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Current Status of Colorectal Cancer: From Prevention to Treatment

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Abstract

The management process of colorectal cancer (CRC) comprises a large number of strategic moments for disease treatment. Key points of progress on this disease research range from the the initial screening phase, where screening tests and maximum population coverage are crucial, to the decision on what is the best personalized treatment at different disease stages. An overview of each of these phases will be conducted, unifying in one article the two main moments of CRC management. The aims are: to provide an updated account of the recommendations on screening and treatment - in both the surgical phase and the radio-chemotherapy phase; to analyze the tests being conducted, and, finally, to provide an account of foundational research and keys for future guidelines.

Introduction

Colorectal cancer (CRC) is the third most common malignant neoplasm worldwide and the fourth leading cause of cancer-related deaths globally, with approximately 746,000 cases. The incidence of CRC varies by geographic regions across the world. Almost 55% of cases occur in developed countries: while more than 40 per 100,000 people suffered from CRC in United States, less than 5 per 100,000 did in Africa and Asia [1]. According to the EUROCARE study, the incidence in Europe in 2012 was estimated at 340,000 [2], and the number of deaths, at approximately 150,000 [3].

However, an improvement in both diagnostic methods and varying treatment strategies has made possible an increase in survival rates, even in advanced stages [4].

Treatment is multidisciplinary for effective disease control. Therapeutic options include surgery as primary treatment strategy and adjuvant chemotherapy for colon cancer in advanced stages. For rectal cancer, total mesorectal excision is recommended and, depending on the stage, adjuvant or neoadjuvant radio-chemotherapy followed by surgery [5].

Nevertheless, there are alternatives within each therapeutic modality. The major focus of CRC research is the study of the ideal time for treatment and of different therapeutic modalities. These factors are determined by the pathological complete response [6].

In the 20th century, CRC remains a major health problem, despite being a potentially curable disease and an important part of prevention programs [7]. Therefore, this article aims at proving a current overview of CRC screening and treatment recommendations, analyzing the tests carried out and highlighting key research in the field.

Preventive Medicine: The Importance of Screening

The objective of CRC screening is to reduce its incidence and mortality through the detection and resection of precursor lesions. It is therefore key for CRC control in the population. So, treatment is most effective when the lesion is diagnosed at an early stage. That is why it is considered a curable disease [8,9].

The importance of screening has been studied, and its role in reducing CRC incidence, demonstrated. Yang, et al. [10] estimated a 30% increase in the percentage of adults subjected to screening over the last three decades. As a result, the incidence of disease decreased to approximately 40 people per 100,000 inhabitants. This decrease was particularly felt for late disease stages. A Cochrane review showed a 16% relative reduction in the risk of death by testing fecal occult blood (FOBT) every two years [11], and different studies showed a reduction of even 32% [12]. Current randomized trials have reported the efficacy of flexible sigmoidoscopy in reducing the incidence and mortality up to 38% in a SCORE study [13], and up to 50% in other studies [14].

CRC screening tests include the detection of FOBT, the DNA blood test, the sigmoidoscopy and the colonoscopy. Other methods such as virtual colonoscopy, immunological detection of feces (FIT) or fecal DNA analysis are being analyzed to improve screening efficiency [15]. Currently, the immunochemical FOBT is the chosen test for screening programs in Europe [16].

Recently, favorable results of DNA tests on blood showed their much higher sensivity to precancerous lesions. An example of this is the methylated Septin 9 marker (SEP T9) [17] which has recently been approved by the FDA for CRC screening in Europe as the first and only blood-based CRC screening test. However, more studies are needed in order to evaluate the assay performance.

Research is underway to improve existing evidence and develop

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new screening techniques [18]. An innovative example is computed tomography (CT), a full-spectrum technique that has improved the sensitivity of conventional CT for adenoma detection purposes [19].

Some studies have designed new hybrid screening strategies using simulation models. An example of this is a model that consists on annual or biennial FITs, starting at age 50, with a single colonoscopy at age 66. This model helped improve compliance at younger ages and reduce the number of complications in colonoscopy at older ages without increasing resources [20]. It could have additional advantages, if its efficacy is truly demonstrated in routine clinical practice studies. In this line, a randomized multicenter trial, COLONPREV, is being conducted to evaluate the effectiveness of colonoscopy and biennial immunochemical test in reducing mortality from colon cancer at 10 years [21].

Another major objective of screening research is finding new parameters for efficient screening strategies based on major risk factors for CRC [22,23]. These models incorporate a lot of variables related to CRC-associated risk factors. Thus, there has to be a balance between prediction accuracy and model simplicity. However, a comprehensive and validated tool is yet to be developed. A current epidemiological review concludes that if the current cost of colonoscopy screening for 50-year old individuals at average risk is considered acceptable, one might as well consider the detection of high-risk patients before that age [24].

In short, current models have made some progress, especially in high-risk groups. It is hoped that a better understanding of the molecular and pathological epidemiology of colon carcinogenesis might contribute towards future research on this field.

Finally, note that in most developed countries screening is part of a national strategy for cancer prevention; but there are communities that have still not developed it, as well as populations that have demonstrated low participation rates [25,26], with the subsequent diagnosis delay [27]. Even so, some innovative investigations are implementing strategies to increase participation levels [28-30]. In addition, a population-based registry would be needed to monitor investments and quality measures, and improve the diagnosis and clinical management of patients with CRC [31].

Healing Treatment: Current Situation and New Research Models

The role of surgery

Laparoscopic surgery: Laparoscopic surgery has represented a huge technical revolution and one of the most important medical advances of the last century. The results of the multicenter randomized trials in 2004 or the COLOR study in 2005 have established the safety of this technique for CRC treatment [32,33]. In relation to open surgery, it has improved the quality of life of patients with CRC without altering their oncologic targets [34]. Over time, it has established itself as the undisputed technique for colon cancer treatment. Its rapid expansion came about thanks to the favorable data on long-term oncological outcomes in trials COLOR II and CLASSIC. These trials collected data for five years, proving laparoscopy was an oncological safe technique in relation to open surgery [35,36]. This was the real breakthrough. It is also important to keep in mind to their advantages in terms of postoperative recovery, fewer wound complications, reduced risk of incisional hernias and subsequent subsequent adhesions [37,38]. It has also been observed in a recent study that patients' quality of life is better after laparoscopic surgery than after open surgery [39].

New surgical possibilities have emerged building on the laparoscopic model, favored by new materials -making enhanced variations possible - as well as new surgical approaches.

Robotic surgery: The great contributions of this technique are both its versatility of movement and its 3D vision, characteristics that favor technical advances. It offers particular advantages for rectal cancer surgery, the area with the greatest laparoscopic technical difficulties. Their distinct features make robots particularly suited to facilitate work in this field. However, what the true benefits of this technique are beyond the surgical time, and whether those outweigh its high economic costs, is still being debated [40]. Both its oncologic outcomes and postoperative recovery seem to present advantages over laparoscopy. However, those have not been demonstrated in controlled trials on rectal cancer [41]. While the use of robotic surgery is promising, its results are still limited to retrospective studies [42]. Randomized clinical trials would be needed to determine the role played by robotic technology.

Rectal cancer surgery: towards organ preservation: Rectal cancer surgery is challenging because it not only involves deciding what systemic treatment to choose, but also what surgical technique to adopt - either the best approach or the best functional reconstruction.

The evidence on the benefits of laparoscopy in rectal cancer makes this technique as oncologically safe as open surgery, and it has advantages over it [43,44]. This data is supported by a meta-analysis of 23 prospective studies. Those showed an increased morbidity and mortality for the open surgery group [45].

Total mesorectal excision (TME) is the universally accepted technique. However, according to the latest recommendations of the multidisciplinary European consensus process on CRC [46], transanal endoscopic surgery or TAMIS [47] might be performed on selected patients in early stages as a more conservative option. In a study of patients with T1 tumors that compared open surgery to transanal surgery, no difference was found in their overall survival to 5 years. A local recurrence rate of 0% was generated by the TME, whereas for transanal surgery that was of about 24% [48]. Two studies achieved good results for T1 tumors, but not for T2 or T3 [49,50]. In addition, transanal excision is associated with a better quality of life and lower genitourinary dysfunction [51]. However, despite its status as a technically reliable option, there is insufficient evidence to recommend this procedure as a standard technique.

There are no randomized trials comparing long-term oncological results between open and laparoscopic surgery in advanced rectal cancers. A study conducted by The American Surgeons Oncology Group study is currently underway [52]. This multicenter randomized phase III trial compares laparoscopy to open surgery in rectal cancers at IIA, IIIA and IIIB stages. As a result, during incoming years there will be available data on the long-term oncologic outcomes of rectal cancer following laparoscopic surgery.

New approaches: Lacy, et al. developed a new approach to rectal cancer that consists of a hybrid surgical technique: transanal surgery with TME. The results presented [53] were promising, showing a high quality of oncologic resection without conversion, and an average of 16 lymph nodes. However, there is no available data on its long-term oncological safety.

Ultimately, the question about these new technical approaches and whether their benefits outweigh those of standard laparoscopic surgery is still unresolved. More comprehensive studies need to be conducted in order to justify the new guidelines; either clearly defining benefits or risks, as well as their economic costs.

Adyuvant/Neoadyuvant Therapy

Colon cancer

Currently, the standard treatment for non-metastatic colon cancer, such as the treatment recommended by the European Society for Medical Oncology (ESMO), is the oncologic resection without adjuvant therapy. In the case of stage III, adjuvant chemotherapy is recommended (FOLFOX, CapeOX 5 fluorouracil/leucovorin or capecitabine) [54].

Stage II: the controversy: However, there is a point of controversy as to whether patients with stage II should receive adjuvant chemotherapy. These patients' overall survival at 5 years is 70%-85% [55]: although surgery is curative, 25% of them will relapse of their disease [56].

However, there is still no available data showing an increase in overall survival compared to surgery alone. Consequently, in most patients no adjuvant treatment is indicated.

The results of the QUASAR trial showed an absolute improvement in survival of only 3.6% in stage II patients who had received fluorouracil and folinic acid [57]. This result means that less than 4% of patients could benefit from adjuvant chemotherapy. Supporting these results, a systematic review of the Cancer Care Ontario Program (CCOPGI) concluded that there was no evidence for treating stage II patients with chemotherapy in a systematic way [58].

Therefore, the decision to administer chemotherapy to stage II patients is based on clinical and pathological markers of risk. However, it has been observed that sometimes patients are not adequately informed about the risks and possibilities of the treatment [59].

The SACURA phase III study has recently been carried out with approximately 2000 patients. It aims at studying the efficacy and safety of UFT - oral chemotherapy - administered over a year as observation. Among other things, the disease-free survival and overall survival and adverse effects will be analyzed [60].

One of the main issues is the scare number of patients who could potentially benefit from adjuvant chemotherapy. This could be resolved with studies that attempt to better identify this potential pool of patients. The introduction of molecular techniques that allow identification of high-risk patients could play an important role in predicting their response to chemotherapy.

Current status of adjuvant chemotherapy: Before 2000 years, 5-FU was the only useful cytotoxic chemotherapy for stage III cases, but from this year on, capecitabine was established to be an equivalent option to 5-FU and leucovorin. The combination FLOLFOX (oxaliplain + 5-FU + leucovorin) was adopted following the results of the MOSAIC trial for adjuvant treatment in stage III patients [61]. Subsequently, it was shown that the combination of capecitabine and oxaliplatin (XELOX), versus that of 5-FU and folinic acid, was valid the disease-free survival in the following 3 years was of 71.0% for capecitabine and oxaliplatin, versus a 67.0% rate for 5-FU and leucovorin [62].

Recently, a number of patients' outcomes from four randomized trials have been published, directly comparing the efficacy of capecitabine with or without oxaliplatin versus leucovorin and fluorouracil with or without oxaliplatin. The results obtained showed that therapy with oxaliplatin improved results regardless of whether capecitabin and leucovorin, or fluorouracil, were administrated. These data add to the evidence that makes oxaliplatin and capecitabine, or fluorouracil and leucovorin, the standard [63].

After disappointing results in studies with addressed therapies, such as interferon, edrecolomab, irinotecan, bevacizumab [64], and most recently cetuximab after the PENTACC-8 results [65], recent studies aim to foccous on toxicity and cost reduction. As an example of these trials, the meta-analysis IDEA is looking for the optimal duration of chemotherapy to reduce both the costs and the toxicity of adjuvant treatments [66].

A summary of selected studies with different approaches to colon cancer is available in table 1 [64].

Rectal cancer

Due to an increased risk of local recurrence and poorer overall prognosis, rectal cancer treatment is different from its colon cancer counterpart. Adjuvant therapy for rectal cancer on stages II (T3-4N0) or III (N1-2M0) is an acceptable option, yet nowadays neoadjuvant or preoperative chemoradiation are preferred because of their increased radiation effectiveness [67].

Neoadjuvant radiotherapy: Phase III randomized trials have shown that neoadjuvant radiotherapy followed by EMT should be the recommended treatment for rectal cancer. This is due to its lower toxicity and higher affectivity in reducing local recurrence in relation to a postoperative treatment [68,69]. The traditional system of radiotherapy for advanced malignancies has daily fractions concurrent with chemotherapy (long course) followed by delayed surgery (between 4 and 8 weeks later) [67]. Another possible option is a short regimen without chemotherapy nor radiotherapy, followed by immediate surgery (one week later).

Two randomized phase III trials have compared the efficacy of short-course radiotherapy to that of chemo-radiotherapy, without finding any differences in local recurrence [70,71].

The multicenter randomized phase III stockholm trail is ongoing. More than 300 patients have been included, receiving three possible treatments: short course radiotherapy (25 Gy in 5 fractions) followed by immediate surgery (1 week); short course radiotherapy followed by surgery after 4-8 weeks, or a long course of radiotherapy 50 Gy in 25 fractions (without chemotherapy) followed by surgery after 4-8 weeks. Intermediate results show that 13% of those patients with delayed surgery had no residual tumor, versus 1% of those in the immediate surgery group [72].

Another interesting approach is being adopted in a randomized trial that aims at determining whether neoadjuvant chemotherapy with FOLFOX and bevacizumab could be replaced by pelvic radiation without compromising R0 resection rates in patients with locally advanced rectal cancer, in terms of pathologic complete response [73]. The results could possibly help define a set of stage II-III patients who could benefit from changes to the current guidelines.

Chemoradiotherapy: The benefit of 5-FU-based chemoradiotherapy was demonstrated by the German CAO/ARO/AIO-94 phase III trial. The results showed a decrease on local recurrence, although with less impact on disease-free survival and on overall survival in the preoperative regime than in the postoperative one [74].

However, some guidelines, such as the NCCN's, support the addition of postoperative adjuvant chemotherapy treated with neoadjuvant therapy, as this approach has obtained favorable results [75]. For example, a meta-analysis of 21 randomized controlled trials supports this practice, demonstrating a 25% reduction in the risk of recurrence in patients when treated with adjuvant 5-FU regimens [76]. Long-term monitoring of the EORTC 22921 study was meant to clarify the optimal time to apply the chemotherapy (5-FU and leucovorin) to the radiotherapy preoperatively, postoperatively, or both. The results revealed that chemotherapy, combined with radiotherapy either concurrently with or after surgery, increased local control rates and, most importantly, that there was no apparent impact on disease free rates or overall survival [77].

Studies on the different modalities of possible chemotherapy regimens focus on neoadjuvant chemoradiotherapy followed by postoperative chemotherapy, presenting it as the definitive treatment [78]. Within this line of research, a Dutch study of only 50 patients evaluated a strategy for short-course radiotherapy followed by 6 cycles

Table 1: A summary of selected studies with different approaches to colon cancer.

Study	Key inclusion criteria	Treatment	Outcomes
Quasar	Stage II	Surgery + QT 5-FU + Folinic acid vs. Surgery + observation	Overall survival: 3.6% vs. 3.1%
Sacura	Stage II	Surgery + QT oral UFT during 1 year vs. surgery + observation	Ongoing
Mosaic	Stage III	5-FLU + Leucovorin vs. FOLFOX 4	DFS: 67.4% vs. 63.3%
Haller, et al. [62]	Stage III	XELOX vs. 5-FU + Folinic acid	Survival in 3 years: 70.9% vs. 66.7%

DFS: Disease Free Survival

Table 2: Clinical trials of rectal cancer [78].

Study	Key inclusion criteria	Treatment	Outcomes
Ngan, et al. [71]	T3,T4	RT short course and immediate surgery RT long course and delayed surgery	DFS: 67% vs. 66% Recurrence: 9% vs. 14.2%
Van Djk, et al. [79]	Stage IV	RT short course + CAPOX + Bebazizumab	pCR: 26%
Tunio, et al. [80]	T4	RQnt QT with capecitabineT + neoadyuv	pCR: 85.4%
Bujko, et al. [70]	Stage IV	NUeoadyuvant RT short course + FOLFOX vs. QRT with 5-F	pCR: 21% vs. 9%
Garcia-Aguilera	T3,T4	RT with 5FU RT with 5 FU followed by FOLFOX x 4 weeks	pCR: 18% vs. 25%

DFS: Disease Free Survival, pCR: Pathologic Complete Response.

of CAPOX plus bevacizumab, beginning at 2 weeks of completion of radiotherapy on stage IV patients. A rate of pathological complete response of 26% was achieved, with a two-year survival of 80% [79].

An Italian study used chemoradiotherapy followed by two 3-week cycles of capecitabine, revealing pathological response rates of 18%, with a disease-free survival of 85.4% at 5 years. However, it should be noted that there was a low prevalence of T4 tumors, what may justify the favorable long-term outcomes [80].

An ongoing clinical trial from the Polish Colorectal Cancer Study Group follows this approach. It is a phase III study comparing preoperative short duration radiotherapy followed by three cycles of FOLFOX, to conventional chemoradiotherapy with 5-FU (NCT00833131). An interim analysis showed an improvement in the rates of complete pathological response in the short duration radiotherapy followed by FOLFOX: 21% vs. 9% for the conventional treatment [81].

In any case, there is a lack of conclusive data on this topic, leaving room for debate about the optimal incorporation of chemotherapy to rectal cancer treatment. Given the lower toxicity and improved compliance in the preoperative setting, there is a growing interest in developing strategies for neoadjuvant treatment.

This favored by the optimal timing of surgery after chemoradiotherapy has raised. The nonrandomized multicenter US study is an example worth highlighting. It included 144 patients at stage II and III of rectal cancer. They were assigned to one of two groups, initially receiving 5-FU-based chemoradiotherapy. After its completion, the first group had surgery within 6-8 weeks, while the second group was reassessed after 4 weeks. As there was evidence of a clinical response, the patients in the second group were treated with two cycles of FOLFOX followed by surgery after 3-5 weeks. There was almost no difference in their pathologic response rate: 18% vs 25%, respectively. From this same dataset, a third group of 48 patients were treated with two new cycles of FOLFOX and delayed surgery 4 additional weeks. Their rates of complete pathological response increased to 31%, without additional complications [82].

A summary of selected studies with different approaches to rectal cancer is available in table 2.

Watch and wait: The adoptions of this strategy after neoadjuvant chemoradiotherapy results in pathologic complete response rates of about 10%-20% [83,84]. Making decisions about which patients are placed into this strategy is a complex process that requires weighting harms and benefits on a case-by-case basis. This difficulty is exacerbated by the conflicting nature of current evidence. For example Smith, et al. [85] found no differences in survival, even reporting an improvement in absolute survival in the group of 80 patients with associated comorbidities. However, other authors have developed a decision-analytic model to evaluate the benefits of surgery versus observation [86].

While interest is increasing, a major limitation is the lack of consensus on how to assess pathologic complete responses [87]. A protocol including both the endoscopic criteria of the ACOSOG study [88] and the histological data defined by Habr Gama [89] would be needed to ensure timely detection of recurrences. Yet other questions remain, such as its long-term oncological safety and what models would help identify patients who could potentially benefit from

this strategy. Future studies could compare these two treatments by moving toward randomized non-inferiority trials.

Conclusions

The incidence and mortality of CRC is diminishing due to increased detection efforts and advances in research on new screening strategies, resulting in diagnoses at earlier disease stages. Still, a growing concern remains regarding low participation rates and the existence of populations with no screening programs in place.

As for its treatment, surgical technique improvements, the incorporation of preoperative radiotherapy and the use of adjuvant chemotherapy seem to confer an additional benefit to most of patients. Currently, surgery for rectal cancer adopts more conservative approaches. Supports by the adjuvant, it tries not to modify the oncological benefits by preserving the organ. It should be added that neoadjuvant treatment offers a unique opportunity for improving the current situation. Thus the possibility exists to improve overall survival results through the differential stratification of therapy, and reduce toxicity through the selective use of different therapeutic modalities.

Optimal population selection is the paradigm for the applicability of different strategies. Beyond the clinical criteria, results drawn from ongoing research studies could help develop long-awaited individualized therapeutic strategies. However, support for clinical research remains essential if our patients' future outcomes are to improve.

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