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Late adverse effects of radiation therapy for rectal cancer – a systematic overview

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Abstract

Purpose. The use of radiation therapy (RT) together with improvement in the surgical treatment of rectal cancer improves survival and reduces the risk for local recurrences. Despite these benefits, the adverse effects of radiation therapy limit its use. The aim of this review was to present a comprehensive overview of published studies on late adverse effects related to the RT for rectal cancer. *Methods.* Meta-analyses, reviews, randomised clinical trials, cohort studies and case-control studies on late adverse effects, due to pre- or postoperative radiation therapy and chemo-radiotherapy for rectal cancer, were systematically searched. Most information was obtained from the randomised trials, especially those comparing preoperative short-course 5×5 Gy radiation therapy with surgery alone. *Results.* The late adverse effects due to RT were bowel obstructions; bowel dysfunction presented as faecal incontinence to gas, loose or solid stools, evacuation problems or urgency; and sexual dysfunction. However, fewer late adverse effects were reported in recent studies, which generally used smaller irradiated volumes and better irradiation techniques; although, one study revealed an increased risk for secondary cancers in irradiated patients. *Conclusions.* These results stress the importance of careful patient selection for RT for rectal cancer. Improvements in the radiation technique should further be developed and the long-term follow-up of the randomised trials is the most important source of information on late adverse effects and should therefore be continued.

The benefits of radiation therapy (RT) in addition to surgery for rectal cancer are well documented and the reduced risk for local recurrences is highlighted [1,2]. Improvements in surgical technique, understanding of rectal anatomy and the embryonic planes, including the mesorectal fascia, have led to the development of the total mesorectal excision (TME) [3], which further reduces the risk of local recurrences. However, RT is still beneficial, also in combination with TME [4,5]. The local recurrence rate of resectable rectal cancers should now have decreased below 10% [6–8], which is a considerable improvement from local recurrence rates of 20–30% reported only a few decades ago [2,9,10]. On a population level, these improvements have resulted in better survival for patients with rectal cancer [6,11,12].

RT is associated with adverse effects [13] and a balance between the beneficial and the negative effects of irradiation is sought. Immediate adverse effects, such as skin erythema, fatigue, nausea, diarrhoea and neurological pain from rectal cancer radiation are well documented [14–19]. With increased length of follow-up and better survival of the rectal cancer patients, attention has been directed to late adverse effects [20–25], as additional RT, whether given pre- or post-operatively, means over treatment of a substantial proportion of the patients.

The aim of this paper was to provide a comprehensive overview of published studies on late adverse effects related to RT for rectal cancer.

Methods

Studies on late adverse effects of radiation therapy for rectal cancer were searched in the databases: Medline through PubMed, Cochrane database of systematic reviews and reference lists of the primary

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and review articles. The search terms used were: radiation therapy; radiotherapy; rectal; rectum; cancer; adverse effects; complications; function; and dysfunction. The type of articles included were meta-analyses, reviews, randomised controlled trials and clinical trials: the types of articles excluded were editorials, letters and practice guidelines. For reviews, the search was limited to English only; no other limitations were applied during the search.

This review focused on external beam radiation therapy, including both preoperative and postoperative RT with total doses of both 25 and 50–60 Gy. Studies on chemo-radiotherapy (CRT) were included, but intraoperative RT (IORT) and brachytherapy were excluded. Late adverse effects were defined as adverse effects persisting or occurring more than 6 months from the start of the RT.

Results revealed no meta-analysis with the primary aim of analysing late adverse effects of RT for rectal cancer: one meta-analysis on the benefits of the RT also included non-colorectal cancer deaths [1]. Another systematic overview included an evaluation of some adverse effects, mainly bowel function and gastrointestinal disorders [2] and one model study balanced gains and losses of RT [26] (Table I). The search for reviews gave 1 878 reviews in English; first, this was reduced to less than 100 articles dealing with some aspects of complications or adverse effects of rectal cancer treatment, and then reduced to ten relevant reviews focusing on late adverse effects of RT for rectal cancer [27–36] (Table I). For randomised controlled trials, 633 references were found on rectal cancer, but only 16 publications fulfilled the criteria of explicitly studying late adverse effects [7,16,20–23,25,37–45] (Table II). For clinical trials, 1 570 references were found for rectal cancer and 14 studies were of substantial high quality to be included in the review [46–59] (Table III).

A list of references for the studies relating to late adverse effects of RT on rectal cancer that are discussed in this paper is presented in Table II & III. The studies were sorted into order of type of study and the year of publication. Information on the RT doses and techniques were also given.

Although there are almost 30 randomised trials on RT for rectal cancer that focus on local recurrence and survival [1,2,60], only a few [16,20–25,40–42,44,45] have evaluated the late adverse effects on follow-up; this particularly applied to the preoperative 5×5 Gy studies. Even though the radiation dose delivered in many trials was the same, the radiation technique and the irradiated volumes varied between the studies. The most important details of the radiation techniques used in the randomised trials on late adverse effects are presented in Table IV. As

Table I. List of meta-analyses and reviews on late adverse effects of radiation therapy for rectal cancer. The publications are listed in order of year of publication and comments are made on the publication.

Reference	Year of publication	Comments
		Meta-analyses
Colorectal Cancer Collaborative Group [1]	2001	Meta-analysis of 22 randomised trials comparing outcomes of surgery including non-colorectal cancer mortality
Glimelius et al. [2]	2003	Systemic overview of 131 scientific articles with the secondary aim of analysing late adverse effects, mainly bowel function and gastrointestinal disorders
Bakx et al. [26]	2006	A model study of 4 randomised trials balancing gains and losses of preop RT 5×5 Gy
		Reviews
Cummings [29]	1986	A critical review of preoperative RT
Gerard et al. [31]	1995	A review on dose volume relationship in the risk of radiation induced rectal complications
Letschert [34]	1995	A review of radiation-induced small bowel complications and its prevention
Coia [28]	1995	A comprehensive review discussing tolerance doses and management on late adverse effects of RT on the GI tract
Camilleri-Brennan et al. [27]	1998	A review of 54 studies on quality of life in rectal cancer surgery, which discusses a few studies including RT and CT
Ooi et al. [35]	1999	A review mainly discussing early adverse effects of RT and CT for rectal cancer, but also commenting on late adverse effects
Johnston et al. [33]	2003	Review considering the management of late adverse effects of pelvic RT
Temple et al. [36]	2003	A review mainly discussing anal and sexual dysfunction of RT for rectal cancer
Fajardo [30]	2005	Pathological description of the effects of RT on normal tissues
Guckenberger and Flentje [32]	2005	Review on late small bowel toxicity after adjuvant treatment for rectal cancer

Abbreviations: RT: Radiation therapy; CT: Chemotherapy; CRT: Chemo radiotherapy; Gy: Gray.

Table II. List of randomised clinical trials on late adverse effects of radiation therapy for rectal cancer. The publications are listed in order of year of publication. Comments are made on the follow-up time in years, type of study, radiation technique, and the late adverse effects reported.

Reference	Year of publication	Follow-up in years	Type of study	Type of radiation	Adverse effects reported
Dahl et al. [37]	1990	5	Examination	Preop 18 × 1.75 Gy vs no RT	BF, U
Frykholm et al. [42]	1993	8–10	Hospital records and interview	Preop 5 × 5 Gy vs postop 25 × 2 Gy for stage II and III	BF, GI, U, D
Holm et al. [41]	1996	5	Register study	Preop 5 × 5 Gy vs no RT	F, GI, U, V
MRC-2 [44]	1996	5	Interview	Preop 20 × 2 Gy vs no RT	GI, U
MRC-3 [45]	1996	5	Interview	Postop 20 × 2 Gy vs no RT	GI, U
Lundby et al. [39]	1997	14	Questionnaire telephone	Postop 25 × 2 Gy vs no RT	BF
Dahlberg et al. [22]	1998	5	Questionnaire	Preop 5 × 5 Gy vs no RT	BF, QLB
Sauer et al. [16]	2004	5	Prospective registration	Preop CRT 28 × 1.8 Gy + 5-FU vs postop 28 × 1.8 Gy + 5-FU	BF, D, GI, H, U
Birgisson et al. [21]	2005	13	Register study	Preop 5 × 5 Gy vs no RT	All organs
Birgisson et al. [23]	2005	13	Register study	Preop 5 × 5 Gy vs no RT	Second cancers
Marijnen et al. [7]	2004	2	Questionnaire	Preop 5 × 5 Gy vs no RT	SF, QL
Peeters et al. [20]	2005	5	Questionnaire	Preop 5 × 5 Gy vs no RT	BF, GI, QL, SF, U, V
Lundby et al. [40]	2005	17	Examination	Postop 25 × 2 Gy vs no RT	BF
Pollack et al. [38]	2006	14	Examination	Preop 5 × 5 Gy vs no RT	BF, QL, GI, U, V
Pollack et al. [25]	2006	14	Examination	Preop 5 × 5 Gy vs no RT	BF
Bujko et al. [43]	2006	4	Examination	Preop 5 × 5 Gy vs preop 28 × 1.8 Gy + 5-FU	F, GI, N, U

Abbreviations: RT: Radiation therapy; CT: Chemotherapy; CRT: Chemo radiotherapy; Gy: Gray; y: Years; 5-FU: 5-fluorouracil; Preop: Preoperative; Postop: Postoperative; BF: Bowel dysfunction; D: Dermatological problems; F: Fractures; GI: Gastrointestinal; H: Haematological; N: Neurological; QL: Quality of Live; QLB: Quality of life related to bowel function; SF: Sexual dysfunction; U: Urinary tract; V: Vascular.

the retrospective hospital record studies often contained incomplete descriptions about the radiation techniques, and more variation in the dose delivered, they were not included in the table, but were commented upon in the text where appropriate.

Results

The late adverse effects due to RT for rectal cancer were gastrointestinal disorders, neurological problems, anal, rectal, urinary and sexual dysfunction, pelvic or hip fractures, thromboembolic diseases and secondary cancers [7,20–23,39,41,42,49,59]. Assessments of quality of life was also the aim of some studies [20,22,38].

The grading systems, whether from the Radiation Therapy Oncology Group (RTOG), European Organisation for Research and Treatment of Cancer (EORTC) or National Cancer Institute (Common Toxicity Criteria (NCI-CTCAE)) [61] were based on a severity scale from no symptoms (grade 0) to death (grade 5) [62]. The RTOG/EORTC late radiation morbidity scoring system for gastrointestinal adverse effects is listed in Table V.

Symptoms on the functional results of the rectum, e.g. gas or faeces incontinence and rectal emptying difficulties, were not mentioned in the scoring systems.

The study design influenced whether mild symptoms (grades 1-2) were detected or not. Studies with interviews, visits and questionnaires detected the mildest symptoms, whereas, register or hospital record studies only detected the more severe symptoms (grades 3-5). Therefore, when different RT trials were compared, it was important to have a proper definition of the study design and instruments used for detecting the problems. Preferably, questionnaires should be designed according to the Late Effects on Normal Tissues (LENT)-Subjective, Objective, Management and Analytic (SOMA) scales (LENT/SOMA scales) [63].

The gastrointestinal tract

The small bowel was the organ that was most often affected by pelvic irradiation [16,21,23,42,64]. The colon, rectum and anus were also affected, but the upper gastrointestinal canal including duodenum, stomach and oesophagus was not. The symptoms resulting from adverse effects of the gastrointestinal tract were diarrhoea, bleeding, abdominal pain and obstruction due to stenosis or adhesions and more rarely malabsorption [64], necrosis, perforation and fistulation [28].

It was mainly the trials with preoperative 5x5 Gy that studied the late adverse effects [7,20–23,25,41].

Table III. List of cohort and case-control studies on late adverse effects of radiation therapy for rectal cancer. The publications are listed in order of year of publication. Comments are made on the follow-up time in years, type of study, radiation technique, and the late adverse effects reported.

Reference	Year of publication	Follow-up in years	Type of study	Type of radiation	Adverse effects reported
Letschert et al. [50]	1990	2	Hospital records	Postop 22–25 ×2 Gy	GI
Birnbaum et al. [46]	1994	3	Examination	Preop 25 ×1.8 Gy	BF
Kollmorgen et al. [49]	1994	2-5	Telephone Questionnaire	Postop CRT vs no RT	BF
Mak et al. [52]	1994	3–21	Hospital records	Postop various	GI, U
Lewis et al. [51]	1995	1	Questionnaire/ Examination	Postop CRT vs no RT	BF
Minsky et al. [54]	1995	3	Questionnaire/ Examination	Preop 28 ×1.8 Gy	BF
Wagman et al. [58]	1998	5	Examination	Preop 27 ×1.8 Gy±CT	BF
Miller et al. [53]	1999	5	Hospital records	Postop CRT	BF, GI
Olagne et al. [56]	2000	3	Questionnaire	Preop 25 ×1.8 Gy	BF
Caffo et al. [47]	2002	3	Questionnaire	Postop 25–30 ×1.8 Gy±5-FU	QL
Dehni et al. [48]	2002	3	Questionnaire/ Examination	Preop 5 ×5 Gy or 25 ×1.8 Gy vs no RT	BF
van Duijvendijk et al. [59]	2002	1	Questionnaire/ Examination	Preop 5 ×5 Gy vs no RT	BF, U
Prabhudesai et al. [57]	2005	1	Questionnaire/ Examination	Preop 5 ×5 Gy vs no RT	BF, D, GI, U
Mohiuddin et al. [55]	2006	2–5	Examination	Preop CRT 46-50 ×1.2 Gy with 5-FU vs 5-FU+irinotecan	D, GI, U

Abbreviations: RT: Radiation therapy; CT: Chemotherapy; CRT: Chemo radiotherapy; Gy: Gray; y: Years; 5-FU: 5-fluorouracil; Preop: Preoperative; Postop: Postoperative; BF: Bowel dysfunction; D: Dermatological problems; GI: Gastrointestinal; QL: Quality of Live; U: Urinary tract.

Studies with long-term follow-up and that examine late adverse effects of RT, other than 5x5 Gy, were the Uppsala study on pre- and postoperative RT [42], and a Danish randomised study on postoperative RT [39]. The studies by the Medical Research Council Rectal Cancer Working Party (MRC) on postoperative RT (MRC-3) [45] or preoperative RT versus no RT (MRC-2) [44] for locally advanced rectal cancers, and the German trial on pre-versus postoperative CRT [16] also reported late adverse effects from the gastrointestinal tract.

Anal and rectal dysfunction. Anal and rectal dysfunction refers mainly to symptoms such as gas, liquids or solid faeces incontinence, rectal emptying problems, frequent bowel movements and diarrhoea.

In 1998, a 5- year follow-up questionnaire study, of the SRCT was published, which compared 84 patients irradiated with preoperative 5x5 Gy and 87 patients treated with only low anterior resection [22]. Bowel frequency more than four times a day occurred in 20% of the irradiated group compared to 8% of the non-irradiated patients. Incontinence to loose stools was seen in 50% of irradiated patients and 24% of non-irradiated, and incontinence to solid stools in 14% irradiated and 3% non-irradiated patients (Table VI). Emptying difficulties were also a common problem for 52% of the irradiated patients and in 36% treated with surgery only. All differences were statistically significant. A 14-year follow-up of the Stockholm I and II trials, including 23 preoperatively irradiated (5x5 Gy) patients and 43 non-irradiated patients, revealed more frequent faecal incontinence (57%) and soiling (38%) in irradiated patients than in non-irradiated patients (26% faecal incontinence and 16% soiling) (Table VI). More bowel movements were seen in irradiated patients (20 a week) than in non-irradiated patients (10 a week) [25].

Bowel dysfunction was analysed in a 5-year follow-up on the Dutch TME trial, incontinence was seen in 62% of the irradiated patients and 38% of the non-irradiated patients (Table VI). Irradiated patients had more frequent bowel movements (3.69 per day) than non-irradiated had (3.02 per day) and were less satisfied with their bowel function. Patients with stomas were more satisfied with their bowel function than those operated with a low anterior resection without stoma, this were independent of RT [20].

In a Polish trial comparing preoperative 5x5 Gy RT and CRT (50 Gy), no differences were seen in the proportion of patients having incontinence to loose stools (72% RT and 65% CRT), difficulties in

Table IV. List of randomised trials on radiation therapy for rectal cancer dealing with late adverse effects. The year of study, type of radiation in each arm, the radiation technique, upper beam limits, and whether or not the irradiation of anal sphincters was made, are presented.

Study	Year	Arm I Dose (Gy)/Fraction (n)*	Arm II Dose (Gy)/Fraction (n)*	RT Technique Beams	Upper beam limits	Irradiation of anal sphincters
Western Norwegian Trial [37]	1976–85	Preop 31.5/18 (159)	no RT (150)	AP–PA	L1/L2	For tumours <5 cm from anus
Uppsala Trial [42]	1980–85	Preop 25/5 (236)	Postop 50/25 (235)	3	L 4	For tumours <10 cm from anus
Stockholm I [25,38,41]	1980–87	Preop 25/5 (424)	no RT (425)	AP–PA	L 2	All patients
MRC-2 [44]	1981–89	Preop 40/20 (139)	no RT (140)	AP–PA	5 cm above tumour	na
MRC-3 [45]	1984–89	no RT (235)	Postop 40/20 (234)	AP–PA	5 cm above tumour	If APR was done
Stockholm II [25,41]	1987–93	Preop 25/5 (272)	no RT (285)	3/4	L 4	All patients
SRCT [21–23]	1987–90	Preop 25/5 (572)	no RT (575)	3/4	L 4	All patients
Dutch TME trial [20,24]	1996–99	Preop 25/5 (924)	no RT (937)	3/4	L 5/S 1	If APR was planned
German trial [16]	1995–02	Preop 50.4/28+CT (421)	Postop 50,4/28+CT (402)	3/4	L 4/L 5	If ≤2 cm from dentate line
Danish [39,40]	1979–85	no RT (250)	Postop 50/25 (244)	AP–PA	L 5	na
Polish trial [43]	1999–02	Preop 25/5 (155)	Preop 50.4/28+CT (157)	3/4	L 5/S 1	All patients

RT: Radiation therapy; CT: Chemotherapy; Gy: Gray; Preop: Preoperative; Postop: Postoperative; L: Lumbar vertebrae; y: years; MRC: Medical research council rectal cancer working party; TME: Total mesorectal excision; SRCT: Swedish rectal cancer trial; APR: Abdominoperineal rectal excision; na: Not available. * Number of patients allocated to each treatment arm. S: Sacral vertebrae; AP–PA: Anterior posterior – Posterior anterior; 3/4: Three or four.

discrimination between gas and stools (59% RT and 66% CRT) and in stool frequency (median 4 RT and 5 CRT) [65].

A 17-year follow-up of a randomised study on postoperative RT (n=15 RT and n=13 no RT) revealed increased bowel frequency, with 80% of the irradiated patients having >2 stools a day compared to 23% of the non-irradiated patients. Faecal incontinence to stools was determined in 60% irradiated and 8% non-irradiated and urgency in 53% irradiated and 0% non-irradiated (Table VI) [40].

In a retrospective case-control hospital record study, analysing postoperative CRT with 3-year follow-up, a great impact on bowel movements, faecal incontinence and rectal emptying was seen [49]. In this study, 83% of the non-irradiated patients had <4 bowel movements a day compared to 22% of the CRT group. Incontinence was seen in 56% of the CRT group and in 7% of the surgery only group. Radiation-induced diarrhoea and malabsorption have been correlated to irradiated small bowel volumes and was worse in those treated with low anterior resection than those treated with abdominoperineal resection [64]. Further, another hospital record study [53] showed that chronic bowel injury, chronic enteritis and proctitis were prevalent in patients treated with postoperative CRT. Proctitis was not a problem in preoperatively irradiated patients as the irradiated rectum was removed during low anterior resection.

Bowel obstructions. An increased risk for small bowel obstructions in irradiated patients has been observed in several studies. In the 5-year follow-up of the Stockholm trials, the frequency of small bowel obstruction was 13% for the irradiated patients and 8.5% for surgery only patients [41]. The occurrence was slightly lower in the 13-year follow-up of the SRCT with 9% of the irradiated patients developing late small bowel obstruction compared to 4% of the surgery only group [21]. A five-year follow-up of the Dutch TME trial revealed that 11% suffered small bowel obstruction, with no difference observed between the irradiated and non-irradiated groups [20]. To diminish the bias of bowel obstruction caused by cancer growth, both the Stockholm Trial and SRCT excluded non-curatively treated patients and patients developing cancer recurrence. In the follow-up of the SRCT, the differences in bowel obstruction became obvious during the latter part of follow-up, with a difference between the groups first being seen after 8 years [21].

Preoperative RT, with 5-fluorouracil, has a non-significantly lower risk (9%) of grades 3-4 late

Table V. RTOG/EORTC late radiation morbidity scoring schema for adverse gastrointestinal effects.

ORGAN TISSUE	0	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
SMALL OR LARGE INTESTINE	None	Mild diarrhoea	Moderate diarrhoea and colic	Obstruction or bleeding requiring surgery	Necrosis/ Perforation Fistula	Death directly related to the radiation effects
		Mild cramping	Bowel movement >5 times daily			
		Bowel movement 5 times daily	Excessive rectal mucus or intermittent bleeding			
		Slight rectal discharge or bleeding				

RTOG: Radiation Therapy Oncology Group.
EORTC: European Organisation for Research and Treatment of Cancer.

gastrointestinal symptoms than postoperative CRT (15%) does, as shown by the German Rectal Cancer Study Group [16]. In a previous trial comparing pre- and postoperative RT, postoperatively treated patients (60 Gy) had a higher risk of bowel obstruction compared to the preoperatively treated patients (25 Gy) [42]. One explanation was that patients previously operated in the pelvis had a larger part of the small bowel within the irradiated volume than those not previously operated [66]. This was especially the case for patients operated with abdominoperineal resection [67].

The Polish study comparing preoperative 5x5 Gy RT to preoperative CRT of 28x1.8 Gy and 5-fluorouracil+leucovorin did not reveal any differences in late adverse effects from the gastrointestinal tract [43].

Other gastrointestinal disorders. Only the Stockholm trials determined an increased risk for fistulas in irradiated patients [41]. Anastomotic strictures were not a problem, when preoperative 5x5 Gy was given; however, postoperative CRT increased the risk of late anastomotic strictures (12%) compared to preoperative CRT (4%, $p = 0.003$) [16].

Urinary tract dysfunction

The surgical treatment for rectal cancer can cause urinary dysfunction such as incontinence, retention, dysuria, frequency and urgency [68,69]. A small study with a follow-up time of more than 12 months compared 20 patients treated with preoperative 5x5 Gy with 12 non-matched historical controls with the LENT SOMA scales [57] and reported more urinary dysfunction problems including increased frequencies and incontinence after irradiation. A late follow-up of the Stockholm trials have also shown increased urinary incontinence in the irradiated patients [38]. However, when the larger randomised studies were analysed, rectal irradiation did not appear to have any major effects on the urinary system [16,20,21,41,42]. Late urinary tract symptoms were reported in 4% of all patients in the Western Norwegian trial [37] and in 3% of all patients in the Uppsala trial, with chronic cystitis as the most common diagnosis [42]. Bladder problems were seen in 2% of the preoperatively treated and 4% of the postoperatively treated patients ($p = 0.21$) in the German study on pre- versus postoperative CRT [16].

Sexual dysfunction

Sexual function after treatment of rectal cancer did not gain much attention until the past decade and was originally directed mainly at male sexual dysfunction [27,70,71]. Of the randomised studies, only the Dutch TME trial analysed the grade of sexual dysfunction between irradiated and surgery only patients [24]. In males, the sexual activities of those who were still active preoperatively decreased to 67% in irradiated patients and 76% in non-irradiated patients: this difference was not statistically significant. A greater difference was seen in females with a reduction to 72% for irradiated patients and 90% non-irradiated patients. Males had greater problems with erection and ejaculation but no differences in vaginal dryness and pain during intercourse were seen in females [24]. A non-randomised case control study with up to 4-years follow-up compared male patients with rectal cancer operated with proctosigmoidectomy to patients operated with the same method but receiving

Table VI. A comparison of faecal incontinence in patients treated for rectal cancer with RT and low anterior resection or low anterior resection alone. The results are from randomised clinical trials that have studied late bowel dysfunction.

	Faecal incontinence		Faecal incontinence Night		Faecal incontinence Loose stools		Faecal incontinence Solid stools	
	Preop RT %	No RT %	RT %	No RT %	RT %	No RT %	RT %	No RT %
Dahlberg et al. [22]	#	#	14	8 ns	50	24*	14	3*
Peeters et al. [20]	62	38*	32	17*	#	#	#	#
Pollack et al. [25]	57	26*	#	#	#	#	#	#
	Postop RT %		Postop RT %		Postop RT %		Postop RT %	
Lundby et al. [39]	49	5*	#	#	#	#	#	#
Lundby et al. [40]	60	8*	#	#	#	#	#	#

RT: Radiation therapy; CRT: Chemo radiotherapy; Preop: Preoperative; Postop: Postoperative; ns: Non-significant; *: Significant ($p < 0.05$), #: Not analysed.

preoperative conventional RT up to 40–50 Gy [71]. Although the study showed impaired sexual function in the irradiated group, this group had more advanced tumour stages with all patients receiving pre- or postoperative chemotherapy compared to only 25% of the surgery only group.

Second cancers

There is currently only one published study on the risk of secondary cancer in patients treated with RT for rectal cancer [23]. The study was based on patients participating in the Uppsala Trial and the SRCT and concluded that irradiated patients had an almost doubled risk of developing second cancers than those treated with surgery only. The follow up time for the SRCT was 14 years with second cancer occurring in 9.5% of the RT patients and 4.3% of the non-RT patients.

The risk was mainly related to second cancers from organs within or adjacent to the irradiated target. There was no individual type of cancer that could be related to the RT, but gynaecologic and prostate cancers were the most common second cancers from organs within or adjacent to the irradiated target. Moreover, irradiated patients with stage I disease were at higher risk of developing second cancer than those treated with surgery only [23].

Quality of life

Although there are specific quality of life questionnaries available for colorectal cancer patients (QLQ-CR38) constructed by EORTC [72] there are no studies on quality of life measuring the late adverse effects of RT for rectal cancer and few studies on early adverse effects [15].

Quality of life has mainly been analysed in association with the bowel function, not using standardised questioners [20,22,38,47]. Because of incontinence and frequent emptying, 30% of the irradiated patients reported restrictions in social life compared to 10% of the surgery only patients [22].

No differences were seen in the quality of life between irradiated and non-irradiated patients participating in the Dutch TME trial [24]. During follow-up, the only difference seen was a lower activity level 3 months postoperatively in irradiated patients compared to surgery only patients [24].

The North Central Cancer Treatment Group randomised patients with T3 or T4 and lymph node positive rectal cancer between postoperative RT (25×1.8 Gy) or CRT (25×1.8 Gy + 5-fluorouracil)[73]. In this trial the Q-TWiST method

(quality-adjusted survival relative to time without symptoms of disease or toxicity) was used to weight the adverse effects of the adjuvant therapy against the recurrence rate and survival. The conclusion was that even though the adjuvant treatment increased the adverse effects the improved outcome in terms of delayed recurrence and increased survival balances the time spent with early and late adverse effects [73].

Fractures

Pelvic insufficiency fractures are a potential complication of pelvic irradiation but are rarely seen after RT for rectal cancer [74,75]. The long-term follow-up of the Stockholm trials [41] revealed a higher risk for femoral neck and pelvic fractures in RT patients when the Stockholm I and II trials were analysed together. The difference was not significant when the trials were analysed separately [41]. Long-term follow-up of the SRCT and the Dutch TME trial has not revealed any increased risk for fractures in the irradiated patients [20,21].

Thromboembolic disorders

Venous thromboembolism was more common in the RT group during follow-up of the Stockholm I and II trials when the trials were analysed together [41]. The increased risk was mainly seen during the first 4 months and would therefore be classed as early adverse effects. This increase in relative risk was not significant when the Stockholm studies were analysed separately [41]. A tendency toward late arteriosclerotic events was also seen in the follow-up of the Stockholm trials [38].

During long-term follow-up of the SRCT and the Dutch TME trial, no differences was seen between the treatment groups regarding venous or arterial or cardiovascular diseases [20,21].

Mortality

When the risk of non-colorectal cancer deaths, potentially caused by the additional RT, was analysed in the meta-analysis by the CCCG [1], an increased risk was also seen in irradiated patients, particularly if irradiated preoperatively. However, this increased risk was only seen during the first months after randomisation, and ascribed to increased risk of postoperative death. No increased risk of late non-colorectal cancer deaths was detected. Similarly, long-term follow-up of the SRCT did not reveal an increased death rate in irradiated patients [76].

Discussion

Late adverse effects of RT for rectal cancer needs to be evaluated carefully, as the surgical treatment itself causes dysfunctional problems that do not exist preoperatively [68]. Thus, only randomised controlled trials can provide reliable information about the late adverse effects. Due to improvements in the surgical technique and RT, and because of different radiation techniques, information on the adverse effects is not always easy to interpret [21]. Further, the addition of chemotherapy makes these relations to RT even more complex [16].

The current understanding of the late adverse effects of RT for rectal cancer is mainly based on randomised trials using short course preoperative 5x5 Gy RT [20–23,25,38,41,42]. The irradiated volumes have been reduced in the most recent trials, with a simultaneous reduction in adverse effects, as can be seen in the Dutch TME trial [20] compared to the follow-up after a comparable time of the SRCT [22] and Stockholm trials [41], particularly, the Stockholm I trial [77]. Besides some of the old trials, generally using rather low RT doses (biologically equivalent dose, BED, <20 Gy [1]), the Stockholm I trial had the largest irradiated volume [77]. It is of concern that some serious adverse effects such as bowel obstruction and second cancers appear more than 5 years from the start of the treatment, and stresses the importance of designing long-term follow-up for all randomised trials on RT for rectal cancer [21].

The aim of RT is to reduce the risk of local recurrence. The target volume of the RT generally includes the primary tumour, the mesorectal and presacral lymph nodes, the lateral lymph nodes along the obturator, medial rectal and internal iliac arteries, and, if the tumour is located in the lower part of the rectum, the nodes along the pudendal and inferior rectal arteries. The mesenteric inferior nodes and lumbar para-aortal nodes were included in the irradiated target in several of the older trials. Although these lymph nodes are at risk of containing tumour cells, these are presently excluded from the irradiated target because of an increased risk for small bowel complications. In addition, it is considered that in most cases involvement of these proximal nodes is a sign of generalized disease. The anal canal is only irradiated in low rectal cancers where an abdominoperineal rectum excision is planned [4].

The radiation technique is also relevant for the radiation burden and as a consequence the risk of adverse effects. One modification resulting in fewer adverse effects is the use of multiple beam techniques, instead of anterior-posterior beams techniques,

which were discarded because of increased postoperative mortality [78,79]. The multiple beam techniques currently used are generally 3- or 4-beam techniques and the irradiated small bowel volume does not differ substantially between the techniques [19]. The target volume is smaller than previously, when e.g. the cranial beam limit was at the second lumbar vertebra [78] and the caudal below the anal verge in all cases [12]. The reason for the higher beam limits was to reach possible metastasis in the para-aortal lymph nodes.

The effect of radiation therapy in resectable rectal cancers is to complement an incomplete resection by devitalising tumour cells that could be left during the operation. The site of local recurrences after TME are mainly located in the lower two thirds of the pelvis and probably represent tumour cell contamination from the primary tumour or metastatic lymph nodes in the mesorectum caused by incomplete mesorectal excision [80].

Bowel dysfunction is the adverse effect most frequently studied, and there is general agreement that irradiated patients have more problems with anal incontinence, urgency or evacuation than those treated with surgery only [20,22,25,40]. There are several possible reasons for increased bowel dysfunction in irradiated patients. Direct irradiation of the small bowel and the distal large intestines can cause mucosal inflammation with increased secretion and lower absorption possibilities and can result in stiffer rectal surroundings decreasing the capacity of the neo-rectum [51]. The sphincter muscles can be affected causing decreased resting pressure and difficulties in holding the faeces, and finally, the sacral and pudendal nerves or the myenteric plexus of the internal anal sphincter can be damaged causing decreased control of the bowel movements [25]. The use of anorectal manometry and anal ultrasound on patients in the Stockholm studies has revealed lower resting pressure, a trend for lower squeeze pressures of the anal sphincter, and increased scarring of the anal sphincter [25]. No differences were seen in the first sensation of rectal filling or in the maximal tolerable volume of rectal filling [25].

Lundby et al. [40] found lower maximal squeeze pressure and rectal capacity on rectal manovolumetry in patients treated with postoperative RT with 25×2 Gy than in those treated with an anterior resection only. These patients had rather high anastomoses located between 9–10 cm from the anus [40]. During anal ultrasonography, the internal anal sphincter was thinner in the RT patients, but no differences were seen in the thickness of the external anal sphincter [40].

Irradiation of the anal sphincters may not be the only cause [20], as irradiated patients from the Dutch TME trial also display increased incontinence, even though the anal sphincters are not entirely irradiated. The lower border of the beams is about 3 cm above the anal verge, excluding at least a major part of the external sphincters from the high doses. The shielding in the Dutch TME trial was also better planned than in the Stockholm trials [77,81]. Furthermore, the surgery on the patients in Stockholm trials was probably not as nerve sparing as the TME technique, as this was before the introduction of TME.

A Dutch study [59] on patients operated with TME, comparing patients treated with RT to patients treated with surgery only, reveals that the rectal compliance was reduced after TME + RT at 4 and 12 months. The result was lower rectal volumes at the thresholds for first sensation and desire to defecate compared to those treated with TME only; however, this was only observed in few patients and the follow-up time was short [59]. No differences were seen in the anal resting pressure or the maximum squeezing pressure between the groups. Unfortunately, the radiotherapy technique was not described exactly for example whether the anal sphincters were irradiated or not.

The type of the neo-rectum made, such as size or type, or whether an end-to-side anastomosis is used, also plays a role in compliance and function. An observational study [48] analysed adverse effects of RT in patients operated with a J-pouch anastomosis and treated with preoperative RT with 25 Gy in one week ($n = 22$) or 45 Gy in 5 weeks ($n = 6$) and compared this with patients treated with surgery only ($n = 97$). This study revealed differences in nocturnal defaecations and diarrhoea in favour of surgery only patients [48].

Of interest is the finding of the Dutch TME trial that patients with stoma were more satisfied with their bowel function than those without a stoma independent to whether the patients were irradiated or not [20]. This is an important observation, as a reconstruction after rectum resection should be weighted against the risk for faecal incontinence. Elderly patients, especially if irradiated, with impaired sphincter function should be given the choice of stoma even though reconstruction with low rectal anastomosis is possible.

Bowel obstruction is a complication commonly observed after pelvic surgery with RT and poses an increasing risk in several studies [21,41,42]. The reasons for this are anatomical as small bowel loops are located in the pelvis close to or within the irradiated target and sometimes receive the same dose as the tumour target. An unpublished study

(Birgisson, unpublished) with hospital records of patients with bowel obstruction, who participated in the SRCT, revealed that irradiated patients were at higher risk of being treated surgically for their bowel obstruction. The main cause of obstruction was in adhesions and not stenosis of the bowel (Birgisson, unpublished). One reason for adhesions in irradiated patients could be that the mesothelium of the visceral peritoneum is more radiosensitive than other structures and is similar in structure to vascular endothelium, which is highly radiosensitive [30].

There are several methods for decreasing irradiation of the small bowel during preoperative RT for rectal cancer [34], the most important are the use of multiple beam techniques [50] and proper shielding [19]. Individual dose planning is important for recognising the localisation of the small bowel, but if done optimally, individual treatment planning is more time consuming than the simplified techniques previously used [19]. Other methods are distension of the urinary bladder [66,82], using a prone position [83], and a belly-board technique [84,85]. More sophisticated radiation modalities such as intensity-modulated RT [82] and proton beam therapy also decrease the radiation dose to the small bowel [86].

Late urinary tract symptoms were rarely seen after rectal cancer surgery with or without RT [16,41,42,44,45].

Fractures of the pelvis and the femoral neck and thromboembolic events were more commonly seen in the long-term follow-up of the Stockholm trials [41], but these results were not be reproduced in the SRCT [21] or in the Dutch TME trial [20]. In the Dutch TME trial and in the non-Stockholm patients in the SRCT, shields covered tissues behind the lumbar vertebrae and parts of the sacrum and tissues lateral to the lower lumbar vertebrae, this was not the case in the Stockholm trials and could explain the difference.

Secondary cancers are a serious adverse effect after RT and CRT [87]. Earlier studies on secondary cancers mainly focus on younger patient groups with expected long-term survival such as patients with Hodgkin's lymphoma [88] and testicular cancer [89]. Patients with rectal cancer are generally older at diagnosis, but with increasing survival of the population, the occurrences of second cancers becomes more relevant. Currently, only one study [23] has evaluated secondary cancers due to RT for rectal cancer, and revealed a doubled risk of secondary cancer in irradiated patients mainly from organs within or adjacent to the irradiated target [23]. This is in concordance with studies on pelvic RT for gynaecological malignancies such as cervical cancer [90].

It is clear that a more individual selection of patients for RT and CRT will be needed. Especially as more patients receive RT because of the positive results from randomised trials, most recently the MRC-07 trial [5] revealed fewer local failures and improved disease free and overall survival after 5x5 Gy preoperative RT than selective postoperative CRT does.

As a result of the benefits of RT, 64% of surgically treated patients in the Uppsala/Örebro health care region of Sweden, received RT in 2003 and 69% in 2004 [91]. With about 20% of rectal cancer patients having T1N0 or T2N0 stage, it appears that most patients that will benefit from RT are treated with it. However, with the adverse effects it may be that too many patients are presently treated with RT [26]. Preoperative RT is more effective and less toxic than postoperative RT [16]; thus, preoperative staging is therefore mandatory but the reliability of the staging is still incomplete. MRI and/or endorectal ultrasound are the preferred imaging techniques [92].

Conclusions

RT for rectal cancer is effective, but has late adverse effects, small bowel obstruction and second cancers that occur long after the RT and can cause major concerns for the patients. Symptoms such as impaired anal and sexual function can have great impact on the well being of many patients. Improvements in radiation techniques appear to reduce the risk of late adverse effects, but further improvements are needed. It is expected that less adverse effects will be seen in the future, even from the treatment currently given, compared to what the trials have indicated. Even so, for the patients to gain sufficiently from the additional RT, good selection through better preoperative staging is mandatory.

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