4. **Rectal Cancer**

Introduction

In 2000, 1 817 new cases of rectal cancer were diagnosed in Sweden. This number has been rather stable during past decades. Rectal cancer constitutes approximately one third of all colorectal cancers. The number is sensitive to the precise definition of the delineation between rectum and colon. At present, most investigators tend to refer cancers with their lower border below 15 cm from the anal verge as rectum and those above as rectosigmoid, i.e. belonging to colon. Several other definitions have also been used. These definitions have meant that cancers extending from about 12 cm up to about 20 cm from the anal verge have been included in the trials. Although different inclusion criteria have thus been used in the trials, this does not really disturb the interpretation of trial data. Precise knowledge of the absolute locoregional failure rate for cancers at different heights from the anal verge is, however, important when it comes to a decision of whether radiotherapy should be given or not in addition to surgery.

Most cancers arising in rectum are adenocarcinomas. Colorectal cancers are staged according to the TNM system, although for decades, the Dukes' staging system was used (Table 1).

Table 1 *Staging system.*

TNM Staging	UICC	Dukes' stages
T1 Involvement of submucosae muscularis propria T2 Invasion into but not penetration through muscularis propria	I	A Tumour has not penetrated beyond musccularis propria
T3 Penetration through muscularis propria and into serosa or pericolic fat, but not into free peritoneal cavity or other organs T4 Invasion of other organs or involvement of free peritoneal cavity N0 No nodal involvement	II	B Tumour has penetrated beyond muscularis propria; no nodal involvement
N1 1–3 pericolic/perirectal nodes involved N2 ≥ 4 pericolic/perirectal nodes involved N3 Any regional nodes along a named vascular trunk involved M0 No distant metastases	III	C Lymph node involvement
M1 Distant metastases	IV	D Distant metastases

The overall 5-year survival figures for rectal cancer have slowly improved [30,112]. Recently, even better survival figures have been reported in certain Swedish Health Care Regions [22,66]. This marked survival improvement for rectal, but not for colon cancer has also been noticed in the most recent update of the Swedish Cancer Registry (Epidemiologiskt centrum, June 2001). At present, the 5-year survival figure is about 70 per cent compared to below 50 per cent some decades ago. Mortality from rectal cancer has also decreased in Sweden during past decades in spite of stable incidence figures.

Between 10 to 15 per cent of all newly diagnosed patients with rectal cancer have a tumour that has grown into adjacent, non-readily resectable organs.

These patients are generally considered as primarily non-resectable. Approximately 15–20 per cent of the patients have already developed distant metastases (stage IV, Dukes' D) at the time of diagnosis. Among patients having undergone apparently curative surgery, the two main reasons for fatal outcome are occult distant metastases not found at surgery and a locoregional recurrence. A locoregional recurrence or a primary rectal cancer not possible to remove is accompanied by severe suffering for the patient with pain, bleeding, soiling, ulceration and fistulation as common symptoms and profoundly deteriorates quality of life [15].

Summary of the earlier report, SBU 129/2

Conclusions

- The previous report stated that a local recurrence of rectal cancer, generally defined as recurrence in the dorsal part of the pelvis is accompanied by severe suffering for the patient, e.g. severe pain that is difficult to control by medication and surgery. Hence, it was considered a major benefit to avoid a local recurrence.
- Radiotherapy (preferably preoperative) was considered indicated in resectable rectal cancers since the results from eleven randomized clinical trials had shown that adjuvant radiotherapy could reduce the risk for local recurrence.
- The report also concluded that the effects of radiotherapy might be dependent upon when it was given in relation to surgery, the fractionation, administration of chemotherapy during the radiotherapy, and the surgical techniques also appeared to be of relevance.
- The report also concluded that external radiotherapy provides valuable palliation in many patients with locally advanced rectal cancer. In isolated cases, treatment appears to lead to prolonged disease-free survival.

Discussion

SBU 129/2 report chiefly reviewed the experience of using preoperative or postoperative radiotherapy in addition to surgery to prevent a local recurrence for a resectable rectal cancer. The report covered the literature until about 1992, although it included a few articles from 1993 and one

from 1994. The report was published in 1996. In addition, some articles about the use of radiotherapy alone or in combination with chemotherapy in locally advanced rectal cancer was mentioned, although the report did not cover most trials in locally advanced or recurrent cases.

The role of radiotherapy in addition to surgery for a rectal cancer has been and still is a very controversial issue in spite of the results of several large clinical trials using adequate methodology. The SBU 129/2 report touched upon some of the problems, but did not make a complete overview of the available knowledge. It did not include the results of several trials reported during the first half of the 1990s.

Literature

The articles on which the conclusions in the SBU 129/2 report were based were classified and graded as follows (number of studies/number of patients).

	1 = High	2 = Moderate	3 = Low	Total
M	1/5 000[1)]	–	–	**1/5 000**
C	20/ 6 054	4/734	8/1 628	**32/8 416**
P	13/1 086	9/396	–	**22/1 482**
R	–	1/144	–	**1/144**
L	–	–	–	**–**
O	16	1	–	**17**
Total	**50/12 140**	**15/1 274**	**8/1 628**	**73/15 042**

[1)] This planned study was incorrectly classified as a meta-analysis; thus, the number of patients was overestimated in the Totals.

Assessment of new literature

Search methods and selection

Radiotherapy for rectal cancer has been the subject to several systematic overviews and other analysis of the collected experience where a systematic approach to the literature was used. Since these overviews have already identified all randomized trials, no further literature search was performed in the situation covered by the meta-analysis. Since the previous SBU report was not complete, a review of the literature from the time period already covered is also included in the present report. All randomized trials were updated through 2001.

The present report mainly concerns three aspects of radiotherapy (RT) for rectal cancer:

1) pre- or postoperative RT to rectal cancer considered to be primarily resectable. Only randomized trials are included in the evaluation. Altogether 27 trials, comparing RT with no RT have been identified and analyzed (a few other small trials, identified by the meta-analysis groups (see below), not providing any data, have not been evaluated). In 19 of these (9 included in SBU 129/2) the RT was given preoperatively [11,29,42,45,52,56,60,61,64,78,81,92,100,101,105,109,111, 114,117] (Table 2) and in 8 (5 included in SBU 129/2) the RT was given postoperatively [4,5,32,40,77,82,122,131] (Table 3). Nine randomized trials have postoperatively used various combinations of chemotherapy and radiotherapy without permitting an evaluation of the role of radiotherapy as such; these trials are also included since they contribute to the understanding of the role of radio(chemo)therapy in rectal cancer [33,41,63,65,75,95,119,120,124] (only 63,75,120 shown in Overview 3). In addition, one trial (previously reviewed) compared preoperative and postoperative radiotherapy [37] (Overview 2). Three other similarly designed trials are ongoing or have completed patient recruitment but no results are known (EORTC, protocol 22921, [57,103,108]). Finally, one trial (not previously reviewed) compared postoperative radiotherapy to the pelvis alone with postoperative radiotherapy to the pelvis, para-aortic nodes and liver [7] (Overview 2).

   Twenty-two of the 27 evaluated trials allowing a comparison between irradiated and not irradiated resectable rectal cancer (excluding three small trials with no data and the two most recent trials, [60,131]) have been included in a meta-analysis based upon individual patient data [21] (Overview 1). In addition, a meta-analysis of the preoperative radiotherapy trials based upon published data only [16] has been performed. Only the former meta-analysis is reviewed in detail, since the two analysis cover the same preoperative radiotherapy trials, and reach the same results and as the latter in addition contains some errors. More recently, a third systematic review has been published [90]. In addition to the previously identified trials, it found one more old randomized trial, however, only providing limited data [111].

2) Preoperative RT, alone or in combination with chemotherapy to primarily non-resectable rectal cancer or locally recurrent cancer.

3) Preoperative RT given to low-lying rectal cancer in order to increase the chances to preserve the anal sphincter function.

Very few randomized trials evaluating RT in situation two and three have been performed. Therefore prospective studies identified through a Medline search were reviewed. In addition, all major journals and the reference lists of identified articles were scrutinized to find further studies. (Only randomized studies shown on Overview 5, 6).

RT alone to early, small rectal cancers is not reviewed as this therapy is hardly used in Sweden and no randomized studies have been performed. For a review, see [43]. In Sweden, rather, a transanal surgical procedure is recommended.

Overview of new studies

Radiotherapy in resectable rectal cancer

Table 2, Preoperative RT

Table 3, Postoperative RT

Overview 1, Radiotherapy in resectable rectal cancer, meta-analysis of individual patient data (after the list of references)

Overview 2, Radiotherapy in resectable cancer, RT-trials either not included in the meta-analysis (see Overview 1) or comparing two different ways of delivering RT (pre- vs postoperative, different targets), (after the list of references)

Overview 3 Postoperative radiotherapy, chemotherapy or radiochemotherapy, randomized trials in stages II + III (trials only comparing two RTCHT regimens are not included in the overview, two of eight trials included in the meta-analysis), (after the list of references)

Local recurrences after surgery-alone

In the randomized trials including a surgery-alone group, the surgery-alone group has, with few exceptions, shown a local recurrence rate exceeding 20 per cent, average 28 per cent (Tables 2 and 3). This figure can thus be considered to represent the results achieved after a follow-up generally exceeding five years using standard rectal cancer surgery worldwide. During the past decade, it has, however, repeatedly been claimed that surgery has not been optimal in the trials generally recruiting patients during the 1980s and that fewer local recurrences can be obtained if surgery is improved. Lower figures were also reported from institutions with devoted and well-trained surgeons (e.g. [31,50,71]). Improved lateral clearance after a careful dissection in the plane outside the fascia surrounding the mesorectum is likely responsible for the markedly lower local recurrence rates. The term total mesorectal excision (TME) is often used for this type of surgery, even if the entire mesorectum is not always excised in high rectal cancers. A concentration of rectal cancer surgery to a colorectal cancer unite and extensive surgical training programmes, have also resulted in low local failure rates (approximately 10–15 per cent after 2–5 years) in unselected Swedish patient populations [24,66] and in Norway [129]. Several individual hospitals have also reported low recurrence rates after having introduced the TME concept (e.g. [3,72]). There are also several reports pointing to the importance of the surgeon for the outcome [80,98]. TME in all patients has only been used in one randomized trial, with a local failure rate of 8 per cent in the surgery-alone group after two years of follow-up [60] (Table 2).

Table 2 *Pelvic recurrences after a combination of surgery and preoperative radiotherapy in rectal carcinoma (controlled trials with a surgery-alone group).*

Trial (ref)	Total Dose, Gy	No. of fractions	BED, Gy	Local recurrences (%) Control group	RT group	Relative reduction, %
Standard surgery						
MRC1 [29]	5	1	7.5	118/275 (43)[1)]	125/277 (45)[1)]	0
	20	10	20.4		128/272 (47)[1)]	0
RTOG [109][5)]	5	1	7.5	33/153 (22)	281/148 (19)	12
Dresden [51]	15.5	5	20.3	9/37 (24)	5/40 (13)	49
St.Marks [45]	15	3	22.5	51/210 (24)[2)]	31/185 (17)	29
Essen [92]	25	13	24.0	7771 (10)	4/56 (7)	30
VASAG II [52]	31.5	18	26.8	40/181 (22)[3)]	37/180 (21)	0
Bergen [56]	31.5	18	26.8	31/131 (24)	24/138 (17)	29
VASAG I [105]	20–25	10	27.5	32/87 (37)[4)]	27/93 (29)	22
North-West [78]	20	4	30.0	58/141 (41)	26/143 (18)	65
Mainz [64]	34.5	15	35.2	21/106 (20)	8/64 (13)	37
Dutch [11]	34.5	15	35.2	18/50 (36)	7/59 (12)	67
EORTC [42]	34.5	15	35.2	49/175 (28)	24/166 (15)	48
MRC2 [81]	40	20	36.0	65/140 (46)	50/139 (36)	22
Brazil [100]	40	20	36.0	16/34 (47)	5/34 (15)	68
Stockholm [114]	25	5	37.5	120/425 (28)	61/424 (14)	50
SRCT [117]	25	5	37.5	150/557 (27)	65/553 (12)	60
TME						
Dutch TME [60]	25	5	37.5	72/907 (8)	23/897 (3)	71

Trials who have not reported local recurrence rates are not included in the table; BED: biological effective dose. See overview 1. The follow-up times have exceeded 5 years, except in the Dutch TME trial where it is 2 years.

1) According to Suwinski et al [115]. In the original publication only actuarial data were given with no difference.
2) Outpatient attenders only reported.
3) Residual and recurrent disease related to the length of follow-up.
4) Autopsy series only reported.
5) Postoperative radiotherapy given in both groups to Dukes' B + C.

Table 3 *Pelvic recurrences after a combination of surgery and postoperative radiotherapy in rectal carcinoma (controlled trials with a no-RT group).*

Trial (ref)	Total Dose, Gy	No. of fractions	BED, Gy	Local recurrences (%) Control group %	RT group	Relative reduction, %
Odense [5]	50	25	35.4	57/250 (23)	46/244 (19)	17
MRC3 [81]	40	20	36.0	79/235 (34)	48/234 (21)	38
ANZ-BCT [77]	45	25	36.9	1/14	2/17	–
GITSG [40]	40–48	23–26	39.4	27/106 (25)	15/96 (16)	36
NSABP R-01 [32]	46.5	26	39.3	45/184 (24)	30/184 (16)	33
NSABP R-02 [131]	50.4	28	39.8	47/348 (14)	27/346 (8)	42
EORTC [4]	46	23	40.8	30/88 (34)	25/82 (30)	13
Rotterdam [122]	50	25	43.8	28/84 (33)	21/88 (24)	41

BED: biological effective dose. The follow-up times exceed 5 years in all trials but the small Australasian trial [77].

Local recurrences after surgery and radiotherapy

Statistically significantly lower local recurrence rates have been seen in most trials comparing preoperative radiotherapy followed by surgery with surgery alone (Table 2) and in some of the trials comparing surgery with or without postoperative radiotherapy (Table 3).

The trials included in the meta-analysis (Overview 1) have used different radiation schedules with different fraction sizes. In the preoperative radiotherapy trials, one group of trials used 1–5 fractions of 5 Gy and another used so called conventional fraction sizes of 1.8–2 (–2.3) Gy. One very small trial fell in between [51]. In the postoperative radiotherapy trials only conventional fractionation (1.8–2.0 Gy) was used. In order to compare doses, the trials were ranked according to the linear quadratic time (LQ-time) model, explained in Overview 1 [21,44]. The preoperative radiotherapy trials were in the meta-analysis arbitrarily grouped in three groups with LQ-times below 20 Gy, between 20 and 30 Gy and above 30 Gy (maximum 37.5) [21]. All postoperative radiotherapy trials fell in the 30+ Gy group (range 35.4–43.8 Gy).

A dose-dependent influence on local failure rates was seen in the preoperative trials and preoperative radiotherapy appeared to be more dose-efficient than postoperative. The latter statement was confirmed in the only trial having directly compared pre- and postoperative radiotherapy [37] (Overview 2). These dose-response relationships, using all available evidence in literature, have also been more extensively analyzed [44,115].

In the above mentioned trials, being part of the meta-analysis, surgery was not standardized [16,21,90]. This was, however, the case in a large cooperative trial initiated in 1996 [60]. The trial showed that the local failure rate was reduced by radiotherapy and also with TME (Overview 2).

Importance of radiation fractionation

The preoperative trials used either a conventional fractionation (10–20 fractions of about 2 Gy) or a few (generally 5) fractions of 5 Gy. A reduction in local failure rates was seen using both schedules (Table 2). No trial has directly compared the two fractionation schemes, and it can thus not be deduced from literature whether one way is superior to another in reducing local failures. Different schedules were used in the trial comparing preoperative and postoperative radiotherapy [37] (Overview 2). Therefore the relative importance of the fractionation can not be evaluated. Besides antitumour activity, the two ways of fractionation have different advantages and disadvantages with respect to normal tissue toxicity and costs.

Survival after surgery and radiotherapy

In the two meta-analysis of the preoperative radiotherapy trials, overall survival was better in patients randomized to radiotherapy [16,21] (Overview 1). When rectal cancer mortality was analysed in the preoperative trials, a highly statistically significant improvement was seen. In the TME trial, follow-up is still too short to allow any meaningful survival analysis (Overview 2) [60].

Postoperative radiotherapy alone has not improved the overall or rectal cancer survival in any of the individual trials, nor in the meta-analysis [21] (Overview 1). The addition of low dose irradiation to the para-aortic nodes and liver did not improve survival in one trial [7] (Overview 2). A survival gain has been reported in some postoperative trials, however,

only when radiotherapy was combined with chemotherapy [40,63,124] (Overview 3). Combined postoperative chemoradiotherapy has also been considered standard therapy in the US for more than a decade [93]. Due to differences in the way the chemotherapy and radiotherapy were given between the trials, a survival gain from chemotherapy alone in one trial [32] and negative results from two recent trials [14,131] (Overview 3), it is impossible to elucidate the relative importance of either modality alone or a particular combination for any survival gain. A continuous infusion of 5-fluorouracil appears to be superior to intermittent bolus injections during the radiotherapy [95] and methyl-CCNU does not add efficacy, only toxicity [41]. A recent report indicates that delaying the start of the radiochemotherapy worsen the results [65]. The relevance of postoperative chemotherapy for colorectal cancer survival was extensively reviewed in the SBU-report of chemotherapy [99]. The report reached the conclusion that postoperative chemotherapy was not routinely indicated in rectal cancer stages II or III.

Toxicity of preoperative and postoperative radiotherapy

Overview 4 Postoperative mortality in randomized trials using multiple fractions of 5 Gy given preoperatively to patients with primarily resectable rectal cancer (after the list of references)

The balance between favourable effects for some patients and potentially negative effects from (neo-)adjuvant therapy to all patients has been of great concern and the topic of many reviews. (See also the SBU-report of chemotherapy [94]). In rectal cancer trials, the greatest concern has been increased postoperative morbidity and mortality from preoperative radiotherapy. Other acute and late effects from both pre- and postoperative radiotherapy have also been seen and are the topic of several clinical and experimental studies, e.g. [12,23,27,37-39,48,51,54,55,62,67-70, 74,84,106,116,123], and subject to several reviews. This report will systematically review the influence from preoperative radiotherapy on postoperative mortality (Overview 4) and the influence on non-colorectal cancer deaths from pre- and postoperative radiotherapy as analyzed in the meta-analysis (Overview 1) [21]. It will also briefly describe the still limited knowledge about late effects.

Influence on postoperative mortality

In the trials using conventionally fractionated preoperative radiotherapy or a single fraction of 5 Gy, no increased mortality was seen. The results of the trials using 3–5 fractions of 5 Gy are shown in Overview 4. An increased postoperative mortality was seen in the two trials using two anterior-posterior (AP-PA) beams, but not in any of the other trials. It thus appears that there is a correlation between the radiation volume and influence on the postoperative course. This has been separately analyzed in a model study [38]. The finding is in a way trivial and not unique to rectal cancer trials, but has created much uncertainty in the interpretation of rectal cancer trial data.

Influence on non-colorectal cancer deaths

In the meta-analysis (not including the TME-trial) using individual patient data [21], a statistically significant increased non-rectal cancer death rate was seen in the preoperatively irradiated group (Overview 1). It was restricted to the first year after randomization. Increased non-rectal cancer deaths were also seen in the postoperative trials, however, this was not statistically significant.

Influence on late toxicity

Several trials have reported that the sphincter function in patients operated with a low anterior resection is poorer in postoperatively [62,68-70] and preoperatively [23] irradiated patients than in those not irradiated. The relevance of the inclusion of the anal canal in the target volume is not known.

An increased risk of postoperative ileus has been seen in trials irradiating large volumes of small bowel, either preoperatively [55] or postoperatively [67,74], but not when smaller volumes were irradiated [37,55,67].

The literature shows that:

- After rectal cancer surgery, a local failure, generally causing severe suffering for the patient, was frequently seen (average 28 per cent in the randomized trials).
- RT, in addition to surgery, could significantly diminish the risk of local failure. Several large randomized trials have shown that preoperative

RT at a moderate dose level could decrease the risk by more than half (50–60 per cent). Postoperative RT decreased the risk by 30–40 per cent at doses that generally are higher than used preoperatively.

- Preoperative RT thus appears to be more effective than postoperative. This has also been seen in a randomized trial directly comparing pre- and postoperative RT.
- Preoperative RT has also slightly improved survival (by about 10 per cent) whereas this has not been seen in the postoperative radiotherapy trials unless the RT was combined with chemotherapy.
- The results after surgery have improved during the latest decade. Although not tested in a randomized trial, it is likely that local failure rates after a follow-up of at least five years at many hospitals have decreased from about 28 per cent to 10–15 per cent.
- A large randomized trial has revealed that preoperative RT significantly decreases the local failure rate (from 8 per cent to 2 per cent after two years) also with more optimized surgery, often called total mesorectal excision (TME). It is too early to evaluate whether survival also is improved.
- Several radiotherapy schedules have been used in the preoperative trials. In the absence of randomized trials comparing different schedules, it is impossible to define the most optimal one. The largest experience from randomized trials comes from a short-term schedule (5 x 5 Gy in one week with surgery in the next week). Postoperatively, it appears as if the efficacy of radiotherapy is increased when combined with concomitant chemotherapy, but this conclusion is based on small and partly conflicting trials. The combination of radiotherapy and chemotherapy has not been sufficiently evaluated preoperatively, but trials are ongoing.
- Preoperative RT can be given with low toxicity. High, and unacceptable toxicity in terms of increased postoperative mortality and increased non-colorectal death rate during the first year has been seen in some pre-operative trials where large volumes received radiation due to suboptimal techniques. Postoperative RT can also be given with acceptable

toxicity. The long-term consequences of RT have been less extensively studied, although they appear to be limited with adequate radiation techniques.

Literature

Radiotherapy in resectable rectal cancer.*

	1 = High	2 = Moderate	3 = Low	Total
M	2/17 878	1/5 974	–	**3**
C	14/12 891	5/1 638	18/3 508	**37/8 666**
P		1/37	–	**1/37**
R	4/4 739	–	1/100	**5/4 839**
L	1	1	–	**2**
O	13	2	–	**15**
Total	**34/20 442**	**10/455**	**19/2 016**	**63/22 913**

*) Studies and patients are not counted more than once in each column or row. Thus, since some patients can be included in several reports, the sums of the totals are lower than the sums of the numbers given within the table.

Radiotherapy in non-resectable rectal cancer

Overview 5 Radiotherapy alone compared to radiotherapy plus chemotherapy in non-resectable rectal cancer (only randomized studies shown), (after the list of references)

There is no uniform definition of what constitutes non-resectability. Overgrowth to organs or tissues not readily resectable like the base of the urinary bladder or the bony pelvis and very large non-mobile tumours generally indicate nonresectability, although some would claim that a multidisciplinary surgical approach would allow a radical resection. Magnetic resonance imaging (MRI) facilitates the evaluation of potential overgrowth [6], but has usually not been used in the trials.

There is no randomized trial that have compared preoperative RT aiming at rendering the tumour resectable through sterilizing the tumour overgrowth with other therapeutic approaches including attempts to extended surgery. Marked tumour regression, even complete, and long-term disease-free survival were seen in trials giving preoperative RT or radiochemotherapy over 4–5 weeks. Thus, the evidence is only indirect

that preoperative radio(chemo)therapy increases the chances of radical resection and cure. If tumour growth in the pelvis can not be controlled, the patients have severe suffering from pain and other symptoms, and the median survival is about 8–10 months.

A great number of trials have reported that preoperative radio(chemo) therapy results in a radical resection in 40–80 per cent of the patients and that 20–30 per cent will become long-term survivors [2,8-10,17-20, 25,26,28,35,36,49,53,59,79,83,85-89,96,97,102,104, 121,125,130]. Four of these trials have in a randomized way compared RT alone with 5-fluorouracil chemotherapy in addition to the RT (Overview 5) [59,86, 96,104]. These trials, all being small and sometimes with defective methodology, do not collectively provide supportive evidence that radiochemotherapy is superior to RT alone. Other trials in patients with a locally unresectable (or locally recurrent) cancer are mainly phase I or phase II trials, generally having explored a combination of concomitant chemotherapy and radiotherapy, or a phase III trial comparing two schedules of chemoradiation. The individual trial data was not reviewed here since, due to its design, it is not add information as to whether radiochemotherapy is superior to radiotherapy alone or whether one combination is superior to another. It is possible that patient selection is as relevant for treatment results as the particular schedule tested. Collectively, the trials give information to the overall results that can be achieved in these patients after preoperative therapy (see above).

The literature shows that:

- In the 10–15 per cent of the patients, who present primarily with a locally advanced, surgically non-resectable tumour, preoperative radiotherapy can cause tumour regression, allowing subsequent radical surgery in a substantial proportion of the patients. Whether radiochemotherapy is more efficient than radiotherapy alone is not clear from the literature since the few randomized trials have not shown any clear superiority.
- Radiotherapy frequently causes symptom relief in a patient with rectal cancer not amendable to surgery.

Literature

Radiotherapy in non-resectable rectal cancer.

	1 = High	2 = Moderate	3 = Low	Total
C	–	–	5/371	**5/371**
P	8/700	7/215	13/337	**28/1 252**
Total	**8/700**	**7/215**	**18/708**	**33/1 623**

Sphincter preservation after preoperative radiation

Overview 6 Randomized trial exploring the potential of increasing sphincter preservation after preoperative radiotherapy (after the list of references)

During the past decade, the indication for preoperative radio(chemo) therapy in a tumour judged to be resectable has not only been to lower local the failure rates but also to facilitate a sphincter-preserving procedure by decreasing the size of the tumour. This has often been ascribed to a down-staging effect by the preoperative therapy, although this term is inaccurate since it is not a decrease in stage, but in size, that is of relevance. The appropriate term should thus be down-sizing. There is at present no firm evidence that sphincter-preserving procedures will be possible more frequently after preoperative therapy and that this will result in improved quality of life [1]. One randomized study of the timing for surgery after preoperative RT reported slightly more sphincter-preserving procedures in the long interval group allowing down-sizing [34] (Overview 6). Slightly more sphincter-saving procedures were also found in a prematurely interrupted NSABP (National Surgical Adjuvant Breast and Bowel) R-03 trial comparing preoperative with postoperative radiochemotherapy (48 per cent vs 39 per cent, significance level not given) [103]. The preoperative therapy tended to be more toxic than the postoperative (grade 4/5 toxicity 34 per cent vs 24 per cent, p = 0.07). A large German trial, presently still recruiting patients, has a similar design [108]. The neoadjuvant therapy is well tolerated in the trial and bears no higher risk for postoperative morbidity. No results concerning sphincter preservation are presently available. Finally, a Polish trial has compared short-course radiotherapy (25 Gy in one week) with immediate surgery and radio-

chemotherapy to 50 Gy with delayed surgery in the group of patients where a down-sizing of the tumour theoretically could facilitate a sphincter preserving procedure [13]. The percentages of sphincter-preserving procedures were the same in the two groups (61 per cent vs 58 per cent, 316 randomized patients. Data presented at the ESTRO-meeting in Prague, September 2002, K. Bujko, abstract 140).

Besides these randomized trials, a large number of phase II trials have been reported [1,46,47,58,73,91,107,118,126-128] (not shown in overview). The trials all claim that more restorative procedures were possible after the preoperative prolonged radiochemotherapy course than would have been the case if no preoperative therapy, or only radiotherapy had been given. Without randomization, these conclusions can not be made, and the treatment results are not detailed. Long-term anal function has rarely been analyzed. In a group of 18 patients with locally advanced primary and recurrent rectal cancer treated with chemoradiotherapy and intraoperative radiotherapy, the functional outcome was generally poor after a median of 24 months after surgery [110].

The literature shows that:

Preoperative radiotherapy, frequently combined with chemotherapy, has been used to increase the chances of sphincter preserving surgery in low-lying tumours. The literature is inconclusive with respect to how frequently this occurs, and the long-term anal function, but several randomized trials are ongoing.

Literature

Sphincter preservation.

	1 = High	2 = Moderate	3 = Low	Total
C	–	1/201	–	**1/201**
P	4/417	2/68	2/58	**8/543**
R	1/53	1/18	–	**2/71**
Total	**5/470**	**4/287**	**2/58**	**11/815**

Literature

The articles on which the conclusions in this report were based were classified and graded as follows (number of studies/number of patients).

	1 = High	2 = Moderate	3 = Low	Total
M	2/17 878	1/5 974	–	**3/9 371**
C	14/12 891	6/1 839	23/3 879	**43/9 238**
P	12/1 117	10/320	15/395	**37/1 832**
R	5/4 722	1/18	1/100	**7/4 910**
L	1	1	–	**2**
O	13	2	–	**15**
Total[1)]	**47/21 612**	**21/957**	**39/2 782**	**107/25 351**

[1)] Studies and patients are not counted more than once in each column or row. Thus, since some patients can be included in several reports, the sums of the totals are lower than the sums of the numbers given within the table.

Conclusions and comments

The synthesis of the literature in rectal cancer is based upon 130 scientific publications. These included three meta-analysis of randomized trials including 9 371 patients, 42 randomized trials including 9 238 patients, 36 prospective trials with 1 832 patients and 7 retrospective analysis including 4 910 patients. Totally, the 105 studies (some studies have been reported more than once; therefore, the number of articles reviewed are higher than the number of studies) included 25 351 patients.

Based upon the literature review, the following conclusions can be reached:

- The results after rectal cancer surgery have improved during the latest decade. The support for this conclusions is fairly strong, even if the TME-concept (TME = total mesorectal excision) has not been tested in randomized trials. ([24](R1), [66](R1), [129](R1).

It is likely that local failure rates after five years of follow-up at hospitals adopting the TME-concept (TME = total mesorectal excision) have decreased from about 28 per cent to 10–15 per cent.

- Preoperative radiotherapy at biological effective doses above 30 Gy decreases the relative risk of a local failure by more than half (50–70 per cent). Postoperative radiotherapy decreases the risk by 30–40 per cent at doses that generally are higher than those used preoperatively.

These conclusions are very strong since they are based upon 27 randomized trials summarized in three meta-analysis. ([16](M2), [21](M1), [90](M1)).

- There is a strong evidence that preoperative radiotherapy is more effective than postoperative. ([21](M1), [37](C1).
- There is a moderate evidence that preoperative radiotherapy significantly decreases the local failure rate (from 8 per cent to 2 per cent after two years) also with TME. ([60](C1)).
- There is a strong evidence that preoperative radiotherapy improves survival (by about 10 per cent). ([16](M2), [21](M1), [117](C1).
- There is no evidence that postoperative radiotherapy improves survival. ([21](M1)).
- There is some indication that survival is prolonged when postoperative radiotherapy is combined with concomitant chemotherapy. ([40](C3), [124](C2)).

The importance of adjuvant chemotherapy or radiotherapy combined with adjuvant chemotherapy for survival is difficult to evaluate since trial results are partly conflicting. ([14](C3), [32](C1), [63](C2), [131](C1))

In the absence of randomized trials comparing different radiation schedules, it is impossible to define the most optimal preoperative one. The largest experience in the trials is with a short-term schedule (5 x 5 Gy in one week with surgery in the next week).

- Preoperative radiotherapy at adequate doses can be given with low acute toxicity. ([11](C3), [37](C1), [42](C1), [60](C1), [64](C3), [76](C1), [78](C1), [81](C2), [100](C3), [116](C1)).
- Higher, and unacceptable acute toxicity has been seen in some preoperative radiotherapy trials using suboptimal techniques. ([45](C2), [114](C1)).
- Postoperative radiotherapy can also be given with acceptable acute toxicity. ([4](C3), [5](C1), [32](C1), [37](C1), [40](C3), [81](C2), [122](C3)).

- The long-term consequences of radiotherapy appear to be limited with adequate radiation techniques, although they have been less extensively studied. Longer follow-up are needed before firm conclusions can be made. ([23](C1), [37](C1), [55](C1), [62](R3), [67](O1), [68](L2), [70](R2), [74](O1)).

Preoperative radiotherapy, preferably preoperative since it is more effective, is routinely recommended for most patients with a rectal cancer since it can substantially decrease the risk of a local failure and increases survival. Whether groups of patients with a very low risk of a local failure (less than a few per cent) can be exempted from the radiotherapy is not properly known.

- In a primarily non-resectable tumour, preoperative radiotherapy can cause tumour regression allowing subsequent radical surgery. This therapy is routinely indicated since it is based on clear evidence from many observational studies. ([2,8-10,17-20,25,26,28,35,36,49,53, 59,79,83,85-89,96,97,102,104,121,125,130]).

- Whether radiochemotherapy is more efficient than radiotherapy alone in primarily non-resectable tumours is not clear, since the results of four small randomized trials are partly conflicting. ([59](C3), [86](C3), [96](C3), [104](C3)).

- Preoperative radiotherapy, frequently combined with chemotherapy, has been used to increase the chances of sphincter preserving surgery in low-lying tumours. The literature is inconclusive with respect to how frequently this occurs, since it is mainly based upon observational studies where patient selection can influence outcome and one inconclusive randomized trial. ([1](R1), [34](C2), [46](P1), [47](P3), [58](P1), [73](P3), [107](P1), [118](P3), [126](P2)).

Several randomized trials are ongoing or have completed patient accrual.

- Radiotherapy frequently produces symptom relief in patients with rectal cancer not amendable to surgery. This conclusion is based upon solid clinical experience.

The literature dealing with palliative effects of rectal cancer radiotherapy has not been specially penetrated in this report.

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Overview 1 *Rectal cancer. Radiotherapy in resectable rectal cancer, meta-analysis of individual patient data.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Colorectal Cancer Collaborative Group, 2001 [21] M	Surgery alone vs surgery and preop or postop RT, meta-analysis of 22 trials.	Trials starting before 1987, 22 of 28 identified trials allowed analysis of individual patient data. 6 350 pts (92% of all) in 14 preop trials, 2 157 pts (99%) in 8 postop trials.

BED: biological effective dose. Calculated as LQ-time = $n.d\left(1 + \frac{d}{\alpha / \beta}\right) - \frac{\gamma}{\alpha}(T - T_k)$ where n = number of fractions, d = dose (Gy) per fraction, α/β = the common linear-quadratic quotient (set to 10 Gy), γ/α = repair rate (set to 0.6 Gy/day), T = the total treatment time (days) and T_k = the initial delay time (days, set to 7 days). The choice of coefficients reflects acute effects (41). Pts: patients; RT: radiotherapy

Results				Conclusion/Comments
		Reduced overall death rate		Preop RT (at BED 30+ Gy)
Preop BED	<20 Gy	5.5% (SE 9.4)	p = 0.6	reduces the risk of local failures
,	20–30 Gy	0.5% (5.3)	p = 0.9	and deaths from rectal cancer.
,	30+ Gy	9.8% (4.7)	p = 0.04	The reduction was seen in all
, all		5.6% (2.9)	p = 0.09	stages and both sexes. It increases
Postop, all	(35+ Gy)	4.6% (5.9)	p = 0.4	non-rectal cancer deaths, being technique dependent (see Overview 3).
		Reduced rectal cancer death rate		The effect on overall survival
Preop BED	<20 Gy	11.2% (11.4)	p = 0.3	is limited.
,	20–30 Gy	1.1% (6.3)	p = 0.9	Preop RT (at BED 20–30 Gy)
,	30+ Gy	21.6% (5.1)	p = 0.00002	slight reduction local failures,
, all		12.9% (3.7)	p = 0.0006	no influence on survival.
Postop, all	(35+ Gy)	8.6% (6.5)	p = 0.2	No significant effects are seen
		Relative reduction isolated local failure		using lower preop doses
Preop BED	<20 Gy	–20.2% (28.8)	p = 0.05 adverse	(BED <20 Gy).
,	20–30 Gy	23.7% (14.5)	p = 0.10	Postop RT (at BED 35+ Gy)
,	30+ Gy	57.4% (6.6)	p <0.00001	reduces risk of local failure
, all		46.0% (6.0)	p <0.00001	(less than preop RT), no
Postop, all	(35+ Gy)	36.9% (9.7)	p = 0.00002	influence on survival.
				M1
		Absolute reduction isolated local failures at 5 yrs		
Preop , all		22.2– 12.5%	p <0.00001	
Postop, all		22.9– 15.3%	p = 0.0002	
		Increase in non-rectal cancer death rate		
Preop BED	<20 Gy	–4.9% (16.2)	p = 0.8 adverse	
,	20–30 Gy	–0.8% (9.7)	p = 0.9 adverse	
,	30+ Gy	–37.2% (11.6)	p = 0.001 adverse	
, all		–15.2% (6.8)	p = 0.02 adverse	
Postop, all	(35+ Gy)	–12.4% (14.3)	p = 0.1	

Overview 2 *Rectal cancer. Radiotherapy in resectable cancer, RT-trials either not included in the meta-analysis (see Overview 1) or comparing two different ways of delivering RT (pre-vs postoperative, different targets).*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Frykholm 1993 [37] C	**A:** Preop RT (5 x 5.1 Gy, BED 37.8) + surgery **B:** Surgery + postop RT (25 x 2 Gy, BED 52.2) to Dukes' B+C	1980–85 A: 236 pts B: 235 pts
Kapiteijn 2001 [60] C	**A:** TME alone **B:** Preop RT (5 x 5 Gy, BED 37.5) + TME	1996–99 1 805/1 861 eligible A: 937 pts B: 924 pts
Bosset 2001 [7] C	**A:** Postop RT pelvis only (50 Gy/25 fr) **B:** Postop RT pelvis (50 Gy), para-aortic nodes + liver (25 Gy/19 fr)	1983–92 451/484 eligible A: 229 pts B: 222 pts

BED: biological effective dose. For calculation see overview 1; CHT: chemotherapy; fr: fractionation; pts: patients; RT: radiotherapy; TME: total mesorectal excision; y: year(s)

Results	Conclusion/Comments
5 y local failure rate A: 13%, p = 0.02 B: 22% No increased postop mortality No survival difference 10 y risk of ileus surgery alone 6% preop RT + surg 5% surg + postop RT 11%, p = 0.01	Short term preop RT is more efficient in reducing local failures than postop conventional RT, and less toxic. Preop RT (3 beams) does not increase postop mortality. **C1**
2 y local failure rate A: 8.2% B: 2.4% p <0.001 **2 y overall survival** A+B 82% p = 0.8 No increased postop mortality	Short term preop RT reduces the risk of local failure also with TME. The relative reduction appears to be higher with TME (71%) than with non-standardized surgery (see Table 1). Preop RT (3 or 4 beams) does not increase postop mortality. **C1**
10 y disease-free and overall survival similar, **10 y local failure rate** 30% both groups	Low dose postop RT to an extended volume does not improve survival. **C1**

Overview 3 *Rectal cancer. Postoperative radiotherapy, chemotherapy or radiochemotherapy, randomized trials in stages II + III (trials only comparing two RTCHT regimens are not included in the overview, two of eight trials included in the meta-analysis).*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
GITSG 7175 1985 [40] included in meta-analysis [21] C	**A:** surgery alone **B:** surg + RT 40–48 Gy **C:** surg + CHT (MF) **D:** surg + RT + 5FU + CHT (MF)	1975–1980 202/227 eligibile A: 58 pts B: 50 pts C: 48 pts D: 46 pts
Krook 1991 [63] Miller 1998 [84] C	**A:** RT 45 Gy ± boost 5.4 Gy **B:** RT + 5FU + CHT (MF)	1980–1986 204/209 eligible A: 100 pts B: 104 pts
Fisher 1988 [32] included in meta-analysis [21] C	**A:** surgery alone **B:** surg + RT 46.5 Gy **C:** surg + CHT (MOF)	1977–1986 555/574 eligible A: 185 pts B: 184 pts C: 187 pats

CHT: Chemotherapy; FLv: 5FU + leucovorin; MF: MethylCCNU + 5FU; MOF: MethylCCNU + vincristine + 5FU; pts: patient(s); RT: radiotherapy; RTCHT: radiochemotherapy; surg: surgery

Results	Conclusion/Comments
5 y local failure rate A: 24% B: 20% C: 27% D: 11% ns **6 y overall survival** A: 28% B: 43% C: 43% D: 57% p = 0.05	Small trial, prematurely interrupted, supports the benefit of postop RTCHT. Increased acute toxicity was seen. **C3**
5 y local failure rate A: 25% B: 14% p = 0.04 **5 y overall survival** A: 47% B: 58% p = 0.04	Supports the benefit of combined radiochemotherapy over radiotherapy alone. Increased acute toxicity, particularly diarrhoea (grade 3–4 22% vs 4%, p = 0.001) **C2**
5 y local failure rate A: 25% B: 16% C: 21% ns **5 y overall survival** A: 43% B: 41% C: 53% p = 0.05	No benefit was seen with post radiotherapy. A survival benefit was seen with chemotherapy alone challenging the results of the GITSG 7175 trial. The benefit was restricted to males. **C1**

The table continues on the next page

Overview 3 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Mansour 1991 [75] C	**A:** RT **B:** CHT (MF) **C:** RT + CHT	1986–? 248 eligible 237 evaluable
Tveit 1997 [124] C	**A:** surgery alone **B:** surg + RT + 5FU	1989–1993 A: 72 pts B: 72 pts
Cafiero 2000 [14] C	**A:** RT 50 Gy **B:** CHT x 1 + RT + CHT x 5 (5FU + levamisol)	1992–1998 A: 108 pts B: 110 pts
Wolmark 2000 [131] C	**A:** CHT (MOF or FLv) **B:** CHT+RT 45 Gy + boost 5.4 Gy + 5FU + CHT	1987–1992 742 pts A: 348 pts B: 346 pts

Results	Conclusion/Comments
Overall survival A: 46% B: 47% C: 50%	Only reported as an abstract. No concomitant chemotherapy was given. Gives no evidence of any survival benefit. **C3**
Local failure rate A: 32% B: 11% p = 0.01 **Overall survival** A: 49% B: 63% p = 0.05	Small trial, but supports the benefit of concomitant radiochemotherapy without prolonged chemotherapy. **C2**
Local failure rate A: 15% B: 21% ns **Projected 5 y survival** A: 56% B: 39% ns	No benefit was seen with chemotherapy in addition to postop radiotherapy. Increased acute toxicity, with sign more severe enteritis (p = 0.03) **C3**
8 y initial local failure rate A: 14% B: 8%, p = 0.02 **8 y overall survival** A = B: 58%, p = 0.9	Radiotherapy with chemotherapy decreases local failure rates but does not improve survival **C1**

Overview 4 *Rectal cancer. Postoperative mortality in randomized trials using multiple fractions of 5 Gy given preoperatively to patients with primarily resectable rectal cancer.*

Author Year (ref no) Design	Radiation	Technique	Postop. mortality
Goldberg 1994 [45] C	3 x 5 Gy	AP-PA, L5	In hospital 30 day
Marsh 1994 [78] C	4 x 5 Gy	3 rotating beams, 10 x 10 cm	Not defined
Frykholm 1993 [37] C	5 x 5 Gy	3 beams, L3	In hospital
Stockholm Rectal Cancer Study Group 1990 [114] C	5 x 5 Gy	AP-PA, L2	30 day
SRCT 1993 [116] C	5 x 5 Gy	3/4 beams, L4	In hospital
Stockholm Colorectal Cancer Study Group 1996 [113] C	5 x 5 Gy	3/4 beams, L4	30 day 60 day
Kapiteijn 2001 [60] Marijnen 2002 [76] C	5 x 5 Gy	3/4 beams, L5	In hospital 30 day

AP-PA: Two anterior-posterior beams; L2–5 = upper beam limit at lumbar vertebra 2–5.

	Results	Conclusion/Comments
Surgery 7% 4%	Surgery + RT 12% p = 0.06 9% p <0.05	Increased risk after palliative surgery. **C2**
No difference		Exact figures not given in the publication. No increased risk. **C1**
5%	2% ns	No increased risk. **C1**
2%	8% p <0.001	This trial used large beams, that resulted in a large radiation burden and a marked increase in postoperative mortality, particularly in the elderly. **C1**
3%	4% ns	Increased postop mortality was seen when AP-PA was given at three hospitals, violating the protocol (3/4 beams 3%, AP-PA 15%). Otherwise no increased risk. **C1**
1% 1%	2% ns 4% ns	Stockholm II overlaps SRCT, the same technique was used, but the Stockholm group did not add any shields covering small bowels. This can be responsible for the tendency seen in Stockholm II but not in the rest of SRCT. **C1**
3% 3%	4% ns 4% ns	No increased risk. **C1**

Overview 5 *Rectal cancer. Radiotherapy alone compared to radiotherapy plus chemotherapy in non-resectable rectal cancer.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Moertel 1969 [86] C	**A:** RT 35–40 Gy + placebo **B:** RT 35–40 Gy + 5FU	A: 33 pts B: 32 pts
Rominger 1985 [104] C	**A:** RT 45–51 Gy + boost **B:** RT 45–51 Gy + 5FU + maintenance CHT	129/147 evaluable A: 65 pts B: 64 pts
Overgaard 1993 [96] C	**A:** RT 50 Gy + boost **B:** RT 50 Gy + weekly 5FU	A: 29 pts B: 30 pts
Jansson-Frykholm 2001 [59] C	**A:** 46 Gy RT **B:** 40 Gy RT split course + Methotrexate + 5FU + Leucovorin	A: 36 pts B: 34 pts

5FU: 5-fluorouracil; LFS: local failure free survival; OS: overall survival; pts: patient(s); RT: radiotherapy; RTCHT: radiochemotherapy; y: year(s)

Results	Conclusion/Comments
Mean survival, months A: 17 B: 25 p <0.05 **3 y survival** A: 9% B: 19% ns	Colon and rectum together (the study also included pts with gastric and pancreatic cancer). This study was early interpreted to show that RTCHT (3 days of 5FU) was superior to RT alone. **C3**
2 y survival A: 36% B: 44% ns No difference in failure pattern More complications in B	No difference between RTCHT and RT, increased risk of complications. **C3**
3 y survival A: 7% B: 16% ns **Acute toxicity** A: 13% B: 33% p = 0.07	Significant palliation in 73%, no difference between groups, except more toxicity with RTCHT. **C3**
LFS at 5 y A: 38% B: 66% p = 0.03 **OS at 5 y** A: 18% B: 29% p = 0.3	Gives some support that RTCHT is superior to RT, but did not have the same RT schedule in the two arms. **C3**

Overview 6 *Rectal cancer. Randomized trial exploring the potential of increasing sphincter preservation after preoperative radiotherapy.*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Francois 1999 [34] C	**A:** RT 13 x 3 Gy, surgery after 2 weeks **B:** same RT, surgery after 6–8 weeks	201/210 eligible A: 99 pts B: 102 pts

Pts: patient(s); RT: radiotherapy

Results	Conclusion/Comments
Sphincter preservating procedure A: 68% B: 76% ns No other differences detected	Downstaging was seen after a long interval, but the only randomized trial completed so far does not provide support for more sphincter preserving procedures. **C2**