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Review

Current treatment of rectal cancer adapted to the individual patient

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ABSTRACT

Preoperative radiochemotherapy and total mesorectal excision surgery is a recommended standard therapy for patients with locally advanced rectal cancer. However, some subgroups of patients benefit more than others from this approach. In order to avoid long-term complications of radiation and chemotherapy, efforts are being made to subdivide T3N0 stage using advanced imaging techniques, and to analyze prognostic factors that help to define subgroup risk patients. Long-course radiochemotherapy has the potential of downsizing the tumor before surgery and may increase the chance of sphincter preservation in some patients. Short-course radiotherapy (SCRT), on the other hand, is a practical schedule that better suits patients with intermediated risk tumors, located far from the anal margin. SCRT is also increasingly being used among patients with disseminated disease, before resection of the rectal tumor. Improvements in radiation technique, such as keeping the irradiation target below S2/S3 junction, and the use of IMRT, can reduce the toxicity associated with radiation, specially long-term small bowel toxicity.

1. Background

Even though surgery has always been the historical backbone of rectal cancer treatment, since the first Northern American experiences of postoperative radiochemotherpy (RCT)[1] and Northern European experiences of preoperative exclusive radiotherapy,[2] it became evident that adjuvant treatment could be an effective way to obtain an outcome improvement.

Preoperative RCT and total mesorectal excision (TME) surgical procedure is a recommended standard therapy for patients with locally advanced rectal cancer (LARC), that is ≥T3 and/or ≥N1 disease. However, subgroup analyses in studies of preoperative treatment have not demonstrated a clinical benefit for patients whose tumors are confined to the bowel wall and who have negative lymph nodes. In the absence of significant survival advantages, it seems appropriate to focus our attention on defining benefits precisely and on selecting

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treatment options according to risk. Compelling reasons not to treat all patients with radiation, either preoperatively or postoperatively, include the risks of substantial toxic effects and long-term complications, specially the detrimental effects on bowel function.

The selection of a treatment modality depends on factors such as tumor histology, size, location, mobility, anatomic constraints, patient age, intercurrent medical disease and the technical expertise of the surgeon and radiation oncologist.

On the other hand, support is growing for the appealing concept of "wait and see" or even better "watch and wait" rather than proceed to radical surgery when a complete clinical response is observed. Hence, the management of patients who achieve a complete clinical response is becoming increasingly controversial.[3]

2. General principles of radiation therapy for rectal cancer

Radiotherapy is given to bulky primary tumor, positive nodes, and subclinical pelvic deposits. In resectable tumors, 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 tumors.

A dose between 45 Gy and 50 Gy at 2 Gy is considered adequate to control subclinical disease, thus, this is the dose needed to sterilize the surgical margins in patients with resectable tumors. In patients with unresectable tumors, the dose to control bulky tumors and to promote RO resectability must be higher, but this is strongly affected by the tolerance of pelvic organs.

It is known that biologically effective dose is related to the overall treatment duration and the fraction size. Short-course large daily fractionations (5 Gy/day, 5 days) should not be affected by repopulation. Biological effects of such a fractionation, according to the linear-quadratic model, are equivalent to 37.5 Gy in 2 Gy fractions.[4]

A prolonged interval before surgery, using preoperative long-course approach, could raise some concerns regarding the probability that metastases may develop in the meantime. Irradiation quickly reduces the number of viable tumor clonogens available for metastasis, thus, it seems reasonable to assume that preoperative RT eliminates the production of new micrometastases during treatment or in the interval between irradiation and surgery.

Concomitant chemotherapy can further reduce the occurrence of systemic metastases, but the exact contribution of chemotherapeutic agents to the final effect of treatment remains largely unknown. Better models to determine the mechanisms of radiosensitization and the therapeutic index of a treatment are needed.

No trial has ever shown that CRT or RT increase sphincter saving,[5,6] with the exception of the randomized Lyon R 96-2 trial which demonstrated not only sphincter preservation but organ (rectum) preservation after 10 years follow-up.[7,8]

3. Evidence of benefits in literature about preoperative radiotherapy: why adding a neoadjuvant treatment to surgery?

Surgical resection is the cornerstone of curative treatment for rectal cancer. Tumors in the upper and middle rectum can usually be managed with low anterior resection or coloanal anastomosis with preservation of the anal sphincter. For lower rectal tumors, with a distal edge of up to 6 cm from the anal verge, abdominoperineal resection (APR) has long been considered to be the standard operation. For patients with small rectal cancers that are confined to the rectal wall (T1 or T2), local excision techniques may offer local control rates that are comparable to APR, while preserving sphincter function, but this can not be considered a standard treatment for T2 rectal cancer. For patients with larger or more invasive tumors, neoadjuvant RCT has been utilized to promote tumor regression in an attempt to convert a planned APR into a sphincter-sparing surgical procedure.

The only definitive indication for neoadjuvant CRT, supported by results of randomized trials, is the presence of T3 or T4 rectal cancer. In 1997 the Swedish trial showed both a 5 year local control and survival improvement by adding preoperative RT (alone, with a short course – SCRT – schedule of fractionation), even if the group of patients underwent non standardized surgery.[9]

TME was developed after the recognition that discontinuous tumor deposits are often present in the lymphovascular tissue that surrounds the rectum (the mesorectum); left in place, such residual deposits are most likely the origin of local treatment failure. With the introduction of the TME, the local recurrence rates have dropped from 40 to 10 percent, approximately. Some physicians claim that adjuvant radiotherapy is not necessary if patients undergo resection with TME; however, it must be emphasized that TME series include patients with T1-2 N0 disease and allow identification and exclusion of patients with more advanced disease, compared with patients treated in the adjuvant trials in which more conventional surgery is performed. In the TME era, the Dutch trial obtained, for a population of T1–3 patients, a significant benefit for the arm adding short course radiation therapy (SCRT) to certified TME surgery (25 Gy in 5 fractions); this benefit remains at 6 year of median follow-up.[10]

Data from randomized trials suggest that the preoperative approach is associated with a more favorable long-term toxicity profile and fewer local recurrences than postoperative therapy The German study CAO/ARO/AIO-94 compared preoperative versus postoperative approach, delivering 45–50.4 Gy in 25–28 fractions with concomitant chemotherapy (CT).The two arms were similar apart from the administration of a boost of 5.4 Gy in the postoperative arm. Preoperative approach significantly decreased toxicity, and local recurrence, moreover, it increased sphincter preservation. The main outcomes remained at 11 years follow up.[11]

In the NSABP trial R-03, preoperative RCT was directly compared to postoperative RCT.[12] Preoperative RCT consisted of one cycle of bolus weekly 5-FU and leucovorin for six weeks, two courses of 5-FU and leucovorin (daily for five days during the first and fifth course of RT) concomitant with 50.4 Gy pelvic

irradiation, surgery, then four cycles of postoperative weekly bolus 5-FU and leucovorin. Postoperative therapy consisted of surgery, one cycle of weekly bolus 5-FU plus leucovorin, two cycles of 5-FU and leucovorin concomitant with pelvic RT as described above, then four cycles of weekly bolus 5-FU and leucovorin. Accrual did not reach planned levels, and the protocol was closed early. In the final analysis of 267 enrolled patients, the clinical pathologic complete response rate after preoperative RCT was 15%. While preoperative therapy was associated with a significantly higher rate of 5-year disease-free survival (DFS, 65 versus 53 percent), there was only a trend toward better overall survival (OS, 75 versus 66 percent, $p = 0.065$), and no difference in locoregional control (5-year cumulative incidence of locoregional recurrence was 11 percent in both arms) or sphincter preservation.

In contrast, Park et al.[13] did not find differences in acute or late toxicity between preoperative and postoperative CRT in 240 locally advanced rectal cancer patients. In this randomized trial, the patients with low-lying tumors, the preoperative CRT arm had a higher rate of sphincter preservation (68% vs. 42%, $p = .008$).

4. International guidelines recommendations: what is worldwide suggested?

Two of the most representative international guidelines, the National Comprehensive Cancer Network (NCCN)[14] and the National Cancer Institute (NCI)[15] suggest preoperative LCRCT as preferable: that seems in line with the traditional clinical approach in North America. The European scenario is quite more various, since the UK and Northern regions seem to prefer more often SCRT schedules while the other countries tend to prefer LCRCT (of course with case variations). Table 1 reports recommendations from the most commonly used national and international guidelines. The International Conference on 'Multidisciplinary Rectal Cancer Treatment: Looking for an European Consensus' (EURECA-CC2) was organized in Italy, with the aim to focus on the main agreement and controversies about the rectal cancer management.[16] For the treatment of intermediate stages there was a moderate consensus that SCRT reduces local relapses, LCRCT was also considered a primary option; for more advanced unresectable lesions, LCRCT was the preferred schedule. A key role of MRI based staging is being introduced now to tailor the preoperative modalities (SCRT/LCRCT) choice, giving more option to LCRCT when the mesorectal fascia is threatened.

The optimal management of clinical T3N0 rectal cancer is unclear. Some of these patients have a sufficiently favorable prognosis, therefore questions have been raised as to the necessity of postoperative adjuvant therapy after upfront TME. Others have questioned the utility of upfront CRT, particularly for those involving the upper rectum, given the favorable low rates of local recurrence after TME alone in the Dutch TME trial and retrospective analyses. On the other hand, as many as one-fifth of these patients may be understaged by preoperative imaging. In a review of 188 patients with TRUS/MRI staged T3N0 rectal cancer patients who received preoperative RCT, 41 (22%) were found to have pathologically positive mesorectal lymph nodes at the time of surgery.[17] Given the downstaging effect of RCT, it is likely that an even larger number of these patients would have been found to have node-positive disease (and recommended for postoperative adjuvant therapy) had surgery been undertaken initially. Thus, given the limitations of current imaging, all patients with cT3N0 rectal cancer by TRUS or MRI should be considered candidates for preoperative CRT.

Another issue emerged from different studies, both including LCRCT and SCRT, is the negative impact on outcome deriving from positive or involved circumferential resection margins (CRM+/close ≤ 1 mm). CRM is defined as the margin created around the mesorectum, which is at risk both from direct involvement by the tumor and from the lymph nodes that lie just under the mesorectal fascia, if not completely removed. There are higher rates of metastatization and even lower survival if CRM is directly involved or if it is inferior to 1 mm.[18] LCRCT has the potential to decrease the CRM positivity rates.[5]

High quality evidence to support a clear benefit from preoperative RCT as compared to initial surgery for other subgroups of patients with rectal cancer is lacking. For instance, preoperative RCT can be an appropriate option for patients with T1/2 tumors and clinically positive nodes. Also, for patients who have distal mobile rectal cancers, not amenable to local excision, preoperative RCT might allow sphincter-preserving LAR rather than an APR in some cases.[19] The German trial of preoperative versus postoperative CRT demonstrated that patients undergoing preoperative CRT were twice as likely to undergo a sphincter-sparing operation (39 versus 19 percent).[20] However, the absolute rates of APR in the two cohorts were not significantly different. In all these settings, patients must understand that there is a possibility that postoperative CRT might not be needed, based upon the final pathologic stage if surgery is performed initially. However, due to the downstaging effect, pathologic nodal staging is unreliable after CRT. Thus, if this approach is followed, a six-month course of postoperative chemotherapy (CT) is recommended.

5. Long-course versus short-course radiochemotherapy

Rectal cancer is considered to have a very long growing time, 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.

Main potential advantages from the use of LCRCT over SCRT are: the safe association with concomitant chemotherapy, the downstaging before surgery, the induction of resectability for originally unresectable lesions, the efficacy in management of mesorectal fascia involvement presentations, and potential increase of sphincter saving rates.

One of the main advantages of LCRCT is the potential downstaging obtainable before surgery. It is quite well known that downstaging is significantly correlated with better

Table 1 – National and International Guidelines for locally advanced rectal cancer.

	World Congress on GI Cancer, 2007	French Guidelines, 2007	Norwegian Guidelines, 2008	EURECA Consensus, 2008	Dutch Guidelines, 2008	Danish Guidelines, 2009	ESMO, 2010	Expert Opinion in Spain, 2011	NCCN, 2012	PDQ, 2012
T3,N0 or anyT N+	LCRTCT (SCRT as an alternative for earlier stages) (RTCT can also be considered for T2N0 disease)	SCRT or LCRTCT (no tx of T3N0 disease with CRM >1 mm)	SCRT (or LCRTCT if CRM ≤3 mm)	If resectable: SCRT or LCRTCT	SCRT (LCRTCT only for positive CRM or ≥4 LNs involved) (include also T2 disease)	LCRTCT for midrectal T3 disease with CRM <5 mm; and for all low-rectal T3 disease	If CRM negative at MRI: RT alone or LCRTCT (as alternative) (Also include T4 disease with vaginal or peritoneal involvement only)	LCRTCT [SCRT as alternative for non-fitting pts or in case of suboptimal LCRTCT) (Include pts with CRM <1 mm)	LCRTCT	LCRTCT
T4,anyN	LCRTCT (SCRT as alternative for earlier stages)	SCRT or LCRTCT	LCRTCT	If not resectable: LCRTCT	SCRT (LCRTCT only for positive CRM or ≥ 4 LNs involved)	LCRTCT for mid- and low-rectal T4 disease	If not resectable: LCRTCT (Also include cT3 disease with CRM positive on MRI)	LCRTCT	LCRTCT (including unresectable lesions)	LCRTCT

Modified by Cellini, F. and V. Valentini (2012). Oncology (Williston Park) **26**(8): 730–735, 741 [24].

CRM = circumferential resection margin; ESMO = European Society of Medical Oncology; EURECA = European Rectal Cancer; LN = lymph node; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; PDQ = Physician Data Query; pt = patient; SCRT = short course radiotherapy; LCRTCT = long course radiochemotherapy; tx = treatment.

outcomes, in particular with highly favorable locoregional control (LRC) rates for pathological complete response.[21,22] Recently, a pooled analysis of randomized trials using preoperative RCT identified a subgroup of patients with better indicators for pathological complete response (pCR), in terms of local control, distant metastases and overall survival.[23]

Another potential effect of downstaging and downsizing is the conversion into resectable an unresectable tumor; this is evident and widely accepted among the international guidelines.[14,16] Some clinical experiences are now trying to evaluate if SCRT with a longer interval before surgery can increase the pCR rates.

The downstaging obtainable with a LCRCT approach has also the potential to increase the sphincter preservation rates, although this is still a debated issue.[24]

5.1. *Concomitant chemotherapy*

An optimized choice of concomitant chemosensitization could enhance LCRCT treatment's efficacy. Several randomized trials and a meta-analysis have directly addressed the question of whether the concurrent administration of CT with conventional fractionation RT is critical to the success of this approach. EORTC 22921 examined both the benefit of concurrent RCT (using a five-day bolus 5-FU and leucovorin regimen during weeks 1 and 5 of RT) versus preoperative RT alone (45 Gy over five weeks) and the contribution of adjuvant CT (four cycles of bolus 5-FU and leucovorin), using a 2×2 factorial design. Compared to RT alone, patients undergoing preoperative RCT had a significantly higher rate of pathologic complete responses (pCR, 14 versus 5 percent), significantly less advanced pT and pN stage, and fewer cases with venous, perineural, or lymphatic invasion.[25] Local failure rates were significantly lower in all three groups receiving CT, regardless of whether it was given prior to or following surgery. Nevertheless, OS was comparable in all four groups, as well as PFS in patients receiving preoperative CRT versus RT alone (56 versus 54 percent) or adjuvant CT versus no adjuvant chemotherapy (58 versus 52 percent, $p = 0.13$).

In the randomized trial conducted by Braendengen el al.,[26] which included 207 patients with T4, non resectable tumors treated between 1996 and 2003 with either RT alone (50 Gy) or CRT (fluorouracil/leucovorin), more pathologic complete responses were found in the CRT arm (16% vs. 7%). CRT also improved local control at 5 years (82% vs. 67; $p = 0.03$), time to treatment failure (63% vs. 44%; $p = .003$) and cancer-specific survival (72% vs. 55%; $p = .02$), compared with RT alone.

The standard association for LCRCT is with 5-FU in continuous infusion,[14] but some evidence reported the equivalence of oral capecitabine.[27,28] The efficacy of the integration of oxaliplatin into the concurrent schedules is still controversial; some evidence suggests no benefit from such association due to increased toxicity without a significant improvement of pCR rates. That was basically reported by the STAR-01[29] and the ACCORD 12[30] trials, whereas the German trial (CAO/ARO/AIO-04)[31] reported on significant improvement for the oxaliplatin-based arm. A clearer picture will be available when all these studies provide long term results. In the mean time, the vast majority of experts agree that oxaliplatin must not be given concurrently with 5FU or capecitabine and radiotherapy.

Associated with a high potential as it is, the use of molecular targeted therapies, like cetuximab and bevacizumab in the neoadjuvant setting, is still under evaluation due to some concerns in terms of efficacy and toxicity and associated risk of postoperative complications. Patient selection, based on gene expression profiles, seems to be a potential key to define the most suitable patients to receive these complex treatments.

5.2. *Direct comparison of LCRTCT vs. SCRT: randomized trials*

Two randomized trials directly compared LCRCT against SCRT: the so-called "Polish trial" evaluated 316 cT3 pts with lesion lying above the anorectal ring; TME was not performed for all patients. As expectable, the LCRCT provided higher rates of pCR (16%-LCRCT; 1%-SCRT), lower rates of positive CRM (4%-LCRCT; 13%-SCRT), and higher rates of acute toxicity (16%-LCRCT; 1%-SCRT) without any significant difference in locoregional control and survival.[5]

Another experience from Australia and New Zealand also randomized patients into two arms: SCRT immediately followed by surgery plus 6 cycles of adjuvant CT, or 50.4 Gy with continuous infusion of 5-FU, 225 mg/m^2, followed by surgery after 4–6 weeks; 326 T3 any N pts were enrolled. Authors found no statistically significant difference for survival (74 vs. 70% at 5 years) or locoregional recurrence (8 vs. 4% at 3 years)[32] (Table 2).

Some studies with the same purpose are also ongoing: the Stockolm III randomizes to LCRT (no concomitant chemotherapy) or SCRT (with immediate surgery) or SCRT (with delayed surgery). Interestingly, an interim report found higher postoperative complication rates correlated to SCRT with immediate surgery (associated to impaired postoperative leukocyte counts).[33,34]

A German trial is comparing now LCRCT vs. SCRT (early surgery). This trial is supposed to accrue over 700 pts.

5.3. *Short course radiotherapy and delayed surgery*

The interest in this scheme has increased in the last few years, as delayed surgery can be performed 6–8 weeks after treatment. In the study by Radu[35] 46 patients with non-resectable rectal cancer were treated between 2002 and 2005. The first group (A) had no metastases ($T_4N_XM_0$), whereas the other two groups (B + C) had metastases ($T_4N_XM_1$). In group (B), patients had predominantly loco-regional disease and were not candidates for CRT due to advanced age or comorbidities. In group (C), CRT was given with the intention to perform surgery of both the primary and the secondary tumor if sufficient regression was seen. SCRT was well tolerated by most patients. Only 3 patients suffered diarrhea grade 4. One patient in group (C) died due to sepsis with fever and neutropenia. All patients underwent delayed surgery. R_0 or R_1 was obtained in 22 patients of group (A) (92%), 4 in group (B) (44%), and 6 in group (C) (46%). Pathologic complete response was seen in 4 patients, 2 in group (A) and 2 in group (C). There were no postoperative deaths.

Table 2 – Randomized studies comparing short-course RT vs. long-course RT.

	BJS 2006 Polish study		JCO 2012 RTOG 01.04	
	5 × 5 + TME	50.4/5FU bolus + TME	5 × 5 + TME 6 adjuvant CT	50.4/5-FU ci + TME 4 adjuvant CT
N	155	157	163	163
Follow-up	4 years		5.9 years	
Local failure	9%	14.2%	7.5%	4.4%
DFS	58%	55%	73%	70%
OS	67%	62%	74%	70%
G3-G4 GI			3.2%	5.1%
G3-G4 Global	10.1%	7.1%	5.8%	8.2%

Ci, continuous infusion; DFS, disease-free survival; GI, gastrointestinal; OS, overall survival. $p \leq 0.05$.

Other group[36] used MRI for the evaluation of the resection margin in patients with contraindication for CT due to age, performance status, or comorbidities. Patients were treated with SCRT and delayed surgery. Forty-three patients, with a mean age of 82 years, were selected. Of the 42 patients who received RT, 26 (61%) could undergo surgery. R_0 was obtained in 22 patients, and R_1 or R_2 in 2 patients each. The treatment was well tolerated. Two patients required hospitalization due to diarrhea. One patient presented with delayed toxicity of the small intestine, which was attributable to RT. After a mean follow-up of 18 months, no local relapse was reported in the R_0 and R_1 groups. Mean survival for the whole population was 23 months, but increased to 44 months in the group of patients who underwent surgery.

The improved survival due to the progress in CT and biologic agents over the last years, has caused surgical procedures to become more frequent among patients with disseminated disease. This has favored the alternate use of SCRT and FOLFOX CT. CT would be administered in weeks 1 and 3, and RT in week 5, followed by two more cycles of FOLFOX in weeks 7 and 9, and surgery in week 11.

6. Watch and wait approach

A proportion of patients who receive preoperative RCT for locally advanced (T3/T4, NX) rectal cancer achieve a complete clinical response and a pathologic complete response in the region of 15–30 percent. The "wait and see" approach is contrary to traditional surgical tenets, although radical external beam RT is considered an acceptable therapeutic option for patients with rectal cancer who are unfit for or refuse surgery. For tumors in the low rectum, surgeons and oncologists have collaborated over many years in the search for less mutilating approaches. Thus, strategies such as preoperative RCT followed by sphincter sparing surgery or local excision, or local excision followed by pelvic RCT have been explored.

Some radiation oncologists have reported that locally applied endocavitary radiotherapy is an accepted method of radical treatment for clinically staged T1 and T2 tumors in the mid and distal rectum. Advocates of this procedure treat until response and accept that lack of response is an indication for surgical excision. This technique requires rigorous patient selection, experience, and operator skill in the delivery of superficial radiation directly to the tumor on repeated occasions. The results of the Lyon experience for 101 T1 tumors demonstrate a local control of 90 percent. However, the outcome for T2 tumors is less favorable with reported local recurrence rates of up to 22% of cases.[37] In a larger series of 44 patients combining external RT and 50 KV contact X-ray therapy, the rate of local failure for T2 tumors was <20%, and no nodal failure was reported.[38]

The evidence from an initial observational study in Brazil[39] has been enthusiastically received in the oncological forum, and support is growing for the concept of "wait and see" when a clinical complete response is observed after neoadjuvant RCT for locally advanced rectal cancer. This concept would be better defined as "watch and wait", meaning that the first step after CRT would be to watch with rectoscopy to eventually find a clinical complete response and follow closely. In their last update, a total of 306 clinically staged T2–T4 patients were treated with RCT, of whom 99 achieved a cCR and only six were described as experiencing a local recurrence.[40] These unique data are very close to the data reported by Papillon in 1990[41] and more recently by Maas.[42]This approach may be particularly relevant to European countries where screening programs for rectal cancer are implemented, which should define a much greater proportion of early T1/T2 tumors, and the fact that we have an increasingly aging population, although the response after neoadjuvant RCT is not easy to assess, being diffusion MRI and/or PET-CT under investigation.[43] These conservative approaches would only be acceptable if close observation and frequent rectoscopy are performed.

The available evidence remains insufficient to support this policy and is not robust enough to risk the well-being of a young, fit patient, although it could be justified in elderly patients with early-stage tumors and considerable comorbidity. Furthermore, CRT followed by endocavitary irradiation would be a good option for selected patients, with the aim of organ (rectum) preservation, and not only sphincter preservation as has been demonstrated in the Lyon R96-2 trial.[7,8] Prospective, randomized studies in this field are clearly required to duplicate the Lyon R96-2 trial, and change the clinical practice..

7. Technical aspects of the treatment

Gastrointestinal toxicity is the main acute toxicity observed in the preoperative setting. Acute grade 3 or greater diarrhea is observed in 12–25% of patients.[44,20] Moreover, several studies

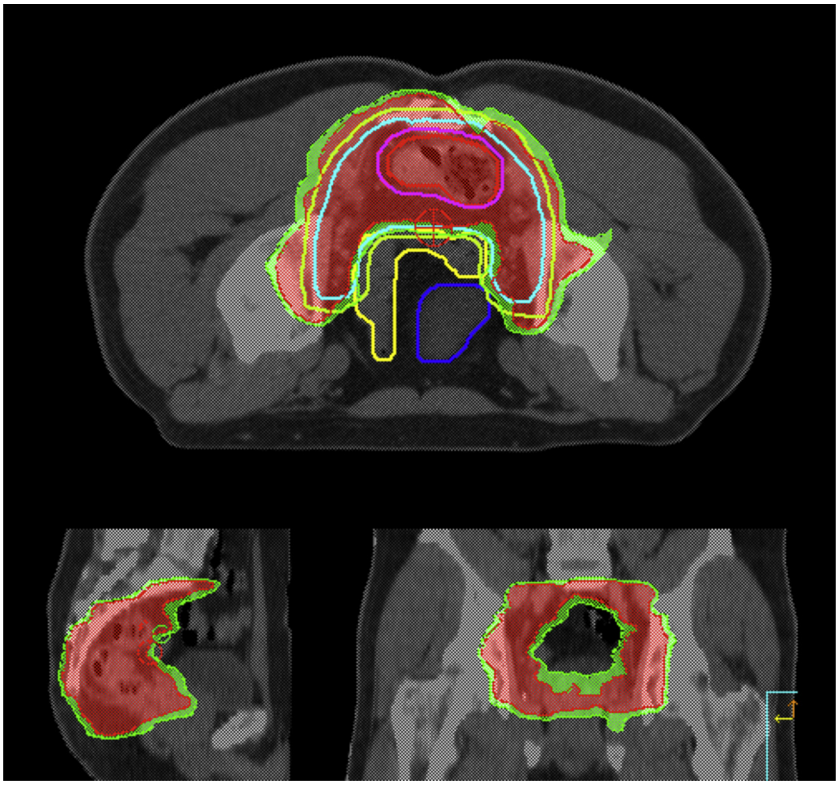

Fig. 1 – Axial, sagittal and coronal computed tomography slices. The 47.5 Gy isodose surface (red) encompasses the CTV, and the 45 Gy isodose surface (green) encompasses de PTV.

have demonstrated a statistically significant association between the development of G3 or greater acute small bowel (SB) toxicity and the volume of SB irradiated.[45–48] V15 have been postulated as a reliable dose-volume parameter to be assessed during dose plan evaluation; patients in whom more than 150 cc of small bowel receive ≥15 Gy appeared to have the greatest risk of grade 3 small-bowel toxicity.

It is now agreed that the target must be kept below the S2/S3 junction in most cases.[49] In the ACCORD 12 trial, 3D conformal RT was used to irradiate small posterior volume to 50 Gy. At 3 years, grade 3 toxicity was less than 5% and the rate of local recurrence was <3% in the Capox arm[6]

In this scenario, intensity-modulated radiation therapy (IMRT) has been proposed as a technique to reduce the toxicity associated with CRT. IMRT could potentially reduce the dose to the small bowel, thereby reducing the gastrointestinal side effects caused by radiation, even when combined with more effective radiation sensitizers. Appropriate delineation of target volumes and organs at risk is critical due to the high degree of conformity achieved with IMRT.[50] Dosimetric studies have shown that IMRT has better normal tissue sparing ability than other radiation techniques[51–54] (Fig. 1). However, only a limited number of clinical studies have been reported to date.[55–57] These prospective trials have demonstrated the feasibility of treating with IMRT and concomitant chemotherapy, but more data regarding acute and long-term toxicity are necessary.

Preliminary results of the RTOG 0822 phase II study of preoperative IMRT with Capecitabine and Oxaliplatin in LARC patients[58] suggest a reduction in ≥ Grade 2 toxicity, but toxicity data analysis is currently being performed toward identifying optimal IMRT planning criteria for future studies. Simultaneously, the University of Navarra Hospital has carried out a prospective study of preoperative chemo-IMRT in rectal cancer.[51,55,56,59] The treatment protocol included simultaneous combination of capecitabine and oxaliplatin (CAPOX) with 47.5 Gy hypofractionated IMRT (2375 Gy/fx). A total of 140 patients with LARC were analyzed. No grade 4 toxicity was reported. Grade 1–2 rectitis was the most frequently observed toxicity (74% of patients), and this could be attributed to oxaliplatine. Grade 3 diarrhea was reported in 13 patients (9%), and grade 3 rectitis in 14 patients (10%). After surgery, 50% of patients achieved a major pathologic response. With a median follow-up of 5.2 years, only three patients presented locoregional failure (2.1%). The 8-year OS and DFS rates were 89% (95% CI: 96.3–105.2) and 78% (95% CI: 88–99.5), respectively, and the distal failure rate was 16%. This treatment protocol is feasible and safe, small bowel toxicity rate is low, and produces major pathological responses in about 50% of the patients. Although no firm conclusions can be drawn from this phase II trial, these results indicate that hypofractionated Capecitabine – IMRT achieve a good clinical outcome in LARC patients.

8. Conclusions

Even if the need for neoadjuvant treatment for locally advanced rectal cancer is clear enough, the optimal strategy has yet to be defined. New clinical evidence is needed to

definitely define which treatment schedule is superior, but also longer follow-up evaluation could be determinant, since for rectal cancer patients (as opposed to pure colon cancer) the trend of local control and survival continues to decrease after 5 years. At present, LCRCT seems to have greater clinical versatility and can allow high personalization of treatment. On the other hand, SCRT can be used in patients with intermediated risk rectal tumors, located more than 5 cm away from the anal margin, with a non-threatened circumferential resection margin and with a low risk of lymph node involvement. The use of a large shared database could favor the individualization of surrogative end-points to address the future research. The Watch and Wait policy after preoperative RCT can be an attractive subject of future research for small tumors, but can not be considered standard treatment at the present time. In order to reduce the intestinal toxicity, keeping the target volume below S2/S3 junction is generally recommended. The use of IMRT in the preoperative setting of LARC patients is based on a strong rationale and dosimetric evidence of small intestine irradiated volume.

Conflict of interest

None declared.

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REFERENCES

1. NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer. *JAMA* 1990;**264**(September (11)):1444–50.
2. Preoperative short-term radiation therapy in operable rectal carcinoma. A prospective randomized trial. Stockholm Rectal Cancer Study Group. *Cancer* 1990;**66**(July (1)):49–55.
3. Glynne-Jones R, Wallace M, Livingstone JI, Meyrick-Thomas J. Complete clinical response after preoperative chemoradiation in rectal cancer: is a "wait and see" policy justified? *Dis Colon Rectum* 2008;**51**(January (1)):10–9.
4. Glimelius B, Gronberg H, Jarhult J, Wallgren A, Cavallin-Stahl E. A systematic overview of radiation therapy effects in rectal cancer. *Acta Oncol* 2003;**42**(5/6):476–92.
5. Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006;**93**(October (10)):1215–23.
6. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Clinical outcome of the ACCORD 12/0405 PRODIGE 2 randomized trial in rectal cancer. *J Clin Oncol* 2012;**30**(December (36)):4558–65.
7. Gerard JP, Chapet O, Nemoz C, et al. Improved sphincter preservation in low rectal cancer with high-dose preoperative radiotherapy: the lyon R96-02 randomized trial. *J Clin Oncol* 2004;**22**(June (12)):2404–9.
8. Ortholan C, Romestaing P, Chapet O, Gerard JP. Correlation in rectal cancer between clinical tumor response after neoadjuvant radiotherapy and sphincter or organ preservation: 10-year results of the Lyon R 96-02 randomized trial. *Int J Radiat Oncol Biol Phys* 2012;**83**(June (2)):e165–71.
9. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. *N Engl J Med* 1997;**336**(April (14)):980–7.
10. Peeters KC, Marijnen CA, Nagtegaal ID, et al. The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. *Ann Surg* 2007;**246**(November (5)): 693–701.
11. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol* 2012;**30**(June (16)):1926–33.
12. Roh MS, Colangelo LH, O'Connell MJ, et al. Preoperative multimodality therapy improves disease-free survival in patients with carcinoma of the rectum: NSABP R-03. *J Clin Oncol* 2009;**27**(November (31)):5124–30.
13. Park JH, Yoon SM, Yu CS, Kim JH, Kim TW, Kim JC. Randomized phase 3 trial comparing preoperative and postoperative chemoradiotherapy with capecitabine for locally advanced rectal cancer. *Cancer* 2011;**117**(August (16)):3703–12.
14. *NCCN clinical practice guidelines in oncology: rectal cancer. (Version 4.2013)*; 2013. http://www.nccn org/professionals/physician_gls/f_guidelines asp#rectal
15. NCI. National Cancer Institute. *PDQ Rectal Cancer Treatment*. Bethesda, MD: National Cancer Institute; 2013. Available at: http://cancergov/cancertopics/pdq/treatment/rectal/HealthProfessional [last modified 02.08.13].
16. Valentini V, Aristei C, Glimelius B, et al. Multidisciplinary Rectal Cancer Management: 2nd European Rectal Cancer Consensus Conference (EURECA-CC2). *Radiother Oncol* 2009;**92**(August (2)):148–63.
17. Guillem JG, az-Gonzalez JA, Minsky BD, et al. cT3N0 rectal cancer: potential overtreatment with preoperative chemoradiotherapy is warranted. *J Clin Oncol* 2008;**26**(January (3)):368–73.
18. Nagtegaal ID, Quirke P. What is the role for the circumferential margin in the modern treatment of rectal cancer? *J Clin Oncol* 2008;**26**(January (2)):303–12.
19. Allal AS, Bieri S, Pelloni A, et al. Sphincter-sparing surgery after preoperative radiotherapy for low rectal cancers: feasibility, oncologic results and quality of life outcomes. *Br J Cancer* 2000;**82**(March (6)):1131–7.
20. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004;**351**(October (17)):1731–40.
21. Capirci C, Valentini V, Cionini L, et al. Prognostic value of pathologic complete response after neoadjuvant therapy in locally advanced rectal cancer: long-term analysis of 566 ypCR patients. *Int J Radiat Oncol Biol Phys* 2008;**72**(September (1)):99–107.
22. Mihaylova I, Parvanova V, Velikova C, Kurteva G. Degree of tumor regression after preoperative chemo-radiotherapy in locally advanced rectal cancer – preliminary results. *Rep Pract Oncol Radiother* 2011;**16**(237):242.
23. Valentini V, van Stiphout RG, Lammering G, et al. Nomograms for predicting local recurrence, distant metastases, and overall survival for patients with locally advanced rectal cancer on the basis of European randomized clinical trials. *J Clin Oncol* 2011;**29**(August (23)):3163–72.
24. Cellini F, Valentini V. Sphincter preservation in the treatment of locally advanced rectal cancers. *Oncology (Williston Park)* 2012;**26**(September (9)):872.
25. Bosset JF, Calais G, Mineur L, et al. Enhanced tumorocidal effect of chemotherapy with preoperative radiotherapy for rectal cancer: preliminary results – EORTC 22921. *J Clin Oncol* 2005;**23**(August (24)):5620–7.

26. Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. *J Clin Oncol* 2008;**26**(August (22)):3687–94.
27. Hofheinz RD, Wenz F, Post S, et al. Chemoradiotherapy with capecitabine versus fluorouracil for locally advanced rectal cancer: a randomised, multicentre, non-inferiority, phase 3 trial. *Lancet Oncol* 2012;**13**(June (6)):579–88.
28. Conde S, Borrego M, Teixeira T, Teixeira R, SA A, Soares P. Neoadjuvant oral VS infusional chemoradiotherapy on locally advanced rectal câncer: prognostic factors. *Rep Pract Oncol Radiother* 2013;**18**(67):75.
29. Aschele C, Cionini L, Lonardi S, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 randomized phase III trial. *J Clin Oncol* 2011;**29**(July (20)):2773–80.
30. Gerard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol* 2010;**28**(April (10)):1638–44.
31. Rodel C, Liersch T, Becker H, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. *Lancet Oncol* 2012;**13**(July (7)):679–87.
32. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol* 2012;**30**(November (31)):3827–33.
33. Pettersson D, Cedermark B, Holm T, et al. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. *Br J Surg* 2010;**97**(April (4)):580–7.
34. Pettersson D, Glimelius B, Iversen H, Johansson H, Holm T, Martling A. Impaired postoperative leucocyte counts after preoperative radiotherapy for rectal cancer in the Stockholm III Trial. *Br J Surg* 2013;**100**(April (7)):969–75.
35. Radu C, Berglund A, Pahlman L, Glimelius B. Short-course preoperative radiotherapy with delayed surgery in rectal cancer – a retrospective study. *Radiother Oncol* 2008;**87**(June (3)):343–9.
36. Hatfield P, Hingorani M, Radhakrishna G, et al. Short-course radiotherapy, with elective delay prior to surgery, in patients with unresectable rectal cancer who have poor performance status or significant co-morbidity. *Radiother Oncol* 2009;**92**(August (2)):210–4.
37. Gerard JP, Roy P, Coquard R, et al. Combined curative radiation therapy alone in (T1) T2–3 rectal adenocarcinoma: a pilot study of 29 patients. *Radiother Oncol* 1996;**38**(February (2)):131–7.
38. Gerard JP, Ortholan C, Benezery K, et al. Contact X-ray therapy for rectal cancer: experience in Centre Antoine-Lacassagne, Nice, 2002–2006. *Int J Radiat Oncol Biol Phys* 2008;**72**(November (3)):665–70.
39. Habr-Gama A, de Souza PM, Ribeiro Jr U, et al. Low rectal cancer: impact of radiation and chemotherapy on surgical treatment. *Dis Colon Rectum* 1998;**41**(September (9)):1087–96.
40. Habr-Gama A, Perez RO, Proscurshim I, et al. Patterns of failure and survival for nonoperative treatment of stage c0 distal rectal cancer following neoadjuvant chemoradiation therapy. *J Gastrointest Surg* 2006;**10**(December (10)):1319–28.
41. Papillon J. Present status of radiation therapy in the conservative management of rectal cancer. *Radiother Oncol* 1990;**17**(April (4)):275–83.
42. Maas M, Beets-Tan RG, Lambregts DM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. *J Clin Oncol* 2011;**29**(December (35)):4633–40.
43. Patel UB, Brown G, Rutten H, et al. Comparison of magnetic resonance imaging and histopathological response to chemoradiotherapy in locally advanced rectal cancer. *Ann Surg Oncol* 2012;**19**(September (9)):2842–52.
44. O'Connell MJ, Martenson JA, Wieand HS, et al. Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. *N Engl J Med* 1994;**331**(August (8)):502–7.
45. Baglan KL, Frazier RC, Yan D, Huang RR, Martinez AA, Robertson JM. The dose-volume relationship of acute small bowel toxicity from concurrent 5-FU-based chemotherapy and radiation therapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2002;**52**(January (1)):176–83.
46. Gunnlaugsson A, Kjellen E, Nilsson P, Bendahl PO, Willner J, Johnsson A. Dose-volume relationships between enteritis and irradiated bowel volumes during 5-fluorouracil and oxaliplatin based chemoradiotherapy in locally advanced rectal cancer. *Acta Oncol* 2007;**46**(7):937–44.
47. Robertson JM, Lockman D, Yan D, Wallace M. The dose-volume relationship of small bowel irradiation and acute grade 3 diarrhea during chemoradiotherapy for rectal cancer. *Int J Radiat Oncol Biol Phys* 2008;**70**(February (2)):413–8.
48. Tho LM, Glegg M, Paterson J, et al. Acute small bowel toxicity and preoperative chemoradiotherapy for rectal cancer: investigating dose-volume relationships and role for inverse planning. *Int J Radiat Oncol Biol Phys* 2006;**66**(October (2)):505–13.
49. Nijkamp J, Kusters M, Beets-Tan RG, et al. Three-dimensional analysis of recurrence patterns in rectal cancer: the cranial border in hypofractionated preoperative radiotherapy can be lowered. *Int J Radiat Oncol Biol Phys* 2011;**80**(May (1)):103–10.
50. Myerson RJ, Garofalo MC, El Naqa I, et al. Elective clinical target volumes for conformal therapy in anorectal cancer: a radiation therapy oncology group consensus panel contouring Atlas. *Int J Radiat Oncol Biol Phys* 2009;**74**(July (3)):824–30.
51. Arbea L, Ramos LI, Martinez-Monge R, Moreno M, Aristu J. Intensity-modulated radiation therapy (IMRT) vs. 3D conformal radiotherapy (3DCRT) in locally advanced rectal cancer (LARC): dosimetric comparison and clinical implications. *Radiat Oncol* 2010;**5**:17.
52. Callister MD, Ezzell GA, Gunderson LL. IMRT reduces the dose to small bowel and other pelvic organs in the preoperative treatment of rectal cancer. *Int J Radiat Oncol Biol Phys* 2006;**66**(3):S290.
53. Guerrero Urbano MT, Henrys AJ, Adams EJ, et al. Intensity-modulated radiotherapy in patients with locally advanced rectal cancer reduces volume of bowel treated to high dose levels. *Int J Radiat Oncol Biol Phys* 2006;**65**(July (3)):907–16.
54. Mok H, Crane CH, Palmer MB, et al. Intensity modulated radiation therapy (IMRT): differences in target volumes and improvement in clinically relevant doses to small bowel in rectal carcinoma. *Radiat Oncol* 2011;**6**(June (8)):63.
55. Arbea L, Martinez-Monge R, Diaz-Gonzalez JA, et al. Four-week neoadjuvant intensity-modulated radiation therapy with concurrent capecitabine and oxaliplatin in locally advanced rectal cancer patients: a validation phase II trial. *Int J Radiat Oncol Biol Phys* 2012;**83**(June (2)):587–93.
56. Aristu JJ, Arbea L, Rodriguez J, et al. Phase I-II trial of concurrent capecitabine and oxaliplatin with preoperative intensity-modulated radiotherapy in patients with locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2008;**71**(July (3)):748–55.

57. Ballonoff A, Kavanagh B, McCarter M, et al. Preoperative capecitabine and, accelerated intensity-modulated radiotherapy in locally advanced rectal cancer: a phase II trial. *Am J Clin Oncol Cancer Clin Trials* 2008;**31**(June (3)): 264–70.
58. Garofalo M, Moughan J, Hong T, et al. RTOG 0822: a phase H study of preoperative (PREOP) chemoradiotherapy (CRT) utilizing imrt in combination with capecitabine (C) and oxaliplatin (O) for patients with locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys* 2011;**81**(2):S3–4.
59. Arbea L, Moreno M, Rodriguez J, et al. Four-week neoadjuvant intensity modulated radiation therapy with concurrent capecitabine and oxaliplatin in locally advanced rectal cancer patients: a single institution experience with long-term follow-up. *Int J Radiat Oncol Biol Phys* 2012;**84**(November (3)):S347.