Perioperative Radiotherapy in Rectal Cancer

Bengt Glimelius and Lars Påhlman

From the Departments of Oncology and Surgery, University of Uppsala, Akademiska Sjukhuset, Uppsala, Sweden

Correspondence to: Dr Bengt Glimelius, Department of Oncology, University of Uppsala, S-751 85 Uppsala, Sweden. Tel: + 46 18 66 30 00. Fax: + 46 18 66 55 28

Acta Oncologica Vol. 38, No. 1, pp. 23–32, 1999

Local failure of rectal cancer is one of the principal causes of morbidity and mortality. In order to lower unacceptably high local failure rates, pre- or postoperative radiotherapy has been extensively investigated. The collected information from all controlled trials reported so far shows that the proportion of local recurrences is reduced to less than half when radiotherapy up to moderately high doses is given preoperatively. This reduction is smaller after postoperative radiotherapy, even if higher doses are used. In addition, there is a positive influence on survival from preoperative radiotherapy. Improved survival has also been seen in trials using postoperative radiotherapy, but only when combined with chemotherapy. With proper radiation techniques, sufficiently high doses can be given preoperatively with little, if any, increase in postoperative mortality and morbidity. Furthermore, late toxicity can be anticipated to be low provided the technique is optimal. The beneficial effects noted so far have been achieved in trials where 'standard' surgery has been used, followed by a local recurrence rate of more than 20% (average 29%, range 23–46%) of the patients. It is, however, possible that the reduction in local failure rates is proportionally even greater added to 'optimal' surgery, although the absolute number of failures prevented is lower.

Received 24 June 1997
Accepted 5 July 1997

Surgery has been the primary treatment for cancer of the rectum with overall survival figures after 5 years below 50%, and with little improvement over the years (1). In patients with a primarily extirpable tumour, perioperative radiotherapy has been extensively investigated and used in order to decrease an often unacceptably high local recurrence rate. Since a local recurrence of a rectal carcinoma is not only extremely disabling but also more or less incurable, a gain in local pelvic control represents an important achievement of an additional treatment even though survival is not likely to be substantially improved.

The rationale for combining surgery and radiation is that surgery removes the bulk of the tumour tissue, whereas radiation therapy kills the tumour cells in the periphery of tumours where they are fewer and the area is well vascularized. With surgery, the most peripherally located tumour cells sometimes have to be left because of the necessity to preserve normal tissues. The main cause of a pelvic failure is lateral spread of microscopic foci of tumour cells that are not removed at surgery (2, 3). Surgical techniques aiming at removing this lateral spread have also resulted in apparently lower local recurrence rates (4–6).

This work presents the collected experience with respect to influence on local failure rates, survival, and acute and late adverse effects from controlled clinical trials conducted so far and discusses the potential value of perioperative radiotherapy in primarily extirpable rectal cancer, also in instances where surgery is 'optimal'.

RADIOBIOLOGICAL ASPECTS

Dose and fractionation

The effects of irradiation in terms of local tumour control and acute and late damage to normal tissues are dependent not only on the total dose, but also on the dose delivered in each fraction and the total treatment time. Several attempts have been made to estimate the biological effects of various radiation schedules. In this review the linear-quadratic (LQ) time formula (7) is used to transform the effects of different radiation schedules to the effects achieved when a conventional fractionation of 2 Gy daily, 10 Gy/week is used.

To achieve a high probability (90% or more) of eradicating subclinical disease from an adenocarcinoma in a surgically undisturbed area, it is necessary to deliver a dose in the order of 50 Gy (8, 9). This dose (50 Gy in 25 fractions during 5 weeks) gives an LQ time of 43 Gy with an $\alpha/\beta = 10$ Gy for both acute responding tissues and tumours. The repair rate (γ/α) is then assumed to be 0.6 Gy/day and the time before proliferation starts (T_k) to be 7 days (7, 10, 11). In order to reduce treatment duration, i.e. to shorten the time period between start of radiotherapy and surgery, it is necessary to give either multiple

 ISSN 0284-186X

fractions per day or higher doses per fraction. With higher doses per fraction, the therapeutic range shrinks due to an increase in the risk of late toxicity (12). A dose of 5.0 Gy daily has, however, been used in several preoperative trials as a suitable alternative both for the patient and the surgeon. Using the coefficients selected above, the acute effects of a total dose of 25 Gy in five 5 Gy-fractions in 5 days corresponds approximately to a dose of 42 Gy in 21 fractions of 2 Gy in 29 days. The LQ times for acute effects for the various regimens used in controlled clinical trials can be found in Table 1. Since the size of each radiation fraction (1.75–5 Gy) and the time between the first and the last fraction (1–40 days) vary considerably between trials, a better estimate of the relative efficacy of the radiation achieved in the different trials is given by LQ times than by the total doses.

Radiotherapy before or after surgery?

The question of whether radiation before or after surgery is to be preferred has long been debated. The most optimal treatment is, for obvious reasons, the one that results in the greatest reduction in local failure rates/the highest improvement in survival and, at the same time, causes the fewest adverse effects both in the short and in the long run. Practical and economic aspects may also be of relevance, particularly if the beneficial effects do not clearly favour one or the other approach, or if there are conflicting tumour and normal tissue effects.

The rationale for additional radiotherapy in patients with an extirpable rectal carcinoma is to kill any tumour cells not removed by surgery. These cells are reasonably fewer before than after surgery because of tumour cell proliferation. For the same cure rate, the efficacy of the radiotherapy must thus be higher after surgery than before in terms of remaining tumour cell fraction. There is also considerable evidence indicating that for a similar result, a higher dose is required postoperatively than preoperatively (13). The assumption of a greater dose-efficacy of preoperative radiotherapy compared to postoperative, has, apart from one study in rectal cancer discussed below, not been tested and confirmed in controlled studies. A higher dose, as required postoperatively to achieve the same tumour cell kill effect, carries the risk of resulting in more severe long-term complications.

If the tumour is inextirpable at diagnosis owing to overgrowth of tumour cells to adjacent organs not possible to remove, the radiotherapy must, of course, be carried out prior to the surgical attempt. In these instances, the radiation dose must be sufficiently high, and the time interval between the radiotherapy and surgery sufficiently long so that down staging permitting subsequent surgery can be achieved. A preoperative approach with a long delay before surgery has also been used in instances where a down-staging effect is desired in order to permit sphincter-preserving surgery rather than a rectal excision (14, 15). Although theoretically attractive, it is possible that this treatment will only result in the surgical procedure appearing to be easier because the tumour bulk is smaller. The margins may not be closer to the tumour without jeopardizing radicality, since the most commonly used dose, about 50 Gy in 5 weeks, only kills subclinical disease (5×5 Gy in 1 week may be as effective). Using higher doses, the goal can be reached, but the risks of late effects on bowel function may then be unacceptably high (see below). Ongoing trials in Europe and the US may perhaps come up with a solution to this problem.

The main reason for choosing postoperative irradiation in rectal cancer is that patients with a high probability of being cured by surgery alone, i.e. those with a tumour in Dukes' stage A (UICC stage I), can be excluded. Patients in whom generalized disease is found at surgery can also be excluded.

One disadvantage with postoperative radiotherapy, not always appropriately recognized, is that those patients who do not have an uneventful recovery after surgery may not initiate their radiotherapy until after a prolonged time period. The extent of this problem is not possible to evaluate from the postoperative trials, since only those with an uncomplicated postoperative course and in shape for randomization within the stipulated time period, e.g. 1 month, will be included. In the Uppsala trial (16) in which patients were randomized prior to surgery, it was actually found that the radiotherapy could be started within six weeks in only half the patients. In about one quarter of the patients, start of treatment had to be delayed for more than eight weeks because of problems during postoperative recovery. This was also the experience in the postoperative trial carried out by the EORTC (European Organization for Research and Treatment of Cancer) (17).

Combination with chemotherapy

The purpose of combining radiotherapy and chemotherapy is to achieve a better tumour effect without simultaneously increasing normal tissue reactions. True clinical synergism has not been shown, at least not in adenocarcinomas of the rectum, and the knowledge on how to combine the two modalities is still limited (18, 19). An increased frequency of severe adverse effects has also been observed with several drug–radiation combinations (19, 20). Despite this, radio/chemotherapy is routinely advocated in rectal cancer by many investigators (see below). The situation is different in squamous cell carcinomas of the anus since randomized controlled trials have shown that the antitumour effect is increased (21–23); despite greater toxicity, combined radiochemotherapy is the standard treatment in anal cancer.

OVERVIEW OF RADIOTHERAPY TRIALS

Local recurrence rate after surgery alone

Variables such as patient selection, the skill and endurance

Table 1

Pelvic recurrence after a combination of surgery and radiotherapy in rectal carcinoma

Irradiation Study	Dose (Gy)/ No. of fractions	LQ time (Gy)	Surgery alone No. of local recurrences/total	(%)	Surgery + radiotherapy No. of local recurrences/total	(%)	p-[1] value	Percent reduction in local failure rates
Preoperative								
Toronto (27)	5/1	7.5	[3]					
MRC1 (28)	5/1	7.5						0
	20/10	20.4	[4]					0
St Marks (31)	15/3	22.5	51/210[5]	(24)	31/185	(17)	*	29
VASOG II (29)	31.5/18	26.8	[3]					
Bergen (32)	31.5/18	26.8	31/131	(24)	24/138	(17)	NS	29
VASOG I (30)	25/10	27.5	32/87[6]	(37)	27/93	(22)	NS	22
North-West (32)[2]	20/4	30.0	46/126	(37)	17/133	(13)	**	65
EORTC (34)	34.5/15	35.2	49/175	(28)	24/166	(14)	**	50
MRC2 (35)[2]	40/20	36.0	65/140	(46)	50/139	(36)	*	22
Stockholm (36)	25/5	37.5	120/425	(28)	61/424	(14)	**	50
SRCT (37)	25/5	37.5	150/557	(27)	63/553	(11)	***	60
Total			544/1851	(29)	297/1831	(16)	***	45
Postoperative								
Odense (38)	50/25	35.4	57/250	(23)	46/244	(19)	NS	17
MRC3 (40)	40/20	36.0	79/235	(34)	48/234	(21)	**	38
GITSG (41)	40–48/23–26	36.0	27/106	(25)	15/96	(16)	NS	36
NSABP (39)	46.5/26	39.3	45/184	(24)	30/184	(16)	NS	33
EORTC (17)	46/23	40.8	30/88	(34)	25/84	(30)	NS	13
Rotterdam (42)	50/25	43.8	28/84	(33)	21/88	(24)	NS	41
Total			266/947	(28)	185/930	(20)	***	29
Preoperative versus Postoperative			Surgery + preoperative radiotherapy		Surgery + postoperative radiotherapy			
Uppsala (16)	25.5/5	38.0	27/209	(13)				
	60/30	46.9			45/204	(22)	*	–

[1] NS = non-significant; * = $p<0.05$; ** = $p<0.01$; *** = $p<0.001$.
[2] Only tethered tumours.
[3] Not reported.
[4] Only actuarial data reported, with no difference between groups.
[5] Outpatient attendees only reported.
[6] Autopsy series only reported.

of the surgeon, follow-up routines, definition of radicality as well as of local failure can all have an influence on local recurrence rates. These variables can explain the substantial variations as reported in the literature, from $<10\%$ to 65% (4, 5, 24–26). In published controlled trials with adjuvant radiotherapy (pre- or postoperative), the local recurrence rate in the surgery alone group has always exceeded 20% (average 29%, range 23–46%, see Table 1). Thus, our knowledge of how much additional radiotherapy reduces local recurrence rates is based upon studies where the average local recurrence rates are close to 30%. Within all series, the rates are higher when the tumour has penetrated the bowel wall and/or has given lymph node metastases, i.e. Dukes' stages B and C (UICC, stages II and III), and if it is situated distally in the rectum.

Local recurrence rate after additional radiotherapy

In trials using low radiation doses, one should not expect significant effects in the light of the dose-response relationship. This notion is corroborated by several early trials (27–30). Local failure rates were, however, not properly analysed in some of these studies (Table 1). Thus a comparison with later trials, where higher doses have been used, cannot be properly made.

As presented in Table 1, all controlled trials with preoperative radiation for which appropriate data are available have reported a lower local failure rate in the irradiated group of patients than in the non-irradiated (31–37). The difference is statistically significant in 6 of the 8 trials. With radiotherapy delivered postoperatively, a reduction in local recurrence rates has also been observed, but statistical significance was only reached in one of six trials (17, 38–42). The relative reduction in local failure rates is usually higher in the preoperative trials (range 22–65% in trials adequately reported) than in the postoperative trials (average 29%, range 13–41%) despite the fact that higher

Table 2

Pelvic recurrence and overall 5-year survival after surgery and postoperative radiotherapy, chemotherapy or both

Study	Additional treatment	No. of local recurrences/total (%)	p-value[1]	5-year survival (%)	p-value
GITSG (41)	0	14/58 (24)		43	
	Chemotherapy	13/48 (27)	NS	56	NS
	Radiotherapy	10/50 (20)	NS	52	NS
	Chemotherapy + radiotherapy	5/46 (11)	NS	59	*
NSABP (39)	0	45/184 (24)		43	
	Radiotherapy	30/184 (16)	NS	41	NS
	Chemotherapy	40/187 (21)	NS	53	*
NCCTG (46)	Radiotherapy	25/100 (25)		47	
	Chemotherapy + radiotherapy	14/104 (14)	*	58	*
ECOG (48)	Chemotherapy	–	–	47	
	Radiotherapy			46	NS
	Chemotherapy + radiotherapy			50	NS
NSABP-R02 (49)	Chemotherapy	(11)		–	
	Chemotherapy + radiotherapy	(7)	NS	–	
Oslo (47)	0	23/72 (30)		49	
	Chemotherapy + radiotherapy	11/72 (12)	*	69	*

[1] NS = non-significant; * = $p < 0.05$.

doses were used postoperatively (corresponding to LQ times between 35.4 and 43.8 Gy) than preoperatively (LQ times between 22.5 and 37.5 Gy in the trials adequately reported).

The results from the randomized trials thus indicate that preoperative irradiation is more efficient in reducing local recurrence rates than postoperative irradiation. Lower local failure rates were also seen after preoperative than after postoperative radiotherapy in the only trial directly comparing the two approaches (16). This result was found even if a higher dose was used postoperatively than preoperatively (Table 1).

Survival after additional radiotherapy

For between 20 and 50% of the patients with recurrent disease, a local recurrence is the only residual tumour. Therefore, at least on theoretical grounds, preoperative radiotherapy should improve survival when the follow-up period is sufficiently long. In a meta-analysis including all controlled trials published up to 1984, a marginally positive effect on 5-year survival of 4.3% was demonstrated (43). Recent trials prescribing higher doses with a more pronounced reduction in local failure rates were not included in the meta-analysis. These trials, now all having a sufficiently long follow-up, also show that survival is improved after preoperative radiotherapy.

The most convincing evidence of a survival benefit is presented in the Swedish Rectal Cancer Trial (SRCT) which was sufficiently large (1 168 patients randomized) to reveal the survival difference with statistical significance. In irradiated patients (5×5 Gy), the overall 5-year survival was 58% compared with 48% ($p < 0.004$) in the non-irradiated group (44). The relative decrease in mortality thus amounts to 21% (95% confidence limits 8–34%). Finally, the overall survival curves in several preoperative trials deviate with increasing follow-up time, but the differences do not reach statistical significance (31, 33–35). In these trials, cancer-specific survival is usually improved in a statistically significant way. In patients randomized to either preoperative radiotherapy or surgery alone in the Stockholm area between 1987 and 1993 (between 1987 and February 1990, the patients participated in the SRCT), a statistically significant survival benefit of radiotherapy was also observed (45) In these patients, no increase in postoperative mortality was seen (see below). In the first Stockholm trial (36), no effect on survival was seen except when the survival data were corrected for postoperative deaths.

None of the trials using postoperative radiotherapy alone has demonstrated any significant impact on survival. Two trials have, however, demonstrated a survival benefit when postoperative radiotherapy was combined with concomitant chemotherapy (41, 46), but not when radiotherapy was given alone (Table 2). Since in another trial it was found that chemotherapy but not radiotherapy improved survival (39), it is likely that the chemotherapy rather than the postoperative radiotherapy is responsible for the survival improvement. A survival benefit, together with a decreased local recurrence rate, has also been reported in a Norwegian trial in which 144 patients were randomized between surgery alone and surgery plus postoperative ra-

diotherapy to 46 Gy together with concomitant 5-FU (47). No survival benefit could be detected in an ECOG study when radiotherapy and chemotherapy was combined sequentially compared to radiotherapy or chemotherapy given alone (48). When postoperative radiotherapy was added to chemotherapy, either methyl-CCNU, vincristine and 5-FU (MOF) or 5-FU and leukovorin, in the NSABP R-02 trial, no influence on survival was noted (49). A small but statistically significant reduction in the percentage of local recurrences as a site of first treatment failure was seen.

A consensus conference sponsored by NIH discussed adjuvant treatment in rectal cancer and recommended that patients with stages II and III tumours should receive adjuvant treatment with postoperative radiotherapy (45–55 Gy in 5–6 weeks) together with chemotherapy (5-FU and methyl-CCNU). The conclusion was based mainly upon the results of three US trials (Table 2). Updated results from these studies were reviewed in a clinical announcement by the NCI (50). It was again stated that postoperative radiotherapy and chemotherapy should be the standard treatment for rectal cancer stages II and III. A subsequent trial indicated that the addition of methyl-CCNU to 5-FU was not required (51). It was also found that continuous infusion of 5-FU was more effective than bolus 5-FU during the radiotherapy.

Acute/subacute toxicity from additional radiotherapy

Before an evaluation of the advantages and disadvantages of various treatment approaches can be made, the adverse effects and resource demands from the additional treatments must also be known. Preoperative radiotherapy can influence postoperative morbidity and mortality. An increased frequency of perineal wound sepsis after abdominoperineal resection was found in several trials (31, 32, 34, 36, 40, 52, 53). In these trials, the hospital stay was usually slightly longer (mean 2 days) in irradiated patients. The increase in perineal wound sepsis was seen both in trials using conventional fraction sizes (1.8-2.3 Gy (32, 34, 40)) and in trials using 5 Gy fractions (31, 36, 37, 52). The anastomotic integrity after a low anterior resection is not influenced by preoperative radiotherapy (31, 34–36, 52, 53).

Both compliance and acute tolerability have improved after preoperative compared with postoperative radiotherapy. Between 12 and 27% of the patients did not receive the planned postoperative dose (17, 38–42), whereas this occurred in less than 10% in the groups of patients randomized to preoperative radiotherapy (28, 29, 31–36, 53) This difference in acute toxicity was seen also in the single trial directly comparing preoperative with postoperative radiotherapy (52). In the AXIS trial, 96% of the patients scheduled for preoperative radiotherapy received the treatment, whereas this figure was 56% among those where postoperative radiotherapy was chosen (AXIS Trial Office, pers comm, 1997).

A higher postoperative mortality in patients receiving preoperative radiotherapy was found in two reports (31, 36). The increased mortality was noticed among patients older than 75 years and in those with metastatic disease at surgery. The deaths were mainly attributable to cardiovascular and infectious causes, i.e. not obviously related to the irradiation. In these trials radiotherapy was given with anterior–posterior beams; a large volume of the body thus received the same dose as the tumour target. In the Uppsala trial (52), the same radiation dose (5×5 Gy) was used as in the Stockholm–Malmö trial (36) but the irradiation technique (3 beams rather than 2 beams) spared parts of the pelvis and abdomen other than the target volume containing the tumour cells. No influence on postoperative mortality was noticed even if no age limit was used (52). Preoperative radiotherapy can thus be delivered without increasing postoperative mortality. It is thought that a large tissue volume, irradiated to a high dose, is likely to be deleterious, at least in elderly patients. This conclusion is supported by results from the SRCT in which no influence on postoperative mortality was found in patients treated with 3- or 4 beams, whereas this was the case at the hospitals where 2 beams, violating the protocol, were used (53). This conclusion is also supported by extended analyses of the Stockholm-Malmö (Stockholm I) and the Stockholm II trials (as mentioned above, the Stockholm II trial overlaps the SRCT). It was then seen that there tended to be an increased postoperative mortality also in the Stockholm II trial where a 4-beam technique was used at all hospitals but one (54). However, the Stockholm group did not use the lead shields for blocking tissues with a minimal risk of harbouring tumour cells, as stipulated in the SRCT protocol. This meant that the irradiated small bowel volume (and total body volume) was somewhat larger in the Stockholm II trial than recommended in the SRCT protocol. It can be anticipated that this difference may be of relevance for the tendency towards increased postoperative mortality (55).

Acute neurogenic pain, a few hours after the irradiation of the lower lumbar region, was reported from one of the trials using 5 Gy fractions preoperatively (52). The pain, which affected only a few of the patients, was usually of short duration but could remain for several months in some. Subacute neurogenic symptoms and signs have developed in some of the affected patients, leading to inability to walk in a few cases. When the entire experience in Uppsala from 1979 through 1994 was reviewed, 19 (4%) out of 550 patients treated with 5×5 (or 5.1) Gy within prospective protocols had reported pain. In six (1%) patients, the pain had a duration of more than a few days, and in four of them, subacute neurogenic symptoms developed. The pain was more common in women than in men, and appeared to occur more often in diabetic patients and in patients with previous neurologic disorders. An extensive re-evaluation of the treatment did not disclose any

technical or human error, and the genesis of this acute adverse effect is still unknown (56). The observation of this complication, probably caused by an effect on the nerves in the lower lumbar region, does, however, indicate the need for an adequate radiation technique with appropriate target volumes and blocking of tissues that have a minimal risk of harbouring tumour cells.

Late radiation-associated toxicity

The most extensive knowledge about the risk of late morbidity has come from the Swedish trials, the Uppsala trial (57, 58), the two Stockholm trials (59) and the SRCT (60). Yet, the knowledge is not complete, and we will have to wait another few years until there is a sufficiently long follow-up in all of the trials. In the Uppsala trial, preoperative radiotherapy (25.5 Gy in 1 week) was compared with postoperative radiotherapy (60 Gy in 7 weeks), whereas in the other trials, preoperative radiotherapy (25 Gy in 1 week) followed by immediate surgery was compared with surgery alone. The target volumes and the radiation techniques have, however, varied considerably between the trials. Besides these trials, late effects have also been reported from trials using postoperative radiotherapy to doses between 40 and 50 Gy in 4–5 weeks. The irradiated volumes have varied also in these trials.

Intestinal obstruction. Late effects from irradiation are dependent upon radiation dose and the irradiated volume of the risk organ. In a report by Letschert et al. (61), postoperative radiotherapy with beams extending high up in the abdomen caused small bowel intestinal obstruction in 30–40% of patients, compared with 5–10% when only the dorsal part of the pelvic cavity was irradiated. Similarly, in the Stockholm I trial, where large anterior–posterior beams were used, an increased incidence of hospital admission due to intestinal obstruction after preoperative radiation was seen, but not in the Stockholm II trial where somewhat smaller beams were used, but with a 4-beam technique reducing the irradiated small bowel volume (59). In the Uppsala trial, all patients with a follow-up period between 5 and 10 years were re-examined for late adverse effects of radiation. Those given preoperative radiotherapy did not differ with respect to bowel obstruction or other possible late adverse effects from those given surgery alone (57). In patients irradiated postoperatively, a higher late morbidity was found also when a technique that largely avoided irradiation of extended small bowel volumes was used. This can also be anticipated since the postoperative dose was higher (60 Gy in 7 weeks) than the preoperative one (25 Gy in 1 week, corresponding to approximately 42–50 Gy in 4–5 weeks). In conclusion, the results so far indicate that late small bowel morbidity will be low provided the irradiation is given with 3 or 4 beams maximally extending up to L3 and the total dose is at most 50 Gy using 2 Gy-fractions (about 25 Gy using 5 Gy fractions).

Diseases related to the genitourinary tract. Neither the Stockholm I and II trials (59) nor the Uppsala trial (57) could detect any increased late morbidity from the genitourinary tract after preoperative radiotherapy to 5×5 Gy. It is thus possible that even higher doses are required to cause a significant increase in the complication rates. The design of the mentioned trials was, however, not optimal to detect minor, although clinically relevant, adverse effects. The Stockholm trials only looked at effects causing hospitalization, and the Uppsala trial did not have sufficient patient numbers. Chronic cystitis was reported to occur considerably more often after postoperative radiotherapy (46 Gy, 10/84, 12%) than after surgery alone (0/88) in one trial (17).

Bowel function. Radiation therapy may theoretically influence bowel function after an anterior resection, either by damaging the sphincters, the remaining part of the rectum or the pudendal nerves. In a 5-year follow-up study of the SRCT, irradiated patients frequently complained about increased urgency, incontinence to gas and loose stools and a frequent need to wear a pad (60). Results from postoperative trials also indicate a negative influence on bowel function (62–64). Chronic diarrhoea was also frequently seen after postoperative radiotherapy (17). Whether this influence on long-term quality of life counterbalances the positive effects by the radiotherapy is not known. They do, however, indicate that optimized techniques should be used. The routine inclusion of the anal canal in the irradiated volume should probably be avoided (55).

Femoral neck and pelvic fractures. The Stockholm group recently reported increased hospitalization for these reasons after preoperative radiation (59). The effect was seen in both trials although it was more marked in the first one. The Stockholm group did not block the dorsal parts of the sacrum and the tissues behind on the lateral beams (59) as was stated in the protocol of the SRCT (55). The relevance of these lead blocks for the prevention of sacral fractures, as seen in the Stockholm trials, is not known.

WHAT IS THE APPROPRIATE TARGET VOLUME AND RADIATION TECHNIQUE?

Ideally, the target volume should include locoregional tissues at risk of containing tumour cells not removed by the subsequent (or preceding) surgery. The radiation technique should also ideally cover the entire target volume with the prescribed dose and, at the same time, minimize dose to tissues outside the target volume. The irradiated volume receiving $>95\%$ of the prescribed dose should thus not be significantly larger than the target volume. Different conformal techniques after individual 3D dose planning may complete this task in an optimal way. Protons, with their superior geometrical properties compared to electrons and photons, would solve the problem even

better (65). In a common disease like rectal cancer, the use of the most optimal procedure in every patient may, however, not be possible for practical and economic reasons. A simplified and less time-consuming procedure has been practised in Uppsala for 17 years, and has proven to be safe and sufficiently robust not to jeopardize the outcome even in patients with unusual constitutions (55). Thus, for practical purposes, three or four rather standardized beams with a few appropriately placed lead shields solve the problem in a clinically satisfactory way.

As detailed above, experience has taught us that overly large irradiated volumes will result in unexceptably high rates of both acute and late toxicities. Since the primary aim of the perioperative radiotherapy is to decrease local failure rates, even if survival also may be positively influenced, the target volume should cover only locoregional tissues at risk of containing tumour cells when surgery has been carried out. Exclusion of the tissues above the promontorium will not influence the pelvic recurrence rate, although this may diminish the positive influence on colorectal cancer-specific survival. Even if the Uppsala experience has been favourable with respect to both acute and late toxicities (16, 55, 57), the upper border of the target volume has successively been lowered. The change has emerged through the years as a consequence of the results of the trials. At present, we recommend that the upper border should be just below the promontorium (see Figure). It is not known whether even smaller target volumes, such as, for example, used by Marsh et al. (33), are sufficient. The anal canal has not been included in the target volume in Uppsala, except when the SRCT was running (see above), in tumours situated above 6–8 cm from the anal verge.

The beam limits based upon an imagined planning target volume (PTV) are illustrated in Fig. 1. The appropriate size of the target volume and the radiation technique has not been subject to any randomized controlled clinical trial. The relevance of using this technique as compared to other techniques is, however, supported by the application of biological models (55).

CONCLUSIONS

Until more efficient chemotherapy regimens are available, radiation therapy should be included in rectal cancer treatment, primarily since it reduces the local failure rate. Contrary to the opinion held in the US (50), we believe that radiotherapy is more effective given preoperatively. Preoperative radiotherapy also improves survival, although the magnitude of the survival benefit is rather limited. We also question the routine use of simultaneous radiochemotherapy, because the scientific evidence in rectal cancer is weak and limited to two small, randomized trials (41, 46). The chemotherapy component is, however, of relevance for the survival benefit seen in those and other trials, mainly influencing distant metastases rates but to some extent also local failure rates. We do not recommend the short preoperative 5×5 Gy schedule to be combined with simultaneous chemotherapy, but it can readily be combined with postoperative chemotherapy for stages at high risk of distant failure. This approach was used at several Swedish centres in a large Nordic adjuvant chemotherapy trial (B. Glimelius, unpublished observation).

Using a preoperative approach, there is, however, concern about irradiating patients with a Dukes' stage A lesion and those with metastatic disease disclosed at surgery. Dukes' A lesions can now be identified with reasonable accuracy by using intraluminal ultrasonography before surgery (66, 67) and thus patients are spared radiotherapy. This requires, however, that surgery is prop-

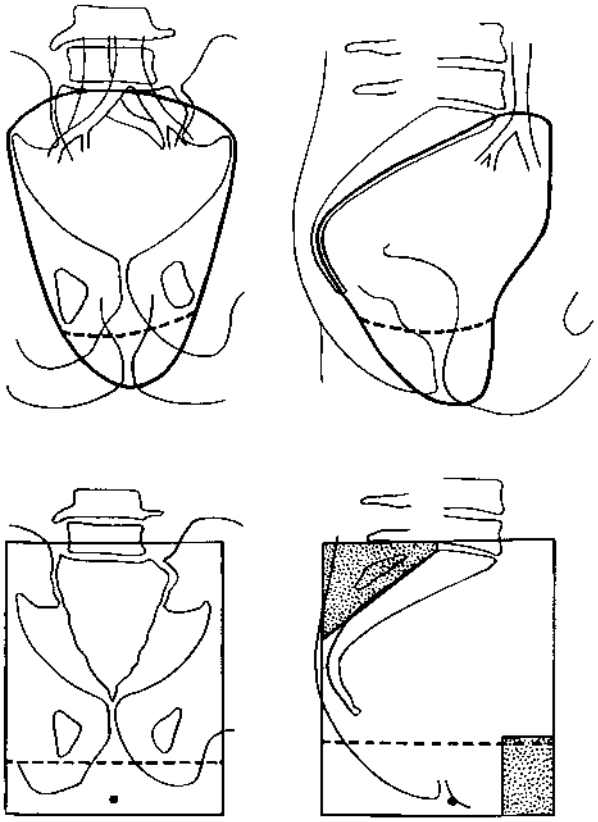

Fig. 1. Illustration of the planning target volume (PTV) (above) and the beam limits (below) used with a 4-beam 'box' technique, as presently recommended in Sweden. The lower portion of the target includes the anal canal only in low-situated tumours when a rectal excision is the likely surgical procedure. The beam limits are defined in the simulator. No PTV is defined in an individual patient. A dose optimization is performed in a single transverse section and based on a manually obtained contour of the patient. Beam energy, beam weights and wedge filters are selected at the dose planning station (55). Shields are placed on the lateral beams in the simulator as indicated in the figure. The caudal shield anterior to the anal orifice is not used when the tumour is situated in the lower anterior part of the rectum.

erly performed so that local failures are kept at a very low level. In the trials reporting a reduced local recurrence rate according to Dukes' stage, the reduction was seen also in Dukes' stage A (36, 45). In these trials, non-irradiated Dukes' stage A patients had an unacceptably high local failure rate of 14 and 11%, respectively, compared with 5 and 3% among irradiated patients.

It is possible that the proportional reduction in local recurrence rate after preoperative radiotherapy is at least as high following 'optimized' surgery, as advocated by Heald and others (4–6), as it is when combined with 'standard' surgery. It is anticipated that the local failure rate will then be very low (0–3%?) (68). This has, however, not been tested in a randomized trial. A presently ongoing Dutch trial tests this hypothesis (C van de Velde, pers comm). When the local failure rate without radiotherapy is 8–10% (local failure rates should be calculated on all patients eligible for rectal cancer surgery where the tumour-bearing bowel segment is removed, and not just those curatively resected), over-treatment is substantial. The radiotherapy therefore must be safe, both in the short and in the long perspective. The dose must also be sufficiently high (>40 Gy when given in 2 Gy fractions, or comparable doses using other fractionation schedules). Therefore, radiotherapy must be given with techniques that exclude volumes not at risk of containing tumour cells. All treatment modalities should be used in an optimal way so that the severely disabling condition, a local pelvic failure of a rectal cancer, can be entirely eliminated.

REFERENCES

1. Stenbeck M, Rosén M, Holm L-E. Cancer survival in Sweden during three decades 1961–1991. Acta Oncol 1995; 34: 881–91.
2. Adam IJ, Mohamdee MO, Martin IG, et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. Lancet 1994; 344: 707–11.
3. Ny IOL, Luk ISC, Yuen ST, et al. Surgical lateral clearance in resected rectal carcinomas, a multivariate analysis of clinicopathological features. Cancer 1993; 71: 1972–6.
4. Heald RJ, Ryall RDH. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986; 28: 1479–82.
5. MacFarlane JK, Ryall RDH, Heald RJ. Mesorectal excision for rectal cancer. Lancet 1993; 341: 457–60.
6. Enker WE. Total mesorectal excision—the new golden standard of surgery for rectal cancer. Ann Med 1997; 29: 127–33.
7. Fowler JF. The linear-quadratic formula and progress in fractionated radiotherapy. Br J Radiol 1989; 62: 679–94.
8. Denham JW. The radiation dose-response relationship for control of primary breast cancer. Radiother Oncol 1986; 7: 107–23.
9. Fletcher GH. Subclinical disease. Cancer 1984; 53: 1274–84.
10. Fowler JF. How worthwhile are short schedules in radiotherapy?: a series of exploratory calculations. Radiother Oncol 1990; 8: 165–81.
11. Withers HR, Taylor JMG, Maciejewski B. The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 1988; 27: 131–46.
12. Fletcher GH. Hypofractionation: lessons from complications. Radiother Oncol 1991; 20: 10–5.
13. Glimelius B, Isacsson U, Jung B, Påhlman L. Radiotherapy in addition to radical surgery in rectal cancer: evidence for a dose-response effect favouring preoperative treatment. Int J Radiat Oncol Biol Phys 1997; 37: 281–7.
14. Minsky BD, Cohen AM, Enker WE, Pary P. Sphincter preservation with preoperative radiation therapy and coloanal anastomosis. Int J Radiat Oncol Biol Phys 1995; 31: 553–9.
15. Gerard J-P, Baulieux J, Francois Y, et al. The role of radiotherapy in the conservative treatment of rectal carcinoma. Acta Oncol 1998; 37: 247–52.
16. Påhlman L, Glimelius B. Pre- or postoperative radiotherapy in rectal carcinoma: a report from a randomized multicenter trial. Ann Surg 1990; 211: 187–95.
17. Arnaud JP, Nordlinger B, Bosset JF, 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: 352–7.
18. Lawrence TS, Davis MA, Maybaum J. Dependence of 5-fluorouracil-mediated radiosensitization on DNA-directed effects. Int J Radiat Oncol Biol Phys 1994; 29: 519–23.
19. Tannock F. Treatment of cancer with radiation and drugs. J Clin Oncol 1996; 14: 3156–74.
20. Overgaard M, Bertelsen K, Dalmark M, et al. A randomized feasibility study evaluating the effect of radiotherapy alone or combined with 5-fluorouracil in the treatment of locally recurrent or inoperable colorectal carcinoma. Acta Oncol 1993; 32: 547–53.
21. UKCCCR Anal Cancer Trial Working Party. Epidermoid anal cancer: results from the UKCCCR randomised trial of radiotherapy alone versus radiotherapy, 5-fluorouracil, and mitomycin. Lancet 1996; 348: 1049–54.
22. Flam M, John M, Pajak TF, et al. Role of mitomycin in combination with fluorouracil and radiotherapy, and of salvage chemoradiation in the definitive nonsurgical treatment of epidermoid carcinoma of the anal canal: results of a phase III randomized intergroup study. J Clin Oncol 1996; 14: 2527–39.
23. Bartelink H, Roelofsen F, Eschwege F, et al. Concomitant radiotherapy and chemotherapy is superior to radiotherapy alone in the treatment of locally advanced anal cancer: Results of a phase III randomized trial of the European Organization for Research and Treatment of Cancer Radiotherapy and Gastrointestinal Cooperative Groups. J Clin Oncol 1997; 15: 2040–9.
24. Gunderson L, Sosin H. Areas of failure found at reoperation (second or symptomatic look) following 'curative surgery' for adenocarcinoma of the rectum. Cancer 1974; 34: 1278–92.
25. Phillips RKS, Hittinger R, Blesovsky L, Fry JS, Fielding LP. Local recurrence following'curative' surgery for large bowel cancer: I. The overall picture. Br J Surg 1984; 71: 12–6.
26. Påhlman L, Glimelius B. Local recurrences after surgical treatment for rectal carcinoma. Acta Chir Scand 1984; 150: 331–5.
27. Rider WD, Palmer JA, Mahoney LJ, Robertson CT. Preoperative irradiation in operable cancer of the rectum: report of the Toronto trial. Can J Surg 1977; 20: 335–8.

28. Duncan W, Smith AN, Freedman LS, Alderson MR, Arnott SJ, Bleehen NM. 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: 21–5.
29. Higgins G, Humphrey E, Dwight R, Roswit B, Lee L, Keehn R. Preoperative radiation and surgery for cancer of the rectum. VASOG Trial II. Cancer 1986; 58: 352–9.
30. Roswit B, Higgins G, Keehn R. Preoperative irradiation for carcinoma of the rectum and rectosigmoid colon: report of a National Veterans' Administration randomized study. Cancer 1975; 35: 1597–602.
31. Goldberg PA, Nicholls RJ, Porter NH, Love S, Grimsey JE. 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: 1602–6.
32. Horn A, Halvorsen JF, Dahl O. Preoperative radiotherapy in operable rectal cancer. Dis Colon Rectum 1990; 33: 823–38.
33. Marsh PJ, James RD, Schofield PF. Adjuvant preoperative radiotherapy for locally advanced rectal carcinoma. Results of a prospective, randomized trial. Dis Colon Rectum 1994; 37: 1205–14.
34. Gerard A, Buyse M, Nordlinger B, et al. Preoperative radiotherapy as adjuvant treatment in rectal cancer. Ann Surg 1988; 208: 606–14.
35. 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: 1605–10.
36. Stockholm Rectal Cancer Study Group. Preoperative short-term radiation therapy in operable rectal carcinoma. A prospective randomized trial. Cancer 1990; 66: 49–55.
37. Swedish Rectal Cancer Trial. Local recurrence rate in a randomized multicentre trial of preoperative radiotherapy compared to surgery alone in resectable rectal carcinoma. Eur J Surg 1996; 162: 397–402.
38. Bentzen SM, Balslev I, Pedersen M, et al. Time to loco-regional recurrence after resection of Dukes' B and C colorectal cancer with or without adjuvant postoperative radiotherapy. Br J Cancer 1992; 65: 102–7.
39. 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: 21–9.
40. 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: 1610–4.
41. Gastrointestinal Tumor Study Group. Prolongation of the disease-free interval in surgically treated rectal carcinoma. New Engl J Med 1985; 312:1464–72.
42. Treurniet-Donker AD, van Putten WLJ, Wereldsma JCJ, et al. Postoperative radiation therapy for rectal cancer. Cancer 1991; 67: 2042–8.
43. Buyse M, Zeleniuch-Jacquotte A, Chalmers TC. Adjuvant therapy of colorectal cancer. Why we still don't know. JAMA 1988; 259: 3571–8.
44. Swedish Rectal Cancer Trial. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997; 336: 980–7.
45. Stockholm Colorectal Cancer Study Group. Randomized study on preoperative radiotherapy in rectal carcinoma. Ann Surg Oncol 1996; 3: 423–30.
46. Krook JE, Moertel CG, Gunderson LL, et al. Effective surgical adjuvant therapy for high-risk rectal cancer. New Engl J Med 1991; 324: 709–15.
47. Tveit KM, 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. Br J Surg 1997; 84: 1130–5.
48. Mansour EG, Lefkopoulou M, Johnson R, Douglass H. A comparison of postoperative adjuvant chemotherapy, radiotherapy or combination therapy in potentially curable resectable rectal carcinoma. An ECOG study Est 4276. Proc Am Soc Clin Oncol 1991; 10: 154 (abstr).
49. Rockette H, Deutsch M, Petrelli N, et al. Effect of postoperative radiation therapy (RTX) when used with adjuvant chemotherapy in Dukes' B and C rectal cancer: results from NSABP R-02. Proc Am Soc Clin Oncol 1994; 13: 193 (abstr).
50. NCI. Clinical announcement. Adjuvant therapy of rectal cancer, 14th March, 1991.
51. O'Connell MJ, Martenson JA, Wieand HS. Improving adjuvant therapy for rectal cancer by combining protracted infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 1994; 331: 502–7.
52. Påhlman L, Glimelius B, Graffman S. Pre- versus postoperative radiotherapy in rectal carcinoma: an interim report from a randomized multicentre trial. Br J Surg 1985; 72: 961–6.
53. 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: 1333–6.
54. Holm T, Rutqvist LE, Johansson H, Cedermark B. Postoperative mortality in rectal cancer treated with or without preoperative radiotherapy causes and risk factors. Br J Surg 1996; 83: 964–8.
55. Frykholm-Jansson G, Isacsson U, Sintorn K, et al. Preoperative radiotherapy in rectal carcinoma—aspects of adverse effects and radiation technique. Int J Radiat Oncol Biol Phys 1996; 35: 1039–48.
56. Frykholm-Jansson G, Sintorn K, Montelius A, Jung B, Påhlman L, Glimelius B. Acute lumbosacral plexopathy after preoperative radiotherapy in rectal carcinoma. Radiother Oncol 1996; 38: 121–30.
57. Frykholm G, Glimelius B, Påhlman L. Pre- 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: 564–72.
58. Graf W, Ekström K, Glimelius B, Påhlman L. A pilot study of factors influencing bowel function after colorectal anastomosis. Dis Colon Rectum 1996; 39: 593–600.
59. Holm T, Singnomklao T, Rutqvist L, Cedermark B. Adjuvant preoperative radiotherapy in patients with rectal carcinoma. Adverse effects during long term follow-up of two randomized trials. Cancer 1996; 78: 968–76.
60. Dahlberg M, Glimelius B, Graf W, Påhlman L. Preoperative irradiation affects the functional results after surgery for rectal cancer. Dis Colon Rectum 1998; 41: 543–9.
61. Letschert JGJ, Lebesque JV, de Boer RW, Hart AAM, Bartelink H. Dose-volume correlation in radiation-induced late small-bowel complications: a clinical study. Radiother Oncol 1990; 18: 307–20.
62. Lewis WG, Williamson MER, Stephenson BM, et al. Potential disadvantages of postoperative adjuvant radiotherapy after anterior resection for rectal cancer: a pilot study of sphincter function, rectal capacity and clinical outcome. Int J Colorectal Dis 1995; 10: 133–7.

63. Lundby L, Jensen VJ, Overgaard J, Lauerberg S. Long-term colorectal function after postoperative radiotherapy for colorectal cancer. Lancet 1997; 350: 564.
64. Kollmorgen CF, Meagher AP, Wolff BG, Pemberton JH, Matenson JA, Ilstrup DM. The long-term effect of adjuvant postoperative chemoradiotherapy for rectal carcinoma on bowel function. Ann Surg 1994; 220: 676–82.
65. Isacsson U, Montelius A, Jung B, Glimelius B. Comparative treatment planning between proton and x-ray therapy in locally advanced rectal cancer. Radiother Oncol 1996; 41: 263–72.
66. Beynon J, Mortensen NJ, Foy DMA, Channer JL, Virjee J, Goddard P. Preoperative assessment of local invasion in rectal cancer: digital examination, endoluminal sonography or computed tomography? Br J Surg 1986; 73: 1015–7.
67. Lindmark G, Kraaz W, Elvin A, Glimelius B. A critical evaluation of the endosonography in the staging of rectal cancer. Radiology 1998; 204: 533–8.
68. Glimelius B. Role of radiotherapy in addition to optimal surgery. In: Søreide O, Norstein J, eds. Rectal cancer surgery, optimisation, standardisation, documentation. Berlin: Springer-Verlag, 1997: 373–83.