

Low and Medium Rectal Cancer Treatments: Realities and Prospects

Bouchra Amaoui^{1, *}, Mohamed Ouazni², Slimane Semghouli³

¹Service of Radiotherapy, Regional Center of Oncology, Agadir, Morocco

²Faculty of Medicine and Pharmacy, Ibn Zohr University, Agadir, Morocco

³Departement of Health Techniques, Institute of Nursing Professions and Health Techniques, Agadir, Morocco

Abstract

Today, the treatment of rectal cancer must take into account the tumor stage, prognosis at diagnosis, tumor response and patient characteristics. The treatment must be carcinological with sphincter preservation. This study aims to present the reality and perspectives for the treatment of rectal cancer. New surgical techniques, such as total excision of the transanal mesorectal by video and robot-assisted surgery, have emerged to overcome the challenge of navigating the deep and narrow spaces of the pelvis. Medical imaging, particularly functional MRI, has led to better clarification and assessment of the tumor response to treatments. Patients showing a complete response after neoadjuvant chemoradiotherapy treatment may even avoid surgery as part of a close monitoring strategy. The locoregional toxicity of radiotherapy and remote relapses remain a major problem. The administration of preoperative chemotherapy without radiotherapy in small tumors may be an option with similar results. A new personalized approach to the treatment of rectal cancer is feasible with functional conservation and adaptation of treatment to prognostic factors.

Keywords

Rectal Cancer, Radio-chemotherapy, Neo-adjuvant, Watch and Wait

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1. Introduction

Viewed globally, the five-year prevalence of cancer is estimated at 43.8 million in 2018. Colorectal cancer in women is one of the three main types of cancer in terms of incidence and ranks second in terms of mortality. Colorectal cancer (1.8 million cases, or 10.2% of the total) is the third most frequently diagnosed cancer. It is the second leading cause of death (881,000 deaths, or 9.2% of the total) after lung cancer (1.8 million deaths, or 18.4% of the total) [1].

For the past ten years or so, concomitant chemo-radiotherapy and optimization through surgery with total mesorectal excision (TME) with at least adjuvant chemotherapy is the standard treatment for stages II and III. This protocol has reduced the risk of locoregional recurrence from 25% to 5% with a risk of distant metastasis and death of 35% at 5 years.

In addition, this therapeutic strategy seems to over treat small tumors at the expense of complication and impact on the quality of life [2].

One of the main reasons for this evolution is the progress made in terms of means of diagnosis and the treatment response evaluation including magnetic resonance imaging (MRI). Those allow correctly staging the initial disease, specifying the quality predictive factors for the surgery and, above all, correctly evaluate the treatment response [3]. In this work, we will present recent developments and controversies in the care of rectal cancer treatment.

2. Contribution of Magnetic Resonance Imaging (MRI)

Diagnostic MRI with diffusion sequences can accurately

* Corresponding author

E-mail address: bamaoui73@gmail.com (B. Amaoui)

calculate lateral resection margin and correctly stage the tumor. A lateral resection margin <1mm is correlated with a major risk of locoregional recurrence [2-3]. Assessment of the radiological response by MRI after neo-adjuvant

treatment is an excellent prognostic indicator. Actually there is a correlation grade system between the histological response and MRI.

Table 1. Radiological evaluation (MRI) of the tumor response after neo-adjuvant treatment of rectal cancer [2, 3, 17, 18].

TRG Grade	Response	Definition
TRG1	Complete	Absence of residual tumor no tumor signals.
TRG2	Good	Hypo-intense dense fibrosis very little residual tumor.
TRG3	Moderate	≈50% fibrosis or necrosis intermediate residual tumor signal.
TRG4	Slight	Fibrosis or minority mucin predominant tumor.
TRG5	None	Tumor identical to the initial tumor.

This breakthrough paved the way for clinical trials that indicate treatment intensification in poor responders or de-escalation in good responders.

3. Surgical Innovation

Since the 1990s, neo-adjuvant radio-chemotherapy (50Gy in 25 fraction of 2Gy) with standardized mesorectal excision has been the standard for all non-metastatic rectal tumors [4-5]. Currently surgery knows several advances that aim to reduce the sequelae and complications of standard surgery.

3.1. Laparoscopic Surgery

Laparoscopy in rectal cancer surgery is developing in most industrialized countries. It has reduced postoperative complications, the hospital stay, the fast return to normal activity with less aesthetic sequelae and without compromising the carcinologic surgery (complete lateral resection margin >1mm) [6-9].

The randomized COLOR II Phase III trial compared Laparoscopic surgery to laparotomy in 1044 patients. This trial showed no difference in terms of local recurrence between the two techniques (15% at 3 years). But, it proved that the quality of life was better in patients operated by Laparoscopy [10]. Other North American and Australian randomized trials found similar results in the hands of expert surgeons [8, 11, 12].

3.2. Transanal Total Mesorectal Excision

It is a minimally invasive surgery for the low rectal tumors. It brings a better visibility of the mesorectum and especially the lower limit of the resection. Several non-randomized studies have reported the non-inferiority of this technique compared to laparotomy in terms of risk of locoregional recurrence with acceptable side effects. But the surgical technic required a long learning curve [13-14].

3.3. Robotic Surgery

Robotic-assisted surgery is asserting itself in rectal cancer, as for prostate surgery. It allows a better visibility of the small

pelvis. The series and the only meta-analysis published on this technique did not report any inferiority compared to laparotomy [14-16]. Assisted surgery respects the standards of the carcinologists such as the total mesorectal excision and the pelvic lymphadenectomy.

4. Neo-adjuvant Strategies

4.1. Time of Response Evaluation Treatment

In the Stockholm III trial, the study compared the short radiotherapy protocol (5×5Gy) to the standard protocol (25×2Gy) with immediate surgery or after 4 weeks for the short arm. He reported a better complete response rate for arms operating after 4 weeks with lower toxicity than in the arm with surgery at less than 4 weeks. [2].

In 2018, a meta-analysis compared the impact of the delay between surgery and neo-adjuvant treatment with short protocol radiotherapy (more than 4 weeks or less than 4 weeks). It analyzed 5 randomized trials with 1244 patients and confirmed the same results with a complete histological response rate (pCR) RR = 0.49 95% CI (0.31-0.78) p = 0.003, a down staging RR = 2.69 95% CI (1.37-3.0) p<0.00001 and a reduction in postoperative complications RR = 0.81 95% CI (0.7-0.95) p = 0.008. In addition, this meta-analysis found no significant difference in terms of sphincter preservation, quality of life and overall survival [19-20].

4.2. Watch and Wait Strategy

In the 2000s, a Brazilian retrospective series [17, 21] was published which analyzed for the first time the results of patients who had a complete response after concomitant radio-chemotherapy and who were not operated on. The authors of this study called it the Wait-and-Watch strategy, which consists of 12-month follow-up and follow-up by clinical-radiological examinations (Digital rectal examination-Rigid Sigmoidoscopy with biopsy) every six weeks [20, 22, 23] They reported a rate of:

a) Survival without recurrence of 68% at 5 years.

b) Loco-regional relapses at 11%.

c) Overall survival of 78% at 5 years.

A meta-analysis examined individual data from eleven studies involving 602 patients who received radiotherapy with the Wait and watch approach. The results obtained confirmed a correlation between the initial stage and the local recurrence rate. The risk of local recurrence at 3 years was respectively 19%, 31% and 37% for T1-T2, T3 and T4 [24].

A second meta-analysis confirmed these findings with an organ preservation rate of 78% and local relapse of 25% without impact on overall survival (95%) or on disease-free survival (87%) [25].

The complete response is usually obtained after 10 weeks of radiotherapy. These studies show that lateral resection margin less than 1 mm is a major risk factor for locoregional recurrence.

4.3. Neoadjuvant Treatment Without Radiotherapy

An American trial analyzed the results of 32 patients with a T3N0 tumor who were treated with first-line chemotherapy (Six Folfox cycle with four Bevastizumab cycles) with clinical evaluation and MRI before surgery. Thirty patients had a complete response to chemotherapy and R0 surgery with total mesorectal excision. In addition, no case of locoregional recurrence was observed at 4 years of follow-up. Currently several randomized trials are being recruited to compare arms with only chemotherapy to concomitant radio-chemotherapy:

A. The French trial NORADO I [2] aim to show the non-inferiority at 3 years in terms of progression-free survival between neo-adjuvant chemotherapy (Folforinox) compared to the standard arm (Capecitabin RT 50Gy) in patients with low rectal tumor CT3N0, T1T3N1.

B. The Chinese trial FORWAR [26] compared three arms: Folfox arm without radiotherapy, the second arm with concomitant chemotherapy with unique 5 FU and the third arm with concomitant radio-chemotherapy with Folfox. The three arms were followed by TME surgery. The three-year result was in favour of the third arm in terms of complete histological response (arm1-6%, arm2-14% and arm 3-27.5%). In addition, there was no significant difference in terms of overall survival and survival without recurrence. But the digestive and hematological toxicity was more important in the arms with radiotherapy.

The FORWAR trial paved the way for another clinical trial to intensify chemotherapy for radiotherapy with or without surgery [26]. Currently ESSAI GRECCAR 21 is being recruited and its main objective is to compare the rate of organ preservation one year after surgery. This study is stratified into two arms:

a) The first with 4Folforirox then concomitant radio chemotherapy (50Gy plus Capicetabine).

b) The second with only concomitant radio chemotherapy (50 Gy plus Capicetabine).

The response evaluation (Rectoscopy + MRI) will be done in 10 weeks after the end of the radiotherapy and will be followed according to the results by standard surgery (TME) or lumpectomy [27].

Another French OPERA trial randomizes a dose escalation of radiotherapy with chemoradiotherapy and contact therapy (45Gy in five weeks in a pelvic volume and 90Gy contact therapy) compared to chemoradiotherapy (45Gy in five weeks in a pelvic volume and a 9Gy supplement) with also a rectal preservation objective. The surgical or "Watch and wait" strategy is decided based on the response assessed by MRI, rectoscopy and rectal touch at 14 weeks from the start of treatment. In the event of a sub complete response, the decision may be postponed to a second evaluation in weeks 20. The main objective is the rectal preservation rate without stoma and without tumor recurrence that is not operable at 3 years [18].

5. Conclusion

This study summarizes recent evidence and controversies on timely and innovative aspects of the treatment of locally advanced lower and middle rectal cancer. The therapeutic strategy is evolving towards an individualization of treatments. Therapeutic de-escalation without radiotherapy or surgery is possible for small tumors or for correct tumor responses after neo-adjuvant treatment. On the other hand, a therapeutic intensification is recommended for tumors that are at the limit of resectability or for poor responses to treatment.

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