Adjuvant versus Neoadjuvant Radiochemotherapy for Locally Advanced Rectal Cancer

A Progress Report of a Phase-III Randomized Trial (Protocol CAO/ARO/AIO-94)

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Aim: The standard treatment for patients with clinically resectable rectal cancer is surgery. Postoperative radiochemotherapy is recommended for patients with advanced disease (pT3/4 or pN+). In recent years, encouraging results of preoperative radiotherapy have been reported. This prospective randomized phase-III trial (CAO/ARO/AIO-94) compares the efficacy of neoadjuvant radiochemotherapy to standard postoperative radiochemotherapy. We report on the design of the study and first results with regard to toxicity of radiochemotherapy and postoperative morbidity.

Patients and Methods: Patients with locally advanced operable rectal cancer (uT3/4 or uN+, Mason CS III/IV) were randomly assigned to pre- or postoperative radiochemotherapy: A total dose of 50.4 Gy (single dose 1.8 Gy) was applied to the tumor and the pelvic lymph nodes. 5-FU (1,000 mg/m^2/d) was administered concomitantly in the first and fifth week of radiation as 120-h continuous infusion. Four additional cycles of 5-FU chemotherapy (500 mg/m^2/d, iv bolus) were applied. Radiochemotherapy was identical in both arms except for a small-volume boost of 5.4 Gy in the postoperative setting. Time interval between radiochemotherapy and surgery was 4–6 weeks in both arms. Techniques of surgery were standardized and included total mesorectal excision. In addition, stratification according to surgeons involved has been provided for. Primary endpoints of the study are 5-year overall-survival, local and distant control, secondary endpoints include rate of curative (R0) resections and sphincter saving procedures, toxicity of radiochemotherapy, surgical complications and quality of life.

Results: As of 15th November 2000, 628 patients were randomized from 26 participating institutions: 310 patients were randomized to postoperative radiochemotherapy, 318 patients to preoperative radiochemotherapy. Acute toxicity (WHO) of radiochemotherapy was low, with less than 15% of patients experiencing Grade 3 or higher toxicity: The principal toxicity was diarrhea, with 12% in the postoperative radiochemotherapy arm and 10% in the preoperative radiochemotherapy arm having Grade-3, and 1% in either arm having Grade-4 diarrhea. Erythema, nausea and leukopenia were the next common toxicities, with less than 3% of patients in either arm suffering Grade 3 or greater leukopenia or nausea. Postoperative complication rates were similar in both arms, with 12% (postoperative radiochemotherapy) and 13% (preoperative radiochemotherapy) of patients, respectively, suffering from anastomotic leakage, 4% (postoperative radiochemotherapy) and 3% (preoperative radiochemotherapy) from postoperative bleeding, and 6% (postoperative radiochemotherapy) and 5% (preoperative radiochemotherapy) from delayed wound healing.

Conclusion: The patient accrual of our trial is satisfactory, neoadjuvant radiochemotherapy is well tolerated and bears no higher risk for postoperative morbidity.

Key Words: Rectal cancer · Neoadjuvant/adjuvant radiochemotherapy · Phase-III trial

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Adjuvante und neoadjuvante Radiochemotherapie beim lokal fortgeschrittenen Rektumkarzinom: Ein Zwischenbericht über die Phase-III-Rektumkarzinomstudie (Protokoll CAO/ARO/AIO 94)

Ziel: Die Standardbehandlung des operablen Rektumkarzinoms ist die sofortige Operation. Eine postoperative Radiochemotherapie wird für Patienten mit fortgeschrittenen Tumoren (pT3/4 oder pN+) empfohlen. In den letzten Jahren wurden vielversprechende Ergebnisse durch eine präoperative Bestrahlung erzielt. Wir beschreiben das Design einer prospektiv randomisierten Phase-III-Studie (CAO/ARO/AIO-94), die die Wirksamkeit einer neoadjuvanten Radiochemotherapie mit der postoperativen Standardbehandlung vergleicht, und berichten über erste Ergebnisse zur Toxizität der Radiochemotherapie und zur postoperativen Komplikationsrate.

Patienten und Methoden: Patienten mit lokal fortgeschrittenem operablen Rektumkarzinom (uT3/4 oder uN+, Mason CS III/IV) wurden auf den prä- oder postoperativen Radiochemotherapiearm randomisiert: Tumor(-bett) und pelvines Lymphabflussgebiet erhielten 50,4 Gy (Einzeldosis: 1,8 Gy). In der ersten und fünften Bestrahlungswoche erfolgte eine simultane 5-FU-Chemotherapie in einer Dosierung von 1000 mg/m^2/Tag, appliziert als 120-stündige Dauerinfusion. Vier weitere Zyklen 5-FU (500 mg/m^2/Tag, appliziert als Bolusgabe) schlossen sich an. Das Radiochemotherapieregime war in beiden Armen (bis auf einen Boost von 5,4 Gy im postoperativen Radiochemotherapiearm) identisch. Das Intervall zwischen Radiochemotherapie und Operation betrug in beiden Armen 4–6 Wochen. Die Operationstechnik war standardisiert und beinhaltete die totale Entfernung des Mesorektums. Außerdem erfolgte eine Stratifizierung nach beteiligten Chirurgen. Primäre Endpunkte der Studie sind das 5-Jahres-Überleben, die lokale und systemische Tumorkontrolle; sekundäre Endpunkte umfassen die Rate an R0-Operationen und kontinenzerhaltenden Verfahren, die Toxizität der Radiochemotherapie, die postoperative Komplikationsrate und die Lebensqualität.

Ergebnisse: Bis 15. November 2000 wurden 628 Patienten in 26 beteiligten Zentren randomisiert: 310 Patienten in den postoperativen Radiochemotherapiearm, 318 Patienten in den präoperativen Radiochemotherapiearm. Die Akuttoxizität war insgesamt gering; bei weniger als 15% der Patienten trat eine Grad-3- oder -4-Toxizität nach WHO auf. Die häufigste Nebenwirkung war die Diarrhö, die mit Grad 3 bzw. 4 bei 12% bzw. 1% im postoperativen Arm und mit 10% bzw. 1% im präoperativen Arm auftrat. Hauterythem, Übelkeit und Leukopenie waren weitere häufige Nebenwirkungen, Grad-3-Leukopenie und Übelkeit wurden bei weniger als 3% beobachtet. Die postoperative Komplikationrate war in beiden Armen ähnlich; nach sofortiger Operation (postoperative Radiochemotherapie) entwickelten 12% der Patienten, nach präoperativer Radiochemotherapie 13% eine Anastomoseninsuffizienz, bei 4% (postoperative Radiochemotherapie) und 3% (präoperative Radiochemotherapie) traten postoperative Blutungen, bei 6% (postoperative Radiochemotherapie) und 5% (präoperative Radiochemotherapie) Wundheilungsstörungen auf.

Schlussfolgerung: Die Patientenrekrutierung verläuft sehr zufriedenstellend. Die neoadjuvante Radiochemotherapie wird gut toleriert und erhöht die postoperative Komplikationrate nicht.

Schlüsselwörter: Rektumkarzinom · Neoadjuvante/adjuvante Radiochemotherapie · Phase-III-Studie

Introduction

Adjuvant treatment for rectal cancer is one of the major controversies in oncology today. The basic issues of whether or not to give radiotherapy, the timing of radiotherapy – preoperative versus postoperative –, whether or not to combine radiotherapy with concomitant chemotherapy and what regimen should be used in the individual patient, are of utmost importance, as rectal cancer is one of the most frequent cancer types in the western world. Currently, practice differs from Europe to the USA, between countries in Europe, and even between institutions within the same country.

In the last three decades, randomized studies have extensively investigated the role of radiotherapy in rectal cancer. At least two conclusions can be drawn from the data available by now: First, the combination of postoperative radiotherapy and 5-fluorouracil-(FU-)based chemotherapy has been shown in several trials to reduce local recurrence rates and to improve overall-survival compared with (conventional) surgery alone or surgery plus postoperative radiotherapy [4, 6, 18, 27, 34]. This prompted a National Cancer Institute Consensus Conference in the USA in 1990 [26] and a German Cancer Society Consensus Conference in 1999 [15] to recommend postoperative combined radiochemotherapy for patients with UICC Stage II and III rectal cancer as standard treatment. Second, preoperative radiotherapy is highly effective and can result in marked tumor shrinkage. In T4 tumors primarily not amenable to radical surgery preoperative radiotherapy in conventional fractionation, possibly combined with concurrent chemotherapy, is standard treatment in many institutions [22, 31, 35]. Recent results of the Swedish Rectal Cancer Trial in operable tumors have shown reduced local recurrence rates and improved overall survival with a short-term preoperative 5×5 Gy regimen compared with surgery alone [33]. Due to the short overall treatment time and the option of immediate surgery this concept is now used frequently in patients with operable carcinoma of the rectum throughout Europe. However, major radio- and tumorbiological shortcomings, among others the short interval between radiation therapy and surgery, which does not allow for significant tumor shrinkage and sphincter preservation in low lying tumors, and the high single dose, that may induce more acute and late toxicity, have also prompted criticism [24].

In 1995, we initiated a protocol comparing preoperative conventionally fractionated radiotherapy and concurrent 5-FU-chemotherapy with standard postoperative combined modality treatment in locally advanced (UICC Stage II/III) resectable rectal cancer (protocol CAO/ARO/AIO-94). Primary endpoints of this study are 5-year overall and relapse-free survival, locoregional and distant control, secondary endpoints include the rate of curative (R0) resections and sphincter saving procedures, acute and late toxicity of radiochemotherapy, surgical complications and quality of life.

As it has become increasingly clear in recent years that the surgeon himself is an important prognostic factor in controlling the local tumor and reducing morbidity [8, 11], optimized surgery and quality control are pivotal when assessing the effect of any (neo-)adjuvant therapy. Thus, techniques of surgery are strictly standardized and quality-controlled in our trial and include total mesorectal excision for tumors of the lower and middle part of the rectum [5]. In addition, stratification according to surgeons involved has been provided for. Pre-randomization assessment of intended surgical procedure (sphincter preservation possible or not) was included to evaluate the efficacy of preoperative radiochemotherapy to enable sphincter-sparing surgical procedures in low lying tumors. In this progress report we describe the rationale and design of our trial, the baseline characteristics of the patients, the acute toxicity of radiochemotherapy as well as postoperative complications for each treatment arm, to judge the feasibility of the trial.

Patients and Methods

Design of the Trial and Radiochemotherapy Regimen

This phase-III trial comparing standard adjuvant with neoadjuvant radiochemotherapy in operable carcinoma of the rectum was commenced in February 1995 under the auspices of the German Cancer Society. Candidates are patients with biopsy-proven operable primary rectal cancer staged to be UICC Stage II or III. Every effort is made to identify and exclude UICC Stage I and IV patients before randomization. Patients eligibility requirements and exclusion criteria are listed in Table 1.

After providing appropriate informed consent, eligible patients are randomized centrally at the Tumor Center of the University of Erlangen-Nürnberg to arm I (postoperative radiochemotherapy) or arm II (preoperative radiochemotherapy) as indicated in Figure 1. Stratification is performed according to the individual surgeon involved. Patients in arm I undergo immediate surgery. Chemotherapy is to begin after recovery from surgery within 4 weeks postoperatively and consists of six cycles of 5-FU. During radiotherapy 5-FU is scheduled as 120-hour continuous intravenuous infusion of 1,000 mg/m^2/day during the first and fifth week of radiotherapy. Outside concurrent radiochemotherapy, four more cycles of 5-FU are to be administered as bolus injection at a dose of 500 mg/m^2/day for five consecutive days repeated every 4 weeks for a total of six cycles. Radiotherapy is applied concurrently to the first and second or second and third cycle of chemotherapy. A total of 50.4 Gy (specified to the isocenter) is delivered in 28 fractions (single dose: 1.8 Gy) using a three- or four-field box technique with individually shaped portals in the prone position. Radiation therapy is designed to include the entire tumor bed, the perirectal, presacral and the internal iliac nodal groups. Thus, the superior border extends to the L5/S1 junction, the distal border is at the bottom of the obturator foramen after low anterior resection or includes the perineal scar after abdominoperineal resection (up to 45 Gy). Anteriorly, the border of the field extends to the dorsal wall of the bladder and the prostate/vagina. Posteriorly the sacrum has to be included. The lateral margins are designed to be 1–2 cm lateral of the linea terminalis. An additional boost is given to the tumor bed at 5.4 Gy for 3 days. Radiotherapy and chemotherapy are identical in the preoperative radiochemotherapy arm (arm II) except for the small volume boost that is omitted in this arm. Surgery is scheduled 4–6 weeks after completion of preoperative concurrent radiochemotherapy and four cycles

Table 1. Inclusion and exclusion criteria.

Tabelle 1. Einschluss- und Ausschlusskriterien.

Inclusion criteria
• Patients with histologically confirmed adenocarcinoma or mucinous adenocarcinoma of the rectum
• Tumor distal border located within 16 cm from anocutaneous line (as measured by means of an rigid rectosigmoidoscope)
• Age < 75 years
• Endosonographically > uT2 or uN+, stenosing or clinically advanced tumors (Mason CS III/IV)
• Tumor must be clinically resectable by anterior resection or abdominoperineal resection and R0 resection must be most likely
• Tumor has not arisen from chronic inflammatory bowel disease or hereditary polyposis disease
• Approved informed consent must be signed and dated before randomization
Exclusion criteria
• Patients with malignant disease of the rectum other than adenocarcinoma or mucinous adenocarcinoma
• Previous chemotherapy, radiotherapy, or immunotherapy to the pelvis
• Recurrent rectal cancer
• Locally advanced T4 rectal cancer not amenable to R0 resection
• Distant metastases (even if synchronously resectable)
• Synchronous colorectal cancer lesions
• Other previous or concurrent malignancies except basal cell carcinoma or spinocell carcinoma of the skin or in situ carcinoma of the cervix
• Any other morbidity or situation with contraindication for (neo-)adjuvant radiochemotherapy (e.g. cardiac failure, kidney failure, cirrhosis of the liver, immunsuppressive treatment, HIV-infection)
• Pregnant women or unreliable contraception
• Wish to bear children in female patients
• Patient declines randomization

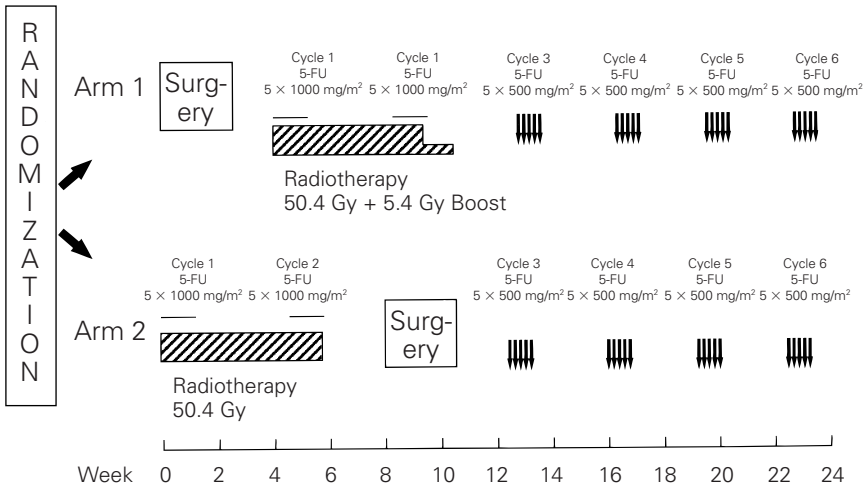

Figure 1. Design of the two-arm Rectal Cancer Study (Protocol CAO/ARO/AIO-94) comparing preoperative to postoperative radiochemotherapy in locally advanced rectal cancer (UICC Stage II/III).

Abbildung 1. Design der zweiarmigen Rektumkarzinomstudie (Protokoll CAO/ARO/AIO-94) zur adjuvanten und neoadjuvanten Radiochemotherapie des lokal fortgeschrittenen Rektumkarzinoms (UICC-Stadium II/III).

of 5-FU bolus injections are to be started within 3–4 weeks after surgery.

Pathological Examination

All resection specimen are examined according to a standardized protocol details of which will be published separately and which has been summarized by Hermanek recently [9, 10]. This results in a prospective standardized collection of pathology data including UICC TNM categories and stage grouping, number of examined and involved lymph nodes, status of resection margins as well as changes in the primary tumor following preoperative radiochemotherapy. Data are documented in a standardized form and are evaluated by a reference pathologist (C.W.) as to completeness and plausibility.

Assessment of Acute Toxicity and Perioperative Morbidity

During the (neo-)adjuvant period, patients are monitored for signs of hematologic and non-hematologic toxicity, physical examinations as well as blood cell counts and blood chemistry are performed every week, and chemotherapy dose is modified accordingly (leukocyte count 3,500–2,500 per µl or platelet count 100,000–80,000 per µl: reduction of the next course by 30%; leukocyte count < 2,500 per µl or platelet count < 80,000 per µl: delay of the next chemotherapy course until recovery). Toxicity is graded according to WHO's common toxicity criteria. This rates toxicities from 0 to 4, with 0 being the least and 4 the greatest toxicity. Perioperative and 30-day postoperative complications are obtained with regard to anastomotic leakage, wound healing impairment, postoperative bleeding, ileus, fistula to bladder, small bowel or vagina, cardiovascular complications and perioperative mortality.

Follow-up, Criteria for Recurrences, Late Sequelae and Quality of Life Assessment

The study protocol states that all patients are to be reevaluated at 3-month intervals for 2 years and every 6 months thereafter, for a total of 5 years. Evaluations consist of pertinent medical history, physical examination, complete blood counts and blood chemistry including carcinoembryonic antigen levels at every follow-up visit. Proctoscopy (if rectum is in place) is performed at 3-month intervals in the first year, at 6-month intervals in the second year and once per year thereafter. A follow-up schedule for abdominal ultrasound, computerized tomography studies of the abdomen and pelvis and chest X-rays is also defined at regular intervals. Histologic confirmation of locoregional and distant relapse is encouraged. Alternate acceptable criteria include sequential enlargement of a mass in radiologic studies. Isolated elevation of carcinoembryonic antigen levels, liver function test elevations or "suspicious" findings alone are not considered treatment failure. 1, 3 and 5 years after completion of therapy an evaluation of late treatment-related toxicity is scheduled with emphasis on skin reactions, stenosis or insufficiency at the anastomotic site and chronic side effects with regard to the small or large bowel and the bladder. Quality of life assessments take place before and after adjuvant treatment as well as 1, 3 and 5 years thereafter by means of the EORTC QLQ-C30 questionnaire [1, 17].

Quality Assurance

A quality-assurance program continuously controls information submitted on entry forms. Reference institutions (for surgery: R.R., Hannover; for radiochemotherapy: R.F., Rostock; for pathology: C.W., Leipzig) obtain copies of original treatment records, and may request any other pertinent information, including pathology specimen, simulation and portal films, dosimetry calculations etc., to confirm compliance with the treatment protocol. Moreover, institutional performance relative to data submission is reviewed every 6 months in more detail for arbitrarily selected patients at regular study meetings.

Statistical Analysis

This study is designed to have a power of 80% to detect a 10% increase in 5-year overall survival in the preoperative radiochemotherapy group with a significance level of 0.05 (two-sided). The sample size required to detect this difference is 340 patients per treatment arm. An estimated rate of ineligible patients of 10–15% is expected in both arms, thus, 750–800 pa-

tients need to be randomized. The respective endpoints are evaluated according to an "intent to treat" analysis as well as with regard to the actual treatment mode and within the per protocol population. In this preliminary analysis we only investigated safety issues, but not efficacy. Thus, this is not an interim analysis requiring adjustment of significance levels for statistical tests comparing treatment efficacy.

Results

CAO/ARO/AIO-94 protocol opened for accrual in February 1995. As of November 2000, 628 patients were randomized in 26 participating institutions (see appendix): 310 patients were randomized to the postoperative radiochemotherapy arm, 318 patients to the preoperative radiochemotherapy arm. Table 2 shows the patients' and tumor characteristics by randomization group. Age and gender are well balanced between the treatment arms. Pathologic tumor evaluation after surgery reveals a slightly higher percentage of UICC Stage-I and -II tumors, plus 18 patients with a pathologic complete response, and a lower percentage of tumors with positive lymph nodes (UICC Stage III) in the neoadjuvant radiochemotherapy arm, most probably due to "downstaging" effects of preoperative radiochemotherapy. In 22 and 18 patients, respectively, metastatic disease was discovered prior to or at the time of surgery (UICC Stage IV). Noteworthy is the rate of 18% of UICC Stage-I tumors in the immediate surgery group. These patients were staged clinically by means of endorectal ultrasound to have UICC Stage-II/III disease and were thus entered into the protocol, but turned out to have pT1–2 pN0 disease, and were consequently excluded from postoperative radiochemotherapy. As the same clinical staging error should apply to the preoperative radiochemotherapy group, the percentage of 18% also represents the risk of "overtreatment", when radiochemotherapy is applied preoperatively before pathologic confirmation of locally advanced, i. e. Stage-II and -III disease.

Table 2. Patients- and tumor characteristics by randomization group. [a]The final stage based on histopathologic assessment of the resected specimen is given for the two treatment arms.

Tabelle 2. Patienten- und Tumorcharakteristik nach Randomisationsgruppe.

	Adjuvant radiochemotherapy	Neoadjuvant radiochemotherapy
Number of patients	310	318
Median age (years)	60	59
Gender (male/female)	206/104	228/90
UICC stage (pathologic[a])		
No tumor	1 (0.3%)	18 (6%)
Stage I	57 (18%)	67 (21%)
Stage II	85 (27%)	92 (29%)
Stage III	115 (37%)	76 (24%)
Stage IV	24 (8%)	19 (6%)
Not known	28 (9%)	46 (14%)

Acute Toxicity of Radiochemotherapy

Complete toxicity information for concurrent radiochemotherapy and four additional 5-FU maintenance cycles is available for 162 patients in arm I (for a total of 972 cycles) and for 230 patients in arm II (for a total of 1,380 cycles). As this study is ongoing, not all patients have already completed treatment and not all case report forms have been received, which automatically results in missing data. Figure 2 demonstrates the highest grade toxicity for any course of therapy in the respective treatment arm. The principal toxicity was diarrhea, with 12% in the postoperative radiochemotherapy arm and 10% in the preoperative radiochemotherapy arm having Grade-3, and 1% in either arm having Grade-4 diarrhea. Erythema, nausea and leukopenia were the next common toxicities with fewer than 3% of patients in either arm suffering Grade-3 or greater leukopenia or nausea. One patient died from pulmonary embolism while receiving therapy in the postoperative radiochemotherapy arm and three patients died while receiving therapy in the preoperative radiochemotherapy arm. Arm-II deaths included two cases of myocardial infarction, that occurred during or shortly after the first 5-FU chemotherapy cycle, and one case of pulmonary embolism.

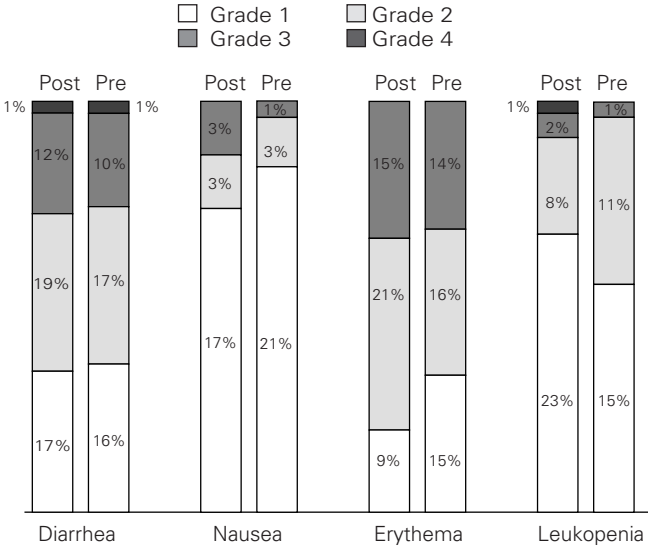

Figure 2. Acute toxicity of radiochemotherapy. The highest grade (WHO) for any of the two concomitant radiochemotherapy cycles or the four additional chemotherapy cycles is plotted. Grade-0 toxicity is not plotted, thus, numbers in the respective columns do not add up to 100%.

Abbildung 2. Akuttoxizität der Radiochemotherapie. Angegeben ist der jeweils höchste Toxizitätsgrad (WHO), der während der zwei simultanen Radiochemotherapiekurse oder der vier weiteren Chemotherapiekurse erreicht wurde. Grad-0-Toxizität wird in den jeweiligen Säulen nicht dargestellt, sodass sich die Zahlen nicht zu 100% addieren.

Table 3. Postoperative complications.

Tabelle 3. Postoperative Komplikationen.

	Adjuvant radiochemotherapy (n = 280)	Neoadjuvant radiochemotherapy (n = 258)
Anastomotic leak	12%	13%
Postoperative bleeding	4%	3%
Delayed wound healing	6%	5%
Intestinal obstruction	1%	3%
Fistula to bladder	1%	1%
Fistula to small intestine	1%	0%
Retrovaginal fistula	2%	1%
Cardiovascular	3%	2%
Other	4%	6.5%
Total	34%	34.5%

Postoperative Complications

Data for surgical mortality and morbidity are available for 280 and 258 patients in the postoperative and preoperative radiochemotherapy arm, respectively. In total, there were five surgical deaths, three patients died after immediate surgery (1%) from cardiac failure (n = 2) or sepsis (n = 1). Two patients died after preoperative radiochemotherapy and surgery (0.8%) from cardiac failure (n = 1) or sepsis (n = 1). Overall postoperative complication rates were similar in both arms, with 34.0% of patients in the immediate surgery arm and 34.5% of patients after preoperative radiochemotherapy suffering from surgical complications. Table 3 shows the distribution of complications in both treatment groups. For integrity at the anastomotic site any grade, including only radiologically verified leakage without clinical symptoms, is given. Most of the complications were minor and could be treated conservatively, with only 14 patients in the immediate surgery arm (5%) and 17 patients in the preoperative radiochemotherapy arm (6.5%) requiring reoperations due to postoperative complications.

Discussion

Rationale of the Study: Potential Advantages of Pre- and Postoperative Radiochemotherapy

The interest in preoperative radiochemotherapy for resectable tumors of the rectum is based not only on the success of adjuvant radiochemotherapy in the postoperative setting, but also on the numerous potential advantages of delivering radiation treatment preoperatively. Among those are "downstaging" or "downsizing" effects that possibly enhance the rate of curative (R0) surgery in locally advanced rectal cancer [31, 35], and may enable sphincter preservation in low lying tumors [7, 20, 32, 36]. In addition, a certain dose of irradiation seems to be more effective if given preoperatively compared with postoperatively, most probably due to the fact that oxygen tension within the tumor may be higher prior to surgical compromise of the regional blood flow [28, 29]. As the small bowel in an unviolated abdomen will be mobile and less likely to be tethered within a pelvic radiation portal, preoperative irradiation may also cause less acute and late toxicity. On the other hand, a major concern regarding preoperative radiation therapy is that patients with early stage tumors (UICC Stage I) will receive unnecessary treatment. Moreover, neoadjuvant treatment usually postpones definitive surgery considerably and may also be associated with increased postoperative morbidity.

Prospective randomized trials comparing the efficacy of preoperative radiochemotherapy to standard postoperative radiochemotherapy resectable UICC Stage-II and -III rectal cancer were initiated in the United States by the Radiation Therapy Oncology Group (RTOG 94-01) [21] and the NSABP (R-03) [14] as well as in Germany (CAO/ARO/AIO-94). Unfortunately, both US trials suffered from lack of accrual and have already been closed. The accrual of the German multicenter study is going well with a total of 628 patients having already been recruited until November 2000. The preliminary results with regard to baseline characteristics of patients, toxicity of radiochemotherapy and postoperative morbidity clearly demonstrate the feasibility of our trial. We will discuss some important aspects of our progress report.

Risk of Overtreatment of Early Stage Tumors in the Neoadjuvant Radiochemotherapy Arm

Accurate pretreatment staging is imperative with the use of preoperative multimodal treatment to avoid unnecessary treatment in early stage rectal carcinoma. According to data from the literature, staging of rectal cancer by digital examination is accurate in only 40–60% of the cases [25]. Accuracy of computed tomography is estimated between 50 and 75% [19]. Accuracy of endoluminal ultrasound is reported to be 75–94% for tumor penetration and 72–83% for nodal metastases [2]. In our study, pretreatment evaluation of the tumor by transrectal ultrasound is mandatory for non-stenosing lesions. Thus, only 18% of patients in the immediate surgery arm, staged preoperatively to have tumor penetration through the bowel wall (uT3) or lymph node metastasis (uN+), turned out to have pT1–2 pN0 tumors on pathologic evaluation of the resected specimen. As this overstaging error should also apply to the preoperative radiochemotherapy arm, the risk of "overtreatment" in the neoadjuvant radiochemotherapy arm probably lies between 15 and 20%. This rate seems quite acceptable, especially if one takes into account that the experience of investigators with this method may vary considerably within a multicentric study. As more experience is acquired quality should increase in the future. Moreover, innovative techniques, including three-dimensional endosonography, may further improve accuracy of staging [13].

Toxicity of Radiochemotherapy

Overall treatment-related toxicity was low with less than 15% of all patients experiencing Grade-3 or higher side effects. This figure also mirrors the high quality of radiation treatment, in-

cluding conformal radiotherapy and 3-D treatment planning, and underlines the low toxicity profile of a conventionally fractionated radiotherapy regimen. WHO Grade-4 toxicity was restricted to three patients in the postoperative radiochemotherapy arm (two patients with severe diarrhea necessitating hospitalization and intravenous rehydration, one patient with leukopenia < 1000 per µl) and to two patients in the preoperative radiochemotherapy arm (both with severe diarrhea). Noteworthy, however, are the two patients in the preoperative arm who died from myocardial infarction that had occurred in close relation to the administration of 5-FU chemotherapy. Although this cardiotoxic effects of 5-FU are rare, a close monitoring of patients during chemotherapy and exclusion of patients with cardiac symptoms or a previous history of severe heart disease seems advisable. Advocates for neoadjuvant radiochemotherapy have often claimed a lower treatment-related toxicity with the preoperative approach [23, 30]. Albeit in our study overall toxicity was quite similar for both arms, we noted a tendency towards reduced gastrointestinal acute side effects in the preoperative radiochemotherapy arm. Whether or not this may also translate to the more relevant consequential late effects needs to be awaited.

Postoperative Complications

Before starting the trial, some surgeons were concerned that postoperative morbidity and mortality would increase after preoperative radiochemotherapy. Higher postoperative complication rates were described in the early Swedish series using short-course preoperative radiation therapy with high single fractions to shorten the time interval to surgery [3, 12]. Although these rates have been markedly reduced in recent years by more sophisticated radiation techniques (multiple fields, reduced treatment volume), the current trial of the Dutch ColoRectal Cancer Group comparing optimized surgery with total mesorectal excision (TME) alone to preoperative short course radiation (5×5 Gy) plus total mesorectal excision in rectal cancer has again revealed some adverse effects of this irradiation regimen at the time of surgery (especially with regard to infective complications and intraoperative blood loss) [16]. Conversely, in our study, surgical complications were similar in both arms, with no compromise of the anastomotic integrity and no increased rate of infective or other complications following preoperative radiochemotherapy. We conclude from these findings that our regimen of conventionally fractionated preoperative radiochemotherapy, plus a rest period of at least 4 weeks before surgery to allow for tumor shrinkage and recovery from toxic side effects, does not affect surgical morbidity.

Conclusion

Due to the premature closure of the RTOG 94-01- and the NSABP R-03-protocol in the United States this phase-III trial is the only one worldwide that continues to recruite patients to evaluate the potential advantages of preoperative radiochemotherapy over standard postoperative radiochemotherapy in resectable Stage-II/III rectal cancer. This present interim analysis regarding toxicity data, surgical complications and treatment-related deaths obviously confirms feasibility. Recruitment is going well with more than 620 patients randomized until November 2000. Based on an actual accrual rate of 150 patients per year, the expectation is that the trial will close in autumn 2001 with a total of 800 patients included. After that, further reporting will take place.

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Appendix

Participating Institutions

I. Surgery

Zentralklinikum Augsburg
Klinik für Allgemein- und Viszeralchirurgie

Evangelische Diakonissenanstalt Bremen
Chirurgische Klinik

Klinikum Coburg, I. Chirurgische Klinik
Allgemein-, Viszeral und Gefäßchirurgie

Klinikum der Carl-Gustav-Carus-Universität Dresden
Klinik und Poliklinik für Viszeral-, Thorax- und Gefäßchirurgie

Städtisches Klinikum Dresden-Friedrichstadt
Klinik für Allgemein- und Abdominalchirurgie

Klinikum der Friedrich-Alexander-Universität Erlangen-Nürnberg
Chirurgische Klinik mit Poliklinik

Waldkrankenhaus St. Marien Erlangen
Chirurgische Abteilung

Klinikum der Johann-Wolfgang-Goethe-Universität Frankfurt
Zentrum der Chirurgie
Klinik für Allgemeinchirurgie

Krankenhaus Nordwest Frankfurt
der Stiftung Hospital zum heiligen Geist
Chirurgische Klinik

Wald-Klinikum Gera
Allgemeine, Viszerale und Kinderchirurgie
Chirurgisches Zentrum

Georg-August-Universität Göttingen
Klinik und Poliklinik für Allgemeinchirurgie

St. Elisabeth-Krankenhaus Halle
Abteilung für Allgemein- und Viszeralchirurgie

Martin-Luther-Universität Halle-Wittenberg
Medizinische Fakultät, Klinik für Allgemeinchirurgie, Klinikum Kröllwitz

Medizinische Hochschule Hannover
Klinik für Abdominal- und Transplantationschirurgie
Zentrum Chirurgie

Klinikum Hannover-Siloah
Zentrum für Minimal Invasive Chirurgie
Chirurgische Klinik

Klinikum der Friedrich-Schiller-Universität Jena
Allgemeine und Viszerale Chirurgie
Chirurgische Klinik

Christian-Albrechts-Universität zu Kiel
Klinik für Allgemeine Chirurgie und Thoraxchirurgie

Universitätsklinikum Leipzig
Chirurgische Klinik und Poliklinik I
Zentrum für Chirurgie

Klinikum Landshut
Chirurgische Klinik

Universitätsklinikum Leipzig
Chirurgische Klinik und Poliklinik II,
Klinik für Abdominal-, Transplantations- und Gefäßchirurgie

St. Elisabeth-Krankenhaus Leipzig
Abteilung für Chirurgie

Friedrich-Ebert-Krankenhaus Neumünster
Chirurgische Klinik

Universität Regensburg
Klinik und Polikinik für Chirurgie

Diakoniekrankenhaus Rotenburg
I. Chirurgische Klinik für Allgemein-, Viszeral- und Thoraxchirurgie

Krankenhaus der Barmherzigen Brüder
St. Veit, Österreich
Chirurgische Abteilung

Krankenanstalt Mutterhaus der Borromäerinnen, Trier
Abteilung für Chirurgie

Paul-Gerhardt-Stiftung Wittenberg
Klinik für Allgemein-, Viszeral und Gefäßchirurgie

II. Radiotherapy

Zentralklinikum Augsburg
Klinik für Strahlentherapie

Evangelische Diakonissenanstalt Bremen
Klinik für Strahlentherapie

Zentralkrankenhaus St.-Jürgen-Straße Bremen
Klinik für Strahlentherapie

Gemeinschaftspraxis Dres. Romahn, Brinster, Latz
am Klinikum Coburg
Praxis für Strahlentherapie, Radiologie und Diagnostische Radiologie

Klinikum der Carl-Gustav-Carus-Universität Dresden
Klinik und Poliklinik für Strahlentherapie und Radioonkologie

Städtisches Klinikum Dresden-Friedrichstadt
Abteilung für Strahlentherapie

Klinikum der Friedrich-Alexander-Universität Erlangen-Nürnberg
Klinik und Poliklinik für Strahlentherapie

Klinikum der Johann-Wolfgang-Goethe-Universität Frankfurt
Zentrum der Radiologie
Abteilung für Strahlentherapie

Krankenhaus Nordwest Frankfurt
Radioonkologische Klinik

Wald-Klinikum Gera
Klinik für Stahlentherapie und Radioonkologie

Georg-August-Universität Göttingen
Klinik und Poliklinik für Strahlentherapie und Radioonkologie

Martin-Luther-Universität Halle-Wittenberg
Medizinische Fakultät, Klinik und Poliklinik für Strahlentherapie

Medizinische Hochschule Hannover
Abteilung für Strahlentherapie und spezielle Onkologie

Klinikum der Friedrich-Schiller-Universität Jena
Klinik für Radiologie
Abteilung Strahlentherapie

Christian-Albrechts-Universität zu Kiel
Radiologische Universitätsklinik
Klinik für Strahlentherapie

Radiologische Gemeinschaftspraxis Kiel
Strahlentherapie

Landeskrankenhaus Klagenfurt, Österreich
Strahlentherapeutisches Institut

Klinikum Landshut
Abteilung für Strahlentherapie

Universitätsklinikum Leipzig
Klinik und Poliklinik für Strahlentherapie und Radioonkologie

Friedrich-Ebert-Krankenhaus Neumünster
Abteilung für Strahlentherapie und Radiologie

Universität Regensburg
Klinik und Poliklinik für Stahlentherapie

Diakoniekrankenhaus Rotenburg
Abteilung für Strahlentherapie und Radiologie

Krankenanstalt Mutterhaus der Borromäerinnen, Trier
Abteilung für Strahlentherapie

III. Internal Medicine

Zentralklinikum Augsburg
II. Medizinische Klinik

Evangelische Diakonissenanstalt Bremen
Medizinische Klinik, Hämatologie und internistische Onkologie

Klinikum Coburg, I. Medizinische Klinik
Abteilung für Internistische Gastroenterologie

Städtisches Klinikum Dresden-Friedrichstadt
I. Medizinische Klinik

Gemeinschaftspraxis Dres. Wolf, Freidt
Praxis für Innere Medizin, Hämatologie und Internistische Onkologie
Dresden

Medizinische Hochschule Hannover
Abteilung Hämatologie und Internistische Onkologie

Klinikum Hannover-Siloah
Medizinische Klinik III für Hämatologie und Onkologie

Klinikum Landshut, Medizinische Klinik I

Friedrich-Ebert-Krankenhaus Neumünster
Medizinische Klinik

Universität Regensburg
Klinik und Poliklinik für Chirurgie und Innere Medizin I, Proktologische Ambulanz

IV. Pathology

Zentralklinikum Augsburg
Institut für Pathologie

Zentralkrankenhaus Bremen-Nord
Institut für Pathologie

Klinikum Coburg, Abteilung für Pathologie

Klinikum der Carl-Gustav-Carus-Universität Dresden
Institut für Pathologie

Städtisches Klinikum Dresden-Friedrichstadt
Institut für Pathologie

Klinikum der Friedrich-Alexander-Universität Erlangen-Nürnberg
Institut für Pathologie

Klinikum der Johann-Wolfgang-Goethe-Universität Frankfurt
Senckenbergisches Institut für Pathologie

Krankenhaus Nordwest Frankfurt
Institut für Pathologie

Wald-Klinikum Gera
Abteilung für Pathologie

Georg-August-Universität Göttingen
Pathologisches Institut

Martin-Luther-Universität Halle-Wittenberg
Medizinische Fakultät, Institut für Pathologie

Medizinische Hochschule Hannover
Pathologisches Institut

Städtisches Krankenhaus Hannover-Nordstadt, Pathologisches Institut

Klinikum der Friedrich-Schiller-Universität Jena
Institut für Pathologie

Christian-Albrechts-Universität zu Kiel
Institut für Allgemeine Pathologie und Pathologische Anatomie

Klinikum Landshut, Pathologisches Institut

Universitätsklinikum Leipzig
Institut für Pathologie

Gemeinschaftspraxis Dres. Rosenkranz, Uhl
Institut für Pathologie am Elsapark
Leipzig

Kreiskrankenhaus Rendsburg
Akademisches Lehrkrankenhaus für die Universität Kiel, Pathologisches Institut

Universität Regensburg, Institut für Pathologie

Diakoniekrankenhaus Rotenburg
Institut für Pathologie

Gemeinschaftspraxis Prof. Mäusle, Dres. Uhl, Hinkedey
Pathologisches Institut, Trier

Kaiser-Franz-Josef-Spital Wien, Österreich
Pathologisch-bakteriologisches Institut

Paul-Gerhardt-Stiftung Wittenberg
Klinikbereich Paul-Gerhardt-Stift
Institut für Pathologie