Radiotherapy in rectal cancer

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Radiotherapy has an established role in the treatment of rectal cancer. In primary resectable cancer, numerous randomised trials have shown that particularly pre-operative, and to some extent also postoperative, radiotherapy substantially reduces the risk of local failure. This is seen also with total mesorectal excision. Secondary to the reduction in local failures, there is also a slight improvement in survival after pre-operative radiotherapy or postoperative radiochemotherapy. Using appropriate techniques, the morbidity of radiotherapy is low. In non-resectable cancer, radiotherapy may cause down-staging, allow surgery, and may cure some patients. Whether radiochemotherapy is more efficient has yet to be firmly established. The role of pre-operative radio(chemo)therapy to permit more sphincter-preserving procedures with adequate long-term function is not defined.

The 5-year survival for colorectal cancer has slowly improved during recent decades. Recently, even better survival has been reported for rectal cancer, constituting approximately one-third of all colorectal cancers, in certain populations[1,2]. This marked survival improvement for rectal, but not for colon, cancer has also been noticed in the most recent update of the Swedish Cancer Registry (Epidemiological Centre, Stockholm, Sweden, personal communication 2002). At present, 5-year cancer-specific survival is about 70% compared with below 50% some decades ago. It is likely that both better surgical techniques and greater use of radiotherapy have contributed to the most recently seen improvements in rectal cancer survival. The same therapeutic changes have not occurred in colon cancer, although it is likely that increased use of adjuvant chemotherapy introduced during the 1990s[3] will soon also have an impact on survival.

Between 10–15% of all newly diagnosed patients with rectal cancer have a tumour that has grown into adjacent, non-readily resectable organs. These patients are generally considered as primarily non-resectable. Approximately 15–20% of the patients have already developed distant metastases at the time of diagnosis. Among those having undergone apparently curative surgery, the two main reasons for fatal outcome are occult distant metastases not found at surgery and a locoregional recurrence. A locoregional failure has been frequently seen even after locally curative surgery, and is likely the result of inadequate

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lateral clearance[4]. A locoregional recurrence or a primary rectal cancer that cannot be removed is also accompanied by severe suffering for the patient, with pain, bleeding, soiling, ulceration and fistulation as common symptoms, all of which profoundly reduce the patient's quality-of-life[5].

The present report concerns, firstly, radiotherapy given either pre- or postoperatively to a primary rectal cancer considered to be operable. In this situation, the aim is to prevent a local recurrence by eradicating the cancer cells not (to be) excised during surgery, as well as to improve survival. Radiotherapy has the possibility to eradicate entirely subclinical deposits of cancer cells that are not readily removed by surgery without extensive morbidity, provided the dose is adequate. Secondly, pre-operative radiotherapy, alone or in combination with chemotherapy, applied to a primarily non-resectable rectal cancer as well as a locally recurrent cancer is reviewed. In this situation, the aim of radiotherapy is to cause down-staging, allowing subsequent surgery, in order to avoid severe morbidity and, in some cases, to cure. Thirdly, pre-operative radiotherapy given to a low-lying rectal cancer in order to increase the chances of preserving anal sphincter function is reviewed. Radiotherapy alone to early, small rectal cancers is not included. Radiotherapy has no documented role in colon cancer, and so this is not discussed either.

Radiotherapy in primarily operable rectal cancer

Radiotherapy for rectal cancer has been the subject of two systematic overviews, one based upon published data only[6], and the other based upon individual patient data (Table 1)[7]. Altogether, 25 trials (22 were included in the meta-analysis) have been identified that have compared radiotherapy in one group with no radiotherapy in another. Of these, 17 have compared pre-operative radiotherapy with no pre-operative radiotherapy and 8 have compared postoperative radiotherapy with no postoperative radiotherapy (chemotherapy was invariably used in some of the trials; Table 2). In addition, one trial compared pre-operative and postoperative radiotherapy[8]. Four other similarly designed trials are on-going or have completed patient recruitment but no results are known. Finally, one trial compared postoperative radiotherapy to the pelvis alone with post-operative radiotherapy to the pelvis, para-aortic nodes, and liver[9].

The trials have used different radiation schedules with different fraction sizes. In the pre-operative trials, one group of trials used 1–5 fractions of 5 Gy and another used so-called conventional fraction sizes of 1.8–2.0 (or 2.3) Gy. In the postoperative trials, only conventional fractionation (1.8–2.0 Gy) was used. In order to compare doses, the trials were ranked according to the linear quadratic time (LQ-time) model, explained in Table 1. The pre-operative trials were in the meta-

Table 1 Radiotherapy in operable rectal cancer, results of a systematic overview

Reference	Colorectal Cancer Collaborative Group[7], 2001
Treatment groups	Surgery alone *versus* surgery and preop or postop RT, meta-analysis of 22 trials starting before 1987. 6350 patients in 14 preop trials 2157 patients in 8 postop trials

Results

Treatment group		Reduced overall death rate (SE)			Reduced rectal cancer death rate (SE)			Relative reduction isolated local failure (SE)			Increase in non-rectal cancer death rate (SE)		
Preop BED	< 20 Gy	6%	(9)	$P = 0.6$	11%	(11)	$P = 0.3$	–20%	(29)	$P = 0.05$	5%	(16)	$P = 0.8$
Preop BED	20–30 Gy	1%	(5)	$P = 0.9$	1%	(6)	$P = 0.9$	24%	(15)	$P = 0.10$	1%	(10)	$P = 0.9$
Preop BED	30+ Gy	10%	(5)	$P = 0.04$	22%	(5)	$P = 0.00002$	57%	(7)	$P < 0.00001$	37%	(12)	$P = 0.001$
Preop, all		6%	(3)	$P = 0.09$	13%	(4)	$P = 0.0006$	46%	(6)	$P < 0.00001$	15%	(7)	$P = 0.02$
Postop all	(35+ Gy)	5%	(6)	$P = 0.4$	9%	(7)	$P = 0.2$	37%	(10)	$P = 0.00002$	12%	(14)	$P = 0.1$

Conclusion/comments	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 (see Table 5). The effect on overall survival is limited. Preop RT (at BED 20–30 Gy) results in a slight reduction of local failures, but has no influence on survival. No significant effects are seen using lower preop doses. Postop RT (at BED 35+ Gy) reduces the risk of local failure (less than preop RT), but has no influence on survival.

BED, biological effective dose, calculated as:

$$\text{LQ-time} = \quad n \times d \left(1 + \frac{d}{\alpha/\beta} \right) - \frac{\gamma}{\alpha} (T - T_k)$$

where n = number of fractions, d = dose (Gy) per fraction, α/β = the common linear-quadratic quotient (set to 10 Gy), γ/α = repair rate (set to 0.6 Gy/day), T = the total treatment time (days) and T^k = the initial delay time (days, set to 7 days). The choice of coefficients reflects acute effects. RT, radiotherapy; SE, standard error.

Table 2 Pelvic recurrences after a combination of surgery and radiotherapy in rectal cancer (controlled trials with a surgery-alone/no radiotherapy group)

Trial[a]	Total dose (Gy)	Fractions (*n*)	BED[b] (Gy)	Local recurrences[c] Control group	Local recurrences[c] RT group	Relative reduction
Pre-operative						
Standard surgery						
MRC1	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%)	28/148 (19%)	12
St Marks	15	3	22.5	51/210 (24%)	31/185 (17%)	29
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
Dresden	15.5	5	20.3	9/37 (24%)	5/40 (13%)	49
North-West	20	4	30.0	58/141 (41%)	26/143 (18%)	65
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[18]	25	5	37.5	120/425 (28%)	61/424 (14%)	50
SRCT 17	25	5	37.5	150/557 (27%)	65/553 (12%)	60
TME surgery						
Dutch TME[13]	25	5	37.5	72/907 (8%)	23/897 (3%)	71
Postoperative						
Odense	50	25	35.4	57/250 (23%)	46/244 (19%)	17
MRC3	40	20	36.0	79/235 (34%)	48/234 (21%)	38
GITSG[20]	40–48	23–26	39.4	27/106 (25%)	15/96 (16%)	36
NSABP R-01[23]	46.5	26	39.3	45/184 (24%)	30/184 (16%)	33
NSABP R-02[25]	50.4	28	39.8	47/348 (14%)	27/346 (8%)	42
EORTC	46	23	40.8	30/88 (34%)	25/82 (30%)	13
Rotterdam	50	25	43.8	28/84 (33%)	21/88 (24%)	41

[a]For remaining references, see the meta-analysis[7].
[b]See Table 1 for an explanation of the calculation of biological effective dose (BED).
[c]Total recurrences, and not only those occurring as an initial event.

analysis[7] arbitrarily placed in three groups with LQ-times below 20 Gy, between 20 and 30 Gy and above 30 Gy (maximum 37.5 Gy). All postoperative trials fell in the 30+ Gy group (range 35.4–43.8 Gy).

Local recurrences after surgery alone

In the randomised trials including a surgery-alone group, the surgery-alone group has, with two exceptions, shown a local recurrence rate exceeding 20% (average 28%; Table 2). This figure represents the results achieved after a follow-up generally exceeding 5 years using standard rectal cancer surgery world-wide. During the past decade,

however, it has been repeatedly claimed that surgery has not been optimal in the trials generally recruiting patients during the 1980s and that fewer local recurrences can be obtained if surgery is improved. Lower figures were also reported from institutions with devoted and well-trained surgeons[10,11]. Improved lateral clearance after a careful dissection in the plane outside the fascia surrounding the mesorectum is likely responsible for the markedly lower local recurrence rates. The term total mesorectal excision (TME) is often used for this type of surgery, even if the entire mesorectum is not always excised in high rectal cancers. A concentration of rectal cancer surgery to a colorectal cancer unit and an extensive surgical training programme have also resulted in low local failure rates (approximately 10–12% after 2–5 years) in unselected patient populations[2,12]. TME has consistently in all patients only been used in one randomised trial, with a local failure rate of 8% in the surgery-alone group after 2 years of follow-up[13].

Local recurrences after surgery and radiotherapy

Statistically, significantly lower local recurrence rates have been seen in most trials comparing pre-operative radiotherapy followed by surgery with surgery alone, and in some of the trials comparing surgery with or without postoperative radiotherapy (Table 2). When all trials were analyzed in a meta-analysis, a dose-dependent influence on local failure rates was seen in the pre-operative trials (low doses have very low, if any, activity) and pre-operative radiotherapy appeared to be more dose-efficient than postoperative (a lower pre-operative dose is more efficient than a higher postoperative). The latter statement was confirmed in the only trial having directly compared pre- and postoperative radiotherapy (Table 3)[8]. These dose-response relationships, using all available evidence, have been more extensively analyzed[14,15].

In the above-mentioned trials, being part of the meta-analyses[6,7], surgery was not standardized. In the collected analyses, and in analyses of the pre-operative trials having sufficient patient numbers, a reduction was seen in all stages and at all tumour heights. In the postoperative trials, only stages II and III were included.

Even if, on theoretical grounds, it was likely that pre-operative radiotherapy at a sufficiently high radiation dose would be at least as effective in combination with more optimized surgery, like TME, leaving fewer and smaller peripherally located tumour deposits behind than standard surgery, the magnitude of the benefit was not known, and the balances between toxicity (and costs) and efficacy were unclear, a large co-operative trial was initiated[13]. In a multicentre setting, the trial could show that the local failure rate was further significantly reduced by radiotherapy (Table 3).

Table 3 Radiotherapy in operable rectal cancer: summary of results of randomised trials not included in the meta-analysis

Reference	Treatment groups	Patient population	Results	Conclusion/comments
Uppsala[8], 1993	(A) Preop RT (5 × 5.1 Gy, BED 37.8) + surgery	1980–1985	**5-year local failure rate** (A) 13%, (B) 22%, $P = 0.02$	Short-term preop RT is more efficient in reducing local failures than postop conventional RT, and less toxic
	(B) Surgery + postop RT (25 × 2 Gy, BED 52.2) to stages II + III	(A) 236 patients (B) 235 patients	No increased postop mortality No survival difference	
			10-year risk of ileus Surgery alone 6% Preop RT + surgery 5% Surgery + postop RT 11%, $P = 0.01$	Preop RT (3 beams) does not increase postop mortality
TME[13,39], 2001	(A) TME alone	1996–1999 1805/1861 eligible	**2-year local failure rate** (A) 8.2%, (B) 2.4%, $P < 0.001$	Short-term preop RT reduces the risk of local failure also with TME. The relative reduction appears to be higher with TME (71%) than with non-standardised surgery (see Table 2 and Fig. 1)
	(B) Preop RT (5 × 5 Gy, BED 37.5) + TME	(A) 937 patients (B) 924 patients	**2-year overall survival** (A + B) 82%, $P = 0.8$	
			No increased postop mortality	Preop RT (3 or 4 beams) does not increase postop mortality
Bosset[9], 2001	(A) Postop RT pelvis only (50 Gy/25 fractions)	1983–1992 451/484 eligible	**10-year disease-free and overall survival** Similar	Low dose postop RT to an extended volume does not improve survival
	(B) Postop RT pelvis (50 Gy), para-aortic nodes + liver (25 Gy/19 fractions)	(A) 229 patients (B) 222 patients	**10-year local failure rate** 30% both groups	
Lyon[48], 1999	(A) RT 13–3 Gy, surgery after 2 weeks	1991–1995 201/210 eligible	**Sphincter preserving procedure**	Down-staging is seen after a long interval, but the only randomised trial completed so far does not provide strong support for more sphincter preserving procedures.
	(B) Same RT, surgery after 6–8 weeks	(A) 99 patients (B) 102 patients	(A) 68%, (B) 76%, NS No other differences detected	

BED, biological effective dose – for calculation see Table 1; CHT, chemotherapy; RT, radiotherapy; TME, total mesorectal excision.

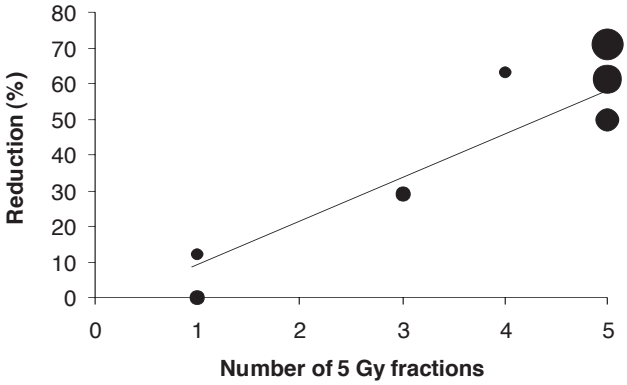

Fig. 1 The relative reduction in local failure rates according to number of 5 Gy fractions. The size of the symbols is proportional to the number of patients in the trials. The three large trials giving 5 fractions are, from the top, the TME trial[13], the Swedish Rectal Cancer trial[17] and the Stockholm I trial[18]. The line is drawn by hand. Reprinted from Glimelius and Isacsson[16] with the permission of Taylor and Francis.

Importance of radiation fractionation

As mentioned above, and shown in Table 2, the pre-operative trials used either a conventional fractionation (10–20 fractions of about 2 Gy) or a few (generally 5) fractions of 5 Gy. A reduction in local failure rates was seen using both schedules. No trial has directly compared the two fractionation schemes, and it thus cannot be deduced from literature whether one way is superior to another in reducing local failures. Different schedules were used in the trial comparing pre-operative and postoperative radiotherapy[8], revealing the superiority of pre-operative 5 × 5.1 Gy (biological effective dose [BED] 37.8 Gy) to postoperative 30 × 2 Gy (BED 47.8 Gy) radiotherapy, but the relative importance of the fractionation can not be evaluated. Besides antitumour activity, the two ways of fractionation have different advantages and disadvantages with respect to normal tissue toxicity and costs[16].

In the trials using one or multiple fractions of 5 Gy, a clear dose-response relationship can be seen (Fig. 1). It can also be seen that the relative reduction in local failure rates was higher in the TME trial[13], having better lateral clearance, than in the Swedish Rectal Cancer Trial[17] and the Stockholm I trial[18]. This supports the notion given above that the relative efficacy of radiotherapy is higher with good surgery[19].

Survival after surgery and radiotherapy

In the two meta-analyses of pre-operative radiotherapy trials, overall survival was better in patients randomised to radiotherapy (see Table 1

for the analysis based upon individual patient data)[6,7]. When rectal cancer mortality was analyzed in the pre-operative trials, a highly statistically significant improvement was seen. In the TME trial[13], follow-up is still too short to allow any meaningful survival analysis, but no difference was seen after 2 years (Table 3).

Postoperative radiotherapy alone has not improved overall or rectal cancer survival in any of the individual trials, nor in the meta-analysis (Table 1)[7]. The addition of low-dose irradiation to the para-aortic nodes and liver did not improve survival in one trial (Table 3)[9]. A survival gain has been reported in some postoperative trials, but only when radiotherapy was combined with chemotherapy (Table 4)[20–22]. Due to differences in the way the chemotherapy and radiotherapy were given between the trials, with a survival gain from chemotherapy alone in one trial[23] and negative results from two recent trials[24,25], it is impossible to elucidate the relative importance of either modality alone or a particular combination for any survival gain. A recent report indicates that delaying the start of the radiochemotherapy worsens the results[26].

Toxicity of pre-operative and postoperative radiotherapy

Toxicity from various treatments is important, particularly when one treatment, like radiotherapy, is given in addition to another treatment, like surgery, to improve treatment results. Patients already cured by the surgery will then be overtreated, and only subjected to toxicity. The balance between favourable effects to some patients and potentially negative effects from a (neo-)adjuvant therapy to all patients has been of great concern and the topic of many reviews[27]. In rectal cancer trials, the greatest concern has been increased postoperative morbidity and mortality from pre-operative radiotherapy. Other acute and late effects from both pre- and postoperative radiotherapy have also been seen and are the topic of several studies[8,28–38].

Analyses of the trials have shown that the toxicities are dependent upon the radiation technique, *i.e.* lower risks were seen in trials where the radiation burden was smaller, either because of smaller target volumes or better conformed techniques. This finding is not unique to rectal cancer trials, and has created much uncertainty in the interpretation of rectal cancer trial data. Most studies having explored different toxicities have used 5 × 5-Gy fractions pre-operatively, and thus knowledge of both acute and late toxicity in relation to both surgical and radiation techniques is much more pronounced using this than other fractionation schedules.

In the trials using conventionally fractionated pre-operative radiotherapy or a single fraction of 5 Gy, no increased postoperative mortality was seen. The results of the trials using 5 fractions of 5 Gy are shown in Table 5. An increased postoperative mortality was seen in the trial using two anterior-

Table 4 Postoperative radiotherapy, chemotherapy or radiochemotherapy: results of randomised trials in rectal cancer stages II + III (trials only comparing two RT-CHT regimens are not included in the table)

Reference	Treatment groups	Patient population	Results	Conclusion/comments
GITSG 7175[20] 1985	(A) Surgery alone (B) Surg + RT 40–48 Gy (C) Surg + CHT (MF) (D) Surg + RT + 5-FU + CHT (MF)	1975–1980 202/227 eligible (A) 58 patients (B) 50 patients (C) 48 patients (D) 46 patients	**5-year local failure rate** (A) 24%, (B) 20%, (C) 27%, (D) 11%, NS **6-year overall survival** (A) 28%, (B) 43%, (C) 43%, (D) 57%, $P = 0.05$	Small trial, prematurely interrupted, supports the benefit of postop RT-CHT. Increased acute toxicity was seen
NCCTG 794751[21,33] 1991	(A) RT 45 Gy ± boost 5.4 Gy (B) RT + 5-FU + CHT (MF)	1980–1986 204/209 eligible (A) 100 patients (B) 104 patients	**5-year local failure rate** (A) 25%, (B) 14%, $P = 0.04$ 5-year overall survival (A) 47%, (B) 58%, $P = 0.04$	Supports the benefit of combined RT-CHT over RT alone Increased acute toxicity, particularly diarrhoea (grade 3—4 22% *versus* 4%, $P = 0.001$)
NSABP-R01[23] 1988	(A) Surgery alone (B) Surgery + RT 46.5 Gy (C) Surgery + CHT (MOF)	1977–1986 555/574 eligible (A) 185 patients (B) 184 patients (C) 187 patients	**5-year local failure rate** (A) 25%, (B) 16%, (C) 21%, NS **5-year overall survival** (A) 43%, (B) 41%, (C) 53%, $P = 0.05$	No benefit was seen with postop RT. A survival benefit was seen with CHT alone challenging the results of the GITSG 7175 trial. The benefit was restricted to males
ECOG-EST[51] 1991	(A) RT (B) CHT (MF) (C) RT + CHT	1986–? 248 eligible 237 evaluable	**Overall survival** (A) 46%, (B) 47%, (C) 50%, NS	Only reported as an abstract. No concomitant CHT was given. Gives no evidence of any survival benefit
Tveit[22], 1997	(A) Surgery alone (B) Surgery + RT + 5-FU	1987–1991 (A) 72 patients (B) 72 patients	**Local failure rate** (A) 32%, (B) 11%, $P = 0.01$ **Overall survival** (A) 49%, (B) 63%, $P = 0.05$	Small trial, but supports the benefit of concomitant RT-CHT without prolonged CHT
Cafiero[24], 2000	(A) RT 50 Gy (B) CHT–1 + RT + CHT–5 (5-FU + levamisol)	1992–1998 (A) 108 patients (B) 110 patients	**Local failure rate** (A) 15%, (B) 21%, NS **Projected 5-year survival** (A) 56%, (B) 39%, NS	No benefit was seen with CHT in addition to postop RT. Increased acute toxicity, with sign more severe enteritis ($P = 0.03$)
NSABP-R02[25] 2000	(A) CHT (MOF or FLv) (B) CHT + RT 45 Gy + boost 5.4 Gy + 5-FU + CHT	1987–1992 694/742 eligible (A) 348 patients (B) 346 patients	**8-year initial local failure rate** (A) 14%, (B) 8%, $P = 0.02$ **8-year overall survival** (A) = (B) 58%, $P = 0.9$	RT with CHT decreases local failure rates but does not improve survival

CHT, chemotherapy; 5-FU, 5-fluorouracil; FLv, 5-FU + leucovorin; MF, methylCCNU + 5-FU; MOF, methylCCNU + vincristine + 5-FU; RT, radiotherapy; RT-CHT, radiochemotherapy; NS, not significant.

Table 5 Radiotherapy volumes in trials using 5 × 5 Gy and postoperative mortality

Volume	Stockholm[18] Mid L2 2-beams	Uppsala[8] Mid L3 3-beams	SRCT[17] Mid L4 3/4 beams	Stockholm II[30] (As SRCT, but no shields)	TME[39] Mid L5 3/4 beams
PTV (L)	1.5	1.2–1.4	1.3	1.3	1.0–1.2
$TV^{95\%}$ (L)	5.6	2.1–2.4	2.1	2.5	1.6–1.9
$TV^{95\%}$ bowel (L)	1.8	0.5	0.4	0.5	0.3
Energy imparted (J)	310	210–250	190	270	140–170
Increased postop mortality	Yes	No	No	Tendency	No

L2–5, upper beam limit at lumbar vertebra 2–5; PTV, planning target volume; TV, treated volume. The variability in the volumes seen in two trials depends upon whether the anal canal was included in the target or not. See also Frykholm-Jansson *et al*[29].

posterior (AP–PA) beams, but not in any of the other trials. It thus appears as if there is a correlation between radiation volume and influence on the postoperative course. This has been separately analyzed in a model study[29].

In the meta-analysis (not including the TME-trial) using individual patient data[7], a statistically significantly increased non-rectal cancer death rate was seen in the pre-operatively irradiated group (Table 1). It was restricted to the first year after randomisation. Increased non-rectal cancer deaths were also seen in the postoperative trials, but these were statistically non-significant.

Pre-operative radiotherapy has generally been better tolerated than postoperative. This was also seen in the single trial comparing pre- and post-operative radiotherapy[8]. In all pre-operative trials, *i.e.* irrespective of whether conventional fractions of about 2 Gy or high fractions of 5 Gy were used, more perineal complications after an abdominoperineal resection were seen in irradiated patients[16,39].

There is still limited knowledge of the late effects of radiotherapy. Again, most of the knowledge comes from the Swedish trials using 5 × 5 Gy[8,31,40]. Several trials have described that the sphincter function in patients operated with a low anterior resection is poorer in postoperatively[35–37] and pre-operatively[38] irradiated patients than in those not irradiated. In order to diminish this risk, the anal canal should not be included in the target volume unless the tumour is situated in the lowest third of the rectum[41].

Increased risk of postoperative ileus has been seen in trials irradiating large volumes of small bowel, either pre-operatively[31] or postoperatively[28,34], but not when smaller volumes were irradiated[8,28,31].

Radiotherapy in inextirpable rectal cancer

In these patients, a surgical resection can be suspected to leave gross residual disease behind. There is no uniform definition of what constitutes irresectability. Overgrowth to organs or tissues not readily

Table 6 Radiotherapy alone compared with radiotherapy plus chemotherapy in non-resectable rectal cancer: results of randomised trials

Reference	Treatment groups	Patient	Results population	Conclusion/comments
Moertel[43] 1969	(A) RT 35–40 Gy + placebo (B) RT 35–40 Gy + 5-FU	(A) 33 patients (B) 32 patients	**Mean survival (months)** (A) 17, (B) 25, $P < 0.05$ **3-year survival** (A) 9%, (B) 19%, NS	Colon and rectum together (the study also included patients with gastric and pancreatic cancer). This study was interpreted early to show that RT-CHT (3 days of 5-FU) was superior to RT alone
Rominger[44] 1985	(A) RT 45–51 Gy + boost (B) same RT + 5-FU + maintenance CHT	129/147 evaluable (A) 65 patients (B) 64 patients	**2-year survival** (A) 36%, (B) 44%, NS No difference in failure pattern More complications in (B)	No difference between RT-CHT and RT, increased risk of complications
Overgaard[45] 1993	(A) RT 50 Gy + boost (B) Same RT + weekly 5-FU	(A) 29 patients (B) 30 patients	**3-year survival** (A) 7%, (B) 16%, NS **Acute toxicity** (A) 13%, (B) 33%, $P = 0.07$	Significant palliation in 73%, no difference between groups, except more toxicity with RT-CHT
Frykholm[46] 2001	(A) 46 Gy RT (B) 40 Gy RT split course + methotrexate + 5-FU + leucovorin	(A) 36 patients (B) 34 patients	**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 that RT-CHT is superior to RT, but did not have the same RT schedule in the two arms

5-FU, 5-fluorouracil; LFS, local failure-free survival; OS, overall survival; RT, radiotherapy; RT-CHT, radiochemotherapy; NS, not significant.

resectable, like the base of the urinary bladder or the bony pelvis, and very large non-mobile tumours, generally indicate irresectability, although some would claim that a multidisciplinary surgical approach would allow a radical resection.

There is no randomised trial that has compared pre-operative radiotherapy aiming at rendering the tumour resectable through sterilizing the tumour overgrowth with other therapeutic approaches, including attempts at extended surgery. Marked tumour regressions, even complete, and long-term disease-free survival were early seen in trials giving pre-operative radiotherapy or radiochemotherapy during 4–5 weeks. Thus, the evidence is only indirect that pre-operative radio(chemo)therapy increases the chances of radical resection and cure. If tumour growth in the pelvis can not be controlled, the patients will suffer severely from pain and other symptoms, and median survival is about 8–10 months.

A great number of trials have reported that pre-operative radio(chemo)-therapy results in a radical resection in 40–80% of patients and that

20–30% will become long-term survivors (see Glimelius[42], and references quoted therein). Four of these trials have, in a randomised way, compared radiotherapy alone with 5-fluorouracil chemotherapy in addition to the radiotherapy (Table 6)[43–46]. These trials, all being small and sometimes with defective methodology, do not collectively provide supportive evidence that radiochemotherapy is superior to radiotherapy alone.

All other trials in patients with a locally irresectable (or locally recurrent) cancer are phase I or phase II trials, generally having explored a combination of concomitant chemotherapy and radiotherapy, or phase III trials comparing two schedules of chemoradiation. The individual trial data are not reviewed here since, due to their design, they do not add information as to whether radiochemotherapy is superior to radiotherapy alone or whether one combination is superior to another[42]. It is possible that patient selection is as relevant for treatment results as the particular schedule tested.

Sphincter preservation

During the past decade, the indication for pre-operative radio(chemo)-therapy in a tumour judged to be resectable has not only been to lower local failure rates but also to facilitate a sphincter-preserving procedure by decreasing the size of the tumour. This has been ascribed to a down-staging effect by the pre-operative therapy, although this term is inaccurate since it is not a decrease in stage, but in size, that is of relevance. The appropriate term should be down-sizing. There is, at present, no firm evidence that sphincter-preserving procedures will be possible more frequently after pre-operative therapy and that this will result in improved quality-of-life[47]. One randomised study noticed slightly more sphincter-preserving procedures in the long-interval group (Table 3)[48]. Slightly more sphincter-saving procedures were also found in the prematurely interrupted NSABP R-03 trial comparing pre-operative with postoperative radiochemotherapy (48% *versus* 39%, significance level not given)[49]. The pre-operative therapy tended to be more toxic than the postoperative (grade 4/5 toxicity 34% *versus* 24%, $P = 0.07$). A large German trial, presently still recruiting patients, has a similar design[50]. The neo-adjuvant therapy is well tolerated in the trial and bears no higher risk for postoperative morbidity. No results concerning sphincter preservation are presently available.

Besides these randomised trials, a large number of phase II trials have been reported (see Glimelius[42], and references quoted therein). The trials all claim that more restorative procedures were possible after the pre-operative prolonged radiochemotherapy course than would have been the case if no pre-operative therapy, or only radiotherapy, had been

given. In the lack of randomisation, these conclusions can not be made, and treatment results are not detailed.

The concept of pre-operative prolonged radio(chemo)therapy to allow a restorative procedure needs to be considered seriously, but also critically[42]. The two crucial questions are: (i) how often this will be the case; and (ii) what the long-term functional outcome will be? If the tumour is so close to the sphincter that a restorative procedure with a colo-anal anastomosis will leave tumour cells behind, the sphincters must be irradiated to a dose of about 50 Gy, even if sensitized with chemotherapy. This treatment carries a risk of a far-from-optimal late function, even if this has not been properly analyzed.

Key points for clinical practice

Based upon the literature review, the following conclusions can be reached:

- After rectal cancer surgery, a local failure generally causing severe suffering for the patient was frequently seen
- Radiotherapy in addition to surgery significantly diminishes the risk of local failure. Large, randomised trials have shown that pre-operative radiotherapy can decrease the relative risk by more than half (50–70%). Postoperative radiotherapy decreases the risk by 30–40% at doses that generally are higher than those used pre-operatively
- Pre-operative radiotherapy thus appears to be more effective than postoperative. This has also been seen in a randomised trial comparing pre- and postoperative radiotherapy
- Pre-operative radiotherapy has also slightly improved survival rates (by about 10%) whereas this has not been seen in the postoperative trials unless the radiotherapy was combined with chemotherapy
- The results after surgery have improved during the past decade (sharp dissection in an embryonic plane rather than a blunt dissection, surgical teaching programmes, feedback from pathology examinations, quality assurance). Although not formally tested in a randomised trial, it is likely that local failure rates after long follow-up at many hospitals adopting the TME concept have decreased from about 30% to 10–15%
- A large, randomised trial has revealed that pre-operative radiotherapy significantly decreases the local failure rate (from 8% to 2% after 2 years) also with TME. It is too early to evaluate whether survival also is improved
- Several radiotherapy schedules have been used in the pre-operative trials. In the absence of randomised trials comparing different radiation

schedules, it is impossible to define the most optimal pre-operative one. The largest experience in the trials is with a short-term schedule (5 × 5 Gy in one week with surgery in the next week)

- Pre-operative radiotherapy can be given with low toxicity. Higher, and unacceptable, toxicity (postoperative mortality and non-colorectal cancer deaths during the first year) has been seen in some pre-operative trials where unnecessarily large volumes received radiation due to suboptimal techniques. Postoperative radiotherapy can also be given with acceptable toxicity. The long-term consequences of radiotherapy have been less extensively studied, although they appear to be limited with adequate radiation techniques
- Radiotherapy, preferably pre-operative since it is more effective, is routinely recommended since it can substantially decrease the risk of local failure. Whether groups of patients with a very low risk of local failure (less than a few per cent) can be exempted from the radiotherapy is not properly known
- In the 10–15% of the patients who primarily present with a locally advanced, surgically inextirpable tumour, pre-operative radiotherapy can cause tumour regressions allowing subsequent radical surgery in a substantial proportion of the patients. This therapy also is routinely indicated in previously non-irradiated patients who develop a local recurrence. Whether radiochemotherapy is more efficient than radiotherapy alone is not clear from the literature since the few randomised trials have not shown any clear superiority
- Radiotherapy frequently causes symptom relief in a patient with rectal cancer not amenable to surgery
- Pre-operative radiotherapy, frequently combined with chemotherapy, has been used to increase the chances of sphincter-preserving surgery in low-lying tumours. The literature is inconclusive with respect to how frequently this occurs, and the long-term anal function, but several randomised trials are on-going

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