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REVIEW

Adjuvant and Neoadjuvant Radiotherapy and Concurrent Radiochemotherapy for Rectal Cancer

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Radical surgery with negative margins remains the most important prognostic factor in the treatment of rectal cancer. Combined modality treatment is the recommended standard adjuvant therapy for patients with locally advanced rectal cancer in the USA and in Germany. During the last decade substantial progress has been made in treatment modalities: surgical management currently includes a broad spectrum of operative procedures ranging from radical operations to innovative sphincter-preserving techniques. Specialized groups have reported excellent local control rates with total mesorectal excision (TME) alone. New and improved radiation techniques (conformal radiotherapy, intraoperative radiotherapy) and innovative schedules (protracted intravenous infusion, chronomodulated infusion) and combinations (oxaliplatin, irinotecan) of chemotherapy may have the potential to further increase the therapeutic benefit of adjuvant treatment. Moreover, the basic issue of timing of radio-(chemo-)therapy - preoperative versus postoperative - within a multimodality regimen is currently being addressed in prospective trials. Evidently, the current monolithic approaches, established by studies conducted more than a decade ago, to apply either the same schedule of postoperative radiochemotherapy to all patients with stage II/III rectal cancer or to give preoperative intensive short-course radiation according to the Swedish concept for all patients with resectable rectal cancer irrespective of tumor stage and treatment goal (e.g. sphincter preservation), need to be questioned. This review will discuss different irradiation settings in more recent and ongoing studies of perioperative radiotherapy for rectal cancer and will focus on the issue which patient should receive radiotherapy at all, and if so, how and when? (Pathology Oncology Research Vol 8, No 1, 7–17, 2002)

Keywords: rectal cancer, radiotherapy, radiochemotherapy

Introduction

Adjuvant treatment for rectal cancer is one of the major controversies in oncology today. The questions of whether or not to give radiotherapy, which patients may benefit from pre-, post- or intraoperative radiotherapy, whether or not to combine radiotherapy with concomitant chemotherapy and what regimen should be used, 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.

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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 until now: (1) Radiotherapy combined with 5-Fluorouracil-chemotherapy is more effective than radiotherapy alone in the adjuvant setting. This prompted a National Cancer Institute Consensus Conference in the USA in 1990[1] and a German Cancer Society Consensus Conference in 1999[2] to recommend postoperative combined radiochemotherapy for patients with UICC-stage II and III rectal cancer as standard treatment. These recommendations are, however, challenged by more recent reports of extraordinarily low local failure rates following improved surgical techniques, including total mesorectal excision (TME), even without the addition of adjuvant therapy.[3,4] (2) Preoperative radiotherapy is highly effective and can result in marked tumor shrinkage. In T4-tumors primarily not amenable to radical surgery and in locoregional recurrent

disease, preoperative radiotherapy in conventional fractionation with concurrent chemotherapy, possibly also combined with intraoperative radiotherapy (IORT), is standard treatment in many institutions. Intensive, short-course preoperative radiotherapy according to the Swedish concept (5 × 5 Gy) is now used frequently in patients with resectable rectal cancer due to the short overall treatment time and the option of immediate surgery. However, major radio- and tumorbiological shortcomings have also prompted criticism. Current clinical trials investigate the role of preoperative short-course radiotherapy with TME as integral part of surgery and the role of combined preoperative as compared to postoperative radiochemotherapy for resectable stage II and III rectal cancer.

This review will discuss the more recent and ongoing studies of perioperative radiotherapy for rectal cancer and will comment on the question: Which patient should receive radiotherapy – to what end and how?

Local Control After Surgery Alone – Indications For Radiotherapy

The occurrence of a locoregional relapse substantially influences the overall prognosis. Evaluation of our own data demonstrated that the 5-year overall survival rate after curative surgery was 85% for patients without local recurrence. Otherwise, the 5-year survival rate dropped to 23% for patients with local relapse.[4] The risk of local relapse is clearly related to the depth of tumor extension through the bowel wall and the presence or absence of nodal involvement. A retrospective analysis of more than 770 patients, operated on between 1984 and 1996 at the Department of Surgery of the University of Erlangen, demonstrated an overall local recurrence rate of 14% and an overall 5-year survival rate of 71,2 % after curative surgery without adjuvant radiotherapy (*Table 1).* Local control and survival were excellent in stage I disease, but decreased markedly with more extensive tumor penetration (> pT3a/b) and nodal involvement. While it is clear from these data that patients with stage I disease do not generally require adjuvant treatment after curative surgery, and that those with multiple lymph node involvement (stage III) urgently do, it is less clear whether all patients with stage T3N0 rectal cancer will benefit from adjuvant radiotherapy. As we and others have demonstrated,[6] the extent of tumor invasion into perirectal fat as well as other anatomic and biologic determinants like lymphatic, vascular or neural invasion, tumor grade, integrity of the radial resection margin and location of the tumor in the upper, middle or lower part of the rectum can substantially influence the risk for local recurrences. For the subset of patients with histologically favorable T3N0 rectal cancer with minimum invasion into the perirectal tissue (pT3a/b), there is probably little benefit of adjuvant radiotherapy. However, only prospective clinical trials including a surgical control arm employing modern surgical procedures can definitively determine the best treatment strategy in these settings.

Table 1. **Five-year local failure rates and 5-year overall survival rates after curative surgery (R0) alone according to tumor stage and perirectal invasion depth. Data from 775 patients operated on from 1/1984 to 12/1996 at the Dept. of Surgery; University of Erlangen, Germany (personal communication: S. Merkel, W. Hohenberger).**

	5-Year local failure (%)	*5 –Year overall survival (%)*
All patients (n = 776)	14	71,2
UICC stage I		
pT1 pN0 (n = 60)	1,7	94,9
pT2 pN0 (n = 145)	6,5	87,9
UICC stage II		
pT3a / b pN0 (n = 128)	4,4	87,8
pT3c pN0 (n = 60)	14,8	74,4
pT3d pN0 (n = 43)	18,0	67,2
pT4 pN0 (n = 20)	10,6	63,5
UICC stage III		
pT1-4 pN1 (n = 183)	18,3	66,8
pT1-4 pN2 (n = 137)	32,3	35

pT3a-d = perirectal tumor invasion depth < 1mm (a), > 1-5 mm (b), > 5-15 mm (c), > 15 mm (d).

The scenario becomes increasingly complex if one considers that local recurrence rates after surgical excision of a rectal cancer vary enormously in reported series. Figures less than 5% contrast with figures of more than 30%. These differences can not be explained exclusively by patient selection or different definitions of radicality or local failure, but also suggest an influence of the experience and skills of the individual surgeon. The German Study Group Colorectal Carcinoma (SGCRC) has recently demonstrated a huge difference in local recurrence rate among institutions and individual surgeons, ranging from 5% to 55%, and has thus established the surgeon himself as an important prognostic factor in rectal cancer.[7,8] Therefore, every effort should be made in the future to incorporate technical surgical requirements into guidelines and to assure their proper implementation into daily practice. The answer to the question, "which patients should be offered adjuvant radiotherapy," not only non depends on tumor characteristics but also on the results obtained by surgery alone. If modern surgical procedures, including total mesorectal excision, are strictly applied and the institution, in general, has a low local failure rate (<10-15%) with surgery alone, adjuvant radiotherapy may be applied in a risk-adapted manner, at least in subgroups of stage II rectal cancer.

Standard Treatment In Resectable Rectal Cancer: Postoperative Radiochemotherpy

The combination of postoperative radiotherapy and 5-fluorouracil-based chemotherapy has now been shown in several randomised trials to reduce local recurrence rates and to improve overall-survival compared with (conventional) surgery alone or surgery plus postoperative radiotherapy (*Table 2*). In 1990, the results of two randomized trials, the GITSG and the Mayo/NCCTG, led to a National Institutes of Health Consensus Conference recommendation that all patients with stage II or III rectal cancer should receive postoperative combined modality treatment.[1] Further trials by the GITSG[12] and Mayo/NCCTG[13] investigated the need for semustine in the chemotherapy regimen and found that it added no benefit to the 5-FU-regimen. In addition, 5-FU-continuous infusion rather than bolus injection was shown to be superior in terms of the development of overall recurrences, distant metastases, and 4-year overall survival.[13] In 1999, the German Cancer Society Consensus Conference has adopted the recommendation of postoperative combined modality treatment for patients with stage II and III rectal cancer outside clinical trials.[2] However, as poor quality of surgery in these previous trials with local failure rates up to 30% led to major criticism among surgeons, it was also concluded in the recent German Consensus, that the role of adjuvant treatment in rectal cancer needs to be re-defined within randomized studies that include modern surgical procedures (TME) and a surgical control arm. The Dutch Colorectal Cancer Group is currently conducting a two-arm randomized study of total mesorectal excision with or without short course preoperative radiotherapy in primary rectal cancer. This trial, which includes strict quality control of operative and histopathogical techniques, will clarify whether the extraordinarily low local failure rates reported in some mono-institutional series with optimized surgery alone can be reproduced in a large, randomized multicenter study and whether radiotherapy reduces local recurrences even if surgery is optimized. The accrual was excellent and was closed in January 2000 with more than 1800 patients included. Preliminary results with regard to local failure rates in both arms were recently published and indicated a highly significant reduction of local failure when preoperative radiotherapy was added to surgery (2.4% versus 8.2% with TME-surgery alone, $p<0.001$).[14]

The results of the recently published NSABP-R-02 trial,[15] which compared postoperative chemotherapy alone with postoperative radiochemotheray in locally advanced rectal cancer, are likely to spur further discussions in the oncology community concerning the role of adjuvant radiation therapy as part of standard treatment of locally advanced rectal cancer after surgical resection. Although the addition of radiotherapy was associated with a significant reduction in locoregional recurrences, from 13% for postoperative chemotherapy alone to 8% for the combined modality therapy ($p=0.02$), there was no significant benefit in relapse-free and overall survival.

However, the wholesale elimination of radiation therapy as a component of standard adjuvant treatment in advanced rectal cancer would certainly seem to be premature. First of all, the NSABP R-02 trial has once again confirmed the high efficacy of radiotherapy to improve local control - even in a situation, where local failure rates were commonly low after surgery. In the preceding NSABP R-01 protocol,[16] as much as 25% of patients experienced a locoregional recurrence after surgery alone, a rate, that has now been reduced to 13% by evidently more appropriate surgery and adjuvant chemotherapy and further reduced to

Table 2. **Randomized postoperative radiation and chemotherapy trials of rectal cancer**

Trial and Trial Arms	*Local Failure (%)*	*Distant Failure (%)*	*5-Year Overall Survival (%)*
GITSG (1986) [9]			
Surgery alone	24	34	44
Surgery + RT	20	30	52
Surgery + CT	27	27	50
Surgery + RCT	11	26	59
NSABP R-01 (1998) [16]			
Surgery alone	25	26	48
Surgery + CT	21	24	58
Surgery + RT	16	31	50
Mayo/NCCTG (1991) [10]			
Surgery + RT	25	46	48
Surgery + RCT	14	29	57
Tveit et al. (1997) [11]			
Surgery alone	30	39	50
Surgery + RCT	12	33	64
NSABP R-02 (2000) [15]			
Surgery + CT	13	29	65
Surgery + RCT	8	31	66

Abbreviations: RT: Radiation Therapy, CT: Chemotherapy, RCT: Radiochemotherapy

8% by the addition of postoperative radiation. Given the dismal prognosis of patients with pelvic recurrences and the substantial morbidity and attenuation in quality of life associated with it, the prevention of such failures alone is a worthy outcome. Therefore, it is pivotal to identify those patients with particularly high risk of local failure. Interestingly, the NSABP R-02 study found that potential benefit from radiation therapy would have occurred in patients less than 60 years of age and in those undergoing abdominoperineal resection. Thus, not every patient with advanced rectal cancer, who is now eligible for postoperative combined treatment protocols, will be so in the future. However, until innovative clinical trials have established the optimal therapy for the respective subgroups of patients with curatively resected rectal cancer, postoperative combined modality therapy remains the benchmark to which other approaches need to be compared. From the radiotherapeutic point of view, we merely wish to suggest for the design of upcoming studies:

- to ensure not only surgical but also radiotherapeutic quality control and to allow only the most recent and modern radiation techniques with 3D-treatment planning and multiple field techniques to reduce acute and late toxicities, which were considerable in former studies due to inappropriate techniques and may have compromised the efficacy of radiation therapy.[17,18]
- to shorten the interval between surgery and postoperative radiotherapy to 4-6 weeks maximum. In most protocols, including the NSABP R-02, irradiation was only initiated 50 to 80 days after surgery. This delay probably enhances the repopulation of tumor cells and may create a tumor burden that is too great to be eradicated with a standard total irradiation dose of 45-50 Gy.[19]
- to make use of the radiosensitizing properties of 5-fluorouracil by either a bolus injection 30 minutes before radiotherapy fractions or, probably even more effective, by a continuous intravenous infusion during the whole course of radiotherapy.

Several studies are currently being carried out to improve the systemic treatment component in postoperative radiochemotherapy, mainly by modulators to bolus 5-FU- based chemotherapy. Preliminary results of a four-arm intergroup trial, INT 0114, showed no significant differences in local control and survival among patients receiving either 5-FU bolus, 5-FU+folinic acid, 5-FU+levamisol or 5-FU+folinic acid+levamisol.[20] However, gastrointestinal toxicity was higher in folinic acid containing regimens. The largest German adjuvant rectal cancer trial (*Forschungsgruppe Onkologie Gastointestinaler Tumore* – FOGT 2) is comparing 5-FU+levamisol to 5-FU+levamisol+folinic acid or 5-FU+levamisol+interferon alpha as systemic treatment added to 50.4 Gy of radiotherapy.[20] Toxicity was highest in the interferon containing arm, long term results are pending. Future trials in rectal cancer should also address combination chemotherapy regimen given concurrently or sequentially with radiation, such as 5-FU with either irinotecan or oxalipaltin. These combinations have already shown superior response rates compared to 5-FU alone in metastatic colorectal cancer.[22,23]

Preoperative Radiation Therapy

Among the potential advantages of the preoperative approach are downstaging and downsizing effects that possibly enhance curative (R0) surgery in locally advanced, e.g. T4-rectal cancer, and sphincter preservation in low-lying rectal cancer. Moreover, neoadjuvant therapy may be advantageous also in resectable rectal cancer as sterilization of the tumor cells prior to surgery may reduce the risk of tumor cell spillage during surgery. The small bowel in an unviolated abdomen will be mobile and less likely to be within a pelvic radiation portal, the irradiated volume does not require coverage of the perineum, as in the cases after abdominoperineal resection, and there is no irradiation of the anastomotic region. Thus, preoperative irradiation may cause less acute and late toxicity and more patients will receive full-dose radiation therapy.[24,25] 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. This may improve the radiosensitivity of the tumor by decreasing the more radioresistent hypoxic fraction. A major concern for preoperative radiation therapy is that patients with early stage tumors or disseminated disease will often receive unnecessary treatment, necessitating improved imaging techniques that allow more accurate selection of patients. Moreover, neoadjuvant treatment usually postpones definitive surgery considerably and may also be associated with increased postoperative morbidity. Technically, there are two approaches to preoperative radiation therapy. The first one is an intensive short-course radiation with large fractions, e.g. 5 x 5 Gy, for one week followed by surgery within one week. The second includes 5 to 6 weeks of conventional fractionation (1.8-2.0 Gy), possibly combined with concurrent chemotherapy, and surgery 4 to 6 weeks later.

Intensive Short-Course Therapy

In an attempt to improve results in „resectable“ rectal cancer, a number of studies with various preoperative fractionation schedules, mainly intensive, short courses of radiation, were carried out in the 1970‘s and 1980‘s. The results of these trials were reviewed by Påhlman et al.[26] In

summary, while a significant decrease in local failure was shown at least in studies with higher doses, e. g. 25 Gy in five fractions, either no significant improvement in survival was observed or the benefit was restricted to subgroups.

The Swedish Rectal Cancer Trial, conducted between 1987 and 1990, was the first randomized trial to show a survival advantage for the total patient group according to an intention-to-treat analysis.[27] One thousand one hundred sixty-eight patients with resectable rectal cancer were randomized to one of the two treatment arms: surgery alone or 25 Gy in five fractions followed by surgery within one week. The addition of preoperative radiation significantly decreased the rate of local failure from 27% to 12% ($p<0.001$) and improved 5-year survival from 48% to 58% ($p=0.004$). This benefit was seen in all stages. Thus, the results of this large study with a clear and simple design once again supported the oncological paradigm that survival is improved by better local control. Due to short overall treatment time, early operation, low costs and patients convenience the concept of a one-week preoperative radiation therapy has been adopted in many institutions in resectable rectal cancer. However, major radio- and tumorbiological shortcomings have also prompted criticism:[28,29]

- First of all, since surgery is performed only one week after the completion of radiation therapy, significant tumor shrinkage („downstaging“) is very unlikely and a major goal of preoperative treatment, the preservation of the sphincter, is less likely to be achieved. Prolonging the interval between radiation therapy and surgery has been studied in a recent French trial in which patients with low lying rectal cancer were randomized to undergo surgery either within the first two weeks after radiation therapy (39 Gy in 13 fractions) or only after 6 weeks.[30] The long interval between radiation and surgery was associated with a significant better clinical tumor response (71.7% vs. 53.1%, $p=0.007$) and pathologic downstaging (26% vs. 10.3%, $p=0.005$) and sphincters were more likely to be preserved if surgery was delayed (76% vs. 68%, $p=0.27$).
- The high single dose (5Gy) used in the Swedish concept has been criticized for inducing more acute and late toxicity. In some patients radiotherapy-induced lumbosacral plexopathy led to an inability to walk and to persistent pain[31]– an adverse effect that is unknown after more conventional fractionation. Moreover, although postoperative mortality might not been increased after preoperative short course radiotherapy, provided more sophiticated multiple-field radiation techniques are used, an interim analysis of the current Dutch TME trial indicated an increased infection rate, higher blood loss during operation and an increased rate of perineal wound healing complications after short-term preoperative radiotherapy (5×5Gy).[14] Conversely, the first results of the German Rectal Cancer Study (Protocol CAO/ARO/AIO 94) comparing preoperative to postoperative radiochemotherapy with conventional fractionation and with a 6 week interval to surgery suggest even a reduced rate of postoperative morbidity in the neoadjuvant arm.[32] Recent data also indicated that there is a substantial change in bowel function (median bowel frequency, incontinence for loose stools, urgency etc.) after high-dose preoperative radiotherapy in the long term,[33] thus emphasizing the need for further optimizing radiation techniques and for identifying the risk-groups for local failures to avoid substantial overtreatment.
- Furthermore, due to short overall treatment time, short course, intensive radiation therapy can not be combined with adequate doses of systemic chemotherapy. Thus, the potential of radiosensitizing effects of concurrent chemotherapy to enhance local tumor response and to simultaneously treat occult distant metastases remains unexploited.

Conventional Preoperative Radiation Therapy with or without Concurrent Chemotherapy T4-Rectal Cancer

Several institutions have applied preoperative radiation in conventional fractionation in the treatment of fixed (T4) rectal lesions.[34-38] The goal is to convert („downsize“) the tumor, which is clinically not amenable to a curative resection at presentation, to a resectable status. Minsky et al. compared preoperative radiotherapy (50.4 Gy) with or without 5-FU/high-dose folinic acid and showed that 90% of the patients with initially „unresectable“ tumors were converted to resectable lesions by preoperative combined therapy as compared with only 64% of those who received radiation therapy alone.[39] Moreover, a complete pathologic response was found in 20% of patients receiving combined modality therapy as compared to 6% receiving radiotherapy alone, indicating an enhancement of radiation-induced downstaging by concomitant 5-FU-based chemotherapy. Several phase II trials of preoperative radiochemotherapy, including our own study at the University of Erlangen,[38] confirmed overall and complete resectability rates between 79 and 100% and 62 and 94%, respectively, and overall-survival rates in the range of 69% at 3 years and 51% at 5 years (*Table 3*). All these studies demonstrate the feasibility of tumor shrinkage in T4 rectal cancer with preoperative multimodality regimen, allowing for potential curative resections. Thus there is no real controversy about this type of treatment, although there are still few evidence-based data with regard to the optimal doses of radiation and chemotherapy as well as the type of 5-FU administration and combination with other cytotoxic agents. In a subset of patients, even more aggressive attempts to achieve a local

***Table 3*. Selected series of preoperative radiochemotherapy in locally advanced T4 – rectal cancer**

Series	*No. of patients*	*RT (Gy)*	*CT*	*Resectability rate/complete resection (R0)(%)*	*pCR (ypT0N0) (%)*	*Local failure (%)*	*Distant failure (%)*	*Overall survival (%)*
Chan et al. (1993)[34]	46	40	5-FU 20 mg/kg/d PVI day 1–4, 15–18 Mitomycin 8 mg/m^2/d1	100/ 89	4	16 (2 years)	41 (2 years)	73 (2 years)
Minsky et al. (1993) [35]	20	46,8 + Boost to 50,4 (IORT 16 Gy in 6 pts)	5-FU 200–375 mg/m^2/5 d IV 200 mg/m^2/5 d Bolus 2 cycles	95/85	20	26 (crude incidence)	30 (crude incidence)	69 (3 years)
Marsh et al. (1996) [36]	18	45 + Boost to 50,4 - 55,8	5-FU 250 - 375 mg/m^2/d PVI (chronomodulated for duration of RT)	94/94	28	n.g.	n.g.	60 (4 years)
Videtic et al. (1998) [37]	29	54 (medium cumulative dose)	5-FU 225 mg/m^2/d PVI for duration of RT	79/62	13	n.g.	n.g.	n.g.
Rödel et al. (2000) [38]	31	50,4 + Boost to 55,8-59,4	5-FU 1000 mg/m^2/d PVI d 1–5, 29–33	94/84	3	23 (crude incidence)	26 (crude incidence)	51 (5 years)

Abbreviations: RT: Radiotherapy, CT: Chemotherapy, IORT: Intraoperative Radiation Therapy, pCR: pathologic complete remission, PVI : protracted venous infusion, n.g.: not given

tumor control, including preoperative radio-chemo-thermo-therapy[40] or intraoperative radiation boost techniques may be indicated.

Enhancing Sphincter preservation

Another major goal of neoadjuvant therapy is the conversion of a low-lying tumor, that was declared by the surgeon to require an abdominoperineal resection (APR), into a lesion amenable to sphincter-preserving procedures. Technically, two surgical approaches have been used after preoperative therapy: local excision and a low anterior resection with or without a coloanal anastomosis. While the first technique should be restricted to patients with clinical stage T1/T2 lesions or to those who are medically unsuitable for radical surgery,[41] the second approach has the advantage of allowing a more complete resection of the tumor and the perirectal soft tissue. It must be emphasized, however, that equivalent local control and survival rates compared to conventional APR as well as the quality of long-term rectal function is of the utmost importance in this setting.

Minsky reviewed five series[42-46] that have reported on patients with clinically resectable rectal cancer who underwent a prospective clinical assessment by their surgeons and were declared to need an APR.[47] All have applied conventional doses of radiation therapy, two used concurrent chemotherapy. A sphincter-sparing approach, mostly low anterior resection with coloanal anastomosis, was accomplished in 23% to 85% of patients, local control ranged from 83 to 100% and sphincter function was declared to be „perfect“ (71%) or „good to excellent“ (85%) in two studies, respectively. However, these preliminary data have to be interpreted with caution. In the aforementioned French trial of preoperative radiation in low-lying rectal cancer the overall recurrence rate was 9% and 12% in those patients in which sphincter preservation seemed impossible at presentation, but who had an anterior resection following preoperative downsizing of their tumor.[30] Further studies to adequately select patients for the respective treatment alternatives are urgently needed.

Preoperative Versus Postoperative Radiochemotherapy

The interest in preoperative radiochemotherapy for resectable tumors of the rectum is based not only on the success of adjuvant radiochemothera-

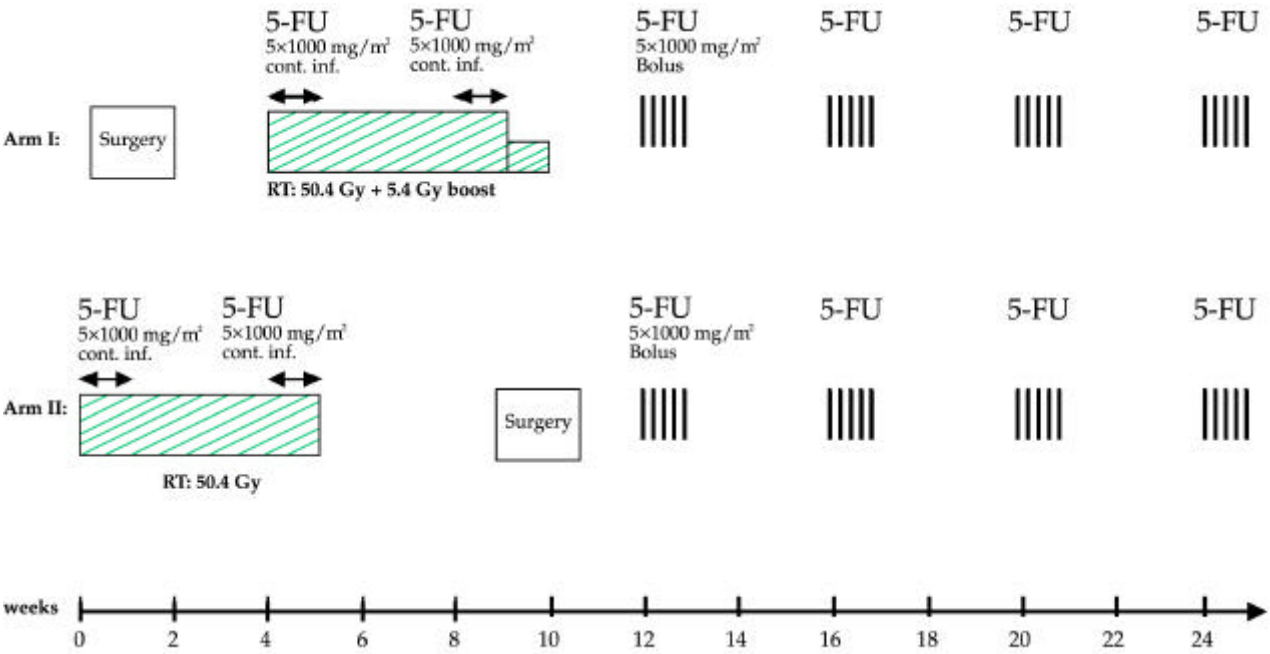

Figure 1. Design of the two-arm German Rectal Cancer Study (Protocol CAO/ARO/AIO 94) comparing preoperative to postoperative radiochemotherapy in locally advanced rectal cancer (UICC-stage II/III).

py in the postoperative setting, but also on the many aforementioned advantages of delivering radiation treatment preoperatively. Until recently, the only randomized trial that directy compared preoperative to postoperative radiation therapy in rectal cancer was the Uppsala trial, which was carried out between 1980 and 1985 in Sweden. [48] In the preoperative arm, patients received intensive short-course radiation (five fractions of 5.1 Gy to a total dose of 25.5 Gy in one week). Postoperatively conventional radiation therapy (2 Gy to a total of 60Gy with a 2-week split after 40 Gy) was applied. Preoperative radiation significantly decreased local failure rate (13% vs. 22%, p=0.02), however, there was no significant difference in 5-year survival rates (42% vs. 38%).

Prospective randomized trials comparing the efficacy of preoperative radiochemotherapy to standard postoperative radiochemotherapy in UICC-stage II and III rectal cancer were initiated both in the United States through the Radiation Therapy Oncology Group (RTOG 94-01) and the NSABP (R-03) as well as in Germany (Protocol CAO/ARO/AIO 94). Unfortunately, both U.S. trials suffered from lack of accrual and have already been closed. The accrual of the German multicenter study is going well and more than 650 of 800 planned patients have already been recruited until September 2000. The design and treatment schedule is depicted in *Figure 1*. Techniques of surgery are standardised and include total mesorectal excision for tumors of the lower and middle part of the rectum. In addition, stratification of all the surgeons involved has been provided for. Endpoints include local and distant control, 5-year overall and relapse-free survival, rate of curative (R0) resections and sphincter saving procedures, toxicity of radiochemotherapy, surgical complications due to treatment mode and quality of life. First results regarding surgical morbidity and toxicity of radiochemotherapy suggest a reduced rate of gastointestinal side-effects in the neoadjuvant setting and no increase of postoperative complications following preoperative radiochemotherapy.[32]

The concurrent use of chemotherapy as part of the preoperative regimen is another important point, as it is not clear by now whether data from postoperative radiochemotherapy in resectable rectal cancer can be extrapolated to the preoperative setting. The European Organization for Research and Treatment of Cancer (EORTC-study 22921) is currently conducting a four arm trial that treats all patients with preoperative radiation in conventional fractionation and tests whether preoperative concurrent radiochemotherapy, postoperative chemotherapy, or bolth are superior to preoperative radiation alone.[49] Up to date, 550 patients have been recruited, another 400 are still necessary.

Intraoperative Radiotherapy

Most experience with intraoperative radiotherapy (IORT) has been gained with locally advanced primary tumors or with isolated pelvic relapses, when the method was used as a boost after preoperative external beam radiation therapy and in addition to extensive surgery. The rational for using IORT is the possibility of delivering a

high-dose to a small tumor-containing area without damaging the surrounding normal tissue. As the radiation dose for microscopic residual disease should exceed 60 Gy[50] and even higher to reach tumorcidal dose for macroscopic tumor, external beam radiotherapy is limited by normal tissue tolerance, especially with regard to the small bowel. IORT may help to overcome this problem by direct visualization and irradiation of the persistent tumor (R2), the positive resection margins (R1) or the area at risk for tumor persistence. Exclusion of dose-limiting structures such as the small bowel by shielding, retraction or operative mobilization and the higher biological effectivness of single-dose IORT have the potential of improving the therapeutic ratio of local control versus toxicity. Peripheral neuropathy and ureteral stenosis are the most important dose-limiting factors to be considered.[51] Animal and clinical data suggest that the IORT threshold doses for complications appear to be 15 Gy for neuropathy and 12 Gy for ureteral stenosis, respectively.[51] Classically, intraoperative radiotherapy has been delivered by a linear acceleration based electron beam (IOERT), but similar effects can be reached with high-dose-rate brachytherapy (Ir^{192}) using afterloading techniques (HDR-IORT).[52] The latter has the potential advantage, that, due to the increased flexibility of the applicators, there are virtually no anatomic or technical constrains that might impair proper application.

Several IORT series for locally advanced primary and recurrent rectal cancer have been published (for review: 51, 53). A combined approach using maximal resection with IOERT (10-20 Gy) and either pre- or postoperative external beam radiotherapy (50.4-54.4 Gy) with or without chemotherapy was first evaluated at the Mayo Clinic and the Massachusetts General Hospital. Updated analyses from the Majo Clinic have documented the efficacy in 56 primary advanced [54] and in 123 recurrent colorectal cancer patients.[55] Three-year actuarial rates of local control and overall survival were 84% and 55% for locally advanced primary and 75% and 39% for recurrent tumors, respectively. In historical case controlled studies, local relapses, especially after R0 and R1 resection of primary advanced cancer, were reduced with IORT by more than 65% compared to treatment without IORT and survival rates were improved by up to 12%.[56] Favourable prognostic factors on disease control and survival for patients with primary cancer included negative resection margins or only microscopic versus gross residual disease, the use of concomitant chemotherapy and preoperative rather than postoperative external beam radiation therapy. Thus, the preferred sequencing is now usually preoperative external beam irradiation plus chemotherapy followed by maximal resection and IORT. Recent reports from the Memorial Sloan-Kettering Cancer Center,[57] using HDR-IORT, and from the Eindhoven group in the Netherlands,[58,59] and the Heidelberg group in Germany[60] have confirmed that this aggressive multimodality treatment is versatile, safe and effective, with local control rates of up to 82% at 3 years for

Table 4. **Standard and experimental (neo-)adjuvant treatment in rectal cancer according to tumor stage, clinicopathological factors and treatment goal (sphincter preservation)**

	Standard treatment	*Experimental treatment*
UICC-stage I		
T1-2 N0, G1/2, < 3 cm	Local excision	Local excision + R(C)T (especially if pT2 or pT1 with L1,V1)
T2 N0, sphincter preservation at presentation possible	Anterior Resection (AR)	
T2 N0, sphincter preservation at presentation not possible	Abdominoperineal Resection (APR)	Preoperative R(C)T + AR with coloanal anastomosis
UICC-stage II		
T3 N0	AR/ APR + RCT+CT	R(C)T + AR/AR with coloanal anastomosis in low lying tumors + CT Resection with TME only +/- CT (especially in pT3 with minimal perirectal invasion < 5mm)
T4 N0	RCT + AR/APR/Exenteration + CT	Hyperthermia + RCT + Surgery +IORT + CT
UICC-stage III		
TX N1,2	AR/APR + RCT + CT	R(C)T + AR/AR with coloanal anastomosis in low lying tumors + CT
Local relapse	RCT + AR/APR/Exenteration	Hyperthermia + RCT + Surgery +IORT + CT

Abbreviations: RT: Radiotherapy, CT: Chermotherrapy, RCT: Radiochemotherapy, TME: Total mesorectal excision

primary and 39% at 5 years for recurrent rectal cancer, respectively. Major concerns, however remain the high risk of local failure when a gross resection is not surgically feasible and the commonly high rate of systemic failure (> 50%). Future directions should therefore include optimization of preoperative treatment to maximize tumor shrinkage and enable complete resection and the incorporation of effective concomitant and maintenance chemotherapy schedules.

Conclusion And Future Perspectives

Is there a standard adjuvant treatment of rectal cancer? The pros and cons have extensively been discussed in recent controversies.[61,62] According to Consensus Conference recommendations in the USA and in Germany,[1,2] postoperative radiochemotherapy remains the treatment of choice in stage II and III resectable rectal cancer. Conversely, a Paris Consensus Conference in 1994 suggested, that „the benefits observed with preoperative radiation incite to test preoperative treatment with radiotherapy and chemotherapy".[63] Since then, new data have been collected and progress has been made both in surgery and perioperative radio-(chemo)therapy. Surgical management now includes a broad spectrum of operative procedures ranging from radical operations (exenteration with en-bloc resection of involved organs, abdominoperineal resection) to innovative sphincter-preserving techniques (local excision, low anterior resection with coloanal anastomosis). Better knowledge of distal microscopic lymphatic spread within the mesorectum has led to the use of total mesorectal excision for mid and low rectal cancer. With this „optimized" surgery, local control rates have been markedly increased and local failure rates above 20% are now no longer acceptable. Technical advances in radiotherapy, including tumor- and radiobiologically optimized fractionation, intraoperative radiation therapy, 3-D treatment planning and intensity-modulated radiation therapy will further allow application of more sophisticated treatment volume to reduce irradiation of normal tissue and increase the therapeutic index.[64] Moreover, innovative ways of administration of chemotherapeutic agents, including continuous and chronomodulated infusion of 5-FU, as well as the emerging role of additional agents, e.g. oxaliplatin or irinotecan, need to be incorporated in multimodality regimens.

Evidently, the current monolithic approaches, established by studies more than a decade ago, to either apply the same schedule of postoperative radiochemotherapy to all patients with stage II/III rectal cancer or to give preoperative intensive short-course radiation according to the Swedish concept for all patients with resectable rectal cancer irrespective of tumor stage and treatment goal (e.g. sphincter preservation), need to be questioned. The inclusion of different multimodal treatments into the surgical oncological concept, adapted to the tumor location and stage and to individual patient's risk factors is mandatory. *Table 4.* summarizes current standard treatment concepts and considers promising experimental options. Clearly, future developments will aim at identifying and selecting patients for the ideal treatment alternatives. Thus, clinicopathological and molecular features as well as accurate preoperative imaging and staging methods (endorectal ultrasonography, magnetic resonance imaging, PET) will take an important and integrative part in multimodality treatment of rectal cancer.

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