Radiotherapy in rectal cancer: technical aspects and regimens

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Introduction

Rectal cancer presentation differs greatly at diagnosis and this influences both prognosis and treatment choices. It varies according to the extension of the tumor through the rectal wall in the mesorectum, the presence of involved lymph nodes inside and outside the mesorectum, its location in the rectum, whether stenosis and/or perforation are present, the histological type and grade, and the presence of distant metastases.

During the past decades a broad spectrum of treatment modalities have been examined such as postoperative chemoradiotherapy with different 5-fluorouracil (5FU)-based schedules, preoperative radiotherapy short course (5 Gy in 5 days), long course (alone or in combination with 5FU-based regimens or with new drugs), and intraoperative radiotherapy (IORT) in primary disease, and combinations of new drugs in metastatic disease. These modalities are used differently in different parts of Europe and in North America, even if based upon the same evidence from the studies performed in different parts of the world.

The aims of this manuscript are to review the best evidence in the literature, focusing on the main advantages that a particular approach promotes for the different presentations of rectal cancer.

Radiotherapy efficacy background and technique

Radiotherapy is given to the bulky primary tumor, to the positive nodes, and/or to the subclinical pelvic deposits, trying to promote R0 resectability, downstaging and downsizing or to prevent recurrence in the tissues beyond the ' future' or ' actual' surgical margins, respectively.

Gross disease represents tumors of approximately 10^{9-12} clonogens and subclinical tumor deposits are frequently assumed to have an amount of cells in the order of 10^6 or 10^7 cells (between 10^0 and about 10^8). The dose which allows a 10-fold reduction in the number of tumor cells (D_{10}) is around 7 Gy at 2 Gy per fraction [1–4]. Therefore, a dose between 45 and 50 Gy at 2 Gy is considered adequate to control subclinical disease. In order to control bulky tumors the dose must be higher and this is deeply affected by the tolerance of pelvic organs. In resectable patients the main goal is to sterilize the surgical margins and the tissues at risk for subclinical disease outside them, or to increase sphincter saving rates by tumor downsizing in low laying tumours. Thus, no dose higher than 50 Gy is needed, whereas in unresectable or recurrent tumors the goal is to promote R0 resectability and a higher dose is required. Also in R2 postoperative patients, where the goal is to achieve long-term control, higher doses are required. In the preoperative setting, a meta-analysis concluded that biologically effective doses above 30 Gy resulted in a statistically significant reduction in local-regional recurrences [5].

Furthermore, it is known that changes in the biologically effective dose are related to the overall treatment duration and the fraction size. Rectal cancer is considered to have a very long growing time [6,7], but retrospective analyses of rectal cancer trials show that the growth rate for subclinical tumor deposits has an average doubling time for microscopic foci not longer than 14 days and could be as short as 4 days, and also that the tumor control probability curves for local control were shifted to higher doses as the overall duration of the preoperative radiation therapy was increased [8]. Short-course large daily fractionations (5 Gy/day, 5 days) should not be affected by repopulation. The biological effects of such a fractionation according to the linear-quadratic (LQ) model is equivalent to 37.5 Gy in 2 Gy fractions [9, 10].

A prolonged interval before surgery using preoperative long-course approach could raise some concerns regarding the probability that metastases may develop in the meantime. Withers and Haustermans [11] reported that about 80% of patients with no lymph node metastases will be free of metastases, even when

the primary tumor is large enough to penetrate the full thickness of the bowel wall. It seems that a mass containing about 10^9 or 10^{10} malignant cells, is needed before metastatic dissemination begins. The probability of metastases from a tumor with a volume 10 times smaller (e.g. 10^8 cells) should be low (e.g. 1%), and rare from a mass 100 times smaller (10^7 cells). Irradiation quickly reduces the number of viable tumor clonogens available for metastasis: 1 or 2 D_{10} (D_{10} = 7 Gy using 2 Gy per fraction) reduce clonogen numbers 10-fold and 100-fold, respectively. Thus, it seems reasonable to assume that preoperative radiotherapy can quickly eliminate any concerns regarding the development of new micrometastases during radiation therapy or in the interval between irradiation and surgery, even if heterogeneity in patient and tumor characteristics may impair the use of a simple proportionality between the number of clonogens and the metastatic process [12].

It is not easy to evaluate the role of concomitant chemotherapy in enhancing the ' actual meaning' of the radiation dose. A 20% reduction in the incidence of metastases by chemotherapy would reflect the elimination of all micrometastases containing less than 10^2–10^3 clonogenic cells, a situation that may exist in about 20% of the patients who harbor subclinical metastases [11]. Thus, it could be assumed that the contribution to the radiation dose could be in the range of 2–3 D_{10}; but, the mechanisms by which conventional chemotherapeutic agents produce radiosensitization remain largely unknown. 5FU has been used extensively with radiation [13]. 5FU has both DNA-directed (through the inhibition of thymidylate synthase) and RNA-directed (through incorporation into the 3 species of RNA) effects, and radiosensitization is mainly a result of inhibition of thymidylate synthase. The main mechanisms by which 5FU could increase radiation sensitivity is through the killing of S phase cells, which are relatively radioresistant [14]. Radiosensitization increases when the cells have inappropriate progression through the S phase in the presence of drug, from a disordered S-phase checkpoint. It seems that the crucial events producing sensitization occur after the classic G1 checkpoint in the cell cycle, which is consistent with the lack of dependence on p53 [15]. Radiosensitization under non-cytotoxic conditions occurs only when cells are incubated with drug before radiation, and many clinical and laboratory studies have suggested that 5FU should be given continuously during a course of fractionated radiation if radiosensitization of most fractions is to be achieved [16]. Better models to determine the mechanisms of sensitization and the therapeutic index of a treatment considering the irradiated site, the volume irradiated and the fraction size are needed [16].

The knowledge of the location of loco-regional failures after surgery addresses the design of the pelvic radiation beams [17–19]. These should include residual disease in the soft-tissues of the pelvis and residual nodal disease. Usually two volumes are treated, the whole pelvis, which should adequately cover the primary tumor/tumor bed as well as the primary nodes at risk, and the primary tumor itself. Whole pelvic and boost fields are usually treated with 3–4-field techniques. Field shaping by blocks is used to spare additional small intestine anteriorly and superiorly, the posterior muscle and soft tissues behind the sacrum, and inferior to the symphysis pubis. Innovative conformal techniques using 3D treatment planning are used for dose escalation programs [20]. The use of intensity-modulated radiotherapy (IMRT) may further lower the dose to the critical structures while maintaining adequate doses in the planning target volume [21]. Protons have been also suggested for these purposes [22]. With conventional fractionation (1.8–2 Gy fractions, 5 days per week), the doses most commonly used are 45–50.4 Gy in 5–6 weeks, with a boost of 5.4 Gy to the primary tumor or tumor bed. Large daily fractionation, 25 Gy in 5 days has mainly been used in the preoperative setting, but practiced also postoperatively [23]. In the incomplete resection (R1 or R2 resection), postoperative radiation doses of more than 60 Gy are required. Complications of pelvic radiation therapy are a function of the volume irradiated, overall treatment time, fraction size, radiation energy, total dose, technique and sequence of radiotherapy [24].

Early rectal cancer

Early localized tumors (3–5% of rectal cancers) include small, exophytic, mobile tumors without adverse pathologic factors (i.e., high grade, blood or lymphatic vessel invasion, colloid histology, or the penetration of tumor into or through the bowel wall) and are adequately treated with a variety of local therapies such as local excision or endocavitary radiation.

Most investigators have used intracavitary irradiation alone or a combination of temporary Iridium-192 implant and external beam radiation for more advanced tumors (more than cT2 and or N+) [25–28]. Intracavitary treatment, introduced by Papillion and colleagues in Lyon, France, irradiated early tumors with a low-energy X-ray unit, placed through a 4-cm

Table 1
Local excision and postoperative radiation therapy: survival, salvage and functional results

Selected series	Enrolled patients	%T3	%5FU	5-year survival	Local failures salvaged with APR
U Florida [34]	45	2	4	88%[a]	1/5 (20%)
NE Deaconess [35]	48	10	54	94%[b]	3/4 (75%)
MD Anderson [36]	46	33	17	–	–
U Pennsylvania [37]	16	32	0	94%[c]	2/2 (100%)
MGH [38]	47	0	55	74%[d]	5/9 (55%)
Catholic University [39]	21	0	0	81%	1/2 (50%)
Fox Chase [40]	21	19	10	77%	3/4 (75%)
CALGB [41]	51[f]	0	100	85%[e]	4/7 (57%)
MSKCC [42]	39	21	51	70%	5/8 (62%)
Vancouver [43]	23	9	0	77%[a]	3/7 (43%)
Princess Margaret Hospital [44]	73	11	0	67%	11/14 (78%)

[a] cause specific, [b] crude, [c] 3-year actuarial, [d] 5-year disease free, [e] 6-year actuarial survival.
[f] Analysis is limited to the 51 of 110 patients (all with T2 disease) who underwent a local excision and received post-operative radiation therapy + chemotherapy

proctoscope almost against the tumor and generally, 50-kV X-rays, in doses of 30 Gy per treatment, are given using this "contact" approach. Three or four such treatments over 1 month are given. Using this technique, local failure rates ranged in the literature between 10% and 15%, but it is affected by patient selection: some reports local control of 54–56% for T3 or T2 [25,27–30]. Overall 5-year survival ranges between 65% and 81%. Since most institutions do not have a 50-kV radiation machine there is a limited experience with this technique.

Local excision has been performed both pre- and postradiation therapy. The main advantage of a local excision prior to radiation is that pathologic details such as margins, depth of bowel wall penetration, and histological features can be characterized. Patients with pT1 tumors without adverse pathologic factors have a low rate of local failure (5–10%) and positive nodes (<10%) and usually do not need adjuvant therapy. On the contrary, when adverse pathologic factors are present or the tumor invades into or through the muscularis propria, the local failure rate raises to at least 17% and the incidence of positive nodes to above 10% [31]. Many conservative surgical approaches are practiced; recently, Transanal Endoscopy Microsurgery (TEM) has emerged as a reliable option [32]. Regardless of the technique, excision should be full thickness, non-fragmented, and have negative margins [33].

In series of local excision followed by postoperative therapy, the average local failure rate increases with T stage: pT1, 5%; pT2, 14%; pT3, 22% (Table 1). The high local failure rates for pT3 tumors suggest that they are treated more effectively with radical surgery and pre- or postoperative therapy. There are some experiences with preoperative radiation + 5FU-based concomitant chemotherapy followed by local excision [45–50]. Most series are limited to highly selected patients with cT3 disease who are either medically inoperable or refuse radical surgery [45, 50].

Salvage of local failures is possible after local excision and radiotherapy, and at least half of the patients who undergo a salvage abdominoperineal resection (APR) can be cured [36,37,39,40,42]. A close follow-up is recommended. The few series that have investigated sphincter function report favorable outcomes [36,37,39,40,42,45,50].

Locally advanced rectal cancer

Preoperative radiotherapy

The potential advantages of the preoperative approach include decreased tumor seeding, less acute toxicity, increased radiosensitivity due to more oxygenated cells, and enhanced sphincter preservation [51]. The main disadvantage is related to overtreatment of patients with early stages (pT1-2N0) or undetected metastatic disease, even if imaging modalities (endorectal ultrasound and high-resolution phased-array magnetic resonance imaging [MRI]) allow better spatial resolution, and identification of the anal sphincter and the mesorectal fascia, predicting negative

circumferential margins [52–54]. In the last years, preoperative therapy has gained a large acceptance as a standard therapy for rectal cancer.

There are more than 15 randomized trials of preoperative radiation therapy without concurrent chemotherapy for clinically resectable rectal cancer [5,10,55,56] (Table 2). All used low to moderate doses of radiation and most showed a decrease in local recurrence. The Swedish Rectal Cancer Trial is the only one out of eight studies with more than 500 patients, which reported a survival advantage for the total treatment group [64].

Many have tried to interpret these data. Three meta-analyses report conflicting results [5,55,56]. All of them revealed a decrease in local recurrence. However, the analysis by Camma et al. [55] reported a survival advantage, whereas the analysis by Munro and Bentley [56] did not. The Swedish Council of Technology Assessment in Health Care (SBU) performed a systematic review of radiation therapy trials [10]. They analyzed data from 42 randomized trials and 3 meta-analyses, 36 prospective studies, 7 retrospective studies and 17 other articles, for a total of 25,351 patients. The main conclusion was that preoperative radiotherapy at biologically effective doses above 30 Gy decreases the relative risk of local failure by 50–70%, and by 30–40% for postoperative radiotherapy at doses that are usually higher than those used preoperatively (similar to the Colorectal Cancer Collaborative Group) [5]; that survival is improved by about 10% using preoperative radiotherapy. Long-term consequences of radiotherapy appear to be limited with adequate techniques, although longer follow-up is needed before firm conclusions can be drawn.

The Dutch CKVO 95-04 trial randomized 1805 patients with clinically resectable (cT1-3) disease to surgery alone (with a total mesorectal excision (TME)) or short course of preoperative radiation followed by TME [66]. A quality assurance program evaluated surgery and radiotherapy. Radiation significantly decreased local recurrences (8% vs 2%), but there was no difference in 2–year survival (82%). With longer follow-up, 5-year local failure was 12% with TME alone and still significantly lower (6%) in combination with preoperative radiation, whereas 5-year survival was still the same, 63% and 64%, respectively [75]. The circumferential margins (CM) are an important negative prognostic factor and support the preoperative approach because, even if patients with positive CM received 50 Gy postoperatively, this did not compensate for positive margins [76]. 1530 Dutch patients entered onto the study were analyzed for complications [75,77]. In the preoperative arm, acute toxicity events were observed in 26% of the patients; in 7% there was a grade 2 or 3 complication. The overall postoperative complication rate was 48% in the radiation arm versus 41% in the surgery-only group ($p=0.008$). This difference was mainly attributable to the difference in perineal wound healing (29% vs 18%, respectively) [77]. 990 randomized patients without a recurrence during the first 2 years were investigated for health-related quality of life (HRQL) and sexual functioning. Irradiated patients recovered more slowly from defecation problems than TME-only patients ($p=0.006$) and had a negative effect on sexual functioning in males ($p=0.004$) and females ($p<0.001$). Irradiated males had more ejaculation disorders ($p=0.002$), and erectile functioning deteriorated over time ($p<0.001$). However, these radiotherapy related side effects were reported not to affect HRQL seriously [75]. A cost–benefit analysis suggested that prevention of a local recurrence reduces long-term health care costs, even if survival was not changed [78].

It is not possible to accurately compare the local control and survival outcomes of short-course preoperative radiation with conventional preoperative combined modality therapy used more recently, because there is a more favorable patients' selection in the series using short-course radiation. The conventional preoperative combined modality therapy regimens are now generally limited to patients with cT3 and/or N+ disease, whereas most trials that used short-course preoperative radiation included patients with cT1–3 disease.

Two randomized trials have examined whether chemotherapy improves the results of preoperative radiation in patients with cT3 rectal cancer. The EORTC 22921 is a 4-arm randomized trial of preoperative 45 Gy with or without concurrent bolus 5FU/leucovorin followed by surgery with or without 4 cycles of postoperative 5FU/leucovorin. A significant decrease in local recurrence was observed in 3 chemotherapy groups: 8.8%, 9.6%, 8.0% with either preop RT-CT, postop CT and both, vs 17.1% without ($p=0.002$). Five years overall survival was not affected by chemotherapy at the median follow-up of 5.4 years: 66% vs 65% ($p=0.798$) for preop RT-CT vs preop RT; 67% vs 63% ($p=0.132$) for postop CT vs nil. An increased rate of pT0 (14% vs 5%, $p=0.0001$) and sphincter saving surgery (56% vs 52%, $p=0.05$) was observed in preop RT-CT vs preop RT; 58% of patients received planned adjuvant CT. The authors stated that in view of the benefit of preop RT-CT on conservative surgery and the bad compliance of postop CT, preop RT-CT might be preferred [79].

Table 2
Randomized trials of preoperative radiotherapy

Study	Selection Criteria	Tot. Dose (Gy)	Fractions (*N*)	Enrolled Pt		Crude Local Control			5 years Survival		
				RT (*n*)	Surgery (*n*)	RT (%)	Surgery (%)	$p < 0.05$	RT (%)	Surgery (%)	$p < 0.05$
Hypofractionation											
Rider ' 77 PMH [57]	Resectable, 0–15 cm	5	1	65	60	–	–	–	40	35	no
Duncan ' 84 MRC [58]	Resectable, 0–15 cm	5	1	277	275	55	57[a]	no	42	38	no
Stockholm I ' 95 [59]	Resectable, no LE, 0–15 cm	25	5	424	425	86	72	yes	46	42	no
Marsh ' 94 Northwest RCG [60]	Resectable, tethered or fixed 0–13 cm	20	4	143	141	87	64	yes	38	30	no
Goldberg ' 94 St.Marks [61]	Resectable, 0–12 cm	15	3	228	239	83	76	yes	39	40	no
Sause ' 94 RTOG [62]	Resectable, tethered or fixed, 0–13 cm postoperative RT II-III stage	5	1	148	153	81	78	no	54	54	no
Stockholm II ' 96 [63]	Resectable,<80 no LE, 0–15 cm	25	5	272	285	88	75	yes	39[c]	36[c]	no
Swedish Trial ' 97 [64]	Resectable,<80 no LE, 0–15 cm	25	5	553	557	88	73	yes	58	48	yes
Herrmann ' 99 Dresden [65]	Resectable, 0–15 cm postoperative RT if T4,R1/R2, perforation	16.5	5	47	46	87	76	no 0.08	40	28	yes
Dutch ' 01 [66]	Resectable,<80 no LE, 0–15 cm certified TME	25	5	924	937	97	91	yes	82[b]	82[b]	no
Conventional fractionation – intermediate dose 20–40 Gy											
Stearns ' 74 MSKCC [67]	Resectable, rectum	20	8	376	414	–	–	–	57	58	no
Higgins ' 75, VASAG I [68]	Resectable, M+,rectum & sigmoid	20 (25)	10	347	353	–	–	–	35	29	no
Duncan ' 84, MRC I [58]	Resectable, 0–15 cm	20	10	272	275	53	57[a]	no	40	38	no
Kutzner ' 84 Mainz [69]	n.a.	34.5	15	69	106	87	80	yes	35	23	yes
Higgins ' 86 VASOG II [70]	Rectum and Rectosigmoid Resectable by APR	31.5	18	180	181	79	78	no	–	–	no
Gerard ' 88 EORTC [71]	Resectable, 0–15 cm	34.5	15	231	228	80	69	yes	52	49	no
Reis Neto ' 89 PUCC [72]	Resectable, 0–14 cm	40	20	34	34	85	53	yes	70	29	yes
Dahl ' 90 Norway [73]	Resectable, 0–15 cm	31.5	18	159	150	85	79	no	57	58	no
MRC ' 96 [74]	Partially or fixed 0–15 cm planned 450 pts	40	20	139	140	64	54	yes	34	27	no

RT: radiotherapy arm; Surg: surgery arm; Frac: radiotherapy Fractions; LE: local excision; n.a.: not available; TME: total mesorectal excision
[a] % rate at 5 year,
[b] 2-year survival;
[c] 10-year survival

The second trial (FFCD 9203) compared preoperative 45 Gy with or without bolus 5FU/leucovorin, and all patients receive postoperative chemotherapy [80]. An improvement in the pCR rate was observed (12% vs 4%, $p \leqslant 0.0001$) but no difference in the sphincter preservation rate (52% vs 53%). Overall survival at 5 years was the same (67%), local recurrence was lower in preop RT-CT: 8% vs 16% of preop RT. Grade 3+ toxicity was increased (15% vs 3%, $p \leqslant 0.0001$).

Besides local control and survival, also acute toxicity, sphincter preservation and function, and quality of life are important. For sphincter preservation, preoperative therapy may decrease the volume of the primary tumor. When the tumor is located in close proximity to the dentate line, shrinking of the tumor volume may allow the surgeon to perform a sphincter conserving procedure more easily. However, sphincter preservation is unlikely when the tumor directly invades the anal sphincter.

One of the most important controversies with preoperative therapy is whether the degree of downsizing is adequate enough to enhance sphincter preservation. In prospective clinical studies evaluating this endpoint, the surgeon examines the patient prior to the start of preoperative therapy and declares the type of operation required. Some groups have measured the distance between the lower pole of the tumor to the anorectal ring by double contrast barium enema or by MRI [81].

Bujko et al. randomized 316 patients with cT3 rectal cancer to 5 Gy × 5 followed by surgery (median 8 days) or conventional preoperative combined modality therapy (50.4 Gy plus bolus 5FU/leucovorin daily × 5, weeks 1 and 5) followed by surgery (median 78 days) [82]. The tumors did not infiltrate the anorectal ring. Sphincter-saving surgery was performed in 61% of patients treated with a short course and 58% with a long course + concurrent chemotherapy (p = NS). Local control and survival results have not yet been reported.

Comparing the rates of sphincter-saving surgery in the randomized study arms published since 2000, there is a substantial similarity in the outcomes: 67% in the TME-alone arm of the CKVO 95–04 trial, 61% and 65% in the short-course arms of the Polish and of the CKVO 95–04 trials, respectively, 51% in the long-course radiotherapy-only arm of the FFCD trial, and 51% and 58% in the long course + concurrent chemotherapy arms of the FFCD and Polish trials, respectively. The similarity supports that sphincter-saving surgery is not related to the previous treatment but to technical skill, to traditional oncologic principles and to risk attitudes of the surgeons.

The analyses of sphincter preservation after preoperative chemoradiotherapy in 247 consecutive patients with locally advanced resectable carcinoma of low-medium rectum (cT3N–/+), treated within four phase II studies between 1990 and 2002 and who were referred to only three surgical teams, showed an overall improvement in sphincter-saving rate from 78% to 93% ($p < 0.001$) across the studies [83]. Looking at the patients having a distance between the anal-rectal ring and the lower pole of the tumor between 0 and 30 mm, sphincter saving surgery was feasible in 44% of patients in the group who received radiotherapy plus mitomycin-C and 5FU, 52% in the group of radiotherapy plus cisplatin and 5FU, 65% in the group of radiotherapy plus raltitrexed, and 84% in the group of radiotherapy plus raltitrexed and oxaliplatin ($p < 0.001$). Surgeons kept the same criteria in performing sphincter-saving surgery across the studies. Moderate soilage after the sphincter saving procedure was recorded in 4–6% of the patients, without any statistical difference between groups. Even if the surgeons' skill in performing sphincter-saving surgery could have improved in the years in spite of sustaining the same surgical criteria, the higher rate of this sphincter-saving observed in the latest schedules suggests an impact of the new drugs in promoting sphincter saving surgery.

No short-course randomized trials have addressed the issue of sphincter preservation, because it was not an endpoint of these trials. An analysis of 1316 patients treated in 2 Swedish trials of short-course radiation showed a correlation between downstaging and the interval between the completion of radiation and surgery [84]. In the Dutch CKVO 95-04 trial no downstaging was observed [85]. Whether increasing the interval between the end of intensive short-course radiation and surgery to more than 4 weeks will increase downstaging is not known. This question is being addressed in the ongoing Stockholm III trial.

Conventional doses and techniques of radiation are recommended when the goal of preoperative therapy is sphincter preservation. Multiple field techniques, a total dose of 45–50.4 Gy at 1.8 Gy/fraction, 4–7 weeks of interval between surgery and the completion of radiation are the main features of long-course preoperative radiotherapy. Data from the Lyon R90-01 trial of preoperative radiation suggest that an interval of more than 2 weeks following the completion of radiation increases the chance of downstaging [86].

As SBU pointed out [10], at this moment the literature is inconclusive in evaluating the role of

preoperative radiotherapy alone or with concurrent chemotherapy in promoting sphincter-saving surgery in low-lying tumors, although the German trial recently showed a favorable impact of preoperative chemoradiotherapy in a subgroup of the patients [87].

Although pre-operative therapy may adversely affect sphincter function [88] the impact is most likely less than using postoperative combined modality therapy [89]. In four preoperative series which report functional outcome, the majority (~75%) have good to excellent sphincter outcome [83,86,90–93]. Anyway, sphincter preservation without good function is of questionable benefit: in a series of 73 patients who underwent surgery, Grumann et al. reported that the 23 patients who underwent an APR had a more favorable quality of life compared with the 50 who underwent a low anterior resection [94].

Although some series show no correlation [95, 96], many series report that patients who achieve a pathological complete response (pCR) following preoperative radiotherapy ± concurrent chemotherapy have improved long-term outcomes including local control, metastases-free survival, and overall survival, independently of their initial clinical T and N stage [83,86,90–93,97]. In patients who achieve less than a pCR there is heterogeneity in the definitions of the presence of residual tumor, e.g. stage pT3 has been defined varying from gross disease remaining in the perirectal fat to a few foci of microscopic residual disease outside the bowel wall. New pathological score systems can be predictive of outcome [98–100].

In one series, patients with T1-3 disease who had a biopsy proven complete response did not receive any surgery: 5-year overall and disease-free survival rates were 98% and 84% [101]. Local excision after major clinical response is under investigation in some trials. New imaging is still weak in predicting pathological response: neither post-treatment ERUS [102,103] nor physical examination (with an accuracy of 25%) [104] are sufficiently adequate. The use of positron emission tomography (PET) scan [105,106] and diffusion MRI [107] are being investigated. In any case, in most series with cT3 patients who received preoperative therapy, radical surgery has still been considered necessary to fully evaluate if a pathologic response has been achieved.

Analyses of biopsies using selected molecular markers such as c-K-ras [108], thymidylate synthase [109], p27kip1 [110], p53 [111,112], apoptosis [113], DCC [111], EGFR [114,115], and Ki-67 [116] have had varying correlation to identify patients who may best respond to preoperative therapy. Since these studies are retrospective and usually do not examine multiple markers, at present the need for combined treatments should still be based solely on T and N stage.

Postoperative radiotherapy

The main advantage with this approach is the better selection of the patients based on pathologic staging. Post-operative therapy remains a common approach, particularly in North-America, despite the advances in pre-operative imaging techniques. The primary disadvantages include an increased toxicity related to the amount of small bowel in the radiation field [24], a potentially more radio-resistant hypoxic post-surgical bed and, if the patient has undergone an APR, the radiation field has to be extended to include the perineal scar.

Five randomized trials have reported data on the use of adjuvant post-operative radiation therapy alone in stages pT3 and/or N1–2 rectal cancer [117–120]. None showed an improvement in overall survival. In the Mayo Clinic/NCCTG trial 79-47-51 there was no surgery only control arm [121]. In two series, one of the arms included radiation plus chemotherapy (GITSG) [118] or chemotherapy alone (NSABP R-01) [120]. Two studies show a decrease in local failure: NSABP R-01 (16% vs. 25%, $p=0.06$) [120] and the Medical Research Council (21% vs. 34%, $p=0.001$) [122]. No survival advantage was observed from pelvic radiation plus elective para-aortic and liver radiation versus pelvic radiation alone [123].

In 1990, the NCI Consensus Conference, analyzing the postoperative North American chemoradiotherapy studies, stated that combined modality therapy was the standard post-operative treatment for patients with pT3 and/or N1–2 disease [124]. The standard design consisted of 6 cycles of chemotherapy with concurrent radiation during cycles 3 and 4. A 10% survival advantage from continuous infusion (CI) 5-FU versus bolus 5-FU combined with radiotherapy was reported in the Intergroup/NCCTG trial [122]. The INT–0144 postoperative adjuvant rectal trial also tested this question [125]: the patients were randomized to 3 arms: arm 1 = bolus 5-FU → CI 5-FU/RT → bolus 5-FU, arm 2 = CI 5-FU → CI 5-FU/RT → CI 5-FU, and arm 3 = bolus 5-FU/LV/Levamisole → bolus 5-FU/LV/Levamisole/RT → bolus 5-FU/LV/Levamisole. The lowest incidence of grade 3+ hematological toxicity was seen in arm 2 (4%). However, there was no significant difference in local control or survival. Given these results, CI 5-FU with radiation is considered as standard and either arm 1 or 2 is a reasonable choice. If arm 1 is chosen, the bolus chemotherapy segment should be the Roswell

Park (weekly) rather than the Mayo Clinic regimen (monthly).

A randomized trial by Lee et al. suggested that radiation should start during cycle 1 rather than during cycle 3 [126]. Even if this interesting result opens a new debate, a number of patients who did not receive the treatment arm were randomized to, thus, more data are needed before recommending a change in sequence.

Recently, the 6th edition of the American Joint Commission on Cancer (AJCC) staging system subdivides stage III into IIIA (T1–2N1), IIIB (T3–4N1), and IIIC (TanyN2), based on a pooled analysis of Intergroup and NSABP postoperative trials, and a retrospective analysis of the American College of Surgeons National Cancer Database (NCDB) database [127]. In these analyses, the 5-year survival of no radiotherapy arms by stages IIIA, B, and C was 81%, 57%, and 49% in the pooled analysis and 55%, 35%, and 25% in the NCDB database, respectively. Although radiation does not improve the survival achieved with chemotherapy alone in stages pT3N0, T1–2N1 disease, local control data are requested before recommending chemotherapy alone for this subset of patients. If the local control rate without radiation is acceptable, then for pT3N0 upper rectal cancers patients, who undergo a total mesorectal excision and have at least 12 nodes examined, radiation therapy can be avoided. The 4–5% benefit in local control with radiation may not be worth the risks, especially not in women of reproductive age.

Acute toxicity is usually high with postoperative therapy: e.g., the incidence of grade 3+ toxicity in the combined modality arms of the GITSG and Mayo/NCCTG 79-47-51 trials was 25–50%. Furthermore, the percentages of patients who completed the prescribed 6 cycles of chemotherapy in those trials were only 65% and 50%, respectively [128].

To reduce toxicity, the contribution of adjuvant chemotherapy in the postoperative combined treatment has been questioned. Two European randomized trials support the argument. The Norwegian trial compared surgery alone with surgery plus postoperative radiochemotherapy and a less resource-demanding 5FU-regimen (bolus injection) administered exclusively during the radiotherapy period. Five-year overall survival and disease-free survival rates were significantly better in the combined treatment arm (64% vs 50% and 64% vs 46%, respectively) [129]. Furthermore, the acute and long-term toxicity of the combined regimen was low. A Hellenic trial tested the addition of four cycles of chemotherapy with 5FU and leucovorin to postoperative concomitant radiotherapy with 5FU bolus infusion. No statistical difference in 3-year overall and disease-free survival was seen (70% vs 68% and 77% vs 73%, respectively). Concomitant radiotherapy and adjuvant four cycles of chemotherapy were more toxic than postoperative radiochemotherapy alone arm (32% vs 5%, $p < 0.0001$) [130].

Preoperative and postoperative therapy have been compared in four randomized trials. The Uppsala trial used short-course radiation (5.1 Gy × 5) versus 60 Gy postoperatively with conventional fractionation [131]. The preoperative arm treatment resulted in significant decrease in local failure (13% vs 22%) with no difference in survival (42% vs 38%). The other 3 randomized trials selected patients with T3-4 disease and used conventional radiation doses and concurrent 5-FU-based chemotherapy. Two are from the United States (INT 0147, NSABP R0-3) and one from Germany (CAO/ARO/AIO 94). Unfortunately, low accrual resulted in early closure of both the NSABP R-03 and INT 0147 trials.

The German trial completed the planned accrual of over 800 patients and compared preoperative combined modality therapy (with CI 5-FU) vs. postoperative combined modality therapy [87]. Patients were stratified by the surgeon, in order to overcome surgical bias. The preoperative group had a significant decrease in local failure (6% vs 15%, $p = 0.006$), acute toxicity (27% vs 40%, $p = 0.001$), chronic toxicity (14% vs 24%, $p = 0.012$) compared with postoperative group. In 194 patients judged by the surgeon to require an APR and randomized to receive preoperative combined modality therapy, a significant increase in sphincter preservation (39% vs 20%, $p = 0.004$) was observed. With a median follow-up of 40 months there was no difference in 5-year survival (74% vs 76%).

At the present time, given the improved local control, acute and long-term toxicity profile, and sphincter preservation rate reported in the German trial, patients with cT3 rectal cancer who require combined modality therapy should receive it preoperatively, even if we need confirmation of more long-term follow-up data.

Unresectable rectal cancer

Adenocarcinomas of the rectum beyond a surgical resection (R0) are defined as unresectable. The evaluation of resectability depends on the extent of the operation the surgeon is able to perform as well as on the morbidity the patient is willing to accept. Unresectable rectal cancer is a heterogeneous disease and it is not unequivocally related to cT4 stage: it can range from a tethered or ' marginally resectable' cancer

Table 3
Selected clinical studies of chemoradiation in patients with unresectable rectal carcinoma

Study	Enrolled patients	ERT dose Gy	Concurrent chemotherapy	Radical surgery %	Local control %	5-year survival %
Landry [132]	20	50	5FU	100	90	92 (3y)
Chen [133]	31	55.8	5FU CI	100	84	68 (3y)
Minsky [134]	36	50.4	5FU/LV	97	86	76 (4y)
Rodel [135]	31	50.4	5FU	84	74	51
Ratto [136]	47	45–48	5FU CI + MMC	88	77	59
Mohiuddin [137]	38	45–60	5FU Bolus/PVI	84	79	71
Sanfilippo [138]	45	45	5FU PVI	62	76 (4y)	50 (4y)

n.a.: not assessed; y: years; ERT: external radiation therapy; 5FU: 5-fluorouracil; LV: leucovorin; MMC: mitomycin C; CI: continuous infusion (4–5 days); PVI: prolonged infusion (whole radiotherapy course).

to a fixed cancer with direct invasion of adjacent non-resectable organs or structures. The heterogeneity of the presentation and the absence of an uniform definition of resectability may explain some of the variations in outcomes seen among the series [10].

All patients with primarily unresectable disease should receive preoperative combined modality therapy in the range of 50–54 Gy plus 5FU-based chemotherapy to enhance R0 resectability even if the scientific evidence for adding chemotherapy is low [10] (Table 3). Experience to increase the dose using concomitant or sequential boosts has been practiced [20,135,139]. Although 50–90% will be able to undergo a resection with negative margins, depending on the degree of tumor fixation, many still develop a local recurrence. Given the limitation of the total radiotherapy dose which can be delivered to the bulky tumor in the pelvis [140]and the frequent problem of local recurrence, the surgeon should be aggressive not to risk leaving microscopic residual tumor [141]. Extended surgery is still recommended even if there is a favorable response after the preoperative therapy.

To increase the local control a large single dose of irradiation is delivered to a surgically exposed area, while uninvolved and dose-limiting tissues are displaced [142]. Intra-operative radiation therapy (IORT) can be delivered by two techniques: electron beam and brachytherapy. Brachytherapy is commonly delivered by the high-dose rate (HDR) technique and the dose rate is similar to that used for electron beam IORT [143–145]. The results (and recommended dose) of IORT depend on whether the margins of resection are negative or whether there is microscopic or gross residual disease. In general, series have used 10–20 Gy.

At the MGH, in patients who received preoperative therapy followed by IORT and had negative margins, local failure rates decreased from 18% without IORT to 11% with IORT. In patients with positive margins, local failures decreased from 83% without IORT to 43% with IORT if there was gross residual disease, and to 32% with IORT if there was microscopic residual disease; 5-year disease-free survival was 63% for patients with negative margins and 32% for patients with positive margins [146]. Reports from other centres have revealed similar results [147–151]. At the MGH, 40 of the 95 patients with T4 disease who received preoperative irradiation and underwent complete resection, had an IORT boost and 55 did not because it was not practiced due to either a favorable response or because it was not technically feasible [152]. Regardless of the response to preoperative therapy, higher local failure rates were seen in patients not receiving IORT (responders: 16% vs 0%, and non-responders: 12% vs 27%). These data support, but do not prove, that IORT should be delivered independent of the extent of tumor downstaging in this setting.

It is difficult to clearly separate treatment-related complications from disease-related complications in patients with unresectable primary and/or recurrent rectal cancers. Treatment-related complications range from 15% to 50% in most series and is highest in patients with the most advanced disease. Complications such as delayed healing, an increase in infection rates, fistula formation, and neuropathy may be the result of recurrent tumor, aggressive surgery, radiation, or a combination of these. IORT-related toxicity increases with IORT doses >20 Gy. In a series from the Netherlands, 79 patients reported fatigue (44%), perineal pain (42%), sciatic pain (21%), walking difficulties (36%), and voiding dysfunction (42%) [153]. In addition, functional impairment consisting of requiring help with basic activities (15%), sexual inactivity (56%), loss of former lifestyle (44%) and

loss of professional occupation (40%) were noted. The University of Navarra reported peripheral neuropathy up to 5 years after IORT [154].

Recurrent tumor

Usually, patients with local recurrence have a very unfavorable prognosis. Symptoms include pain, hemorrhage, pelvic infection and obstructive symptoms. The median survival ranges between 1 and 2 years [155].

The incidence of failure sites were analyzed in 155 patients at the University of Wurzburg [156]. They are similar for APR vs low anterior resection (LAR): local + nodal: 61% vs 66%, isolated lymph node: 4% vs 5%, internal iliac and presacral nodes: 47% vs 59%, and external iliac: 7% vs 2%. Local recurrence was most commonly seen in the presacral pelvis and in patients who underwent an LAR; the anastomosis was involved in 93%.

Attempts to classify localized pelvic recurrences according to the tumor location within the pelvis have been practiced. At the Mayo Clinic, 106 patients with local recurrence treated by IORT and postoperative radiotherapy were stratified during the surgical procedure according to the infiltration of the tumor to none (F0), one (F1), two (F2), or >2 pelvic sites (F3) [157]. This classification system significantly correlated with survival. At the Catholic University of the Sacred Heart, Rome, 47 patients with locally recurrent, non-metastatic rectal carcinoma were treated with preoperative chemoradiation ± IORT and were classified by CT scan according to the Mayo Clinic system [158]. A further (F4) class was added when tumor infiltrated small bowel or bone structures. The CT-based classification system significantly predicted R0 resectability ($p = 0.01$) and survival ($p = 0.008$).

As with primarily unresectable disease, patients should receive preoperative combined modality therapy, but the role of higher doses is less clear, probably due to the heterogeneity of the patient population. Negative margins seem to predict better outcome. In the MGH series of 40 patients, the 5-year local control was higher with negative margins (56%) versus positive margins (13%); the overall 5-year survival was 40% in those with negative margins versus 12% with positive margins [152]. Similar results were reported in 74 patients treated at Memorial Sloan Kettering [144]: the 5-year local control was 43% (negative margins) versus 26% (positive margins), and 5-year survival was 36% versus 11%, respectively. In a report from Olso, 107 patients with isolated pelvic recurrence received 46–50 Gy preoperatively [159]. Regardless of the volume of residual disease, there was no significant difference in local recurrence or survival whether or not they received IORT. In summary, in contrast to patients who have negative or microscopically positive margins, it is unclear if those with macroscopic positive margins benefit from aggressive therapy.

Although the combination of adjuvant therapy and TME has significantly lowered the incidence of local recurrence, there is a subset of patients previously irradiated who present with only local recurrence. In these patients, re-irradiation would be expected to be associated with a high risk of late toxicity. Few studies have analyzed the role of radiation retreatment in pelvic recurrence. Data from Mohiuddin and colleagues suggests re-irradiation with doses of 30 Gy, and if the small bowel can be excluded from the irradiation field, 40 Gy can be used for limited volumes [160]. A multi-center Italian trial of 59 patients with recurrent disease who had received <55 Gy were retreated preoperatively with concurrent 5-FU plus 30 Gy (1.2 Gy BID) to the GTV plus a 4-cm margin [161]. A boost was delivered, with the same fractionation schedule to the GTV plus a 2-cm margin (10.8 Gy). Grade 3+ acute and late toxicities were 5% and 12%, respectively. With a median follow-up of 36 months, local failure was 48%, median survival 42 months, and 5-year actuarial survival 39% (R0: 67% vs. R1–2: 22%).

Palliation

Medically inoperable patients, patients who refuse surgery or patients with such advanced local disease that resection would compromise a vital pelvic structure are proposed for radiation therapy alone. In most series, patients have received pelvic radiation therapy followed by a boost with either external beam or brachytherapy. Brierley et al. treated 229 patients who refused surgery or had unresectable or medically inoperable disease with external beam only (40–60 Gy) [162]. The overall 5-year survival was 27%; according to the mobility of the primary tumor it was 47% for mobile lesions, 27% partially fixed and 4% fixed. These data support that patients with mobile or partially fixed rectal cancers who are medically inoperable should receive aggressive pelvic radiation therapy as a component of their therapy.

Gerard and associates treated 63 patients with cT2–3 tumors with the combination of external beam, intracavitary, and brachytherapy [163]. Patients with cT3 disease had 20% 5-year local failure and 35% 5-year survival.

Pelvic radiation offers effective palliation. Crane et al. reported that 94% of 80 patients with metastatic disease who received pelvic radiation, had complete resolution of pelvic symptoms and the 2-year pelvic symptom-free control was 82% [164]. The Princess Margaret Hospital reported in a subset of 84 patients who received >45 Gy frequent symptom control: pain, 89%; bleeding, 79%; neurological, 52%; mass effect, 71%; discharge, 50%; urological, 22%; other, 42% [59]. In the Thomas Jefferson University series, complete plus partial symptomatic relief was pain (65%+28%), bleeding (100%), and mass effect (24%+64%), respectively [160]. The duration of the palliation was 8–10 months.

Conclusions

Significant evidence has been collected in the past years, which support the positive role of radiotherapy in the treatment of rectal cancer. Technical advances in radiotherapy and improvements in the sequencing of radiotherapy, chemotherapy, and surgery will offer further advantages. Clinicopathological and molecular features and the development of more accurate preoperative imaging and staging methods will also contribute to tailor the treatments according to the patient' s characteristics.

But some controversies still remain. Can we develop more accurate imaging techniques and/or molecular markers to identify patients with different risk factors? Is chemotherapy necessary with preoperative radiation and after surgery and in which patients? Will new systemic agents improve the results of combined modality therapy regimens? These and other questions support further clinical investigations.

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