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Neoadjuvant Radiochemotherapy for Rectal Cancer

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Key Words
Rectal cancer · Radiotherapy · Chemotherapy · Toxicity

Abstract
During the past few decades, significant progress has been achieved in the management of rectal cancer with the introduction of total mesorectal excision. The role of radiotherapy in improving local control and survival has been investigated extensively. Randomized trials of preoperative radiotherapy reported statistically significant lower local recurrence rates with either short regimens (25 Gy in 5 fractions) or conventionally fractionated regimens (45–50 Gy in 25 fractions) and some also showed a survival improvement. Preoperative radiotherapy appears more effective in terms of local control and toxicity compared to postoperative therapy. Several recent studies show that 5-FU-based chemotherapy enhances tumor response to radiotherapy and preoperative chemoradiotherapy is being increasingly used for stage II and III disease.

There are four major goals in the treatment of a patient with rectal cancer: local control, long-term survival, preservation of anal sphincter, bladder and sexual function and finally maintenance or improvement of quality of life. These goals are best achieved through a multimodality approach delivered by a multidisciplinary team. Surgery remains the cornerstone of all therapy and continues to develop towards the ultimate goals of improved local control maintaining good quality of life. In the early series the local recurrence rates after standard surgery were around 30–50%. With extensive surgical training programs and the introduction of total mesorectal excision (TME), several studies in the 1990s reported rates of 8–15% with TME.

Information concerning the depth of tumor penetration through the rectal wall, lymph node involvement and presence of metastatic disease is of crucial importance when planning a curative treatment. Preoperative staging is used to determine the indication for neoadjuvant treatment. Local excision is likely to be curative for most patients with a tumor limited to the submucosa (T1N0M0), but once the tumor invades the muscularis propria (T2), radical resection is recommended. In patients with transmural and/or node-positive disease (T3/T4 and/or N1), preoperative chemoradiotherapy followed by radical resection according to the principles of TME has become widely accepted [1].

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Table 1. Randomized trials of preoperative radiotherapy in rectal cancer (controlled trials with a surgery-alone group)

Trial	Total dose Gy	Fractions	BED Gy	Local recurrences (%)		Relative reduction, %
				control group	RT group	
Standard surgery						
MRCI	5	1	7.5	118/275 (43)	125/277 (45)	0
	20	10	20.4		128/272 (47)	0
RTOG	5	1	7.5	33/153 (22)	281/148 (19)	12
Dresden	15.5	5	20.3	9/37 (24)	5/40 (13)	49
St. Marks	15	3	22.5	51/210 (24)	31/185 (17)	29
Essen	25	13	24.0	7/71 (10)	4/56 (7)	30
VASAG II	31.5	18	26.8	40/181 (22)	37/180 (21)	0
Bergen	31.5	18	26.8	31/131 (24)	24/138 (17)	29
VASAG I	20–25	10	27.5	32/87 (37)	27/93 (29)	22
North-West	20	4	30.0	58/141 (41)	26/143 (18)	65
Mainz	34.5	15	35.2	21/106 (20)	8/64 (13)	37
Dutch	34.5	15	35.2	18/50 (36)	7/59 (12)	67
EORTC	34.5	15	35.2	49/175 (28)	24/166 (15)	48
MRC2	40	20	36.0	65/140 (46)	50/139 (36)	22
Brazil	40	20	36.0	16/34 (47)	5/34 (15)	68
Stockholm	25	5	37.5	120/425 (28)	61/424 (14)	50
SRCT	25	5	37.5	150/557 (27)	65/553 (12)	60
TME						
Dutch TME	25	5	37.5	72/907 (8)	23/897 (3)	71

Preoperative Radiotherapy

The rationale for preoperative radiotherapy is: for T3 tumors to sterilize tumor deposits outside the mesorectal fascia, to downstage fixed T4 tumors and make a curative procedure possible and for resectable but low rectal cancers (requiring abdominoperineal resection) to downsize enough for sphincter preservation. Preoperative radiotherapy has the theoretical advantage of treating an undisturbed tumor bed which should have a smaller proportion of hypoxic cells and therefore should be more radiosensitive. In addition, radiation fields are usually smaller and acute and long-term toxicity is not severe [2].

Nineteen randomized studies of preoperative radiotherapy have been published so far (table 1). The surgery-alone group, with a few exceptions, has shown local recurrence rates exceeding 20% (on average 28%). Most of these trials showed statistically significant lower local recurrence rates (local recurrence was reduced by 40–50% with preoperative radiotherapy). Radiotherapy was given either with conventional dose and fractionation (20–25 fractions of 1.8–2 Gy to a total dose of 45–50 Gy) or as a short schedule of 5 fractions of 5 Gy each (total dose 25 Gy). Reduction in local failure was seen with both regimens [3]. The two fractionation schedules have not been directly compared and it is not known which is the most effective. The short scheme of preoperative radiotherapy is certainly convenient for the patients without significantly increased acute toxicity. It has a proven efficacy in local tumor control as has most recently been shown by the Dutch trial. A cost utility analysis reported a cost-effectiveness ratio of USD 25,000 per quality-adjusted life-year. However, this scheme does not contribute to downstaging of locally advanced rectal tumors, and it cannot be administered concomitantly with chemotherapy while there is some concern regarding late toxicity.

Three meta-analyses confirmed the significant effect of preoperative radiotherapy on local failure and deaths from rectal cancer. The meta-analysis published in 2001 by the Colorectal Cancer Cooperative Group showed that preoperative radiotherapy at biological doses of >30 Gy reduces the risk of local recurrence by 46%, the 5-year overall mortality by 16% and cancer-related mortality by 29% (table 2). The effect was seen in all stages and both genders. However, the magnitude of benefit on survival is relatively small and criteria are needed to identify patients most likely to benefit from radiotherapy [3].

Table 2. Colorectal cancer collaborative group overview (2001) on randomized trials of preoperative radiotherapy in rectal cancer (meta-analysis of individual patient data)

Aim/study question	Patient population		Results			Conclusion/comments
			%	SE	p	
Surgery alone vs. surgery and preop. or postop. RT, meta-analysis of 22 trials	Trials starting before 1987, 22 of 28 identified trials allowed analyses of individual patient data. 6,360 pts (92% of all) in 14 preop. trials, 2,157 pts (99%) in 8 postop. trials		Reduced overall death rate			Preop. RT (at BED >30 Gy) reduces the risk of local failures and deaths from rectal cancer. The reduction was seen in all stages and both sexes. It increases non-rectal cancer deaths, being technique dependent. The effect on overall survival is limited.
		Preop. BED <20 Gy	5.5	9.4	0.6	
		Preop. 20–30 Gy	0.5	5.3	0.9	
		Preop. >30 Gy	9.8	4.7	0.04	
		Preop. all	5.6	2.9	0.09	
		Postop. all (>35 Gy)	4.6	5.9	0.4	
			Reduced rectal cancer death rate			
		Preop. BED <20 Gy	11.2	11.4	0.3	
		Preop. 20–30 Gy	1.1	6.3	0.9	
		Preop. >30 Gy	21.6	5.1	0.00002	
		Preop. all	12.9	3.7	0.0006	
		Preop. all (>35 Gy)	8.6	6.5	0.2	
			Relative reduction isolated local failure			Preop. RT (at BED 20–30 Gy) slight reduction local failures, no influence on survival. No significant effects are seen using lower preop. doses (BED <20 Gy). Postop. RT (at BED >35 Gy) reduces risk of local failure (less than preop. RT). No influence on survival. M1
		Preop. BED <20 Gy	–20.2	28.8	0.05 adverse	
		Preop. 20–30 Gy	23.7	14.5	0.10	
		Preop. >30 Gy	57.4	6.6	<0.00001	
		Preop. all	46.0	6.0	<0.00001	
		Postop. all (>35 Gy)	36.9	9.7	0.00002	
			Absolute reduction isolated local failures at 5 years			
		Preop. all	22.2–12.5		<0.00001	
		Postop. all	22.9–15.3		<0.0002	
			Increase in non-rectal cancer death rate			
		Preop. BED <20 Gy	–9	16.2	0.8 adverse	
		Preop. 20–30 Gy	–0.8	9.7	0.9 adverse	
		Preop. >30 Gy	–37.2	11.6	0.001 adverse	
		Preop. all	–15.2	6.8	0.02 adverse	
		Postop. all (>35 Gy)	–12.4	14.3	0.1 adverse	

One of the largest studies conducted in the 1980s, the Swedish Rectal Cancer Trial, randomized 1,168 patients with all-stage resectable disease to short-course preoperative radiotherapy (25 Gy in 5 fractions) followed by standard surgery within 1 week of surgery only [4]. In the most recent report with a median follow-up of 13 years, the local recurrence rate was statistically lower following preoperative radiotherapy (9 vs. 26% in the non-irradiated group). The reduction in the local recurrence rate was observed at all tumor locations, although it was not statistically significant for tumors >10 cm from the anal verge. In addition, preoperative radiotherapy resulted in a significant increase in the overall 13-year survival from 30 to 38% and in the cancer-specific survival from 62 to 72%.

In the past decade, it has repeatedly been claimed that surgery was not optimal in the trials that recruited patients in the 1980s. Concentration of rectal cancer surgery to a rectal cancer unit and extensive surgical training programs have resulted in low local recurrence rates only with TME. To investigate the necessity of preoperative radiotherapy with appropriate surgery, the Dutch Colorectal Cancer Group randomized 1,861 patients with resectable rectal cancer to short-course preoperative radiotherapy (25 Gy in 5 fractions in 1 week) immediately followed by TME or TME alone [5]. The study was conducted with the use of standardization and quality control measures to ensure the consistency of surgery, radiotherapy and pathology techniques. With a median follow-up of 2 years, local recurrence was seen in 8.2% following surgery only and 2.4% with the addition of radiotherapy, although overall survival was similar in both groups (82%). The effect was seen for stage II and III tumors located up to 10 cm from the anal verge.

Tumor Response

The effect of radiotherapy on tumor characteristics (reduction in size, necrosis, fibrosis), and consequently on the occurrence of downstaging, depends on treat-

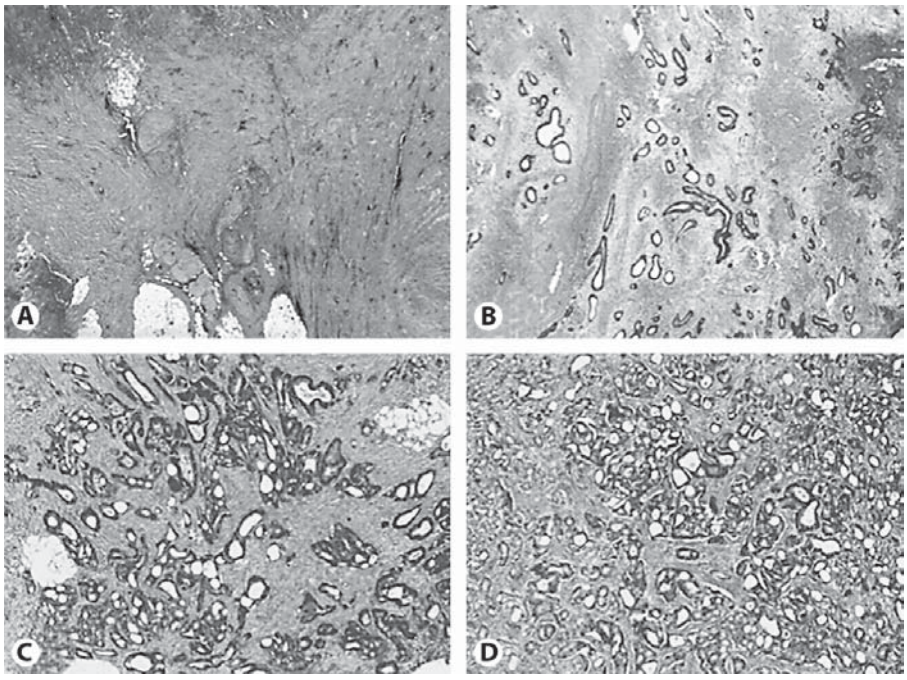

Fig. 1. TRG after preoperative chemoradiotherapy in rectal cancer patients: **A** total regression, no viable tumor cells, only fibrotic mass, TRG 4; **B** dominant fibrosis outgrowing the tumor mass (i.e., >50% tumor regression), TRG 3; **C** dominant tumor mass with obvious fibrosis in 26–50% of the tumor mass, TRG 2; **D** minor regression, fibrosis in only 25% or less of the tumor mass, TRG 1.

ment-related factors as well as tumor-related factors. The total radiation dose, the fraction size, the concomitant administration of chemotherapy and the overall treatment time are associated with tumor response. There is some evidence for a dose-response relationship for rectal cancer. The 2001 Overview indicates that radiotherapy schemes at biological doses >30 Gy are associated with lower recurrence rates improving local disease control by 27% while lower doses have no significant effect on local control [3]. In addition, the Lyon R0-02 trial showed that dose escalation with contact radiotherapy to 85 Gy increased tumor response; mean tumor diameter was decreased from 3.2 to 2.4 cm and the rate of pathologic complete response increased from 2 to 29%. As a result, a sphincter-saving procedure was performed in 79% of patients [6].

In studies in which radiotherapy is delivered as a short scheme of 5 fractions, the overall treatment time is 2 weeks at the most. The interval is too short for the tumor cells to disappear. Analysis of the pathologic tumor characteristics of patients who participated in the Dutch trial showed a small reduction in tumor size, probably due to intratumoral lymphocytic cell death by apoptosis, and the number of recovered lymph nodes but no change in tumor and node classification [7]. Therefore, no downstaging occurs after short-term preoperative radiotherapy. With doses of >40 Gy given with conventional fractionation followed by surgery several weeks later, there is enough time for tumor cells to die resulting in considerable shrinkage. The Lyon R90-01 trial was specifically designed to answer the question of the interval between the end of radiotherapy and surgery and showed a significant increase in tumor response with a long interval of 6 weeks [8].

Assessment of response to radiotherapy by comparing preoperative staging, with endorectal ultrasound, computer tomography or magnetic resonance scans, is likely to overestimate the degree of downstaging. An alternative method is by grading histological changes in the resected specimen. A new system for assessment of tumor response has been recently developed, the tumor regression grading (TRG) scoring with 5 categories, determined by the amount of viable tumor versus fibrosis (fig. 1). TRG was evaluated on surgical specimens of patients treated within the German trial [9]. It was found that complete regression of the primary (TRG 4) was associated with better control of disease in the lymph nodes, sustained local control (100%) and a minor risk to develop distant metastases (DFS 86%). Patients showing an intermediate regression (TRG 2+3) also had an intermediate prognosis (DFS 72%) and poor tumor regression (TRG 0+1) was associated with adverse pathologic features and predicted for an unfavorable outcome (DFS 63%). Although TRG seemed promising in the univariate

Table 3. EORTC 22921 trial: patients' pathological characteristics

Tumor size, mm			
Median	30.0	25.0	p < 0.0001
90% range	10.0–70.0	8.0–110.0	
Tumor stage, patients (%)			
0	25 (5.3)	65 (13.7)	p < 0.001
1	36 (7.6)	49 (10.4)	
2	141 (29.6)	156 (33.0)	
3	233 (48.9)	175 (37.0)	
4	25 (5.3)	18 (3.8)	
Missing	16 (3.4)	10 (2.1)	
Nodes examined			
Mean	9	7	p = 0.046
Range	0.0–45.0	0.0–39	
N stage, n (%)			
N0	288 (60.5)	340 (71.9)	
N1	108 (22.7)	84 (17.8)	
N2	57 (12.0)	34 (7.2)	p < 0.001

analysis, the most important independent prognostic factor for DFS was the pathological T category and the nodal status. In a study from Canada, the post-treatment TNM stage was also a strong prognostic factor for recurrence and survival [10]. By contrast, in a similar study from Padova, tumor response following preoperative chemoradiotherapy was mainly related to the regimen used and only the pretreatment TNM stage was prognostic for the outcome [11].

Adding 5-FU and leucovorin concomitantly with the radiotherapy course significantly decreases tumor size and pTN stage. In most trials of preoperative radiotherapy the complete response rate is around 5–10%, the addition though of chemotherapy resulted in tumor sterilization in 20–30% of patients. Chemotherapy also reduces lymphatic, venous and perineural invasions which have been shown to impact negatively on the outcome while it increases mucin production by the tumors which is considered as a mode of response to therapy [12]. The large EORTC 22921 randomized trial indicates a synergistic effect of chemotherapy on downsizing and downstaging but longer follow-up is needed to assess the impact on local control and survival (table 3).

It seems, therefore, that tumor regression after preoperative chemoradiotherapy is a multifactorial phenomenon. Apart from treatment-related factors, it appears to be associated with smaller, less aggressive disease, and may correspond to the molecular tumor profile regulating tumor response. Apoptosis, apoptosis-related proteins, genes and growth factors may be implicated.

Sphincter-Saving Procedures

Theoretically, the reduction of the tumor bulk induced by preoperative irradiation should improve sphincter preservation in patients with low-lying cancers. This notion seems to be supported by the results of several phase II and two phase III studies [6, 8, 13, 14]. It has also been suggested that the anterior resection rate increases with concurrent chemoradiotherapy. The very recent review of 10 randomized trials involving 4,596 patients showed that tumor shrinkage did not result in a statistically significant higher anterior resection rate (table 4). Subgroups of patients considered to be candidates for abdominoperineal resection before randomization were identified in three trials. A statistically significant higher rate of sphincter-saving procedures was demonstrated in the German trial; however, sphincter preservation was a secondary endpoint [15]. The benefit of sphincter preservation was not confirmed by subgroup analysis in the Lyon R90-01 nor in the Polish study, which were originally designed to address this issue [8, 13].

It should be acknowledged that these trials differed in respect to radiochemotherapy regimens, interval between radiotherapy and surgery, patient populations and the periods of accrual. The distance between the anorectal ring and the lower pole of the tumor certainly lengthens following treatment; however, many surgeons do not perform an anterior resection. One reason might be that they are not convinced by the suggestion of possibility of a shorter surgical distal bowel margin (<1 cm instead of the usually recommended 1–2 cm). In three retrospective studies, there was no association between the length of the distal margin and the risk of local recurrence [16]. By contrast, in many phase II studies, which are single-center studies, the surgeons agreed that the final decision on sphincter preservation has to be based on the tumor status at the time of surgery and not before irradiation and have shown a much higher rate of conservative procedures.

Combined Radiochemotherapy

The rationale for systemic chemotherapy for stage II/III rectal cancer is twofold: 5-FU-based chemotherapy can enhance tumor response to radiotherapy, acting as

Table 4. The AR rates in the randomized trials for respectable rectal adenocarcinoma, in which preoperative irradiation, with or without chemotherapy, resulted in a smaller primary tumor, prior to surgery in the experimental group as compared to the control group

A study name or a name of first author, year of beginning of accrual remarks	Overall quality score[a]	Treatment regimens: experimental group vs. control group	The evidences for tumor shrinkage and higher percentage of CR in an experimental group compared to a control group, respectively, p value	Experimental group no. of patients with ARs/total no. of patients[b] (%)	Control group no. of patients with ARs/total no. of patients[b] (%)	% of treatment effect[c] (95% CI) p value
Trials in which a rate of ARs was the primary endpoint						
Lyon R90-01, 1991	100	The same preoperative irradiation in both groups (39 Gy, 3 Gy/fraction); interval to surgery 6–8 weeks vs. <2 weeks	Clinical PR + CR: 72 vs. 53%, p = 0.007	77/102 (76)	67/99 (68)	8 (–5, +20) 0.27
Polish trial, 1999	100	Preoperative chemoradiation (50.4 Gy, 1.8 Gy/fraction + 2 cycles of 5-Fu, LV, 4–6 weeks interval to surgery vs. preoperative 5 × 5 Gy, immediate surgery	Mean dimension of tumors along bowel axis: 26 vs. 45 mm, p < 0.001; clinical CR: 13 vs. 3%, p < 0.001	91/157 (58)	94/154 (61)	–3 (–14, +8) 0.64
Trials in which a rate of ARs was a secondary endpoint						
CAO/ARO/AIO 94, 1994 Analysis according to actual treatment given	80	Preoperative chemoradiation (50.4 Gy, 1.8 Gy/fraction + 2 cycles of 5-Fu, LV, up to 8 weeks interval to surgery vs. postoperative chemoradiation	Downstaging (p < 0.001)	286/415 (69)	273/384 (71)	–2 (–9, +4) 0.54
NSABP R-03, 1993 40% (45/113) of patients were excluded from analysis	50	1 cycle of 5-Fu, LV + preoperative chemoradiation (50.4 Gy, 1.8 Gy/fraction + 2 cycles of 5-Fu, LV, up to 8 weeks interval to surgery) vs. postoperative chemoradiation	Downstaging: pathological CR + stage I: 33 vs. 16%, p value not given	15/31 (48)	11/37 (30)	+19 (–4, +42) 0.14
Trials in which a rate of ARs was not an endpoint						
MRC 1, 1975 Three-arm study; in single fraction preoperative group no downsizing was seen and therefore this group was combined with surgery-only group	80	Preoperative irradiation 20 Gy, 2 Gy/fraction, interval to surgery <1 week vs. surgery alone or single fraction 5 Gy within 1 week before surgery	Tumor size >4 cm: 46% for multiple fraction group vs. 61% for surgery alone + single fraction group, p = 0.004	57/272 (21)	133/548 (24)	–3 (–9, +3) 0.29
Horn, 1976	33	Preoperative irradiation 31.5 Gy, 1.75 Gy/fraction, interval to surgery 2–3 weeks vs. surgery alone	Median tumor diameter: 32 vs. 43 mm, p < 0.05	50/157 (32)	51/149 (34)	–2 (–13, +8) 0.72
Reis Neto, 1978	0	Preoperative irradiation 40 Gy, 2 Gy/fraction, interval to surgery 1 week vs. surgery alone	After radiotherapy 76% of patients had the tumor mass reduction more than 70% of its initial size	18/34 (53)	22/34 (65)	–12 (–35, +12) 0.27
MRC 2, 1981	100	Preoperative irradiation 40 Gy, 2 Gy/fraction, interval to surgery at least 4 weeks vs. surgery alone	Tumor size >4 cm: 32 vs. 64%, p < 0.001	46/139 (33)	52/140 (37)	–4 (–15, +7) 0.53
EORTC 22921, 1993	100	Preoperative chemoradiation (2 cycles of 5-Fu, LV) vs. preoperative irradiation alone; 45 Gy, 1.8 Gy/fraction and interval to surgery 3–10 weeks in both groups	Smaller tumors after chemoradiation, p < 0.001	263/506 (52)	249/505 (49)	+3 (–4, +9) 0.41
FFCD 9203, 1993	Abstract, assessment is not possible	Preoperative chemoradiation (2 cycles of 5-Fu, LV) vs. preoperative irradiation alone; 45 Gy, 1.8 Gy/fraction and interval to surgery 3–10 weeks in both groups	Clinical CR: 5.7 vs. 2.6%, NS pathological CR: 11.7 vs. 3.7%, p < 0.0001	184/370 (50)	182/363 (50)	0 (–8, +7) 0.94

AR = Anterior resection; CR = complete response; PR = partial response; NS = non-significant.

[a] In order to assessing the quality of trials, the scores attached to each individual item of domains of concealment of treatment allocation and handling of with drawals were summed to produce an overall quality score as the percentage of the maximum score theoretically achievable. [b] Patients who underwent local excision were excluded. Total number of these patients was: experimental arm 3 (0.1%), control arm 8 (0.3%). The number of patients treated with Hartmann's procedures was included in numerators. Total number of these patients was: experimental arm 17 (0.8%), control arm 32 (1.3%). [c] Treatment effect equals: anterior resection rate in experimental arm minus anterior resection rate in control arm; '+' denotes treatment effect better in experimental group, '–' worse in experimental group.

radiosensitizer, and adjuvant systemic chemotherapy for node-positive or high-risk patients can reduce distant relapse rates and improve survival. The proper sequence and combination of treatment modalities is controversial. Over the past two decades, randomized trials in North America have shown the efficacy of postoperative radiotherapy and chemotherapy.

The Gastrointestinal Tumor Study Group trial was the first to show local recurrence, disease-free and overall survival benefit with combination of chemotherapy and radiotherapy in high-risk stage II/III rectal cancers [17]. These results were further supported by the Mayo Clinic Study. The National Cancer Institute Consensus Conference in 1990 concluded that combined modality therapy should be administered to patients with stage II/III rectal cancer [18]. However, these results were not seen in other trials. Of note, the two recent studies from the NSABP R02 and a study from Italy showed decreased local failure rates but no effect on survival. One interesting study showed that protracted venous infusion of 5-FU during radiotherapy improved survival compared to intermittent bolus injections, this could be related to prolonged tumor cell exposure to drug or to higher total doses of 5-FU [19]. Some other phase II and III studies showed no benefit from combination chemotherapy compared to 5-FU alone [20].

In the 1990s there were some indications that preoperative was more effective than postoperative radiotherapy in terms of local control. The study by Frykholm et al. [21] reported lower local failure rate after preoperative compared to postoperative radiotherapy (13 and 22%, respectively); however, there was no difference in survival between the two groups. Two recent studies, INT 0145 and NSABP 03, closed early because of insufficient accrual, but the German Rectal Cancer Group Trial comparing preoperative to postoperative combined chemoradiotherapy was published in 2004 with a median follow-up of 45 months [15]. A 5-year cumulative incidence of local failure of 6% was seen in the preoperative RT arm compared to 13% in the postoperative RT arm, a statistically significant difference, while overall 5-year survival was 76 and 74%, respectively. Toxicity was worse in the postoperative arm with 40% grade 3–4 toxic events compared to 27%.

At the beginning of the 1990s, it became clear that preoperative chemoradiotherapy was a relevant issue for clinical research. The EORTC radiotherapy group demonstrated that a 5-FU dose of 350 mg/m^2/day could be safely administered in combination with a leucovorin dose of 20 mg/m^2/day during the first and fifth week of

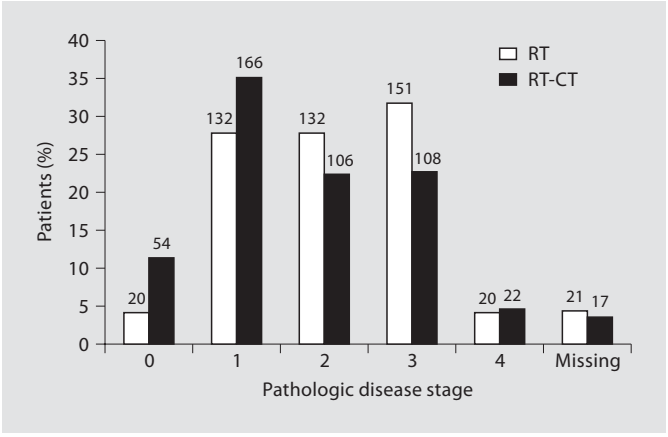

Fig. 2. EORTC 22921 trial. Pathologic disease stage.

radiotherapy to a total dose of 45 Gy. Later the EORTC conducted the four-arm trial 22921 to examine the value of preoperative radiochemotherapy versus preoperative radiotherapy alone and the value of additional postoperative chemotherapy versus none with respect to overall survival and progression-free survival [12]. Preliminary analysis published in 2005 showed that the addition of 5-FU and LV chemotherapy reduced tumor size and pathological stage with slightly increased acute toxicity (fig. 2). The compliance with the radiotherapy protocol and the feasibility of surgery did not decrease. Longer follow-up is needed to assess the true impact on local control and survival. The trial conducted by the Fédération Francophone de Cancérologie Digestive compared preoperative chemoradiotherapy with 5-FU and folinic acid versus radiotherapy and reported lower local recurrence rate with combined treatment without any survival benefit [22]. Interestingly, in all studies, no impact was seen on distant metastases with preoperative chemotherapy. Two possible explanations for this observation were that the chemotherapeutic agents used were administered at doses adequate for radiosensitizing local effect but not adequate to have a systemic effect, and that 5-FU and leucovorin were suboptimal chemotherapy agents.

Several agents are currently being evaluated for their role in an integrated treatment program. These include oral fluoropyrimidines such as Xeloda, irinotecan (CPT-11), oxaliplatin and cetuximab, which is a monoclonal antibody against the epidermal growth factor receptor. Xeloda mimics continuous infusion of 5-FU. The enzyme thymidine phosphorylase is essential for the activation of Xeloda. This is more active in tumor than in normal tissue while radiotherapy upregulates TP in tumor and re-

Table 5. Radiotherapy alone combined with radiotherapy plus chemotherapy in non-resectable rectal cancer

Author/year/design	Aim/study question	Patient population	Results	Conclusion/comments
Moertel, 1969 C	A: RT 35–40 Gy + placebo B: RT 35–40 Gy + 5-FU	A: 33 pts B: 32 pts	Mean survival, months A: 17 B: 25, $p < 0.05$ 3-year survival A: 9% B: 19%, n.s.	Colon and rectum together (the study also included patients with gastric and pancreatic cancer). This study was interpreted early to show that RTCHT (3 days of 5-FU) was superior to RT alone. C3
Rominger, 1985 C	A: RT 45–51 Gy + boost B: RT 45–51 Gy + 5-FU maintenance CHT	129/147 evaluable A: 65 pts B: 64 pts	2-year survival A: 36% B: 44%, n.s. No difference in failure pattern More complications in B	No difference between RTCHT and RT, increased risk of complications C3
Overgaard, 1993 C	A: RT 50 Gy + boost B: RT 50 Gy + weekly 5-FU	A: 29 pts B: 30 pts	3-year survival A: 7% B: 16%, n.s. Acute toxicity A: 13% B: 33%, $p = 0.07$	Significant palliation in 73%, no difference between groups, except for more toxicity with RTCHT.
Frykholm, 2001 C	A: 46 Gy RT B: 40 Gy RT split course + methotrexate + 5-FU + leucovorin	A: 36 pts B: 34 pts	LFS at 5 years A: 38% B: 66%, $p = 0.03$ OS at 5 years A: 18% B: 29%, $p = 0.3$	Gives some support to the view that RTCHT is superior to RT, but did not have the same RT schedule in the two arms. C3

sults in more 5-FU in tumor cells. Studies indicate that Xeloda has an additive activity in combination with radiotherapy while it simplifies chemoradiation and is highly appealing to patients. There are currently several ongoing phase II and III studies in the neoadjuvant setting. Combinations with oxaliplatin and irinotecan are also being investigated and may further improve local and systemic control. These agents have improved overall survival in patients with metastatic colorectal cancer and disease-free survival for patients with completely resected stage II and III colon cancer, while oxaliplatin in addition has a radiosensitizing effect.

Many different concurrent chemoradiotherapy regimens have been evaluated in phase I/II studies during the past 5 years. In the Lyon R0-04 trial, two cycles of oxaliplatin and continuous infusion 5-FU during the first and the fifth week of the radiotherapy course (50 Gy in 5 weeks) resulted in objective clinical response in 75% with pathologic complete response in 15% and sphincter-saving surgery was possible in 65% of the patients [23]. A phase I/II study by the Cancer and Leukemia Group B showed that the addition of weekly oxaliplatin 60 mg/m^2 to continuous infusion of 5-FU 200 mg/m^2 during the radiotherapy showed pathologic complete response in 26% of patients with T3/T4 tumors. Toxicity, grade 3 and 4 diarrhea, was increased, but most patients completed therapy as planned [24]. In another study from the Royal Marsden Hospital, patients with locally advanced rectal tumors received 12 weeks of neoadjuvant oxaliplatin/capecitabine chemotherapy followed by concomitant capecitabine and radiotherapy. TME was performed 6 weeks later and postoperatively 12 more weeks of capecitabine were given. Pathologic complete response was documented in 24% and in an additional 48% of patients only microscopic tumor foci were found on surgical specimens. Distant metastases were seen only in 10% of the patients, although the follow-up was relatively short. Toxicity, though, was not negligible with four toxic deaths as a result of pulmonary embolism and ischemic heart disease [25]. In view of this promising activity, two randomized trials (the NSABP 04 and a multicenter study by the MRC UK) have already been initiated and their results will be very helpful.

Management of Fixed Unresectable Tumors

For locally advanced non-resectable rectal cancers, radiotherapy or combined radiotherapy and chemotherapy achieve marked tumor regression in a significant proportion and facilitates resection. Several trials have reported that preoperative radiotherapy or radiochemotherapy results in radical resection in about 40–70% of patients and that 20–30% will become long-term survivors. Four trials have randomly compared radiotherapy alone with 5-FU chemotherapy concurrent with radiotherapy (table 5). These trials are small and do not provide supportive evidence that radiochemotherapy is superior to radiotherapy alone. However, patient selection may be a very important issue for treatment results. Ferrigno et al. [26] treated 101 patients with fixed or semifixed tumors with radiotherapy, 45 Gy to the whole pelvis and 50.4 Gy to the primary, and concomitant weekly chemotherapy with 5-FU and leucovorin. A complete response was seen in 8% and radical tumor removal with negative margins was achieved in 82% of patients. The actuarial 5-year local control was 76% and distant metastasis was the predominant pattern of failure supporting the need for new chemotherapy agents. Pelvic nodal involvement and incomplete excision were the main adverse prognostic factors. For fixed tumors, high-dose rate intraoperative radiotherapy in combination with preoperative external beam radiotherapy and chemotherapy has also been investigated with some very promising early results. Addition of intraoperative therapy for patients with narrow or microscopic incomplete resection seems to overrule the unfavorable prognostic histological finding. A study from The Netherlands reported 5-year local control of 58% and overall survival of 38% for patients with R1/R2 resections [27].

Toxicity

Complications of pelvic radiotherapy are a function of the volume treated, the overall treatment time, fraction size, total dose, radiation energy and technique. Large field sizes, short overall treatment time, large fraction sizes (>2 Gy), low-energy radiation, the use of a two-field technique and the lack of computerized dosimetry all contribute to an increased incidence of radiation complications [2]. Other patient-related risk factors such as pelvic inflammatory disease, diabetes, hypertension, obesity, previous surgery and concurrent chemotherapy also increase the incidence and severity of complications. Willett et al. [28] reported a series of 28 patients with inflammatory bowel disease (18 with ulcerative colitis and 10 with Crohn's disease) treated with pelvic radiotherapy to 40 Gy or more for colorectal cancer. Severe acute toxicity was seen in 46% which caused 22% of patients to stop treatment. Acute toxicity was similar in ulcerative colitis and Crohn's disease; however, late toxicity was limited to patients with ulcerative colitis. For these patients specialized radiation techniques must be used in an effort to reduce total dose or exclude the small and large bowel from the radiation field.

The most frequent complications which occur in almost all patients include effects on the small bowel (diarrhea, cramping), the large bowel (proctitis, tenesmus, bloody or mucus discharge), the bladder (frequency, dysuria) and hematological toxicity (thrombocytopenia, leukopenia). The mechanism is primarily the depletion of actively dividing cells. In the small bowel, loss of mucosal cells results in malabsorption of fat, carbohydrate, protein and bile salts. These symptoms are transient and resolve within a few weeks after the end of radiotherapy. Concurrent chemotherapy increases gastrointestinal and hematological toxicity; acute grade 3+ toxicity occurred in 22% of patients in the chemoradiotherapy arm and in 4% in the radiotherapy only arm in the INT 0114 trial of postoperative combined modality treatment. The addition of chemotherapy increases acute toxicity more in the postoperative setting compared to preoperative. The German Rectal Cancer Group Trial reported 40% grade 3–4 toxic events in the postoperative group and 23% in the preoperative group [15].

Long-term complications occur less frequently about 6–18 months after completion of radiation. Injury to the vascular and supporting stromal tissues of the bowel is the presumed pathophysiology. The most common complications are due to small bowel damage and include enteritis, proctitis, adhesions and small bowel obstruction requiring surgical intervention. In most series the incidence of mild to moderate late complications range from 8 to 15% and is directly proportional to the volume of small bowel in the radiation field. The effect of radiotherapy on sphincter function has not been properly assessed. However, in a recent prospective study preoperative radiotherapy given with conventional dose and technique had a minimal effect on sphincter function [29]. Patients though who received 25 Gy in 5 fractions in the Swedish trial had a significant increase in bowel frequency, incontinence, urgency and emptying difficulty and this impaired patients' social life 30% of the time compared with 10% with surgery alone [30]. Pelvic radiother-

apy can also have an adverse effect on sexual function especially if given as a short course. Irradiated males who participated in the Swedish trials had more ejaculation disorders than non-irradiated patients and erectile functioning deteriorated over time [31]. Finally, in the same study, an increased risk for second cancers in the irradiated group was seen in organs within or adjacent to the irradiated volume (relative risk 2.04) but not outside.

Improvements in Radiotherapy

In the past two decades, advances in diagnostic imaging, computer technology and accelerator design have resulted in new radiotherapy techniques such as the three-dimensional conformal technique (3D conformal RT) and the IMRT. These techniques include several aspects: appropriate patient immobilization, simulation using a CT simulator, three-dimensional conformal planning using multiple fields, treatment delivery with a high-energy linear accelerator, use of multileaf collimator to conform the treatment volume to the shape of the target and electronic portal imaging to ensure accurate daily setup. As a result, a homogenous dose distribution is maintained throughout the target volume while minimizing the dose to surrounding normal structures. In a report from the Photon Treatment Planning Collaborative Group, it was found that the most important contribution of the three-dimensional treatment planning in rectal cancer was the ability to localize the target volume and normal tissues at all levels [32]. In addition, a decrease in the volume of normal tissues in the radiation fields was also seen. Attempts are being made to selectively subtract the anal sphincter from the high-dose field in order to improve functioning outcome in patients with mid-rectal tumors scheduled for a low anterior resection [33]. Only lately, the IMRT technique with a five-field customized segmented plan has significantly reduced the volume of small and large bowel irradiated to high dose, which could potentially lead to less bowel toxicity [34].

Conclusions

To conclude:

- Significant progress has been achieved in the treatment of rectal cancer over the past 20 years. Combined modality therapy with the integration of optimal surgery, radiotherapy and chemotherapy has resulted in a significant reduction in local recurrence rates and also an improved survival.
- Optimizing outcome after treatment includes minimizing both the recurrence rate and the number of cancer-related deaths, as well as maximizing patients' quality of life. Yet, even as we await future trials to refine our treatment strategies, we must ensure best practices for patients with rectal cancer today.
- Preoperative staging is important and imaging by endorectal ultrasound or magnetic resonance should be routine.
- Surgery for rectal cancer should be performed by surgeons with training in the technique of TEM and adequate experience.
- Finally, pelvic radiotherapy should be planned and delivered by optimal technique and both radiotherapy and surgery need to be coordinated with evolving chemotherapy regimens.

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