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The role of radiotherapy in rectal cancer

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Abstract

In Europe, short-term radiotherapy is increasingly used in the primary management of rectal cancer. In the United States, postoperative chemoradiotherapy is the standard treatment of choice. The rationale and indications for radiotherapy and possible combinations with chemotherapy are discussed and an overview of all of the randomised trials containing radiotherapy as one randomisation arm is given. Three major indications for radiotherapy can be identified: the reduction of local recurrences in mobile rectal cancer, downstaging of the tumour in primary irresectable tumours and downsizing of low-lying tumours in attempts to more frequently perform a sphincter-saving procedure. For reduction of local recurrences, radiotherapy can be given either pre- or postoperatively, although preoperative therapy is more dose-efficient. Short-term preoperative radiotherapy reduces the number of recurrences and improves survival. Improved survival is also reported after postoperative radiotherapy in combination with chemotherapy, however, the relevance of the radiotherapy component is discussed. Although the debate about radiotherapy is still ongoing, we strongly believe that the results demonstrate that short-term preoperative radiotherapy is the treatment of choice for resectable rectal cancer.

Keywords: Radiotherapy; Rectal carcinoma; Randomised trials; Review

1. General introduction

The basic treatment of infiltrating rectal carcinoma is radical surgery with or without sphincter preservation. Despite complete surgical resection of the tumour, 15–50% of the patients will have a local pelvic relapse after conventional surgery [1–3]. A local recurrence causes profound morbidity that severely impairs quality of life and usually leads to death. Symptoms include intractable pain, intestinal obstruction, perforation and septic complications. The high incidence of recurrence after conventional surgery and the acknowledgement of the importance of the circumferential margin [4] has stimulated the introduction of the total mesorectal excision (TME) [5–8], with the aim of reducing local recurrences with minimal morbidity.

The role of additional therapy (either radiotherapy, chemotherapy or the combination of both) in the management of resectable tumours has been an area of debate for a long time. Despite the fact that the first randomised trial investigating the role of radiotherapy was reported in 1959 [9], the question about the optimal treatment together with rectal cancer surgery is not yet resolved. The main reason for this is the marked change in the surgical results with the introduction of the TME concept.

This review discusses the indications and the rationale of radiotherapy, different treatment schedules, timing of treatment, adverse effects and treatment results in rectal cancer. The role of chemotherapy will be discussed for trials that had chemo-radiotherapy as a randomisation option.

2. Indications for radiotherapy

2.1. Reduction of local recurrences

The first and primary indication for radiotherapy in addition to surgery is to prevent local recurrences and, secondary to that, to improve survival. The radiotherapy may prevent the growth of cancer cells, which

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are not (to be) excised during surgery. The efficiency of radiotherapy is limited in cases with a large tumour burden; since only a limited proportion of the cells is killed per given fraction, a high dose is needed to reduce the number of cells in a large tumour. In patients with a positive resection margin in the TME trial (see below), preoperative radiotherapy did not appear to reduce the number of local recurrences after 2 years, whereas it had a significant beneficial effect on the prevention of local recurrences in patients with negative circumferential margins (C.A.M. Marijnen, LUMC, Leiden, The Netherlands). Apparently, the amount of tumour cells in patients with a positive margin was already too large to be cured by the radiation doses that safely can be given in connection with rectal cancer surgery.

Most trials have evaluated the role of radiotherapy in patients who underwent conventional surgery. This procedure implies partially blunt dissection of the rectal fascia, resulting in incomplete removal of mesorectal tissue. The residual tissue potentially contains tumour cells and is the rationale behind the application of radiotherapy. In order to reduce the viability of those tumour cells and consequently to improve local control, radiotherapy can be given either pre- or postoperatively. The issue of which timing is preferable will be addressed later.

The important role of circumferential margin involvement for local recurrences in resectable rectal cancer has been systematically addressed by Quirke and colleagues [4] and was confirmed in the TME trial [72]. With the introduction of TME, the incidence of local recurrences has decreased considerably [6–8]. This can be contributed to the technique by which the entire mesorectum, including the lateral extensions of the perirectal fat, is removed. However, the TME trial showed a beneficial effect of radiotherapy even in patients with wide circumferential resection margins (>1 cm), demonstrating that even after adequate TME tumour cells are left behind. Possibly, these tumour cells are present in lateral lymph nodes.

2.2. Downstaging

A second indication for radiotherapy is to achieve downstaging of the tumour in order to facilitate resection of a locally irresectable tumour. Obviously, preoperative radiotherapy is the only suitable option for this aim. Downstaging after preoperative radiotherapy is dependent on the fraction size and total dose applied. This is directly correlated with the time interval between the first fraction of radiotherapy and the date of surgery (the so-called overall treatment time (OTT)). To allow enough time for tumours to reduce sufficiently in size, the interval between radiotherapy and surgery needs to be at least 4 weeks. Since it is recommended to operate as soon as possible after short-term preoperative radiotherapy to avoid surgical complications, this radiotherapy scheme is not suitable in irresectable large tumours. The choice of treatment is therefore a conventional scheme: 46–60 Gy in 2.0 or 1.8 Gy fractions. This leads to a treatment time of 4–7 weeks and is usually followed by an interval of 4–6 weeks before the operation takes place.

Although Graf and colleagues reported downstaging in patients treated with 5×5 Gy [10], this was not confirmed by a study in the TME trial [11]. A subgroup analysis of the Swedish study showed that downstaging mainly occurred in patients with an interval of more than 10 days between the initiation of radiotherapy and surgery. The issue of postponement of surgery after 5×5 Gy is further addressed in an ongoing Swedish trial, where patients are randomised to a short (<1 week) or a long interval (4–6 weeks) between radiotherapy and surgery.

2.3. Sphincter-saving procedures

In low rectal cancer, the major limitation to preserve the anal sphincter is the difficulty to create an optimal distal security margin. Intraparietal distal spread is usually less than 1–2 cm, indicating that sphincter-preserving surgery is possible in tumours that are at least 1–2 cm above the anal sphincter [12]. Radiotherapy can be used to increase the safety of a sphincter-saving procedure by devitalising tumour cells that might be left behind. Furthermore, it might facilitate this procedure in very low tumours by downsizing.

The timing between radiotherapy and surgery for sphincter-saving procedures was evaluated in a randomised trial with preoperative radiotherapy (13×3 Gy), followed by surgery after a long (6–8 weeks) or short (1–2 weeks) interval [13]. Although a better clinical response was observed in patients with a long interval compared with patients with a short interval, the percentage of sphincter-saving procedures was not significantly different (76% versus 68%, $P=0.27$). In the National Surgical Adjuvant Breast and Bowel Project (NSABP) R-03 trial, preoperative radiotherapy (28×1.8 Gy) combined with chemotherapy (5-fluorouracil (5-FU) and leucovorin) is compared with a similar postoperative treatment [14]. In a preliminary report after the inclusion of 116 patients, it was shown that more sphincter-saving procedures could be performed in the preoperatively irradiated patients. No data on recurrences are available so far. The same question is being addressed in a large ongoing German trial [15].

3. Repopulation

One of the most important factors determining the success or failure of radiotherapy is believed to be the repopulation of tumours by surviving clonogenic tumour cells. This radiobiological phenomenon has

implications for both pre- and postoperative radiotherapy.

Withers and colleagues [16] hypothesised that for treatment times shorter than 3–4 weeks, proliferation of tumour cells had little effect and that it takes time for accelerated repopulation to be switched on in human tumours. This might be one of the pillars of the success of short-term preoperative radiotherapy; the very short treatment time excludes rapid proliferation of tumour cells. For treatment times of more than 4 weeks, both pre- and postoperatively, it is assumed that the effect of proliferation is equivalent to a loss of radiation dose of approximately 0.6 Gy per day [17]. Evaluation of the influence of the OTT in trials with preoperative radiotherapy for rectal cancer indicates that this loss may be even higher and approximately 1 Gy per day [18].

Postoperatively, the length of the time interval before commencement of radiotherapy is usually 4–6 weeks. After resection, the remaining clonogenic tumour cells can be expected to repopulate during the postoperative period; thus, in theory the time interval should be kept as short as medically tolerable to keep the tumour load as low as possible. Even though in breast cancer patients several retrospective studies have failed to show an influence of this interval on local recurrence rates or survival [19–21], repopulation might explain the lesser efficiency of postoperative radiotherapy in rectal cancer patients [22].

Harari and colleagues [23] showed that even in randomised trials where the question of treatment time is addressed, the ideal treatment time is seldom achieved. For preoperative radiotherapy, this is of less importance in trials with an extremely short treatment time such as using 5×5 Gy, since repopulation is not expected to start until after the first week of radiotherapy. In trials with longer preoperative radiotherapy schemes, the probability of exceeding the ideal treatment time is more likely, possibly resulting in less efficient treatment.

4. Fractionation size and dose

In order to achieve a probability of >90% for eradicating subclinical disease, a dose in the order of 50 Gy using conventional fractionation (1.8–2.0 Gy) is considered necessary [24,25]. Especially in rectal cancer, different preoperative radiotherapy doses and fractionation schemes have been used, which complicates the comparison of randomised trials. Therefore, a mathematical model is used to calculate the biological equivalent dose (BED) of various treatment schemes:

$$\mathrm{BED} = n \cdot d(1 + d/(\alpha/\beta)) - \gamma/\alpha \cdot (T - T_k)$$

where n = number of fractions, d = dose per fraction in Grays; T = duration of radiotherapy in days, T_k = time until repopulation starts.

In this model, the α/β, a value that represents the sensitivity of tissue, is considered to be 10 Gy for rectal tumour cells. Furthermore, it is assumed that repopulation starts after 7 days and that subsequent loss of efficiency (γ/α) is 0.6 Gy/day. For all calculations, we assumed an ideal treatment scheme (as short as possible), with the first dose given on a Monday and no treatment interruption apart from the weekends. Table 1 demonstrates that for preoperative radiotherapy, using the parameters mentioned above, 5×5 Gy is the fractionation scheme with the highest BED. This is mainly explained by the short overall treatment time (5 days), which excludes repopulation of tumour cells. For the postoperative treatment schedules, the BED is generally higher. This is in contrast with the disappointing results of postoperative radiotherapy compared with preoperative radiotherapy. Possibly the reason is the fact the interval between surgery and radiotherapy, during which repopulation has probably already started, is not taken into the calculation, thus lowering the chances of eradicating all cells.

5. Pre- versus postoperative radiotherapy

The NIH consensus conference in 1990 [26] concluded that patients with rectal cancer Dukes' B and C (Astler Coller B2 and C) should receive postoperative radiotherapy combined with chemotherapy. Since then, this combination has been considered standard in the USA. In Europe, however, there is no consensus and most institutions give either no adjuvant radiotherapy or preoperative radiotherapy alone.

Preoperative radiotherapy can inhibit the proliferation of non-excised tumour cells, whether they remain locally or spread outside the pelvis during the surgery. Postoperative treatment can affect only those cancer cells that remain within the volume exposed to radiation.

Well-oxygenated tumour cells are more sensitive to radiotherapy than hypoxic cells [27]. Since surgery disturbs the vascularisation and thus the oxygenation of tumour cells, this may contribute to the finding that postoperative radiotherapy is less effective than preoperative treatment with a similar dose.

The appeal of postoperative radiotherapy is that selection of patients to receive adjuvant therapy may be based on those factors known to influence local recurrence. In general, this concerns patients with a T3/T4 tumour or with positive lymph nodes (TNM stage II or III). For preoperative radiotherapy, reliable imaging is necessary to assess tumour and nodal stage. In a review by Stoker and colleagues [28] an accuracy of 75–80% is claimed for endoluminal magnetic resonance imaging (MRI) concerning local spread. The T-staging accuracy of endosonography reaches approximately 85%. The major limitations of all imaging techniques are understaging

Table 1
Radiotherapy trials in rectal cancer including a surgery alone group

Trial	No.	RT	d	T	BED	LR	Survival
Postoperative radiotherapy							
GITSG [53]	108	40/48	2	26/32	36.6/42.6	N.S.	N.S.
NSABP R01 [55]	368	46/53	1.8	36/40	36.9/42.7	0.06	N.S.
EORTC 81-86 [63]	172	46	2	31	40.8	N.S.	N.S.
MRC III [51]	469	40	2	26	36.6	0.001	N.S.
Rotterdam [64]	172	50	2	33	44.4	N.S.	N.S.
Denmark [65]	494	50	2	47	36.0	N.S.	N.S.
Preoperative radiotherapy							
Bergen [66]	309	31.5	1.75	24	26.8	N.S.	N.S.
EORTC 76–81 [67]	466	34.5	2.3	21	34.0	0.003	N.S.
VASOG II [68]	361	31.5	1.75	24	26.8		N.S.
MRC II [45]	279	40	2.0	28	35.4	0.04	N.S.
VASOG I [69]	613	20/25	2.0/2.5	12	21.0/28.3	N.S.	N.S.
MRC I [70]	824	20	2.0	12	21.0	N.S.	N.S.
		5	5	1	7.5	N.S.	N.S.
RCG/ICRF [40]	468	15	5	5	22.5	<0.05	N.S.
NWRCG [48]	284	20	5	4	30.0	<0.001	N.S.
Stockholm I [39]	849	25	5	5	37.5	<0.01	N.S.
Swedish RCT [31]	1168	25	5	5	37.5	<0.001	0.004
TME [32]	1861	25	5	5	37.5	<0.001	N.S.
Preoperative versus postoperative radiotherapy							
Uppsala [35]	471	60	2	40	52.2	0.02	N.S.
		25	5.1	5	37.8		

GITSG, Gastrointestinal Tumor Study Group; RCT, Rectal Cancer Trial; RT, radiotherapy dose; LR, local recurrence; N.S. non-significant; EORTC, European Organization for Research and Treatment of Cancer; TME, total mesorectal excision; MRC, Medical Research Council. Biological Effective Dose (BED) per trial, calculated according to the following formula: $BED = n^*d\,(1 + d/\alpha/\beta) - \gamma/\alpha^*(T - T_k)\,\alpha/\beta = 10$ Gy, $\gamma/\alpha = 0.6$ Gy, d = fraction size, n = number of fractions, T = duration of RT in days, $T_k = 7$ days. LR, P value of difference in local recurrence; Survival: P value of difference in overall survival; VASOG, Veterans Administration Surgical Oncology Group; RCG/ICRF, Rectal Cancer Group/Imperial Cancer Research Fund; NWRCG, North West Region Rectal Cancer Group.

due to microscopic invasion and/or overstaging caused by an inflammatory reaction [29]. Another difficulty in preoperative imaging is the identification of tumour-positive lymph nodes. Both endosonography and endoluminal MRI can fairly easily detect small perirectal lymph nodes, but neither can tell whether these nodes are involved or not [30]. Accuracy ranges from 70 to 80% for both modalities. Therefore, the inclusion of TNM stage I tumours in preoperative radiotherapy is unavoidable as long as staging procedures are not completely reliable. In the Swedish Rectal Cancer Trial (SRCT), as well as in the TME trial, preoperative radiotherapy actually had a positive effect on the local recurrence rate in patients with a TNM stage I tumour [31,32], although this was not statistically significant due to the low number of events.

The importance of the lateral margin involvement for the occurrence of local recurrences [4] and the limited value of preoperative radiotherapy on patients with a positive margin (C.A.M. Marijnen, LUMC, Leiden, The Netherlands), demonstrates the need for different strategies for high-risk patients. Adjusted treatment consisting of chemoradiation preoperatively with a long interval to allow downstaging seems more appropriate, but can only be given when preoperative imaging enables us to predict the risk for positive resection margins. In a recent study, postoperative MRI of the resection specimen was compared with histopathological examination of the specimen, showing that MRI can predict tumour involvement of the lateral resection margin (<1 mm) with a sensitivity of 88% and a specificity of 78% [33]. Another study demonstrated that CRM involvement is highly unlikely when the margin measured on the preoperative MRI exceeds 5 mm [34]. Since many patients have a margin less than 5 mm on the MRI, further investigations are necessary to limit even more the cut-off point of possible margin involvement.

An advantage of preoperative radiotherapy is the fact that patients' *compliance* is better. After surgery, radiotherapy will often be delayed or not be administered at all due to postoperative complications. The only randomised trial in which preoperative radiotherapy (5×5.1 Gy) was compared with postoperative radiotherapy (30×2 Gy) confirmed this difference in compliance. Only 1 patient in the preoperative radiotherapy group was not irradiated, whereas 16% of the patients in the postoperative group did not receive the intended treatment [35]. It was found that the radiotherapy could be started within 6 weeks in less than 50% of the patients and approximately 25% of the patients' treatment was

delayed for more than 2 months due to problems in postoperative recovery.

6. Chemoradiation

The objectives for chemoradiation are the reduction of local and distant recurrences in order to improve survival. Most antineoplastic drugs induce various types of DNA damage: bridges, adducts, strand breaks or base lesions [36]. The administration of chemotherapy in combination with radiotherapy can have an additive effect, in which there is no interaction between the treatment modalities and each strategy is separately effective. More promising is a combination in which a synergistic effect is achieved; the cytotoxic effect of the combination is greater than the sum of the effects of radiotherapy and chemotherapy alone. This is often achieved by sensitisation, for example when repair of radiation-induced DNA damage is inhibited due to the presence of a chemotherapeutic drug. Thus, the presence of a platinum adduct may interfere with repair through a mechanism known as steric hindrance. Another mechanism is the use of antineoplastic agents which causes single-strand breaks in DNA that is already damaged by radiotherapy, resulting in a non-repairable double-strand break. The main chemotherapeutic agents used in chemoradiotherapeutic combinations are platinum salts, 5-fluorouracil, hydroxyurea, mitomycin C and more recently agents like taxanes or topoisomerase inhibitors.

7. Side-effects

Any benefit of adjuvant therapy regarding a reduced local recurrence rate and possible improved survival must be weighed against potential adverse effects in both the short and the long term. Acute side-effects from radiotherapy for rectal cancer include nausea, diarrhoea, cystitis and skin erythema. These side-effects develop to some degree in most patients with a conventional treatment schedule, but are usually transient and resolve within a few weeks. In several reviews [37,38], both acute and late adverse effects are described for pre- and postoperative radiotherapy.

There have been reservations about more serious short- and long-term toxic effects of high fractional doses of preoperative radiation. Reports about increased mortality rates after preoperative radiotherapy caused great concern: In the Stockholm I trial with 5×5 Gy it was 2% in the control group versus 8% in the irradiated group [39]. In the Imperial Cancer Research Fund trial where patients were treated with 3×5 Gy, these percentages were 7 and 12%, respectively [40]. The explanation for this increase is probably a suboptimal treatment technique. In these trials, the treatment was given by two opposed fields, which increases the volume treated with the prescribed dose considerably.

The results of the SRCT [41] and the Uppsala trial [35] suggest that daily 5 Gy fractions can be safely given in patients when an adequate treatment technique is applied. The results of the TME trial demonstrate that high-dose, short-term radiotherapy is safe even in patients older than 80 years and combined with TME [42]. Increase in perineal dehiscence after preoperative radiotherapy has been observed by several authors, both after short-term as well as after long-term preoperative radiotherapy. Although results are difficult to compare due to various definitions of perineal dehiscence, a 2-fold increase is generally reported after radiotherapy [39,43–45]. In general, no difference in anastomotic leakage or re-interventions is observed.

Radiotherapy, either pre- or postoperatively also induces late effects in the gastrointestinal tract. In the pelvis, the small bowel is the most radiosensitive and, therefore, dose-limiting organ. The main factors predisposing to late radiation-induced small bowel complications are total dose, dose per fraction, volume of irradiated small bowel and previous abdominal surgery [46]. The Uppsala trial showed significantly more small bowel complications in the postoperatively irradiated patients (11%) than in the preoperatively treated patients (5%). In the non-irradiated patients, 6% small bowel obstructions were observed, demonstrating that postoperative radiotherapy leads to more small bowel toxicity, whereas short-term preoperative radiotherapy has a similar toxicity as surgery alone [35].

The effect of radiotherapy on long-term anal sphincter function has not been well documented. Dahlberg and colleagues demonstrated in a retrospective study with questionnaires an increase in patients complaining about an impaired social life after preoperative radiotherapy, due to incontinence for loose stools and urgency [47]. However, in this study the entire anal canal was included in the radiation fields, even if the tumour was located high up in the rectum. The prospective quality of life study in the Dutch TME trial might give further insight into this matter.

8. Randomised trials: radiotherapy only

8.1. Preoperative versus postoperative adjuvant treatment

Despite the ongoing debate whether radiotherapy should be given preoperatively or postoperatively, there has only been one trial to address this question [35]. In this trial, patients were randomised to either preoperative radiotherapy (5×5.1 Gy) given to all patients or postoperative radiotherapy (30×2 Gy) to Dukes' B

and C patients. Preoperative radiotherapy resulted in fewer local recurrences after a minimum follow-up of 5 years: 13% versus 22% ($P=0.02$). No difference in overall survival was observed.

8.2. Preoperative radiotherapy versus no radiotherapy

Preoperative radiotherapy has been given either in a conventional scheme with a fraction size of 1.8–2.3 Gy daily over several weeks or with a short scheme with 3–5 fractions and a high dose per fraction (5 Gy). The rationale of using higher doses per fraction is to diminish the overall treatment period and thus prevent repopulation of the tumour cells. All major prospectively randomised trials with preoperative radiotherapy are listed in Table 1. Of these trials, seven showed a statistically significant beneficial effect of radiotherapy on local control. The MRC II trial [45] included only locally advanced tumours and subsequently had a high local recurrence rate. The SRCT is the only individual trial that showed a statistically significant improved overall survival after preoperative radiotherapy (48 versus 58% at 5 years, $P=0.004$) [31]. The NWRCG [48] trial showed improved survival when only curatively operated patients were taken into analysis. The TME trial, with already very low local recurrence rates in the surgery alone arm (8.2%), still showed a significant decrease in local failure in the irradiated patients (2.4%) [32]. The follow-up in the TME trial is too short to observe a difference in survival. Two meta-analyses of the randomised controlled trials both demonstrate that preoperative radiotherapy significantly decreases local recurrence rates and improves overall and cancer-specific 5-year survival versus surgery alone [49,50].

8.3. Postoperative radiotherapy

Adjuvant postoperative radiotherapy is given with doses ranging between 40 and 60 Gy with fraction sizes of 1.8–2.0 Gy. Postoperative radiotherapy has been evaluated in six randomised trials with surgery alone as the control arm. The results are shown in Table 1. The MRC III trial was the only trial to show a significant reduction in the local recurrence rate after postoperative radiotherapy (20×2 Gy) [51]. Survival benefit was not found in any trial. The meta-analysis also did not reveal any survival benefit [50].

Table 2
Combined radiotherapy and chemotherapy trials in rectal cancer

Trial	No.	Randomisation	RT	LR	O.S.
Postoperative radiochemotherapy					
Norway [59]	72	None		0.01	0.05
	72	**RT + bolus 5-FU**	46		
GITSG 7175 [52,53]	58	None			
	48	RT	40 or 48		
	50	5-FU + CCNU			
	46	**RT + 5-FU#**	44	0.005	0.01
NCCTG 86-47-51 [56]	332	RT + bolus 5-FU[a]	50.4–54.0		
	328	**RT + 5-FU cont.**[a]	50.4–54.0		0.005
Intergroup 0114 [58]	421	5-FU + RT	50.4–54.0	N.S.	N.S.
	425	5-FU + LV + RT	50.4–54.0		
	426	5-FU + Lev + RT	50.4–54.0		
	424	5-FU + LV + Lev + RT	50.4–54.0		
NCCTG 79-47-51 [54]	100	RT	50.4		
	104	**RT + bolus 5-FU**	50.4	0.04	0.04
Cafiero [60]	108	RT	50	N.S.	N.S.
	110	RT + 5-FU + Lev	50		
NSABP R02 [71]	348	5-FU + LV or MOF		0.02	N.S.
	346	**RT + 5 FU + LV or MOF**	50.4		
Preoperative radiochemotherapy					
EORTC 72-76 [61]	121	RT	34.5	N.S.	0.06
	126	RT + bolus 5-FU	34.5		

CCNU, lomustine; cont, continuous; N.S., non-significant; No, number of patients; RT, radiotherapy dose; LR, difference in local recurrence; OS, difference in overall survival. For LR and OS the *P* values are given and the superior treatment arm is printed in bold. 5-FU, 5-fluorouracil; LV, leucovorin; Lev, levamisole; MOF, 5-fluorouracil, semustine and vincristine; #, number of overall recurrences, compared with the no treatment arm in a covariate analysis; NCCTG, North Central Cancer Treatment Group.

[a] Initially, a second randomisation for semustine was performed, which was omitted after an interim analysis.

9. Randomised trials: combined radiotherapy and chemotherapy

9.1. Postoperative chemoradiation

Postoperative chemoradiation has been mainly evaluated in the United States (Table 2). Treatment is usually delivered in two phases: concomitant chemoradiation designed to optimise local control and then additional courses of chemotherapy intended to reduce the metastatic risk. In 1990, the American National Institute of Health recommended postoperative radiotherapy combined with chemotherapy as standard treatment for rectal cancer patients TNM stage II and III disease [26]. This recommendation was based on two trials: The Gastrointestinal Tumor Study Group (GITSG 71-75) [52,53] and the North Central Cancer Treatment Group (NCCTG 794751) [54]. The GITSG study was a four-arm study: surgery only, postoperative chemotherapy, postoperative radiotherapy and postoperative chemoradiation with the chemotherapy given over 18 months. Pair-wise comparisons showed superior survival and local recurrence rates in the chemoradiation arm versus the surgery only arm. The NCCTG study compared radiotherapy with postoperative chemoradiation and demonstrated lower local and distant recurrence rates in the combined treatment arm. Survival was significantly increased. A third trial by the NSABP, protocol R01, found a survival benefit using chemotherapy alone [55]. These results suggest that the observed survival benefit after chemotherapy can rather be ascribed to the systemic effect of chemotherapy and not to the improved local control.

Subsequent studies were mainly conducted to improve the chemotherapy regimen and therefore did not include a radiotherapy only arm. These trials revealed that continuous infusion of 5-FU had better results than bolus injections and that the addition of semustine was of no value [56,57]. A later intergroup study evaluated the value of combining either levamisole, leucovorin or the combination with 5-FU [58]. No significant differences could be observed. More recently, some trials have been conducted in Europe: In Norway, 144 patients were randomised for surgery alone or surgery followed by radiotherapy and chemotherapy [59]. The chemotherapy consisted of 5-FU in weeks 1, 3 and 5. An improved local control and better survival was observed in the combined modality arm. An Italian study in 218 patients comparing postoperative radiotherapy with combined radiotherapy and chemotherapy observed increased toxicity, but failed to demonstrate any benefit from the combined treatment [60].

9.2. Preoperative chemoradiation

The European Organization for Research and Treatment of Cancer (EORTC) conducted a trial from 1972 until 1976, in which the combination of preoperative 5-FU and radiotherapy was compared with preoperative radiotherapy alone [61]. Higher postoperative mortality rate was observed in the combined treatment arm. No difference in the recurrence rates or overall survival could be observed.

Three ongoing trials investigate the value of preoperative chemoradiation compared with postoperative chemoradiation. In the NSABP-R03 trial, randomisation took place for pre- or postoperative combined treatment (5-FU and leucovorin) [14]. A preliminary report demonstrated no difference in morbidity between the two treatment arms, but further results concerning recurrence rates are awaited. In the EORTC trial 22921, preoperative radiotherapy is considered as the standard treatment and the additional value of chemotherapy (pre- and postoperatively) is evaluated. The German CAO/ARO/AI094 compares pre- and postoperative chemoradiation. For the last two trials, 5-FU and folinic acid is the chemotherapeutic regimen of choice.

10. Conclusions

With the results of the randomised TME trial available, the discussion about adjuvant therapy for rectal cancer can hopefully be more constructive with a greater consensus between various clinicians. In this trial, it has been demonstrated that extremely low local recurrence rates can be achieved with the combination of TME and short-term preoperative radiotherapy. To our knowledge, it is the first randomised multicentre trial with local recurrence rates below 5%. Follow-up is too short to comment on the effects on overall survival. Similarly, low local failure rates have been reported from two Swedish population-based studies [7,8]. In these two series, including all patients in defined geographical areas, local failure rates were 2–3% in irradiated patients and 10–12% in non-irradiated patients. Selection for radiotherapy, however, was not based upon randomisation.

Although radiochemotherapy leads to improved survival in several trials, we do not believe this is a better choice of treatment. Although comparison between the different trials is notoriously difficult, the 5-year overall survival rate of the radiotherapy arm in the SRCT is similar to that of the best treatment arm in the GITS-G and NCCTG 79-4751 trials. Therefore, we believe that better local recurrence rates and similar survival rates can be achieved with short-term preoperative radiotherapy compared with chemoradiotherapy with less morbidity.

With the extremely low recurrence rates in the TME trial, one might even speculate that overall survival rates will be even better than seen before, but the follow-up is too short to prove this. In the population-based studies mentioned above, overall survival was significantly

superior during the time period when TME surgery was performed compared with when conventional surgery was used, indicating that improved local control consequently leads to an improved survival [7,62].

To further improve survival, the effect of adjuvant postoperative chemotherapy is evaluated in the successor trial of the TME, the so-called PROCTOR trial (Preoperative Radiotherapy and/or Chemotherapy combined with TME surgery in Operable Rectal Cancer). Hopefully, this trial will lead to similarly exciting results as the TME trial has done.

References

1. Kapiteijn E, Marijnen C, Colenbrander A, *et al*. Local recurrence in patients with rectal cancer diagnosed between 1988 and 1992: a population-based study in the west Netherlands. *Eur J Surg Oncol* 1998, **24**, 528–535.
2. Pahlman L, Glimelius B. Local recurrences after surgical treatment for rectal carcinoma. *Acta Chir Scand* 1984, **150**, 331–335.
3. McCall J, Cox M, Wattchow D. Analysis of local recurrence rates after surgery alone for rectal cancer. *Int J Colorectal Dis* 1995, **10**, 126–132.
4. Quirke P, Durdey P, Dixon M, Williams N. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. *Lancet* 1986, **2**, 996–999.
5. Heald R, Ryall R. Recurrence and survival after total mesorectal excision for rectal cancer. *Lancet* 1986, **1**, 1479–1482.
6. Havenga K, Enker W, Norstein J, *et al*. Improved survival and local control after total mesorectal excision or D3 lymphadenectomy in the treatment of primary rectal cancer: an international analysis of 1411 patients. *Eur J Surg Oncol* 1999, **25**, 368–374.
7. Martling A, Holm T, Rutqvist L, Moran B, Heald R, Cedemark B. Effect of a surgical training programme on outcome of rectal cancer in the County of Stockholm. Stockholm Colorectal Cancer Study Group, Basingstoke Bowel Cancer Research Project. *Lancet* 2000, **356**, 93–96.
8. Dahlberg M, Glimelius B, Pahlman L. Changing strategy for rectal cancer is associated with improved outcome. *Br J Surg* 1999, **86**, 379–384.
9. Stearns M, Deddish M, Quan S. Preoperative roentgen therapy for cancer of the rectum. *Surg Gynecol Obstet, 1959, 225–229*.
10. Graf W, Dahlberg M, Osman M, Holmberg L, Pahlman L, Glimelius B. Short-term preoperative radiotherapy results in downstaging of rectal cancer: a study of 1316 patients. *Radiother Oncol* 1997, **43**, 133–137.
11. Marijnen C, Nagtegaal I, Klein Kranenbarg E, *et al*. No downstaging after short-term preoperative radiotherapy in rectal cancer. *J Clin Oncol* 2001, **19**, 1976–1984.
12. Shirouzu K, Isomoto H, Kakegawa T. Distal spread of rectal cancer and optimal distal margin of resection for sphincter-preserving surgery. *Cancer* 1995, **76**, 388–392.
13. Francois Y, Nemoz C, Baulieux J, *et al*. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. *J Clin Oncol* 1999, **17**, 2396.
14. Hyams D, Mamounas E, Petrelli N, *et al*. A clinical trial to evaluate the worth of preoperative multimodality therapy in patients with operable carcinoma of the rectum: a progress report of National Surgical Breast and Bowel Project Protocol R-03. *Dis Colon Rectum* 1997, **40**, 131–139.
15. Sauer R, Fietkau R, Wittekind C, *et al*. Adjuvant versus neoadjuvant radiochemotherapy for locally advanced rectal cancer. A progress report of a phase-III randomized trial (protocol CAO/ARO/AIO-94). *Strahlenther Onkol* 2001, **177**, 173–181.
16. Withers H, Taylor J, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. *Acta Oncol* 1988, **27**, 131–146.
17. Suwinski R, Taylor J, Withers H. Rapid growth of microscopic rectal cancer as a determinant of response to preoperative radiation therapy. *Int J Radiat Oncol Biol Phys* 1998, **42**, 943–951.
18. Glimelius B. Time factor in combined modality treatment. *Radiother Oncol* 2001, **58**, S29.
19. Vujovic O, Perera F, Dar A, *et al*. Does delay in breast irradiation following conservative breast surgery in node-negative breast cancer patients have an impact on risk of recurrence? *Int J Radiat Oncol Biol Phys* 1998, **40**, 869–874.
20. Froud P, Mates D, Jackson J, *et al*. Effect of time interval between breast-conserving surgery and radiation therapy on ipsilateral breast recurrence. *Int J Radiat Oncol Biol Phys* 2000, **46**, 363–372.
21. Nixon A, Recht A, Neuberg D, *et al*. The relation between the surgery-radiotherapy interval and treatment outcome in patients treated with breast-conserving surgery and radiation therapy without systemic therapy. *Int J Radiat Oncol Biol Phys* 1994, **30**, 17–21.
22. Glimelius B, Isacsson U, Jung B, Pahlman L. Radiotherapy in addition to radical surgery in rectal cancer: evidence for a dose-response effect favoring preoperative treatment. *Int J Radiat Oncol Biol Phys* 1997, **37**, 281–287.
23. Harari P, Fowler J. Idealized versus realized overall treatment times. *Int J Radiat Oncol Biol Phys* 1994, **29**, 209–211.
24. Fletcher G. Lucy Wortham James Lecture. Subclinical disease. *Cancer* 1984, **53**, 1274–1284.
25. Denham J. The radiation dose-response relationship for control of primary breast cancer. *Radiother Oncol* 1986, **7**, 107–123.
26. Anonymous. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990, **264**, 1444–1450.
27. Horsman M., Overgaad J. The oxygen effect. In Steel G, ed. *Basic Clinical Radiology*. London, Arnold, 1997, 132–140.
28. Stoker J, Rociu E, Wiersma T, Lameris J. Imaging of anorectal disease. *Br J Surg* 2000, **87**, 10–27.
29. Hulsmans F, Tio T, Fockens P, Bosma A, Tytgat G. Assessment of tumor infiltration depth in rectal cancer with transrectal sonography: caution is necessary. *Radiology* 1994, **190**, 715–720.
30. Lindmark G, Kraaz W, Elvin P, Glimelius B. Rectal cancer: evaluation of staging with endosonography. *Radiology* 1997, **204**, 533–538.
31. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. *N Engl J Med* 1997, **336**, 980–987.
32. Kapiteijn E, Marijnen C, Nagtegaal I, *et al*. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med* 2001, **345**, 638–646.
33. Blomqvist L, Rubio C, Holm T, Machado M, Hindmarsh T. Rectal adenocarcinoma: assessment of tumour involvement of the lateral resection margin by MRI of resected specimen. *Br J Radiol* 1999, **72**, 18–23.
34. Beets-Tan R, Beets G, Vliegen R, *et al*. Accuracy of magnetic resonance imaging in prediction of tumour-free resection margin in rectal cancer surgery. *Lancet* 2001, **357**, 497–504.
35. Frykholm G, Glimelius B, Pahlman L. Preoperative or postoperative irradiation in adenocarcinoma of the rectum: final

treatment results of a randomized trial and an evaluation of late secondary effects. *Dis Colon Rectum* 1993, **36**, 564–572.
36. Nygren P. What is cancer chemotherapy? *Acta Oncol* 2001, **40**, 166–174.
37. Ooi B, Tjandra J, Green M. Morbidities of adjuvant chemotherapy and radiotherapy for resectable rectal cancer: an overview. *Dis Colon Rectum* 1999, **42**, 403–418.
38. Glimelius B, Pahlman L. Perioperative radiotherapy in rectal cancer. *Acta Oncol* 1999, **38**, 23–32.
39. Cedermark B, Johansson H, Rutqvist L, Wilking N. The Stockholm I trial of preoperative short term radiotherapy in operable rectal carcinoma. A prospective randomized trial. Stockholm Colorectal Cancer Study Group. *Cancer* 1995, **75**, 2269–2275.
40. Goldberg P, Nicholls R, Porter N, Love S, Grimsey J. Long-term results of a randomised trial of short-course low-dose adjuvant pre-operative radiotherapy for rectal cancer: reduction in local treatment failure. *Eur J Cancer* 1994, **30A**, 1602–1606.
41. Frykholm G, Isacsson U, Nygard K, *et al*. Preoperative radiotherapy in rectal carcinoma—aspects of acute adverse effects and radiation technique. *Int J Radiat Oncol Biol Phys* 1996, **35**, 1039–1048.
42. Marijnen CAM, Kapiteijn E, van de Velde CJH, *et al*. Acute side effects and complications after short-term preoperative radiotherapy combined with total mesorectal excision in primary rectal cancer. *J Clin Oncol* 2002, **20**, 817–825.
43. Stockholm Colorectal Cancer Study Group. Randomized study on preoperative radiotherapy in rectal carcinoma. *Ann Surg Oncol* 1996, **3**, 423–430.
44. Swedish Rectal Cancer Trial. Initial report from a Swedish multicentre study examining the role of preoperative irradiation in the treatment of patients with resectable rectal carcinoma. *Br J Surg* 1993, **80**, 1333–1336.
45. Medical Research Council Rectal Cancer Working Party. Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer. *Lancet* 1996, **348**, 1605–1610.
46. Letschert J. The prevention of radiation-induced small bowel complications. *Eur J Cancer* 1995, **31A**, 1361–1365.
47. Dahlberg M, Glimelius B, Graf W, Pahlman L. Preoperative irradiation affects functional results after surgery for rectal cancer: results from a randomized study. *Dis Colon Rectum* 1998, **41**, 543–549.
48. Marsh P, James R, Schofield P. Adjuvant preoperative radiotherapy for locally advanced rectal carcinoma. Results of a prospective, randomized trial. *Dis Colon Rectum* 1994, **37**, 1205–1214.
49. Camma C, Giunta M, Fiorica F, Pagliaro L, Craxi A, Cottone M. Preoperative radiotherapy for resectable rectal cancer: a meta-analysis. *JAMA* 2000, **284**, 1008–1015.
50. Colorectal Cancer Collaborative Group. Meta-analysis of preoperative radiotherapy in rectal cancer. *Lancet* 2001, **358**, 1291–1304.
51. Medical Research Council Rectal Cancer Working Party. Randomised trial of surgery alone versus surgery followed by radiotherapy for mobile cancer of the rectum. *Lancet* 1996, **348**, 1610–1614.
52. Douglass H, Moertel C, Mayer R, *et al*. Survival after postoperative combination treatment of rectal cancer (letter). *N Engl J Med* 1986, **315**, 1294–1295.
53. Thomas P, Lindblad A. Adjuvant postoperative radiotherapy and chemotherapy in rectal carcinoma: a review of the Gastrointestinal Tumor Study Group experience. *Radiother Oncol* 1988, **13**, 245–252.
54. Krook J, Moertel C, Gunderson L, *et al*. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med* 1991, **324**, 709–715.
55. Fisher B, Wolmark N, Rockette H, *et al*. Postoperative adjuvant chemotherapy or radiation therapy for rectal cancer: results from NSABP protocol R-01. *J Natl Cancer Inst* 1988, **80**, 21–29.
56. O'Connell M, Martenson J, Wieand H, *et al*. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 1994, **331**, 502–507.
57. Gastrointestinal Tumor Study Group. Radiation therapy and fluorouracil with or without semustine for the treatment of patients with surgical adjuvant adenocarcinoma of the rectum. *J Clin Oncol* 1992, **10**, 549–557.
58. Tepper J, O'Connell M, Petroni G, *et al*. Adjuvant postoperative fluorouracil-modulated chemotherapy combined with pelvic radiation therapy for rectal cancer: initial results of intergroup 0114. *J Clin Oncol* 1997, **15**, 2030–2039.
59. Tveit K, Guldvog I, Hagen S, *et al*. Randomized controlled trial of postoperative radiotherapy and short-term time-scheduled 5-fluorouracil against surgery alone in the treatment of Dukes B and C rectal cancer. Norwegian Adjuvant Rectal Cancer Project Group. *Br J Surg* 1997, **84**, 1130–1135.
60. Cafiero F, Gipponi M, Peressini A, Bertoglio S, Lionetto R. Preliminary analysis of a randomized clinical trial of adjuvant postoperative RT vs. postoperative RT plus 5-FU and levamisole in patients with TNM stage II-III resectable rectal cancer. *J Surg Oncol* 2000, **75**, 80–88.
61. Boulis-Wassif S, Gerard A, Loygue J, Camelot D, Buyse M, Duez N. Final results of a randomized trial on the treatment of rectal cancer with preoperative radiotherapy alone or in combination with 5-fluorouracil, followed by radical surgery. Trial of the European Organization on Research and Treatment of Cancer Gastrointestinal Tract Cancer Cooperative Group. *Cancer* 1984, **53**, 1811–1818.
62. Dahlberg M, Pahlman L, Bergstrom R, Glimelius B. Improved survival in patients with rectal cancer: a population-based register study. *Br J Surg* 1998, **85**, 515–520.
63. Arnaud J, Nordlinger B, Bosset J, *et al*. Radical surgery and postoperative radiotherapy as combined treatment in rectal cancer. Final results of a phase III study of the European Organization for Research and Treatment of Cancer. *Br J Surg* 1997, **84**, 352–357.
64. Treurniet-Donker A, van Putten W, Wereldsma J, *et al*. Postoperative radiation therapy for rectal cancer. An interim analysis of a prospective, randomized multicenter trial in The Netherlands. *Cancer* 1991, **67**, 2042–2048.
65. Balslev I, Pedersen M, Teglbjaerg P, *et al*. Postoperative radiotherapy in Dukes' B and C carcinoma of the rectum and rectosigmoid. A randomized multicenter study. *Cancer* 1986, **58**, 22–28.
66. Dahl O, Horn A, Morild I, *et al*. Low-dose preoperative radiation postpones recurrences in operable rectal cancer. Results of a randomized multicenter trial in western Norway. *Cancer* 1990, **66**, 2286–2294.
67. Gerard A, Buyse M, Nordlinger B, *et al*. Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). *Ann Surg* 1988, **208**, 606–614.
68. Higgins G, Humphrey E, Dwight R, Roswit B, Lee L, Keehn R. Preoperative radiation and surgery for cancer of the rectum. Veterans Administration Surgical Oncology Group Trial II. *Cancer* 1986, **58**, 352–359.
69. Higgins G, Conn J, Jordan P, Humphrey E, Roswit B, Keehn R. Preoperative radiotherapy for colorectal cancer. *Ann Surg* 1975, **181**, 624–630.
70. Medical Research Council Rectal Cancer Working Party. The evaluation of low dose pre-operative X-ray therapy in the management of operable rectal cancer; results of a randomly controlled trial. *Br J Surg* 1984, **71**, 21–25.

71. Wolmark N, Wieand H, Hyams D, *et al*. Randomized trial of postoperative adjuvant chemotherapy with or without radiotherapy for carcinoma of the rectum: National Surgical Adjuvant Breast and Bowel Project Protocol R-02. *J Natl Cancer Inst* 2000, **92**, 388–396.

72. Nagtegaal ID, Marijnen CAM, Klein Kranenbarg E, van de Velde CJH, Han J, van Krieken JM. For the Pathology Review Committee and the Cooperative Clinical Investigators. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: not one mm but two mm is the limit. *Am J Surg Pathol* 2002, **26**(3), 350–357.