



# The Current Role of Radiotherapy in Colorectal Cancer

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During the last two decades, radiotherapy has become an integral part of the multidisciplinary approach in the treatment of patients with colorectal cancer. Currently, radiotherapy is seen mainly as an adjuvant therapy, sometimes in combination with chemotherapy, in a pre- or postoperative setting. Adjuvant radiotherapy alone leads to a significant reduction of local recurrence rates, but an impact on survival is seen only in subset analyses. Combined modality treatment can reduce local recurrence rates even further, and can also reduce the rate of distant relapses and increase survival. The acute toxicity of combined modality is considerably higher. Local radiation can also be used as a component of organ conserving local treatment for selected early lesions. Radiotherapy has been an important palliative treatment modality, diminishing symptoms in cases of inoperable primary rectal cancers or pelvic recurrences. The timing of radiation, surgery and chemotherapy has been under evaluation for years. For patients with locally advanced primary or recurrent malignancies (unresectable due to fixation), the preferred sequence is pre-operative irradiation with or without chemotherapy, followed by surgical resection. For mobile resectable lesions, sequencing issues are being tested in phase III randomised trials.

**Key words:** colon neoplasms, rectum neoplasms, radiotherapy, radiation enteritis

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## INTRODUCTION

THE ROLE of radiotherapy in the treatment of colorectal cancer has considerably fluctuated. Two decades ago, radiation was used only in a very palliative setting, but nowadays radiation also has an important place in curative treatment for colorectal cancer.

In a textbook from 1950, compiled on the statistical report from the Christie Hospital and Holt Radium Institute, Manchester, Paterson, Tod and Russell, described the results of irradiation with orthovoltage equipment from 1940 to 1944 assessed at 5 years and 1934–1938 assessed at 10 years. They concluded that: "Radiation as a method of treating adenocarcinoma of the rectum has gradually been given up. Operable cases are sent for radical surgery, inoperable for palliative colostomy" [1].

After the introduction of cobalt 60 units and linear accelerators, radiation was again applied to patients with rectal cancers. Initially, only patients who were primarily inoperable or who had a local recurrence received radiation. In 1960, the first randomised controlled trial on adjuvant radiation in cancer of the rectum was begun [2]. From that time until the present, radiation has been applied more frequently in all possible treatment settings, varying from radiation as a single modality to pre-operative, intra-operative and postoperative radiation.

## THE ROLE OF RADIOOTHERAPY IN THE CONSERVATIVE TREATMENT OF RECTAL CANCER

In patients with tumour limited to the rectal wall (T1 and T2), conservative management may be an alternative to radical

surgery. The main methods of conservative treatment in recent years have been local excision, electrocoagulation and irradiation.

The role of radiation in conservative treatment was described by Papillon, in a study of 310 patients with a T1 or T2 rectal tumour, who were treated between 1951 and 1983 with intracavitary irradiation alone or combined with an iridium implant [3]. A 50 kV X-ray machine was used to give 3–4 applications with 10–14 day intervals up to doses of 90–120 Gy. After a split of 4–6 weeks, an iridium 192 implantation, delivering a dose of 20 Gy, was applied in patients who initially had ulcerative lesions. The 5 year local failure rate was 5% and the death rate from cancer was 7.7%. In the same publication, 71 elderly, poor risk patients, with T2 and T3 grade I or II adenocarcinomas of the lower rectum, underwent combined external beam therapy (30 Gy in 10 fractions over 12 days, using a cobalt 60 machine with an 120° arc around the sacrum), followed by local irradiation after an interval of 2 months (contact therapy 25 Gy and iridium 192 implant 20–30 Gy). After a follow-up of 3 years, 64.7% of the patients were alive and well (62% with normal anorectal function and 2.7% with a colostomy after operation for a local recurrence). At 5 years, the death rate from cancer was 16% and the death rate from intercurrent disease was 28%. Papillon concluded that radiation may be used as a single modality in elderly patients with T2 or T3 rectal tumours.

However, the role of radiation in combination with limited surgery is still uncertain. An important advantage of a surgical technique is that the specimen can be examined pathologically, allowing adjustment of the treatment when the tumour is less limited than expected. Preliminary results of one study addressing this question were published in 1994 by Minsky and associates [4]. 22 patients with localised, mobile, resectable

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rectal cancer were treated with local excision and postoperative radiation (45–49.5 Gy in fractions of 1.8 Gy to the pelvis followed in 15 patients by a boost of 3.6–10 Gy and in one patient by a brachytherapy boost). The large fields extended from L5 to the bottom of the obturator foramen; with 1.5–2 cm lateral margins on the pelvic side walls, including the sacrum and not including the external iliac nodes. 2 patients received postoperative chemotherapy. After a median follow-up of 37 months, the incidence of local failure increased with higher T stage and tumour size as expected (local failure T1 0%, T2 17%, T3 33%). 4 patients developed local failure (at 6–21 months). 3 of these patients underwent an abdominoperineal rectum resection and were locally controlled. The fourth patient also had distant metastases and abdominal failure, and, therefore, salvage surgery was not performed. In one other patient, abdominoperineal rectum resection was performed for clinically presumed local failure, but no tumour was found. Minsky concluded that complete local excision with postoperative radiation may be an alternative to standard surgery, but only in selected patients. Randomised studies will have to be carried out to establish the results of limited surgery with adjuvant radiation.

### ADJUVANT RADIOTHERAPY IN COLORECTAL CANCER

#### *Pre- and postoperative radiotherapy in colorectal cancer*

Although surgery remains the cornerstone of treatment in colorectal cancer, there is still a high incidence of local recurrence and metastases in patients with modified Astler Collier stages B2, B3 or C (TNM stages T3N0, T4N0, T1–4N1–3) rectal tumours. To improve results, trials have been performed to evaluate the value of adjuvant therapy. Adjuvant radiotherapy has been used both in pre- and postoperative settings. The theoretical advantages of pre-operative radiation are potentially better tumour cell kill because of better oxygenation when compared with the situation after surgery with inevitable vascular alterations, and, in addition, possible damage to cells that may be spread locally or distantly at the time of resection. Alternatively, an advantage of postoperative radiation is the possibility of reducing overtreatment by proper selection of patients. Better staging procedures such as pre-operative ultrasound could improve patient selection for pre-operative studies, especially with tumours of the lower or middle third of the rectum.

A study comparing pre- and postoperative radiation was performed by Pahlman and associates [5–7] (see Table 1). In a randomised multicentre trial on 471 patients with primary operable rectal cancer, high dose fractionated pre-operative radiation (25.5 Gy in 5 fractions in 5–7 days) was compared with high dose postoperative radiation (40 Gy in 20 fractions and after an interval of 10–14 days another 20 Gy in 10 fractions using a shrinking field technique). Postoperative radiation was only given to patients with Astler Collier stage B2, C1 or C2. After a mean follow-up of 6 years (and a minimum follow-up of 3 years), the local recurrence rate was significantly lower after pre-operative radiation (12% versus 21%,  $P = 0.02$ ). No statistical difference was found in overall survival or occurrence of distant metastases. Postoperative complications were slightly higher in the pre-operative radiation group. Perineal wound sepsis after abdominoperineal rectum amputation occurred more frequently in the pre-operatively irradiated group (33% versus 18%,  $P < 0.01$ ). Both pre- and postoperative radiation were well tolerated. The late side effects were acceptable in both treatment arms. The overall risk of developing a small bowel obstruction was 7% (5% in the pre-operative group and 11% in

the postoperative radiation group;  $P < 0.01$ ). Only 3% of the pre-operatively irradiated patients and 7% of the postoperatively treated group needed surgery for small bowel obstruction.

One of the largest studies on pre-operative short term radiation therapy in operable rectal carcinoma was performed by the Stockholm Rectal Cancer Study Group ( $n = 849$ ). They compared pre-operative radiotherapy with no further treatment after surgery [8]. The radiotherapy consisted of 25 Gy in 5 fractions over 5–7 days, delivered through anterior and posterior opposed fields with Co 60 or 8–12 MV photon beams. Surgery was performed 1–7 days after completion of the radiotherapy. Pelvic recurrence was significantly lower in the pre-operatively irradiated group (11%) compared to the surgery only group (25%). There was no significant difference in distant metastases and overall survival. Postoperative morbidity was significantly higher among irradiated patients, mainly due to wound sepsis among the irradiated patients. The postoperative mortality, particularly due to cardiovascular disease, was 8% in the irradiated group and 2% in the surgery alone group.

Another large prospective randomised multicentre trial, comparing pre-operative radiotherapy followed by surgery with surgery alone for rectal cancer, was performed by the Rectal Cancer Study Group in London [9]. From the 468 patients that were randomised in this study, 228 were randomised to radiotherapy. These patients received 3 fractions of 5 Gy over 5 days within 2 days of operation. The treatment was given with two parallel opposed fields, extending from the lumbosacral junction to the perineum and 1.5 cm lateral to the pelvic side walls. The results showed a reduction of local recurrence after pre-operative radiation. Peri-operative mortality, however, was clearly increased in the pre-operatively irradiated group (9% versus 4%;  $P < 0.05$ ). The main cause of mortality was deep vein thrombosis and pulmonary embolism. The cause is uncertain but there might be a relationship with relatively large radiation fields (irradiated with only 2 portals) and the lack of thromboembolic prophylactic measures (only in 10% in both treatment groups).

A more fractionated radiation schedule has been used by the EORTC. In a large randomised trial ( $n = 466$ ), pre-operative radiotherapy (34.5 Gy in 15 fractions) in rectal cancer (T2–4) significantly reduced the local recurrence rate (20% versus 35% for the total group,  $P = 0.02$ ; 15% versus 30% for curatively resected patients,  $P = 0.003$ ). An impact on survival of pre-operative irradiation was only seen in patients treated with a curative aim, with 5 year survival rates of 69% versus 59% ( $P = 0.08$ ). Postoperative mortality was not significantly different between irradiated and non-irradiated patients (4.2% versus 3.4%). Morbidity was slightly higher for pre-operatively irradiated patients [10].

From the multitude of trials with pre-operative radiation as a single adjuvant, it can be concluded that, despite the increase in side effects, the gain in local control is substantial. In patients with a cardiac disease or of old age, special attention should be paid to prevention of thrombosis. Treatment-specific side effects can be reduced by using a multiple field technique.

Postoperative pelvic radiation as a component of adjuvant therapy has also been studied extensively [11–16]. A selection of the randomised studies will be described here (Table 1). In a prospective, randomised multicentre trial in The Netherlands, the effect of postoperative radiation (50 Gy in 25 fractions in 5 weeks) for rectal cancer was studied [11]. An interim analysis in 172 patients showed that the local recurrence rate in the postoperatively irradiated group was lower, but this was not

Table 1. Pre- versus postoperative irradiation—impact on disease control [29]

Sequence XRT/Op'n	No. of patients	Op'n	Incidence local recurrence (%)				P value	Incidence distant meastasis (%)				P value
			CT	XRT	XRT/CT	Op'n		CT	XRT	XRT/CT		
<i>Pre-op versus Postop</i> (crude incidence, local recurrence; 5 year actuarial distance metastasis)												
Swedish trial [5–7]	471	–	–	12 versus 21	–	0.02	–	–	28 versus 37	–	0.30	
<i>Pre-op</i> (5 year actuarial)												
Stockholm [8]	849											
Total		23	–	11	–	<0.01	28	–	23	–	n.s.	
Curative		25	–	11	–	<0.01	23	–	17	–	n.s.	
The Rectal Cancer Group, London [9]	468											
Total		24		17		0.04	–	–	–	–	n.s. <sup>o</sup>	
			–		–							
EORTC [10]	466	35	–	20	–	0.02	–	–	–	–	–	
Total	341	30		15		0.003	22	–	23	–	n.s.	
Curative												
<i>Postop</i> (initial failure, crude incidence)												
The Netherlands [11]	172	33	–	24	–	n.s.	26	–	39	–	n.s.	
NSABP [12]	555	25	21	16	–	0.06	26	24	31	–	n.s.	
GITSG 7175 [13]	227	24	27	20	11	0.08*	34	27‡	30	26‡	–	
NCCTG/Mayo 794751 [14]	204	–	–	25	13.5	0.04	–	–	46	29	0.01	
NCCTG 864751 [16]	680	–	–	–	8 versus 12	0.11†	–	–	–	31 versus 40	0.03†	

Op'n, operation; XRT, external irradiation; CT, chemotherapy; Pre-op; pre-operative; Postop, postoperative; n.s., not significant; n.s.<sup>o</sup>, data not shown but only stated that no statistically significant differences as to distant metastases were observed.

\* XRT versus no XRT; † advantage to XRT+C15FU versus XRT+bolus 5-FU; ‡ GITSG advantage to chemotherapy versus no chemotherapy at 20 versus 30% (distant metastases (DM) only), 27 versus 32% (any DM).

statistically significant (24% versus 33%). No influence on disease-free survival was found.

One of the largest trials studying the value of postoperative radiotherapy was conducted by the NSABP ( $n = 555$ ), comparing surgery alone with surgery combined with postoperative irradiation (46–47 Gy in 26–27 fractions, using parallel opposed fields, with a boost on the perineum up to 51–53 Gy), with surgery combined with adjuvant chemotherapy (5-fluorouracil, semustine and vincristine) [12]. Postoperative radiation resulted in a reduction of local recurrence from 25 to 16% (also see Table 2).

The Gastro Intestinal Study Group (GITSG) reported their experience of a 4 arm randomised study on the role of radiotherapy and or chemotherapy (5-fluorouracil and semustine) on patients ( $n = 227$ ) after complete surgical resection of Astler Collier B2 or C rectal carcinoma (GI-7175) [13]. Patients were randomised to 4 treatment arms: no adjuvant therapy, adjuvant chemotherapy only, adjuvant radiotherapy only and combined modality. Radiotherapy in the irradiation only arm was delivered according to the institutional preference, 40 Gy in 4–4.5 weeks or 48 Gy in 5–5.5 weeks. In the combined treatment arm, radiation consisted of 40 Gy in 4–4.5 weeks or 44 Gy in 4.5–5.5 weeks. The radiation was given 5 days a week using parallel opposed fields. The incidence of local recurrence as the initial pattern of relapse after no adjuvant therapy was not significantly different from the local recurrence rate after radiotherapy only (24% surgery alone versus 20% adjuvant irradiation and 27% adjuvant chemotherapy). Since the total radiation dose was considered to be rather low and the total number of patients per treatment arm was quite low, one cannot conclude from this

study that postoperative adjuvant radiation as a single adjuvant is ineffective. In the GITSG study, the lowest incidence of local relapse was achieved with combined modality irradiation plus chemotherapy at 11% (see also Table 2).

The radiation dose was higher in the randomised trial by the Mayo Clinic and the NCCTG (794551) [14]. 204 patients with rectal carcinoma stage B2 or C were randomly assigned after potentially curative surgery to postoperative radiation alone (45.0 or 50.4 Gy in fractions of 1.8 Gy), or to radiation plus fluorouracil combined with semustine, both before and after postoperative pelvic irradiation and 5-fluorouracil bolus injections on 3 consecutive days in weeks 1 and 5 of postoperative radiotherapy. This trial also demonstrated an advantage of combined modality treatment with regard to both disease control (local and distant) and survival (disease-free and overall) (see also Table 2).

In conclusion, a reduction of local recurrence rate is found in most studies, both after pre- and postoperative radiation. Prevention of local recurrence of rectal carcinoma is very important in terms of quality of life because local recurrences are usually associated with pain, bleeding and obstruction which are difficult to treat.

For patients with a T3 or T4 tumour of the rectum or rectosigmoid, meta-analysis results suggest lower local recurrence rates after pre-operative radiation. Pre-operative radiation is the appropriate treatment for patients with a T3 or T4 tumour of the rectum or rectosigmoid, despite the increase in side effects. Total dose and dose fractionation schedule are still a matter of debate; randomised studies comparing different pre-operative fractionation schedules have not been performed. If

Table 2. Adjuvant postoperative randomised rectal trials. U.S.A.—irradiation and chemotherapy [29]

Group or institution (ref.)	Treatment regimen	XRT total dose/dose per fraction (Gy)	Chemotherapy	No. of patients	Advantage in tumour control		Survival advantage	
					Local	Distant	DF	Overall
GITSG 7175 [13]	1. Op'n alone	None	None	58	—	—	—	—
	2. XRT	40 or 48/1.8	None	50	Yes*	No	Inc.	Inc.
	3. CT	None	5-FU+MeCCNU (10 week cycle–18 months)	48	No	Yes†	Inc.	Inc.
	4. XRT+CT	40 or 44/1.8	5-FU on first and last 3 days on XRT; followed by CT as in arm 3 (adjustment first course)	46	Yes* $P = 0.08$	Yes†	Yes $P = 0.009$	Yes $P = 0.005$
Mayo/NCCTG 79475 [14]	1. XRT	50.4/1.8	None	101	—	—	—	—
	2. XRT+CT	Same	5-FU+MeCCNU 5-FU on first and last 3 days of XRT; 5-FU+MeCCNU 1 course before and after XRT	103	Yes $P = 0.04$	Yes $P = 0.01$	Yes $P = 0.002$	Yes $P = 0.025$
NSABP [12]	1. Op'n alone	None	None	73	—	—	—	—
	2. XRT	47/1.8	None	177	Yes $P = 0.06$	Dec.	Equal	Equal
	3. CT	None	5-FU+MeCCNU+VCR	178	Inc.	Equal	Yes $P = 0.006$	Yes $P = 0.05$
NCCTG 864751 [16]	1. XRT+CT (bolus 5-FU)	50.4 to 54/1.8	5-FU+MeCCNU 1 course before and after XRT 5-FU bolus on first and last 3 days of XRT	332	—	—	—	—
	2. XRT+CT (CI 5-FU)	Same	CT before and after XRT as in arm 1 CI 5-FU during XRT	328	Inc.	Yes $P = 0.11$	Yes $P = 0.03$	Yes $P = 0.005$

Op'n, operation; XRT, external irradiation; CT, chemotherapy; DF, disease-free; Inc, increased survival or tumour control but not statistically significant; Dec, decreased; Yes, marginal or statistically significant improvement; No, no improvement; 5-FU, 5-fluorouracil; CI, continuous infusion; MeCCNU, methylcyclohexylnitrosourea.

\* Local control advantage of XRT versus no XRT,  $P = 0.08$ ; † Distant control advantage to CT versus no CT.

pre-operative treatment is intended to impact significantly on survival and distant metastases as well as on local control, systemic treatment will undoubtedly need to be combined with irradiation and resection.

The role of radiotherapy in more proximal colon cancers is more limited. The potential role of postoperative radiation with or without 5-fluorouracil for high risk colon carcinoma has been described by Willet in 1993 in a study of 203 patients with modified Astler Coller B2, B3, C2 and C3 colon carcinoma [15]. Of the 203 patients, 30 had residual local tumour whereas 173 had no residual disease. The latter 173 patients were compared with a historical control group of 395 patients. Postoperative radiation was delivered to the tumour bed with a 3–5 cm margin up to a dose of 45 Gy in fractions of 1.8 Gy. Using a shrinking field technique, the tumour bed usually received a dose of 50.4–54 Gy, depending on the mobility and the volume of the small bowel in the radiation field. 63 patients received adjuvant chemotherapy, usually 5-fluorouracil. The study showed that local control rates were higher for irradiated patients with B3 and C3 tumours, for patients with tumours associated with abscess or fistula, and for patients with residual disease after resection who were treated with postoperative radiation. Survival trends were also better in irradiated B3 and C3 patients. On the basis of these positive trends and the positive trends for 5-fluorouracil plus levamisole in node-positive colon cancer patients, a U.S.A. intergroup trial is underway comparing 5-

fluorouracil with levamisole with or without tumour bed/nodal irradiation for resected high risk patients (modified Astler Coller B3, C3 and selected C2; T4bN0–2; T3–4aN1–2).

#### Adjuvant postoperative radiation with or without chemotherapy

The role of adjuvant chemotherapy, as reported by Moertel [18], for patients with a high risk of systemic failure of a colon carcinoma, although widely accepted in the U.S.A., is still a matter of debate in Europe. There are studies showing a beneficial effect of adjuvant therapy [12–14, 16, 17] (Table 2). The value of addition of chemotherapy to adjuvant radiotherapy in the previously discussed, large randomised trials on combined modality treatment for rectal cancer will be discussed here.

The NSABP trial, described previously, compared surgery, with surgery combined with postoperative irradiation, and with surgery combined with adjuvant chemotherapy (5-fluorouracil, semustine and vincristine) [12]. The group treated with surgery and adjuvant chemotherapy showed an overall improvement in disease-free survival ( $P = 0.06$ ) and survival ( $P = 0.05$ ), but local relapse as initial failure was impressive at 21%. In patients treated with postoperative radiation only, a reduction in local recurrence from 25 to 16% ( $P = 0.06$ ) was found.

In the previously discussed GITSG study on patients after complete surgical resection of Astler Coller B2 or C rectal carcinoma (GI-7175), no adjuvant therapy was compared with adjuvant chemotherapy only (5-fluorouracil and semustine),

with adjuvant radiotherapy only, and with adjuvant chemotherapy combined with radiotherapy [13]. The combined modality arm showed an advantage in survival ( $P = 0.005$ ) and in time to relapse ( $P = 0.009$ ) as compared to no adjuvant therapy. Unfortunately, the gain in tumour control was accompanied by severe acute toxicity in 61% of the combined modality arm. Analysis of irradiation versus no irradiation showed a decreased local recurrence rate as an initial failure pattern ( $P = 0.08$ ).

The trial performed by the Mayo Clinic and the NCCTG (794551) on 204 patients with rectal carcinoma stage Astler Coller B2 or C after potentially curative surgery, compared postoperative radiation alone (15.0 or 50.4 Gy) with radiation plus 5-fluorouracil combined with semustine, and showed an advantage for the combined modality treatment with regard to disease control (local and distant) and survival (disease-free and overall). Although acute intolerance was higher in the combined modality arm, chronic tolerance was equal [14].

Recently in 1994, a favourable effect of combined modality treatment was reported in a large randomised trial ( $n = 680$ ), using protracted infusion of 5-fluorouracil during postoperative radiotherapy [16]. Patients were randomly assigned to one of four treatment schedules, using a  $2 \times 2$  design, to test two separate questions. Patients received systemic chemotherapy both before and after pelvic irradiation, consisting of 5-fluorouracil with semustine or 5-fluorouracil alone at higher doses. During postoperative radiotherapy, patients received either an intermittent bolus injection of 5-fluorouracil (500 mg/m<sup>2</sup>) on 3 consecutive days during weeks 1 and 5 of radiotherapy or protracted intravenous infusion of 5-fluorouracil (225 mg/m<sup>2</sup>/24 h during the entire course of irradiation or until intolerance). Radiation was started on day 64 in all treatment schedules. Radiation was given using photon beams with a minimal photon energy of 4 MV. Multiple field techniques were used to include the tumour bed and the nodal groups. All patients received at least 45 Gy with a boost of 5.4 Gy on the tumour bed. If the small bowel could be completely excluded from the treatment field, a second cone down was performed applying another 3.6 Gy (total dose 50.4–54 Gy). The results from this study showed a significant decrease in overall tumour relapse rate among the patients treated with protracted venous infusion of 5-fluorouracil during irradiation (47% versus 37%,  $P = 0.01$ ) and a significant decrease in distant metastases (40% versus 31%,  $P = 0.03$ ) as compared with patients who received bolus injections of 5-fluorouracil. A decrease in local recurrence after protracted intravenous 5-fluorouracil infusion was observed, but this was not statistically significant. The significant decrease in distant metastases suggests an improved effect on micrometastases. The improvement in disease-free survival also translated into a difference in 4 year actuarial survival of 70% versus 60% ( $P = 0.005$ ). The addition of semustine to 5-fluorouracil as a systemic therapy did not improve the results.

#### *Pre-operative irradiation with or without chemotherapy*

In conclusion, in most studies on postoperative radiation, with or without chemotherapy, the combined modality arm has shown a higher overall survival and a lower local recurrence rate. In addition to its systemic benefits, another application of chemotherapy is that of a radiosensitiser. In the latter application, the chemotherapy is used in a lower dose with irradiation than that used in the systemic chemotherapy as a component of treatment.

The EORTC has recently initiated a trial studying both

aspects of chemotherapy (E22921) [18], comparing pre-operative pelvic irradiation to pre-operative irradiation, combined with 5-fluorouracil and leucovorin, with or without postoperative adjuvant chemotherapy in T3 and T4 resectable rectal cancer. With regard to which drugs, route and time of delivery, sequencing of radiation and chemotherapy might result in the optimal effect in terms of local control with minor side effects, there are still many questions to be solved.

#### *Intra-operative radiation*

In patients with locally advanced primary rectal cancer or with locally recurrent disease, resection may not be possible. Radiotherapy may offer long term palliation, but this can only be achieved by using high dose external beam irradiation, which means for microscopic residual disease  $\geq 60$  Gy in fractions of 1.8 or 2.0 Gy and for macroscopic residual disease even more. It is often impossible to reach such dose levels with only external beam radiation because of the tolerance of the surrounding normal tissues. In the pelvis, the small bowel is the most important dose-limiting organ.

Intra-operative radiation therapy (IORT) with electrons (IOERT), orthovoltage or brachytherapy might diminish the problems with normal tissue tolerance. The main advantage of IORT is the possibility of mobilising and excluding critical organs or shielding dose-limiting structures from the radiated volume. In addition, the target volume can be defined more accurately because treatment is performed in co-operation with the surgeon under direct view, and, therefore, the irradiated boost volume after 45 to 50 Gy is likely to be smaller.

In the 1970s, IOERT was introduced as a component of treatment for locally advanced colorectal cancers. Several non-randomised studies have been performed to explore the possibilities of IORT [19–22]. Patients selected for IOERT were those in whom surgery and external irradiation, with or without chemotherapy, were not likely to achieve local control.

In the Massachusetts General Hospital from 1978 to 1989, 80 patients with locally advanced primary lesions were considered for combined external beam therapy followed by surgery and IOERT [19]. All patients received pre-operative radiation (45 Gy in 25 fractions followed by a boost on a smaller field up to 50.4 Gy). Patients treated after 1986 also received 5-fluorouracil intravenously for 3 consecutive days during the first and last week of radiotherapy. Surgery was done 4–6 weeks after external beam radiation. If there was no evidence of positive or minimal margins, IORT was not applied. Patients who received IORT were treated with 9–15 MeV electrons with doses ranging from 10 to 20 Gy. Excluding patients with metastatic disease, 42 patients were treated with resection and IORT. The 5-year local control and disease-free survival for the patients who had undergone a complete resection plus IOERT was 88% and 53%, respectively, for those with negative margins and 69% and 47%, respectively for patients with microscopic residual disease. In case of gross residual tumour, these figures were 50% and 17%, respectively.

The most recent results of IOERT for locally recurrent rectal cancer from the Mayo Clinic, using single or combined modality treatment, have shown promising results: IOERT in combination with external beam radiation improved local control and survival as compared with historical controls and data from the literature [21].

#### *Radiation-related complications*

Complication rates, especially small bowel complication rates, have diminished after improvement of radiation techniques.

Currently, a three or four-field technique, using lateral fields as a component of treatment, is applied in pre-operative or postoperative radiation with adjustment of the fields to protect as much small bowel as possible; accurate planning has improved the dose distribution. Serious complications, such as bowel obstruction needing surgical intervention, are seen in only 5–10% of patients receiving high dose postoperative radiotherapy as compared with approximately 5% in patients treated with surgery only.

Letschert and associates have studied the volume effect in radiation-related late small bowel complications in patients treated with postoperative irradiation after radical surgery for rectal carcinoma [23]. They showed that there is a volume effect in radiation-induced diarrhoea, but not for small bowel obstruction at a dose of 50 Gy in 25 fractions. Other studies have shown a volume effect for small bowel obstruction at the same dose level in patients treated with large radiation fields with estimated small bowel volumes of 800 cm<sup>3</sup> after intra-abdominal surgery [24–26]. As might be expected, the combined adjuvant modality of external irradiation and chemotherapy had a higher incidence of acute side effects, especially diarrhoea, but chronic gastrointestinal side effects were not increased.

### PALLIATIVE RADIATION

#### *Irradiation of the primary tumour*

As described earlier, radiotherapy has been used in the past mainly as a palliative treatment. Primary tumours in the rectum and recurrences can cause devastating symptoms, such as haemorrhage, obstruction and pain by nerve involvement with or without destruction of the sacrum. External radiation can diminish these symptoms for 6–9 months or delay the onset of these problems, but rarely results in long term survival. The treatment schedule depends strongly on the life expectancy of the patient.

In the presence of distant metastases, life expectancy is short and, therefore, a hypofractionated schedule is often used in these patients because they will probably not live long enough to develop late radiation complications. A hypofractionated schedule can be more convenient for a patient than a conventionally fractionated schedule, although acute toxicity is usually more severe.

#### *Radiation for distant metastases of colon carcinoma*

Patients with locally advanced stages of colon carcinoma frequently develop liver and lung metastases. In selected patients, metastasectomy is possible, leading to long term survival, and a subgroup may be cured by resection. In the majority, however, palliation is the only possible goal, for which usually chemotherapy is applied. In case of localised symptoms (for instance pain due to bone metastases or diffuse liver metastases), radiotherapy can be useful. Sometimes the number of liver metastases is limited but resection is not technically feasible. The role of high dose conventionally fractionated conformal therapy is currently being studied [27].

### CONCLUSION

The role of radiotherapy in colorectal cancer has changed over the last decade, and will probably continue to change in the future. Radiation has been proven to reduce local recurrence rates in both pre- and postoperative settings, with or without chemotherapy. When irradiation is combined with chemotherapy following resection of rectal cancers, the combined modality treatment also reduces distant metastases and improves survival. Research will continue on the use of radiation for

organ-preserving treatment modalities and on the timing of radiation, surgery and chemotherapy.

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