Strahlenther Onkol 2012 · 188:377–382
DOI 10.1007/s00066-012-0073-8
Received: 14 July 2011
Accepted: 11 January 2012
Published online: 10 March 2012

J. Winkler[1] · L. Zipp[1] · J. Knoblich[2] · F. Zimmermann[1]
[1] Department of Radiation Oncology, University Hospital Basel, Basel
[2] Outpatient Oncology Centre, Lörrach

Simultaneous neoadjuvant radiochemotherapy with capecitabine and oxaliplatin for locally advanced rectal cancer

Treatment outcome outside clinical trials

Neoadjuvant chemoradiotherapy is a standard treatment for locally advanced rectal carcinoma (LARC), especially of the lower two thirds of the organ. This treatment approach offers the best locoregional control and a chance for sphincter preservation in tumours located less that 6 cm from the anal verge [5, 6, 7, 15, 38]. Numerous chemotherapeutic schemes have been tested over the last decade for simultaneous administration with external beam radiotherapy (EBRT), aiming to improve the rates of locoregional control, sphincter-sparing surgery and diminish distant failure [30, 33, 37]. However, it could not be clarified yet which chemotherapy regimen should be applied in order to achieve the maximal therapeutic benefit for the patient, i.e: an excellent tumour control while providing an acceptable quality of life during and after the treatment [44].

Five-fluorouracil (5-FU) based chemotherapy concurrent to EBRT is the current standard neoadjuvant scheme, which was introduced over two decades ago into the treatment of LARC [6] in order to improve local control after radical surgery. An oral pro-drug of 5-FU, capecitabine, has been lately developed and might be more selectively converted into active 5-FU, especially in irradiated tumour tissue [39]. This drug has demonstrated favourable results in comparison to intravenous 5-FU with regard to tumouricidal effects and toxicity profile, while being convenient for administration in an outpatient setting. In the clinical trials (CTR), all known side effects of 5-FU have been also present by administration of capecitabine, however, with less diarrhoea, nausea and high-grade oral mucositis and neutropenia, but with an increased rate of hyperbilirubinemia and hand–foot syndrome [24, 43]. A final report of the first randomized comparison of capecitabine versus 5-FU in combination with irradiation is yet awaited [46].

In the treatment of metastatic colorectal cancer newer generation of chemotherapeutics including oxaliplatin have been assessed and demonstrated superior tumour response rates than single agent 5-FU regimens or its combination with either folinic acid or leucovorin [8, 11]. Considering the radiosensitizing effects of capecitabine and oxaliplatin in vitro [10, 45], simultaneous application of both substances with EBRT was consequently examined in phase I and II trials in the treatment of LACR [9, 17, 20, 21, 26, 29, 35, 36]. Several of those trials have demonstrated a promising efficacy and limited toxicity profile, leading to the quick adoption of this new regimen in the treatment of LARC outside CTR. However, as it was recently discussed by Bekelman et al. [4], the trials may have limited generalizability beyond the setting and subpopulation in which the study is conducted. Thus, we analyzed retrospectively the efficacy and toxicity of this chemoradiotherapy regimen in patients treated outside CTR.

Patients and methods

All consecutive patients with histologically confirmed adenocarcinoma of the rectum of stage II or III according to UICC-TNM classification, treated in neoadjuvant intention from January 2005 to December 2008 with capecitabine, oxaliplatin and EBRT in the University Hospital Basel were evaluated. Pretreatment assessment included a complete history, physical examination, blood count, renal and liver function tests, rigid rectoscopy, biopsy, colonoscopy, endorectal ultrasonography, computed tomography (CT) of the thorax or a chest x-ray, CT of abdomen and pelvis, and, in some patients, pelvic magnetic resonance imaging.

Treatment

Chemotherapy

Treatment was started upon completion of the diagnostic procedures. If the start of EBRT had more than 14 days delay, chemotherapy was started prior to irradiation according to the XELOX scheme: capecitabine 1,000 mg/m^2 twice daily (b.i.d.) on days 1–14 and oxaliplatin 130 mg/m^2 on day 1, repeated once again on day 22 if still no irradiation followed. As soon as EBRT was started, chemotherapy was applied according to the CAPOX schedule (capecitabine 825 mg/m^2 b.i.d. on irradiation days 1–14 and 22–35, oxali-

Tab. 1 Posttreatment surveillance

	Months after completion of the treatment									
	3	6	12	18	24	30	36	42	48	60
History and physical examination, CEA	+	+	+	+	+	+	+	+	+	+
Rectoscopy, sigmoidoscopy		+	+	+	+					
Colonoscopy			+				+			
Chest, abdominal and pelvic computed tomography (CT) scan[a]			+		+		+		+	+

CEA carcinoembryonic antigen [a] Annual CT scan could be replaced by a regular abdominal ultrasound, if the baseline CT scan was without abnormalities and there were no other findings during the follow-up suggestive for a recurrence.

Tab. 3 Stage migration after the neoadjuvant radiochemotherapy

CS	II	II	III	III	III	III	III
cTNM	T3N0M0	T4N0M0	T2N1M0	T3N1M0	T4N1M0	T3N2M0	T4N2M0
ypTNM	(n)	(n)	(n)	(n)	(n)	(n)	(n)
T0N0M0	2[a]	1[a]	1[a]	1[a]			
T1N0M0	1[a]			1[a]			
T2N0M0	3[a]	1[a]		2[a]	1[a]		
T3N0M0	3[b]		1[a]	2[a]	1[a]	1[a]	1[a]
T4N0M0	1[b]						
T0N1M0				1[b]			
T3N1M0	1[c]			3[b]		2[a]	
T4N1M0					1[b]		
T3N2M1				1[c]			

CS initial clinical stage according to UICC-TNM classification; cTNM initial tumour stage according to UICC-TNM classification; ypTNM UICC-TNM stage of the pathological specimen. [a]Regression of initial clinical stage, [b]initial clinical stage remained unchanged, [c]pathological stage is more advanced than clinical stage.

Tab. 2 Baseline characteristics of the 34 patients

Baseline characteristics	Patients (n, %)
Age (years)	
< 50	4 (12)
50–70	17 (50)
> 70	13 (38)
Sex	
Male	25 (74)
Female	9 (26)
Tumour location	
Upper third	3 (9)
Middle third	16 (47)
Lower third	15 (44)
TNM stage	
T2	2 (6)
T3	25 (74)
T4	7 (20)
N0	13 (38)
N1–2	21 (62)
Histological grading	
Well differentiated	1 (4)
Moderately differentiated	29 (86)
Poorly differentiated	4 (12)

Tab. 4 Tumour regression grade after radiochemotherapy according to Dworak

Grade	Tumour regression	Patients (n)	Proportion (%)
0	No regression	1	3
1	Minimal regression	9	27.3
2	Moderate regression	12	36.4
3	Good regression	6	18.2
4	Complete regression	5	15.1

platin 50 mg/m^2 on irradiation days 1, 8, 22 and 29).

Radiotherapy

Megavoltage equipment was used with 6/10/18 MV. Patients were immobilized in the prone position using a belly board. All patients received individual three-dimensional CT-based treatment planning. Radiotherapy was delivered through three to four portal fields to the tumour, corresponding lymphatic region and perirectal soft tissue structures at risk of microscopic disease. All patients received 45–50.5 Gy total dose, given in daily fractions of 1.8 Gy, 5 times a week.

Surgery

Four to six weeks after completion of the chemoradiotherapy, radical surgery encompassing total mesorectal excision (TME) was performed according to a standardised technique as the preferred type of radical resection, with sphincter preservation whenever feasible.

Adjuvant chemotherapy

Adjuvant chemotherapy was recommended for all patients according to the NCCN (National Comprehensive Cancer Network) guidelines. The choice of the chemotherapy regimen was at the discretion of the medical oncologist. Generally, in case of complete or near complete tumour regression, further 4–6 courses of XELOX regimen were recommended.

Evaluation of efficacy and safety

Efficacy

The extent of residual tumour in the surgical specimen was classified according to the UICC-TNM staging system and then compared to the tumour stage determined after the pretreatment evaluation. The histological regression assessment was performed using the grading criteria established by Dworak et al. [14]. In addition, the rates of sphincter preservative surgery, R0 resection (circumferential margins ≥ 2 mm) and the rates of locoregional and distant relapses were estimated as well.

Safety

All reported acute treatment-related toxicities were registered and graded according to Common Toxicity Criteria from National Cancer Institute, Version 2.0 [41]. The follow-up was conducted by a medical oncologist as demonstrat-

ed in ◘ **Tab. 1**, referring to the established NCCN and German Cancer Society guidelines [40].

Results

In the 4-year period from 2005–2008, 34 patients with LARC were treated with neoadjuvant radiotherapy simultaneous with capecitabine and oxaliplatin at the Radiation Oncology Institute, University Hospital Basel. Chemotherapy was administered by the medical oncologists from two institutions. Surgery was performed at four different centres with expertise in rectal cancer, according to the patient's preferences and place of residence. Retrospective data were collected and analyzed. Complete follow-up data up to November 2009 was available for 31 patients: 2 patients had changed their place of residency and 1 refused the follow-up. The mean follow-up for all patients analyzed and for the patients alive was 22 months (range 0–53 months) and 24 months (range 3–53 months) respectively.

Tumour control

The main patients' characteristics are summarized in the ◘ **Tab. 2**. None of the patients relapsed locally. Five (15%) patients relapsed with distant metastases only. One 28-year-old patient diagnosed with a rectal tumour of signet ring adenocarcinoma had progressive disease: peritoneal carcinomatosis was revealed during the scheduled abdominoperineal resection (APR). Retrospective assessment suggests that the tumour stage was initially underestimated. The patient died shortly afterwards due to progressive disease. At the time of last follow-up 88% of the patients (n = 30) were alive, and 82% (n = 28) of all patients analyzed have so far faced no failure. Stage regression according to UICC-TNM classification (◘ **Tab. 3**) and pathological regression of grade 3 and 4 according to Dworak were observed in 18.2% (n = 6) and 15.1% (n = 5) respectively (◘ **Tab. 4**).

Sphincter-preserving surgery was performed in 75% (n = 25) of all patients who underwent surgery and in 53% (n = 8) of 15 patients with tumour in the lower rec-

Strahlenther Onkol 2012 · 188:377–382 DOI 10.1007/s00066-012-0073-8

J. Winkler · L. Zipp · J. Knoblich · F. Zimmermann

Simultaneous neoadjuvant radiochemotherapy with capecitabine and oxaliplatin for locally advanced rectal cancer. Treatment outcome outside clinical trials

Abstract

Background. Phase II trials of neoadjuvant treatment in UICC-TNM stage II and III rectal cancer with capecitabine and oxaliplatin demonstrated favourable rates on tumour regression with acceptable toxicity.

Patients and methods. Retrospective evaluation of 34 patients treated from 2005–2008 outside clinical trials (CTR) with neoadjuvant irradiation (45–50.4 Gy) and simultaneous capecitabine 825 mg/m^2 b.i.d. on days 1–14 and 22–35 and oxaliplatin 50 mg/m^2 on days 1, 8, 22 and 29 (CAPOX). Twenty-six (77%) patients received one or two courses of capecitabine 1,000 mg/m^2 b.i.d. on days 1–14 and oxaliplatin 130 mg/m^2 on day 1 (XELOX) prior to simultaneous chemoradiotherapy.

Results. UICC-TNM stage regression was observed in 60% (n = 20). Dworak's regression grades 3 and 4 were achieved in 18.2% (n = 6) and 15.1% (n = 5) of the patients. Sphincter-preserving surgery was performed in 53% (n = 8) of patients with a tumour of the lower rectum. Within the mean observation of 24 months, none of the patients relapsed locally, 1 patient had progressive disease and 5 patients (15%) relapsed distantly. Toxicity of grade 3 and 4 was mainly diarrhoea 18% (n = 6) and perianal pain 9% (n = 3). Nevertheless, severe cardiac events (n = 2), severe electrolyte disturbances (n = 2), and syncopes (n = 2) were observed as well.

Conclusion. Treatment efficacy and common toxicity are similar to the reports of phase I/II trials. However, several severe adverse events were observed in our cohort study. The predisposing factors for these events have yet to be studied and may have implications for the selection of patients outside CTR.

Keywords

Rectal cancer · Oxaliplatin · Capecitabine · Toxicity

Simultane neoadjuvante Radiochemotherapie mit Capecitabin und Oxaliplatin beim lokal fortgeschrittenen Rektumkarzinom. Therapieergebnisse außerhalb klinischer Studien

Zusammenfassung

Hintergrund. Phase-II-Studien zur neoadjuvanten Therapie des Rektumkarzinoms (UICC-TNM-Stadium II und III) mit Capecitabin und Oxaliplatin zeigten eine günstige Tumorregressionsrate bei akzeptabler Toxizität.

Patienten und Methoden. Retrospektive Auswertung der Daten von 34 Patienten (Nachsorge ◘ **Tab. 1**, Patientencharakteristika ◘ **Tab. 2**), die in den Jahren 2005–2008 außerhalb klinischer Studien eine neoadjuvante Strahlentherapie (45–50,4 Gy) simultan mit Capecitabin 825 mg/m^2 2-mal täglich an den Tagen 1–14 und 22–35 und Oxaliplatin 50 mg/m^2 an den Tagen 1, 8, 22 und 29 (CAPOX) erhielten. 26 (77%) Patienten bekamen 1–2 Zyklen Capecitabin 1000 mg/m^2 2-mal täglich an den Tagen 1–14 und Oxaliplatin 130 mg/m^2 am Tag 1 (XELOX) vor der simultanen Chemoradiotherapie.

Ergebnisse. Eine Regression des UICC-TNM-Stadiums wurde bei 60% (n = 20) beobachtet (◘ **Tab. 3**). Regressionsgrade 3 und 4 nach Dworak wurden in 18,2% (n = 6) und 15,1% (n = 5) der Patienten erreicht (◘ **Tab. 4**). Eine sphinktererhaltende Operation wurde in 53% (n = 8) der Patienten mit einem distalen Tumor realisiert. Innerhalb der Beobachtungszeit von 24 Monaten erlitt keiner der Patienten einen lokalen Rückfall. Eine Patientin zeigte eine kontinuierliche Tumorprogression und 5 Patienten (15%) entwickelten Fernmetastasen im Verlauf. Toxizität (◘ **Tab. 5**) vom Grad (G) 3/4 manifestierte sich überwiegend als Diarrhoe 18% (n = 6) und perianaler Schmerz 9% (n = 3). Es traten jedoch 2 schwerwiegende kardiale Ereignisse, 2 Fälle von schwerer Elektrolytentgleisung und 2 Synkopen auf.

Schlussfolgerung. Die Effektivität und die allgemeine Toxizität in unserem Patientengut sind den Ergebnissen aus den Phase-I/II-Studien ähnlich. Es traten jedoch einzelne schwerwiegende Nebenwirkungen in unserer Kohorte auf. Die hierzu beitragenden Faktoren bedürfen einer weiteren Beobachtung und können Konsequenzen für die künftige Patientenselektion haben.

Schlüsselwörter

Rektumkarzinom · Oxaliplatin · Capecitabin · Toxizität

Tab. 5 Acute toxicity

NCI CTC Grade			
Toxicity	**Grade 1–2 (n, %)**	**Grade 3 (n, %)**	**Grade 4 (n, %)**
Hematologic			
Leucopenia	7 (21)	0	0
Thrombocytopenia	9 (27)	1 (3)	0
Anaemia	6 (18)	0	0
Neurologic			
Paresthesia/dysesthesia	11 (32)	0	0
Skin			
Local toxicity, perianal	10 (39)	2 (6)	0
Hand–foot syndrome	3 (9)	0	0
Allergy (skin rash/exanthema)	1 (3)	0	0
Genitourinary			
Dysuria/pollakisuria	20 (59)	0	0
Renal insufficiency	0	1 (3)	0
Vaginal mycosis	1 (3)	0	0
Gastrointestinal			
Diarrhoea	24 (71)	6 (18)	0
Obstipation	3 (9)	0	0
Nausea	3 (9)	0	0
Anorexia	6 (18)	0	0
Body weight reduction	2 (6)	0	0
Proctitis	7 (21)	0	0
Cholangitis	1 (3)	0	0
Other			
Pain	3 (9)	3 (9)	0
Deep venous thrombosis	0	1 (3)	0
Syncope	0	2 (6)	0
Fatigue	8 (24)	1(3)	0
Infection	3 (9)	0	1(3)
Cardiovascular	0	0	2[a] (6)
Electrolyte dysbalance			
Hypokalemia	2 (6)	0	1(3)
Hyponatremia	1 (3)	1(3)	0

[a]One non-lethal myocardial infarction, one acute cardiac insufficiency with sudden death.

tum. Complete tumour resection was achieved in 31 of 33 patients undergoing surgery (94%).

Toxicity

Treatment-related toxicity in the neoadjuvant setting was predominantly mild (**Tab. 5**). Toxicity of grade 0–2 was mainly diarrhoea 71% (n = 24), dysuria 59% (n = 20), paraesthesia 32% (n = 11), haematological abnormalities 38% (n = 13) and local skin reactions 29% (n = 10). Severe diarrhoea, skin and haematological toxicities were rare. However, there were few but severe treatment-related complications.

Two patients, who had had a previous myocardial infarction, experienced a second myocardial infarction immediately after the first course of chemotherapy before starting combined RCT. One of them died due to this event. The other continued treatment with modified chemotherapy. There were two cases with severe electrolyte imbalances, two syncopes and one case of deep venous thrombosis of lower extremities. One patient had developed a generalized skin rash, which regressed after capecitabine was withdrawn. Another patient with severe diarrhoea refused earlier hospitalisation as well as offered medication. He passed through severe dehydration, electrolyte disturbance, acute renal insufficiency and urosepsis.

Treatment modification (either of chemotherapy or of radiotherapy or both) was necessary in order to prevent or reduce severe toxicity in 32% of the cases (n = 11), with dose reduction of the chemotherapy agents by more than 25% of the originally planned dose in 18% (n = 6) of the patients. Due to treatment-related toxicity 3 patients had an interruption in radiotherapy of 1–3 days, and in another 3 cases radiotherapy was discontinued earlier than intended.

Discussion

The results of our retrospective evaluation of patients treated preoperatively with irradiation in combination with capecitabine and oxaliplatin for LARC outside CTR demonstrate similar results as the reported phase I and II trials in terms of down-staging and down-sizing, pathological regression, sphincter preservation rate, rates of complete resection, local and distant control [9, 17, 21, 26, 29, 35, 36]. However, these parameters of treatment efficacy did not differ markedly from those reported in the trials for simultaneous irradiation with administration of either capecitabine solely or 5-FU with leucovorin [12, 13, 22, 23, 25]. Hence according to our data and to the published phase I and II trials a definitive conclusion favouring one of these treatment approaches could not be made so far. Moreover, one lethal treatment-related and several life-threatening toxicities occurred in our patient cohort, similar to the trial from Chua et al. [9], who initially did not systematically exclude patients with a previous history of cardiovascular disease. The latter study counts even higher rates of fatal and life-threatening events: 9 thromboembolic and cardiac events, 4 of them lethal. Comparable to our observation, cardiac events occurred during administration of XELOX regimen, before the start of simultaneous CAPOX regimen and irradiation. In several other phase I and II trials using capecitabine and oxaliplatin with thoroughly selected patient populations, cardiovascular events occurred as well [17, 21, 26, 29, 34, 35, 36].

The reported incidence of 5-FU-induced cardiac events ranges from 1.2–

18% [27, 28]. In the study of Van Cutsem et al. [42], capecitabine monotherapy was compared with 5-FU and leucovorin (Mayo Clinic regimen), yielding similar rates of cardiac events (3% for each arm). The mechanism of cardiac toxicity either with 5-FU infusion or with capecitabine was closely investigated. It is believed to be primarily based on coronary vasospasm [1, 18]. Whether the addition of oxaliplatin to capecitabine increases the risk for cardiovascular toxicity remains to be elucidated. In a retrospective evaluation Ng et al. [31] concluded that cardiotoxicity of the combination with oxaliplatin exceeds the toxicity of capecitabine monotherapy. In our study, severe cardiac events occurred in 2 of 34 patients (6%) during administration of the XELOX scheme, prior to irradiation. This may be related either to the higher doses of capecitabine and oxaliplatin administered in the XELOX scheme compared to the CAPOX scheme, or to the timing of the first exposition to these substances.

Other rare, severe side effects were two episodes of syncope during the simultaneous chemoradiotherapy, in one case due to severe electrolyte imbalance. The electrolyte imbalances are known to be associated with administration of capecitabine or 5-FU with and without oxaliplatin-based chemotherapy, but may be induced primarily by oxaliplatin [3].

The side effects noticed in our study raise caution for the wide application of this treatment scheme without a careful selection of patients, particularly among elderly patients [16]. Currently available data remains controversial and do not yet provide a clear conclusion whether treatment efficacy outweighs the risk of higher toxicity. The previously reported superiority of neoadjuvant chemoradiaotherapy for LARC with capecitabine and oxaliplatin compared to the results of trials with either 5 FU or capecitabine monotherapy was not observed in the latest phase II trial by Öfner et al. [32]. Moreover, the phase III STAR-01 (Studio Terapia Adiuvante Retto) trial reported increased treatment-related toxicity following the addition of oxaliplatin to 5-FU without affecting primary tumour response [2]. On the other hand, in a phase III trial by Gérard et al. [19], a trend to higher rates of complete tumour regression was seen in the combination of oxaliplatin with capecitabine in comparison to capecitabine alone. The rates of complete and near complete tumour regression in the capecitabine and oxaliplatin arm were similar to those in our present study. However, again in line with our findings, increased high grade toxicity was noted by Gérard et al. [19] in the combined oxaliplatin arm. Thus, the yet awaited results of the large randomized phase III 4-arm NSABP (National Surgical Adjuvant Breast and Bowel Project) R-04 trial aiming to compare simultaneous radiation for resectable rectal cancer either with capecitabine or 5-FU with or without oxaliplatin may provide further help for the evaluation of chemoradiotherapy treatment options for LARC [46].

Thus, outside clinical trials in a non-restricted patient population, the combination of capecitabine and oxaliplatin demonstrates favourable results in terms of complete response, tumour down-staging and down-sizing in order to facilitate a sphincter- and/or organ-preserving surgery without compromising local tumour control. However, the rate of distant metastases still remains high.

Conclusion

Considering several severe complications observed in our analysis and in the previous phase I/II studies while missing clear tumour-related superiority in the latest randomized phase III trial, caution should be taken when administering XELOX or CAPOX outside clinical trials for LARC. In particular, cardiac morbidity should be thoroughly assessed before envisaging a combined capecitabine and oxaliplatin treatment.

Corresponding address

Prof. Dr. F. Zimmermann
Department of Radiation Oncology,
University Hospital Basel
Petersgraben 4, 4031 Basel
Switzerland
zimmermannf@uhbs.ch

Conflict of interest. The corresponding author states that there are no conflicts of interest.

References

1. Ang C, Kornbluth M, Thirlwell MP et al (2010) Capecitabine-induced cardiotoxicity: case report and review of the literature. Curr Oncol 17:59–63
2. Aschele C, Cionini L, Lonardi S et al (2011) Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. J Clin Oncol 29:2773–2780
3. Basso M, Cassano A, Modoni A et al (2008) A reversible coma after oxaliplatin administration suggests a pathogenetic role of electrolyte imbalance. Eur J Clin Pharmacol 64:739–741
4. Bekelman JE, Shah A, Hahn SM (2011) Implications of comparative effectiveness research for radiation oncology. Pract Radiat Oncol 1:72–80
5. Bonnen M, Crane C, Vauthey JN et al (2004) Long-term results using local excision after preoperative chemoradiation among selected T3 rectal cancer patients. Int J Radiat Oncol Biol Phys 60:1098–1105
6. Boulis-Wassif S, Gerard A, Loygue J et al (1984) Final results of a randomized trial on the treatment of rectal cancer with preoperative radiotherapy alone or in combination with 5-fluorouracil, followed by radical surgery. Trial of the European Organization on Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. Cancer 53:1811–1818
7. Braendengen M, Tveit KM, Berglund A et al (2008) Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in non-resectable rectal cancer. J Clin Oncol 26:3687–3694
8. Cassidy J, Clarke S, Diaz-Rubio E et al (2008) Randomized phase III study of capecitabine plus oxaliplatin compared with fluorouracil/folinic acid plus oxaliplatin as first-line therapy for metastatic colorectal cancer. J Clin Oncol 26:2006–2012
9. Chua YJ, Barbachano Y, Cunningham D et al (2010) Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. Lancet Oncol 11:241–248
10. Cividalli A, Ceciarelli F, Livdi E et al (2002) Radiosensitization by oxaliplatin in a mouse adenocarcinoma: influence of treatment schedule. Int J Radiat Oncol Biol Phys 52:1092–1098
11. Gramont A de, Figer A, Seymour M et al (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938–2947
12. De Paoli A, Chiara S, Luppi G et al (2006) Capecitabine in combination with preoperative radiation therapy in locally advanced, resectable, rectal cancer: a multicentric phase II study. Ann Oncol 17:246–251
13. Dunst J, Debus J, Rudat V et al (2008) Neoadjuvant capecitabine combined with standard radiotherapy in patients with locally advanced rectal cancer: mature results of a phase II trial. Strahlenther Onkol 184:450–456
14. Dworak O, Keilholz L, Hoffmann A (1997) Pathological features of rectal cancer after preoperative radiochemotherapy. Int J Colorectal Dis 12:19–23
15. Eich HT, Stepien A, Zimmermann C et al (2011) Neoadjuvant radiochemotherapy and surgery for advanced rectal cancer: prognostic significance of tumor regression. Strahlenther Onkol 187:225–230
16. Fels F, Kraft JW, Grabenbauer GG (2010) Geriatrics and radiation oncology. Part 1: How to identify high-risk patients and basic treatment principles. Strahlenther Onkol 186:411–422

17. Fernandez-Martos C, Pericay C, Aparicio J et al (2010) Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo cancer de recto 3 study. J Clin Oncol 28:859–865
18. Freeman NJ, Costanza ME (1988) 5-Fluorouracil-associated cardiotoxicity. Cancer 61:36–45
19. Gerard JP, Azria D, Gourgou-Bourgade S et al (2010) Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. J Clin Oncol 28:1638–1644
20. Gerard JP, Chapet O, Nemoz C et al (2003) Preoperative concurrent chemoradiotherapy in locally advanced rectal cancer with high-dose radiation and oxaliplatin-containing regimen: the Lyon R0–04 phase II trial. J Clin Oncol 21:1119–1124
21. Glynne-Jones R, Sebag-Montefiore D, Maughan TS et al (2006) A phase I dose escalation study of continuous oral capecitabine in combination with oxaliplatin and pelvic radiation (XELOX-RT) in patients with locally advanced rectal cancer. Ann Oncol 17:50–56
22. Guillem JG, Diaz-Gonzalez JA, Minsky BD et al (2008) cT3N0 rectal cancer: potential overtreatment with preoperative chemoradiotherapy is warranted. J Clin Oncol 26:368–373
23. Habr-Gama A, Perez RO, Sabbaga J et al (2009) Increasing the rates of complete response to neoadjuvant chemoradiotherapy for distal rectal cancer: results of a prospective study using additional chemotherapy during the resting period. Dis Colon Rectum 52:1927–1934
24. Hoff PM, Ansari R, Batist G et al (2001) Comparison of oral capecitabine versus intravenous fluorouracil plus leucovorin as first-line treatment in 605 patients with metastatic colorectal cancer: results of a randomized phase III study. J Clin Oncol 19:2282–2292
25. Kim DY, Jung KH, Kim TH et al (2007) Comparison of 5-fluorouracil/leucovorin and capecitabine in preoperative chemoradiotherapy for locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 67:378–384
26. Koeberle D, Burkhard R, Moos R von et al (2008) Phase II study of capecitabine and oxaliplatin given prior to and concurrently with preoperative pelvic radiotherapy in patients with locally advanced rectal cancer. Br J Cancer 98:1204–1209
27. Kosmas C, Kallistratos MS, Kopterides P et al (2008) Cardiotoxicity of fluoropyrimidines in different schedules of administration: a prospective study. J Cancer Res Clin Oncol 134:75–82
28. Kuchenmeister U, Kirchner R, Mellert J et al (2000) First results of neoadjuvant simultaneious radiochemotherapy in advanced rectal carcinoma. Strahlenther Onkol 176:560–566
29. Machiels JP, Duck L, Honhon B et al (2005) Phase II study of preoperative oxaliplatin, capecitabine and external beam radiotherapy in patients with rectal cancer: the RadiOxCape study. Ann Oncol 16:1898–1905
30. Marquardt F, Rodel F, Capalbo G et al (2009) Molecular targeted treatment and radiation therapy for rectal cancer. Strahlenther Onkol 185:371–378
31. Ng M, Cunningham D, Norman AR (2005) The frequency and pattern of cardiotoxicity observed with capecitabine used in conjunction with oxaliplatin in patients treated for advanced colorectal cancer (CRC). Eur J Cancer 41:1542–1546
32. Ofner D, Devries AF, Schaberl-Moser R et al (2011) Preoperative oxaliplatin, capecitabine, and external beam radiotherapy in patients with newly diagnosed, primary pperable, *c*T(3)NxM0, low rectal cancer: a Phase II study. Strahlenther Onkol 187(2):100–107
33. Rodel C, Arnold D, Becker H et al (2010) Induction chemotherapy before chemoradiotherapy and surgery for locally advanced rectal cancer: is it time for a randomized phase III trial? Strahlenther Onkol 186:658–664
34. Rodel C, Fietkau R, Keilholz L et al (1997) The acute toxicity of the simultaneous radiochemotherapy of rectal carcinoma. Strahlenther Onkol 173:415–421
35. Rodel C, Grabenbauer GG, Papadopoulos T et al (2003) Phase I/II trial of capecitabine, oxaliplatin, and radiation for rectal cancer. J Clin Oncol 21:3098–3104
36. Rodel C, Liersch T, Hermann RM et al (2007) Multicenter phase II trial of chemoradiation with oxaliplatin for rectal cancer. J Clin Oncol 25:110–117
37. Rodel C, Sauer R (2007) Integration of novel agents into combined-modality treatment for rectal cancer patients. Strahlenther Onkol 183:227–235
38. Sauer R, Becker H, Hohenberger W et al (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351:1731–1740
39. Sawada N, Ishikawa T, Sekiguchi F et al (1999) X-ray irradiation induces thymidine phosphorylase and enhances the efficacy of capecitabine (Xeloda) in human cancer xenografts. Clin Cancer Res 5:2948–2953
40. Schmiegel W, Pox C, Reinacher-Schick A et al (2010) S3 guidelines for colorectal carcinoma: results of an evidence-based consensus conference on February 6/7, 2004 and June 8/9, 2007 (for the topics IV, VI and VII). Z Gastroenterol 48:65–136
41. Trotti A, Byhardt R, Stetz J et al (2000) Common toxicity criteria: version 2.0. An improved reference for grading the acute effects of cancer treatment: impact on radiotherapy. Int J Radiat Oncol Biol Phys 47:13–47
42. Van Cutsem E, Hoff PM, Blum JL et al (2002) Incidence of cardiotoxicity with the oral fluoropyrimidine capecitabine is typical of that reported with 5-fluorouracil. Ann Oncol 13:484–485
43. Van Cutsem E, Twelves C, Cassidy J et al (2001) Oral capecitabine compared with intravenous fluorouracil plus leucovorin in patients with metastatic colorectal cancer: results of a large phase III study. J Clin Oncol 19:4097–4106
44. Wolff HA, Gaedcke J, Jung K et al (2010) High-grade acute organ toxicity during preoperative radiochemotherapy as positive predictor for complete histopathologic tumor regression in multimodal treatment of locally advanced rectal cancer. Strahlenther Onkol 186:30–35
45. Wolff HA, Hennies S, Herrmann MK et al (2011) Comparison of the micronucleus and chromosome aberration techniques for the documentation of cytogenetic damage in radiochemotherapy-treated patients with rectal cancer. Strahlenther Onkol 187:52–58
46. http://www.clinicaltrials.gov, accessed 23 February 2012