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Locally advanced rectal cancer: The importance of a multidisciplinary approach

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Abstract

Rectal cancer accounts for a relevant part of colorectal cancer cases, with a mortality of 4-10/100000 per year. The development of locoregional recurrences and the occurrence of distant metastases both influences the prognosis of these patients. In the last two decades, new multimodality strategies have improved the prognosis of locally advanced rectal cancer with a significant reduction of local relapse and an increase in terms of overall survival. Radical surgery still remains the principal curative treatment and the introduction of total mesorectal excision has significantly achieved a reduction in terms of local recurrence rates. The employment of neoadjuvant treatment, delivered before surgery, also achieved an improved local control and an increased

sphincter preservation rate in low-lying tumors, with an acceptable acute and late toxicity. This review describes the multidisciplinary management of rectal cancer, focusing on the effectiveness of neoadjuvant chemoradiotherapy and of post-operative adjuvant chemotherapy both in the standard combined modality treatment programs and in the ongoing research to improve these regimens.

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Key words: Locally advanced rectal cancer; Neo-adjuvant treatment; Radio-chemotherapy; Surgery; Adjuvant treatment; Target drugs

Core tip: In the last three decades, multidisciplinary treatments have significantly reduced both local and distant recurrences due to locally advanced rectal cancer, with a consensual increase in overall survival. Even if surgery still remains the mainstay of treatment, for patients with stage II or III rectal cancer, available data support the use of neo-adjuvant chemoradiotherapy followed by radical resection. In the neo-adjuvant setting, novel biologic agents targeting aberrant pathways in rectal carcinogenesis are currently under study. This review describes the multidisciplinary management of rectal cancer, focusing on evidences supporting this approach and on the ongoing research to improve these regimens.

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INTRODUCTION

Rectal cancer accounts for nearly a third of colorectal cancer cases and the mortality with a mortality of 4-10/100000 per year^[1].

In the last twenty years, new multimodality strategies have been introduced in order to reduce both local and distant risk of recurrences.

As reported in the ESMO 2013 guidelines, from a practical point of view, rectal cancers could be divided into four groups, that can be also used for categorising rectal cancers clinical subgroups: (1) very early (some cT1); (2) early (cT1-2, some cT3), or “good”; (3) intermediate (cT3- some cT4a), or “bad”; and (4) locally advanced (cT3crn +, some cT4a, all cT4b), or “ugly”.

Factors other than clinical T stage, such as tumour height, anterior location, proximity of the tumour or lymph node growths to the mesorectal fascia, size of the mesorectum, cN stage and vascular and nerve invasion are also relevant. It is presently not possible to give a precise definition of which T and N substages belong to these groups.

In recent studies, the term locally advanced (LARC) has been commonly used for the intermediate/bad group, but is best reserved for the truly locally advanced/ugly tumours as used in the most recent European consensus documents^[2-5].

Multidisciplinary treatments have reduced local recurrences due to LARC from 40 to < 10% with an increase in overall survival (OS) from 50% to 75% in the last 40 years^[6]. High-quality surgery still remains cornerstone of the treatment in patients with rectal cancer, and the introduction of total mesorectal excision (TME) has revolutionised the oncologic outcomes of patients with resectable rectal cancer, leading to significantly lower local recurrence rates at 10-year follow-up^[7,8].

In order to improve the outcome, pre- and post-operative combined therapy (radiotherapy +/- chemotherapy) has been used.

Due to a favourable acute and long-term toxicity profile combined with a significant decrease in local failure, neo-adjuvant combined chemo-radiotherapy is now widely used in standard clinical practice for LARC^[9,10].

This review describes the multidisciplinary management of rectal cancer, focusing on the effectiveness of neoadjuvant chemoradiotherapy (CRT) and of post-operative adjuvant chemotherapy both in the standard combined modality treatment programs and in the ongoing research to improve these regimens.

RESEARCH

We extensively reviewed the scientific literature on this topic and studies on the multimodality treatment of LARC have been searched in peer-review journals. We used the MEDLINE and CancerLit databases, and the search was restricted to English-language publications. The search term included the terms “rectal cancer” together with “induction, primary, neoadjuvant, pre-

operative, chemotherapy, radiotherapy, chemoradiation, combined treatment, locally advanced”.

Full articles were obtained and reviewed, and all the included references and related articles were checked for additional appropriate references.

If results were reported or updated in more than one publication, only the most recent one was considered.

LARC: WHAT IS THE ENTITY OF THE PROBLEM?

The occurrence of a locoregional relapse and the development of distant metastases substantially influences the overall prognosis of rectal cancer. The extent of tumour invasion into peri-rectal fat as well as other anatomic and biologic determinants like lymphatic, vascular or neural invasion, tumour differentiation, integrity of the radial resection margin, and location of the tumour in the upper, middle or lower part of the rectum can have an impact on the risk for local recurrences^[11].

An accurate American Joint Committee on Cancer TNM (Classification of Malignant Tumours T = tumor, N = nodes, M = metastasis) tumor staging is essential to identify the patients who might be candidates for upfront surgery *vs* those who might require neo-adjuvant therapy.

Radical surgery represents the principal curative treatment and locoregional tumour control has improved significantly after the introduction of TME, which leads to the complete removal of the intact mesorectum including lymphatic vessels, lymph nodes, nerves, and vascular supply. TME now represents the gold-standard surgical procedure for rectal cancer^[12].

For the last three decades, post-operative radiotherapy +/- chemotherapy has been used widely in an attempt to improve outcome. Post-operative CRT significantly improved both local control and OS when compared with surgery +/- radiotherapy. This prompted a National Cancer Institute Consensus Conference in the United States in 1990 to recommend it for patients with TNM stage II and III rectal cancer as standard treatment^[13].

In recent years, pre-operative neo-adjuvant CRT has been studied more extensively. After showing less acute and long-term toxicity along with an improved local control in a randomised study, pre-operative combined CRT has replaced post-operative CRT as standard treatment for LARC^[9,14].

MANAGEMENT OF LARC IN CLINICAL PRACTICE: STANDARD OF CARE

At present, the clinical management of LARC is performed most effectively by a multidisciplinary team, including GPs, gastroenterologists, medical oncologists, radiation oncologists, radiologists, surgeons and pathologists (Table 1).

Early and accurate determination of tumour location within the rectum and TNM stage are important because

Table 1 Multidisciplinary team involved in the treatment of rectal cancer

Multidisciplinary team-Specialists	Role in the management of LARC
General Practitioner	Colorectal cancer screening, follow-up
Gastroenterologist	Screening, diagnosis (colonoscopy)
Medical Oncologist	Neo-adjuvant and adjuvant treatment, follow-up, management of toxicity
Surgeon	Radical surgery with TME
Radiation Oncologist	Preoperative (or in a few cases post-operative) radio or chemoradiotherapy
Radiologist	Staging, evaluation of response, follow-up
Pathologist	Preliminary diagnosis (on biopsy obtained during colonoscopy) and definitive diagnosis and pathological staging on surgical specimen

LARC: Locally advanced rectal cancer.

such information will determine the type of surgery to be performed and the need for CRT. Endoscopic ultrasound for the earliest tumours (cT1-T2) or rectal magnetic resonance imaging (MRI) for all others is recommended in order to select patients for pre-operative treatment. Pre- or post-operatively complete colonoscopy is also required.

The recommended modalities of treatment for rectal cancers are summarised in Table 2.

EVIDENCES FOR THE USE OF NEO-ADJUVANT TREATMENT IN LARC

In the last three decades several randomised studies were performed in order to compare pre-operative radiotherapy to surgery. These studies showed a decrease in local recurrence rates, even if only the Swedish Rectal Cancer Trial demonstrated an advantage in OS using the short-course pre-operative radiotherapy *vs* surgery alone^[15]. A recent meta-analysis also concluded that pre-operative radiotherapy followed by surgery significantly improved local control and OS when compared with surgery alone^[16]. Moreover, recent data deriving from the 12-year follow-up of the multicentre, randomised controlled TME trial, which randomised patients with clinically resectable disease (T1-3) to radical surgery with TME alone or to a preoperative radiation regimen of 5 × 5 Gy applied immediately before TME surgery, showed that for patients with TNM stage III cancer with a negative circumferential resection margin, 10-year survival was 50% in the preoperative radiotherapy group *vs* 40% in the control-arm receiving surgery-alone group ($P = 0.032$)^[17].

Also the utility to add concomitant chemotherapy to radiation in the neo-adjuvant setting has been investigated^[18]. Two large randomised phase III studies have tested pre-operative CRT and 5-FU-based chemotherapy *vs* radiotherapy alone. Both studies showed that pre-operative CRT might be the preferred option, due to the benefits

Table 2 Clinical management of rectal cancer according to risk categories^[2]

Risk group	Management
Very early (some cT1)	Local excision (TEM) If poor prognostic characteristics are present, (such as high grade, vascular invasion, <i>etc</i>), TME resection (or possibly CRT) can be considered
Early (cT1-2, some cT3), or "good"	Surgery alone (TME) is sufficient, and should result in a few rate of local recurrences (< 3%-4% after 5 yr) If poor prognostic characteristics are present, such as circumferential margin or nodal involvement, post-operative CRT or CT can be added
Intermediate (cT3- some cT4a), or "bad"	Surgery alone results in a high rates of local recurrences (> 8%-10% after 5 yr if surgery alone) Add preoperative RT (5 × 5 Gy) or CRT followed by TME If cCR is obtained with CRT, wait-and-see policy may be considered in selected cases (such as high risk patients for surgery)
Locally advanced (cT3crn +, some cT4a, all cT4b), or "ugly"	Preoperative CRT is needed to achieve high probability of R0 surgery (TEM) and a decrease of local recurrences Preoperative 5 × 5 Gy RT with a delay to surgery can be considered in elderly or in patients with severe comorbidity who cannot tolerate CRT

TEM: Total mesorectal excision; CRT: Chemoradiotherapy; cCR: Clinical complete response; CT: Computed tomography.

on conservative surgery and to the bad compliance to post-operative treatment. Also a significant reduction of local recurrence rate after combined CRT was observed, even if it was not translated into an improvement in disease free survival (DFS) and OS^[19,20].

Similar results derived from the randomised EORTC Radiotherapy Group Trial 22921 by Bosset *et al*^[21] in patients with LARC who received preoperative radiotherapy, the addition of fluorouracil-based chemotherapy preoperatively or postoperatively had no significant effect on survival. However, 5-FU chemotherapy, regardless of whether it was administered before or after surgery, conferred a significant benefit in terms of local control.

Unfortunately, the combined CRT showed increased the toxicity when compared with preoperative radiation alone. However, these side effects were predictable and manageable allowing and not impairing the delivery of full radiotherapy doses.

These findings have been confirmed by a recent Cochrane meta-analysis based on the results of four published studies comparing pre-operative RT alone *vs* pre-operative CRT in patients with resectable stage II and III rectal cancer. The results showed that the addition of chemotherapy to pre-operative radiotherapy significantly increased grade III/IV acute toxicity, while no differences were observed in post-operative morbidity or mortality. Compared to pre-operative RT alone, pre-operative CRT significantly increased the rate of complete pathological response, even if this did not translate into a higher sphincter preservation rate. The incidence of local recurrence at five years was significantly lower in the CRT group compared to RT alone. No statistically significant

differences were observed in 5-years DFS and OS^[22].

Whether pre-operative CRT is preferable than post-operative CRT has been demonstrated by the CAO/ARO/AIO-94 trial, which showed no greater surgical morbidity for CRT, while pre-operative combined modality had a significant decrease in local failure, acute toxicity, chronic toxicity, in addition to a better compliance to treatment, even if no difference in 5-year survival rates was observed^[19,23].

Given the superior overall compliance rate, the improved local control, reduced toxicity, and increased sphincter preservation in low-lying tumours, pre-operative CRT is now the preferred treatment.

Neoadjuvant treatment: A standard of care

For patients with stage II or III rectal cancer (in particular with extramural infiltration and/or regional lymph nodes involvement), available data support the use of neo-adjuvant CRT with continuous infusion 5-FU, followed by radical resection^[9].

Given the superior overall compliance rate, the improved local control, reduced toxicity, and increased sphincter preservation rate in low-lying tumors, pre-operative CRT is now the preferred treatment when compared with post-operative CRT^[9].

Pre-operative CRT is often preferred in patients with resectable rectal cancer due to a significant decrease in local failure, acute toxicity, chronic toxicity, even if no significant differences in term of OS have been observed^[19,23].

There are two different approaches to pre-operative radiation therapy: an intensive short-course radiotherapy with large fractions (5×5 Gy), for 1 wk followed by immediate surgery, or 5-6 wk of conventional fractions (1.8-2.0 Gy), combined with concurrent chemotherapy, and surgery 4-6 wk later (long-course pre-operative radiotherapy).

In clinical practice, in larger tumours (cT3-4 and/or N+) in which the goal is downstaging or downsizing, full course pre-operative CRT (50.4 Gy plus concurrent chemotherapy) is considered the standard treatment. In patients with earlier stages of disease both the two strategies can be considered.

Patients with a cT3N0, cT4N0 and cTxN+ should be considered for a neo-adjuvant CRT. According to most experts, T2N0 distal rectal cancer should also be considered also for a neo-adjuvant CRT. Indeed, in patients with low rectal cancer (0-5 cm from the anal verge) the risk of a positive circumferential resection margin is higher as well as the local recurrence rate. With the strategy of pre-operative CRT or radiotherapy we probably overtreat some cT3N0 patients because of potential over-staging, but experts agree to take this risk as pre-operative CRT is clearly better tolerated and results in a lower regional recurrence rate compared with post-operative radiotherapy or CRT^[2,24].

Surgical treatment and “wait-and-see policy”

High-quality surgery is the cornerstone of the treatment. Preferably, surgery should be done by a team of expe-

rienced surgeons collaborating with a multidisciplinary team in high-volume centres. The main goal of surgical treatment is to achieve clear surgical margins yielding a curative radical resection (R0). TME has become the standard procedure for low rectal cancers resection. It results in higher local control and increased DFS. The surgical approach to resection varies with the location of the tumour. Proximal tumours are resected by a low anterior resection (LAR) and primary anastomosis. Most mid-rectal tumours can also be resected by a LAR, although when the anastomosis is low in the pelvis, a temporary ileostomy or colostomy may be required to divert the fecal stream from the anastomosis and facilitate proper healing. Distal rectal tumours typically require an abdominoperineal resection with permanent colostomy because the anal sphincter cannot be preserved.

Finally, only a small subgroup of superficial, distal rectal tumours with favourable histological features may be resected with local excision, that should go through the muscular layer^[25]. If local excision is required, TEM (transanal endoscopic microsurgery) is the standard procedure. Transanal endoscopic microsurgery appears to be appropriate only for T1 N0 tumors and it has been developed in order to obtain clear margins using transanal excision: in these cases, this approach results in low rates of local relapse^[26,27].

Recently, even if surgery still remains the cornerstone of treatment, the rectal preservation after clinical complete response (cCR) to neo-adjuvant treatment is becoming a point of interest. In fact, approximately up to 20% of the patients who undergo neoadjuvant CRT for LARC obtain a pCR^[28].

It is now widely established that rectal cancer patients obtaining pCR after neoadjuvant CRT have both lower local recurrence rate and improved survival when compared to those with residual tumor^[29].

Several studies investigated the possibility of a “wait-and-see policy” (omission of surgery with follow-up) and showed long-term results as good as that of patients with a pCR after surgery^[30,31]. Several trials investigated the role of “wait-and-see policy” in patients with low rectal cancer who achieved a cCR after CRT: these patients did not receive surgery but only underwent to a close follow-up. The results suggested that the “wait-and-see policy” with strict selection criteria, up-to-date imaging techniques, and close follow-up results in promising long-term results, as good as that of patients with a pCR after surgery^[30-32].

However, accuracy for regression rate and histopathological response is still unsatisfying. Diffusion-weighted MRI prior, during and after CRT may permit early evaluation of response during neoadjuvant CRT, in order to classify patients as “responders” and “non-responders”. Diffusion-weighted MRI seems to predict more sensibly the achievement of a pCR, important prognostic factor by itself, when compared with MRI only^[33,34].

The role of fluorine-18-fluorodeoxyglucose-positron emission tomography/computed tomography (FDG-

PET/CT) is still investigational. Several studies also showed that FDG-PET, especially when combined with MRI, could be more accurate for predicting pathological response^[35].

In conclusion, “Wait-and-see policy”, if assessed with up-to-date imaging techniques, needs further investigations and could form the basis for future large prospective randomised trials with adequate follow-up.

Adjuvant treatment

In the standard combined-modality treatment programs for LARC, CRT and surgery are often followed by 4-6 mo of adjuvant chemotherapy.

The aim of adjuvant treatment is to complement the reduction of local failures achieved through pre-operative treatment with a reduction of distant metastasis and, thereby, increase survival. To date, adjuvant chemotherapy is recommended (and given) by most centres in Western Countries.

The support for the use of adjuvant chemotherapy is provided by a recent pooled analysis of five randomised studies demonstrating a 20% absolute survival benefit with post-operative chemotherapy, administered for 6-18 mo +/- post-operative radiotherapy, compared with observation or post-operative radiation alone^[36].

Adjuvant treatment including fluoropyrimidine-based chemotherapy is effective in those patients who show downstaging (pT1-pT2) after pre-operative treatments (CRT or radiotherapy). An unanswered question is whether adjuvant chemotherapy may be omitted in patients with a good response to pre-operative CRT. Several retrospective studies have shown that patients with a pCR have a better long-term prognosis^[18]. However, a contribution of post-operative chemotherapy to this good long-term outcome cannot be excluded, since patients in these studies generally received adjuvant chemotherapy despite the response to pre-operative treatment. Furthermore, it is not possible to determine whether this better outcome depends on inherent characteristics of these tumors, with response to pre-operative CRT representing just an index of a favourable biological and clinical behaviour, or whether this prognosis is indeed the result of tumor response to pre-operative treatment. Response to pre-operative CRT may also indicate chemosensitivity with intact cell death pathways and a potential positive impact also on the efficacy of post-operative treatment.

At present, adjuvant infusional 5-FU/folinic acid or capecitabine for 6 mo is recommended^[37]. Oxaliplatin-based regimens as post-operative chemotherapy are considered in some cases, in particular in patients in whom 5-FU-based CRT did not lead to a downsizing. The duration is sometimes limited to 4 mo, especially in patients who were exposed to a long course of preoperative CRT. In patients who did not receive neo-adjuvant radiotherapy or CRT, adjuvant treatment should be considered after radical resection of a stage II-III rectal cancer. CRT is

more efficacious in this setting than radiotherapy alone or chemotherapy alone, but the tolerance is however less good than when delivered pre-operatively. In the setting of post-operative CRT a long course radiotherapy (45-50.4 Gy in 1.8 Gy fractions) regimen in combination with chemotherapy (protracted infusion of 5-FU or capecitabine) is usually administered^[24].

Several questions remain unanswered, including whether the incorporation of newer cytotoxic and targeted agents can decrease morbidity and mortality associated with this disease.

ACUTE AND LATE TOXICITY OF PRE-OPERATIVE CRT

Pre-operative CRT and advanced surgical procedures may result in high rates of post-operative complications and long-term morbidity with urinary problems, altered defecation, pain, fatigue and sexual problems^[38,39]. In addition, many patients may have a permanent colostomy.

Late toxicities due to pelvic radiotherapy most often are diarrhoea, faecal incontinence, soiling, abdominal cramping and discomfort, rectal strictures, anal blood and mucus loss, but in general, the reported rate of severe late side effects to the gastrointestinal system is about 5%. The most common delayed severe complications are due to small bowel damage and include enteritis, adhesions and small bowel obstruction requiring surgical intervention. Functional results with respect to sphincter preservation are generally not well documented, but both pre- and post-operative radiotherapy seems to have a negative impact, although contradictory data exist^[40-43]. There does not seem to be a relevant difference between short-course radiotherapy and CRT if both are administered pre-operatively^[41].

Also urogenital dysfunction after rectal cancer treatment is common (about 34% after TME in one report). Surgical damage to the pelvic autonomic nerves is the main cause of urinary dysfunction. The influence of radiotherapy on the urinary function remains controversial^[44].

As with surgery, radiotherapy can lead to increased sexual dysfunction. In males a long-term deterioration of ejaculatory and erectile function is due to late radiation damage to the seminal vesicles and small vessels, respectively. In females, radiotherapy leads to vaginal dryness and reduced sexual satisfaction^[38].

Surgical damage to pelvic autonomic nerves might be involved, in particular to the superior hypogastric plexus and hypogastric nerves during presacral mesorectal dissection (resulting in urinary incontinence, ejaculatory dysfunction in male patients and reduced lubrication in female patients) and to the sacral splanchnic nerves and the inferior hypogastric plexus during dissection of the lateral planes of the mesorectum (leading to urinary retention, erectile disorders in men and reduced labial and vaginal swelling in women)^[45].

FUTURE PERSPECTIVES IN NEO-ADJUVANT AND ADJUVANT SETTINGS - NEW DRUGS AND TARGETED THERAPIES

All the new drugs approved for use in colorectal cancer in the last years (irinotecan, oxaliplatin, capecitabine) have radiosensitizing properties. Several trials are thus investigating the incorporation of these agents in the CRT programs for LARC in order to increase treatment efficacy. Efforts are also being made to increase treatment convenience replacing intravenous administration with oral fluoropyrimidine as well as to address each treatment to specific individual patient and tumour biological characteristics and to develop new strategies.

Comparable results were reported for orally administered capecitabine and intravenously delivered 5-FU^[46]. Both irinotecan and oxaliplatin have been combined with pre-operative radiation and either 5-FU or capecitabine with acceptable toxicities rates, but without a significant benefit in term of downstaging/downsizing or survival^[47,48].

Moreover, the next generation of clinical trials is integrating the novel “targeted” drugs, already used in the metastatic setting, like bevacizumab and cetuximab in both pre-operative and post-operative setting. At present, the role of biologic agents is the subject of ongoing clinical trials^[48].

The Epidermal growth factor receptor (EGFR) is a promising target of antitumor treatment because it participates in cell division, inhibition of apoptosis, and angiogenesis.

EGFR-inhibition in particular may result in radiosensitization^[47] and the toxicity profile of anti-EGFR drugs appears favourable for their use in combination with CRT. Several phase I and II trials suggested that the addition of Cetuximab (an anti-EGFR-1 monoclonal antibody) could be safe and effective, even if only a small percentage of patients achieved a pCR^[49-52]. In particular, K-ras mutational status, which is considered crucial to identify the population of patients who are likely to benefit from the addition of anti-EGFR monoclonal antibodies in the metastatic setting, seems to have a less defined role in this setting: while published data by Grimminger *et al.*^[53] seem to confirm the role of K-ras status as predictive of response to pre-operative CRT with the addition of Cetuximab, Erben *et al.*^[54] failed to show any significant relationship between K-ras mutations and PTEN loss and different response patterns in patients treated with the same chemoradiation regimen.

Lastly, the most important trial assessing the role of addition of cetuximab to preoperative chemoradiation is derived from the EXPERT-C trial, where in ninety K-RAS or B-RAF wild type patients randomised to receive CAPOX for four cycles followed by capecitabine-based CRT or the same regimen plus weekly cetuximab, a significantly higher overall survival (HR = 0.27, $P = 0.034$) and response rate (75% *vs* 93%; $P = 0.0028$) were observed,

although the study failed to reach its primary endpoint that was the improvement in complete response rate (9% *vs* 11%, $P = 1$)^[55].

Angiogenesis is another important therapeutic target in colorectal cancer. Radiosensitizing properties have been described in pre-clinical models and a promising anti-tumour activity has been observed in a small series of patients with the anti-vascular endothelial growth factor antibody bevacizumab combined to 5-FU and pre-operative radiation^[56]. However, safety concerns may be raised for its use prior to surgery with an unresected primary rectal tumour, such as thrombosis, haemorrhage and hypertension.

The most recent data concerning the use of bevacizumab in addition to pre and postoperative CRT with CAPOX is derived from the ECOG 3204 trial. The study enrolled 57 patients, of whom 9 (17%) achieved pathological complete response, and 32 patients (59%) experienced pathological tumour downstaging. It also must be noted that at least 68% of patients experienced acute grade 3-4 toxicity and that 47% of patients who underwent surgery experienced a surgical complication^[57].

In conclusion, tailored treatment programs are being developed based on patient and/or tumour biological features that may predict the activity and toxicity of specific drugs.

Similarly, efforts are being made to develop imaging tools that allow the identification of responding and non-responding patients early during pre-operative CRT, such as diffusion-weighted MRI and FDG-PET^[58].

DISCUSSION

Currently, the optimal treatment of locally advanced rectal cancer has evolved toward a multidisciplinary team modality, which includes GPs, gastroenterologists, medical oncologists, radiation oncologists, radiologists, surgeons and pathologists. The multidisciplinary team modality can optimize treatment strategy by enabling an accurate and integrative evaluation of each case of LARC before the planning of treatment.

Recent evidences also confirmed that the multidisciplinary approach improves patient selection for surgery by enabling accurate classification of the recurrence pattern for each LARC patient, in order to achieve R0 resection, representing the most significant factor affecting long-term survival^[59].

In the neo-adjuvant setting, novel biologic agents targeting aberrant pathways in rectal carcinogenesis are currently under study. Incorporating molecular imaging studies and assaying biologic endpoints in these studies will provide insights on the mechanisms of action of these agents.

It is also clear, that in the face of current and future schedules and the increasing number of therapeutic options, translational research is urgently required for the identification of patient groups, by both clinical-pathological features and molecular and genetic markers, that

will gain maximum benefit from each treatment option. In this time of changing therapeutic approaches, it clearly appears that a common standard for large heterogeneous patient groups will prospectively be substituted by more individualised therapies^[60].

We need also to develop a more rigorous and consistent approach for the evaluation of late toxicity due to surgery and radiotherapy with commonly overlapping toxicities. Quality of life and functional assessment tools report differing levels of late normal tissue dysfunction and the latter approach does not measure the patient perspective.

Further progress depends on the completion of well-designed randomised clinical trials, that will lead to the identification of more active combined CRT regimens for LARC.

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