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REVIEW

Review on adjuvant chemotherapy for rectal cancer – why do treatment guidelines differ so much?

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ABSTRACT

Background. The use of postoperative adjuvant chemotherapy is controversial for rectal adenocarcinoma. Both international and national guidelines display a great span varying from recommending no adjuvant chemotherapy at all, over single drug 5-fluororuacil (5-FU), to combinations of 5-FU/oxaliplatin.

Methods. A review of the literature was made identifying 24 randomized controlled trials on adjuvant treatment of rectal cancer based on about 10 000 patients. The trials were subdivided into a number of clinically relevant subgroups.

Results. As regards patients treated with preoperative (chemo) radiotherapy, four randomized studies were found where use of adjuvant chemotherapy showed no benefit in survival. Three trials were found in which a subset of patients received preoperative (chemo) radiotherapy. Two of these trials showed a statistically significant benefit of adjuvant chemotherapy. Twenty trials were identified in which the patients did not receive preoperative (chemo) radiotherapy, including five Asian studies in which a statistically significant benefit from adjuvant chemotherapy was reported.

Conclusions. Most of the data found did not support the use of postoperative adjuvant chemotherapy for patients already treated with preoperative (chemo) radiotherapy. For patients not treated preoperatively, several studies support the use of single agent 5-FU chemotherapy. Treatment guidelines seem to differ according to if preoperative chemoradiation is considered of importance for use of adjuvant chemotherapy and if adjuvant colon cancer studies are considered transferrable to rectal cancer patients regardless of the molecular differences.

Adenocarcinoma of the rectum (RC) is a common cancer, with 100 000 new cases in Europe per year [1] and 40 000 in the US [2]. Approximately 30% of the RC patients are diagnosed at stage III, and 25% at stage II. Of the stage II patients, 40% are considered to be at a high-risk of recurrence [3,4]. Previously, local recurrence rate (LRR) was reported to be as high as 30%. However, due to the introduction of TME surgery [5,6], and preoperative long-course chemoradiotherapy (CRT) or short-course radiotherapy (SCRT) [7–9], as well as the implementation of multi disciplinary team-conferences [10], LRR has been reduced to less than 10% [11,12]. Furthermore staging by means of MRI [13,14] has improved treatment stratification. However, the benefit of SCRT/CRT in terms of reduced LRR, has not prolonged overall survival (OS) [15,16]. Therefore, the focus on improving outcome has changed from lowering LRR only, to a reduction of distant recurrences, which still occurs in 35% of the patients treated with surgically curative intent [17], and usually leads to death of the patient. Therefore, there might be a potential benefit from postoperative adjuvant chemotherapy as demonstrated for colon cancer (CC). The combined treatment modalities for RC however, differ from the treatment of CC, in terms of different surgical technique and CRT. In CC adjuvant single agent 5-fluororuracil (5-FU) chemotherapy has led to an increase in OS, approximately 10% for patients

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with the TNM stage III disease [18], and a further 5% gain by adding oxaliplatin [19–21].

Against this background, many oncologists extrapolate the benefits of adjuvant chemotherapy shown in CC to the treatment of RC. In RC, however, the efficacy of adjuvant chemotherapy is not equally well documented and the effect and use is still controversial. This is reflected in international and national treatment guidelines, which differ considerably in their recommendations as shown in Table I.

The aim of this review was to evaluate adjuvant chemotherapy for RC in terms of improvement in OS or disease-free survival (DFS); especially separating studies with and without preoperative SCRT/CRT. Furthermore we wanted to investigate why international and national guidelines differ so much.

Methods

Data sources

A systematic search according to a pre-specified protocol (Appendix 1, available online at http://informahealthcare.com/doi/abs/10.3109/0284186X.2014.993768) was performed using electronic databases, reference lists of articles obtained and conference abstracts. Furthermore scanning of clinicaltrials.gov and consultation of experts in the field were performed. Some limits were applied for language (cf. "selection criteria"). The searches in databases were performed by two of the authors (LØP and CQ) in Pubmed, Embase and Web of Science. The primary search was performed 1 November, 2013. An additional search was performed 1 September 2014. Relevant abstracts, or abstracts not yet indexed, were included, cf. Figure 1.

Study selection criteria

1) Randomized controlled trials (RCT) with a mandatory control-arm; 2) 5-FU-based postoperative adjuvant regimens; 3) Intravenous or oral administration of postoperative adjuvant chemotherapy; 4) For "non-English articles", an abstract of their contents with relevant data for RC patients regarding OS and/or DFS must have been available.

Results

The literature search identified 307 274 abstracts, where 8109 were duplicates from the Embase, PubMed and Web of Science. In total 22 165 titles were screened with 22 022 studies not fulfilling the study selection criteria. After stepwise exclusion of 107 studies which did not fulfill the study selection criteria and with the addition of two studies from the reference list, 38 studies remained for in-depth analysis. Further 14 studies did not fulfill the criteria and thus 24 studies were included in the final analysis, cf. Table II.

The studies were performed in Caucasian (n = 16) and Asian cohorts (n = 8). The studies varied in size, from 57 to 1243 RC patients. Four studies were on adjuvant chemotherapy with preoperative therapy and 10 studies were on adjuvant chemotherapy without preoperative therapy. Three studies evaluated adjuvant chemotherapy in a mixed cohort of patients with and without preoperative therapy.

Discussion

During these past three decades, numerous randomized adjuvant colorectal chemotherapy trials have been reported. However, most of them have included rather few RC patients. Studies have been performed with Asian or Caucasian patients, however from other malignant diseases it is known that these populations may differ in their response to treatment, both regarding its efficacy [56] and its toxicity [57].

Also several meta-analyses and systematic reviews have been published. Most recently a Cochrane review showed a significant gain in OS in RC patients treated with single agent 5-FU as adjuvant chemotherapy with a HR of 0.83 [55]. However, the interpretation of these results from this review is difficult as it included trials conducted during several decades, with patients at all stages and all treatment modalities and did not distinguish between patients receiving RT/CRT and those not.

Table I. International and national guidelines on postoperative adjuvant chemotherapy for rectal cancer.

	ESMO	NCCN	Norway	Sweden	Finland	Denmark	Spain	Dutch	NICE
Year	2013 [22,23]	2012 [2]	2013 [24]	2014 [25]	2009 [26]	2013 [27]	2013 [28]	2014 [29]	2011 [30]
RC High-risk stage II	FU/5FU	5FU/Ox#	No	5FU	5FU-Ox§	5FU(+ Ox)	Yes*	No	Yes
RC stage III	FU/5FU	5FU/Ox	No	5FU(+ Ox)	5FU-Ox	5FU(+ Ox)	Yes*	No	Yes
After preop. CRT**	n.s.	Yes	No	No	n.s.	Yes	No	No	n.s.

ESMO, European Society for Medical Oncology; 5-FU, 5-Flurouracil; NCCN, National Comprehensive Cancer Network, USA; n.s., Not stated; Ox, Oxaliplatin.* If no CRT was given **Does the guideline recommend use of postoperative adjuvant chemotherapy after preoperative (chemo) radiotherapy. # recommended for stage 0, 1 & 2. §Unknown if all stage II or only high-risk stage II.

Table II. Included trials. *Studies included patients with both colon and rectal cancer. Only patients with rectal cancer are included here. Either the authors published the separate data or provided them for the Cochrane analysis [55]. **$p \leq 0.05$.

Year	Author	n = (Total/RC)	Stage	Regimen	Hazard ratio	OS	Result	DFS	Result
Asian studies									
1991	Matsuda [31]	2450/1243*	n.s.	Observation	0.97	5y OS	No diff.		n.s.
				Adj FT	(0.77–1.23)				
1995	CCSGJ [32]	1004	n.s.	Observation	0.66	5y OS	60.2%	5y DFS	57%
				Adj 5-FU+ MMC	(0.52–0.84)	**	73.6%	**	73%
				Adj. 5-FU+ MMC+ MMC IP		**	70.7%	**	72%
1996	Ito [33]	173/77*	II-III	Observation	1.33	5y OS	No diff.	5y DFS	63%
				Adj. HCFU	(0.68–2.59)			**	77%
1998	Kodaira [34]	794	II-III	Observation	0.93	5y OS	66.3%	5y DFS	59%
				Adj UFT+ MMC	(0.73–1.19)		70.1%	**	69%
2002	Kato [35]	320/143*	II-III	Observation	0.66	5y OS	66.7%	5y DFS	60%
				Adj UFT	(0.35–1.25)		75.9%	**	76%
2004	Watanbe [36]	1429/669*	II-III	Observation	0.88	5y OS	No diff.	5y DFS	No diff.
				Adj HCFU + 5FU+ MMC	(0.57–1.36)				
				Adj HCFU + 5FU+ MMC+ immunotherapy					
2011	Hamaguchi [37]	606/274	III	Observation	0.60	5y OS	72.1%	5y RFS	56%
				Adj UFT	(0.38–0.97)	**	85.3%	**	69%
Studies with preoperative chemoradiotherapy (CRT)									
2006	EORTC 22921 [38]	1011	II-III	RT - surgery - observation	0.85	5y OS	63.2%	5y DFS	52%
				CRT - surgery - observation	(0.69–1.04)				
				RT - surgey - adj 5FU			67.2%		58%
				CRT - surgery - adj 5FU					
2010	Cionini [39]	634	II-III	CRT - surgery - observation	No HR	5y OS	69.8%		n.s.
				CRT - surgery - adj 5FU			68.0%		
2013	Proctor/Script [40]	470	II-III	RT/CRT* - surgery - observation	0.88	5y OS	75.9%	5y DFS	58%
				RT/CRT* - surgery - adj 5FU or cape	(0.59–1.31)		74.4%		62%
2014	Chronicle [41]	113	I-II-III	CRT - surgery - observation	1.18	3y OS	88%	3y DFS	71%
				CRT - surgery - adj capox	(0.43–3.26)		89%		78%
Studies without preoperative radiotherapy									
1981	Grage [42]	233/64*	II-III	Observation	0.41	5y OS	p = 0.05	5y DFS	p = 0.04
				Adj 5FU	(0.20–0.84)	**		**	
1985	Hafstrøm [43]	421/137	II-III	Observation	No HR	5y OS	No diff.		n.s.
				Adj oral 5FU					
1988	Fisher [44]	574	II-III	Observation	0.79	5y OS	43%	5y DFS	p = 0.006
				Postop RT	(0.61–1.03)	**		**	
				Postop RT with adj SFV			53%		
1988	Thomas [45]	202/106	II-III	Observation	0.75	OS	36%		n.s.
				Adj FS	(0.49–1.14)		46%		
				(Postop RT)					
				(Postop CRT - adj FS)					
1990	Hafstrøm [46]	334/99*	III	Observation	0.71	5y OS	34%		n.s.
				Adj FCV	(0.43–1.17)		49%		
1991	Krook [47]	204	II-III	Postop RT	0.71	OS-gain	29%		n.s.
				Postop CRT - adj FS	(0.55–0.92)	**			
1996	Kornek [48]	57	II-III	Observation	0.42	5y OS	54%	5y RFS	46%
				Adj intraabd. mitoxantrone and iv 5FU	(0.17–1.04)		70%		68%
1999	Athanassiou [49]	220	II-III	Postop CRT	No HR	3y OS	73.3%	3y DFS	68%
				Postop 5FU x1 - CRT - 5FU x 3			77%		70%
2003	Cafiero [50]	218	II-III	Postop RT	1.33	5y OS	p = 0.18	5y DFS	p = 0.66
				Postop RT - adj 5FU + FA	(0.90–1.96)				
2005	Glimelius [51]	2224/691*	II-III	Observation	0.90	5y OS	No diff.		n.s.
				Adj 5FU with FA, levamisole or both.	(0.74–1.10)				
Studies with AND without preop RT									
1992	Li [52]	423	n.s.	Observation	No HR	5y OS	28.8%		n.s.
				Preop RT			34.4%		
				Adj CT			47.5%		
				Preop RT - adj CT		**	52.4%		
2001	Taal [53]	1029/299*	II-III	Observation	0.95	5y OS	p = 0.13		n.s.
				Adj 5FU+ lev	(0.66–1.36)				
2007	Quasar [54]	3239/948*	I-II-III	Observation	0.77	5y OS	p = 0.05	RR	0.68
				Adj 5FU+ FA	(0.60–0.99)	**		**	

FA, folinic acid; FCV, 5FU CCNU and vincristine; FLv, 5FU and folinic acid; FS, 5FU semustin; FSV, 5FU semustin, vincristin; HCFU, carmofur; IP, intraportal; Lev, levamisole; n.s., not stated; RFS, recurrence free survival; RR, relative risk of recurrence; UFT, uftoral.

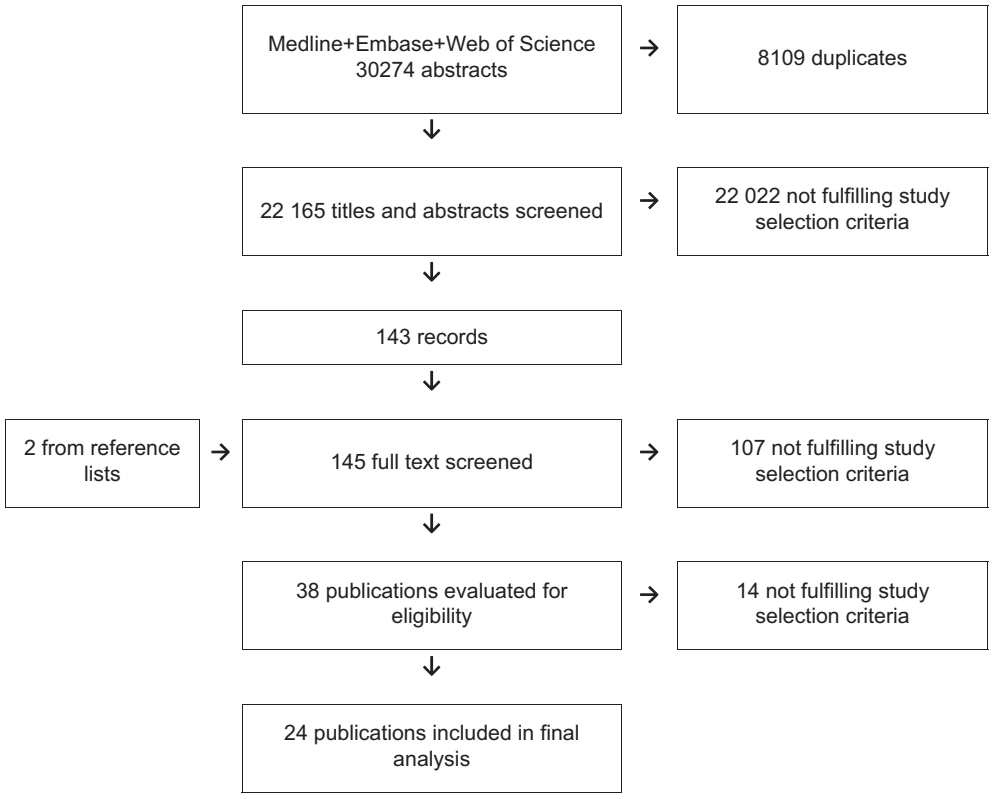

Figure 1. Study flowchart.

Adjuvant studies with preoperative treatment

In most Western countries, preoperative RT/CRT is recommended in patients with locally advanced RC [2,23].

Preoperative treatment can be delivered in different treatment schedules. One option is SCRT with 25 Gy in 5 fractions delivered in one week with immediate surgery. This regimen was mainly used in the *PROCTOR/SCRIPT* trial [40], with more than 80% of the patients treated with SCRT. This trial evaluated the effect of adjuvant chemotherapy with either 5-FU infusion or capecitabine after SCRT and surgery. The trial showed no benefit from adjuvant chemotherapy, neither on OS or DFS.

Preoperative SCRT with 5 Gy $\times$ 5 and delayed surgery 6–8 weeks later is still being investigated in RCTs [58] with no prospective data on adjuvant chemotherapy available.

The most used option for CRT consists of approximately 50 Gy in 25 fractions with concomitant 5-FU-based chemotherapy. Three prospective trials have studied adjuvant chemotherapy in RC patients after long-course CRT [38,39,41]. None of these showed a statistically significant benefit from postoperative adjuvant chemotherapy. The *EORTC 22921*-trial was a 2 $\times$ 2 factorial design with four randomized groups that evaluated chemotherapy added to preoperative long-course RT and adjuvant single agent 5-FU postoperative chemotherapy. In the study, no significant gain from adjuvant chemotherapy (5-year OS 67% vs. 63% HR 0.85) was described in their primary analysis [38]. A recent update of the study, with a median follow-up time of 10.4 years, confirmed the results of the primary analysis, with no benefit of adjuvant chemotherapy [17]. The *Cionini*-trial included 634 patients in a randomized trial with CRT and surgery versus CRT, surgery and postoperative adjuvant chemotherapy with single agent 5-FU. Their final abstract included both 5- and 10-years OS showing neither statistically significant differences between the two arms regarding OS, nor any differences as to the incidence of distant recurrences [39]. The *CHRONICLE trial* [41] evaluated the effect of adjuvant chemotherapy with CAPOX after CRT and surgery. The trial was closed prematurely because of slow accrual rate and showed no benefit of adjuvant chemotherapy after CRT. Due to interpretation of early data from the *EORTC 22921* study, it has been argued that the type of preoperative treatment might influence the selection of those who would benefit from adjuvant chemotherapy [59]. The hypothesis was that patients with SCRT would gain from adjuvant chemotherapy, whereas patients treated with CRT would not [60]. However, in order to confirm this hypothesis, an eight-arm design would have been needed [61]. Neither the *CHRONICLE*

nor the *PROCTOR/SCRIPT* trials have gained enough of essential pieces of information in order to be able to confirm that hypothesis [40].

Retrospective analyses have indicated that the time of start of adjuvant chemotherapy is important [62]. In CC patients, surgical treatment is usually performed within a few weeks after diagnosis and the adjuvant treatment can often start 4–6 weeks later, i.e. a delay of less than two months from diagnosis. In RC, planning and delivery of RT, particularly in case of long-course CRT preoperatively with extended time interval before surgery in order to allow for maximal tumor regression, it can be argued that the patients with subclinical tumor deposits do not receive any efficient systemic chemotherapy until several months later. This delay might be a reason why adjuvant chemotherapy does not benefit RC patients receiving CRT [63]. Studies using induction chemotherapy followed by radiotherapy and surgery or even preoperative chemotherapy without radiotherapy are ongoing [64,65]. Another important issue in the interpretation of these trials, is the fact that a surprisingly weak adherence is often found to the current protocol. In the *EORTC 22921*-trial 25% of the patients assigned to the postoperative adjuvant chemotherapy never started treatment and less than 50% completed the prescribed dose and number of courses of chemotherapy [17]. In the clinical setting, the same issue occurs with more than one third of patients scheduled for postoperative adjuvant chemotherapy failing to initiate the treatment [66].

It has been discussed whether it is possible to identify a subgroup of RC patients who will benefit from postoperative adjuvant chemotherapy. Some argue that patients with good response to CRT also will benefit from adjuvant chemotherapy [67,68]. Others argue that patients with good response have an excellent prognosis per se and do not need adjuvant chemotherapy [69,70]. Finally others suggest using the histological classification to identify high-risk patients and offer adjuvant chemotherapy [71]. However, all these data are retrospective analyses and may be biased. So far, no prospective RCTs according to the histological classification have been performed.

A possible beneficial subgroup is the high-lying tumors, who might respond more like CC to adjuvant chemotherapy. In the subgroup analysis from the *EORTC 22921*-trial, patients with a tumor located above 5 cm from the anal verge had a significant gain in OS from adjuvant chemotherapy (HR 0.64, 95% CI 0.42–0.96) [67]. The subgroup analysis from the *PROCTOR/SCRIPT*-trial showed a significant gain in OS for patients with tumors above 10 cm from the anal verge (HR of 0.55, 95% CI 0.33–0.94) [40]. In a Swedish retrospective study, data from 436 patients were analyzed. They found an OS benefit in patients with tumors located >10 cm from the anal verge (HR 0.54, 95% CI 0.3–0.9) [72]. However, in the recent update from the *EORTC* trial, with updated data on this subgroup in their supplementary material, there was no longer any significant gain from adjuvant chemotherapy in patients with tumors above 5 cm from the anal verge [73].

Although no single RCT phase III supports the use of adjuvant chemotherapy after RT/CRT, adjuvant chemotherapy is still being strongly recommended [2]. The only trial that might support the use of adjuvant chemotherapy (5-FU) after SCRT/CRT is the *Quasar* trial. The study included both CC and RC patients, and about 50% of the rectal cancer patients had received radiotherapy [54]. A subgroup analysis of this study showed that RC patients treated with radiotherapy either pre- or postoperatively had a significant reduction in risk of death (RR 0.69 95% CI 0.49–0.98) [75]. A meta-analysis of the *Quasar-*, *Cionini-*, *PROCTOR/SCRIPT-* and *CHRONICLE* trials, is planned.

For CC, the combination of 5-FU and oxaliplatin is superior to single drug 5-FU as adjuvant therapy in several studies [19–21]. Preoperative oxaliplatin in combination with CRT have been tested in five large RCTs. Two of these used both pre- and postoperative adjuvant 5-FU and oxaliplatin and these studies were both presented at the ASCO 2014 annual meeting. The German *CAO/ARO/AIO-0* trial included 1265 patients and compared mFOLFOX with bolus 5-FU as adjuvant treatment after CRT and surgery [76]. After a median follow-up time of 50 months a statistical significant increase in DFS was found favoring the combination-arm (HR 0.79, 95% CI 0.64–0.98). However, at present there are no differences in OS at three years (88%) and five years (78%). The *PETACC-6* trial randomized 1094 patients after CRT and surgery to CAPOX or capecitabine. An interim analysis presented showed no difference in three-year DFS (74.5% vs. 73.9%) [77]. In both studies only about 60% of patients received all planned chemotherapy cycles. The *ADORE* trial, an Asian randomized phase II trial, randomized 321 RC patients, stage II or III, to adjuvant bolus 5-FU or FOLFOX after CRT and TME. The authors found a statistically significant improvement in three-year DFS from 62.9% to 71.6% (HR 0.66, 95% CI 0.43–0.99) [78]. In the *CHRONICLE-study* [41], described above, patients were randomized between observation and adjuvant CAPOX and did not evaluate the additional use of oxaliplatin as the above studies. The same 5-FU schedule was used in both arms of the PETACC-6 trial, where no difference in DFS was seen, whereas the bolus schedule of 5-FU was used both in the ADORE trial and in the German

CAO/ARO/AIO-04 in the control arms, where a statistically significant gain in DFS was seen. The bolus schedule of 5-FU is shown to be inferior in the metastatic setting [79] and thus it can be considered if the gain in DFS in the ADORE trial and in the German *CAO/ARO/AIO-04* trial is not solely driven by the addition of oxaliplatin.

These recent data may potentially change the present treatment recommendations; however before any definite conclusion can be made, final survival data must be presented.

Adjuvant studies without preoperative chemoradiotherapy

The literature search found several Asian trials on adjuvant chemotherapy without preoperative CRT, and according to the inclusion criteria seven of these trials were included. Of the seven, two of them showed significant gain in five-year OS. The *Hamaguchi*-trial from 2011 included 606 stage III colorectal cancer patients. Patients were randomized after surgery to no further treatment or one year of adjuvant uracil and tegafur (UFT). Results showed no improvement in OS for CC patients, but for the 274 RC patients a statistical significant improvement in OS was shown (HR 0.60 95% CI 0.38; 0.97) [37]. Ten western RCTs included patients without preoperative treatment. Of the 10, three of them showed significant improvement in five-year OS. Finally in three trials CRT treated patients were included, with the *Quasar* trial being the largest. This study included more than 3000 patients with CRC and 948 of these had RC. The majority of the patients (>90%) had stage II disease. The subgroup analysis of patients with preoperative treatment is mentioned above, but for all RC patients included, a statistically significant improvement in five-year OS was shown (HR 0.77 95% CI 0.60; 0.99) [54].

For patients who are not treated with preoperative treatment, it has been argued that the gain from adjuvant chemotherapy is only shown in older studies without the use of standardized TME-surgery, which is now a mandatory standard for RC patients planned for definitive surgery [22]. No RCT has been published with patients having TME-surgery and adjuvant chemotherapy without preoperative treatment. Postoperative ischemia in the surgical field, which theoretically would be greater with TME-surgery than with colonic surgery, may reduce delivery of chemotherapy. It has also been argued that the opposite is the matter and that the effect of chemotherapy to remove distant micro-metastases is not impaired [80]. As the majority of patients in many countries are treated with preoperative treatment, and adjuvant chemotherapy often is a standard, a future RCT is unlikely to be performed.

Can results from colon cancer studies automatically be extrapolated to rectal cancer patients?

In light of the missing adjuvant data from RC trials, adjuvant study results from CC are often extrapolated to RC patients. This raises the question if RC and CC can be considered similar or if there are major differences in tumor biology and response to chemotherapy. It is frequently stated that RC and CC have different gene expression profiles, different cytokeratin profiles, different level of microsatellite instability (MSI) and mutations in BRAF and KRAS [81,82]. Many studies however show a gradual change from rectum to proximal colon [83,84]. If there is a major difference, it seems to be between proximal CC compared to distal CC and RC, with the main difference being MSI tumors that have a preferential proximal colon location and BRAF mutations that have a preferential colon location. If MSI tumors are excluded, few differences are seen between gene expression in RC and CC [82,85]. Several studies have shown minor differences between distal CC and RC, whereas large differences are found between proximal CC and distal CC/RC [82,86–88]. Based on tumor biology, the question of how much adjuvant chemotherapy benefits CRC patients should probably rather separate between proximal CC and distal CC/CC patients or according to MSI status. Metastatic CC and RC in general respond similarly to chemotherapy and primary tumor site is not predictive of response or survival. One exception is a study by Boisen et al. where the addition of palliative bevacizumab seemed to benefit patients with RC [89]. Benefit of chemotherapy in a metastatic setting can however differ from the adjuvant setting; irinotecan-based chemotherapy, bevacizumab and cetuximab prolong survival in metastatic CRC, whereas no benefit of these drugs has been found in the adjuvant setting [90]. Based on the above data, we consider that CC study results should probably not automatically be extrapolated to RC patients in the adjuvant setting.

Why do guidelines differ?

Only one of the nine guidelines mentioned in Table I, has cited the grade of evidence (IIB) used for their recommendations [23]. A number of guidelines conclude that the literature available for RC is poor and therefore do not recommend the use of adjuvant chemotherapy. Many other guidelines however seem to extrapolate data from CC and based on these data

recommend the use of adjuvant chemotherapy. As far as we can judge, the main reason for the major differences in guidelines seems to be if the authors believe that adjuvant CC data can be extrapolated to RC or if the authors do not believe this is correct. NCCN guidelines [2] are even wider in RC than in CC as it is restricted to high-risk stage II for CC whereas in RC recommendations include all stage II patients. Updated new guidelines should specify if perioperative chemoradiation will influence their recommendation and if they believe that adjuvant CC data can be extrapolated to rectal cancer patients.

Conclusion

Postoperative adjuvant chemotherapy for patients with RC may be divided into two clinical settings – patients who have been treated with preoperative SCRT/CRT and patients who have not received preoperative therapy. Currently, most available data do not support the routine use of adjuvant chemotherapy for patients who have received preoperative SCRT/CRT. For patients not treated preoperatively, the evidence from the Quasar study and Asian trials support the use of single agent 5-FU chemotherapy for stage II and III disease. The main reason for the major differences in guidelines seems to be if the authors believe that adjuvant CC data can be extrapolated to RC or not. Molecular studies indicate that results from CC studies should probably not be automatically extrapolated to RC patients.

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Supplementary material available online

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