Preoperative radiotherapy for rectal cancer: hypofractionation with multiple fractions (15-25 Gy)

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Abstract

Preoperative radiotherapy lowers local recurrence rates after rectal cancer surgery, as seen in several randomised trials. Postoperative radiotherapy is also effective, although a higher radiation dose is required. In addition, preoperative, but not postoperative (unless combined with chemotherapy) radiotherapy also improves survival slightly. Since the toxicity profile also favours preoperative therapy, this is a more attractive approach. The trials have also shown that a sufficiently high biological dose is required to achieve any influence on local failure rates. If the dose at each radiation fraction is higher (e.g. 5 Gy), the radiation can be given much faster (during one week) than if a 'conventional' fraction size of about 2 Gy is used (4-5 weeks). Surgery can also safely be performed immediately after the end of the short radiation course, but not until several weeks later after conventional radiotherapy. This adds to the practicability of the short schedules.
An inappropriate radiation technique was used particularly in one trial using multiple 5 Gy fractions. This resulted in unacceptable acute and late toxicity. However, several other trials have shown that the treatment is safe. Preoperative 5 x 5 Gy is one of the most extensively investigated oncological treatments with proven efficacy. Since the total dose is comparably low (25 Gy), the decreased therapeutic ratio of using fraction sizes above 2 Gy appears to have no clinical relevance. The experience indicates, however, that every therapeutic modality should be used in an optimal way.
Key words: Rectal neoplasms, radiotherapy, dose response relationship, adjuvant, treatment outcome.

Riassunto

RADIOTERAPIA PREOPERATORIA DEL CANCRO DEL RETTO

Numerosi studi randomizzati hanno dimostrato la possibilità, da parte della radioterapia preoperatoria, di ridurre l'incidenza di recidive locali, Anche la postoperatoria ha dimostrato una efficacia in tal senso, anche se richiede l'utilizzo di dosi più elevate. Inoltre, la radioterapia preoperatoria è anche in grado di ottenere un lieve miglioramento della sopravvivenza, mentre un simile risultato, con la radioterapia postoperatoria, si ottiene solo in associazione alla chemioterapia. Se si considera anche la minor tossicità radioindotta associata, il trattamento radiante preoperatorio sembra al momento la alternativa più promettente. È stato inoltre documentato un evidente rapporto dose-effetto tra "dose biologica" ed impatto sul controllo locale. L'uso di dosi

Introduction

Both surgery and radiotherapy can be used to achieve locoregional control of a rectal cancer. Since the mechanisms of failure differ between these two techniques it is theoretically tempting to use them together (1). Surgery hardly never fails to take the tumour bulk out, but it may fail in the periphery whereas radiotherapy can kill micrometastases in the periphery but can hardly sterilise the tumour bulk.
In a tumour considered resectable, the use of radiotherapy is aimed at eradicating suspicious microscopic populations of tumour cells that cannot be excised without a major risk of complications or poor function postoperatively. Radiotherapy can easily be delivered to a defined tissue volume with negligible damage to both non-irradiated and irradiated tissues. A sufficient radiation dose is required in order to have high probability to eradicate all non-removed tumour cells. There is, however, no need to cause any down-staging since the tumour is already resectable, unless there is a desire to increase the chances of sphincter preservation. Therefore, the radiation could theoretically be given using a few high fractions in order to have practical advantages.
Alternatively, in the case of a fixed tumour, where it is likely that the tumour cannot be resected radically because of tumour overgrowth to adjacent organs, the rationale of radiotherapy is to achieve shrinkage of the tumour. In the latter situation, there is no role for a limited number of high fractions since maximum tumour

per frazione elevate (ad esempio 5 Gy) permette di eseguire il trattamento, rispetto ai frazionamenti convenzionali (3 Gy), in tempi nettamente inferiori (1 settimana versus 4-5). Inoltre, utilizzando schemi di trattamento abbreviati, l'intervento chirurgico può essere eseguito subito dopo il termine della radioterapia, al contrario di quanto avviene per i trattamenti convenzionali che richiedono un intervallo di diverse settimane. Ciò favorisce, sotto il profilo pratico, gli schemi di breve durata. In uno studio che utilizzava multiple frazioni da 5 Gy è stata utilizzata una tecnica di trattamento inadeguata, con il seguente riscontro di un'elevata incidenza di effetti collaterali acuti e tardivi. Tuttavia, una serie di ulteriori studi ha dimostrato la fattibilità di questo tipo di trattamento. Lo schema di 5 frazioni da 5 Gy rappresenta una delle schedule più estesamente sperimentate. La riduzione della dose totale, rispetto ai trattamenti standard, non è associata ad un impatto clinico negativo. L'esperienza indica, semmai, che ogni modalità terapeutica richiede una qualità ottimale di trattamento.

Parole chiave: Neoplasie del retto, radioterapia, correlazione dose-risposta, adiuvante, risultato della terapia.

regressions may not be seen until after a prolonged time period.

Several questions have been addressed in large randomised trials regarding the efficacy and safety of irradiation in rectal cancer. In the randomised trials reported during the latest decades, the surgery alone group has shown a local recurrence rate exceeding 20%, average 28% (see Tab. I). This figure probably represents the result achieved using standard rectal cancer surgery worldwide. Many researchers have claimed that surgery has not been optimal in the trials and that fewer local recurrences can be obtain if surgery is improved. Lower figures have also been reported from institutions with devoted and well-trained surgeons (2, 3). A concentration to a colorectal cancer unit and a surgical training programme have also resulted in low local failure rates in unselected patient populations (4, 5). In some centres, an even more radical procedure has been used than usually is the case, but with such a radical surgery, there is a definite risk of increased morbidity regarding sexual and bladder func-

Tab. I – PELVIC RECURRENCE AFTER A COMBINATION OF SURGERY AND RADIOTHERAPY IN RECTAL CARCINOMA (CONTROLLED TRIALS WITH A SURGERY ALONE GROUP). TRIALS USING HYPOFRACTIONATION (5 GY) ARE INDICATED IN BOLD

Study	*Irradiation* *Dose (Gy)/ Number of fractions*	*LQ time (Gy)*	*Surgery alone* *Number of local recurrences/total (%)*		*Surgery + radiotherapy* *Number of local recurrences/total (%)*		*P value*[a]	*Percent reduction in local failure rates*
Preoperative								
Rider et al (13)	5/1	7.5	c)					
Duncan et al (14)	5/1	7.5	d)				0	
	20/10		d)				0	
RTOG[b] (15)	5/1	7.5	33/153	(22)	28/148	(19)	NS	12
Goldberg et al (16)	15/3	22.5	51/210[e]	(24)	31/185[e]	(17)	NS	29
Higgins et al (62)	31.5/18	26.8	c)					
Horn et al (42)	31.5/18	26.8	31/131	(24)	24/138	(17)	NS	29
Roswit et al (63)	25/10	27.5	32/87(f)	(37)	27/93[f]	(22)	NS	22
Marsh et al (17)	20/4	30.0	58/141	(41)	26/143	(18)	**	63
Gérard et al (24)	34.5/15	35.2	49/175	(28)	24/166	(14)	**	50
Kutzner et al (64)	34.5/15	35.2	21/106	(20)	9/69	(13)	NS	34
MRC2 (43)	40/20	36.0	50/132	(38)	41/129	(32)	NS	16
Sao Paulo (65)	40/20	36.0	16/34	(47)	5/34	(15)	**	68
SRCSG (18)	25/5	37.5	120/425	(28)	61/424	(14)	**	50
SRCT (19)	25/5	37.5	131/557	(24)	51/553	(9)	***	61
Postoperative								
Balslev et al (45)	50/25	35.4	57/250	(23)	46/244	(19)	NS	17
MRC3 (66)	40/20	36.0	69/235	(29)	46/234	(20)	**	31
GITSG (46)	40-48/22	36.0	27/106	(25)	15/96	(16)	NS	36
Wolmark et al[e] (67)	45/25	36.3	47/348	(14)	27/346	(8)	*	42
Fisher et al (47)	46.5/26	39.3	45/184	(24)	30/184	(16)	NS	33
Arnaud et al (68)	46/23	40.8	30/88	(34)	25/84	(30)	NS	13
Treuniet et al (69)	50/25	43.8	28/84	(33)	21/88	(24)	NS	41

a) NS = p>0.05, * = p < 0.05, ** = p < 0.01, *** = p < 0.001
b) Postoperative radiotherapy given in both groups to Dukes' B + C
c) Not reported
d) Only actuarial data reported, with no difference between groups
e) All patients had postoperative chemotherapy

tion (6). It is doubtful that the long-term results using a 'super-radical' surgical approach will ever turn out favourable in comparison with a well-designed radiotherapy protocol as an adjunct to a 'radical' surgical approach. Recognising the advantages and disadvantages of various treatment modalities, it appears unwise to treat microscopic tumour deposits with a surgical knife.
This paper will review the experience using high-dose fractionated radiotherapy preoperatively for primary resectable rectal cancer and relate the results to other radiation schedules.

Adjuvant radiotherapy; radiobiological considerations

Based upon data mainly obtained from studies on breast and head-and-neck cancer, the minimum dose required to kill micrometastases (less than a few millimetres in diameter) with a high probability is about 50 Gy given in 5 weeks if delivered preoperatively (7, 8). A higher dose (60-70 Gy) is required if the radiotherapy is given postoperatively to achieve similar effects on micrometastases (8). The main reason for this difference is probably repopulation of tumour cells in the time interval between surgery and the start of radiotherapy (7), but an additional explanation is a hypoxic state of tumour cells in the surgical bed.
Not only the total radiation dose but also the dose at each fraction and the overall treatment time have to be taken into consideration when the effects on tumour cells and on normal tissues are calculated. All these three parameters have varied considerably between the rectal radiotherapy trials. By estimating the biological effect of the irradiation it is possible to compare different regimens with each other. In this review, we use the linear-quadratic (LQ) formula with a time correction factor for immediate effects (9). In the LQ-time estimations, the common linear-quadratic quotient, a/ß, was chosen as being 10 Gy for tumour and immediate effects and 3 Gy for late effects, and the repair ratio g/a as being 0.6 Gy/day and the initial delay time T_K as 7 days (9, 10). The most commonly used schedule in radiotherapy is 1.8 or 2 Gy given daily 5 days a week. This schedule, arrived at empirically, is considered to be a practical regimen and to give the highest therapeutic ratio in the treatment of most malignant tumours. To deliver a dose of 50 Gy, the patients have to be treated for 5 weeks. Due to postirradiation oedema, surgery should not be carried out until after 4 weeks after the end of this irradiation. In order to reduce the treatment time, a higher dose at each fraction has been used. A dose of 25 Gy, 5 Gy per day for 5 days, corresponds approximately to the effects attained when conventional irradiation to 40-50 Gy is given, according to the LQ formula. After one week of irradiation, no oedema is present, giving that surgery can be performed the following week. The duration of treatment will then be shorter, which may have practical advantages. However, the therapeutic ratio, which is of major importance if the total dose is close to normal tissue tolerability, will be decreased. A narrow therapeutic ratio might be acceptable as a practical compromise if the dose is lower, e.g. when the aim is to kill microscopic tumour cell deposits. In curative radiation treatments, the use of high fraction doses should be abandoned.
With modern high voltage radiotherapy equipment in combination with appropriate dose planning, it is possible to deliver doses of up to 60-70 Gy in 6-8 weeks to limited volumes of the abdomen. If the irradiated volume has to be larger because of the extent of the tumour, the upper dose limit should not exceed 45-55 Gy in 4-6 weeks (11, 12). This means that the likelihood of eradicating subclinical disease in surgically undisturbed, preoperative, areas can be high. Postoperatively the likelihood of curing subclinical disease is lower (8).

Adjuvant radiotherapy; results

Effect on local recurrence rates

In Table I all controlled trials reported hitherto using pre- or postoperative radiotherapy are summarized and compiled with regard to the LQ formula. The trials using hypofractionation with 5 Gy fractions are highlighted in bold. A clear dose-response relationship concerning reduction in local recurrence rates can be seen in the preoperative trials. No major effects on local recurrence rates have been found in trials where low doses (LQ times <30 Gy) have been used (13-15). This is in agreement with that a dose corresponding to a LQ $time_{acute}$ about 35 - 40 Gy (with the assumptions given above), is required before there is a high probability of killing micrometastases.
Seven trials have used hypofractionation with 5 Gy fractions given 1-5 times a week (13-19), and, in the six trials presenting complete data, a clear dose-response relationship in the relative reduction in local failure rates is observed (Fig. 1). In the trial using 3 x 5 Gy, the Imperial Cancer Research Fund trial (16), an effect on the local recurrence rate was found but not of the same magnitude as in the trials using 4 x 5 Gy (17) or 5 x 5 Gy (18, 19).
It appears from the data in Table I that postoperative radiotherapy has had less good effects than preoperative irradiation, and that approximately 15-20 Gy higher doses are required postoperatively to reach the same reduction in the local failure rate as has been achieved with preoperative regimens (1, 10). The effect of preoperative and postoperative radiotherapy has only been compared in one randomised trial, the Uppsala trial (20,

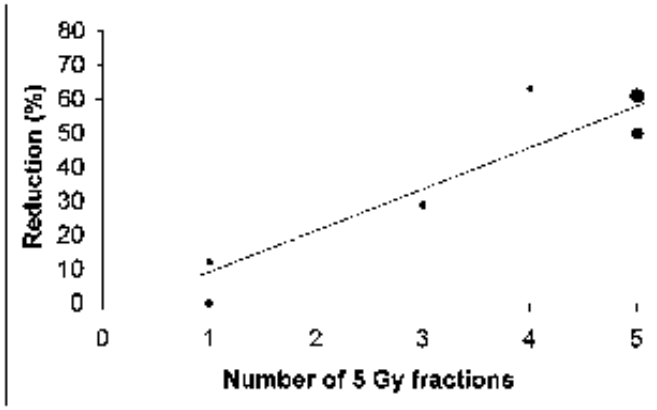

Fig. 1: The relative reduction in local failure rates according to numbers of fractions. The size of the symbols is proportional to the number of patients in the trials (14-19). The line is drawn by hand. The Dutch TME-trial, preliminarily reported after a follow-up of 2 years, showed a relative reduction of 71%.

21). Patients received either preoperative radiotherapy, totally 25.5 Gy in five fractions (LQ time 38.0), with surgery in the following week, or postoperative irradiation (2 Gy to 60 Gy, LQ-time 46.9). After a minimum of 5 years' follow-up, a reduced local recurrence rate was found in the preoperatively irradiated group (12%) compared with the postoperative group (21%) ($p < 0.02$) (20). In this trial the highest dose ever used in a postoperative setting was delivered, but only to patients with a tumour in Dukes' stage B or C.

In conclusion, the effect of radiotherapy on the local recurrence rates is dose-dependent and preoperative irradiation is more dose-effective than postoperative. Further, 4 or 5 fractions of 5 Gy are at least as effective as 20 conventional fractions if given preoperatively and as 30 fractions given postoperatively. The preliminary results of the Dutch TME-trial, providing further evidence of the efficacy of 5 fractions of 5 Gy, will be described below.

Influence on survival

Both surgery and radiotherapy are local treatment modalities and cannot possibly affect occult metastases in distant organs. On the other hand, if a local recurrence is prevented and if such a recurrence is the first and only sign of a residual tumour, the combination of surgery and radiotherapy will have an impact on survival after prolonged follow-up. Survival data from the trials where moderate/high radiation doses have been used preoperatively are presented in Table II. Again, the trials using high dose fractions are marked in bold. In the Swedish Rectal Cancer Trial (SRCT), totally 1,168 patients were included between 1987-1990. Patients with a resectable rectal cancer were randomly allocated to receive 5 x 5 Gy preoperatively in one week followed by surgery in the next week, or to undergo surgery alone. After a minimum follow-up of 5 years, 48% of the patients in the surgery alone group were alive, compared with 58% in the irradiated group (19). This was the first trial using preoperative radiotherapy to report a survival benefit, which can be explained, firstly, that the trial was large enough to detect small but clinically relevant differences in survival, secondly, the dose was high enough (see above), and thirdly, a proper technique not jeopardising the outcome of the surgery was used (see below). If the survival curves were corrected for postoperative deaths in the Stockholm/Malmö trial (see below), the cancer specific survival was increased among the irradiated patients (22). In s report from the Stockholm group an improvement of survival was noted in the so called Stockholm II trial (23), in which the majority of the patients, those randomised prior to February 1990, were included in the SRCT (19). Superior cancer-specific survival and a tendency for an overall survival benefit were also noted in the two other trials using 3 or 4 fractions of 5 Gy (16, 17). No statistically significant overall survival benefit supporting radiotherapy was obtained in the EORTC trial, but the

Tab. II – SURVIVAL IN RELATION TO PERCENTAGE REDUCTION IN LOCAL RECURRENCE RATES. ONLY RANDOMISED TRIALS USING 'HIGH-DOSE' RADIOTHERAPY ARE PRESENTED. TRIALS USING HYPOFRACTIONATION (5 GY) ARE INDICATED IN BOLD

Trial	Dose Gy/ number of fractions (LQ time, Gy)		% reduction in local recurrence	Improved survival with irradiation	
				Overall	Cancer-specific
Goldberg et al (16)	15/3	(22.5)	29%	No[a)]	Tendency
Marsh et al (17)	20/4	(30.0)	63 %	Tendency	Yes
Gérard et al (24)	34.5/15	(35.2)	50%	No	Yes
MRC2 (43)	40/20	(36.0)	16 %	No	No
Sao Paulo (65)	40/20	(36.0)	68%	Yes	–[b)]
SRCSG (18)	25/5	(37.5)	50%	No a)	Yes
SRCT (19)	25/5	(37.5)	61%	Yes	Yes

a) A positive influence on cancer-specific deaths was counter balanced by increased postoperative mortality due to toxicity.
b) Not presented in this very small trial including only 68 patients.

survival curves are diverging as the period of follow-up lengthens (24). Two meta-analyses, one based upon published data (25) and one upon individual patient data (26), have recently confirmed that preoperative radiotherapy, to moderately high doses (LQ-times >30 Gy) statistically significantly improves overall and cancer-specific survival. Low radiation doses are ineffective.

Sphincter-preservation

A rationale to use prolonged radiotherapy in the preoperative setting has been claimed to be an increased chance of preserving sphincter function in very low rectal cancers (27). A French trial compared radiotherapy (39 Gy in 13 fractions) followed by a short (2 weeks) or a prolonged (6 to 8 weeks) interval before surgery and found that a longer interval resulted in increased tumour down-staging (28). Several studies have also reported this effect from chemo-radiation, but none has tested the combined approach in a random fashion against radiotherapy alone (29-34). It is, however, difficult to interpret these data since the trials have been ongoing during the same time period as when we have learned that a closer distal margin is sufficient.
Moreover, there are series with surgery alone or preoperative short-term radiotherapy followed by immediate surgery with the same high percentage of sphincter preservation (4, 5, 35, 36). It is too early to recommend this combined treatment, since long-term results are not available, and there can be a risk of higher local failure rates due to too narrow margins. Also, the anal function 5-10 years after combined radio-chemotherapy is not known, and in individual patients, it may not be superior to having a stoma.

Adjuvant radiotherapy; safety

Postoperative mortality after preoperative radiotherapy

The adverse effects after radiotherapy are mainly dependent on three factors, the irradiated volume, the total dose, and the treatment time. By definition, only preoperative, but not postoperative radiotherapy can have an impact on complications to surgery, and the most dreadful one is increased postoperative mortality. In the Uppsala trial (25.5 Gy in one week), where the irradiation technique was designed to avoid irradiation of those parts of the pelvis and abdomen that were not included in the target volume, no influence on postoperative mortality was noted (20). However, during the same time period, the parallel Stockholm-Malmö trial described an increase in postoperative mortality (8% vs 2%, $p < 0.001$) in the irradiated group, despite the fact that the dose was similar to that in Uppsala (18). It is likely that the differences in radiation techniques between the two Swedish trials are responsible for the differences in postoperative mortality (12). In the Stockholm-Malmö trial a two-beam technique was used and in the Uppsala trial a three-beam technique was used. In the Stockholm-Malmö trial the upper limit of the beams was at the level of the second lumbar vertebra, whereas it was at the mid third vertebra in the Uppsala trial. Large volumes of the abdomen were then unnecessarily irradiated in the Stockholm-Malmö trial. The trial from St. Mark's Hospital, also using a two-portal technique and 5 Gy fractions, similarly found an increased postoperative mortality rate among elderly patients (above 75 years of age) and in those with generalised disease discovered at surgery (16).
One important factor why the SRCT was initiated, was to evaluate the question of influence on postoperative mortality, due to the conflicting results presented from the Uppsala and the Stockholm-Malmö trials. It was mandatory to use a three- or four-beam technique, but for unexplained reasons, four hospitals used the two-beam technique. Again, an increased postoperative mortality was noted among patients treated with the two-beam technique compared with the patients treated according to the protocol (37), supporting the conclusion that a large treated volume and a high radiation dose prior to surgery may be too much of a burden for an elderly patient. The mortality in the surgery alone arm and among the patients irradiated with a three- or four-beam technique was, however, exactly the same (2.6% vs 2.6%). The Stockholm group has reported a tendency towards increased postoperative mortality also in the Stockholm II trial, using four beams and an upper beam limit at the mid fourth lumbar vertebra (38). However, the Stockholm group again simplified the technique and did not include any shields (39), as prescribed in the SRCT protocol. This again resulted in an increased radiation burden to the abdomen. As will be described below, no increased mortality could be seen in the Dutch TME-trial, confirming the SRCT evidence. The conclusion drawn is that radiotherapy, once decided upon, should be properly planned and meticulously monitored during the treatment course.

Postoperative morbidity after preoperative radiotherapy

Healing of the bowel anastomosis and the surgical wound after preoperative radiotherapy has been another concern. In all controlled randomised trials, no increase in anastomotic dehiscence has been found after preoperative radiotherapy (16, 22, 24, 37). Moreover, experimental data indicate that preoperative irradiation will not have an adverse impact on anastomotic healing (40, 41).
Most trials in which preoperative radiotherapy has been used, have reported an increased risk of an infection of the perineal wound in patients operated upon with an

abdominoperineal excision; an increase from 10% to 20% (20, 22, 24, 37, 42, 43). This complication is thus reported both in trials using multiple 5 Gy fractions and in those using conventional fractions of about 2 Gy. Such a wound infection is not a disaster for the patient and in most patients it will heal within one or two months. The rare complication, a perineal sinus, has not been more common if radiotherapy has been given (21, 39).

Acute neurogenic pain a few hours after irradiation of the lower lumbar region has been noticed in the Uppsala trial (20). The pain was usually of short duration, but could persist for several months, and some of the affected patients developed persistent neuropathy with symptoms like inability to walk. In a review of the total experience in Uppsala from 1980 to 1994, 19 (3%) reported pain out of a total of 550 patients treated with 5 x 5 Gy within protocols (44). The pain lasted for more than a few days in 6 patients (1%), and in 4 of them subacute neurogenic symptoms developed. The origin of this acute, potentially dangerous adverse effect is still unknown. The dose, 25 Gy in one week, is not of that magnitude that damage of the nerves could be expected. It may represent an extreme sensitivity to high radiation doses in a susceptible patient, and therefore, it is essential to avoid hot spots in the region of the lower lumbar nerves. It should be noted that it could be seen also after conventional fractionation sizes (12). Further, this complication, although rare, indicates that the target volume should not be above the sacral promontory.

Tolerance to treatment

In all trials using multiple fractions of 5 Gy (16-20) the preoperative treatment has been well tolerated and very few patients who were allocated to the preoperative irradiation did not receive the treatment. In contrast, in the Uppsala trial (20), the postoperative irradiation was completed without any complications in only 9% of the patients. Several patients had to be hospitalised for parenteral nutrition because of diarrhoea or the treatment was discontinued because of fatigue and infectious complications. Only about half of the patients completed the postoperative irradiation within the scheduled time period. Similar difficulties have been reported from other postoperative (chemo)radiotherapy trials (45-48).

Late adverse effects

When postoperative radiotherapy has been given, small bowel loops adherent in the pelvic cavity are at risk of being damaged from the radiotherapy. Several techniques have been used to prevent the small bowel from falling down into the lesser pelvis (49, 50). Despite this, there have been several reports on late morbidity due to intestinal obstruction after postoperative radiotherapy (11, 45, 51). Another late adverse effect of radiation therapy is chronic diarrhoea, and together with small bowel obstruction, these effects have been related to the volume of the small bowel included in the treatment volume. If radiotherapy extends high up in the abdomen, the risk of small bowel obstruction has been reported to be as high as 30-40%, which should be compared with 5-10% when only the dorsal part of the pelvic cavity is included (11). The direct correlation between the target volume and the adverse effect on small bowel obstruction has also been demonstrated in the preoperative Stockholm-Malmö trial (5x5 Gy), where an increase in small bowel obstruction was found among the patients irradiated with two beams extending up to L2 (39). This has not been found in patients treated according to the SRCT protocol (52). Also, in the Uppsala trial all patients have been followed up extensively and re-examined with respect to late adverse effects of irradiation. An increase in small bowel obstructions or other possibly late adverse effects was not seen among patients who received preoperative radiotherapy (21). However, in the group of patients treated with postoperative radiotherapy, a significantly higher incidence of late irradiation-related adverse effects was found.

Radiotherapy may also be detrimental to the sphincter function, but this has so far not been extensively investigated. There are indications that both postoperative radiotherapy (53-55), and preoperative radiotherapy (56) will negatively influence the anal function. A questionnaire study among all survivors from the SRCT who were operated upon with a sphincter saving resection noticed an altered sphincter function (56). In the SRCT, the anal sphincters were included in the target volume. The reasons for this malfunction are unclear, but the irradiation might damage either the sphincters or the pudendal nerves. It is important to take this notice in consideration, and exclude the sphincters from the target if not necessary, as in mid and high rectal tumours. The appropriate target volume has been more extensively discussed (1).

Conclusions

The collected experience indicates that if radiotherapy is to be used, preoperative treatment is to be preferred, since it is more dose-effective. Moreover, the treatment should be given with a sufficiently high dose and with a technique avoiding large volumes including areas not at risk of containing tumour cells. In addition, since postoperative radiotherapy is less effective, has more adverse effects and is more resource demanding than preoperative schedules, it is difficult to understand that postoperative radiotherapy continues to be recommended even if it, when combined with chemotherapy, improves survival (57). Rather, the most logical approach would seem to be to use an appropriate surgical proce-

dure with the most optimal radiotherapy, i.e. 'high-dose' preoperative irradiation, and integrate chemotherapy postoperatively in order to further improve the results.
By recommending a preoperative approach it is important to exclude patients with a low risk of having a local recurrence, i.e. those with a T 1 or T 2 lesion as well as those with metastatic disease. However, since patients with low rectal tumours have a higher risk of developing a local recurrence than those with tumours situated higher up in the rectum, we recommend that preoperative radiotherapy is given in all cases where the surgical procedure will be an abdominoperineal excision.
With preoperative radiotherapy a reduction in local recurrence rates of more than 50% has been noticed. However, in all trials where adjuvant radiotherapy has been tested, surgery can be claimed to be inaccurate (1, 58). There is, however, much evidence indicating that the relative reduction seen after preoperative radiotherapy in the randomised trials will be at least of the same magnitude if the surgery is performed in a more optimal way. Since more optimal surgery, as compared with so called standard surgery, results in fewer recurrences, the absolute number of patients who benefit will, however, be reduced. This issue was addressed in the recently completed randomised Dutch multicentre trial, where TME-surgery was mandatory. The trial included 1861 patients, mainly from Holland with some contributions from hospitals in Sweden and other countries. The quality control of surgery, radiotherapy and pathology was at a very high level. Preliminary results from the trial were released at a meeting in Nordwijk in April 2001. Median follow-up was 25 months. Preoperative radiotherapy (5 x 5 Gy) statistically significantly reduced local recurrences from about 8% to 2% (p >0.001) in the group of patients who had an R0 or an R1 resection. The relative reduction was 71%. The relative reduction did not differ significantly according to tumour height, i.e. a reduction was seen also in high tumours (10-15 cm) although it then did not reach statistical significance. Low-lying tumours had the highest local failure rates. Overall survival did not differ between groups at this early time point. Whether a long-term survival benefit ultimately will show up by reducing local failures by less than ten percentage points can only be speculated upon. I has thus been demonstrated, also in a randomised trial, that with good surgery and preoperative radiotherapy, a previously very common and to most affected patients severely disabling condition, namely local rectal cancer failure, could more or less be eradicated. Population-based series from Uppsala (4), after a minimum follow-up of 5 years, and Stockholm, Sweden (5), after a follow-up of 2 years, could also disclose virtually identical results.
The Dutch trial has again shown that preoperative radiotherapy according to the Swedish model (5x5 Gy in one week) followed by surgery the next week is very safe (59). Updated results were presented at the meeting in Nordwijk, confirming that there is no difference in postoperative mortality between irradiated and non-irradiated patients. Subgroup analyses showed that elderly patients who were operated upon >3 days after the end of the radiotherapy had higher postoperative mortality than those operated upon earlier or than those non-irradiated. Whether this is a true finding or not is not known. Irrespective of this, surgery should not unnecessarily be delayed beyond the first few days after the last radiation fraction, as was originally stipulated (20).
Other important aspects of adjuvant radiotherapy are compliance and economic considerations. If a treatment is recommended, compliance needs to be high, and in this respect, the collected experience again indicates that preoperative treatment is to be preferred. The economic aspects also have to be considered, i.e. in practice the number of fractions given. The short preoperative schedules, proven to be effective and safe, provided the technique is appropriate, are more cost-effective than the schedules using conventional fractionation. If many patients are to be irradiated, this will have a substantial impact on the resources. On the other hand, the short preoperative schedules have been criticised because intolerable adverse effects have been seen in one trial, however, due to inappropriate radiation technique. In the trials using adequate techniques, as was practically possible during the 1980s, some adverse effects have also been noted. The patients in these trials have, however, been followed longer and more carefully than those in any other trial using conventional fractionation. Thus, we do not have an answer to the question whether the short schedules have more late toxicity than the conventional ones. Since toxicity is not only dependent upon fraction size, but also upon total radiation dose, it may well be that the short schedules turn out to be favourable also with respect to late toxicity. The decreased therapeutic index using high fraction sizes is of great importance when the dose is close to normal tissue tolerability, but may be of no practical relevance if the dose is lower. The dose level in the preoperative trials is only aimed at killing microscopic disease, and not macroscopic tumours. Further, the continuous technical development (60, 61) together with a better understanding of the most appropriate target volume tell that the radiotherapy today can be given with even less risk of toxicity than was the case in e.g. the Swedish Rectal Cancer Trial.

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