Neoadjuvant Radiochemotherapy and Surgery for Advanced Rectal Cancer

Prognostic Significance of Tumor Regression*

Hans Theodor Eich[1], Anna Stepien[1], Christian Zimmermann[1], Martin Hellmich[3], Ralf Metzger[2], Arnulf Hölscher[2], Rolf-Peter Müller[1]

Purpose: Preoperative radiochemotherapy is widely used in the treatment of locally advanced rectal cancer. The predictive value of response to neoadjuvant treatment remains uncertain. We retrospectively evaluated the impact of downstaging and tumor regression as prognostic factors and its influence on the ability to perform sphincter-sparing surgery.
Patients and Methods: A total of 72 consecutive patients with advanced rectal cancer were included in this retrospective analysis. All patients were treated with preoperative 5-fluorouracil-based chemotherapy and pelvic radiation with a total dose of 50.4 Gy followed by surgery 6 weeks later.
Results: A sphincter-preserving procedure could be performed on 42 patients, and in all 72 patients complete resection (R0) was achieved. A pathological complete response (ypT0, ypN0) was achieved in 8 (11%) patients. None of the patients showing a complete pathological response relapsed or died during the follow-up period. At a median follow-up of 28 months, 65 patients were alive, none of these patients had local recurrence and 15 patients had metastatic disease. Patients showing a complete pathological response had a significantly better 2-year disease-free survival compared to patients with ≥ 10% residual tumor cells ($p = 0.024$). Patients < 65 years showed a significantly better response rate, compared with those > 65 years of age ($p = 0.036$). Acute toxicity was moderate.
Conclusion: Preoperative radiochemotherapy is an effective and safe treatment for patients with locally advanced rectal cancer. Pathological parameters after preoperative radiochemotherapy, including tumor regression grading, could be correlated with disease-free survival. The impact of tumor regression grading needs to be further validated in prospective clinical trials.

Key Words: **Radiotherapy · Rectal carcinoma · Neoadjuvant radiochemotherapy · Prognostic factors**

Strahlenther Onkol 2011;187:225–30
DOI 10.1007/s00066-011-2113-1

Neoadjuvante Radiochemotherapie und Operation fortgeschrittener Rektumkarzinome: Tumorregression stellt prognostischen Faktor dar

Hintergrund: Die präoperative Radiochemotherapie (RChT) gefolgt von einer Operation stellt heute die Standardbehandlung für Patienten mit lokal fortgeschrittenem Rektumkarzinom dar. Der Vorhersagewert des Ansprechens auf eine neoadjuvante RChT ist nicht definiert. Wir untersuchten retrospektiv die Bedeutung des Tumoransprechens (Downstaging) und der Tumorregression als prognostische Faktoren und ihren Einfluss, eine sphinktererhaltende Operation zu ermöglichen.
Material und Methode: Die vorliegende Analyse umfasst 72 konsekutive Patienten mit fortgeschrittenen Rektumkarzinomen, die im Zeitraum Januar 1999 bis Dezember 2006 eine neoadjuvante RChT erhielten. Die Behandlung bestand aus einer perkutanen Radiotherapie mit 50,4 Gy und einer simultanen 24-h-Dauerinfusion von 5-Fluorouracil (Woche 1 und 5) gefolgt von einer radikalen Tumorresektion. Neben dem Ansprechen des Tumors im Sinne eines Downstagings wurden mögliche prognostische Faktoren analysiert.
Ergebnisse: Nach einer medianen Nachbeobachtungszeit von 28 Monaten kam es bei keinem Patienten zu einem Lokalrezidiv und bei allen 72 Patienten gelang eine komplette Resektion (R0). Das Ansprechen auf die neoadjuvante RChT im Sinne einer histopathologischen Tumorregression konnte als relevanter Prognosefaktor für das krankheitsfreie Überleben herausgearbeitet werden (Abbildung 1). 8 Patienten (11%) erreichten eine histopathologische komplette Remission (ypT0, ypN0). Darüber hinaus

*Presented at the 15th Annual Meeting of the German Society for Therapeutic Radiology and Oncology (DEGRO), Bremen, 11–14 June 2009.

[1]Department of Radiation Oncology, University of Cologne, Germany,
[2]Department of General, Visceral and Cancer Surgery, University of Cologne, Germany,
[3]Institute of Medical Statistics, Informatics, and Epidemiology, University of Cologne, Germany.

Received: December 7, 2009; accepted: April 15, 2010
Published Online: March 7, 2011

zeigten Patienten unter 65 Jahre ein signifikant besseres Ansprechen auf die präoperative RChT im Sinne eines Downstagings als Patienten über 65 Jahre (p = 0,036). Die Akuttoxizität der neoadjuvanten Therapie ist moderat.
Schlussfolgerung: Die neoadjuvante RChT mit anschließender radikaler Resektion ist eine effektive und sichere Behandlung lokal fortgeschrittener Rektumkarzinome. Die Tumorregression konnte mit dem krankheitsfreien Überleben korreliert werden. Inwieweit die Tumorregression als valider Prognoseparameter angesehen werden kann, muss in prospektiven klinischen Studien überprüft werden.

Schlüsselwörter: **Radiotherapie · Rektumkarzinom · Neoadjuvante Radiochemotherapie · Prognostische Faktoren**

Introduction

Locally advanced rectal cancer is one of the most frequent tumors. Rectal cancer has an annual incidence of 22 per 100,000 men and 16.4 per 100,000 women. Most of the patients are male and the mean age is between 60–65 years.

Prospective trials that have investigated the potential advantage of preoperative radiochemotherapy with 5-fluorouracil (5-FU) over radiotherapy (RT) alone have shown that the addition of chemotherapy to preoperative RT results in downsizing and pathological downstaging and improves local control but has no significant effect on survival of patients. Based on these clinical data, preoperative radiochemotherapy followed by surgery is the standard treatment for locally advanced rectal cancer [1, 2, 4, 9, 15, 16, 23, 26, 28].

The purpose of this analysis was to evaluate the Cologne experience of patients who received neoadjuvant radiochemotherapy for locally advanced rectal cancer. Factors associated with pathologic tumor response following preoperative therapy and the prognostic impact of pathologic response on overall and disease-free survival (DFS) were evaluated. Furthermore, a possible correlation between the occurrence of acute- or long-term toxicities [20, 21, 22, 29] and the treatment planning procedure (2D vs. 3D) was determined.

Patients and Methods

Study Design and Treatment

This study comprises a retrospective review of 72 consecutive patients, who received neoadjuvant radiochemotherapy at the Department of Radiation Oncology, University of Cologne, Germany, between January 1999 and December 2006. Surgery was performed in 46 patients at the Department of General, Visceral, and Cancer Surgery, University of Cologne, Germany, and in 26 patients at nonacademic referral hospitals (n = 10).

The regime was used for locally advanced rectal cancer stage II–III according to the UICC classification which were resectable and had no distant metastases. RT was delivered with 10–15 MV photon beams at 1.8 Gy/fraction up to 50.4 Gy in 28 daily fractions for 5 days a week. Patients were treated in prone position with a belly-board immobilization device. Doses were always prescribed according to the International Commission on Radiation Units and Measurements reference point. Ninety-five percent of the planning target volume (PTV) had to be covered by at least 95% isodose line in all patients. A three-field box technique was usually used; all treatments fields were individually configured with multileaf collimators (MLC). Radiation treatment planning consisted of 2D techniques in 52 patients (72%) and 3D techniques in 20 patients (28%). Preoperative chemotherapy was given as a 120-hour continuous infusion in two 5-day courses during the first and fifth week of radiotherapy. 5-FU was given at a dose of 650 or 1000 mg/m^2 body area per day. Patients older than 70 years achieved a reduced 5-FU dose of 650 mg. Surgery followed 4–6 weeks after the completion of the preoperative treatment and clinical restaging [12, 18]. Standardized surgery which included total mesorectal excision (TME) was used. Postoperative chemotherapy of patients with pre- and postoperative N+ status was scheduled depending on the patient's condition 4–6 weeks after surgery and was delivered in four courses (5-FU 500 mg/m^2 every 4 weeks).

Preoperative Clinical Staging

All patients underwent a complete history, physical examination, digital rectal examination, transrectal rectoscopy with biopsy, full colonoscopy when possible, computed tomographic (CT) scan of the chest, abdomen and pelvis, and endosonography. The distance between the tumor from the anal verge was determined by rigid rectoscopy. T-stage was primarily defined within the transrectal ultrasound. Every visible lymph node in the transrectal ultrasound and/or in the CT was classified as positive [25].

Histopathologic Staging and Assessment of Tumor Regression

Histopathologic staging was performed according to the pTNM classification of the UICC [31]. Tumor regression of the primary tumor was semiquantitatively determined by the amount of viable tumor vs. the amount of fibrosis, ranging from no evidence of any treatment effect to a complete response with no viable tumor identified, as described by Müller and Junker [14]. Tumor regression grade (TRG) I was defined as no regression; TRG IIa as more than 10% residual tumor cells; TRG IIb, as less than 10% residual tumor cells; TRG III, as total regression (no viable tumor cells). Tumor downstaging was defined by a comparison in the pretreatment TN stage (determined by clinical, radiographic, and ultrasound staging) to the pathologic stage [30].

Follow-Up

Follow-up examinations were recommended at 3-month intervals for 2 years, then at 6-month intervals for 3 years. Evalua-

tions consisted of physical examination and blood tests. Recto- and colonoscopy, abdominal ultrasound, CT of the abdomen, and chest radiograph were applied according to the guidelines of the German Cancer Society [13, 27]. Histologic confirmation of local and distant recurrence was encouraged. Alternate acceptable criteria included sequential enlargement of a mass in radiologic studies.

Statistical Analysis

The X^2 trend test for ordered categories was used for ordered prognostic factors with more than two categories. For dichotomous variables, the ordinary X^2 test was used. The prognostic factors were evaluated for overall survival (OS) by log-rank test [18] and Cox regression analysis. Survival was defined as the time between diagnostic biopsy and last follow-up or death. Survival curves were estimated according to the Kaplan–Meier method [17]. A p level ≤ 0.05 was considered significant. Data was analyzed using SPSS statistical software (Release 15.0, SPSS Inc. Chicago, IL, USA).

Results

Patient Characteristics

A total of 72 patients received the full course of multimodal therapy. Patient and tumor characteristics are displayed in Table 1. Tumor resection was performed in all 72 patients. Complete resection (R0) was achieved in all patients. The surgical procedures included abdominoperineal resection in 20 patients (28%), low anterior resection in 40 patients (56%), anterior resection in 5 patients (7%), intersphincter resection in 1 patient (1%). Two patients (3%) received a full rectal wall excision by transanal endoscopic microsurgery. Four patients (6%) with simultaneous liver metastases received preoperative treatment based on the strong patients wish. Two of these patients, each with two liver metastases, were treated with radiofrequency ablation, 1 patient with three metastatic lesions with hemihepatectomy, and another patient with five metastases was treated with atypical liver segmentectomy.

Table 1. Patients and tumor characteristics.

Tabelle 1. Patienten und Tumorcharakteristika.

Number of patients		72
Age range (years)		31–81
Median age (years)		59
Sex		
	Male	41 (58%)
	Female	31 (42%)
Tumor localization		
	< 6 cm from anus	20 (28%)
	6–12 cm from anus	37 (51%)
	> 12–16 cm from anus	15 (21%)
Histology		
	Adenocarcinoma	70 (97%)
	Signet-ring cell carcinoma	2 (2%)
	Undifferentiated carcinoma	1 (1%)
cT stage		
	cT2	7 (10%)
	cT3	50 (69%)
	cT4	15 (21%)
cN stage		
	cN0	28 (39%)
	cN1	41 (57%)
	cN2	3 (4%)
Dukes stage		
	UICC I	4 (6%)
	UICC II	23 (32%)
	UICC III	44 (61%)
	UICC IV	—

Survival

At a median follow-up of 28 months, 90% of the patients were alive. The 2-year OS was 93% ± 3.2% and 2-year DFS was 78% ± 5.3%. Patients with complete pathologic response were characterized by significantly improved 2-year DFS (p = 0.024; Figure 1). The 2-year DFS for patients with intermediate (less than 10% residual tumor cells) or complete tumor regression (ypT0, ypN0) was 100% compared with 82% ± 9.4% for patients with 10% residual tumor cells and 76% ± 14.8% for patients with poor response (> 10% residual tumor cells). The 2-year DFS for patients who achieved a downstaging was 78.7% ± 6.8% and for patients without downstaging 81.6% ± 7.5% (n.s.). Fifteen patients (21%) developed distant metastases (lung 8, liver 4, bone 2, lymph node 1). Seven patients (10%) died. Causes of death were distant metastasis≤patients and independent of the primary tumor or treatment in 2 patients.

Pathological Response

The pre- and posttherapeutic histopathological tumor stages (both UICC) are summarized in Table 2. Downstaging was achieved in 42 patients (58%). A complete remission (ypT0, ypNo) was achieved in 8 patients (11%): 1 of these patients had an initial UICC stage of I, 2 patients stage II, and 5 patients stage III. Of the 44 tumors (61%) examined for tumor regression, 8 tumors (18%) showed no viable tumors cells in the rectal wall (TRG III), whereas in 9 tumors (21%) no regressive changes could be found (Table 3).

Sphincter Preservation

For the group as a whole, sphincter preservation (SP) was possible in 59% (n = 42), and an abdominoperineal resection (APR) was required in 41% (n = 29) of cases. SP was possible in 28 patients of the group who achieved downstaging (n = 42). No correlation was observed between downstaging and sphincter preservation. There was also no correlation between SP and the pretreatment distance from the anal verge

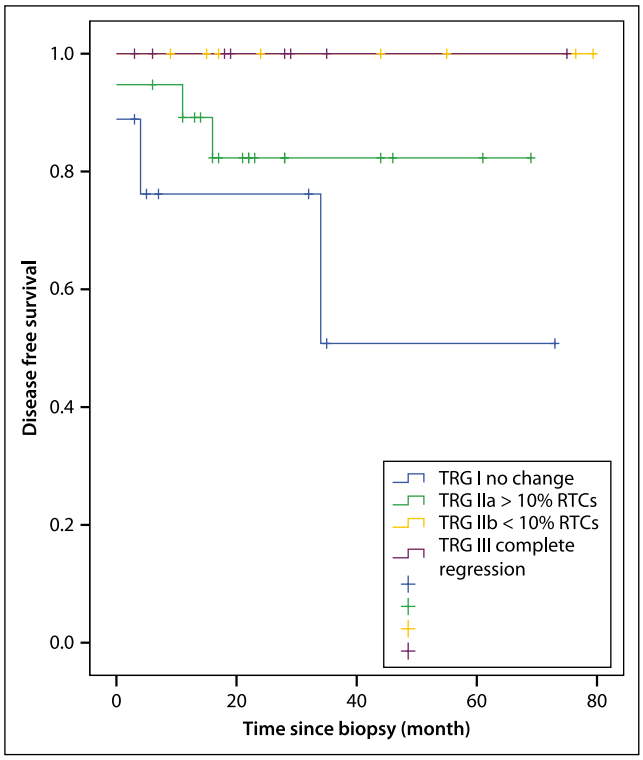

Figure 1. Disease-free survival of 44 patients with rectal carcinoma after preoperative radiochemotherapy and curative resection (R0), according to tumor regression grading (TRG). The 2-year survival was: TRG I = 76.2% ± 14.8%, TRG IIa = 82.3% ± 9.4%, TRG IIb and III = 100% (p = 0.024).

Abbildung 1. Krankheitsfreies Überleben von 44 Patienten mit Rektumkarzinom nach präoperativer Radiochemotherapie bezüglich der Tumorregression (TRG) . Das 2-Jahres-Überleben betrug: TRG I = 76,2% ± 14,8%, TRG IIa = 82,3% ± 9,4%, TRG IIb and III = 100% (p = 0,024).

(Table 4). However, a correlation between SP and T stage (p = 0.027) could be defined (Table 5).

Correlation Between Age and Tumor Staging

Interestingly, a relationship between downstaging and the patients' age was observed. Among patients < 65 years, 33 patients (46%) showed downstaging in comparison to 9 patients (13%) in the group of patients > 65 years (p = 0.036).

Toxicity of Radiation and Chemotherapy

The intensity of clinical adverse events was graded according to the National Cancer Institute Common Toxicity Criteria (NCI-CTC) [29]. The most frequent acute side effects were mild (grade 1 and 2) erythema (6%) and mucositis (3%). Gastrointestinal toxicity (enteritis) was observed in 10 patients. There was no case of radiogenic cystitis. No hematological grade 3 or 4 toxicity was encountered during therapy. Five patients had perioperative wound complications. The overall rates of long-term toxic effects during the 28-month follow-up were low. One patient suffered delayed wound healing. Four patients (7%) reported some form of fecal incontinence, 6 patients complained about perianal pain, 1 patient about erectile dysfunction, and 3 patients had chronic diarrhea [5, 7, 8].

Discussion

This retrospective study presents the outcome of 72 consecutive patients, who received neoadjuvant radiochemotherapy for locally advanced rectal cancer comparable to the regimen of the German Rectal Cancer Group [26]. The following results emerge from this study:

- Preoperative radiochemotherapy induces a significant downstaging with 8 patients (11%) achieving a pathological complete response (pCR) of the tumor (ypT0ypN0).
- Tumor regression revealed by the histopathological examination serves as a good prognostic index for disease-free survival.
- Sphincter sparing was achieved in 59% of all patients. It was clearly related to the depth of tumor invasion.

The results in our experience include a 11% complete response and a 58% downstaging rate. This correlates to other studies which present complete remissions in 7–30% with a comparable regimen [6, 12, 15, 26]. In the German Rectal Cancer Trial, a pCR rate of 8% was achieved [26]. Janjan et al. [12] presented the results of preoperative radiochemotherapy in 117 patients with locally advanced rectal cancer: 45 Gy in 25 fractions over 5 weeks with continuous infusion of 5-FU (300 mg/m^2/day). Surgery was performed 6 weeks later. They reported an impressive pCR rate of 27% and a downstaging rate of 62% [12]. The pCR rate was identified as a prognostic factor for patients undergoing neoadjuvant radiochemotherapy for rectal cancer [24]. The long-term outcome of patients exhibiting pCR is favorable (local relapse rate 1.6%, 5-year cancer-specific survival 94%) [3]. Two-drug regimens were shown to be associated with higher pCR rates in an analysis of several trials including a total 3,157 patients [10]. Furthermore, molecular targeted agents such as cetuximab, an antibody targeting the epidermal growth factor receptor (EGFR), seems to be attractive in neoadjuvant regimens and are currently pursued. However, in the German MARGIT Phase II trial, which enrolled 50 patients, the addition of cetuximab in combination with capecitabine, irinotecan, and radiotherapy failed to increase the pCR rate (8%) as well as the downstaging rate (45%) [11].

In the present analysis, complete pathological regression was significantly associated with an improved disease-free survival rate. The differences in disease-free survival were accounted for by the development of distant metastases. However, freedom from distant metastases was achieved in all ypT0ypN0 patients after a median of 28 months. Rödel et al. [24] assessed the impact of tumor regression grading (TRG) in a cohort of rectal carcinoma patients treated by preoperative radiochemotherapy. TRG was evaluated in surgical specimens of 385 patients treated within the preoperative radiochemotherapy arm of the CAO/ARO/AIO-94 trial. The 5-year disease-free survival

was 86% for patients when no viable tumor cells were detected, 75% for patients with intermediate pathologic response, and 63% for patients with a morphologically unaltered tumor mass (p = 0.006) [24]. The authors recommended including TRG into the pathologic evaluation. Another positive predictor for the patient outcome could be toxicity during treatment. Wolff et al. [32] reported on a statistically significant correlation between high-grade acute organ toxicity during preoperative radiochemotherapy and complete tumor regression after total mesorectal excision in multimodal treatment of locally advanced rectal cancer.

Sphincter preservation (SP) is another important goal of preoperative therapy. In the presented analysis, SP is rather low at 59% of all patients. This correlates with the reported data by Janjan et al. [12], where SP was possible in 59% (n = 69), and an abdominoperineal resection was required in 41% (n = 48). However, in the CAO/ARO/AIO-94 study [26], the abdominoperineal resection rate was only 26% in the preoperative radiochemotherapy arm. The lower rate of SP in our retrospective analysis could be influenced by a number of variables, including the specific criteria used for SP by the referring surgeon and referral bias. There was no correlation between SP and the site of surgery (university hospital vs. nonacademic referral hospital) and there was no correlation between DFS and site of surgery. SP was clearly related to the depth of tumor invasion. However, in the present analysis the rates of complete resection and sphincter sparing surgery did not differ between the groups with and without downstaging. No statistical relationship was observed when SP was considered relative to the pretreatment distance from the anal verge. This is possibly also caused by the large variety of referring surgeons in this limited number of patients with different experience in the surgical management of rectal carcinoma [19]. Janjan et al. [12] clearly demonstrated that preoperative radiochemotherapy allowed sphincter sparing surgery in over 40% of patients whose tumors were located < 6 cm from the anal verge who otherwise would have required colostomy.

Table 2. Preoperative vs. postoperative UICC staging.

Tabelle 2. Präoperatives vs. postoperatives UICC-Stadium.

	Postoperative					Σ
Preoperative	**ypT$_0$N$_0$M$_0$**	**I**	**II**	**III**	**unknown**	
I (T$_2$N$_0$M$_0$)	1 (1%)		2 (3%)	0	0	5 (7%)
II (T$_3$N$_0$M$_0$,T$_4$N$_0$M$_0$)	2 (3%)	9 (12%)		6 (9%)	1 (1%)	24 (33%)
III (T$_{2-4}$N$_{1-2}$M$_0$)	5 (7%)	6 (9%)	19 (26%)		0	43 (60%)
Σ	8 (11%)	17 (24%)	27 (38%)	19 (26%)	1 (1%)	72 (100%)

Table 3. Histopathologic regression rating for clinical responder and nonresponder. RTC: residual tumor cells; responder: patients who achieved downstaging; nonresponder patients who did not achieve downstaging.

Tabelle 3. Histopathologischer Regressionsgrad in der „Responder"- und „Nonresponder"-Gruppe. RTC: residuelle Tumorzellen; Responder: Patienten mit Downstaging; Nonresponder: Patienten ohne Downstaging.

Histopathologic regression	Clinical responder	Clinical nonresponder	Σ	p
No regression	3 (7%)	6 (14%)	9	0.031
> 10% RTC	10 (23%)	9 (20%)	19	
< 10%RTC	6 (14%)	2 (5%)	8	
No residual tumor cells	8 (18%)	0 (0%)	8	
Σ	27 (62%)	17 (38%)	44	

Table 4. Surgery with or without preservation of the sphincter in rrelation to the pretherapeutic localization of the tumor.

Tabelle 4. Operation mit oder ohne Sphinktererhalt in Bezug auf die prätherapeutische Tumorlokalisation.

	< 6-cm from anus	6–12 cm from anus	> 12 cm from anus	Σ	p
Without sphincter preservation	11 (15%)	14 (20%)	4 (5%)	29 (40%)	NS
With Sphincter preservation	9 (13%)	23 (32%)	11 (15%)	43 (60%)	
Σ	20 (28%)	37 (52%)	15 (20%)	72	

Table 5. Correlation between T stage and sphincter preservation.

Tabelle 5. Korrelation zwischen T-Stadium und Sphinktererhalt.

	pT0	pT1	pT2,3	pT4	Σ	p
Without sphincter preservation	1	1	24	3	29	0.027
With sphincter preservation	7	3	31	1	42	
Σ	8	4	55	4	71[a]	

[a]One additional patient with no information about posttherapeutic histopathologic tumor stage.

Conclusion

Neoadjuvant radiochemotherapy with 5-FU and 50 Gy pelvic irradiation represents the standard treatment for patients with locally advanced rectal cancer. This procedure achieves high rates of tumor regression. Pathological parameters after preoperative radiochemotherapy including TRG have been correlated with disease-free survival. The impact of TRG needs to be further validated in prospective clinical trials.

References

1. Bosset JF, Calais G, Mineur L, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preleminary results – EORTC 22921. J Clin Oncol 2005;23:5620–7.
2. Bosset JF, Collette L, Calais G, et al. for EORTC Radiotherapy Group Trial 22921. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114–23.

3. Capirci C, Valentini V, Cionini L, et al. Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long-term analysis of 566 ypCR patients. Int J Radiat Oncol Biol Phys 2008;72:99–107.
4. Colorectal cancer colaborative Group (CCC). Adjuvant radiochemotherapy for rectal cancer. A systemic overview of 8507 patients from 22 randomised trials. Lancet 2001;358:1291–1304.
5. Dörr W, Herrmann T. Second tumors after oncologic treatment. Strahlenther Onkol 2008;184:67–72.
6. Dunst J, Debus J, Rudat V, et al. Neoadjuvant capecitabine combined with standard radiotherapy in patients with locally advanced rectal cancer: mature results of a phase II trial. Strahlenther Onkol 2008;184:450–6.
7. Füller J, Guderian D, Köhler C, et al. Lymph edema of the lower extremities after lymphadenectomy and radiotherapy for cervical cancer. Strahlenther Onkol 2008;184:206–11.
8. Georg D, Georg P, Hillbrand M, et al. Assessment of improved organ at risk sparing for advanced cervix carcinoma utilizing precision radiotherapy techniques. Strahlenther Onkol 2008;184:586–91.
9. Gerad JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol 2006;24:4620–5.
10. Hartley A, Ho KF, McConkey C, et al. Pathological complete response following pre-operative chemoradiotherapy in rectal cancer: analysis of phase II/III trials. Br J Radiol 2005;78:934–8.
11. Horisberger K, Treschl A, Mai S, et al. Cetuximab in combination with capecitabine, irinotecan, and radiotherapy for patients with locally advanced rectal cancer: results of a Phase II MARGIT trial. Int J Radiat Oncol Biol Phys 2009;74:1487–93.
12. Janjan N, Khoo V, Abbruzzese J, et al. Tumor downstaging and sphincter preservation with preoperative chemoradiation in locally advanced rectal cancer; The M.D. Anderson Cancer Center Experience. Int J Radiat Oncol Biol Phys 1999;44:1027–38.
13. Juninger T, Hossfeld, Sauer R, et al. Adjuvante Therapie bei Kolon- und Rektumkarzinom. Dtsch Ärztebl 1999;96: 698–700.
14. Junker K. Therapieinduzierte morphologische Veränderungen bösartiger Lungentumoren. Pathologe 2004;25:475–80.
15. Kaminsky-Forrett MCh, Conroy T, Luporsi E, et al. Prognostic implication of downstaging following preoperative radiation therapy for operable T3-T4 rectal cancer. Int J Radiat Oncol Biol Phys 1998;42:935–41.
16. Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al. Dutch Colorectal Cancer Group. Preoperatve radiotherapy, combined with total meorectal excision for resectable cancer. N Engl J Med 2001;345:638–46.
17. Kaplan El, Meier P. Non-parametric estimation from incomplete observation. J Am Stat Assoc 1958;53:457–81.
18. Mantel N. evaluation of survival data and two new rank order statistics arising in its consideration. Cancer Chemother Rep 1994;73:163–70.
19. Martling AL, Holm T, Rutqvist TE, et al. Effect of surgical training programme on outcome of rectal cancer in the country of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. Lancet 2000;356:93–6.
20. Milani V, Pazos M, Issels RD, et al. Radiochemotherapy in combination with regional hyperthermia in preirradiated patients with recurrent rectal cancer. Strahlenther Onko. 2008;184:163–168.
21. Müller AC, Ganswindt U, Bamberg M, et al. Risk of second malignancies after prostate irradiation? Strahlenther Onkol 2007;183:605–9.
22. Rischke HC, Momm F, Henke M, et al. Does radiation prevent 5-fluorouracil-induced colitis in the early phase of radiochemotherapy? A case report and literature review. Strahlenther Onkol 2007;183:459–63.
23. Roedel C, Hohenberger W, Sauer R. Adjuvante und neoadjuvante Therapie des Rektumkarzinoms. Strahlenther Onkol 1998;174:497–504.
24. Roedel C, Martus P, Papadoupolus T, et al. Prognostic significance of tumor regression after preoperative chemoradiotherapy for rectal cancer. J Clin Oncol 2005;34:8688–96.
25. Roedel C, Sauer R, Fietkau R. The role of magnetic resonance imaging to select patients for preoperative treatment in rectal cancer. Strahlenther Onkol 2009;185:488–92.
26. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–40.
27. Schmiegel W, Reinacher-Schick A, et al. [Update S3-guideline „colorectal cancer" 2008]. Z Gastroenterol 2008;46:799–840.
28. Schwedish Rectal Cancer Trial Group. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997;336:980–7.
29. Seegenschmiedt MH, Sauer R. Systematik der akuten und chronischen Strahlenfolgen. Strahlenther Onkol 1993;169:83–98.
30. Shia J, Guillem JG, Moore HG. Patterns of morphologic alteration in residual rectal carcinoma following preoperative chemoradiation and their association with long-term outcome. Am J Surg Pathol 2004;28:215–23.
31. Wittekind Ch, Klimpfinger M, Sobin LH. Union Internationale Contre le Cancer. Springer, Berlin 2004: 5–38.
32. Wolff HA, Gaedcke J, Jung K, et al. High-grade acute organ toxicity during preoperative radiochemotherapy as positive predictor for complete histopathological tumor regression in multimodal treatment of locally advanced rectal cancer. Strahlenther Onkol 2010;186:30–5.

Address for Correspondence
Priv.-Doz. Dr. Hans Theodor Eich
Department of Radiation Oncology
University of Cologne
Kerpener Str. 62
50937 Cologne
Germany
Phone (+49/221) 478-5449, Fax: -6158
e-mail: hans.eich@uk-koeln.de