The role of radiotherapy in rectal cancer

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Introduction

Surgery is the predominant therapy for rectal cancer. During the past 10–20 years, radiotherapy and, more recently, radiochemotherapy have been increasingly used together with surgery in the primary management of patients with rectal cancer. The purpose of the radiotherapy has varied between four different clinical situations: (1) to lower local failure rates and improve survival in resectable cancers; (2) to allow surgery in primarily non-resectable cancers; (3) to facilitate a sphincter-preserving procedure in low-lying rectal cancers, and (4) to cure patients without surgery in those with either a very small cancer or in those at a very high surgical risk.

Clinical experience and trials have shown that radiotherapy has an established role in many patients in the first two situations, for some patients in the fourth situation [1], and, possibly, for patients in the third situation. Radiotherapy alone is best documented, although many would now claim that radiochemotherapy is superior in many situations.

This article will critically review present knowledge on the use of radiotherapy together with surgery in rectal cancer.

Resectable cancers to improve treatment results

Preoperative therapy

In patients with a resectable cancer, generally 85 to 90% of these patients will have a newly diagnosed rectal cancer, radio(chemo)therapy has been extensively used to lower unacceptably high local failure rates seen after surgery alone [2–4]. Large randomised trials have shown that preoperative radiotherapy can substantially decrease local failure rates (Table 1) and, unless counterbalanced by increased postoperative mortality seen particularly in one trial [5], slightly improve overall survival (Table 2) [6]. The survival benefit was seen only in trials using a moderately high biologically effective dose (LQ-times above 30 Gy, see Table 1). The survival benefit has been confirmed in two recent meta-analyses [7,8].

In the randomised trials reported during the past 10–20 years, the surgery-alone group has shown a local recurrence rate exceeding 20%, average 28% (see Tables 1 and 3). Many researchers have claimed that surgery has not been optimal in the trials and that fewer local recurrences can be obtained if surgery is improved. Lower figures have also been reported from institutions with devoted and well-trained surgeons [9,10]. A concentration of patients to a colorectal cancer unit and a surgical training programme have also resulted in low local failure rates in unselected patient populations, particularly when combined with preoperative radiotherapy [11,12]. In some centres, an even more radical procedure has been used than usually is the case, but with such a radical surgery, there is a definite risk of increased morbidity regarding sexual and bladder function [13].

There is much evidence indicating that the relative reduction in local recurrence rates that is seen after preoperative radiotherapy in the randomised trials will be at least of the same magnitude if the surgery is performed in a more optimal way. Improved lateral clearance will likely result in not only cell deposits being less frequently left, but also that the deposits, on average, are smaller. With the radiation doses used together with rectal cancer surgery, the likelihood of eradicating smaller rather than larger deposits is higher, even if still subclinical. Since more optimal surgery, compared with so-called standard surgery, results in fewer recurrences, the absolute number of patients who benefit will be reduced. This issue has been addressed in the recently completed multicentre trial administered from Leiden, Holland, where total mesorectal excision (TME)-surgery was mandatory. The results of the trial including 1861 patients have been preliminarily reported at the 1st Multidisciplinary Colorectal Cancer Congress in Holland in April 2001. It was then demonstrated that with good

Table 1
Pelvic recurrences after a combination of surgery and preoperative radiotherapy in rectal carcinoma (controlled trials with a surgery-alone group)

Preoperative trial [Ref.]	Total dose (Gy)	Number of fractions	Biological effective dose (Gy)[e]	Control group total recurrences	RT group total recurrences	Relative reduction
PMH [86]	5	1	7.5	NR	NR	NR
MRC1 [87]	5	1	7.5	118/275[a]	125/277[a]	0
	20	10	20.4		128/272[a]	0
St. Marks [66]	15	3	22.5	51/210[b]	31/185	29
VASAG II [88]	31.5	18	26.8	40/181[c]	37/180	0
Bergen [69]	31.5	18	26.8	31/131	24/138	29
VASAG I [89]	25	10	27.5	32/87[d]	27/93	22
North-West [90]	20	4	30.0	58/141	26/143	65
EORTC [70]	34.5	15	35.2	49/175	24/166	48
MRC2 [71]	40	20	36.0	65/140	50/139	22
Brazil [91]	40	20	36.0	16/34	5/34	68
Stockholm [92]	25	53	7.5	120/425	61/424	50
SRCT [6]	25	53	7.5	150/557	65/553	60

NR, Not reported.
[a] According to Suwinski et al. [93].
[b] Outpatient attenders only reported.
[c] Residual and recurrent disease related to the length of follow-up.
[d] Autopsy series only reported.
[e] Calculated as linear quadratic (LQ)-time $= n \cdot d\left(1 + \frac{d}{\alpha/\beta}\right) - \frac{\gamma}{\alpha}(T - T_k)$ 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 [16].
EORTC, European Organization for Research and Treatment of Cancer.
MRC, Medical Research Council.
PMH, Princess Margaret Hospital.
RT, radiotherapy.
SRCT, Swedish Rectal Cancer Trial.
VASAG, Veterans Administration Surgical Adjuvant Group.

Table 2
Survival after a combination of surgery and preoperative radiotherapy in rectal carcinoma (controlled trials with a surgery-alone group)

Preoperative trial [Ref.]	LQ-time[a]	Relative reduction in local failures	Colorectal cancer survival	Overall survival
PMH [86]	<30 Gy	NR	Similar	Similar
MRC1 [87]		0	Similar	Similar
St. Marks [66]		29	Similar	Similar
VASAG II [88]		0	Similar	Similar
Bergen [69]		29	Similar	Similar
VASAG I [89]		22	Similar	Similar
North-West [90]	30 + Gy	65	Tendency	Tendency
EORTC [70]		48	Tendency	Similar
MRC2 [71]		22	Tendency	Tendency
Brazil [91]		68	Improved	Improved
Stockholm [92]		50	Improved	Similar[b]
SRCT [6]		60	Improved	Improved

NR, not reported.
[a] See Table 1.
[b] Counterbalanced by increased postoperative mortality.
Abbreviations, see Table 1.

surgery and preoperative radiotherapy, a previously very common and, to most affected patients, severely disabling condition, namely local rectal cancer failure, could more or less be eradicated. The magnitude of the benefit from radiotherapy must await a longer follow-up; after a median follow-up of 2 years, 2% local failures were seen in the combined group vs 8% in the TME only group. This is a highly statistically significant difference ($P < 0.0001$). These results are virtually identical to those seen in two Swedish pop-

Table 3
Pelvic recurrences after a combination of surgery and postoperative radiotherapy in rectal carcinoma (controlled trials with a surgery-alone group)

Postoperative trial [Ref.]	Dose (Gy)	Number of fractions	Biological effective dose (Gy)[a]	Control group total recurrences	RT group total recurrences	Relative reduction
Odense [78]	50	25	35.4	57/250	46/244	17
MRC3 [94]	40	20	36.0	79/235	48/234	38
GITSG [18]	40–48	23–26	39.4	27/106	15/96	36
NSABP R-01 [20]	46.5	26	39.3	45/184	30/184	33
EORTC [95]	46	23	40.8	30/88	25/82	13
NSABP R-02 [23]	50.4	28	39.8	47/348	27/346	42
Rotterdam [96]	50	25	43.8	28/84	21/88	41

[a] See Table 1 for an explanation of the calculation.
EORTC, European Organization for Research and Treatment of Cancer.
MRC, Medical Research Council.
GITSG, Gastrointestinal Tumor Study Group.
NSABP, National Surgical Adjuvant Breast and Bowel Project.
RT, radiotherapy.

ulation-based studies after a comparable follow-up time [11,12]. It is too early to evaluate any influences on overall survival in the TME-trial, although, so far, no difference has been detected. The Dutch trial also again showed that preoperative radiotherapy according to the Swedish model (5 × 5 Gy in one week) followed by surgery is safe [14]. The time interval between the end of the radiotherapy and surgery should be short, as was the case in the Swedish Rectal Cancer Trial (SRCT), and not exceeding 3–4 days in order to keep the toxicity levels low [6].

Postoperative radiotherapy

Randomised trials have also shown that postoperative radiotherapy may decrease local failure rates, although to a lesser extent than those rates reached following preoperative radiotherapy [8,15,16], but without any influence on overall survival. This was also seen in the only trial that compared preoperative and postoperative radiotherapy [17]. Postoperatively, radiochemotherapy, rather than radiotherapy alone, has been used in several of the trials and has shown a tendency to decrease local failure rates and significantly improve survival compared with surgery alone or surgery and postoperative radiotherapy (Table 4) [18–21]. A survival benefit was, however, seen by postoperative chemotherapy alone without any radiotherapy in one trial (National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol R-01) [20].

Based upon the results of three of the randomised trials mentioned above [18–20], a US National Institute of Health (NIH) Consensus conference in 1990 recommended postoperative radiochemotherapy as standard treatment for rectal cancer in stages II and III [22]. It is, however, possible that the survival benefit can mainly be ascribed to the systemic effects of the chemotherapy component and not to improved local control. The Gastrointestinal Tumor Study Group (GITSG) trial was severely under-powered to reveal any benefit from either radiotherapy or chemotherapy alone [18]. The conclusion is further supported by a follow-up trial by the NSABP (Protocol R-02). In the trial including 694 patients, the radiotherapy had no beneficial effect on disease-free or overall survival, although it reduced the incidence of locoregional relapse from 13% to 8% at five-years of follow-up ($P = 0.02$) [23]. The role of the radiotherapy component in the postoperative radiochemotherapy treatment as regards the survival gain may thus be questioned. Postoperative radio(chemo)therapy has never been tested with TME, and it is thus impossible to tell whether the relative effects will be the same as seen in the trials using 'standard' surgery. The advantage with postoperative therapy is that only those at high risk to recur will be treated, but it is not known whether the therapy will decrease the risk in, e.g. those with lateral margin involvement (<1 mm). The preliminary results from the Dutch TME trial illustrate that radiotherapy will not be sufficient. This was also seen in the Uppsala trial performed 15–20 years ago [17]. Several randomised trials are now testing preoperative therapy, often using the Swedish 5 × 5 Gy schedule, against selective postoperative radiochemotherapy.

In a Norwegian trial, 144 patients were randomised to surgery alone and postoperative radiotherapy with bolus 5-fluorouracil (5-FU) given only during the radiotherapy [21]. A clear benefit con-

Table 4
Influence on local failure rates and survival in rectal carcinoma by postoperative radiotherapy, chemotherapy or both (controlled trials)

Trial [Ref.]	Number of patients	Surgery alone		Radiotherapy		Chemotherapy		Radiochemotherapy	
		LF (%)	S (%)	LF (%)	S (%)	LF (%)	S (%)	LF (%)	S (%)
GITSG [18]	202	24	43	20	52	27	56	11	59[a]
NCCTG [19]	204			25	47			14[a]	58[a]
NSABP-R01 [20]	555	25	43	16	41	21	53[a]		
ECOG-EST [24]	237			–	46	–	47	–	50
Norway [21]	144	32	49					11[a]	63[a]
NSABP-R02 [23]	694					13	64	8[a]	64

[a] Denotes a statistically significant difference against the control group ($P < 0.05$).
LF = local failure; S = overall survival.
NSABP, National Surgical Adjuvant Breast and Bowel Project.
GITSG, Gastrointestinal Tumor Study Group.
ECOG, European Co-operative Oncology Group.
NCCTG, North Central Cancer Therapy Group.

cerning both local control rate and survival was seen, indirectly supporting the relevance of the concomitant administration. In another US trial (Eastern Co-operative Oncology Group, ECOG study EST 4276), only reported as an abstract, no influence on either local control rate or survival was seen from sequential postoperative radiotherapy and chemotherapy compared with surgery alone [24]. A Hellenic group studied the value of adding three cycles of bolus 5-FU and leucovorin after one cycle of the same regimen and radiotherapy with bolus 5-FU [25]. No difference could be seen in the trial including 220 patients, excluding a major influence on survival of the postoperative chemotherapy component. No influence on local control rates or survival could be seen in a large randomised trial including 1696 patients from the addition of either leucovorin or levamisole to 5-FU and radiotherapy [26]. Thus, there is no evidence that modulated 5-FU is superior to 5-FU alone when combined with radiotherapy, as is the case when chemotherapy is used alone for metastatic disease [27]. If radiochemotherapy is used postoperatively, protracted infusion of 5-FU is superior to bolus 5-FU during the radiotherapy [28].

Taken together, it is not possible to clearly state that a combination of chemotherapy and radiotherapy, given postoperatively to rectal cancer patients in stages II and III, is superior to either modality alone, although this may be the case.

Non-resectable cancer to allow subsequent surgery

In patients with a primarily non-resectable cancer, i.e. a cancer where a surgical resection most likely would result in gross residual cancer, preoperative radio(chemo)therapy has been used to cause tumour regression to allow radical surgery. Radical surgery has been possible in 30–70% of the patients. Three randomised trials have in this situation explored whether radiochemotherapy is superior to radiotherapy alone [29–31]. One early trial in gastrointestinal cancer including rectal cancer revealed that survival was slightly prolonged after combined treatment [29], whereas two subsequent trials could not detect any statistically significant differences [30,31]. An increased toxicity was shown when 5-FU was added to the radiotherapy. These small trials cannot exclude any clinically meaningful gain from combining radio- and chemotherapy in this setting. Major toxicity, both acute and late, was also seen in a randomised trial comparing two radiochemotherapy schedules [32]. The use of more appropriate radiation techniques and improved supportive activities may prevent the increased toxicity seen. Several large phase II studies have later shown that preoperative radiochemotherapy can safely be given to patients with non-resectable or locally recurrent rectal cancer [33–37].

Based upon favourable treatment results in these and other similar phase II trials, preoperative radiochemotherapy has been regarded as 'standard' therapy [33,38]. Clinicians have been impressed by apparently more favourable results than seen after radiotherapy alone. This together with extrapolations from the results of the postoperative trials in resectable cancers favouring radiochemotherapy, has resulted in a widespread use of the combined approach. This may be correct, but the scientific evidence is not strong. It could also be argued that if there is a beneficial effect of adding chemotherapy to radiotherapy after surgery, then it should be reasonable to have it before surgery. Increased toxicity may,

however, be more deleterious prior to surgery than after.

In a pilot study in primarily irresectable rectal cancer, a resectability rate of 71% was found using split-course radiotherapy (2 Gy to 40 Gy) with simultaneous sequential methotrexate, 5-FU and leucovorin (MFL) compared with 34% in a historical control group treated with radiotherapy (2 Gy to 46 Gy) only [39]. Even if the combination treatment appeared to be considerably better, it was important to compare the combined treatment with conventional irradiation in a randomised trial, since historical comparisons are difficult and the newer treatment is more toxic and resource demanding. When the results of the randomised trial were analysed [40], resectability rates were high in both groups (85 versus 75%, a non-significant difference). Greater surgical experience and aggressiveness are likely to be responsible for the improved treatment results. Local disease-free survival was, however, significantly superior in the combined group (66% compared with 38% at 5 years, $P = 0.03$), giving support to the notion that radiochemotherapy is more efficacious than radiotherapy alone. However, the radiotherapy schedules were different. Besides this, toxicity was higher, although manageable, with the combined treatment. For these reasons, a new trial has been initiated where the radiotherapy schedule is identical in the two groups. Three European trials, an EORTC trial (EORTC 22921), a French trial in resectable cancer and a Nordic trial in non-resectable rectal cancer, are presently testing the still unanswered question whether radiochemotherapy is superior to radiotherapy.

Locally advanced rectal cancer

An increasing number of phase II trials combining radiation and chemotherapy have been performed in patients with 'locally advanced' rectal cancer. 5-FU has been used most extensively [33–37,41–45] [46–52], although lately other drugs have also been used [53–55].

The results in a phase II trial are mainly dependent upon two factors, patient selection and treatment efficacy. The difficulties in clinically evaluating stage and resectability suggest that patient selection may be a major determinant of the results in the trials rather than the treatment. The distinction between a primarily non-resectable cancer (stage T_4 with overgrowth to non-resectable organ(s)), and a tethered/locally advanced cancer (stage T_3 and certain T_4's) is clear in theory, but difficult in practice. This is the reason why it is virtually impossible to draw conclusive efficacy data from non-randomised comparisons.

The results have, in general, improved in more recent years. This improvement has been seen in resectability rates, sphincter-preserving procedures (see also below), disease-free and overall survival, and, most recently, in the pathological complete remission (pCR) rate. In some trials, a pCR has been seen in 20–30% of the patients operated upon. Intuitively, this may be a relevant surrogate endpoint in order to pick up promising regimens for further testing [56]. It requires standardisation. Furthermore, the proportions of pCR are sensitive to inclusion criteria. In the earlier trials, most or all patients had locally inextricable disease (generally large T_4's), whereas in several of the most recent series, the majority have had ultrasonographically staged T_3 (uT_3). Although ultrasonography is an accurate method to evaluate tumour growth through the bowel wall [57], there is a tendency to overestimate growth through the muscular layer. Thus, as a group, ultrasonographically-staged tumours are smaller than clinically-staged ones. Recent claims of higher efficacy (more pCRs) using newer combinations should be interpreted with caution. Consequently, yet another phase II trial will not increase knowledge about the efficacy of a particular schedule.

Improved sphincter preservation

During the past decade, preoperative radio(chemo) therapy in a tumour judged to be resectable has increasingly been used to facilitate a sphincter-preserving procedure by decreasing the size of the tumour. This has often been ascribed to a downstaging effect, although this term is inaccurate since it is not a decrease in stage, but in size, that is of relevance. The cells that must be targeted are those distal to the macroscopic tumour and left behind if a sphincter-preserving procedure is performed, but removed with an abdominoperineal resection. This does not change the stage. The appropriate term should thus be down-sizing. For this purpose, radiochemotherapy has gained much popularity and is usually preferred to radiotherapy alone [52,58–63]. This conclusion is entirely based upon phase II data with no randomised trials. Again, it is thus not possible to judge whether radiochemotherapy will more often lead to a sphincter-preserving procedure than radiotherapy alone. Furthermore, there is actually no firm evidence that sphincter-preserving procedures will be possible more frequently after preoperative therapy and that this will result in an improved quality of life [64]. The Lyon group randomised 201 patients to a short interval (less than two weeks) or a long interval (6 to 8

weeks) after preoperative radiotherapy (39 Gy in 13 fractions), and noticed a tendency for more sphincter-preserving procedures to be found in the long interval group (76% versus 68%, $P = 0.3$) [65].

The concept of preoperative prolonged radio (chemo)therapy to allow a restorative procedure needs to be considered seriously, but also critically. The two crucial questions are, firstly, how often will this be the case and, secondly, what is the long-term functional outcome? It is possible that the chances have been overestimated and the risks underestimated. It is also possible that the proportion of patients who may benefit is greater with a less experienced surgeon than with a subspecialised, devoted colorectal cancer surgeon. It may feel safer to preserve the sphincter if the tumour is smaller and apparently further away from the sphincter. If the tumour is so close to the sphincter that a restorative procedure with a coloanal anastomosis will leave tumour cells behind, the sphincters must be irradiated to a dose of about 50 Gy, even if sensitised with chemotherapy. This treatment carries the risk of a far-from-optimal late function, even if this has not been properly analysed. Claims that the sphincters need not be irradiated to that dose only indicate that a sphincter-preserving procedure would have been possible even without the preoperative therapy.

Acute and late toxicity from radiotherapy

Of great relevance, particularly when the therapy is given as a (neo)-adjuvant therapy to surgery, is the acute and late toxicity from the additional therapy. Increased postoperative mortality after preoperative therapy has been of great concern. Although this has been seen in some trials [5,66], it has now been established that, properly given, preoperative radiotherapy is safe in this respect [14,67] (Dutch TME-trial Office, data presented in April 2001). It is important not to use unnecessarily large target volumes to conform the radiation beams to the target [68], and not to delay the surgery beyond a few days when 5 × 5 Gy is given.

Other acute concerns have been delayed perineal wound healing and increased anastomotic leakage rates. Delayed wound healing with perineal sepsis has been seen in virtually all preoperative radiotherapy trials, i.e. it is not restricted to trials using 5 Gy fractions [67,69–71]. It is usually of limited clinical relevance, although it prolongs the hospital stay by a few days. Anastomotic leakage rates are not increased, confirming the lack of influence by radiation on the strength of colon anastomoses in animals [72,73].

Acute neuropathic pain has been reported in some patients a few hours after a few 5 Gy fractions [74]. The risk of pain is dependent upon the volume of the spinal nerves being irradiated. The pain may, in rare instances, remain and may sometimes progress to a subacute neuropathy. In the few instances where this has occurred, it has generally been reversible.

When postoperative radiotherapy has been given, small bowel loops adherent in the pelvic cavity are at risk of being damaged from the radiotherapy. Several techniques have been used to prevent the small bowel from falling down into the lesser pelvis [75,76]. Despite this, there have been several reports on late morbidity due to intestinal obstruction after postoperative radiotherapy [77–79]. Another late adverse effect of radiation therapy is chronic diarrhoea, and together with small bowel obstruction, these effects have been related to the volume of the small bowel included in the treatment volume. If radiotherapy extends high up in the abdomen, the risk of small bowel obstruction has been reported to be as high as 30–40%, which should be compared with 5–10% when only the dorsal part of the pelvic cavity is included [77]. A direct correlation between the target volume and small bowel obstruction has also been demonstrated in the preoperative Stockholm–Malmö trial (5 × 5 Gy), where an increase in small bowel obstruction was found among the patients irradiated with two beams extending up to the second lumbar vertebra [80]. This has not been found in patients treated according to the SRCT protocol [81]. Also, in the Uppsala trial, all patients have been followed-up extensively and re-examined with respect to late adverse effects of irradiation. An increase in small bowel obstructions or other possibly late adverse effects was not seen among patients who received preoperative radiotherapy [17]. However, in the group of patients treated with postoperative radiotherapy, a significantly higher incidence of late irradiation-related adverse effects was found even if the radiation technique tried to avoid unnecessary irradiation of the small bowel.

Radiotherapy may also be detrimental to the sphincter function, but this has so far not been extensively investigated. There are indications that both postoperative radiotherapy [82–84], and preoperative radiotherapy [85] will negatively influence the anal function. A questionnaire study among all the survivors from the SRCT who were operated upon with a sphincter-saving resection noticed an altered sphincter function [85]. In the SRCT, the anal sphincters were included in the target volume. The reasons for this malfunction are unclear, but the irradiation might damage either the sphincters or the pudendal

nerves. It is important to take this into consideration, and exclude the sphincters from the target if not necessary, as in mid and high rectal tumours [15].

Conclusions

Radiotherapy has an established role in primary management to lower local failure rates in extirpable rectal cancers. The most recent evidence illustrates that the relative efficacy of preoperative radiotherapy is likely to be as high in connection with a more adequate surgical procedure, like TME as in less optimised procedures. The absolute benefit will, however, be smaller. Whether a minimal absolute reduction exists for routine use of preoperative radiotherapy in relation to toxicity and costs is not known. Since TME-like surgery alone will result in comparably few local recurrences, toxicity must be low, prompting the use of adequate radiation techniques.

Preoperative radiotherapy is more efficient and carries less toxicity than postoperative radiotherapy, although this knowledge is not always recognised. It is likely that preoperative radiotherapy and postoperative radiochemotherapy have the same effects on local recurrence rates and survival in combination with standard surgery, although the latter carries a much greater burden for the patients and the society. Whether postoperative radio(chemo)therapy will prevent recurrences in those with an R1/2 resection after TME is not known.

Radiotherapy also has an established role in primarily inextirpable rectal cancers to increase the chances of achieving local radical surgery. It is possible that radiochemotherapy is more efficient than radiotherapy alone in this situation, but the scientific support for this notion is not particularly strong. An optimal chemoradiation schedule is not known.

Preoperative chemoradiation has gained most popularity in low-lying rectal cancers to achieve more sphincter-preserving procedures. This concept is attractive, but needs to be proven in properly controlled trials. It is possible that the chances to increase sphincter preservation have been overestimated, and the late consequences of the therapy in the truly low-lying tumours are underestimated.

Even if the large conclusive trials during past 10–20 years have improved our knowledge about the effects of radiotherapy in primary rectal cancer, there is a continuous need for better planned trials with a conclusive design.

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