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The Value of Adjuvant Radio(chemo)therapy for Rectal Cancer

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Radiotherapy has been used extensively as an adjuvant treatment with surgery for patients with rectal cancer. Present knowledge indicates that preoperative radiotherapy is more dose-efficient than postoperative radiotherapy in reducing local recurrence rate. Provided the dose is sufficiently high, the reduction exceeds 50% in all Dukes' stages and after both abdominal perineal excision and anterior resection. The effect on survival has not yet been proven but there are indications that survival may be slightly improved using preoperative radiotherapy, although the magnitude of this improvement is probably less than with postoperative chemotherapy. Of concern with all adjuvant treatments are the potential side-effects, and it appears that postoperative radiotherapy has more side-effects than preoperative radiotherapy, even if the reduction of local recurrences is less and proper radiation techniques are utilised.

Key words: rectal cancer, radiotherapy
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INTRODUCTION

IN THE literature, the outcome after surgery for rectal cancer differs markedly between patient series for both local recurrence rates and survival. Patient selection, definition of radicality and recurrence, the skill of the surgeon and follow-up procedures are factors influencing this difference. In order to improve treatment results, various additional treatments, such as radiotherapy, chemotherapy and immunotherapy, have been tested. Since colorectal cancer is a common disease in the western world, even proportionally small improvements in outcome will affect many individuals. The optimal treatment schedule for adjuvant radiotherapy in rectal cancer surgery is not yet resolved. This review discusses treatment results after additional radiotherapy following rectal cancer surgical resection, timing of the treatment and acute and late adverse effects.

TIMING OF RADIOTHERAPY

The rationale of using radiotherapy in addition to surgery is that small tumour deposits, which for anatomical reasons cannot be excised, are left in the periphery after surgery. It has been shown convincingly that the major cause of pelvic failure is a lateral spread of microscopic tumour cells not removed at surgery [1, 2]. In contrast, radiotherapy cannot eradicate the bulk of the tumour. In order to achieve a probability of >90% of irradicating subclinical disease, a dose in the order of 50 Gy using conventional fractionation is considered necessary, based upon results obtained mainly from studies on breast and head and neck cancer [3]. The number of tumour cells to be killed by radiotherapy is probably fewer before rather than after surgery due to tumour cell proliferation. Therefore, to obtain the same efficacy, the dose needs to be higher with postoperative treatment. From the results of all randomised controlled radiotherapy trials, it can also be seen that reduction of local recurrence rates is higher if radiotherapy is given preoperatively rather than postoperatively (Table 1). The table includes all trials in which local recurrence rates have been reported.

Apart from total dose, the effect of radiation is also dependent upon the dose at each fraction and the total treatment time. Since different schedules have been used in the different trials, the biological effects of the various schedules must be estimated for proper comparisons between the trials. In Table 1, the trials have been ranked according to the linear quadratic (LQ) formula, assuming that the α/β for the tumour is 10 Gy [4]. It can be seen that a lower dose has generally been used in the trials using preoperative radiotherapy, which further supports the hypothesis that preoperative radiotherapy is more efficient than postoperative irradiation.

This question of whether preoperative radiotherapy is better than postoperative has been specifically addressed in a Swedish trial [17]. Patients were recruited between 1980 and 1985, and 471 patients were randomly allocated to receive either preoperative radiotherapy (5 × 5.1 Gy in 1 week, LQ time 38.0) followed by surgery the following week, or surgery followed by postoperative radiotherapy (60 Gy in 7–8 weeks, LQ time 46.9) to patients with a Dukes' Stage B or C tumour. The local recurrence rate was 12% in the preoperative group compared with 21% ($P < 0.02$) in the postoperative group [17]. Only 1 patient allocated to preoperative radiotherapy did not receive the intended treatment because of refusal. Among the patients allocated to postoperative radiotherapy, 16% did not receive the treatment due to postoperative complications and fatigue. According to the study design, treatment should ideally start within 4–6 weeks after surgery, but for only 50% of the patients did treatment begin within 6 weeks, and for 24% it did not start

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

Study	Dose (Gy)/ Number of fractions	LQ time	Surgery alone Number of local recurrences/total (%)		Surgery + radiotherapy Number of local recurrences/total (%)		*P* value
Pre-operative irradiation							
St Marks [5]	15/3	22.5	51/210	(24)	31/185	(17)	NS
Bergen [6]	31.5/18	26.8	31/131	(24)	24/138	(17)	NS
North-West [7]	20/4	30.0	58/141	(41)	26/143	(18)	<0.01
EORTC [8]	34.5/15	35.2	49/175	(28)	24/166	(14)	<0.01
MRC2* [9]	40/20	36.0	50/132	(38)	41/129	(32)	NS
Stockholm [10]	25/5	37.5	120/485	(28)	61/424	(14)	<0.01
SRCT [11]	25/5	37.5	131/557	(24)	51/553	(9)	<0.01
Postoperative irradiation							
Odense [12]	50/25	35.4	57/250	(23)	46/24	(19)	NS
MRC3 [9]	40/20	36.0	69/235	(29)	46/234	(20)	<0.05
GITSG [13]	40–48/22	36.0	27/106	(25)	15/96	(16)	NS
NSABP [14]	46.5/26	39.3	45/184	(24)	30/184	(16)	NS
EORTC [15]	46/23	40.8	30/88	(34)	25/84	(30)	NS
Rotterdam [16]	50/25	43.8	28/84	(33)	21/88	(24)	NS

LQ, linear quadratic formula, NS, non-significant. NS, $P > 0.05$. *Only tethered tumours.

until more than 2 months after surgery, usually due to problems with postoperative recovery [18]. This study, where the highest postoperative dose ever reported as an adjuvant treatment was used, also shows that the dose must be considerably higher if given postoperatively to reach the same efficacy as if given preoperatively.

RADIATION SCHEDULE

In order to reach a dose of 40–50 Gy, patients have to be treated for 4.5 weeks if the treatment is given with conventional fractionation, i.e. 1.8–2.0 Gy daily. After this treatment, surgery cannot be performed for 3–4 weeks, giving a total preoperative treatment period of 2 months. This is considered to be a difficult period for both the patient and the surgeon. In addition, the costs are high. The rationale of using higher doses per fraction, such as the 5 Gy fractions to a total dose of 25 Gy extensively used in Sweden [10, 11, 17], is to diminish the treatment period and to be able to operate much earlier. This use of high fraction doses is of great concern because of its decreased therapeutic ratio, particularly with respect to late adverse effects (see below). An alternative approach to shorten treatment times, which has not yet been investigated in rectal cancer irradiation, would be to give multiple fractions each day.

EFFECT ON SURVIVAL

Using preoperative radiotherapy at moderate doses, reduction in local recurrence rate exceeds 50%. Since about 20% of the patients with recurrent disease have local recurrence only, preoperative radiotherapy should improve survival after prolonged follow-up. In a meta-analysis, where all control trials published up to 1984 were included, a marginal positive effect on 5-year survival of approximately 4% was demonstrated [19]. However, in this meta-analysis, recent trials with higher radiotherapy doses were not included. In the preoperative EORTC trial, there were non-significant differences in survival increasing with follow-up time [8]. Moreover, in the Stockholm trial, survival was better in the group of patients who received preoperative radiotherapy, provided survival curves were corrected for postoperative deaths (see below) [10]. In a recent update of all patients in the Stockholm area, where some patients were included in the Swedish Rectal Cancer Trial [20], a statistically significant benefit of preoperative radiotherapy has been observed after a minimum follow-up of 3 years.

No trial using postoperative radiotherapy alone has shown any significant effect on survival. However, in two trials where postoperative radiotherapy was combined with chemotherapy (5-fluorouracil (5-FU) and methyl-CCNU), a survival benefit was demonstrated in the combined treatment arm [13, 14]. A third trial, also from the U.S.A. has demonstrated that chemotherapy in addition to radiotherapy improves survival [21]. The effects on local recurrence rate in those trials are in accordance with Table 1, i.e. a non-significant reduction. It is, therefore, tempting to believe that the survival benefit is an effect of the chemotherapy rather than of the postoperative radiotherapy.

IS ADJUVANT RADIOTHERAPY SAFE?

Acute adverse effects

In two trials, an increased postoperative mortality has been reported among patients receiving preoperative radiotherapy [5, 10]. Both trials used 5 Gy fractions daily with a two-portal irradiation technique. With such a technique, a large volume of the body will receive the same dose as the tumour volume. The excess in mortality was mainly noted among patients older than 75 years, and predominantly among those having generalised disease. In the Uppsala trial, where the same radiation dose and schedule was used with a three-portal technique, no increased postoperative mortality was found, despite no age restriction [18]. When the irradiation is given with three or four portals, the volume of the body that receives the prescribed dose is much less than using two portals. The causes of death among the patients in the two trials who reported an increased postoperative

mortality were mainly cardiovascular and infectious. The relationship between irradiation and cardiovascular diseases is not apparent, but it appears that irradiation to a large body volume can be deleterious, particularly to elderly patients. In a recently published Swedish trial, where 1168 patients were included, it was again noted that the same high-dose radiotherapy (5 × 5 Gy within 1 week) did not influence postoperative mortality, provided the treatment was given with a three- or four-portal technique [22].

In all trials using moderate or high-dose preoperative radiotherapy, a higher incidence of perineal wound infections has been reported among patients operated upon with an abdominal perineal excision [10, 18, 22]. The magnitude of this phenomenon is an increase from 10% in the group not irradiated to 20% in the group which received irradiation. In these trials, the length of the hospital stay was approximately 2–3 days longer among the irradiated patients [22], but no increase in anastomotic dehiscences was observed among irradiated patients. Moreover, other known complications after pelvic surgery, such as deep vein thromboses, urinary tract infections and abdominal wound infections, have not increased when preoperative radiotherapy has been used.

In one trial, using 5 Gy fractions preoperatively, acute neurogenic pain of the lower lumbar region occurred immediately after irradiation [17]. The pain was usually of very short duration, but remained for several months in some patients. 32 patients reported pain among the 550 patients who were treated with 5×5 Gy within prospective protocols since 1979. In 6 (1%) patients, the pain duration was more than a few days, and 4 patients developed subacute neurogenic symptoms in a 6-month period, leading to an inability to walk properly in 3 patients. Acute pain was more common in women than in men, and occurred predominantly in patients with other diseases such as diabetes or previous neurological disorders. The reason for this potentially severe side-effect is still unknown, but general opinion among radiotherapists is that considerably higher doses need be used to cause acute damage to the peripheral nerves.

The acute toxicity from postoperative radiotherapy has been prospectively studied in the Uppsala trial [18]. Treatment was completed without any complications in only 9%. In 7 patients, treatment was interrupted due to fatigue and infectious complications. Fatigue, diarrhoea, skin reactions, urinary disorders and nausea were frequently seen during the treatment period. Most patients were treated on an outpatient basis, but 5 patients had to be hospitalised for parenteral nutrition due to diarrhoea. According to the protocol, the prescribed treatment schedule including the split should be 52 days (42 days + 8–10 days split), but only 49% of the patients completed the postoperative irradiation within this period. Similar difficulties were noticed in the Danish trial [12]. Only 85% of the patients who started the postoperative irradiation completed the treatment.

Late adverse effects

Since higher doses are used postoperatively, it should be expected that patients having postoperative radiotherapy will have more late morbidity, such as intestinal obstruction and/or diarrhoea, than those irradiated preoperatively. Postoperative adhescence may also influence complication rates [23, 24]. The extent of this problem seems to be related to the volume of small bowel included in the treatment volume [25]. Several attempts have been made to diminish the amount of small bowel included within the irradiated volume [26]. In the Uppsala trial, all patients with a follow-up period of 5–10 years were re-examined for late adverse effects of radiotherapy [24]. In that trial, a group of patients had no radiotherapy (Dukes' stage A tumours allocated to postoperative radiotherapy). Therefore, it was possible to compare preoperative irradiation (5×5 Gy in 1 week) with surgery alone as well as with postoperative radiotherapy. The cumulative risk of having a small bowel obstruction was just below 10% in the surgery alone group and in the preoperatively irradiated group [24]. However, among those receiving postoperative radiotherapy, the cumulative risk of having a small bowel obstruction was nearly 20%, with a follow-up period of 10 years. These figures are in accordance with other reports, where the incidence of small bowel obstruction increased by 30–40% if the beams extended high up the abdomen [12, 25]. If the treatments were given with multiple pelvic fields, the risk of small bowel obstructions decreased substantially [21, 25].

Another observation in the Uppsala trial is that patients who received a low anterior resection might have a slightly worse long-term outcome, in terms of bowel function, after irradiation (manuscript in preparation). Due to the small patient sample, it is not clear whether this is an effect of postoperative or preoperative irradiation. Theoretically, the irradiation might damage the sphincters or the pudendal nerves. These questions will be addressed in the Swedish Rectal Cancer Trial.

CONCLUSION

"Optimised surgery" results in a very low frequency of local recurrences, as demonstrated by Heald and others [27, 28]. In the Swedish Rectal Cancer Trial, we can identify institutions with very low local recurrence rates and those with high recurrence rates. The magnitudes of the decrease in the recurrence rates with preoperative irradiation are similar (approximately 65%) in institutions with different outcomes, indicating that recurrence can almost be eradicated if optimised surgery is combined with adjuvant radiotherapy (data not presented). When radiotherapy is used in association with optimal surgery, overtreatment is, however, substantial. This means that radiotherapy must be safe, both in the postoperative period and in the long term. Since the dose must be sufficiently high (at least 40–45 Gy given with conventional fractionation or comparable doses using other schedules), it is also important that the radiotherapy technique is optimised. The experience of using 25 Gy in 1 week in the Uppsala region since 1979 indicates that the treatment is sufficiently safe [17, 24]. However, the experience at other institutions [10], where the same dose was used but with a sub-optimal technique, shows that this treatment may be potentially hazardous. Also, our knowledge of late adverse effects from this high-dose fractionated treatment is still limited. Therefore, longer follow-up of more patients is needed. Long-term follow-ups of other preoperative schedules have not yet been published.

It is important for the surgeons to identify risk groups. First, the tumour has to be properly evaluated preoperatively, so that patients with inappropriate tumours can be withdrawn from an adjuvant protocol. The short preoperative treatment, used extensively in Sweden, is not optimal for fixed tumours, and should be exclusively restricted to patients with a primarily resectable tumour. Of concern are patients with Dukes' stage A lesions, where radiotherapy is probably superfluous provided the surgery is optimal. These patients can easily be detected with endorectal ultrasound and thus withdrawn from adjuvant radiotherapy [29]. However, in the Uppsala region, a small number of patients have developed local failure during the last 8 years in whom ultrasonography indicated a Dukes' stage A

tumour and where no radiotherapy was given. Moreover, the highest recurrence rates are reported among those where the tumour is situated in the lower third of the rectum and where an abdominal perineal excision is the treatment option. Since that procedure is a difficult operation, particularly in males, we advocate that preoperative radiotherapy should be used in all patients, i.e. irrespective of tumour size, where an abdominal perineal excision is planned.

It has been extensively discussed whether radiotherapy should be used preoperatively or postoperatively. In the U.S.A., the consensus is that all patients with a Dukes' B or C lesion should have postoperative chemoradiotherapy [30]. In contrast, we believe that preoperative radiotherapy should be used, simply because it is more effective. As discussed above, the survival benefit seen in the American trials is probably a chemotherapeutic effect. Therefore, the next step should be to combine preoperative radiotherapy with chemotherapy in the most optimal way. An ongoing Nordic trial is currently testing this strategy.

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