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TOPIC HIGHLIGHT

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Neo-adjuvant radiotherapy in rectal cancer

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Abstract

In rectal cancer treatment, attention has focused on the local primary tumour and the regional tumour cell deposits to diminish the risk of a loco-regional recurrence. Several large randomized trials have also shown that combinations of surgery, radiotherapy and chemotherapy have markedly reduced the risk of a loco-regional recurrence, but this has not yet had any major influence on overall survival. The best results have been achieved when the radiotherapy has been given preoperatively. Preoperative radiotherapy improves loco-regional control even when surgery has been optimized to improve lateral clearance, *i.e.*, when a total mesorectal excision has been performed. The relative reduction is then 50%-70%. The value of radiotherapy has not been tested in combination with more extensive surgery including lateral lymph node clearance, as practised in some Asian countries. Many details about how the radiotherapy is performed are still open for discussion, and practice varies between countries. A highly fractionated radiation schedule (5 Gy × 5), proven efficacious in many trials, has gained much popularity in some countries, whereas a conventionally fractionated regimen (1.8-2.0 Gy × 25-28), often combined with chemotherapy, is used in other countries. The additional therapy adds morbidity to the morbidity that surgery causes, and should therefore be administered only when the risk of loco-regional recurrence is sufficiently high. The best integration of the weakest modality, to date the drugs (conventional cytotoxics and biologicals) is not known. A new generation of trials exploring the best sequence of treatments is required. Furthermore, there is a great need to develop predictors of response, so that treatment can be further individualized and not solely based upon clinical factors and anatomic imaging.

Key words: Chemotherapy; Chemoradiotherapy; Local control; Multidisciplinary; Organ preservation; Radiotherapy; Randomized trials; Rectal cancer

Core tip: Neo-adjuvant radiotherapy is beneficial to many rectal cancer patients since it reduces the risk of a local failure. Provided surgery is optimized, it does not substantially improve overall survival. This review describes the results of the randomized trials that form the basis for the present treatment recommendations. It also pinpoints reasons for differences in the care of rectal cancer patients seen worldwide. Finally, the concept of organ preservation is critically discussed.

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INTRODUCTION

Colorectal cancer is the third most common cancer worldwide and the second or third most common cause of cancer death. One third of the cancers arise in the rectum, the rest in the colon and most cases are adenocarcinomas. Survival has for decades been less favourable

in rectal than in colon cancer, but this is no longer the case[1-4]. Efforts to decrease rectal cancer loco-regional recurrence rates by better staging, improved surgery and incorporation of radiotherapy are the most likely reasons for the presently slightly better 5-year survival rates in rectal cancer. The local recurrence rates have also decreased from 30%-40% a few decades ago down to 5%-10% or even lower in some recent studies, and this has influenced survival in certain population-based studies. Survival still differs extensively between countries, and differences in therapy traditions are probably a major reason for this[5].

Radical removal of the primary rectal cancer, together with all regional tumour cell deposits are prerequisites for cure, although occasional local recurrences can be salvaged by (chemo)radiotherapy [(C)RT] and secondary surgery. Avoidance of persistent or recurrent tumour in the pelvis is important, even if cure cannot be achieved since uncontrolled pelvic growth is usually associated with severe symptoms. Even if overall survival is not improved, improved local control is a legitimate outcome of different interventions in rectal cancer. The primary tumour in the bowel is usually not the major problem unless it grows extensively towards organs not readily removed. In these patients, preoperative therapy with the aim of sterilizing macroscopic tumour cells in the periphery of the tumour is required. The most prevalent clinical problem is rather to eradicate the microscopic tumour cell deposits, adjacent to the primary which the surgeon does not always manage to remove with a standard surgical approach, today usually encompassing a total (or partial) mesorectal excision (TME). In Japan and other Asian countries, more extensive surgery with lateral node excision is performed in patients with high risk tumours[6], whereas in the western world, pre- or previously also postoperative (C)RT have been used to kill the subclinical tumour cells not removed by surgery. The (C)RT is then administered as adjuvant therapy after surgery, and as neo-adjuvant therapy before surgery.

An important aim is, thus, to treat so that the risk of residual disease in the pelvis is very low or preferably less than 5% in the population, in which curative treatment is intended. This should be possible in all but the few ($\leqslant$ 10%) cases, who present with a fixed tumour growing into a non-readily resectable organ. At the same time, as little acute and late morbidity as possible should be aimed at. Surgery, particularly if extensive, may give rise to substantial morbidity and the additional treatments, whether given pre- or post-operatively, increase both acute and late morbidity. Thus, all additional treatments, as well as more extensive surgery, should be given only when the expected gains are sufficiently large to motivate the increased morbidity.

This review about the value of radiotherapy to improve loco-regional control and overall survival in rectal cancer is based upon a systematic approach to the scientific literature. The available literature has been identified in several systematic overviews and meta-analyses[7-11]. It gives in addition some personal comments on observed developments during the past decades about sphincter- or organ preservation, where we lack good evidence of beneficial effects from controlled clinical trials.

Diagnosis and staging of rectal cancers

Appropriate diagnosis and staging are fundamental as regards choice of therapy. Tumours with distal extension to 15 cm or less from the anal margin (as measured by rigid sigmoidoscopy) are classified as rectal, and more proximal tumours as colonic. Others, *e.g.*, in Japan[12], prefer to separate colon and rectal cancers at the peritoneal reflection, or about 9-12 cm from the anal verge. Since the localization of the tumour in relation to other organs and structures and thus, the distance from the anal verge, is important for outcome and treatment, cancers between 10 and 15 cm are, in this author's opinion, best discussed as rectal cancers since radiotherapy (RT) is an important component of therapy, even if this is less common than for lower rectal cancers (0-10 cm)[13]. Lateral lymph node involvement is, however, rare in tumours above the peritoneal reflection[14].

Rectal MRI is recommended for staging in order to select preoperative treatment and extent of surgery, although endoscopic ultrasonography can be used for the earliest tumours[15,16]. If MRI and ultrasound are combined, a study claimed that accuracy was improved[17]. The TNM staging system should be used. At present, the latest version 7 from 2010 is preferred by most, even if it shows marked interobserver variations in defining stages Ⅱ and Ⅲ[18]. There is a need for further subclassification of clinical stage T3 (cT3) (Table 1) in order to individualize therapy, *i.e.*, to decide whether surgery alone is appropriate or whether preoperative RT alone or with chemotherapy (CRT) should be recommended.

Subdivision of rectal cancer with different therapeutic strategies

In order to define the extent of surgery and whether neo-adjuvant (or preoperative) (C)RT is required, rectal cancers can be divided into four groups, very early (some cT1), early (cT1-2, some cT3), intermediate (most cT3, some cT4) and locally advanced (some cT3, most cT4). Other factors than clinical T-stage, such as tumour height, closeness to the mesorectal fascia (mrf), potentially the circumferential margin (crm) (preoperatively, the term mrf is better than crm, since the crm cannot be defined until after surgery[19]), nodal (cN)-stage and vascular and nerve invasion are also relevant. It is not possible to precisely define which T and N sub-stages that belong to these groups. The terms "very favourable", "favourable or early or good", "intermediate or bad", and "locally advanced or ugly" can be used for categorizing the rectal cancers into these clinical subgroups. This subdivision (Table 2) is clinically relevant since primary treatment differs.

In many recent studies, the term "locally advanced" has been used for the "intermediate/bad" group, but is

Table 1 Tumor node metastasis-7 classification (2010) with subclassification of stage T3

TNM	Extension to
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Submucosa
T2	Muscularis propria
T3	Subserosa/perirectal tissue
T3a[1]	Less than 1 mm
T3b	1-5 mm
T3c	5-15 mm
T3d	15+ mm
T4	Perforation into visceral peritoneum (a) or invasion to other organs (b)
N1	1-3 regional nodes involved
N1a	1 lymph node
N1b	2-3 lymph nodes
N1c	Small deposits in the fat
N2	4 or more regional nodes involved
N2a	4-6 lymph nodes
N2b	7 or more lymph nodes
M1	Distant metastases
M1a	1 distant organ or set of lymph nodes
M1b	More than 1 organ or to the peritoneum

[1]This subclassification is based upon an evaluation using magnetic resonance imaging prior to treatment decision is clinically valuable, and recommended in this review. It can be used also in the histopathological classification but is not validated and not incorporated in TNM version 7. TNM: Tumor node metastasis.

Table 2 Subgrouping of localized rectal cancer assessed by magnetic resonance imaging[1] and the recommended primary treatment

Favourable "good" group	Intermediate "bad" group	Advanced "ugly" group
Mid/upper rectum	Mid/upper rectum	
T1-3b	T3c/d	T3 mrf positive
Low rectum T1-2, T3a	low rectum also	T4 with overgrowth
N0	includes T3b	to prostate, seminal
mrf clear	T4 with peritoneal or	vesicles, base of urinary
	vaginal involvement	bladder, pelvic side walls
	only	or floor, sacrum positive
	N1/N2	lateral lymph nodes
	mrf clear	
5 yr LFR[2] < 10%	5 yr LFR[2] 10%-20%	5 yr LFR[2] 20%-100%
5 yr DFR[3] < 15%	5 yr DFR[3] 15%-60%	5 yr DFR 30%-80%
Primary surgery	Preop 5 × 5 Gy with	Preop CRT or 5 × 5 Gy
(TME)[4]	immediate surgery[5]	with delayed surgery[6]

[1]The algorithm (modified from[102] with permission from the publisher Informa) does not primarily address the risk of systemic disease, although this risk also increases with the presence of many of "the risk factors"; however, not necessarily parallel to the local failure rate (LFR). The algorithm is also "too simplified", in that a other factors like size of the mesorectum, anterior or posterior location, extramural vascular invasion (EMVI+) are also relevant. [2]Calculated in the group of patients planned for surgery, *i.e.*, irrespective of the surgical outcome. The table are valid if the surgeon is an experienced rectal cancer surgeon and no pre-treatment is given. [3]The 5-year risk of distant failure (DFR) is also given, although this risk is not well established. Risk factors detectable on magnetic resonance imaging for distant failure are N2 (versus N0 and N1), EMVI+, mrf+ and all T4 (a and b, see Table 1). These are also the risk factors used in the ongoing trial[88], where patients at high risk failing systemically are included. [4]A local procedure is possible in a few patients [chiefly pT1, sm1 (+ 2), N0]. This group is in the text referred to as "very favourable". [5]Preoperative chemotherapy (CRT) is also a valid option according to international clinical guidelines[21]. [6]CRT means chemoradiotherapy to 50.4 Gy in 1.8 Gy fractions with 5-fluorouracil (capecitabine). 5 × 5 Gy with delayed surgery should be used only in patients not fit for CRT.

best reserved for the truly "locally advanced/ugly" tumours[9,13,20]. Even if there is variability in what is called locally advanced there is consensus about the need to subgroup along these lines[13,21,22]. Subgrouping is an important step towards individualized therapy. Major discrepancies do, however, exist as regards which treatment is selected for these subgroups (Table 2).

Different treatment principles in the world

There is marked difference in how the subclinical tumour deposits often seen in tumours below the peritoneal reflection are managed in Asia and in the rest of the world. Surgical removal of the lateral nodes on one or both sides has been the preferred option in Asia[6,23], whereas the rest of the world has explored the value of radiation, in addition to surgery for the primary tumour in the bowel, to kill the tumour deposits. Since radiation does not selectively irradiate the lateral nodes, but also includes the primary tumour and the mesorectal nodes, the need for a meticulous surgical dissection technique has not been the same in the Western world as in Asia. Both extensive surgery and additional radiotherapy increase morbidity. It is not known which of the two alternatives is most efficient in eradicating all tumour cells, *i.e.*, preventing a local failure and which alternative results in the least morbidity since no randomized studies have compared the two strategies. Inter-trial comparisons have reported that the results are similar at specialized centres[24]. It is, however, probably more efficient to remove all subclinical cancer deposits using radiation rather than surgery, unless one can dissect in a surgical plane. The morbidity caused by extensive surgery is very different from that caused by external RT and less extensive surgery, although the relevance of this on patient well-being differs between cultures.

In the Western world, preoperative RT was mainly explored in Europe whereas postoperative RT was explored in the US. A few small studies showed that postoperative CRT was better than postoperative RT in preventing local recurrence and that combined treatment was more effective than surgery alone. A NIH Consensus Conference and a subsequent NCI report in the early 1990s stated that postoperative CRT should be standard treatment in rectal cancer stages Ⅱ and Ⅲ[25,26].

In Europe, several randomized trials compared surgery alone versus preoperative RT and surgery. These studies showed a relative reduction in local failure rates of 50%-60% if the radiation dose was moderately high (Table 3). If the radiation dose was lower, corresponding to a biologically effective dose (BED) below 30 Gy[7], no or a more limited effect was shown. As a consequence, preoperative RT was recommended as routine therapy in many European countries[13](Table 3).

Table 3 Major randomized radiotherapy trials in primary rectal cancer[1]

Study	Inclusion time	No of patients	Treatments			Radiation technique[2]	Increased postop death	Local recurrence			Increased survival	Comments
			Surgery alone	Preop (C)RT	Postop (C)RT			Surgery alone	Preop RT + surgery	Postop RT		
Pre-TME era												
MRC1[91]	1975-78	824	Yes	5 Gy × 1 2 Gy × 10		AP-PA	No	43%	45% 47%		No	Very low radiation dose, no benefit
EORTC[92]	1976-81	466	Yes	2,3 Gy × 15		AP-PA	No	28%	14%[1]		No	Decreased local recurrence risk
Bergen[93]	1976-85	169	Yes	1.75 Gy × 18		AP-PA	No	24%	17%		No	Marginally decreased local recurrence risk, comparably low dose
Stockholm Ⅰ[94]	1980-87	849	Yes	5 Gy × 5		AP-PA	Yes	28%	14%[2]	-	No	Increased postop death (8% *vs* 2%), large target, suboptimal technique, decreased local recurrence risk. Increased risk late complications
Uppsala[95]	1980-85	471	-	5.1 Gy × 5	2 Gy × 30	3D-C on RT	No	-	13%[1]	22%	No	Preop 5 Gy × 5 is better than postop RT (60 Gy). Increased risk of late complications after postop RT
S:t Marks[96]	1980-84	395	Yes	5 Gy × 3		AP-PA	Yes	24%	17%		No	Increased postop death (9% *vs* 4%)
MRC2[97]	1981-89	279	Yes	2 Gy × 20		AP-PA	No	46%	36%[1]		No	Slightly reduced risk of local failure, tendency to improved survival (HR = 0.79, 95%CI: 0.6-1.04)
North-West[98]	1982-86	284	Yes	5 Gy × 4		3D-C on RT	No	41%	18%[3]		No	Decreased local recurrence risk, 10 x 10 cm beams
SRCT[53,55]	1987-90	1110	Yes	5 Gy × 5		3D-C on RT	No	27%	12%[3]	-	Yes	Decreased local recurrence risk, no increased acute toxicity, some late toxicity after 10-15 yr
Stockholm Ⅱ[99]	1987-93	557	Yes	5 Gy × 5		3D-RT	Yes	25%	12%[3]	-	Yes	Overlaps to a large part SRCT, simplified radiation technique, tendency to increased postop mortality (4% *vs* 1%). Lower local recurrence risk, increased survival as in SRCT. Increased risk of late complications
Post-TME era												
EORTC 22921[38]	1993-03	1011	-	RT CRT[3]	RT CRT	3D-C on RT	No		17% 9%[2]		No	2 × 2 design, chemotherapy in addition to RT gives fewer local recurrences as first event than RT alone irrespective of whether concomitant (9%) or postoperative (10%), or both (8%), increased toxicity, no increased survival
FFCD 9203[37]	1993-03	742	-	RT CRT		3D-C on RT	No		17% 8%[1]		No	Preop CRT results in fewer local recurrences than preop RT, increased toxicity, no survival difference
AIO-94[30,100]	1995-02	823	-	CRT	CRT	3D-C on RT	No		6%[2]	13%	No	Preop CRT is less toxic and gives fewer local recurrences than postop CRT, no difference in survival
TME[54,101]	1996-99	1861	Yes	5 Gy × 5		3D-C on RT	No	11%	5%[3]		No	No increased postop mortality. Decreased local recurrence risk even with TME, no improved survival, some risk of increased late complications after 5-10 yr
LARCS[39]	1998-03	207	-	RT CRT		3D-C on RT	No		33% 18%[1]		Yes	The only study in "ugly" rectal cancers, preop CRT gives better local control and better disease and cancer specific survival, tendency towards better survival (66% *vs* 53% after 5 yr). Increased acute and possibly late toxicity from CRT
MRC-CR07[31]	1998-05	1350	-	5 Gy × 5	CRT if CRM+	3D-C on RT	No		5%[2]	11%	Yes	Preop 5 Gy × 5 better than postop CRT if CRM+, marginally increased survival. No increase in late complications (3-5 yr)

Polish[33]	1999-02	312	-	5 Gy × 5 CRT	3D-C on RT	No	11% 16%	No	First study that shows less risk of acute toxicity from 5 × 5 compared with preop CRT, no difference in local recurrence and survival or late complications (3-5 yr)
TROG[34]	2001-06	326	-	5 Gy × 5 CRT	3D-C on RT	No	7% 4%	No	Same design as the Polish study, same results

[1]Only large studies of relevance for present treatment recommendations are included. Patients with tumours considered to be resectable were included in all studies but one (LARCS). Staging has varied considerably over the years, but most included patients belonged to the intermediate group (bad) except in the LARCS study where most tumours were locally advanced (ugly). [2]AP-PA, anterior posterior beams with no blocking, meaning high radiation doses to large normal tissue volumes, 3D-CRT, 3D-conformed radiotherapy, 3 or 4 beams with blocking of normal tissues that did not contain tumour cells. 3D-RT (in the Stockholm Ⅱ study) means 4 beams but no blocking. [3]CRT means chemoradiotherapy with 1.8-2 Gy daily to 45-50.4 Gy. RT means the same radiotherapy as in the CRT arm without chemotherapy. [a]$P < 0.05$, [b]$P < 0.01$, [c]$P < 0.001$. TME: Total (or partial) mesorectal excision; CRT: Chemotherapy.

How is the radiotherapy best given?

For about two decades, four questions have been particularly discussed, *viz*. (1) should the RT be given before or after surgery; (2) should it be long-course or short-course; (3) should the long-course RT be given alone or with chemotherapy? In Europe researchers were not universally convinced of the advantages of adding concomitant chemotherapy considering the increased toxicity[27], as stated in the US documents. Furthermore; (4) could sphincter-saving surgery be increased after preoperative CRT? More recently, a fifth question; and (5) has attracted much interest, *viz*. if it is possible to avoid major surgery, *i.e.*, to preserve the organ, in patients who respond well to the preoperative CRT.

Pre- or postoperative radiotherapy?

A randomized trial showed at an early stage that preoperative short-course RT (5 fractions of 5 Gy in one week) was more effective and less toxic than postoperative long-course RT (Table 3). In the trial[28,29], significantly fewer local recurrences (13% *vs* 22%, $P < 0.05$) was seen in the group of patients randomized to the brief preoperative schedule than to an "optimized" postoperative schedule (high total radiation dose, 60 Gy in 7-8 wk, only given to high risk groups, stages Ⅱ + Ⅲ). Subsequently, several trials comparing preoperative CRT with postoperative CRT were initiated. The only completed trial[30] again showed that preoperative therapy was more efficient and less toxic than postoperative. In the trial, fewer local recurrences (6% *vs* 13%, $P < 0.01$) were seen in the group receiving preoperative CRT (Table 3). The preoperative treatment was also less toxic. No difference in survival was detected. Superiority of preoperative short-course RT over postoperative CRT was also shown in the MRC-CR07-trial; local recurrences were less commonly seen in the preoperatively irradiated group (5% *vs* 11%, $P < 0.01$)[31]. Most of the world has now accepted that additional (C)RT in rectal cancer should be given before, *i.e.*, neo-adjuvant, rather than after surgery. An analysis of data from the randomized studies also indicated that preoperative RT is more dose-efficient than postoperative RT[32].

Short- or long-course radiotherapy?

The question of whether the preoperative RT is best given as a short-course (5 Gy × 5) schedule or as long-course conventionally fractionated RT (1.8-2.0 Gy × 25-28) has been ongoing since the first results of the Uppsala trial were published in 1985[28], and the matter has not yet been settled. The potential advantages and disadvantages of the two fractionation schedules are presented in Table 4. The most recent RT trial in rectal cancer in Sweden, the Stockholm Ⅲ trial recently closed patient entry (Jan 2013). It has compared the different fractionation schedules in 845 patients randomized to either 5 Gy × 5 with immediate surgery, 5 Gy × 5 with delayed (4-8 wk) surgery and 2 Gy × 25, likewise with delayed surgery. Results of the primary outcome, local recurrences, will be available in 2015. Two other trials including 316 and 326 patients, respectively, could not find any differences in local recurrence rates, disease-free (DFS) and overall survival (OS) between the groups randomized to short-course RT alone or long-course CRT[33,34]. A German trial[35] with a similar design was initiated in 2004. No data has yet been released.

The short-course schedule has gained much popularity in Northern European countries where the health care system is rarely dependent upon private initiatives, whereas the long-course schedule is preferred in countries where physician and hospital budgets are influenced by the number of treatments given. Reimbursement has thus influenced routines, although this is seldom officially admitted. Many concerns have been expressed about the long-term consequences of hypofractionated RT. There is considerable evidence that the short-course schedule results in long-term morbidity, and the scale of that morbidity is well known[36]. The long-term morbidity of CRT, whether given pre- or

Table 4 Main differences between and potential advantages of short-course and long-course preoperative radiotherapy in intermediate (bad) rectal cancers[1]

	Short-course	Long-course
Total (physical) radiation dose	25 Gy	45-50.4 Gy
Fraction size/number of fractions	5 Gy/5	1.8-2 Gy/23-28
Radiation duration	1 wk	4.5-5.5 wk
BED[2], acute effects	37.5 Gy	37.5-44.4 Gy
BED[2], late effects	66.7	72-84 Gy
Overall treatment time	About 10 d	10-14 wk
Demands of radiation resources	Planning + 5 fractions	Planning + 23-28 fractions
Concomitant chemotherapy[3]	No	Yes
Acute toxicity	Minimal	More
Late toxicity	Present, considered limited in the "bad" group	Present, but not extensively studied. Anticipated to be higher than after short-course
Down-sizing/down-staging	No[4]	Yes[5]

[1]In locally advanced (ugly) tumours, long-course CRT is the preferred option although short-course RT with a delay to surgery is an option if CRT is not tolerated because of high age or co-morbidity; [2]Biologically effective dose according to the time-corrected linear quadratic model. Major uncertainties exist in the relative biological efficacy of the fractionation schedules concerning the acute, antitumour effects. The parameters selected for the acute effects were those used in the meta-analyses from 2001[7], even if they can be criticized and probably are incorrect. For late effects, an α/β of 3 Gy with no time correction is used. The anticipated antitumour effects do not thus differ substantially and late toxicity is at least not higher with short-course RT; [3]Improved local control with long-course RT, increased acute toxicity and probably also late toxicity. Should not be given with short-course RT; [4]Seen after short-course RT with delayed surgery; [5]Not relevant in these intermediate tumours (unless organ-preservation is aimed at), however, relevant in locally advanced (ugly) tumours. BED: Biologically effective dose.

postoperatively has not been studied systematically with the result that the extent of late morbidity is not precisely known. Both options, short-course 5 Gy × 5 and long-course CRT are considered valid in the intermediate group of rectal cancers, according to recent clinical guidelines[13,21]. The demands of radiation resources and the acute toxicity are much higher using long-course CRT than using short-course 5 Gy × 5. It is possible to conclude from the randomized trials that they have similar efficacy and do not differ in the risk of late toxicity; therefore, it is surprising to this author that they are considered equally valid (Table 4).

Radiotherapy alone or with chemotherapy?

Three randomized trials, two in the intermediate group[37,38] and one in the locally advanced, ugly group[39], have provided an answer to the third question. Local control was better in the combined treatment arm in all three studies, whereas a significant survival gain was only seen in the trial including locally advanced cancers[9,39]. Whenever a patient with a locally advanced, ugly rectal cancer receives preoperative treatment, CRT should be used unless the patient cannot tolerate this treatment. It should, however, be recognized that the gains from the chemotherapy addition are rather limited and come with a rather high price with significantly increased acute toxicity[11], and in all probability also increased late toxicity (see below).

The drug most extensively used to sensitize the RT has been 5-fluorouracil (5-FU), although oral capecitabine gives the same potentiation of the effects, and is more convenient[40]. Other oral fluoropyrimidines such as UFT[41,42] have also been explored, but have not yet been the subject of randomized trials. Combinations of 5-FU and other cytotoxic drugs such as oxaliplatin and irinotecan, and targeted drugs, have been extensively explored during the past decade. Multiple phase Ⅱ studies in so-called "locally advanced rectal cancer" have claimed superior results [more down-sizing, higher pathological complete (pCR) rates]. It is likely that these apparently favourable results depend upon the inclusion of mainly early or intermediate cancers. Five large randomized trials have failed to show any superior results from the addition of oxaliplatin[43-47]. When cetuximab was added to CRT with capecitabine and neo-adjuvant chemotherapy with capecitabine-oxaliplatin in a randomized phase Ⅱ study, the primary endpoint, pCR rate, was not increased, but more radiological responses (89% *vs* 72%, $P = 0.002$) and improved OS (96% *vs* 81% at 3 years, $P = 0.04$) were seen in the KRAS wild-type population ($n = 90$)[48]. These results need confirmation.

Sphincter preservation, organ preservation

Trials, again chiefly run in Europe, have explored whether long-course (C)RT with a delay before surgery could increase sphincter preservation rates, whereas others took it for granted that this was the case. The trials could not show that this occurred to any meaningful extent[49]. The hopes about improved chances of sphincter saving influenced routines in many countries, particularly in Southern Europe, Germany and the United States. At present, hopes about organ preservation (see below) influence treatment decisions at many centres.

TREATMENT ACCORDING TO RISK GROUP

Very favourable rectal cancer

In the earliest rectal cancers, chiefly the malignant polyps [Haggitt 1-3, T1 sm 1(-2?) N0], a local procedure, *e.g.*, using the transanal endoscopic microsurgery (TEM) technique, is sufficient for cure[50,51]. If the resection is not radical (R0), there are signs of vessel invasion, poor differentiation or if the tumour infiltrates more deeply into the submucosa (Haggit 4, T1) or is a T2 tumour, the risk of recurrence is too high (≥ 10%) and the patient should be recommended postoperative CRT or, more safely, major (TME) surgery. If the cancer diagnosis is biopsy-verified, presurgical CRT is preferred if the intent is to perform a local procedure[50]. As an alternative to local surgery, alone or with CRT, local RT (brachytherapy

or contact therapy using the Papillon technique) can be used. Experience of these treatments is limited outside specialized centres[52] and more prospective studies are required before they could be a part of clinical routines.

Favourable, "good" rectal cancers

In these cases cT1-2, some early cT3, N0 [cT3a(-b) and clear mrf (mrf-) according to MRI], "good" group, surgery alone using the TME technique is appropriate, since the risk of local failure is low unless the tumour is at the level of the levators[13]. Although the large randomized trials have indicated that short-course RT even further reduces local recurrence rates[31,53,54], surgery alone is recommended since the addition of preoperative RT results in overtreatment of too many individuals[13].

Intermediate, "bad" rectal cancers

In this group most cT3 [cT3(b)c+ without threatened or involved mrf (mrf-) according to MRI], some cT4 (*e.g.*, vaginal or peritoneal involvement only, N+), preoperative RT is recommended since the risk of local failure is not negligible (> 8%-10%), even if proper surgery is performed. Even in the absence of signs of extramural growth on ultrasound or MRI (cT2) in very low tumours (0-5 cm), preoperative RT may be indicated because the distance to the mrf or the levator muscles is very small. Surgery alone, often an abdomino-perineal excision, will then again result in unacceptably high local recurrence rates. Twenty-five Gy delivered during one week and followed by immediate surgery (< 10 d from the first radiation fraction) has in randomized trials reduced the risk of local failure by 50%-70% *vs* surgery alone[31,53-55]. The relative efficacy is likely to be the same irrespective of tumour height, although this was not seen in the TME trial[54]. CRT to 46-50.4 Gy, 1.8-2.0 Gy/fraction with 5-FU (bolus, continuous infusion or peroral) is an alternative, although it is more demanding and not proven to be more effective[33,34,37,38]. CRT is preferred in low rectal cancers even at centres that otherwise use 5 Gy × 5. It must be stressed that RT (or CRT) cannot compensate for poor surgery. Surgery should aim at clear resection margins (crm-); therefore, in low rectal cancers requiring an abdomino-perineal excision, it is important to do the dissection so that a "waist" is avoided. As described above, two European trials[37,38] showed that the addition of 5-FU improved local control with a reduced risk of local failure as first event. After 5 years these were 17% in the preoperative RT arms alone and 8%-9% in the CRT arms. In the EORTC trial, the same reduction was seen whether the chemotherapy was administered concomitantly with the RT, only postoperatively or both pre- and postoperatively. Two randomized trials (Polish, TROG 1.04) could not detect any statistically significant differences in local recurrence rates, DFS and OS after preoperative 5 × 5 Gy or preoperative CRT (5-FU + 50.4 Gy)[33,34]. In the TROG study, numerically more recurrences were seen in the group randomized to 5 Gy × 5 (6/48 *vs* 1/31, P = 0.21)[34]. In the MRC-CR07-trial including 1350 patients, preoperative 5 × 5 Gy was randomly compared with postoperative CRT if the crm was positive. Local recurrence rates favoured the preoperative arm (5% *vs* 17%, $P < 0.001$)[31]. DFS was also superior in the preoperative arm (HR = 0.76, $P = 0.01$) whereas OS did not differ significantly (HR = 0.91, $P = 0.04$).

Locally advanced, "ugly" rectal cancers

In the locally advanced, frequently non-resectable cases [cT3 mrf+, cT4 with overgrowth to other organs (cT4b)], preoperative CRT, 50.4 Gy, 1.8 Gy/fraction with concomitant 5-FU-based therapy should be used[9,13,39], followed by radical surgery 6-8 wk later. In a Nordic randomized trial (cT4NXM0), local control was significantly better after 5 years in the CRT arm (5-FU + 50 Gy) than in the RT only arm (82% *vs* 67%, $P = 0.03$). Also DFS and cancer-specific survival were significantly better in the combined modality arm, whereas OS did not differ significantly (66% *vs* 53%, $P = 0.09$)[39].

In very old patients (≥ 80-85 years) and in patients not fit for CRT, 5 × 5 Gy with a delay of approximately 8 wk before surgery is an alternative option, based upon three retrospectively analyzed patient series revealing favourable results[56-58]. A randomized trial will in all probability never be performed in this patient group, which is not considered to tolerate standard therapy.

Organ preservation?

Apart from the earliest tumours that can be treated with a local procedure or local RT, as described above, it has become increasingly popular to give CRT, then wait and restage the tumour[59-62]. If no signs of remaining tumour/no viable tumour cells are found when biopsies are performed, major surgery is not performed and the patient is monitored closely for at least 5 years. The hypothesis is that potential lymph node metastases have been eradicated parallel with the response of the primary tumour. Although this occurs in some patients, this strategy has not been the subject of properly controlled prospective studies. This excellent response will not be frequent in the intermediate and locally advanced cases[63,64], but only in early cases. The cell kill effect of available CRT schedules is too small.

No major surgery and no rectal excision in very low tumours can be clearly beneficial for individuals who run a high risk of surgical therapy or who cannot accept a stoma. However, the disadvantages for many patients are seldom discussed. In most patients with an early rectal cancer, a low anterior resection alone is the reference treatment. Cure rates are high and morbidity is only a result of the surgery. If these patients are treated with the aim of organ preservation, all will receive CRT with its acute morbidity. Patients who respond with a clinical complete remission (cCR), and are not operated are the ones potentially having a benefit of a wait-and-see approach, although they will all suffer from the long-term toxicity that can be seen after CRT. If the tumour is located in the lower rectum, at least part of the sphincters

must be included in the irradiated volume, and suboptimal anal function can be a result. Those who do not achieve a cCR or those who recur during follow-up will require major surgery. These patients will thus suffer the morbidity from both CRT and major surgery. It is presently not possible to know the proportion of patients who do not require major surgery. With the CRT schedules available today, the group of patients having a true advantage is most probably much smaller than the group of patients who suffer extra morbidity.

Radiation therapy volumes and doses

In the "intermediate/bad" group, with the aim of lowering the risk of local failure, the primary tumour with the mesorectum and lymph nodes outside the mesorectum, at risk to contain tumour cells more than exceptionally should be irradiated[65,66]. In the "early/good" group before or after a local procedure, only mesorectal nodes are at sufficient risk to be involved. The appropriate dose to subclinical disease should with 5-FU chemotherapy be at least 45 Gy in 1.8-2.0 Gy fractions. The relative reduction in local failure rates is then in the order of 50%-60%, and subsequently there is room for improvement. A boost of about 4-6 Gy in 2-4 fractions to the primary tumour is sometimes given[67]. A brachytherapy boost has also been tried; however, without any apparent advantage[68]. The clinical problem is not the primary tumour in the bowel, unless you aim at organ preservation (see above).

In the "locally advanced/ugly" tumours, the target is basically the same as in the intermediate group, although the primary tumour extends more laterally and more lymph nodes can be at risk. In these patients, a lateral boost to areas where it can be difficult to surgically remove all cells can be indicated[69]. It is not primarily motivated to boost the centre of the tumour, *e.g.*, where the PET-uptake is the highest, if this can surgically be removed.

The entire mesorectum is in most cases at great risk of having tumour deposits and should be included in the clinical target volume (CTV). In high tumours it is sufficient to include the 4 cm distal to the tumour. Besides the mesorectal nodes, the presacral nodes up to the level of S1-2 should be included in CTV. If presacral nodes are radiologically involved, the upper border of CTV should be even higher. Local recurrences above S1-2 are infrequent[70-72]. The lateral nodes, including the internal iliac nodes up to the bifurcation of the common iliac arteries should be included in tumours below the peritoneal reflection, *i.e.*, in tumours up to about 9-12 cm from the anal verge[73]. The risk of lateral node involvement in the Western world is not precisely known, but studies from Asia show that these lymph nodes are rarely involved in low-mid rectal pT1-2 tumours and in high tumours irrespective of T-stage[14,74]. External iliac nodes should only be included if an anterior organ such as the urinary bladder, prostate or female sexual organs are involved. The medial inguinal nodes need only to be prophylactically included when the tumour grows below the dentate line[75].

The ischiorectal fossae should be included only when the levator muscles and the internal and external sphincters are involved. The fascia inside the levators is considered to be a strong barrier to tumour cell penetration[76]. Other opinions have been expressed[65].

Late toxicity from rectal cancer radiotherapy

The prevention of a local failure with the severe morbidity this may have must be weighed against the morbidity from (C)RT that all treated patients can develop. From the Swedish and Dutch randomized trials, the morbidity after 5 × 5 Gy RT is well described and reviewed in[36]. Increased risks of poor anal and sexual function, small bowel toxicity with obstruction and secondary malignancies have been reported. Studies have tried to estimate what minimal absolute gain should be present for patients to prefer RT. These studies are difficult to interpret, although many patients accept an absolute 3% difference in local recurrence risk for the known morbidity risks of RT[77].

After having treated rectal cancer patients for over 30 years, and thus, seeing many patients with a local recurrence during the first part of the period, and being actively involved in research aimed at estimating the extent of late toxicity up to 20 years after the RT, it is my opinion that an absolute risk reduction of approximately 5% motivates the recommendation to irradiate. The recommendations given above, as well as in recent consensus statements[13,21] reflect this opinion. Furthermore, and very importantly, the RT we give today, and the RT that routinely can be given in only a few years[66,78,79], will mean even less late toxicity than that seen in the follow-up studies of the RT deli vered during the 1980s-1990s. Better understanding of internal movements will also allow more precise delivery of the radiation dose[80] and of dose-response relationships for *e.g.*, faecal incontinence[81].

An important question is the late toxicity from 5 × 5 Gy compared with the late toxicity seen after 46-50 Gy in 25-28 fractions, usually administered with 5-FU. The long-term morbidity from 5 Gy × 5 up to at least 10 years follow-up (with yesterday's techniques) is known from studies including thousands of patients. This knowledge is not as solid from CRT. The Polish[33] and the MRC-CR07 trials[31] could not detect any differences between 5 × 5 Gy and CRT to 46-50 Gy after 4 years of follow-up. The short-course schedule uses a high fraction size of 5 Gy, compared with 1.8-2.0 Gy, whereas the total dose is less (25 Gy compared to 46-50 Gy). Both the fraction size and the total dose are relevant. The relationship between total dose, fraction size and late toxicity is, however, complex.

Another question is whether the addition of 5-FU increases late toxicity. In one of the two larger randomized trials in the intermediate risk group[37,38], the addition of 5-FU negatively affected global QoL, social functioning and diarrhoea. Almost 60% of the patients suffered from faecal incontinence, impairing their social life[82]. In the trial in locally advanced/ugly cancers, more patients

had a stoma or a poor anal function in the CRT group than in the RT group (89% *vs* 70%, $P = 0.046$)[83]. If this means that the addition of chemotherapy results in more late toxicity or if this difference reflects the survival of patients with more advanced tumours in the CRT group cannot be deduced. No differences in QoL were seen after 4-8 years[84].

CONCLUSION

During the past three decades, a severely disabling condition for many rectal cancer patients, viz a local failure with uncontrolled growth of the cancer in the perineum and pelvis has disappeared, although, unfortunately, not yet at all centres. Multiple trials have confirmed the superiority of what can presently be considered as recommended care and treatment (Table 2). A multidisciplinary approach has been a must in this development, at present formalized as (weekly) multidisciplinary team (MDT) meetings, during which all patients are discussed before the first treatment decision, postoperatively, and at critical time points during the course of the disease. Many countries have successfully launched quality assurance and quality control programmes in rectal cancer surgery[85,86]. It is important that, besides surgical details, RT and CRT details are also fully integrated in the programmes.

Practically all details in the care of the patients have been the subject of prospective, frequently randomized trials. It should, however, also be recognized that many uncertainties about what is the best treatment still exist. Furthermore, alternative approaches to attain low local failure rates and improved survival together with as little negative consequences from the disease and its treatment as possible, also exist.

The trials have repeatedly shown that RT, whether alone or with chemotherapy, should be given before surgery to have the best efficacy and least toxicity. This was shown as early as 1985, but is only recently unanimously agreed upon. It is also a belief that systemic treatment, being the weakest part of the therapy, should be given before and not after the surgery in order to have greatest efficacy. Progression of the local primary should then not occur during the systemic treatment, presently requiring a duration of 5-6 mo. The discovery that the short-course schedule results in substantial down-staging, is tolerable and permits full chemotherapy starting soon after the RT[56,87], has led to the next generation of studies, such as the multicentre "RAPIDO" trial[88]. Patients with ugly rectal cancers at high risk to recur are randomized to the present standard, CRT, surgery and adjuvant chemotherapy (even if not all consider this standard[89]) and an experimental arm with 5 × 5 Gy, neo-adjuvant chemotherapy and surgery at the end. A Polish study, likewise in locally advanced, unresectable rectal cancer, with a similar design is also ongoing[90]. In an interim analysis after 97 randomized patients, no major differences in acute toxicity and local efficacy were seen between the control group receiving CRT (50.4 Gy with 5-FU/FA/oxaliplatin) and the experimental group (5 × 5 Gy followed by 3 FOLFOX-4 cycles preoperatively). No postoperative therapy is scheduled.

During the past 30 years, a better understanding of the molecular mechanisms involved in tumour development and progression has placed great expectations on improved diagnosis, staging, prognostic evaluation and selection of the individually best therapy. Much new and valuable information has been created, but no new clinically valuable markers have been identified. The number of mm's from the most peripheral part of the rectal tumour to the mrf (or crm postoperatively) is most informative. No predictor of which pre- (or post-)operative treatment to choose is available. The efforts to translate basic knowledge into clinically useful information must be intensified or explored along other paths. Sampling of representative and sufficient tumour material for diagnosis and research prior to, during and after therapy may help. Functional imaging showing where to sample, may be helpful. We need predictors and must find better ways of identifying them than has been possible in the past.

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