Chemotherapy in rectal cancer

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Introduction

During the last decade, advances in surgery, specifically the use of meticulous sharp dissection of the mesorectum (total mesorectal excision, TME) together with pre- or post-operative radiotherapy have markedly improved local control in patients with rectal cancer. Local relapse rates above 10–15% are now no longer acceptable. However, this progress was achieved by optimal use of all therapeutic modalities: radiation, surgery and chemotherapy. Systemic chemotherapy has at least two important roles in this multi-modality approach:

- addition to radiotherapy in pre- and post-operative chemoradiation, aiming to enhance efficacy of radiation (resulting in favourable local control)
- adjuvant systemic chemotherapy after completion of radio(chemo)therapy, aiming to eradicate micrometastasis and therefore reduce rate of distant relapse

As the role of chemotherapy in combination with radiotherapy is extensively discussed in the article by Dr Valentini [1], the present article focuses on the systemic treatment options.

Role of adjuvant chemotherapy as single modality

In stage II or III rectal cancer, three trials evaluated the role of surgery alone or with chemotherapy in addition to radiation and chemoradiation (Table 1). The GITSG trial showed no influence on local failure rate, but a trend towards improved survival for chemotherapy modalities [2]. Furthermore, in the NSABP R01 trial, post-operative chemotherapy with Methyl-CCNU, Vincristine and 5-Fluorouracil (5-FU) (MOF regimen) resulted in a significant improvement in overall survival [3]. This survival benefit was mainly observed in male patients receiving MOF, and therefore, the subsequent NSABP R02 trial randomised male patients to receive chemotherapy with MOF or 5-FU whereas female patients received 5-FU treatment. All patients were randomised to receive either chemotherapy alone or chemotherapy combined with chemoradiation [4]. As a result of chemoradiation, the local failure rate was significantly reduced (13% vs. 8%, $P=0.02$) by additional radiation, but this relatively small benefit of 5% did not translate into improved overall survival when compared to resection and chemotherapy without radiation. There was no difference in comparison of either chemotherapy regimen. In conclusion, these trials indicate that arms with chemotherapy alone will not alter local relapse rate but lead to an improvement in overall survival.

Role of adjuvant chemotherapy in combination with radiotherapy

In order to obtain both optimal local control and reduction of distant relapses, two US trials [2,5] and a Norwegian study [6] were designed to compare bimodality of chemotherapy and radiation versus single modality (resection +/– radiation or chemotherapy). As in the GITSG trial, the NCCTG trial demonstrated a significant reduction of both local relapse rates and a survival benefit of 10% absolute difference for patients who were treated with chemotherapy. The Norwegian trial underlined the finding that this approach should be favoured. However, these data have to be interpreted carefully due to the extensively high local relapse rates.

Both US trials used 5-FU in combination with Methyl-CCNU and in both trials 5-FU was administered as bolus. Subsequent trials showed that the addition Methyl-CCNU (which has a high mutagenic potential) leads to increased toxicity, but not to an increase in therapeutic efficacy when compared to 5-FU alone [8]. As a consequence, this information prompted a National Institutes of Health consensus conference, convened in 1990, to recommend post-operative adjuvant chemoradiotherapy as standard treatment for patients with rectal cancer classified as AJCC stage II (i.e. a tumour penetrating the rectal

Table 1
Randomised trials with a single chemotherapy regimen in adjuvant treatment of stage II/III rectal cancer

Trial	regimen	Local failure	Distant metastasis	5y OS
GITSG [2] (n = 227)	Resection	24% } P = 0.08	34%	43%
	Resection + RT	20%	30%	52% } P<0.05
	Resection + 5-FU/MeCCNU	27%	27%	56%
	Resection + RT-5-FU/MeCCNU	11%	26%	59%
NSABP R-01 [3] (n = 574)	Resection + RT	25% } P = 0.06	26%	43% } P <0.05
	Resection + RT	16%	31%	41%
	Resection + MOF	21%	24%	53%
NSABP R-02 [4] (n = 694)	Resection + CT*	13% } P = 0.02	29%	64%
	Resection + RCT	8%	31%	64%
NCCTG/Mayo [5] (n = 204)	Resection + RT	25% } P = 0.04	46% } P = 0.01	81%# } P = 0.005
	Resection + RT + 5-FU/MeCCNU	13%	29%	91%#
Norwegian Trial (Tveit) [6] (n = 144)	Resection	30% } P = 0.01	39%	
	Resection + RT + 5-FU	12%	33%	
Italian trial [7] (n = 218)	Resection + RT	20% n.s.	38% n.s.	
	Resection + 5-FU/LEV + RT + 5-FU/LEV (RT and CT sequential)	22 %	27%	

RT: radiotherapy; 5-FU: 5-fluorouracil; 5y OS: 5-year overall survival; LEV: levamisole; CT: chemotherapy

wall, without regional lymph-node involvement) or stage III (i.e. any tumour with regional lymph-node involvement) [9].

What is the optimal regimen in post-operative chemotherapy with radiation?

O' Connell and colleagues were the first to successfully optimise the post-operative simultaneous chemotherapy regimen in combination with radiation. In a randomised trial, a patient group receiving continuous infusion of 5-FU (225 mg/m^2) yielded significantly improved progression-free survival, distant metastasis rate and overall survival [10]. These results were surprising because of their impact on the endpoint overall survival and generated the hypothesis that a more active simultaneous chemotherapy should not only improve the effect of radiotherapy (and therefore local control) but also seems to have a larger impact on early distant metastasis than expected. However, further improvement of modulation 5-FU with folinic acid (FA) and/or levamisole was not possible in a 4-arm Intergroup trial (INT0114) in which no arm was superior to the bolus 5-FU [11].

In conclusion, the former NCI schedule should no longer be used as a reference schedule for adjuvant chemo-/chemoradiation (which should itself only be replaced by pre-operative chemoradiation). The NCI schedule started 4–8 weeks after resection with two cycles of bolus 5-FU (without FA). Radiotherapy was not started before day 63 with bolus 5-FU, followed by two more cycles of post-chemoradiation therapy with 450 mg/m^2 bolus 5-FU. In view of the O' Connell results, 5-FU should be administered as a continuous infusion during the whole period of radiation (as in the CAO/ARO/AIO-94 trial), followed by systemic chemotherapy which is discussed separately. Furthermore, recent data from Korea indicates that an early onset of therapeutic modalities after resection results in an improvement in disease-free survival when compared to a later start [12]

Pre-operative radiotherapy as the novel standard of care

Despite optimal surgery, several randomised studies have found lower rates of local failure with pre-operative radiotherapy than with TME surgery alone. However, only the Swedish Rectal Cancer Trial, which evaluated a short course of pre-operative irradiation in 1168 patients (25 Gy, delivered in five fractions), found an advantage in overall survival [13]. The authors of a subsequent meta-analysis also concluded that the combination of pre-operative radiotherapy and surgery, as compared with surgery alone, significantly improves local control and overall survival [14]. The Dutch Colorectal Cancer Group reported that the addition of short-course pre-operative radiotherapy to optimal surgery with TME reduced the rate of local recurrence but did not improve 2-year survival [15].

Table 2
Effects of pre-operative chemoradiation versus radiation alone in rectal cancer

Trial	Regimen		pCR (%)	Sphincter preservation (%)	Local failure rate (%)	5y DFS	5y OS
Frykholm (n = 70) [8][a]	RT				17	38	18
	RT/FU/Mtx				44	66	29
						P = 0.03	
FFCD trial (n = 762) [18]	RT	5-FU/FA 4#	3.7	52	16.5	56	66
	RT/5-FU	5-FU/FA4#	11.7	53 n.s.	8.0	59n.s.	67n.s.
			P <0.05		P = 0.003		
EORTC trial (n = 1011) [19]	RT		} 5	} 55	17.1	} 54	} 65
	RT	chemo			9.6 } P = 0.002		
	RT/5-FU		} 11	} 52 n.s.	8.8	} 56 n.s.	} 66 n.s.
	RT/5-FU	chemo			8.0		
Polish trial [16]	RT (5 x 5)		1	61			
	RT/5-FU		16	58 n.s.			

[a] Primarily staged as irresectable; pCR: pathological complete response; 5y DFS: 5-year disease-free survival; 5y OS: 5-year overall survival; 5-FU: 5-fluorouracil; FA: folinic acid; RT: radiotherapy

Conventional radiation with 45–50.4 Gy administered in daily fractions of 1.8 Gy for 5–6 consecutive weeks offers the chance of tumour shrinkage and downsizing/downstaging of large tumours. Ongoing trials suggest that pre-operative ' long time' radiation is indicated when maximal tumour shrinkage is required prior to surgery, i.e. in locally advanced T4-disease and tumours of the lower part of the rectum when sphincter preservation is attempted. A Polish trial addressed this treatment approach in comparison of pre-operative 5×5 radiation (vs. conventional radiation) and a significant higher rate of tumour downsizing and a lower rate of incomplete (R1) resections was yielded. However, sphincter preserving was not improved in this trial [16].

The recently published German AIO/CAO/ARO-94 trial [17] finally addressed the question whether (chemo)radiotherapy should be given post- or pre-operatively. The findings in 799 patients clearly indicate that pre-operative administration is less toxic and enables sphincter preservation in a higher number of patients although this was not a primary endpoint. Furthermore, the local failure rate was significant lower (6%) with pre-operative chemoradiation when compared to the 13% in the post-operative group ($P < 0.006$). These effects were not limited to the ' high-risk' groups only, but also for T3N0-1 tumours.

However, the question about the role of chemotherapy in these novel standards is:

- Is chemotherapy necessary as a part of (chemo)-radiation pre-operatively and does it influence local control and overall prognosis?
- Will chemotherapy, given as systemic treatment post-operatively, be able to reduce rate of distant metastasis?
- Is an onset of early systemic treatment beneficial?

Pre-operative radiation or chemoradiation? (Table 2)

Many patients with locally advanced disease show T4 stages with involvement of adjacent structures where a R0 resection is unlikely or they present low-lying tumours where sphincter preservation is an issue. For this patient group, pre-operative (chemo)radiation was administered frequently. Due to the modulating effect of chemotherapy on tumour cells and therefore enhanced sensitivity for radiation damage, chemoradiotherapy was expected to be superior to radiotherapy alone. This hypothesis is supported by a single published trial that showed superiority in local control after chemoradiotherapy in primarily irresectable disease [8]. This year, two large randomised trials from the EORTC [19] and the French FFCD group [18] addressed that question by randomisation between 45 Gy. conventional radiotherapy (25 fractions/5 weeks) versus 5-FU modulated radiation of the same dose and regimen. 5-FU was administered as bolus injection of 350 mg/m^2 day 1–5 on weeks 1 and 5 in both trials. In two arms of the 2×2 factorial EORTC trial and in both

Table 3
Correlation of local relapse rates to disease-free and overall survival[a]

Trial	Regimen		Local failure rate (%)	Distant metastasis (%)	5y DFS (%)	5y OS (%)
	pre-operative	post-operative				
Frykholm (n=70)[b] [8]	RT		17		38 } P=0.03	18
	RT/FU/Mtx		44		66 } P=0.03	29
FFCD trial (n=762) [18]	RT	5-FU/FA 4#	16.5 } P=0.003		56 } n.s.	66 } n.s.
	RT/5-FU	5-FU/FA 4#	8.0 } P=0.003		59 } n.s.	67 } n.s.
EORTC trial (n=1011) [19]	RT		17.1	38	} 54	} 65
	RT	chemotherapy	9.6	34	} 54	} 65
	RT/5-FU		8.8 } P=0.002	35	} 56 n.s.	} 66 n.s.
	RT/5-FU	chemotherapy	8.0 } P=0.002	31	} 56 n.s.	} 66 n.s.
CAO/ARO/AIO-94 trial (n=823)[c] [17]	–	RT/FU + FU bolus	13 } P=0.006	36 } n.s.	68 } n.s.	76 } n.s.
	RT/5-FU	FU bolus	6 } P=0.006	38 } n.s.	65 } n.s.	74 } n.s.
Dutch 5×5 trial (n=1861)	–	–	11.4			64.3 } n.s.
	RT 5×5	–	5.8			63.5 } n.s.

[a] 5y DFS: 5-year disease-free survival; 5y OS: 5-year overall survival; n.s.: non significant; RT: radiotherapy; 5-FU: 5-fluorouracil; Mtx: methotrexate; FA: folinic acid.
[b] Primarily staged as irresectable.
[c] Median follow-up 46 months.

arms of the FFCD study, systemic 5-FU/FA was given post-operatively as systemic adjuvant treatment.

As expected, the addition of chemotherapy enhances radiation effects, resulting in significant higher rates of tumour eradication (pathologic complete response, pCR) and in a significant reduction of local relapse rate. Tumour eradication was seen in 11% and 16% respectively in the chemoradiation arms whereas it was rarely observed after radiation alone. Local failure rates for radiation alone were in the range of 17% and therefore more than twice as high when compared to radiation with chemotherapy. However, although pre-operative radiotherapy significantly reduced tumour size, pTN stage and significant decreased lymph node invasion, rates of sphincter preserving surgery could not be improved; this in contrast with the findings of the German trial where pre-operative chemoradiation could improve rates of sphincter preservation – but when compared to no treatment. However, the importance of this finding is difficult to interpret due to variability in terms of assessment of operability, patient selection and others.

The major advantage of the pre-operative 5 × 5 Gy radiation is the fast completion of peri-operative modalities. However, this short period does not cause significant tumour shrinkage in advanced disease. The Polish trial of Bujko compared a short pre-operative radiotherapy with conventional 5-FU modulated chemoradiation. Chemoradiation did lead to tumour eradication in more than 10%, but so far, an increase in curative (R0) resection or sphincter preserving surgery could not be shown [16].

In conclusion, pre-operative concomitant chemotherapy should be used as standard when it is combined with 45(–50.4) Gy. Although pre-operative chemoradiation significantly reduces tumour size and stage and significantly reduces local failure rates (which is a major problem and therefore the main reason for chemotherapy), there is no benefit in terms of improved disease-free survival or overall survival. Even the absolute reduction of 5–7% for local relapses does not alter the relapse rate of 40–45% after five years.

The German CAO/ARO/AIO group [17] also showed that pre-operative continuous infusion of 5-FU could significantly reduce local relapse rate from 13% to 6% (when compared to no pre-operative treatment), but this reduction did not influence disease-free or overall survival.

These data stress the importance in controlling distant relapses. In all trials with pre-operative treatments, rates of local relapse are now 6–8% as a result of a continuously improved and now almost optimal locoregional management of surgery and radiotherapy. However, rates of distant metastasis are 31–38% (Table 3) with a 5-year overall relapse rate

of 40–45%, although in the majority of trials patients were treated with systemic chemotherapy. The 5-year overall survival rates for stage II/III rectal cancer are lower than for stage III colon cancer due to distant metastasis. As a consequence, further improvement can only be achieved if the rate of distant metastasis is reduced. Even if the local relapse rate will be (hypothetically) 0%, the overall prognosis with more than 30% distant relapses would not be altered.

Ways to improve chemotherapy

5-FU with or without FA was and still is the cornerstone (and almost the only active drug) in treatment of colorectal cancer for more than 40 years. Optimisation of 5-FU treatment by modulation with levamisole and FA as well as different ways of administration (bolus, infusional) leads to slightly improved outcomes in both adjuvant treatment of colon cancer and treatment of metastatic colorectal cancer. Due to the findings of O' Connell [10], even the modification of post-operative concomitant 5-FU administration with radiotherapy yielded an improved in overall survival so that the optimal way of chemotherapy should not be underestimated.

Standard treatment with pre-operative chemoradiation allows optimisation of chemotherapy either pre-operatively or after resection as ' typical' adjuvant chemotherapy.

Pre-operative chemotherapy

The above mentioned trials clearly indicate that pre-operative chemotherapy leads to significantly better local control and this could lead to lower rates of distant metastasis. Furthermore, retrospective data indicates that patients with complete eradication of tumour cells (pathological complete regression) have a favourable prognosis. Analysis of tumour specimens in randomised trials (the German CAO/ARO/AIO-94 trial and the (not fully recruited) US NSABP R 03 trial) comparing pre-operative chemoradiation with no chemoradiation underline these findings (Figs. 1, 2). In the German trial, a correlation between grade of tumour regression with disease-free survival was shown. In addition, the rate of pathological response was associated with a better outcome in the analysis of the NSABP R03 protocol [20,21].

However, it is still unclear whether a good pathological response is a predictive marker for the combined treatment response or a prognostic marker for a favourable prognosis. Despite that, the optimisation of pre-operative chemotherapy should lead to a consistently higher rate of pathological responses.

Capecitabine mimics the pharmacokinetics of continuous 5-FU infusion while avoiding the potential complications associated with central venous access and reducing the time patients need to spend receiving treatment in infusional centres. Moreover, capecitabine is preferentially converted to the active 5-FU metabolite within tumour cells by exploiting the higher activity of the enzymatic activity in tumour tissue compared with normal tissue [22]. Consequently, capecitabine was evaluated in numerous phase II trials in pre-operative chemoradiation (Table 4). Toxicity was predominantly diarrhoea (grade 3 and 4: 7%) and hand-foot-syndrome. Not surprisingly, the schedule leads to radiographical downstaging of tumours and pathological complete response rates of 11–24% and therefore seems to be as active as 5-FU [23–27].

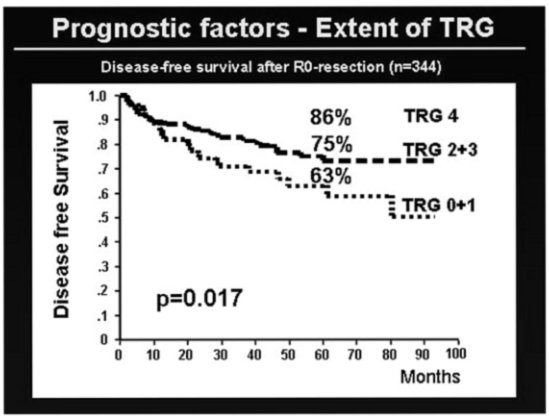

Fig. 1. Tumour regression grading in correlation to disease-free survival. German CAO/ARO/AIO-94 trial [20].

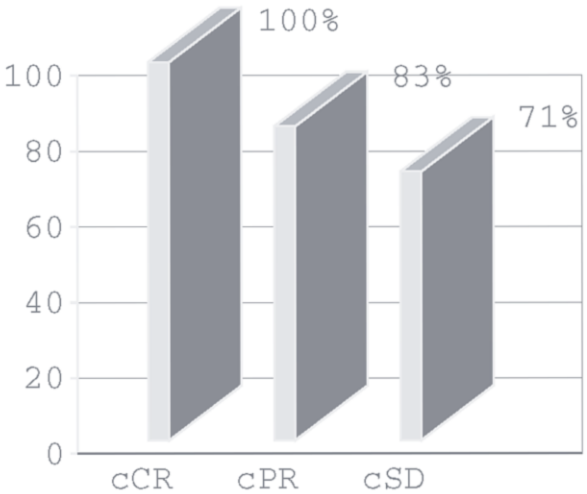

Fig. 2. Correlation of pathological response to disease-free survival. NSABP R 03 trial [21].

Table 4
Phase II trials of pre-operative chemoradiation with novel drugs: Capecitabine

Trial	N	regimen	Main toxicity	pCR*
Kim [23]	45	45 Gy/25 fractions, followed by a 5.4 Gy/3 fractions boost, capecitabine 825 mg/m^2 twice daily, day 1–14 and 22–35, folinic acic 20–mg/m^2/d	Grade 3: hand-foot syndrome 7%, diarrhoea 4%, fatigue 4%	11%
Kim [24]	95	50 Gy over 5 weeks (46 Gy to whole pelvis + 4 Gy boost), capecitabine daily 825 mg/m^2 twice daily day 1–40	Grade 3: diarrhoea 3%, neutropenia 1%	12%
Dunst [25]	98	50.4 Gy in 28 fractions and 5.4 Gy boost, capecitabine 825 mg/m^2 twice daily from first to last day of radiotherapy	Grade 3: diarrhoea 4%, leuko- and lymphopenia 10%, hypopotassemia 4%, local skin erythema in the radiation fields 1%, bilirubin increase 1%, hypocalcemia 1%, hyponatremia 1% Grade 4: hyperglycemia 1%	57%
De Paoli [26]	53	45 Gy/25 fractions and 5.4 Gy boost, capecitabine 825 mg/m^2, twice daily, 7 days/week	Grade 3: diarrhoea 7%	24%
Dupuis [27]		45 Gy/25 fractions, 5 weeks, capecitabine 825 mg/m^2 twice daily from first to last day of radiotherapy	Grade 3: diarrhoea 4%, local skin reaction 4%	24%

Oxaliplatin and irinotecan are also excellent candidates for inclusion into neoadjuvant regimens because of their rapid cytoreductive capacity.

Oxaliplatin is an attractive combination partner to 5-FU because of lack of similar acute dose-limiting side effects. Moreover, recent *in vitro* and *in vivo* preclinical and clinical studies have demonstrated oxaliplatin to be a potent radiosensitising agent [28]. Several phase II trials (Table 5) have incorporated Oxaliplatin with 5FU/FA [29–32], capecitabine [33–36], UFT/FA [27–38] and Raltitrexed [39,40]. The results indicate that these combinations are feasible and show interesting activity with pCR rates of 15% to 28%. These rates are higher compared to 5-FU.

About the same pathological response rates were seen in 5-FU/irinotecan and capecitabine/irinotecan regimens [41–49] (Table 6). As expected, irinotecan-containing regimens seem to be more difficult to handle due to (dose-related) grade 3 and 4 diarrhoea in 10–28% of patients (Tables 4–6).

Recently, the novel ' targeted' therapies have entered treatment of metastatic colorectal cancer. Bevacizumab, which has become standard first-line treatment, has preclinically demonstrated synergistic activity with both chemotherapy and radiation [49]. Cetuximab is active in systemic treatment of colorectal cancer and is a very potent radiosensitiser that has improved survival in patients with head and neck cancer (with concomitant radiotherapy). Both Bevacizumab and Cetuximab are now tested in phase I/II trials [50].

Post-operative chemotherapy

There is no standard post-operative adjuvant chemotherapy in patients with rectal cancer and data on adjuvant chemotherapy in rectal cancer treatment remain controversial. As mentioned above, in a former post-operative trial the use of continuous infusional versus bolus 5-FU resulted not only in improved relapse-free but also in overall survival. Furthermore, the addition of chemotherapy to radiotherapy in all trials with post-operative treatments resulted in the reduction of distant metastasis and improved overall survival. In most of these trials, chemotherapy was given only during radiotherapy.

The role of a ' real' adjuvant chemotherapy after simultaneous chemoradiation was investigated in a German and a Greek trial without showing a clear benefit from therapy versus observation or for 6 versus 12 months administration of 5-FU [51,52] (Table 7).

More evidence is coming from the UK QUASAR trial where 3238 patients of whom 91% had stage II (most ' high-risk') colorectal cancer were randomised to receive either a 5-FU/FA regimen or observation. The 5-year recurrence rate and the overall survival favoured the chemotherapy arm by an absolute increase of 4% and 3% respectively. A relevant subgroup of 29% had rectal cancer, and this subgroup of relatively early stages had a higher benefit than patients with colon cancer (Fig. 3) [54].

There are almost no data on adjuvant post-operative chemotherapy after pre-operative treatment

Table 5
Phase II trials of pre-operative chemoradiation with novel drugs: Oxaliplatin

Trial	N	regimen	Main toxicity	pCR*
Gérard [29]	40	50 Gy over 5 weeks with a concomitant boost, oxaliplatin 130 mg/m (2) on day 1 and 29 followed by 5-day continuous infusion of fluorouracil 350 mg/m^2 and L-folinic acid 100 mg/m^2	Grade 4: diarrhoea 2.5%, mucositis 2.5% Grade 3: fatique 7.5% diarrhoea 5%, rectitis 5%, neutropenia 2.5%	15%
Carraro [30]	22	45 Gy/25 fractions, followed by a 5.4 Gy boost, oxaliplatin 25 mg/m^2/day in 30-min infusions, followed by bolus LV 20 mg/m(2)/day and bolus 5-FU 375 mg/m(2)/day. All drugs were given on 4 days during Weeks 1, 5 and 10 (after radiochemotherapy), single oxaliplatin dose of 50 mg/m^2 was also given on the third week of radiotherapy	Grade 4: neutropenia 4.5%, leukopenia 4.5%, anaemia 4.5%, one treatment-related death (4,5%) Grade 3: diarrhoea 27%, cutaneous toxicity 14%, vomiting 4,5%, neutropenia 4.5%, leukopenia 4.5%, thrombocytopenia 4.5%, anorexia 4,5% chemoradiotherapy)	25%
Alonso [31]	53	50.4 Gy/28 fractions, oxaliplatin 60 mg/m^2 on day 1 every week (weeks 1–6), continuous infusion of 5-FU 200 mg/m^2/day on days 1–5	Grade 3: diarrhoea 7.5% Grade 4: cardiac (miocardial infarct) 2%	23%
Aschele [32]	25	50.4 Gy/28 fractions, oxaliplatin 60 mg/m2 and continuous infusion 5-FU 225 mg/m2/day	Grade 3: diarrhoea 16%	28%
Rödel [33]	26	50.4 Gy/28 fractions, oxaliplatin 50 mg/m^2 on days 1, 8, 22, and 29, capecitabine 825 mg/m^2 twice daily day 1–14 and 22–35	Grade 3: diarrhoea 8%, Skin, local toxicity, perianal 8%	19%
Glynne-Jones [34]	84	45 Gy/25 fractions, capecitabine 650 mg/m^2 twice daily 7 days/week during RT, oxaliplatin 130 mg/m^2, days 1 and 29	10% pts had G3–4 diarrhoea and 2% had G3–4 lethargy	18%
Duck [35]	31	1.8 Gy/fraction, total dose 45 Gy, 5 weeks, 5 days a week, oxaliplatin 50 mg/m^2 weekly for 5 weeks, capecitabine 825 mg/m^2 twice a day, each day of radiation.	Grade 3–4 diarrhoea 22%	6 (1/17)
Tucci [36]	14	1.8 Gy daily up to 45 Gy followed by a 5-fraction boost up to 54 Gy in 6 weeks, capecitabine 825 mg/m^2 bid (days 1 to 40), oxaliplatin 60 mg/m^2 every 2 weeks (3 administrations)	Grade 3 diarrhoea 21%	28
Aschele [37]	15	50.4 Gy – 28 fractions, oxaliplatin 60 mg/m^2, tegafur-uracil (200-250-300-350 mg/m^2/day, Monday through Friday for all the duration of RT) combined with weekly	Grade 3: diarrhoea 16%	19% (2/11)
Wang [38]	63	45 Gy in 20 fractions over 28 days, tegafur-uracil 200 mg/m^2/day and folinic acid 45 mg/day on day 1–28, tegafur-uracil 250 mg/m^2/day and folinic acid 45 mg/day day 36–63 grade 3–4: diarrhoea 9%, leucopenia 3%	25%	
Casado [39]	43	50 Gy over 5 weeks with a concomitant boost approach, three courses of raltitrexed 3 mg/m2 followed by oxaliplatin 130 mg/m2 every 21 days	Grade 3: diarrhoea 7% neutropenia 7%	18%
Gambacorta [40]	48	50 Gy, 5 d/wk for 5 weeks, raltitrexed 3 mg/m^2 and oxaliplatin 60 to 130 mg/m^2 days 1, 19, and 38 Grade 3 acute toxicity occurred in 18.7%	28%	

Table 6
Phase II trials of pre-operative chemoradiation with novel drugs: Irinotecan

Trial	N	regimen	Main toxicity	pCR*
Metha [41]	32	45 Gy/25 fractions, followed by a 5.4 Gy boost, irinotecan 50 mg/m^2 days 1, 8, 15, and 22, 5-FU 200 mg/m^2 daily, 7 days per week, days 1–33	Grade 3: diarrhoea 28%, mucositis 21%, rectal sores (skin) 21%, abdominal cramping 9%, nausea/vomiting 3%	37%
Mitchell [42]	28	45 to 54 Gy, 1.8 Gy daily, irinotecan 50 mg/m^2 on days 1, 8, 15, 22, 5-FU continuous infusion, 300 mg/m^2 initially, and subsequently, 225 mg/m^2/day on days 1–5 weekly during radiation	Grade 3–4 diarrhoea 27%	21%
Navarro [43]	34	45 Gy/25 fractions for 5 weeks, irinotecan 50 mg/m^2 on days 1, 8, 15, 22, 29, 5-FU 225 mg/m^2/day 5 day continuous infusion on days 1–5 weekly during the period of RT	Grade 3: diarrhoea 12%, vomiting 5.9%, radio-dermatitis 2.9%, leukopenia 2.9% Grade 3–4 neutropenia 5.9%	20%
Levine [44]	31	45 Gy/25 fractions for 5 weeks, irinotecan 60 mg/m^2 once per week, during weeks 1, 2, 3 and 4, continuous infusional 5FU at 200 mg/m^2 per day including weekends	Grade 3: diarrhoea 3%	21%
Alonso [45]	39	50.4 Gy/28 fractions, irinotecan 50 mg/m^2 on day 1 every week (weeks 1–6), continuous infusion of 5-FU 200 mg/m^2/day on days 1–5	n.a.	20%
Klautke [46]	37	45 Gy/25 fractions for 5 weeks and boost of 5.4 Gy, irinotecan 40 mg m^{-2}day 1, 8, 15, 22, 29, continuous infusion 5-FU 250 mg/m^2/day days 1–43	Grade 3: diarrhoea 23%, thrombocytopenia 2%, leukopenia 8% Grade 4: diarrhoea 5%, leukopenia 2%, one extrapontine myelinolysis due to severe electrolyte imbalance 2 weeks after completion of therapy	22%
Klautke [47]	23	50.4 Gy, 1.8 Gy fractions with a local boost of 5.4 Gy, irinotecan 40 mg/m^2 day 1, 8, 15, 22, 29, 36, Capecitabine was given daily throughout treatment (d1-43) 1500 mg/m^2/day	Grade 3–4: diarrhoea 10%	18%
Willeke [47]	12	45 Gy/25 fractions for 5 weeks and boost of 5.4 Gy, irinotecan 50 mg/m^2 days 1, 8, 15, 22, 29, capecitabine 500 mg/m^2 twice daily days 1–38	Grade 3: diarrhoea 11%, nausea/vomiting 3%, increased activity of transaminases 3% Grade 4: leukopenia 6%	18%

Table 7
Randomised trials with systemic chemotherapy following post-operative chemoradiation in rectal cancer UICC stage II/III[a]

Trial	Regimen	Local failure (%)	Distant metastasis (%)	5-year OS (%)
Fountzilas [51] (n = 220)	S/5.FU RT	13	25	73
	S/5-FU RT → FU/FA bolus	13	23	77
Queißer [52] (n = 263)	S + 5-FU/FA + RT/5-FU → 4# bolus 5-FU/FA	15	35	76 (years)
	S + 5-FU/FA + RT/5-FU → 10# bolus 5-FU/FA	11	35	70 (years)
Akasu [53] (n = 276)	S	13	78% (3 yrs.)	
	S + UFT/FA	8	91% (3 yrs.) P = 0.005	

[a] S: surgery; 5-FU: 5-fluorouracil; RT: radiotherapy; FA: folinic acid; #: cycles; OS: overall survival

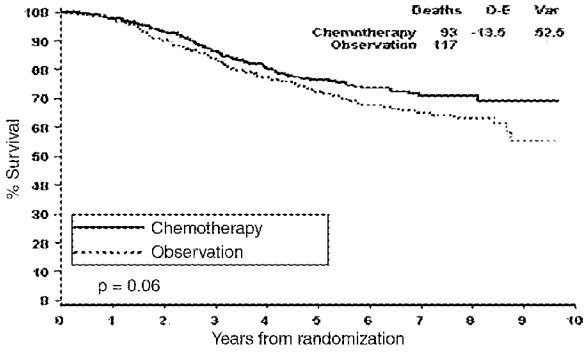

Fig. 3. QUASAR-study: chemotherapy versus observation in patients with stage II (high-risk) rectal cancer [54].

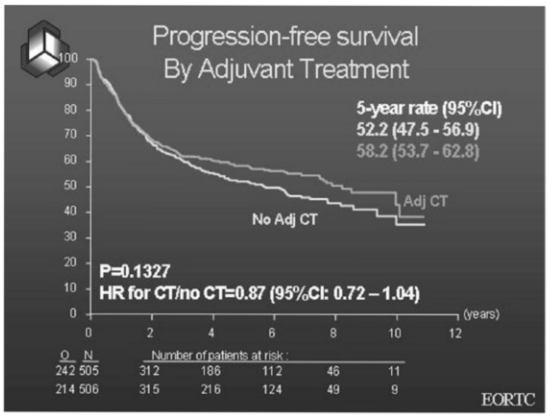

Fig. 4. EORTC trial: 2×2 factorial design: Post-operative observation versus systemic chemotherapy (5-FU/FA). 5-year disease-free survival [19].

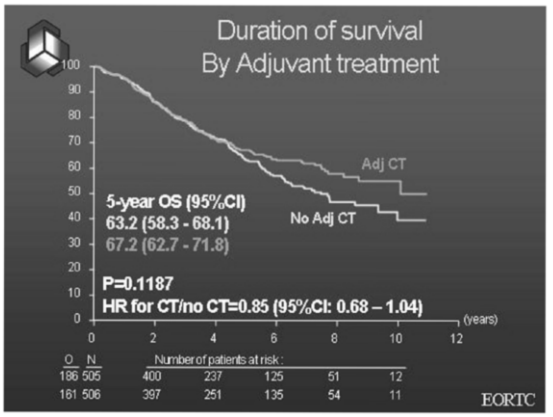

Fig. 5. EORTC trial: 2×2 factorial design: Post-operative observation versus systemic chemotherapy (5-FU/FA). 5-year overall survival [19].

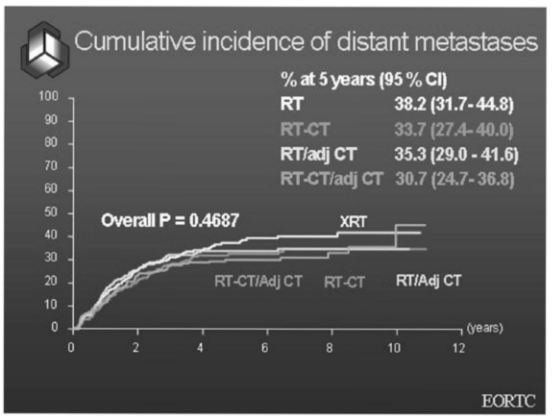

Fig. 6. EORTC trial: 2×2 factorial design: Post-operative observation versus systemic chemotherapy (5-FU/FA). Cumulative incidence of distant metastasis [19].

with (chemo)radiation. In patients treated with 5 × 5 pre-operative radiation, post-operative chemotherapy has not been evaluated so far but is currently investigated in a randomised trial (PROCTOR trial, capecitabine versus observation). Interestingly, a Japanese study (NSAS-CC01) shows that chemotherapy alone after optimal resection may also improve prognosis; after TME and lateral lymph node dissection, a regimen using UFT could improve overall survival when compared to TME alone in stage III patients – without any radiotherapy in any treatment arm [53].

The EORTC trial presented at this year' s ASCO meeting is the only trial that randomised between chemotherapy and observation only after conventional radiotherapy. In the 2 × 2 factorial design, patients received either 4 cycles of bolus 5-FU/FA post-operatively versus observation (with the other randomisation pre-operative chemoradiation versus radiation alone as discussed above). Interestingly, the arms with chemotherapy had a trend to improved 5-year progression-free (52.2% vs. 58.2%; 95% CI: 0.72–1.04; P = 0.1327) and overall survival (63.2% vs. 67.2%, 95% CI: 0.68–1.04, P = 0.1187). As expected, the rate of distant metastasis was mainly reduced by chemotherapy, and the combination arm with pre-operative chemoradiation followed by systemic treatment was the most effective treatment (Figs. 4–6) [19]. Interestingly, post-operative chemotherapy compensated for the lack of pre-operative chemoradiation on local failure (local relapse rate for chemoradiation with no adjuvant chemotherapy 8.7%; for radiation followed by chemotherapy: 9.6%).

Although these data show that 5-FU/FA bolus regimens are beneficial in reducing distant metastasis and may improve overall survival, the benefit is limited. The high distant relapse rates (e.g. 36% in the German trial, as displayed in Table 2) indicate that 5-FU/FA is not active enough. In adjuvant colon cancer therapy for stage III (and II), oral

fluoropyrimidines (e.g. X-ACT trial) [55] and/or the combination of 5-FU with oxaliplatin (MOSAIC trial and NSABP C 07 trial, [56,57]) have replaced the former standard bolus administration of 5-FU/FA after resection by improving both toxicity and/or efficacy. Novel combination regimen allowing more convenient administration (e.g. XELOX, Capecitabine and oxaliplatin [58]) and/or combinations with ' targeted' therapies (e.g. bevacizumab and cetuximab) are under investigation and may be transferred to adjuvant systemic therapy of rectal cancer.

How to further improve treatment of rectal cancer?

The findings that a more intensive pre-operative chemoradiation may lead to a better prognosis lead to a variety of phase II trials currently investigating combination protocols (Fig. 7). So far, only two protocols with pre-operative chemoradiation followed by post-operative chemotherapy have finished accrual (German CAO/ARO/AIO-04, UK CORE trial) with results being awaited soon.

The open questions of intensification of pre-operative chemoradiation and post-operative adjuvant treatment are addressed by the design of the currently discussed multinational PETACC-6 trial (Fig. 8). Primary endpoint is disease-free survival at three years after pre-operative capecitabine/oxaliplatin modulated chemoradiation, followed by TME and another 18 weeks of adjuvant capecitabine/ oxaliplatin or capecitabine modulated radiation, followed by TME and adjuvant systemic therapy with capecitabine. Secondary endpoints are rate of pathological response rates, sphincter preservation, local failure rate and toxicity.

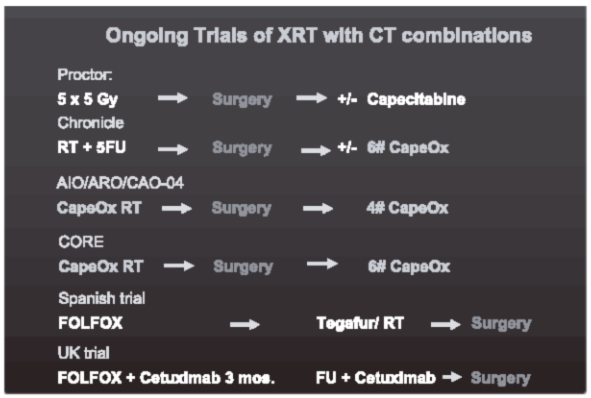

Fig. 7. Ongoing trials of combinations of pre-operative and/or post-operative chemotherapy.

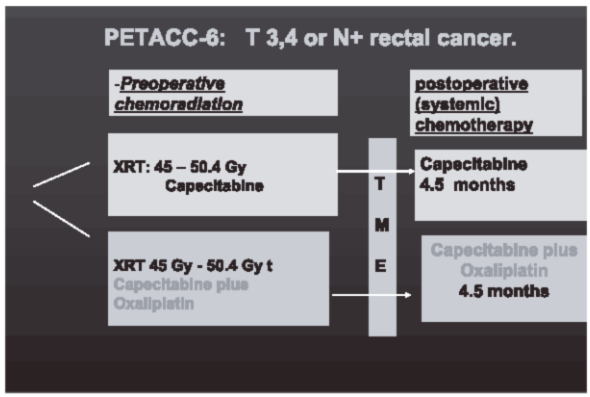

Fig. 8. Design of the PETACC-6 trial.

However, the next generation of clinical trials is about to start now and will integrate the novel ' targeted' drugs like bevacizumab and cetuximab in both pre-operative and post-operative setting. Furthermore, the early onset of highly active systemic combination treatment before chemoradiation and TME is currently investigated in phase II trials. Chemotherapy as first treatment in a multimodal setting may lead to further improvement by preventing early dissemination of micrometastasis and may enable a reduction of radiation fields by pre-radiation tumour shrinkage. This approach indicates that advanced rectal cancer has become a real ' multimodal entity' , requiring all improvement in the fields of surgery, radiation and chemotherapy for the optimal local control and in chemotherapy to reduce onset of distant metastasis and therefore improve overall prognosis.

However, in the face of current and future schedules and the increasing number of therapy options and intensities, translational research is urgently required for the identification of patient groups, by both clinical-pathological features and molecular and genetic markers, that will gain maximum benefit from each treatment option. In this time of changing therapeutic standards, it clearly appears that a common standard for large heterogeneous patient groups will prospectively be substituted by more individualised therapies in the future.

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