Neoadjuvant Capecitabine Combined with Standard Radiotherapy in Patients with Locally Advanced Rectal Cancer

Mature Results of a Phase II Trial*

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Purpose: The objective of this expanded phase II trial was to confirm the safety results of the preceding phase I study and establish the efficacy of neoadjuvant radiochemotherapy with capecitabine in rectal cancer in a multicenter setting.
Patients and Methods: 96 patients (63% male, age 34–81 years) with advanced rectal cancer (cT3–4 or cN+) from seven university centers in Germany were recruited. All were to receive a total irradiation dose of 50.4–55.8 Gy with conventional fractions. Capecitabine was given at an oral dosage of 825 mg/m^2 bid on each day of the radiotherapy period with the first daily dose applied 2 h before irradiation, followed by surgery 6 weeks later.
Results: Most of the patients suffered from an advanced primary tumor (cT3: 57%, cT4: 40%) with lymph node involvement in 60%. After neoadjuvant treatment, with a mean of 99% of the scheduled radiation dose actually delivered, a clinical response rate of 68% (95% confidence interval: 57–78%) was observed. Out of 87 evaluable patients undergoing surgery, a sphincter-preserving procedure could be performed in 51% and R0 resection in 94%. A pathologically complete response was achieved in six patients (7%, 95% confidence interval: 3–14%). The comparison of initial diagnosis and pathologic findings showed a downstaging in 61%. Acute toxicity with > 5% incidence of NCI (National Cancer Institute) grade $\geq$ 3 included lymphopenia (12%), leukopenia (6%), and diarrhea (7%). Mild to moderate hand-foot syndrome occurred in 12% only. After a median follow-up of 48 months, the 5-year overall survival and tumor control data were, with regard to patient selection, in the expected range with an overall survival of 65%, a relapse-free survival of 47%, and a local recurrence rate after 5 years of 17%.
Conclusion: The data clearly confirm that capecitabine is an adequate substitute for 5-fluorouracil in preoperative chemoradiation of rectal cancer with a favorable safety profile.

Key Words: Capecitabine · Rectal cancer · Radiotherapy · Neoadjuvant therapy · Phase II study

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Präoperative Radiochemotherapie mit Capecitabin beim lokal fortgeschrittenen Rektumkarzinom: Langzeitergebnisse einer Phase-II-Studie

Ziel: Diese multizentrische Phase-II-Studie sollte Effektivität und Toxizität einer neoadjuvanten Radiochemotherapie mit Capecitabine prüfen.
Patienten und Methodik: 96 Patienten (davon 63% männlich, Alter 34–81 Jahre) mit lokal fortgeschrittenem Rektumkarzinom (cT3–4 oder cN+) aus sieben deutschen Universitätskliniken wurden rekrutiert. Alle erhielten eine präoperative Radiotherapie (50,4–55,8 Gy in konventioneller Fraktionierung mit 5 × 1,8 Gy) und zusätzlich 2 × täglich 825 mg/m^2 Capecitabin während der

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gesamten Radiotherapie (erste Dosis 2 h vor Radiotherapie, keine Pause am Wochenende). 6 Wochen nach der Radiochemotherapie war die Resektion geplant.

Ergebnisse: 97% der Patienten hatten T3/T4-Tumoren (T3: 57%; T4: 40%). Lymphknotenbefall (cN+) lag in 60% vor. Die präoperative Therapie war gut durchführbar (mittlere Strahlendosis 99%, mittlere Capecitabindosis 96% der geplanten Dosis). Die klinische Ansprechrate betrug 68% (95%-Konfidenzintervall: 57–78%) und entsprach der Studienhypothese. Von 87 auswertbaren operierten Patienten wurden 94% R0-reseziert; ein Sphinktererhalt war in 51% möglich. Sechs Patienten (7%, 95%-Konfidenzintervall: 3–14%) hatten eine histologisch komplette Remission (ypT0) im Resektat. Ein Downstaging wurde in 61% erreicht. Akute Nebenwirkungen CTC-Grad $\geq$ 3 (Common Toxicity Criteria) mit einer Frequenz von > 5% wurden für Lymphopenie (12%), Diarrhö (7%) und Leukopenie (6%) beobachtet. Ein Hand-Fuß-Syndrom trat in 12% auf und war jeweils nur mild (Grad 1–2). Die 5-Jahres-Überlebensrate betrug 65%, das rezidivfreie Überleben 47% und die lokale Kontrolle nach 5 Jahren 83%.

Schlussfolgerung: Die Daten dieser multizentrischen Phase-II-Studie bestätigen, dass die Kombination von präoperativer Radiotherapie und Capecitabin eine wirksame und nebenwirkungsarme Behandlung beim lokal fortgeschrittenen Rektumkarzinom darstellt. Capecitabin eignet sich als Ersatz für eine kontinuierliche 5-Fluorouracil-Infusion.

Schlüsselwörter: Capecitabin · Rektumkarzinom · Strahlentherapie · Neoadjuvante Therapie · Phase-II-Studie

Introduction

Simultaneous radiochemotherapy is increasingly used in a variety of cancer types for mainly improving local control [12, 21, 25, 31]. In locally advanced rectal cancer, preoperative radiochemotherapy with 5-fluorouracil (5-FU) improves local control and reduces the risks of acute and late toxicity as compared to postoperative radiochemotherapy [28]. Thus, preoperative radiochemotherapy with continuous infusional 5-FU has become standard of care in rectal cancer, especially in tumors of the lower and middle rectum.

Capecitabine, a 5-FU prodrug, has demonstrated efficacy comparable to intravenous 5-FU in metastatic colorectal cancer as well as in the adjuvant setting in colon cancers [1, 2, 33–35]. Capecitabine has been investigated in a variety of protocols in rectal and other gastrointestinal cancers in combination with radiotherapy [14]. We here report the results of a phase II study with long-term follow-up.

Patients and Methods

The phase II study was conducted in seven German radiotherapy centers. The institutional review board approval was gained and each patient provided written informed consent before being recruited into the trial.

Eligibility Criteria

Patients between 18 and 80 years of age with histologically confirmed rectal adenocarcinoma and indication for preoperative combined radiochemotherapy (i.e., stage cT3, cT4, fixative tumors, primarily inoperable tumors) were eligible for this study. Liver metastases were allowed, if they were thought to be resectable. Further exclusion criteria are listed in Table 1.

Study Design and Treatment

The primary endpoint was the clinical objective response rate 4–6 weeks after completion of radiochemotherapy. Secondary endpoints included the pathologically complete response rate, the proportion of R1 resections and sphincter-sparing procedures, as well as further evaluation of the safety profile.

Study treatment was started within 14 days after screening assessment. A total irradiation dose of 50.4 Gy was delivered in conventional fractionation (daily fractions of 1.8 Gy over a period of 5–6 weeks). Three-dimensional conformal techniques with high-energy photons (10–15 MV) and belly boards were used. T4 tumors were either treated with 50.4 Gy plus 5.4 Gy external-beam boost or 45 Gy plus an intraoperative radiotherapy (IORT) boost of 10 Gy. Capecitabine was administered

Table 1. Exclusion criteria.

Tabelle 1. Ausschlusskriterien.

- Distant metastasis (except solitary, resectable liver metastases)
- Previous chemotherapy
- Previous radiotherapy of the pelvic region
- Pregnant or lactating patients
- Women of childbearing potential who lacked a reliable contraceptive method
- Significant cardiac disease
- History of neurologic or psychiatric disorders
- Poor performance status (ECOG > 2)
- Liver cirrhosis
- Serious, uncontrolled infections
- Malabsorption syndrome
- Lack of physical integrity of the upper gastrointestinal tract
- Participation in another clinical trial within 4 weeks of the start of treatment
- Absolute neutrophil count < 2×10^9/l
- Platelet count < 100×10^9/l
- Creatinine levels > 1.6 mg/dl
- Total bilirubin levels > 1.5 mg/dl
- Transaminase or alkaline phosphatase levels > 2.5 times the upper limit of normal

twice daily at a planned total dose of 1,650 mg/m^2/d, administered continuously (including weekends and eventual breaks in irradiation) for the duration of radiotherapy, "Flat dosing" was applied, rounding the total daily dose to the nearest number of 500-mg tablets. The first daily dose was administered about 2 h before radiotherapy, with the second dose given about 10 h after the first, within 30 min after the end of a meal.

Patients underwent radical resection of rectal cancer (TME) within 8 weeks after completion of radiochemotherapy. Adjuvant chemotherapy with 5-FU/leucovorin was applied, if indicated, according to general recommendations in Germany, outside the scope of the study protocol procedures.

Evaluation of Efficacy

Response to the preoperative treatment was assessed with computed tomography according to RECIST criteria 4–6 weeks after radiotherapy immediately prior to planned surgery. A pathologically complete response was defined as the absence of viable tumor cells in the tumor specimen, including regional lymph nodes determined with standard histological procedures.

Statistical Aspects

The objective clinical response rate after 5-FU-based radiochemotherapy is expected to be around 70%. Thus, the capecitabine-containing regimen tested in this trial would be considered to be not sufficiently active, if the response rate was < 60%, but very promising in case of a response rate > 75%. According to these assumptions a single-stage design by Fleming required a sample size of 83 evaluable patients in order to achieve a power of 90% and a type I error of 0.05 [10].

Results

Patient, Tumor and Treatment Characteristics

A total number of 96 patients from seven German university centers entered the study between June 2001 and November 2003 (Table 2). Two were cetegorized as nonevaluable, as they did not receive any treatment according to the protocol (one because of the flood in Saxony in 2002, the other due to the development of distant metastasis just before the onset of the scheduled curative therapy).

40% of the patients were scheduled to receive a total dose of 50.4 Gy, 46% the additional boost of 5.4 Gy, while twelve patients from a single institution were treated with IORT. Three patients (3%) had to be withdrawn from treatment prematurely, because of an incomplete intestinal obstruction, a radiation colitis, and a (preexisting) cardiomyopathy, the seriousness of which became known only after the start of radiotherapy. The actual mean external radiation dose delivered amounted to 51.9 Gy. Overall, the patients received 99.4% of the planned radiation dose (range: 71–104%). The mean overall treatment duration was 40.2 days (planned: 38 days). Treatment interruptions due to acute toxicity were necessary in 3%. The amount of actually received dose of capecitabine based on 94 patients was quite near to the theoretical value according to the protocol with mean and median values of 96% and 100.7%.

Efficacy

88 patients were evaluable for the primary criterion of clinical response according to the requirements of the protocol. Six complete and 54 partial remissions were observed. This corresponds to a response rate of 68%, (95% confidence interval: 57–78%), which is well within the expectations at the study design stage.

Five patients did not undergo surgery, two of them due to a finding of persisting nonresectability after neoadjuvant treatment, another one due to a poor performance status combined with a clinical finding of progression. One patient died before surgery due to gastrointestinal complications, thrombosis, and pneumothorax. A fifth patient refused surgery because of personal reasons. As one further patient withdrew his consent to submit the surgical data, 87 evaluable patients remained, in 44 of whom a sphincter-preserving procedure could be performed (51%). Liver metastases were detected in four patients, with no hepatic resection performed in any of these. The surgical result was classified as R0 in 82 patients (94%). A pathologically complete response was achieved in six patients (7%, 95% confidence interval: 3–14%), with one additional documented case of carcinoma in situ. pT and pN stages are

Table 2. Patient and baseline tumor characteristics.

Tabelle 2. Patienten- und Tumorcharakteristika.

	Number (n)	Proportion (%)
Patients	94	100
Sex		
Male	59	63
Female	35	37
Age (years)		
Median	65	
Range	34–81	
Performance status		
ECOG 0	65	70
ECOG 1	29	30
ECOG 2	0	0
Clinical stage		
T2	2	2
T3	54	57
T4	38	40
N0	32	34
N1	42	45
N2	16	17
NX	4	4
Grading		
G1	8	9
G2	61	65
G3	12	13
GX	13	14

Table 3. Pathologic staging at surgery.

Tabelle 3. Pathologisches Staging bei der Operation nach Radiochemotherapie.

	Patients (n)	Proportion (%)
Patients	87	100
ypT0	6	7
ypTis	1	1
ypT1	5	6
ypT2	27	31
ypT3	42	48
ypT4	6	7
ypN0	60	69
ypN1	15	17
ypN2	11	13
ypNX	1	1

Table 4. Tumor downstaging (pathologic ypT and ypN category after surgery vs. initial clinical cT and cN category). ↓: downstaging; ⟷: unchanged stage; ↑: stage increase. NA: not available.

Tabelle 4. Downstaging (Vergleich von postoperativer pathologischer ypT- und ypN-Kategorie und initialer cT- und cN-Kategorie). ↓: Downstaging; ⟷: keine Stadienänderung; ↑: Stadienerhöhung. NA: nicht verfügbar.

T-stage[a]	N-stage	Patients (n = 87) n (%)
↓	↓	27 (31)
↓	⟷	22 (25)
↓	↑	6 (7)[b]
↓	NA	4 (5)
⟷	↓	12 (14)
⟷	⟷	13 (15)
⟷	↑	3 (3)[b]

[a] T-stage increase did not occur

[b] In two cases, the N-stage increased from 1 to 2; the other eight patients with an increasing N-stage had an initial clinical N0 finding

described in Table 3. The comparison of clinical T- and N-stage at the time of initial diagnosis with the pathologic findings is presented in Table 4. Overall, 53 patients (61%) experienced downstaging in the primary and/or the lymph node regions, without a simultaneous stage increase in another site. The overall T downstaging rate, as second primary objective of the trial, is 63%, when based on an intention-to-treat population, i.e., all patients with information available at this time point, with a 95% confidence interval ranging from 53% to 73%.

Toxicity

Figure 1 shows the occurrence and severity of selected NCI (National Cancer Institute) toxicity criteria, those with a total incidence of > 15% of patients as well as hand-foot syndrome as the dose-limiting toxicity detected in the preceding phase I trial. Myelosuppression was the most frequent toxicity observed in about half of the patients. The most relevant adverse effect was diarrhea which was associated with severe symptoms in seven patients (7%; 6% grade 3, 1% grade 4). On the other hand, with an overall incidence of 12%, hand-foot syndrome proved to be an almost negligible problem with the capecitabine dosage scheme chosen. Local erythemas were frequent, but only one single severe case was reported.

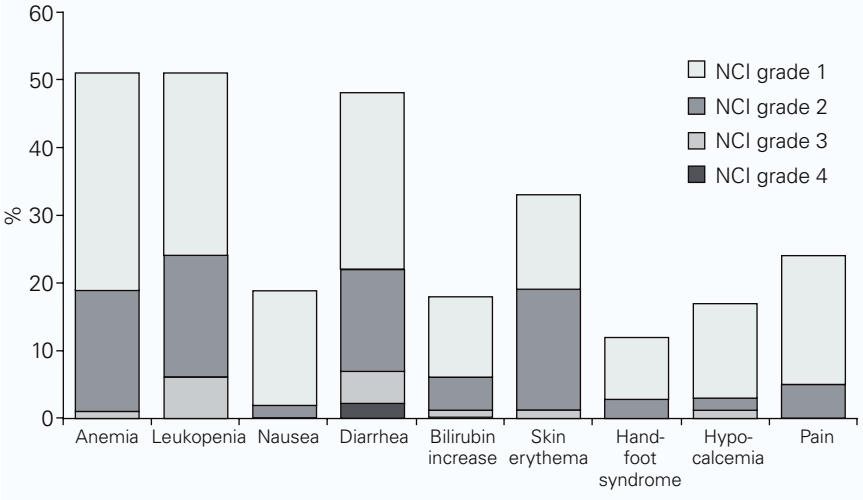

Figure 1. Maximum NCI CTC toxicity grade by patient during chemoradiation therapy.

Abbildung 1. Maximale Toxizität (CTC-Grade) während präoperativer Radiochemotherapie.

Overall Survival, Relapse-Free Survival, and Local Control

Data on survival and local control were analyzed after a median follow-up of 48 months in surviving patients. The Kaplan-Meier curve for survival showed a plateau after 4 years with an overall survival of 65% at 5 years (Figure 2). The 5-year relapse-free survival was 47%. The local control rate after 5 years amounted to 83% (Figure 3).

Discussion

On the basis of the German Rectal Cancer Study and the data of the EORTC study, preoperative radiochemotherapy with 5-FU can be considered the standard of care for T3–4 rectal cancers with a high chance of downstaging and local control [13, 29]. The local failure rates after this preoperative regimen are in the range of 6% after 5 years. In this phase II study, capecitabine was used as substitute for

continuous infusional 5-FU during a preoperative radiochemotherapy regimen in locally advanced rectal cancer. The dosage of the drug was chosen on the basis of the preceding phase I study and the objective of this subsequent expanded phase II study was to confirm the data with regard to efficacy and toxicity in a multiinstitutional setting [8]. The cumulative capecitabine dose delivered with this regimen over 6 weeks is identical to the total dose which is recommended for the drug as monotherapy without radiation in metastatic breast or colorectal cancer (2,500 mg/m^2/d for 2 weeks, then 1 week break). This suggests that systemically effective doses of capecitabine can safely be combined with radiotherapy without increasing the specific local toxicity of pelvic irradiation. If combined with radiation in the head-and-neck region, however, the maximum tolerated dose of capecitabine is lower.

The toxicity of the combined regimen was, as expected, low and the safety data confirm the results of other recent phase I/II studies in rectal cancers. The most frequent nonhematologic severe toxicity was diarrhea (6% grade 3 and 1% grade 4). This was in fact the only grade 4 toxicity. Severe diarrhea is often the dose-limiting toxicity if pelvic radiation with large target volumes is combined with chemotherapy. The figures from this trial compare favorably with the data from other studies. In the German Rectal Cancer Trial, which used continuous infusional 5-FU in the 1st and 5th week of radiotherapy, grade 3–4 diarrhea was the predominant type of acute toxicity and occurred in 12% of patients in the preoperative arm and 18% of the patients in the postoperative arm, respectively [29, 30]. Other phase II studies using 5-FU concurrent with radiation have reported similar results.

With regard to efficacy, the observed response data confirmed the study hypothesis. The clinical response rate of 68% is in accordance with data from other studies with 5-FU or capecitabine and was exactly in the prospectively estimated range. A complete pathohistological response on subsequent surgery (pCR) after radiochemotherapy was observed in 7% of the patients. This is comparable to studies with single-agent 5-FU [5].

Over the past 3 years, a variety of other, mainly phase II studies with comparable design, all of them smaller than our study, have been published [3, 4, 6–9, 11, 16, 19, 20, 22–24, 32, 36–38]. A synopsis of the data is demonstrated in Table 5. Overall, the toxicity profile in these studies was favorable and histologically complete response rates up to about 20% have been reported. Thus, these studies have shown comparable results suggesting that the combination of capecitabine and pelvic radiation is safe and effective and that capecitabine can replace continuous infusional 5-FU. Our study is the first of these studies with long-term follow-up and this is, to our knowledge, the

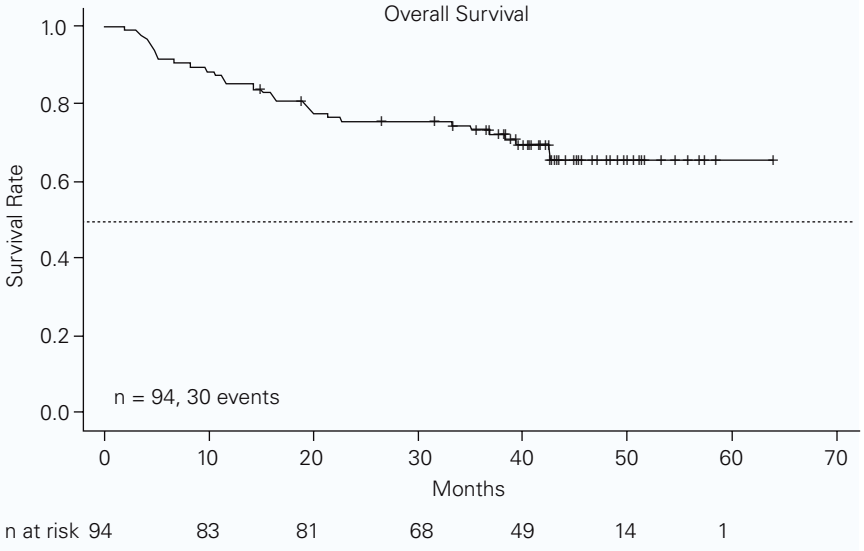

Figure 2. Overall survival of the study population.

Abbildung 2. Gesamtüberleben.

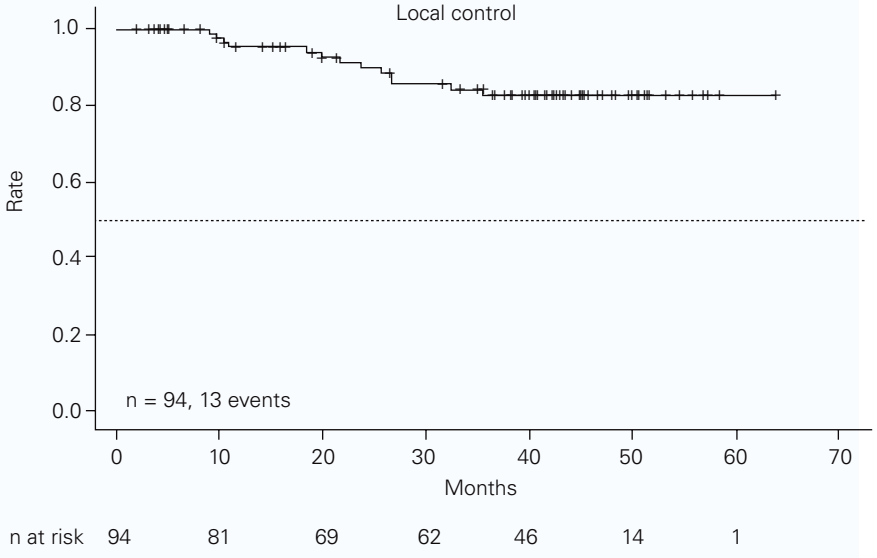

Figure 3. Local control.

Abbildung 3. Lokale Tumorkontrolle.

Table 5. Preoperative radiochemotherapy with capecitabine as single agent. Results from phase I/II studies. FD/TD: fraction dose/total dose; IMRT: intensity-modulated radiotherapy; NR: not reported; pCR: pathologically complete response; PTV: planning target volume.

Tabelle 5. Präoperative Radiochemotherapie mit Capecitabinmonotherapie. Daten von Phase-I/II-Studien. FD/TD: Einzeldosis pro Fraktion/Gesamtdosis; IMRT: intensitätsmodulierte Radiotherapie; NR: nicht angegeben; pCR: histologisch komplette Remission; PTV: Planungszielvolumen.

Authors	Study design	Patients (n)	Dose of capecitabine (mg/m^2)	Radiation dose FD/TD (Gy)	Grade 3 diarrhea (%)	pCR rate (%)
Dunst et al. 2002 [8]	Phase I	69	2 × 250–1,000	1.8/50.4–54.0	4	4
Kim et al. 2002 [16]	Phase II	38	2 × 825	1.8/45.0–50.4	4	31
Dupuis et al. 2007 [9]	Phase II	51	2 × 825	1.8/45.0	6	24
Kocakova et al. 2004 [19]	Phase II	43	2 × 825	1.8/45.0–50.4	NR	21
Shen et al. 2004 [32]	Phase II	71	2 × 825	1.8/60	3	15
Wong et al. 2004 [38]	Phase II	18	2 × 825	1.8/50.4	11	17
Lin et al. 2005 [23]	Phase II	53	2 × 825	1.75/52.5	13	17
Chau et al. 2006 [3]	Phase II	68	2 × 825	1.8/45.0–54.0	6	24
De Paoli et al. 2006 [6]	Phase II	53	2 × 825	1.8/45	< 4	24
Veerasarn et al. 2006 [36]	Phase I	27	2 × 700–1,000	1.8/45	7[a]	14
Velenik et al. 2006 [37]	Phase II	57	2 × 825	1.8/45	NR	9
Craven et al. 2007 [4]	Phase II	70	900	1.8/45	NR	9
Desai et al. 2007 [7]	Phase II	32	1,330	1.8/42–50	15	11
Freedman et al. 2007 [11]	Phase I	8	2 × 825	2 × 1.8–2.2/45–55[b]	(38[c])	0
Korkolis et al. 2007 [20]	Phase II	30	2 × 825	1.8/50.4	0	23
This study	Phase II	96	2 × 825	1.8/50.4–55.8	7[d]	7

[a] Grade 3 diarrhea was only observed at the 2 × 1,000 mg/m^2 level; 2/12 patients (16%) developed grade 3 diarrhea at this level
[b] 28 fractions with IMRT and an integrated simultaneous boost (1.8 Gy to whole PTV, 2.2 Gy to boost PTV, total doses 45/55 Gy)
[c] Study was stopped due to acute toxicity
[d] 1 patient (1%) with grade 4 diarrhea

first report on survival and local control. The 5-year overall survival of 65% in our study is inferior to the 76% 5-year survival in the German Rectal Cancer Study, but it must be kept in mind that our study included a much higher proportion of cT4 tumors (40% cT4 in contrast to 6% in the German study). This negative patient selection might also explain the relatively high rate of local recurrences (17% cumulative risk of local recurrence after 5 years). Future trials are necessary to evaluate the efficacy of other drugs or multiple drug combinations [15, 17, 18, 26–28]. Moreover, a possible impact of timing of daily capecitabine administration and radiation should be further investigated [39].

Conclusion

The results of this expanded phase II study have confirmed the data of the preceding phase I as well as data from other studies in a multicenter setting. The efficacy in terms of clinical and pathologic response rates was in the estimated range and similar to those reported with single-agent 5-FU. With regard to patient selection, the overall survival and local control compare favorably with studies using 5-FU as radiation sensitizer.

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