node negative) can be effectively treated with surgical resection and 90% are expected to survive at 5 years[4]. Therapeutic approach and prognosis differs significantly in more advanced rectal cancers (stage Ⅱ and Ⅲ, T3/4, node negative or positive). Local recurrence rates are significantly higher with more advanced lesions compared to early disease (13% *vs* 5%) and 5-year survival is markedly decreased (35% *vs* 90%)[4,5]. As a result, a more aggressive approach combining radical surgical resection with total mesorectal excision (TME), radiotherapy and chemotherapy is used to treat locally advanced rectal cancers. Neoadjuvant chemoradiotherapy has now become a standard practice in the United States and Europe after the seminal German rectal cancer trial, which showed lower local recurrence rates in neoadjuvant chemoradiotherapy group compared to postoperative chemoradiotherapy[6]. Neoadjuvant chemoradiotherapy has led to an increase in sphincter sparing operations and better quality of life as a result of pre-operative downstaging, and decreased risk of local recurrence[7].

Although mortality and local recurrence rates have improved dramatically over the past decades as a result of more accurate preoperative staging modalities [magnetic resonance imaging (MRI), endoscopic ultrasound] and surgical techniques (TME), the rate of systemic relapse is still unacceptably high and contributes significantly[8]. About a third of patients with advanced rectal cancer will eventually develop distant metastases[6]. In order to prevent this, postoperative adjuvant chemotherapy has been employed in the management of locally invasive treatment of rectal cancer and is now incorporated into most treatment protocols in the west. Various national and international guidelines (National Comprehensive Cancer Network, American Society of Clinical Oncology, European Society of Medical Oncology, National Institute of Clinical Excellence) recommend postoperative chemotherapy with either capecitabine or 5-FU for a total of 6 mo for stage Ⅱ and Ⅲ rectal cancers irrespective of surgical pathology results[9]. Despite the widespread use of this approach, the evidence for beneficial effects of postoperative chemotherapy is conflicting. Indeed, the long-term results (10 years of follow-up) of the European Organisation for Research and Treatment of Cancer (EORTC) 22921 randomised trial published in 2014 showed no benefit of postoperative adjuvant chemotherapy after preoperative chemoradiotherapy prompting the authors to question the validity of current recommendations[10]. Whether or not postoperative chemotherapy should be given is an important clinical dilemma for healthcare professionals, as chemotherapy is associated with significant systemic toxicity, which may lead to diminished quality of life[11]. The present review provides an update on the current evidence-base for treatment of rectal cancer with adjuvant chemotherapy, discusses the strengths and pitfalls of recent research and suggests improvements for future studies.

DIFFERENCES BETWEEN COLON AND RECTAL CANCER

Current recommendations for adjuvant chemotherapy treatment of rectal cancer are based on the evidence, which is largely extrapolated from studies in colon cancer[12-14]. However, it is now known that clinical course and biology of colon and rectal cancers differ significantly. Rectal cancers have distinct gene expression profile, fewer BRAF mutations and less microsatellite instability[15-17]. Furthermore, colon and rectum posses distinct embryological origins as well as anatomical and physiological characteristics. Clinically, rectal cancers have a worse prognosis in the early stages of disease, but longer survival in more advanced stages compared to colonic tumours of the same stage[18]. Finally, it is more difficult to achieve complete resection of rectal cancers with circumferential margin involvement, due to multi organ involvement, compared to colonic cancers[19]. As a result, it is scientifically justifiable to consider colonic and rectal cancers as distinct diseases and therefore the benefits of adjuvant chemotherapy cannot be assumed to be equal in both conditions.

POSTOPERATIVE CHEMOTHERAPY IN COMBINATION WITH SURGERY ALONE

The value of postoperative chemotherapy in patients treated only with curative surgery has been investigated in a large number of trials. The Cochrane systematic review and meta-analysis (2012) of 21 RCTs comparing postoperative chemotherapy with observation alone found significant improvement in both overall (HR = 0.83, 95%CI: 0.76-0.91) and disease-free survival (HR = 0.75, 95%CI: 0.68-0.83)[20]. Data, pooled from almost 10000 patients, showed that 5-FU based postoperative chemotherapy was associated with risk reduction of 17% and 25% in overall and disease-free survival respectively. Only 5 out of 21 trials showed significantly

positive results, which implies that large numbers of study participants are needed to discern a small, but clinically important, difference. Of note, nine trials were conducted in Japan. Despite considerable differences in populations and treatment practices of rectal cancer in the west and in Asian countries (infrequent use of neoadjuvant chemoradiotherapy and different surgical technique in Japan), the authors of the Cochrane review found similar results both for Western and Japanese studies. It is unclear which groups of patients benefit most from chemotherapy, as only three trials reported results based on TNM stage. The QUASAR trial (*n* = 3239, 948 with rectal cancer) found significantly prolonged overall and disease survival in patients with stage Ⅱ (node negative) disease[12]. In contrast, a subgroup meta-analysis of three trials, which included patients with stage Ⅲ disease showed no significant improvement in overall survival, but longer disease-free survival[21-23].

The results should be interpreted with caution as the heterogeneity of the studies was high, most likely due to variable TNM stages (Duke's stages A to C). In addition, the studies were conducted over the course of the past three decades, during which surgical and oncological treatment practices have changed considerably. Indeed, there is an argument that postoperative chemotherapy without preoperative treatment was only found beneficial in older studies not employing TME surgery[24]. No RCTs in the TME era have evaluated the value of postoperative chemotherapy and are unlikely to be performed as neoadjuvant treatment has become a "gold standard" approach. Finally, postoperative radiotherapy was administered alongside chemotherapy in some of the studies, hence individual contribution of chemotherapy to increased survival is difficult to determine.

POSTOPERATIVE CHEMORADIATION AFTER SURGERY ALONE

Therapeutic utilisation of the synergistic effects of radiation and chemotherapy has dominated the treatment of cancer for many decades. The benefits of chemoradiation for rectal cancer was established in a number of trials (NSABP R-01, GITSG-7175, NCCTG-794751, GITSG-7180) in 1980s and early 1990s and is now a recommended optimal treatment modality in patients undergoing curative surgical resection[25-28]. The GITSG-7175 study (*n* = 227) was the first trial to show lower recurrence rates (33% *vs* 55%), but no effect on overall survival in patients treated with radiotherapy and fluorouracil with semustine (methyl-CCNU) compared to surgery alone and had to be terminated prematurely as a result of these findings[25]. The following NCCTG trial randomised 204 patients to either chemoradiation (FU-semustine) or radiotherapy. In contrast to GITSG trial, chemoradiotherapy was found to be associated with significant reduction (46%) in cancer related deaths compared to radiotherapy alone[27]. Based on these studies National Institute of Health in 1990 produced the guidance recommending that all rectal cancers with stages Ⅱ and Ⅲ should be treated with a combined pelvic irradiation and concomitant chemotherapy[29].

To date, only the GITSG-7175 trial compared postoperative chemotherapy alone *vs* chemoradiotherapy and found no significant difference in survival and local recurrence rates[25]. The results of the NASPB R01 trial (*n* = 555) showed that chemotherapy, when compared to surgery alone or radiotherapy, is associated with significantly prolonged disease-free survival[28]. Since postoperative radiotherapy has not been shown to prolong survival in rectal cancer, it is reasonable to believe that chemotherapy when combined with radiotherapy is responsible for reducing the risk of systemic dissemination of rectal cancer. The seminal trial, which compared preoperative with postoperative chemoradiation showed that patients achieve significantly better local control and have lower levels of systemic toxicity, although overall survival is similar in both approaches[6]. As a result of the findings of this trial, preoperative chemotherapy has gradually become a mainstay approach to treatment of locally advanced rectal cancer.

POSTOPERATIVE CHEMOTHERAPY AFTER NEOADJUVANT (CHEMO)RADIOTHERAPY AND SURGERY

Although postoperative chemotherapy with or without radiotherapy prolongs survival in patients treated with surgery alone, the evidence is much more conflicting in the setting of neoadjuvant treatment. Since majority of the patients in the West nowadays receive neoadjuvant chemoradiotherapy, the most pertinent question regarding the benefit of postoperative chemotherapy remains unanswered by the studies described above. In light of several systematic reviews reporting no benefit of neoadjuvant chemoradiotherapy when compared to radiotherapy alone in terms of disease free and overall survival, the role of postoperative chemotherapy has come into question[30,31]. Five recent European trials (CHRONICLE, QUASAR, EORTC 22921, PROCTO-SCRIPT, I-CNR-RT) enrolling 3143 patients with stage Ⅱ and Ⅲ rectal cancer investigated the benefits of postoperative chemotherapy after neoadjuvant chemoradiotherapy and surgery (Table 1)[10,12,32-34]. Four out of five trials reported negative results and only QUASAR study found significantly increased survival in the postoperative chemotherapy group. EORTC 22921 trial (*n* = 1011) employed 2 × 2 factorial design comparing the effectiveness of postoperative 5-FU and leucovorin based chemotherapy after preoperative chemoradiation or radiotherapy alone[10]. No difference in overall and disease-free survival was reported at 5 and 10 years of follow up. In the Italian trial (I-CNR-RT), 635 patients were treated with preoperative chemoradiotherapy

Table 1 Trials comparing adjuvant chemotherapy with observation after neoadjuvant treatment

	Sample size	Accrual period	Total mesorectal excision	Preoperative treatment	Adjuvant treatment	Adherence (%)	Overall survival (adjuvant *vs* observation)	Disease-free survival (adjuvant *vs* observation)	Local recurrence (adjuvant *vs* observation)
EORTC 22921	1011	1993-2003	36.80%	25 doses of 1.8 Gy and fluorouracil-based chemotherapy	Four courses every 3 wk of fluorouracil and folinic acid	42%	51.8% *vs* 48.4%, $P = 0.32$	47% *vs* 43.7%, $P = 0.29$	11.7% *vs* 11.8%
CHRONICLE	113	2004-2008	NR	45 Gy and fluorouracil-based chemotherapy	Six courses every 3 wk of oxaliplatin and oral capecitabine	48.10%	89% *vs* 88%, $P = 0.75$	78% *vs* 71%, $P = 0.56$	Not reported
PROCTOR-SCRIPT	437	2000-2013	All patients	25 doses of 1.8-2.0 Gy and fluorouracil-based chemotherapy	Six courses of fluorouracil and folinic acid OR 12 courses of fluorouracil and folinic acid OR eight courses every 3 wk of oral capecitabine	73.60%	80.4% *vs* 79.2%, $P = 0.73$	62.7% *vs* 55.4%, $P = 0.13$	7.8% *vs* 7.8%, $P = 0.69$
I-CNR-RT	634	1992-2001	NR	25 doses of 1.8 Gy and fluorouracil-based chemotherapy	Six courses of fluorouracil and folinic acid	58.50%	70% *vs* 69.1%, $P = 0.77$	62.8% *vs* 65.3%, $P = 0.88$	4.5% *vs* 6.4%
QUASAR	3239 (948 with rectal cancer)	1994-2003	NR	Radiotherapy (21%)	Thirty doses of intravenous FU with high or low dose folinic acid	58.00%	HR = 0.8 (0.6-1.07)[1]	HR = 0.69 (0.51-0.94)[1]	19.8% *vs* 27.2%

[1]Hazard ratios were obtained from Cochrane review by Petersen *et al*[20]. HR: Hazard ratios; FU: Fluorouracil; NR: Not reported.

and then were randomised into observation and postoperative chemotherapy groups[33]. The investigators found no difference in 5-year survival and the distant metastases rates. PROCTO-SCRIPT trial ($n = 437$) patients treated with preoperative chemoradiotherapy were randomised into observation and treatment arms, which consisted of 5-FU plus leucovorin or capecitabine regimes[34]. The trial was stopped prematurely due to slow accrual and showed no benefit of postoperative chemotherapy in terms of overall survival. Another trial (CHRONICLE, $n = 112$), which was also terminated early due to slow accrual, found no survival advantage in patients treated postoperatively with capecitabine and oxaloplatin (XELOX)[32]. QUASAR trial was the only study to show borderline significant benefit of adjuvant chemotherapy after preoperative radiotherapy, however only 21% of patients with rectal cancer or both (rectal/colon) had radiotherapy[12].

In all of the studies above, adjuvant chemotherapy was associated with only marginal benefit, which was not statistically significant. None of the trials were large enough to detect a 5% difference in 5-year survival, hence the likelihood of type Ⅱ error was high[35]. As a result, Breugom *et al*[36] performed a meta-analysis of available studies using patient-level data. Unfortunately, the authors were not able to obtain the data from the QUASAR trial investigators. The analysis of 1196 patients with stage Ⅱ and Ⅲ rectal cancer with R0 resection showed no significant effect of adjuvant chemotherapy on overall survival, disease-free survival and distant metastases. In subgroup analysis, patients with tumours located 10-15 cm from the anal verge seemed to benefit from adjuvant chemotherapy as disease-free survival was significantly prolonged (HR = 0.59, 95%CI: 0.40-0.85; $P = 0.005$) and rates of distant metastases were lower (HR = 0.61, 0.40-0.94; $P = 0.025$). There was no survival difference between stages Ⅱ and Ⅲ.

A meta-analysis performed by Petrelli *et al*[37], which included 16 randomised and non-randomised studies (a total of 5457 patients) found that overall adjuvant chemotherapy had significantly positive effects on disease-free and overall survival and distant metastasis rates. However, the validity of the results is limited due to significant bias of non-randomised studies. Indeed, in stratified analyses significant benefit was observed only in the non-randomised studies. Study participants who received chemotherapy were often younger, had node negative disease and showed good response to preoperative chemotherapy. In addition, median follow up rates were often shorter than 5 years, which could have exaggerated overall and disease-free survival in the short term.

The findings of these studies beg two questions question: Are current recommendations for adjuvant chemotherapy in rectal cancer valid? Or, are the findings of the

studies reliable enough to change current practice?

POTENTIAL PITFALLS OF THE CURRENT EVIDENCE

Although the RCTs described above are generally held to have robust designs, there are some important considerations to be made when interpreting the results. Poor adherence to postoperative chemotherapy is a well-recognised problem in the treatment of colorectal cancer. Of the patients assigned to the adjuvant chemotherapy group in the EORTC 22921 trial 25% did not start the adjuvant treatment, with similar figures in other studies. The numbers are even smaller for completion rates of chemotherapy with only around half of the patients fully complying with the treatment. Although this may reflect a real life scenario, it is pertinent to determine the effects of optimal chemotherapy treatment so that clinicians and patients can make the informed decision regarding the need for adjuvant chemotherapy. Breugom *et al*[34,36] argued that the results of the trials could have not been affected by poor adherence as PROCTOR-SCRIPT trial showed no benefit of chemotherapy for patients who completed all cycles. Unfortunately the number of patients in this group (n = 159) is too small to detect the clinically meaningful difference.

Another important consideration is a change of surgical practices over long accrual periods. Most trials commenced recruitment in the early 1990s (EORTC 22921, I-CTR-RT, QUASAR). Surgical practices have changed considerably since then and the type of surgery patients received in the trials poorly reflect current standards. For instance, in the EORTC 22921 trial TME was performed in only 36.8% of patients, which contrasts with the contemporary practices where TME is performed virtually in all patients with locally advanced rectal cancers[38]. Furthermore, abdominoperineal resection rate was 47.2% in the intervention arm in the CHRONICLE study, which is significantly higher proportion compared to the United Kingdom National Bowel Cancer Audit Programme (24%)[39]. These deviations from current treatment practices raise concerns about the applicability of the study findings to today's management of rectal cancer.

One of the most important shortcomings of the present studies is the use of inadequate imaging modalities. All of the RCTs relied on CT staging before the commencement of neoadjuvant treatment. Endoscopic ultrasound was only performed in 67% of patients in the EORTC 22912 trial and only in a selected proportion in I-CNR-RT study. The accuracy of the CT based-TNM staging is not perfect and the risk of overstaging is high[40]. Hence, it is likely that many patients were over-treated. Furthermore, CT does not enable accurate assessment of circumferential resection margin (CRM), which is an independent prognostic factor for disease-free survival[41-43] (Figure 1). The best modality to assess the extent of CRM is MRI, however no chemotherapy trials have reported the use of MRI[44] (Figure 1).

Furthermore, lymph node status was determined using pathological staging. Earlier studies have indicated that preoperative chemoradiotherapy may reduce the number of lymph nodes available for pathological examination and thus may affect the accuracy of staging[45-49]. There is a theoretical risk that some patients with metastatic lymph nodes are not identified on pathological staging and are at risk of systemic dissemination[49]. In particular, proximal node involvement carries a significant risk of distant metastasis[49]. Advanced imaging modalities, such as PET and MRI may enable accurate assessment of lymph node involvement before neoadjuvant chemoradiotherapy and would subsequently guide clinicians in deciding whether or not adjuvant therapy is necessary (Figure 2).

The timing of adjuvant chemotherapy may also have a considerable effect on survival outcomes and has been largely overlooked in the present studies. Several meta-analyses showed that the longer the chemotherapy is delayed the shorter survival is in patients with colorectal cancer[50,51]. One of the reasons why colon cancer responds to adjuvant chemotherapy and rectal does not may be prompt administration of adjuvant chemotherapy[9]. Stoma and prolonged preoperative radiotherapy especially in combination with chemotherapy for rectal cancer means that adjuvant chemotherapy may not start until months later. Adverse consequences of delayed chemotherapy are also supported by animal studies, in which surgery was shown to increase the number of circulating neoplastic cells and promote metastatic growth[52]. In addition, surgery has been shown to enhance the production of oncogenic growth factors, such as transforming growth fact - alpha[53,54].

Finally, the most informative analysis of these trials by Breugom *et al*[34,36] is not without limitations. Out of 2195 patients available from four trials, only 1196 were included. These included patients only with stage Ⅱ and Ⅲ disease who had R0 resection, hence the meta-analyses does not address the question whether responders to neoadjuvant chemoradiotherapy achieve any benefit from adjuvant chemotherapy (see below). In addition, QUASAR, which was one of the largest trials and showed positive effects, was not included in the analysis.

WHO MIGHT BENEFIT FROM POSTOPERATIVE CHEMOTHERAPY?

Several studies have suggested that not all the patients with rectal cancer benefit from adjuvant chemotherapy and that only certain groups may respond to treatment. The degree of bowel wall penetration and nodal involvement has been shown to be one of most important predictive factors for local relapse, distant metastasis and survival[4,5,55]. For example, in a pooled analysis

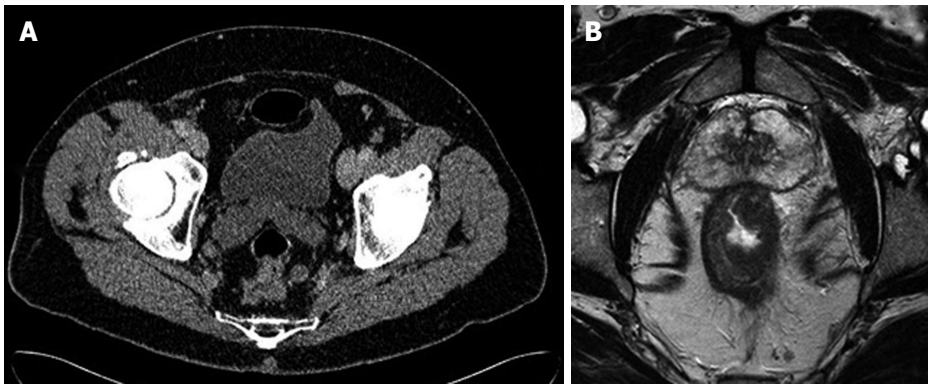

Figure 1 Computed tomography (A) and magnetic resonance imaging (B) of the T3 rectal cancer. Note poor quality of circumferential margin on the computed tomography scan compared to the magnetic resonance imaging.

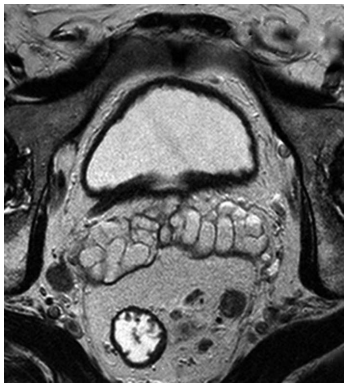

Figure 2 Magnetic resonance imaging of the T3 rectal cancer showing lymph node involvement.

of five randomised control trials in the United States, which included 3791 patients with rectal cancer, 5-year overall survival for T1-2N0 stage was 90%, for T3-4N0 60%, T4N1 30%[4]. Many studies have been conducted to investigate the benefits of chemotherapy in certain subgroups of patients, however the results haven been rather conflicting. Most of the evidence comes from post-hoc subgroup analyses of randomised control trials or retrospective/prospective non-randomised studies, hence is subject to inherent weaknesses of these designs.

The exploratory analysis of the early results (5 years of follow up) of the EORTC 22921 trial has showed that only patients downstaged to ypTN0-2 benefit from adjuvant chemotherapy, while patients with ypTN3-4 do not[56]. In line with this, two other studies by De Stefano *et al*[57] and Janjan *et al*[58] found that patients who responded to preoperative chemoradiotherapy benefited from adjuvant chemotherapy, however no benefit was observed in the non-responders group. Such observations also have sound scientific basis, since rectal cancers are highly heterogenous tumours and preoperative chemotherapy may enable to predict favourable tumour biology, which may respond to subsequent adjuvant chemotherapy.

On the other hand, there have been several reports to suggest that downstaged ypTNM0-2 tumours follow a more indolent course postoperatively and do not require additional chemotherapy. Three studies have shown that patients with good response to preoperative chemotherapy had excellent 5-year survival (90% survival) irrespective whether adjuvant chemotherapy was given or not[59-61]. Hence, additional chemotherapy may not be necessary and potentially harmful. This is also supported by the results of the long term outcomes of EORTC 22921 trial[10]. The investigators showed that although there appeared to be a survival advantage in patients with downstaged tumours in the short term, this benefit was transient and the survival curves equalised after 10 years.

Unfortunately, in a majority of patients a highly favourable response to preoperative chemotherapy is not observed and they are at greater risk of local and distant recurrence as well as shorter survival[62]. As a result, it appears logical to treat these patients aggressively with adjuvant chemotherapy[55,59,63-65]. Unfortunately, Breugom *et al*[36] in the meta-analysis of five trials (described above) showed no benefit of adjuvant chemotherapy neither in stage Ⅱ nor in stage Ⅲ, however there was no data available for stage 0 and Ⅰ disease. The differing results in the studies above may reflect variations in chemotherapy regimes used. Poor response to neoadjuvant treatment, which is usually fluoropyridine-based, indicates unfavourable tumour pathology and, unsurprisingly, administration of fluoropyridines during postoperative period may bring no benefit due to tumour resistance. In these cases, more aggressive combined therapy may have a role. A retrospective analysis of 160 rectal cancers with ypN0 stage showed that patients with T3-4 disease have significantly longer disease-free and overall survival if adjuvant FOLFOX (Oxaliplatin with fluorouracil and folinic acid) or XELOX (capecitabine with oxaliplatin) regimens were given, while those with T0-2 appeared to show no benefit from adjuvant chemotherapy[64]. Randomised controlled trials are needed to determine whether non-responders may benefit from a more aggressive adjuvant treatment.

Location of rectal cancer in relation to anal verge was also found to have significance when aiming to predict which patients may benefit from adjuvant chemotherapy. In the subgroup analysis, Breugom *et al* reported that tumours occurring 10-15 cm from the anal verge have longer disease-free survival if adjuvant chemotherapy is administered (HR = 0.59, 95%CI: 0.40-0.85, *P* = 0.005). No significant interaction between distance from the anal verge and treatment group was found for more distal tumours. The authors proposed that this observation might be as a result of the arbitrary definition of rectum and that tumours in proximal rectum are in fact biologically similar to colonic ones. Bujko *et al*[35] suggested several anatomical reasons why low lying rectal cancer may have poor prognosis compared to higher ones. The authors argued that higher proportion of low lying rectal cancers involve a circumferential margin. In addition, lower cancers receive both systemic and portal venous drainage and hence are at risk of systemic dissemination. Finally, internal iliac and obturator nodes are at risk of involvement in low lying rectal cancers, which are not routinely removed in the West.

ADJUVANT CHEMOTHERAPY AGENTS: PAST, PRESENT AND FUTURE

Fluoropyrimidine-based agents

Fluoropyrimidine-containing agents have formed the basis of adjuvant chemotherapy in rectal cancer. 5-FU can be administered either bolus or by continuous intravenous infusion. The NCCTG trial involving 660 patients with locally advanced rectal adenocarcinoma showed that protracted venous infusion of 5-FU (PVI FU) alongside pelvic irradiation was associated with significantly reduced distant metastases rate (31% *vs* 40%) and increased overall survival[66]. In contrast, a larger study (*n* = 1917) by Smalley *et al*[67] found no significant differences between three trial arms (5-FU bolus plus leucovorin, 5-FU bolus plus infusion, 5-FU only) (United States intergroup study). There appears to be limited evidence to favour PVI FU over simple bolus FU in rectal cancer bearing in mind higher costs, inconvenience and requirement for a central line.

An attractive alternative to PVI FU is an oral agent called capecitabine. Capecitabine requires 3-step enzymatic activation *in vivo*, one of which preferentially occurs in tumours, hence capecitabine offers a highly targeted approach. Trials, mainly investigating the effectiveness of capecitabine in the neoadjuvant setting, show non-inferiority to intravenous 5-FU regimens in terms of disease-free and overall survival and distant and local recurrences[68,69]. A phase Ⅲ German trial randomised 392 patients to receive either capecitabine or intravenous 5-FU in the perioperative period (231 patients received postoperative adjuvant chemotherapy). The results showed significantly lower distant metastases rates with capecitabine compared to 5-FU (19% *vs* 28%), however similar 5-year survival (76% *vs* 67%)[70]. Aside from higher risk of hand-foot syndrome, capecitabine offers a great substitute to intravenous 5-FU regimes and obviates the need for a central line and is already recommended by the National Comprehensive Cancer Network guidelines.

Oxaliplatin-based regimens

Oxaloplatin is a third-generation 1,2 diaminocyclohexane platinum analogue, which prevents replication and transcription of DNA. The MOSAIC and NSABP C07 trials showed significant improvement in overall survival in patients with advanced colon cancer[71,72]. Based on these encouraging results, several trials were carried out to determine the benefits of oxaliplatin in addition to standard fluopyridinamine-based regimens in rectal cancer (ACCORD12/0405-Prodige, CAO/ARO/AIO-04, ADORE, STAR-01, NSAPB R-04, PETACC-6)[73-78]. While some studies reported significant improvement in pathological response and disease-free survival[76,78], others found no superiority of oxaliplatin, but instead an increased risk of acute toxicity[74,75,77,79]. Only four trials reported the data on survival. Recently published results of ADORE trial showed significant improvements in 3-year disease-free survival in FOLFOX group (5-FU, oxaliplatin, leucovorin) compared to (5-FU and leucovorin) (71.6% *vs* 62.9%, HR = 0.657, 95%CI: 0.434-0.994; *P* = 0.047)[78]. Toxicity was more commonly seen in FOLFOX group, however there was no difference in frequency of grade 3 and grade 4 events. Similar results were reported in the CAO/ARO/AIO-04 trial, which showed significant increase in the proportion of patients achieving pathological complete response (17% *vs* 13%) and improved 3-year disease survival[76]. In contrast, interim results of PETACC-6 trial reported in a conference abstract did not show survival advantage in FOLFOX group[79]. CHRONICLE trial reported no benefit of oxaliplatin, however the study was considerably underpowered[32]. Three trials did not find improvement in pathological complete response (NSAPB R-04, ACCORD 12/0405-Prodige, STAR-01), however no data on survival were available. Although the evidence for oxaliplatin use in rectal cancer is limited, adjuvant chemotherapy incorporating oxaliplatin is widely used and is recommended by a number of international guidelines.

Irinotecan and biological agents

Irinotecan is a plant alkaloid, which inhibits DNA replication and repair by blocking topoisomerase Ⅰ. Although irinotecan has been used with success in metastatic colon cancer, no benefit was found for stage Ⅲ[80,81]. Only one trial investigated the benefits of irinotecan in rectal cancer[82]. The study recruited only 225 patients out of expected 3250 and was terminated because of the competing trial on bevacizumab. The investigators reported no benefit of addition of irinotecan to fluorouracil and leucovorin in neoadjuvant or adjuvant settings. Hence, currently irinotecan has no proven role

in treatment of rectal cancer.

Biological agents such as anti-VEGF agent, bevacizumab, and monoclonal antibodies, cetuximab and panitumumab, which target epidermal growth factor receptor have been successfully used in metastatic colon cancer in patients who failed on first line chemotherapy regimens[83-85]. Although approved by FDA, NICE currently does not support their use[86]. The role of bevacizumab in non-metastatic rectal cancer is unknown. The on-going phase Ⅱ BACCHUS trial is comparing FOLFOX with bevacizumab *vs* FOLFOXIRI with bevacizumab in the neoadjuvant setting in patients with locally advanced rectal cancer. However, the trial does not directly test the independent benefits of bevacizumab and its role in adjuvant setting is not under investigation.

FUTURE DIRECTIONS AND TRIALS IN PROGRESS

Unfortunately, a definite answer regarding the effectiveness of adjuvant chemotherapy is unlikely to be forthcoming in the near future. Most on-going trials compare different chemotherapeutic agent combinations or intensification regimes (PETACC-6, NSAPB R04, AERO-R98) and do not include an observation arm. Hence, the fundamental issue of whether or not adjuvant chemotherapy is effective is unaddressed. The only phase Ⅲ trial (NCT01941979) registered in the http://clinictrials.gov.uk website (accessed February 2015), which includes an observation arm is currently open and recruiting. The trial compares FOLFOX *vs* observation alone in patients with T3-4, N1, M0 who were treated with preoperative chemotherapy and showed poor response. The rationale of the study is based on the previous observations that only certain groups of patients with rectal cancer may benefit from adjuvant chemotherapy[57,87].

Since rectal cancer is a highly heterogenous disease, more trials are needed to take a targeted approach when evaluating the benefits of adjuvant chemotherapy. It is still unclear what role adjuvant chemotherapy has in patients who responded well to preoperative chemotherapy as the evidence is conflicting. Hence, ideally a separate trial investigating adjuvant chemotherapy is needed in this patient population. At the other end of the spectrum, the optimal management of patients who did not show improvement with preoperative chemoradiotherapy is also unclear. The use of adjuvant chemotherapy in non-responders appears to be unsupported by current evidence. However, there is scope for a more aggressive approach employing intensification regimens and combination treatments, including oxaliplatin and bevacizumab.

Reporting of the results based on stage may not be sensitive enough since there is high variability in prognosis within each TNM stage[88]. Valentini *et al*[89] produced nomograms based on the data from five major European RCTs on adjuvant chemotherapy in rectal cancer (n = 2795), which take into account a large number of clinical and pathological variables. Using these nomograms to stratify patients with rectal cancer into low, intermediate and high risk groups may help identify with high accuracy patient subgroups, which would benefit from adjuvant chemotherapy, however a randomised control trial is needed to determine their benefit.

Accurate clinical staging before and after administration of preoperative chemotherapy is vital to avoid over-staging and subsequent overtreatment. CT and EUS assessment is far from adequate and instead MRI should be employed. Particular areas of interest are circumferential margin involvement and lymph node status, as these are the most important predictors of poor survival[43,49].

THE ROLE OF BIOMARKERS

It has been increasingly recognised that all cancers in general, including rectal cancer, are highly heterogenous diseases requiring personalised therapies. Identification of reliable biomarkers could potentially aid clinical decision-making regarding the need for adjuvant chemotherapy. Many studies have identified dozens of biomarkers (microsatellite instability, p53, KRAS, BRAF, thymidylate synthase) in colon cancer and a 12-gene recurrence score assay (Oncotype DX Colon Cancer Assay) has been validated in the QUASAR trial as a reliable predictor for distant recurrence[90,91]. Whether similar assays can be used in rectal cancer is not known due to biological differences of colon and rectal cancer and requires separate validation. Biomarker analysis of the PROCTO-SCRIPT trial specimens is planned, which will hopefully help to identify patients who would benefit from adjuvant chemotherapy[34].

CONCLUSION

Adjuvant chemotherapy for rectal cancer has been a subject of controversy in recent years. The results of major trials, published in the last couple of years, do not support the use of postoperative chemotherapy after neoadjuvant chemoradiotherapy, however many clinicians throughout the world are understandably reluctant to abandon adjuvant chemotherapy. Concerns exist regarding the quality of the studies including inadequate staging modalities, out-dated chemotherapeutic regimens, non-TME surgical approaches and small sample sizes. It is becoming evident that not all patients with rectal cancer need adjuvant treatment. Identification of groups at risk using advanced imaging modalities, nomograms and biomarkers is the future of personalised treatment of rectal cancer. Hopefully, these questions will be answered in the near future. In the meantime, patients should be informed of benefits and risks of postoperative chemotherapy and the decision regarding the need for further treatment should be made

on individual basis.

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