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Hot Topic

Adjuvant chemotherapy for rectal cancer: Current evidence and recommendations for clinical practice

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ABSTRACT

While adjuvant chemotherapy is an established treatment for pathological stage II and especially stage III colon cancer, its role in the multimodal management of rectal cancer remains controversial. As a result, there is substantial variation in the use of this treatment in clinical practice. Even among centres and physicians who consider adjuvant chemotherapy as a standard treatment, notable heterogeneity exists with regard to patient selection criteria and chemotherapy regimens. The controversy around this topic is confirmed by the lack of full consensus among national and international clinical guidelines. While most of the clinical trials do not support the contention that adjuvant chemotherapy may improve survival outcomes if pre-operative (chemo)radiotherapy is also given, these suffer from many limitations that preclude drawing definitive conclusions. Nevertheless, in the era of evidence-based medicine, physicians should be guided by the available data and refrain from extrapolating results of adjuvant colon cancer trials to inform treatment decisions for rectal cancer. Patients should be informed of the evidence gap, be given the opportunity to carefully discuss pros and cons of all the possible management options and be empowered in the decision making. In this article we review the available evidence on adjuvant chemotherapy for rectal cancer and propose a risk-adapted decisional algorithm that largely relies on informed patient preferences.

Introduction

Rectal cancer is the 8th most common tumour and the 9th leading cause of cancer-related deaths worldwide [1]. While substantial heterogeneity exists with regard to the anatomical landmarks used for the definition of these tumours, rectal cancers account for approximately 40% of all colorectal malignancies overall. Of note, they are the most common colorectal tumour in people < 50 years, and incidence in this population is on the rise [2,3].

While 310,394 individuals were estimated to have died of rectal cancer worldwide in 2018 [1], survival outcomes have substantially improved over the past decades. According to statistics from the Surveillance, Epidemiology, and End Results Program (SEER), 5-year relative survival rates for all-stage rectal cancer patients in the US increased from 59.8% in 1986–1992 to 66.7% in 2007–2013 [4]. Taking into account the risk of stage migration bias, this improvement is especially noticeable for patients with stage III disease, the 5-year relative survival rates in this group being 54.9% and 70.3%, respectively.

The improved outcome over time of non-metastatic rectal cancer patients is to be largely attributed to a number of factors including advances and standardisation of pathological examination, imaging techniques, neoadjuvant treatments and surgical procedures, as well as routine implementation of a multidisciplinary decision-making approach [5–8]. Furthermore, the increased ability to stratify tumours at baseline according to their prognosis has allowed optimising the use of available therapies with resulting maximisation of outcome for high-risk patients and reduction of unnecessary treatment-related toxicities for low-risk patients [9].

The mainstay of treatment for non-metastatic rectal cancer is surgery according to the technique of total mesorectal excision (TME) [10]. In patients with locally advanced tumours (as defined, depending on the risk classification system, by ≥ T3/N + stage or additional risk

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factors such as tumour location, depth of mesorectal invasion, extramural vascular invasion, mesorectal fascia threatening/involvement and lateral node invasion) neoadjuvant (chemo)radiotherapy is also routinely delivered to reduce the risk of local tumour recurrence [11–16]. While both surgery and neoadjuvant (chemo)radiotherapy are established therapies for locally advanced tumours, the role of adjuvant chemotherapy in this setting is still highly debated with substantial variation in practice among healthcare providers.

This review article aims to analyse the role of adjuvant chemotherapy in rectal cancer, to critically appraise the available data, and to provide physicians with some guidance regarding management options and treatment decisions.

Why is adjuvant chemotherapy attractive in rectal cancer?

Pelvic recurrence has historically been a major cause of treatment failure and morbidity in rectal cancer patients undergoing surgical resection especially for locally advanced tumours. In studies conducted in the 1970s and 1980s, 15% to 40% of patients were reported to have experienced local tumour recurrence [17–19]. Beyond the obvious impact on survival, this also had important implications in terms of quality of life as locally recurring patients frequently suffered a number of tumour-related disabling symptoms including, among others, pain, fistulation, ureteric obstruction, infection, neurologic deficits and lympho-vascular complications [20,21].

Since neoadjuvant radiotherapy (either short-course radiotherapy or long-course chemoradiotherapy) and TME have been widely implemented in routine clinical practice, the pattern of rectal cancer recurrence has substantially changed. Pelvic failure has dramatically reduced, occurring in less than 5–10% of cases [22]. On the other hand, neither neoadjuvant (chemo)radiotherapy nor optimal quality surgery has shown a beneficial impact of similar magnitude on the risk of developing extra-pelvic metastases. As a result, these still occur in approximately 25% of patients and are now up to 5–6 times more frequently than local recurrences [22,23] (Table 1).

This major shift in the causes of treatment failures following curative intent treatment provides a strong rationale for use of adjuvant chemotherapy. Administering systemic chemotherapy after surgery may allow targeting micrometastases and circulating tumour cells that cannot be adequately addressed by neoadjuvant radiotherapy and radiosensitising dose chemotherapy. If successful sterilisation of these micrometastases is achieved, this is expected to translate into reduced risk of distant failure and improved survival [24,25]. Further support to the contention that adjuvant chemotherapy may be beneficial for rectal cancer patients is provided by the results of adjuvant trials in colon cancer. In this setting, single agent fluoropyrimidine-based treatment has been shown to improve recurrence-free survival and overall survival (OS) by 35% and 22%, respectively, in patients with stage II and III disease [26]. Also, further reduction in the risk of recurrence (HR ranging from 0.80 to 0.82) and death (HR ranging from 0.83 to 0.88) was reported with the use of doublet, oxaliplatin-based chemotherapy as compared to fluoropyrimidine alone [27–29]. As a result, adjuvant chemotherapy (either oxaliplatin-based or single agent fluoropyrimidine depending on tumour risk factors, patient comorbidities and preference) is a standard treatment following curative intent resection of stage II and III colon cancer.

Table 1
Local and distant recurrence rates by type of treatment (surgery alone *vs* pre-operative radiotherapy and pre-operative radiotherapy *vs* chemoradiotherapy) in selected clinical trials without adjuvant chemotherapy before and after routine use of total mesorectal excision.

Trial	5-yr local recurrence rate		5-yr distant recurrence rate	
	Surgery alone	*Pre-op SCRT*	*Surgery alone*	*Pre-op SCRT*
Stockholm I	28%	14%	37%	30%
Swedish	27%	11%	25%	23%
Stockholm II	25%	12%	28%	29%
Dutch TME*	11%	6%	28%	26%
	Pre-op RT	*Pre-op CRT*	*Pre-op RT*	*Pre-op CRT*
EORTC 22,921^	22%	11%	37%	32%

Abbreviations: *CRT: long-course chemoradiotherapy; Pre-op: pre-operative; RT: long-course radiotherapy; SCRT: short-course radiotherapy.*

* 6% of patients undergoing an R0 resection received adjuvant treatment.

^ Only patients randomised to the arms without adjuvant chemotherapy are included.

What are the available data on adjuvant chemotherapy for rectal cancer?

Adjuvant chemotherapy versus observation after surgery alone

Before the routine implementation of a multimodal treatment approach including neoadjuvant (chemo)radiotherapy, a number of adjuvant chemotherapy randomised trials were conducted both in Western countries and in Japan [30–46]. The results of these trials are largely ambigous and influenced by notable heterogeneity with regard to some key variables such as sample size, type of patients included (colorectal or rectal only cancer patients), type of chemotherapy (fluoropyrimidine alone or in combination with other agents such as leucovorin, levamisole, mitomycin-C, semustine, lomustine, vincristine, or immunotherapy agents), route of chemotherapy administration (systemic or regional), and treatment modality (chemotherapy alone or in combination with radiotherapy).

In 2012, a Cochrane Collaboration *meta*-analysis attempted to address the uncertainty around adjuvant chemotherapy in rectal cancer by collecting data from these randomised studies [47]. Data were analysed from 20 trials (including 8530 patients) for disease-free survival (DFS) and from 21 trials (including 9221 patients) for OS. Bearing in mind the existence of a moderate inter-trial heterogeneity, this *meta*-analysis showed a statistically significant benefit for adjuvant chemotherapy in terms of both DFS (HR 0.75; 95% CI: 0.68–0.83) and OS (HR 0.83; 95% CI: 0.76–0.91). Of note, no difference in the effect of adjuvant chemotherapy was observed between Western and Japanese patients while a meaningful analysis by tumour stage (i.e., stage II versus stage III) could not be done in light of the small number of trials reporting outcome data separately for these patients.

Although this *meta*-analysis represented a milestone in the development of evidence-based recommendations in this setting, applicability of its results to current clinical practice is very limited. Many of the included trials were conducted before TME was widely implemented in routine care. Furthermore, only in a small minority of cases (from the EORTC 22,921 and QUASAR trials) a multimodal treatment including neoadjuvant (chemo)radiotherapy was actually delivered. As a result, patients analysed in the *meta*-analysis cannot be considered as fully representative of the current rectal cancer population. In fact, they might have carried a substantially higher risk of both local and distant recurrence, this likely enhancing the chances of adjuvant chemotherapy impacting favourably on survival.

Adjuvant chemotherapy versus observation after pre-operative (chemo) radiotherapy

The question as to whether adjuvant chemotherapy is beneficial also to patients who have received pre-operative treatment with short-course radiotherapy or long-course chemoradiotherapy has been addressed by four randomised phase III trials (Table 2).

The first trial to start recruitment was the Italian I-CNR-RT study in 1992 [48]. In this trial eligibility was restricted to patients aged ≤ 75 years with cT3/4 tumours as assessed by digital rectal examination, abdomino-pelvic CT scan and/or endorectal ultrasonography, while thoracic metastases were ruled out by chest x-ray.

Table 2
Clinical trials of adjuvant chemotherapy following pre-operative (chemo)radiotherapy and surgery for rectal cancer.

Trial	N pts	Accrual	Main eligibility criteria	Baseline staging	Study design	Primary endpoint	Primary hypothesis	Starting ACT	Completing ACT	5-yr DFS	5-yr OS
I-CNR-RT (1992-2003)	634	100%	≤75 yrs, cT3-4, prior CRT	DRE, rigid rectoscopy, CT AP, chest X-ray, (ERUS optional)	Observation *vs* 5FULV	OS	+10% in 5-yr OS	91.4%	< 58.4%	62.8%ˆ *vs* 65.3%ˆ HR 0.98 p = 0.88	70.0%ˆ *vs* 69.1%ˆ HR 1.04 p = 0.77
EORTC 22921 (1993-2003)	1011	100%	≤80 yrs, cT3-4, prior SCRT or CRT	DRE, rigid rectoscopy, CT AP, chest X-ray, (ERUS optional)	Observation *vs* 5FULV	OS	+10% in 5-yr OS	73.1%	42.9%	52.2% *vs* 58.2% HR 0.87 p = 0.13	63.2% *vs* 67.2% HR 0.85 p = 0.12
PROCTOR/SCRIPT (2000-2013)	437	52%	ypStage II-III after SCRT or CRT	Inclusion after surgery	Observation *vs* 5FULV/Cape	OS	+10% in 5-yr OS	94.5%	73.6%	55.4% *vs* 62.7% HR 0.80 p = 0.13	79.2% *vs* 80.4% HR 0.93 p = 0.73
CHRONICLE (2004-2008)	113	14%	Any ypStage, CRM > 1mm, after CRT	Inclusion after surgery (CT TAP before ACT)	Observation *vs* CAPOX	DFS	+10.5% in 3-yr DFS	92.6%	48.1%	71.3%* *vs* 77.5%* HR 0.80 p = 0.56	87.8%* *vs* 88.8%* HR 1.18 p = 0.75
ADORE (2008-2012)	321	100%	ypStage II-III after CRT	Inclusion after surgery (CT TAP before ACT)	5FULV *vs* FOLFOX	DFS	+8% in 3-yr DFS	92.5% *vs* 91.3%	87.6% *vs* 88.1%	56.8%° *vs* 68.2%° HR 0.63 p = 0.02	76.4%° *vs* 78.1%° HR 0.73 p = 0.21
R98 TRIAL (1999-2005)	357	59.5%	cStage II/III, CRM > 0mm, (prior (C)RT in 69%)	CT AP or liver US, chest X-ray, ERUS	5FULV *Vs* FOLFIRI	DFS	+11% in 5-yr DFS	96.6% *vs* 95.0%	87.6% *vs* 77.7%	58% *vs* 63% HR 0.80 p = 0.15	74% *vs* 75% HR 0.87 p = 0.43
E5204 TRIAL (2006-2009)	355	17.0%	cStage II/III, prior CRT	na	FOLFOX *vs* FOLFOX + Bev	OS	na	98.3% *vs* 97.2%	71.6% *vs* 59.2%	88.3% *vs* 83.7% HR 0.72 p = 0.88	71.2% *vs* 76.5% HR 1.25 p = 0.30

ˆ Survival outcomes in the resected population.
* 3-yr survival rates.
° 6-yr survival rates.
Abbreviations: ACT: adjuvant chemotherapy; AP: abdomen-pelvis; Bev: bevacizumab; Cape: capecitabine; CRM: circumferential resection margin; CRT: long-course chemoradiotherapy; CT: computed tomography; DFS: disease-free survival; DRE: digital rectal exam; ERUS: endo-rectal ultrasound; FP: fluoropyrimidine; HR: hazard ratio; pts: patients; na: not available; OS: overall survival; SCRT: short-course radiotherapy; TAP: thorax-abdomen-pelvis; TME: total mesorectal excision; yrs: years.

Patients were randomly allocated to observation or adjuvant chemotherapy with six cycles of 4-weekly 5-FU bolus and folinic acid. The primary endpoint was OS, and the trial was powered to detect an improvement of 10% at 5 years. Randomisation occurred before pre-operative treatment which consisted of chemoradiotherapy (45 Gy in 25 fractions and 2 cycles of 4-weekly 5-FU bolus and folinic acid). Of note, no specific recommendation was made for the use of the TME technique. The study completed recruitment after 11 years with 634 eligible patients but failed to meet the initial hypothesis. OS at 5-years was 66.9% in the chemotherapy arm versus 67.9% in the control arm (HR not reported, p = 0.879). DFS at 5 years in the same groups was 63.6% and 60.8%, respectively (HR not reported, p = 0.416). Similar results were observed when only the group of patients who had actually undergone surgery was analysed. Notably, only 51.8% of eligible patients received at least 3 cycles of adjuvant chemotherapy in the investigational arm. Also, no clinico-pathological features were associated with benefit from adjuvant chemotherapy in subgroup analyses.

The EORTC 22,921 was the largest study of adjuvant chemotherapy (n = 1011), conducted between 1993 and 2003 [32]. It included patients aged ≤ 80 years with cT3/4 tumours as assessed by the same staging modalities used in the I-CNR-RT trial. Eligible patients were randomly allocated to four treatment arms according to a 2x2 factorial design: pre-operative radiotherapy followed by surgery and adjuvant chemotherapy, pre-operative chemoradiotherapy followed by surgery and adjuvant chemotherapy, pre-operative radiotherapy followed by surgery alone, and pre-operative chemoradiotherapy followed by surgery alone. In this study, pre-operative radiotherapy consisted of 45 Gy in 25 fractions, pre-operative chemotherapy of 2 cycles of 4-weekly 5-FU bolus and folinic acid, and adjuvant chemotherapy of 4 cycles of 3-weekly 5-FU bolus and folinic acid. Surgery according to the principles of TME was specifically recommended only during the last 4 years of recruitment. In line with the I-CNR-RT trial, the primary endpoint was

OS and the trial was designed to detect a 10% difference at 5 years. Yet, investigators reported only a numerically, but not statistically significant, survival advantage for patients who had received adjuvant chemotherapy. The rates of 5-year OS were 67.2% in the adjuvant chemotherapy group and 63.2% in the observation group (HR 0.85; 95% CI: 0.68–1.04, p = 0.12) while the rate of 5-year DFS were 58.2% and 52.2%, respectively (HR 0.87; 95% CI: 0.72–1.04, p = 0.13). Similarly to the I-CNR-RT trial, compliance to adjuvant chemotherapy was poor with only 42.9% of patients completing treatment as per study protocol. Of note, a statistically significant association between pathological tumour downstaging (i.e., ypT0-2) after pre-operative treatment and benefit from adjuvant chemotherapy was initially observed but not subsequently confirmed after longer follow-up [49,50].

The PROCTOR/SCRIPT trial was conducted between 2000 and 2013 and included patients aged ≥ 18 years with ypStage II and III tumours [51]. In contrast to the I-CNR-RT and EORTC 22,921 trials, randomisation was carried out after pre-operative treatment and surgery. Patients could have received either short-course radiotherapy (25 Gy in 5 fractions) or long-course chemoradiotherapy (45–50 Gy with concurrent 5-FU) and randomisation included observation or adjuvant chemotherapy with 5-FU and leucovorin (either 6 cycles of the Mayo regimen or 12 cycles of the Nordic regimen) or capecitabine (8 cycles). Of note, TME and pathological examination of the resection specimens were standardised and recommended throughout the study period, with approximately two thirds of patients being confirmed to have had high-quality surgery. In line with the I-CNR-RT and EORTC 22,921 trials, the trial was designed to show a 10% difference in OS at 5 years. While 840 patients were required to address this statistical hypothesis, the trial closed due to poor accrual after only 437 eligible patients (52%) were recruited. No difference was observed in 5-year OS between the observation group (79.2%) and the adjuvant chemotherapy group (80.4%) (HR 0.93; 95% CI: 0.62–1.39, p = 0.73). Only a numerical difference was reported for the analysis of 5-year DFS (55.4% versus 62.7%, respectively) (HR 0.80, 95% CI: 0.60–1.07, p = 0.13). In this trial, 73.6% of patients in the adjuvant chemotherapy group completed the planned number of chemotherapy cycles.

The Chronicle trial was launched in 2004 [52]. It included patients aged > 18 who had been treated with pre-operative, fluoropyrimidine-based chemoradiotherapy (at least 45 Gy) and surgery, irrespective of the post-treatment tumour pathological stage. Up to 12 weeks of pre-operative fluoropyrimidine-based chemotherapy were also allowed. Patients were randomised between observation and 6 cycles of adjuvant CAPOX chemotherapy. In contrast to other trials, the primary endpoint was DFS and the study was designed to detect a 10.5% improvement in 3-year DFS. Only 113 out of 800 planned patients (14.1%) were recruited and the study was prematurely discontinued due to slow accrual. The rate of DFS at 3 years was 71.3% in the observation group and 77.5% in the adjuvant chemotherapy group (HR 0.80; 95% CI: 0.38–1.69, p = 0.56). OS figures at the same time point were 87.8% and 88.8%, respectively (HR 1.18; 95% CI: 0.43–3.26, p = 0.75). In this study, adjuvant chemotherapy was completed by 48.1% of patients.

Individual patient data from these trials were pooled in a *meta*-analysis [53]. To account for inter-trial differences in study design and eligibility criteria, the primary objective was to compare OS between observation and adjuvant chemotherapy in patients who had had an R0 resection for ypStage II or III tumours located ≤ 15 cm from the anal verge (n = 1196). In accordance with the results of each trial, no benefit in terms of either OS (HR 0.97; 95% CI: 0.81–1.17, p = 0.775) or DFS (HR 0.91; 95% CI: 0.77–1.07, p = 0.230) was shown. In contrast with the general assumption that adjuvant chemotherapy can efficiently target micrometastases and reduce the risk of distant failure, the cumulative incidence of distant recurrences was almost identical in both treatment groups (36.5% in the observation group versus 35.5% in the adjuvant chemotherapy group, HR 0.94; 95% CI 0.78–1.14, p = 0.523). Of note, in subgroup analyses of DFS and distant recurrence, the effect of adjuvant chemotherapy appeared stronger for patients with high tumours (between 10 and 15 cm from the anal verge) (HR 0.59; 95% CI: 0.40–0.85, p = 0.005 and HR 0.61; 95% CI: 0.40–0.94, p = 0.025, respectively). No statistically significant interaction, however, was found between treatment arm and tumour location for either outcome measure (p = 0.107 and p = 0.126, respectively).

Single agent versus combination adjuvant chemotherapy after pre-operative (chemo)radiotherapy

Doublet, oxaliplatin-based, adjuvant chemotherapy is a standard treatment for patients with colon cancer, especially in the setting of pathological stage III disease [27–29]. The role of combination versus single agent adjuvant chemotherapy in rectal cancer after pre-operative (chemo)radiotherapy has been investigated in three randomised clinical trials (Table 2).

The ADORE trial was a randomised phase II trial conducted between 2008 and 2012 in South Korea [54]. In this study, patients with ypStage II-III tumours after pre-operative, fluoropyrimidine-based, chemoradiotherapy and radical (i.e., R0) TME +/- extended lymph node dissection were randomised between 4 cycles of fluorouracil plus leucovorin (modified Mayo regimen) or 8 cycles of FOLFOX. The primary endpoint was 3-year DFS, and the statistical assumption was that using combination therapy would translate into an absolute 8% improvement. By recruiting 321 eligible patients, the trial showed better outcomes for the oxaliplatin-treated group. The rates of DFS at 3 years were 62.9% and 71.6% in the single agent and combined treatment arm, respectively (HR 0.657; 95% CI: 0.434–0.994, p = 0.047). Superiority of the combination treatment was recently confirmed in an updated analysis; at 6 years 68.2% of patients in the oxaliplatin arm and 56.8% of patients in the monotherapy arm were alive and free of recurrence (HR 0.63; 95% CI: 0.43–0.92, p = 0.018) [23]. Interestingly, in both initial and updated subgroup analyses, the numerical DFS advantage at 3 (+10.3% for ypStage II, +9.3% for ypStage III) and 6 years (+8.3% for ypStage II, +14.9% for ypStage III) met the criteria for statistical significance only in the group of patients with ypStage III tumours (HR 0.60, p = 0.040 at 3 years, HR 0.59, p = 0.019 at 6 years), bearing in mind that patients with ypStage II tumours accounted for only 38.3% of the entire study population. It should be noted that, in striking contrast to previous trials, 87.9% of randomised eligible patients completed all the planned cycles of adjuvant chemotherapy. Finally, although it was a secondary endpoint, OS did not differ between treatment arms (6-year OS 76.4% in the monotherapy group and 78.1% in the combination therapy group (stratified HR 0.73; 95% CI: 0.45–1.19, p = 0.21).

The French R98 Intergroup trial was conducted between 1999 and 2005 [55]. Patients were eligible for this study if they had undergone surgery for cStage II-III rectal cancer. Pre-operative treatment was not mandatory but radiotherapy or fluoropyrimidine-based chemoradiotherapy were recommended and ultimately received by 69% of patients. Also, in > 75% of cases TME was performed. Randomisation was between single arm fluoropyrimidine therapy (either 6 cycles of the Mayo regimen or 12 cycles of the LV5-FU2 regimen) and FOLFIRI chemotherapy (12 cycles). The study was designed to detect an 11% 5-year DFS advantage with the use of FOLFIRI. Due to slow accrual, recruitment was halted when only 357 of the 600 (59.5%) patients who were needed to formally address the statistical hypothesis were randomised. The study failed to meet its primary endpoint as no difference in 5-year DFS was observed between the two arms (58% in the control arm versus 63% in the investigational arm, HR 0.80, p = 0.154). In subgroup analyses, risk reduction of recurrence/death with FOLFIRI appeared numerically larger for patients with cStage III tumours (HR 0.74) than for those with cStage II tumours (HR 0.94). OS was very similar between the two arms. Of note, full compliance with the pre-planned chemotherapy treatment was reported for 87% and 77% of patients in the monotherapy and combination therapy arm, respectively.

The E5204 trial has been reported as an abstract only [56]. Eligibility criteria of this US study were similar to the R98 Intergroup trial as recruitment was restricted to patients with cStage II-III rectal tumours who had undergone pre-operative fluoropyrimidine-based (+/- oxaliplatin) chemoradiotherapy. Patients were randomised between 12 cycles of mFOLFOX6 and mFOLFOX6 plus bevacizumab. The statistical design was quite ambitious as the primary endpoint was 5-year OS and 2088 patients had to be recruited. Recruitment was very slow, and the trial was closed after only 355 (17%) patients were randomised. Results showed no difference in either 5-year OS (88.3% with mFOLFOX6 versus 83.7% with mFOLFOX6 plus bevacizumab, stratified HR 0.72; 95% CI: 0.41–1.26, p = 0.876) or 5-year DFS (71.2% versus 76.5%, respectively, stratified HR 1.25; 95% CI: 0.82–1.90, p = 0.299).

Two other randomised phase III trials (i.e., CAO/ARO/AIO-04 and PETACC-6) compared doublet oxaliplatin-based chemotherapy versus single agent fluoropyrimidine chemotherapy as adjuvant treatment for rectal cancer [57,58]. The administration of oxaliplatin during pre-operative chemoradiotherapy in the investigational arm, however, makes the results very difficult to interpret. Notably, these trials produced conflicting results with the CAO/ARO/AIO-04, but not the PETACC-6 study, suggesting a DFS advantage from the addition of oxaliplatin to fluoropyrimidine-based therapy.

How to make sense of the available evidence?

The results of these studies suggest overall that, in contrast to colon cancer, the role of adjuvant chemotherapy in the modern management of rectal cancer remains controversial. This conclusion, however, sharply contrasts with the longstanding common belief that data from colon cancer adjuvant trials should be extrapolated to inform treatment decisions for rectal cancer. How can this discrepancy be explained? Why does adjuvant chemotherapy work in colon cancer but may not work in rectal cancer?

Despite the direct anatomical relationship, many differences exist between the colon and the rectum, as well as between tumours arising from these segments of the large bowel. While the rectum shares the embryological origin from the hindgut with the left-sided colon, the right-sided segments of the colon arise from the midgut [59]. Furthermore, distal rectal cancers are known to have a unique venous drainage system and pattern of metastatisation [60,61]. In terms of molecular characteristics, differences between colon and rectal tumours have also increasingly emerged. The integrated comprehensive molecular analysis of the Cancer Genome Atlas Network identified two main molecular entities (i.e., hypermutated and non-hypermutated tumours), while it suggested that non-hypermutated tumours (which account for the vast majority of rectal cancers) are similar in terms of copy number variation, DNA methylation and gene-expression patterns irrespective of the site of origin [62]. Other studies, however, have found that rectal tumours are enriched in APC, ERBB2, FBXW7, STK11, TP53 mutations and MGMT, TLE3, TOPO1, and TUBB3 expression compared to colon cancers [63,64]. Differences between colon and rectal tumours have also been reported in terms of mRNA/microRNA expression and proteomics [65–67], and different microbiota profiles have been found in proximal versus distal colorectal cancers [68].

Beyond these considerations, the clear inconsistency between the evidence before and after the adoption of the modern multimodal treatment supports the contention that, even assuming a similar magnitude benefit of adjuvant chemotherapy for colon and rectal cancer, at least part of this may be offset by pre-operative (chemo)radiotherapy in the latter. While the main effect of pelvic radiotherapy and low-dose radiosensitising chemotherapy is in the reduction of the risk of local recurrence (risk more than halved) [69–71], it is possible that the same treatments may also reduce the occurrence of distant metastases. We acknowledge that this hypothesis is largely speculative and needs confirmation. Nevertheless, it should be noted that among the group of radically resected (i.e., R0 surgery) patients of the Dutch TME trial (where no adjuvant chemotherapy was planned), a lower rate of distant recurrence (19% versus 24%, p = 0.06) was reported in the pre-operative short-course radiotherapy arm as compared to the surgery alone arm [69]. Also, in the same trial use of pre-operative radiotherapy improved OS only for patients with stage III tumours who are known to have the highest risk of metastatisation and death. Additional support to this hypothesis is provided by the outcome data from the two surgery-only arms of the EORTC 22,921 trial where a numerically lower rate of distant failure was observed in patients who had been treated with pre-operative chemoradiotherapy as compared to those who had received radiotherapy only (33.4% versus 39.6%) [32] (Table 1).

The above discussed hypotheses imply that, as a result of either inherent characteristics of their tumours or the interfering effect of pre-operative treatments, rectal cancer patients do not benefit from adjuvant chemotherapy. Another interpretation, however, could be that the randomised phase III trials conducted so far had too many limitations to be able to demonstrate a survival benefit even if this actually existed. First of all, slow recruitment affected all studies causing either prolonged accrual or, in most cases, early discontinuation. Trials spanned nearly 3 decades with resulting substantial intra- and inter-trial heterogeneity in terms of staging modalities, surgical techniques and adjuvant chemotherapy regimens, and sub-optimal quality of the same. Also, patient compliance to adjuvant chemotherapy was poor with a non-negligible proportion of patients never starting treatment and many more not being able to complete the assigned course of therapy. Last but not least, all main statistical hypotheses likely overestimated the survival advantage of adjuvant chemotherapy, this meaning limited power to demonstrate lower but still clinical meaningful survival advantages (Table 2). As a result, caution should be used when using these results as definitive evidence that adjuvant chemotherapy does not have any role in rectal cancer patients previously treated with pre-operative (chemo)radiotherapy.

Clinical guidelines recommendations and real-world data

The uncertainty regarding the role of adjuvant chemotherapy in rectal cancer is largely reflected by the variegated recommendations from national and international clinical guidelines.

While most guidelines ultimately suggest or recommend using adjuvant chemotherapy, substantial differences still exist across them especially with regards to the strength of the recommendation and the criteria for patient selection. According to the ESMO guidelines it is reasonable to discuss with patients risks and benefits of treatment and consider fluoropyrimidine monotherapy or doublet oxaliplatin-based therapy in those with pathological high-risk stage II and stage III tumours [14]. The same treatment options are recommended by the JSCCR guidelines for high-risk stage II and stage III patients, but it is not specified whether patient selection should be according to the clinical or pathological stage [72]. The NCCN and Ontario guidelines recommend administration of adjuvant chemotherapy (preferably doublet oxaliplatin-based treatment especially in presence of high-risk features) in all patients with clinical (instead of pathological like indicated in the ESMO guidelines) stage II or III tumours [15,73]. More cautious are the Australian guidelines that highlight the lack of robust data to support routine use of adjuvant chemotherapy and suggest that any or most of the beneficial effects of this treatment are possibly restricted to patients with either clinical or pathological stage III tumours of the upper rectum [74].

Not surprisingly, physicians' and patients' attitude towards the use of adjuvant chemotherapy are similarly heterogeneous. Using data from the Swedish Rectal Cancer Registry, Tiselius et al reported remarkable variation in the use of adjuvant chemotherapy among patients < 75 years who had undergone surgical resection for stage III rectal tumours between 1995 and 2002 [75]. While 42% of patients overall received adjuvant chemotherapy, this figure differed substantially between counties ranging from 13% to 77%. Real-world data from the US

reveal that, despite longstanding recommendations from the NCCN guidelines [76], a non-negligible proportion of adjuvant chemotherapy "eligible" patients, at least in the past decade, did not receive this treatment. A retrospective analysis of the NCCN Colorectal Cancer Database showed that 17% of patients with cStage II and III tumours treated between 2005 and 2010 were not treated with adjuvant chemotherapy because no consultation with the medical oncologist took place after surgery, chemotherapy was not recommended, or it was discussed/recommended but possibly declined by the patient [77]. Another study using data from the SEER database (1998–2007) revealed that adjuvant chemotherapy was used in only 61.5% of patients aged 66 to 80 who had received chemoradiotherapy and surgery for pathologic stage I-III tumours [78]. Younger patients, patients with no post-operative readmission and those with ypStage III disease were most likely to receive adjuvant chemotherapy. It is fair to note, however, that use of adjuvant treatment as well as prescription of an oxaliplatin-based regimen increased significantly over time in line with the recommendations from the NCCN guidelines and possibly as a result of general concerns about undertreatment of patients who receive pre-operative therapy and surgery only.

Who are the patients who may benefit most from adjuvant chemotherapy?

In this complex scenario, the question as to whether there are subgroups of patients who could benefit from adjuvant chemotherapy and how these should be identified has become increasingly relevant.

TNM stage is the strongest and most commonly used risk factor in rectal cancer. The routine use of pre-operative (chemo)radiotherapy for locally advanced tumours (i.e., ≥T3 or N+) as defined by pelvic MRI, however, adds significant complexity to the interpretation and use of tumour stage as a decision-driving risk factor for adjuvant chemotherapy. Not surprisingly, controversy exists around the question of whether patient selection should be based on the clinical stage (i.e., cTNM) at baseline or on the pathological stage after pre-operative treatment (i.e., ypTNM). While either selection criterion has substantial limitations, the latter should be preferred. MRI is the gold standard for staging and treatment response assessment of rectal cancer. Its diagnostic accuracy, however, is still suboptimal especially with regards to the lymph node status. In a *meta*-analysis of 21 studies the diagnostic odds ratio for N stage was only 8.3%, this meaning high risk of under- and over-staging and resulting under- and over-treatment, respectively [79]. On the other hand, selecting patients based on the pathological stage means factoring response to pre-operative (chemo)radiotherapy into the decision making and this is a double-edged sword. While this approach allows better prognostication, the dilemma of whether pathological stage is predictive of benefit from adjuvant chemotherapy remains. It is still not clear whether tumour downstaging after pre-operative treatment indicates that micrometastases are also sensitive to, and therefore likely to be sterilised by, adjuvant chemotherapy or that the tumour has such a good prognosis (due to low risk of micrometastatisation) that adjuvant chemotherapy, even if effective, is unlikely to impact meaningfully on outcome (i.e., impressive HRs translate into marginal absolute advantages). Similarly, uncertainty remains as to whether lack of response to pre-operative treatment indicates that micrometastases are resistant to, and therefore unlikely to be sterilised by, adjuvant chemotherapy or that the tumour has such a bad prognosis (due to high risk of micrometastatisation) that, even if marginally effective, adjuvant chemotherapy (especially if oxaliplatin-based) is likely to impact meaningfully on outcome (i.e., modest HRs translate into substantial absolute advantages). Many retrospective studies, subgroup analyses of clinical trials and *meta*-analyses have analysed the effect of adjuvant chemotherapy according to the pathological stage (the patient group of interest ranging from complete responders to patients with stage III tumours) after pre-operative treatment but the results are largely inconsistent [80–83]. The only available prospective evidence is provided by the abovementioned subgroup analysis of the phase II ADORE trial that appears to suggest that only patients with ypStage III tumours could benefit from an oxaliplatin-based chemotherapy [23,54].

Other parameters indicating the degree of response to pre-operative (chemo)radiotherapy, including tumour regression grade or the NAR score have been validated as strong prognostic factors and could help in the decision making [84–86]. There are no studies, however, to suggest that these could also act as predictive factors for adjuvant chemotherapy. Furthermore, it should be noted that, as an indicator of tumour downstaging, the NAR score inherently relies on the accurate definition of tumour stage at baseline [87].

Recommendations for clinical practice

The suboptimal quality of the completed trials and the results of the same make adjuvant chemotherapy in rectal cancer one of the most controversial topics in modern clinical oncology. It is clear though that no strong recommendation can be made for its regular use, and physicians should refrain from using data from colon cancer trials to guide management choices in routine practice. This approach can be no longer justified in the evidence-based era. Instead, a risk-adapted decisional algorithm that largely relies on informed patient preferences should be pursued.

In view of the lack of supportive prospective data and the otherwise very good prognosis of their tumours, patients who achieve pathological complete response or have ypStage I disease after pre-operative (chemo)radiotherapy should be proposed observation only after surgery. In these circumstances, adjuvant chemotherapy is likely to represent an overtreatment with toxicities largely overweighting benefits if any. In all other patients, a possible beneficial effect of adjuvant chemotherapy cannot be excluded. Therefore, physicians should actually inform these patients of the evidence gap and carefully discuss with them all the possible management strategies. They should highlight potential risks and benefits of observation versus treatment and empower patients in the decision making. If patients are willing to receive adjuvant chemotherapy, single agent fluoropyrimidine treatment appears the most reasonable option for those with ypStage II tumours, while either single agent fluoropyrimidine or doublet, oxaliplatin-including therapy could be considered for patients with ypStage III tumours. In these cases, however, the choice of regimen should be made following a detailed discussion on the potential incremental survival benefit and increased risk of treatment-related toxicities, especially permanent peripheral sensory neuropathy, with the addition of oxaliplatin (Fig. 1).

If the decision has been made to administer adjuvant chemotherapy, a relevant practical question is for how long this treatment should be continued. In most historical colon and rectal cancer trials adjuvant chemotherapy has been administered for 6 (if no pre-operative treatment or only short-course radiotherapy was delivered) or 4 months (if pre-operative long-course chemoradiotherapy was given). The IDEA collaboration trial has recently suggested that 3 months of adjuvant oxaliplatin-based chemotherapy may be as effective as but less toxic than 6 months, at least in low-risk colon cancer patients [88]. Rectal cancer patients, however, were recruited in only one of the six IDEA trials (i.e., SCOT) where they also accounted for a minority of the study population (18%) [89]. Furthermore, pre-operative short-course radiotherapy but no long-course chemoradiotherapy was allowed. Subgroup analysis of this trial showed that, while the non-inferiority HR for rectal cancer was lower than for colon cancer (i.e., HR 0.926 versus 1.021, favouring 3 months of treatment), the 95% CI for the former was much wider (i.e., 0.711–1.205 versus 0.914–1.14), likely due to the low numbers, and largely crossed the non-inferiority boundary. Therefore, physicians should be discouraged to use data from the IDEA collaborative analysis to inform rectal cancer management and, if oxaliplatin-based adjuvant chemotherapy were to be used,

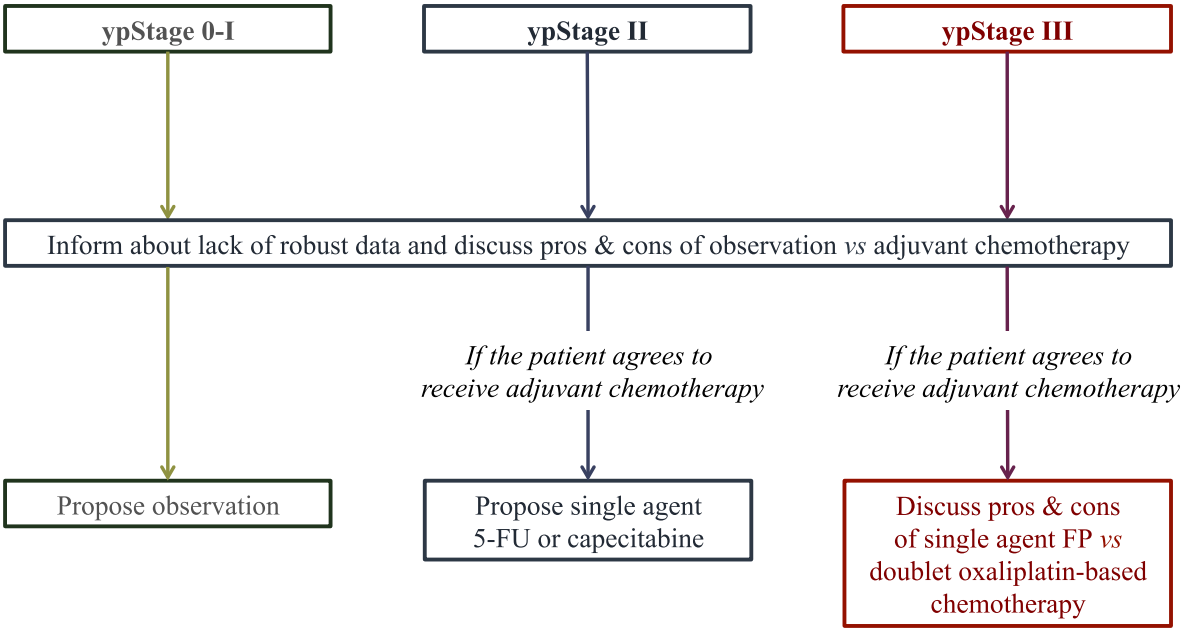

Fig. 1. Proposed recommendations for clinical practice.

Table 3
Ongoing ctDNA-based, adjuvant clinical trials in rectal cancer.

Trial	Sample size	Main eligibility criteria	Study design	Primary endpoint
NCT03415763	764	≤75 yrs, cStage III	In ypStage 0-I pts: FP *vs* observation (non-inferiority) In ypStage II-III pts: FOLFOX/CAPOX *vs* observation (superiority)	3-yr DFS
ACTRN12617001560381 (DYNAMIC-Rectal)	408	Locally advanced tumours treated with pre-op CRT + TME	Conventional risk-based adjuvant chemotherapy *vs* ctDNA-based adjuvant chemotherapy	Reduction in the proportion of pts receiving adjuvant chemotherapy
NCT03748680	64	(y)pStage I-II colon or rectal cancer, detectable ctDNA 2 weeks after surgery	CAPOX/FOLFOX + intensified follow-up schedule *vs* intensified follow-up schedule only	3-yr DFS

Abbreviations: ctDNA: circulating tumour DNA; DFS: disease-free survival; FP: fluoropyrimidine; CRT: long-course chemoradiotherapy; pts: patients; TME: total mesorectal excision; yrs: years.

practice should be in line with the design of the ADORE trial (i.e., 4 months of treatment following pre-operative chemoradiotherapy) [54].

Future perspectives and conclusions

After decades of clinical research, the exact role of adjuvant chemotherapy in the modern multimodal management of rectal cancer remains an unsolved puzzle. Furthermore, early closure of most clinical trials suggests that no solution is likely to be found unless novel and more appealing study designs are proposed to re-engage physicians and patients and to revive their interest in this clinical question.

A game changer could certainly be the analysis of circulating tumour (ct)DNA. While the clinical potential of this biomarker has long been recognised in many tumour types, only recently data have become available also for rectal cancer [90]. In a recent study of 159 patients treated with pre-operative chemoradiotherapy, detection of post-operative ctDNA was the strongest independent prognostic factor, being associated with a significantly lower rate of 3-year DFS (33% versus 87%, HR 13.0, $p < 0.001$) [91]. In another study of 123 patients treated with neoadjuvant treatment and surgery, high levels of circulating free DNA at baseline were associated with shorter time to recurrence (HR 2.48, $p = 0.007$) and DFS (HR 2.43, $p = 0.015$) [92]. These data are certainly interesting, yet demonstration is still needed to support a cf/ctDNA-driven use of adjuvant chemotherapy. Trials investigating the feasibility of ctDNA-driven adjuvant chemotherapy in this setting are ongoing (Table 3).

The increasing consideration given to the use of pre-operative systemic chemotherapy either before or after (chemo)radiotherapy (i.e., "total neoadjuvant therapy") could substantially reduce the interest to investigating further the role of adjuvant chemotherapy in rectal cancer [13,93]. Many centres have already adopted this practice which is now endorsed by clinical guidelines [14,15]. Nevertheless, it should be noted that no randomised data are yet available to back such a treatment paradigm shift. All randomised studies conducted so far actually failed to show any advantage for a strategy of "total neoadjuvant therapy" compared to standard pre-operative treatment while results from other trials are still awaited [94–100]. More interesting appears the option of delivering neoadjuvant systemic chemotherapy without radiotherapy [101]. Therefore, despite supported by a strong rationale, adding pre-operative systemic chemotherapy to standard (chemo) radiotherapy should still be considered an investigational approach. Moving systemic chemotherapy from the post-operative to the pre-operative setting, especially without accurate patient selection based on robust prognostic/predictive factors, may just represent a simplistic way to circumvent the unsolved issue of adjuvant chemotherapy with a non-negligible proportion of patients being still at risk of over-treatment. As a result, in the absence of any strong supporting data, the

current uncertainty regarding the role of adjuvant chemotherapy in rectal cancer may soon turn into a bigger dilemma around the actual value of *peri*-operative systemic chemotherapy in this disease.

Declaration of Competing Interest

The Authors do not have any conflict of interest to disclose.

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