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Colorectal Cancer

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Published in London, United Kingdom







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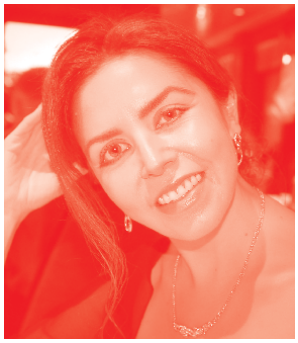

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http://dx.doi.org/10.5772/intechopen.87596
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First published in London, United Kingdom, 2021 by IntechOpen
IntechOpen is the global imprint of INTECHOPEN LIMITED, registered in England and Wales, registration number: 11086078, 5 Princes Gate Court, London, SW7 2QJ, United Kingdom
Printed in Croatia

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library

Additional hard and PDF copies can be obtained from orders@intechopen.com

Colorectal Cancer
Edited by Alberto Vannelli
p. cm.
Print ISBN 978-1-83881-102-0
Online ISBN 978-1-83881-103-7
eBook (PDF) ISBN 978-1-83881-117-4

Meet the editor

Dr. Vannelli graduated from the Faculty of Medicine and Surgery, University of Milan, Italy, in 1997, where he also specialized in General Surgery in 2003. He worked for more than ten years at the National Cancer Institute in Milan. Currently, he directs general surgery at Valduce Hospital, Como, Italy. Dr. Vannelli is involved in the multidisciplinary management of patients with colorectal cancers. His research focuses on multidisciplinary clinical research in colorectal neoplasms and upper gastrointestinal cancers. He has participated as a speaker at national and international meetings and has published several publications in peer-reviewed journals. In 2012, Dr. Vannelli founded Erone Onlus to assist cancer patients and their families. He collaborates with the School of Specialization in General Surgery at the Emergency Department of the University of Milan.

Contents

Preface

Colorectal cancer is the third leading cause of cancer death in the world, and its incidence is steadily increasing in developing nations. Yet, the majority of colorectal cancer is sporadic and largely attributable to the constellation of modifiable environmental risk factors characterizing westernization (e.g., obesity, physical inactivity, poor diets, alcohol drinking and smoking). As such, the burden of colorectal cancer is shifting towards low-income and middle-income countries as they become westernized. This book examines state-of-the-art research relating to the etiology, diagnosis, prevention and treatment of colorectal cancer. Section 1 presents the epidemiological aspect. Section 2 discusses imaging in diagnosis and treatment. Sections 3 and 4 explore surgery and related aspects. Section 5 concludes with a discussion of palliative care.

Given the complex physiopathology of colorectal tumors, treatment and management approaches should not be limited to a single specialty but should involve a number of specialties (surgery, gastroenterology, radiology, biology, oncology, radiotherapy, nuclear medicine, physiotherapy) in an integrated fashion. This book encompasses this concept, as Jim Valvano remembers: "Cancer can take away all of my physical abilities. It cannot touch my mind, it cannot touch my heart, and it cannot touch my soul."

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Section 1

Epidemiology

Chapter 1

Public Health: Prevention

Azmawati Mohammed Nawi

Abstract

Nowadays, colorectal cancer prevention strategies play an essential role in reducing the incidence and mortality of the cases. A well-designed and establishment of the clinical pathway of screening programme needed in all country. Types of screening tools used may vary between the country with the use of FOBT and colonoscopy. The standard guideline related to screening programme such as for high-risk group should be emphasized more as compared to the low-risk group. The uptake of screening for CRC should be highlighted more as the program have showed a significantly reduction of the cases and mortality. The barrier of CRC screening uptake mainly due to poor awareness, discomfort, low physician recommendation, low socioeconomic and improper screening programme. Therefore others prevention strategies beside screening program such as health education and interactive intervention strategies need to be empower.

Keywords: screening, prevention, FOBT, colonoscopy, fecal test

1. Introduction

Colorectal cancer (CRC) incidence and mortality rates vary across worldwide, with distinct gradients across human development levels were seen, pointing towards an increasing burden in countries in transition. In general, CRC incidence and mortality rates are still rising rapidly in many low-income and middle-income countries, particularly in Eastern Europe, Asia, and South America. While stabilizing or decreasing trends are seen in highly developed countries such as Japan, the United States and Australia, where rates remain among the highest in the world [1].

CRC mortality can be reduced if cases are detected and treated early. When identified early, CRC is more likely to respond to effective treatment and can result in a greater probability of surviving, less morbidity, and less expensive treatment. On the other hand, CRC screening aims to identify individuals with abnormalities suggestive of cancer or pre-cancer who have not developed any symptoms and to refer them for diagnosis and treatment. Nonetheless, a screening program is a far more complex public health intervention compared to early diagnosis [2].

2. Colorectal cancer screening programs

CRC screening programs are currently underway in most European countries, Canada, specific regions in North and South America, Asia, and Oceania. The most comprehensive screening strategies were based on fecal occult blood testing, and more recently, the fecal immunochemical test (FIT) [3]. While other options for CRC screening are fecal immunochemical test annually, guaiac-based fecal occult

blood test annually, multi-target stool DNA test every three years, colonoscopy every ten years, computed tomography colonography every five years, and flexible sigmoidoscopy every five years [4].

CRC screening programs are designed for populations according to risk stratification. In general population-based screening, these programs are offered to the

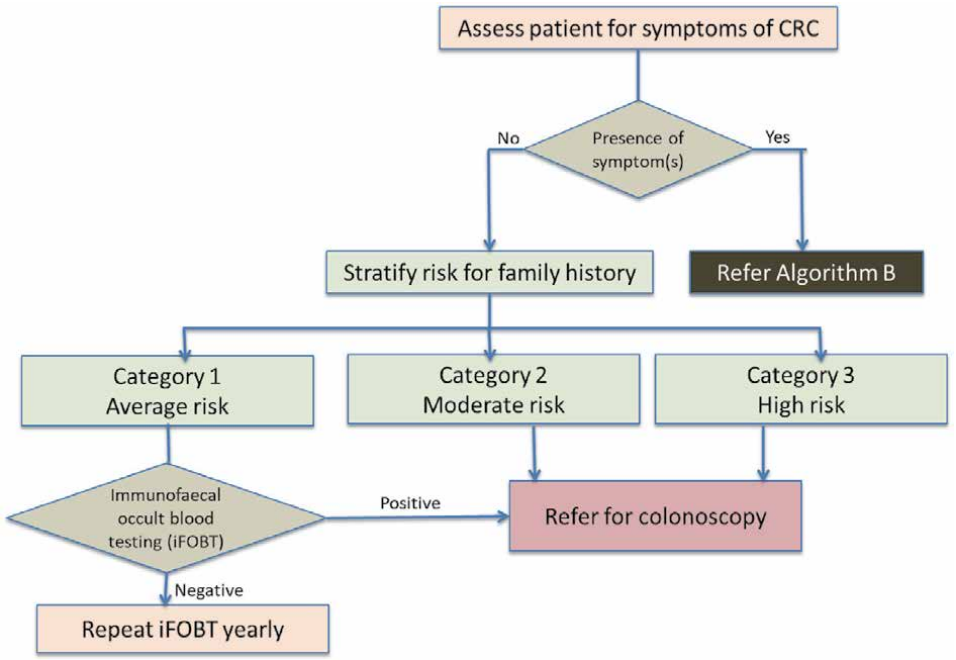

Figure 1.
Clinical pathway of screening for colorectal carcinoma. Source: Kamil et al. [6].

Category	Description	Screening recommendation
Category 1 Average risk	No family history and age >50 years	- Perform IFOBT - Stop screening at age 75
Category 2 Moderate risk	Family history of CRC either: - ≥ 1 FDR - 1FDR and > 1 SDR - > 3 and one of them must be FDR	- FDR with CRC diagnosed at age <60 years, colonoscopy should be performed at age 40 or 10 years younger than affected relative (whichever is younger) If normal, repeat every 3-5 years - FDR with CRC diagnosed at ≥60 years, colonoscopy should be performed at age 40 years. If normal, repeat every 10 years. - Stop screening at age 75
Category 3 High risk	Family history of: - CRC at age < 50 years - FAP - Lynch syndrome - Peutz-Jegher Syndrome - Juvenile polyposis - MAP	- For family history of CRC diagnosed at age <50 years, colonoscopy should be performed at age 40 or 10 years younger than affected relative (whichever is younger) If normal, repeat every 3-5 years. Stop screening at age 75.

Figure 2.
Risk categories for family history with CRC. Source: Kamil et al. [6].

population with average risk. While in a certain country, opportunistic CRC screening is provided at primary healthcare centres, also catering those with average risk. Therefore, most uptakes are due to routine recommendation offered by attending doctors, despite low.

Most of the significant CRC guidelines recommend screening of CRC to start at the age of 50 years old. For instance, the US Preventive Task Force recommends screening for CRC to begin at the age of 50 years and continues until age 75 years. The decision to screen for CRC in adults aged 76 to 85 years should be individualized, taking into account the patient's overall health and prior screening history [5]. For examples, according to Malaysian guideline, screening of colorectal carcinoma (CRC) should be offered at the age of 50 years and continues until age 75 years for the average-risk population. Immunochemical fecal occult blood test (iFOBT) is the preferred method to screen for CRC in an average-risk community. If iFOBT is positive, an early colonoscopy is necessary. Whereas, if iFOBT is negative, the yearly test should be performed (**Figures 1** and **2**) [6].

These screening tests are not only effective in the early discovery of malignant tumors, but also serves as a preventive procedure whereby polyps that could potentially become malignant can be found and removed before becoming cancerous [2].

3. Colorectal cancer screening modalities

There were several screening tests available for CRC which vary in terms of their performance accuracy, complication rates, screening uptake as well as costs associated with screening. Among several options available are fecal occult blood test (FOBT), flexible sigmoidoscopy (FS), colonoscopy, colon capsule endoscopy (CCE), and computed tomographic colonography (CTC).

3.1 Fecal test

Fecal test is a non-invasive tool for CRC screening in general population. It can detect presence of blood, proteins e.g. enzyme M2-PK and DNA. Fecal occult blood refers to blood in the feces that is not visibly apparent. A fecal occult blood test (FOBT) is designed to identify hidden or small quantities of blood in fecal sample. There are two main types of FOBTs: guaiac-based fecal occult blood test (gFOBT) and immunochemical fecal occult blood test (iFOBT) which is also known as fecal immunochemical test (FIT).

FOBT has qualitative and quantitative testing methods. In a meta-analysis of fair to high quality evidence, the pooled sensitivity to detect CRC was 74% (95% CI 62-83) for quantitative test methods and 79% (95% CI 61-90) for qualitative test methods [5]. Immunochemical FOBT (iFOBT) and guaiac-based FOBT (gFOBT) are two methods of qualitative FOBT. The sensitivities of iFOBT and gFOBT are 0.67 (95% CI 0.61-0.73) and 0.54 (95% CI 0.48-0.60) respectively. The specificities of iFOBT and gFOBT are comparable at 0.85 (95% CI 0.83-0.87) and 0.80 (95% CI 0.78-0.82) respectively [7].

Overall, screening with FOBT (either iFOBT or gFOBT) has a 16% reduction in the risk of CRC mortality (RR = 0.84, 95% CI 0.78-0.90) as compared to unscreened population [8], while screening with iFOBT can reduce CRC mortality by 22% as compared to screening with gFOBT [9].

Other fecal test include fecal M2-PK enzyme detection and fecal DNA tests. Fecal M2-PK has a pooled sensitivity and specificity of 79% (95% CI 73 to 83) and 80% (95% CI 73 to 86) respectively [10]. On the other hand, quantitative fecal DNA

test has a higher sensitivity at 92% (95% CI 84 to 97) to detect CRC [5]. These two fecal tests for CRC screening are, however, not widely used locally in screening for general population due to high cost incurred.

3.2 Flexible sigmoidoscopy (FS)

FS needs less rigorous bowel preparation and can be performed as a clinic-based procedure without the need for sedation. Small polyps can be biopsied during procedure but excision of larger lesions (>1 cm) may be performed during subsequent colonoscopy.

In two randomized controlled trial studies conducted in the United States and the United Kingdom, sigmoidoscopy reduces the CRC incidence by 18-26% and mortality by 26-30% in general population. The reduction in mortality, however, was limited to distal colon, with no significant effect in the proximal colon [11, 12].

3.3 Colonoscopy

Colonoscopy is the screening modality that has the ability to visualize the colonic mucosa directly, perform biopsy and excise polyps. It can detect proximal lesions that would be missed by screening sigmoidoscopy and has been shown to reduce risk of cancer in the right colon, while for those who has had colonoscopy especially for screening, the risk of CRC is strongly reduced by 91% up to 10 years [13]. In different study, it was also found that screening colonoscopy was associated with a substantial and comparably decreased mortality risk for both right-sided (65% reduction) and left-sided (75% reduction) cancers within a large community-based population [14].

According to the American College of Gastroenterology Guidelines, the preferred CRC prevention test (screening test) with strong recommendation is colonoscopy every 10 years, beginning at age of 50 based on the evidence of effectiveness, cost-effectiveness and acceptance by patients [15]. The National Cancer Comprehensive Network Clinical Practice Guidelines for Colorectal Cancer Screening also stated that colonoscopy is currently the preferred screening method. It is also the required procedure for confirmation of positive findings from other screening tests [16].

However, based on the updated Asia Pacific Consensus on Colorectal Cancer report in 2013, colonoscopy is recommended for those with an increased risk of CRC based upon the family history of CRC and other related risk factors for CRC. This recommendation has been suggested by the panel in view of colonoscopy being an invasive, labour intensive and more expensive method for CRC screening [17].

3.4 Colon capsule endoscopy (CCE)

CCE is used to obtain images of the colon by using video cameras embedded in an ingested capsule. The technique is less invasive but does not allow biopsy or polyp removal.

The sensitivity in detection of polyps >6 mm and > 10 mm increased substantially between development of first-generation (CCE-1) and second-generation (CCE-2) of CCE. CCE-2 and CCE-1 detect polyps >6 mm with sensitivity of 86% (95% CI 82–89%) and 58% (95% CI 44–70%) respectively, and specificity of 88.1% (95% CI 74.2%–95.0%) and 85.7% (95% CI 80.2%–90.0%) respectively. While for larger polyps >10 mm, CCE-2 and CCE-1 had sensitivity of 87% (95% CI 81–91%) and 54% (95% CI 29–77%) respectively, and specificity of 95.3% (95% CI, 91.5%–97.5%) and 97.4% (95% CI 96.0%–98.3%) respectively [18]. These high specificity

values for detection of polyps by CCE seem to be achievable with a 10-mm cutoff and in a screening setting.

3.5 Computed tomographic Colonography (CTC)

CTC uses multiple thin slice computed tomographic data to construct images of the bowel mucosa in two or three dimensions in detecting polyps. It requires bowel preparation similar to conventional colonoscopy and during the procedure, air or carbon dioxide is introduced into the rectum via a rubber catheter. No sedation is required and patient is usually able to return to work post procedure.

Estimated sensitivities for patients with polyps or adenomas ≥6 mm were 75.9% (95% CI 62.3–85.8) and 82.9% (95% CI 73.6–89.4), with corresponding specificities 94.6% (95% CI 90.4–97.0) and 91.4% (95% CI 84.1–95.5) respectively. On the other hand, estimated sensitivities for patients with polyps or adenomas ≥10 mm were 83.3% (95% CI 76.8–89.0) and 87.9% (95% CI 82.1–92.0), with corresponding specificities 98.7% (95% CI 97.6–99.3) and 97.6% (95% CI 95.0–98.9) respectively [19].

The major drawbacks of CTC are that it is non-therapeutic, with the need for colonoscopy after the identification of polyps for excision and tissue diagnosis. Other reasons include argument for radiation exposure, presence of flat adenomas that are more likely to be missed by CTC than colonoscopy, and issues of incidental extra-colonic pathological findings that may arise [19, 20].

4. Colorectal cancer screening uptake

Participation in screening has varied greatly among different regions. The Netherlands showed the highest participation rate (68.2%) and some areas of Canada showed the lowest (16%). Participation rates were highest among women and in programs that used the iFOBT test. The iFOBT test has been the most widely test used in screening program worldwide nowadays. The advent of this test has increased participation rates and the detection of positive results [13].

In a large scale study conducted in Asia Pacific region, 27% of respondents aged 50 years and older had undergone previous CRC testing; the Philippines (69%), Australia (48%), and Japan (38%) had the highest participation rates, whereas India (1.5%), Malaysia (3%), Indonesia (3%), Pakistan (7.5%), and Brunei (13.7%) had the lowest rates [21].

5. Barriers for colorectal cancer screening

Community with cancer tends to present to cancer services in the later stages of the disease, and this late presentation has severe, often fatal, consequences. Therefore, increasing awareness about cancer signs and symptoms could contribute to earlier presentation and improvements in cancer outcomes Despite the prevalence of colorectal cancer and the many screening tests available, the number of people going for these screening tests are very low [22]. This is rather alarming and many studies have been conducted worldwide to discover and analyze the causes of low turnout for colorectal cancer screening [23].

5.1 Poor knowledge of CRC symptoms and risk factors

A majority of the studies found that the largest barrier towards colorectal cancer screening is poor knowledge of the general public towards the risk factors,

symptoms and screening tests available for CRC. A recent multi-center, international study involving 14 countries or regions in the Asia Pacific region reported considerable deficiencies in knowledge of CRC symptoms and risk factors, and suggested that this could lead to poor uptake of CRC screening tests. One research indicates that there is a lack of awareness among community about CRC symptoms, i.e. only 40.6% of 2379 participants recognized 'blood in stool' as a warning sign for CRC. Other causes of delayed detection and diagnosis include denial, negative perceptions of the disease, the over-reliance on traditional medicine, misperceived risk, emotional barriers and negative perceptions towards screening. Cancer awareness campaigns and their evaluation are sparse in low- and middle-income countries.

Studies from Hong Kong, Australia and USA also reported low levels of knowledge of CRC [22]. Other than that, those with poor educational backgrounds are more likely to have language and communication barriers, and have a harder time understanding materials or recommendations. Also identified being the male gender to have poorer CRC knowledge, as females have better health knowledge due to their traditional role as carers. With particular focus to a multiracial country, the language barrier becomes a prominent problem. Subjects have complained of the limited language diversity in cancer screening awareness material, hence result in poorer understanding. This in particular would be a problem for the older generation, as many are less multilingual than the younger generation; and this becomes a large problem as CRC has a higher prevalence among those above 50 years of age [23]. Few Asian countries have established nationwide CRC awareness and screening programs, with Taiwan, Korea, Singapore and Japan being the only Asian countries that have existing national CRC screening guidelines and programs [23].

5.2 Lack of physician's recommendation

Another major factor of poor knowledge within the population is the severe lack of physician's recommendation to do CRC screening [23]. In Asia Pacific region, countries with low CRC screening participation were found to have the lowest physician recommendation rate [21]. According to an American study, failure of a clinician to suggest screening was identified as the most important barriers to CRC screening [24].

The most common barrier was "unavailability of the test". The two most common patient factors are "patient in a hurry" and "poor patient awareness". This may be related to the low availability of the test in the primary care setting and poor awareness and understanding of the importance of colorectal cancer screening among patients.

5.3 Lack of access of CRC screening

A notable category of barriers that people face that hinders them from CRC screening participation is access barriers. One of them is financial constraints. Another is time constraint. In a busy clinic, long patient waiting time may lead to patient in a hurry and refusal despite being recommended. It is known that the conventional gFOBT is troublesome and embarrassing for patients to do. Another drawback of the test is patient has to be on certain food restriction and the test has to be repeated at least twice. Therefore, many countries have now moving towards using immunological test since it is less troublesome and better detection rate [25].

Many stated that they were too busy, or the tests were too time consuming. Thirdly, there is limited access to centers that provide such screening tests [23]. The most common barrier for screening is because FOBT test is unavailable in the primary care clinic. FOBT is in fact easily available and free in certain health care facilities but only few health clinics have this test. In most of the primary care health clinics, the test needs to be sent to nearest hospital laboratory and because of that it become tedious and not commonly ordered [25].

Majority of patients will come to primary care as their first consult. Wellness clinic has been implemented in primary care clinics. This clinic is meant for patients to come for screening. However, the programme in the certain clinic is mainly targeting on screening cardiovascular risk factors such as diabetes, hypertension and hypercholesterolaemia. Little is done for cancer screening. Cervical cancer screening has the highest patient uptake (43%) because of the incorporation of Pap smear programme in maternal and child health clinic which is run in primary care facilities [25].

5.4 Patient's negative perception towards CRC screening

There are many people who do not perceive that they are at risk of getting CRC. This low perceived risk is attributable to several factors, such as not having a family history of CRC, not experiencing any signs or symptoms, living a healthy or low-risk lifestyle or being free from health problems in general [23]. Another barrier that many studies report is the negative perception towards screening methods, with a more negative view towards more invasive procedures such as endoscopic-based procedures. Among the negative views reported were fear, pain experienced or perceived pain towards screening procedures, feeling of embarrassment, health damage, inconvenience and lack of confidence in screening efficacy. Fear of test result is a common barrier for any test. It is especially when most people relate cancer to untreatable and fatal disease. A study in Italy also showed the same finding where being concern with the test result is the most important reason of patient's noncompliance.

5.5 Others factor

Throughout the world there are widespread differences in CRC screening implementation status and strategy. Differences can be attributed to geographical variation in CRC incidence, economic resources, healthcare structure and infrastructure to support screening such as the ability to identify the target population at risk and cancer registry availability. Despite well-developed CRC screening guidelines, implementation of screening is markedly different among countries and regions worldwide [26]. What is more, there is also inequitable access to CRC screening, at least in relation to socioeconomic status and ethnicity. The mechanism, however, is not well understood [27].

6. Intervention related to CRC screening

Table 1 showed some evidence from previous studies on CRC screening and intervention modalities. Mixed of intervention through telephone counseling, a mail invitation, email/text-message reminder, health talk, video and brochure are some intervention has been done and showed a positive finding on CRC screening uptake. The government needs to take action for CRC screening programme and

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
1	2010	San Francisco, United States	RCT. Participants were randomized to (1) basic intervention: culturally tailored brochure plus FOBT kit (n = 765); (2) enhanced intervention: brochure, FOBT plus telephone counseling (n = 768); or (3) usual care (n = 256).	Culturally tailored telephone counseling by community health advisors employed by a community-based organization, culturally tailored brochures, and customized FOBT kits.	Usual care (no further description).	1789 Latino and Vietnamese primary care patients at a large public hospital, aged 50-79.	Self-reported receipt of FOBT or any CRC screening at 1-year follow-up.	1358 individuals (718 Latinos and 640 Vietnamese) completed the follow-up survey. Self-reported FOBT screening rates increased by 7.8% in the control group, by 15.1% in the brochure group, and by 25.1% in the brochure/telephone counseling group ($p < 0.01$ for differences between each intervention and usual care and for the difference between brochure/telephone counseling and brochure alone). For any CRC screening, rates increased by 4.1% in the usual care group, by 11.9% in the FOBT/brochure group, and by 21.4% in the brochure/telephone	An intervention that included culturally tailored brochures and tailored telephone counseling increased CRC screening in Latinos and the Vietnamese. Brochure and telephone counseling together had the greatest impact.	[28]

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DOI: http://dx.doi.org/10.5772/intechopen.94396

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
								counseling group ($p < 0.01$ for differences between each intervention and usual care and for the difference between the basic and the enhanced intervention).		
2	2014	Florida, United States	Ecological study. From cases reported to the Florida Cancer Registry.	SaTScan ver 9.1.1, a free cluster-detection software application was used to describe spatial clusters of CRC	NA	36,094 cases with CRC diagnosed at late stages from 1996 through 2010 in Florida, aged more than 50.	Clusters of CRC	Much of analysis was underpowered and that no single method detected all clusters of statistical or public health significance.	The high risk area is potentially a priority area for a screening intervention. Cluster detection can be incorporated into routine public health operations, but the challenge is to identify areas in which the burden of disease can be alleviated through public health intervention.	[29]
3	2013	Washington, United States	RCT. 4-group, parallel-design, randomized, controlled	EHR-linked mailings ("automated"), automated plus	Usual care; involved services to promote CRC screening,	4675 patients attended to 21 primary care medical centres in	The proportion of participants current for screening in both	Compared with those in the usual care group, participants in the	Compared with usual care, a centralized, EHR-linked, mailed	[30]

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
			comparative effectiveness trial with concealed allocation and blinded outcome assessments.	telephone assistance ("assisted"), or automated and assisted plus nurse navigation to testing completion or refusal ("navigated"). Interventions were repeated in year 2.	including guidelines, patient handouts, and an annual systems delivered involved services patient-tailored "birthday letter" with previous completion and subsequent due dates for immunizations, screening tests, and long-term care tests (such as influenza shots, CRC screening, or hemoglobin A1c tests).	Washington, not current for CRC screening, aged 50 to 73.	years, defined as colonoscopy or sigmoidoscopy (year 1) or fecal occult blood testing (FOBT) in year 1 and FOBT, colonoscopy, or sigmoidoscopy (year 2).	intervention groups were more likely to be current for CRC screening for both years with significant increases by intensity (usual care, 26.3% [95% CI, 23.4% to 29.2%]; automated, 50.8% [CI, 47.3% to 54.4%]; assisted, 57.5% [CI, 54.5% to 60.6%]; and navigated, 64.7% [CI, 62.5% to 67.0%]; $P < 0.001$ for all pair-wise comparisons). Increases in screening were primarily due to increased uptake of FOBT being completed in both years (usual care, 3.9% [CI, 2.8% to 5.1%]; automated, 27.5% [CI, 24.9% to 30.0%]; assisted, 30.5% [CI, 27.9% to 33.2%]; and navigated, 35.8% [CI, 33.1% to 38.6%]).	CRC screening program led to twice as many persons being current for screening over 2 years. Assisted and navigated interventions led to smaller but significant stepped increases compared with the automated intervention only. The rapid growth of EHRs provides opportunities for spreading this model broadly.	

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No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
4	2011	Massachusetts, United States	RCT. We randomly allocated patients to receive a patient navigation–based intervention or usual care.	Intervention patients received an introductory letter from their primary care provider with educational material, followed by telephone calls from a language-concordant navigator. The navigators offered patients the option of being screened by fecal occult blood testing or colonoscopy.	Usual care (no further description).	465 patients from 4 community health centers and 2 public hospital–based clinics who were not up-to-date with CRC screening, aged 52 to 74.	The primary outcome was completion of any CRC screening within 1 year. Secondary outcomes included the proportions of patients screened by colonoscopy who had adenomas or cancer detected.	During a 1-year period, intervention patients were more likely to undergo CRC screening than control patients (33.6% vs. 20.0%; $P < .001$), to be screened by colonoscopy (26.4% vs. 13.0%; $P < .001$), and to have adenomas detected (8.1% vs. 3.9%; $P = .06$). In prespecified subgroup analyses, the navigator intervention was particularly beneficial for patients whose primary language was other than English (39.8% vs. 18.6%; $P < .001$) and black patients (39.7% vs. 16.7%; $P = .004$).	Patient navigation increased completion of CRC screening among ethnically diverse patients. Targeting patient navigation to black and non–English-speaking patients may be a useful approach to reducing disparities in CRC screening.	[31]

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
5	2014	Chicago, United States	RCT. Patient-level randomized controlled trial conducted in a network of community health centers.	The intervention group received (1) a mailed reminder letter, a free FIT with low-literacy instructions, and a postage-paid return envelope; (2) an automated telephone and text message reminding them that they were due for screening and that a FIT was being mailed to them; (3) an automated telephone and text reminder 2 weeks later for those who did not return the FIT; and (4) personal telephone outreach by a CRC screening navigator after 3 months.	Usual care; included computerized reminders, standing orders for medical assistants to give patients home fecal immunochemical tests (FIT), and clinician feedback on CRC screening rates.	450 patients who were previously negative for FOBT from March 2011 through February 2012. aged 51 to 75.	Completion of FOBT within 6 months of the date the patient was due for annual screening.	Intervention patients were much more likely than those in usual care to complete FOBT (82.2% vs. 37.3%; $P < .001$). Of the 185 intervention patients completing screening, 10.2% completed prior to their due date (intervention was not given), 39.6% within 2 weeks (after initial intervention), 24.0% within 2 to 13 weeks (after automated call/text reminder), and 8.4% between 13 and 26 weeks (after personal call).	This intervention greatly increased adherence to annual CRC screening; most screenings were achieved without personal calls. It is possible to improve annual CRC screening for vulnerable populations with relatively low-cost strategies that are facilitated by health information technologies.	[32]
6	2010	Atlanta, United States	RCT. Community intervention trial.	The three interventions are 1) one-on-one education 2)	Control group; Participants attended the introductory	African-American men and women, aged ≥50 years.	Post intervention increase in CRC knowledge and obtaining a	257 participants completed the intervention and were available for	The current results indicated that group education could increase	[33]

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
				group education, and 3) reducing out-of-pocket costs (financial support). Two of the interventions were educational, and the third intervention responded to financial barriers (participants were offered financial reimbursement up to $500 for out-of-pocket expenses incurred for CRC screening, including transportation and other nonmedical expenses).	session but received no intervention other than accepting the contents of the gift bag with the educational pamphlets. They received pretesting (at the introductory session), post-testing, and follow-up on a schedule identical to that of the participants in the other cohorts.		screening test within 6 months.	follow-up 3 months to 6 months later. Among completers, there were significant increases in knowledge in both educational cohorts but in neither of the other 2 cohorts. By the 6-month follow-up, 17.7% (11 of 62 participants) of the Control cohort reported having undergone screening compared with 33.9% (22 of 65 participants) of the Group Education cohort (P = .039). Screening rate increases in the other 2 cohorts were not statistically significant.	CRC cancer screening rates among African Americans. The screening rate of <35% in a group of individuals who participated in an educational program through multiple sessions over a period of several weeks indicated that there still are barriers to overcome.	
7	2011	Georgia and Florida, United States	RCT. Health plan members intervention trial.	Intervention practices received 1) academic detailing (2	Usual care; at patient level - participants received neither	Members of a large health plan (Aetna's health maintenance	Primary: Self-reported completion of any CRC screening test	Among 443 active participants, 75.8% were ages 52 to 59 years, 80.9%	Interventions combining a patient-directed decision aid and	[34]

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
				physician detailers conducted 2 sessions for each practice that included information about colon cancer and screening tests, practice-specific screening rates, clips of the decision aid, and the development of practice-specific plans to address requests for screening) to facilitate CRC testing once patients were activated by the 2) decision aid (a personalized letter, the decision aid in DVD and VHS formats with instructions for viewing, stage-targeted brochures, Aetna-specific copayment and referral	academic detailing nor decision aid. All Aetna members (including those in our study's intervention and usual care groups) annually received brief mailed reminders from Aetna encouraging them to obtain CRC screening.	organization [HMO] product) from selected metropolitan areas in Georgia and Florida, aged 52 to 75.	at 12 months. Secondary: The effect of the decision aid in the subtrial of nonrespondents.	were white, 62.1% were women, and 46.4% had college degrees or greater education. Among 380 active participants with known screening status at 12 months based on survey results, 39% in the intervention group reported receiving CRC screening compared with 32.2% in the usual care group (unadjusted odds ratio [OR], 1.34; 95% confidence interval; [CI], 0.88-2.05; P = .17). After adjusting for baseline differences and accounting for clustering, the effect was somewhat larger (OR, 1.64; 95% CI, 0.98-2.73; P = .06). Claims analysis produced similar effects for active	practice-directed academic detailing had a modest but statistically nonsignificant effect on CRC screening rates among active participants	

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DOI: http://dx.doi.org/10.5772/intechopen.94396

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
				information, CRC screening options chart, and the decision aid survey).				participants. The intervention was more effective in those who had incomes >$50,000 (OR, 2.16; 95% CI, 1.07-4.35) than in those who had lower incomes (OR, 1.25; 95% CI, 0.53-2.94; P = .03 for interaction).		
8	2016	Texas, United States	Quasi experiment. Two arm parallel non-equivalent control group design in which participants were randomly allocated to three education intervention delivery groups in a 1:1:1 ratio.	Eligible subjects were randomized to either 1) promotora (P), 2) video (V), or 3) combined promotora and video (PV) education, and also received no-cost screening with fecal immunochemical testing or colonoscopy and navigation.	Controls were recruited from a similar county, received no intervention.	Population from community and clinic sites in Texas, aged 50-75.	6 month self-reported CRC screening.	784 subjects (467 in intervention group, 317 controls) were recruited; mean age was 56.8 years; 78.4% were female, 98.7% were Hispanic and 90.0% were born in Mexico. In the worst case scenario analysis (n = 784) screening uptake was 80.5% in the intervention group and 17.0% in the control group [relative risk 4.73, 95% CI: 3.69–6.05, P < 0.001]. No	A multicomponent community-wide, bilingual, CRC screening intervention significantly increased CRC screening in an uninsured predominantly Hispanic population.	[35]

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
								educational group differences were observed. Covariate adjustment did not significantly alter the effect.		
9	2017	Hamadan, Iran	1) FGD and IDI. Focused group discussion and in-depth interview were held among physicians and adult population. 2) RCT. Cluster intervention trial.	A multi-component intervention was developed and piloted. In final intervention trial stage, participants received either 1) education and free FOBT, or 2) education only, or 3) free FOBT. Education materials were reminder pack that contains postcards and pamphlet, and an educational video with title "Being a winner in life: how to prevent CRC cancer".	Controls received only questionnaire (regarding the determinants of the CRC screening behaviors).	Patients in 8 health centres in Hamadan, aged 40-70.	4 month CRC screening.	The preliminary evaluation findings revealed that during the 4-month follow up period, CRC screening rates were 87.1%, 61.3%, 54.8 and 1.6% for participants assigned to education with free FOBT, only education, only free FOBT and control group, respectively. Adults in either of the 3 intervention groups were significantly more likely to undergo screening compared to adults in the control group. There were significant differences in CRC	Intervention Mapping (IM) is a useful process in the design of a theory-based intervention addressing CRC screening among Iranian population.	[36]

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DOI: http://dx.doi.org/10.5772/intechopen.94396

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
								screening uptake between intervention groups and control (P < 0.001).		
10	2010	United States	RCT. Randomized from nation-wide database.	A narrative intervention within educational message was used to promote colorectal cancer screening i.e. first-person narrative from a similar other (i.e., an individual who matched participants in gender, age, and race), who described a personal experience with the colon cancer screening decision.	Control participants did not receive a narrative.	Participants were recruited from Survey Sampling International (SSI), aged 49-60.	Perceptions of the impact of the barriers on screening, risk perception, knowledge, and interest in screening.	Compared to participants who received only the educational message, participants who received the message along with a narrative reported that the barriers to screening would have less of an impact on a future screening experience.	The narrative also increased risk perception for colorectal cancer and interest in screening in the next year.	[37]
11	2011	Germany	RCT. Randomized from German statutory health insurance scheme.	Intervention group received 38 pages brochure with evidence based risk information on	Controls received official information leaflet of the German colorectal cancer	Insured people who were members of the target group for colorectal cancer	The primary end point was "informed choice," comprising "knowledge,"	The response rate for return of both questionnaires was 92.4% (n = 1457). 345/785 (44.0%) participants in the	Evidence based risk information on colorectal cancer screening increased informed choices	[38]

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
				colorectal cancer screening and two optional interactive internet modules on risk and diagnostic tests.	screening programme	screening, age 50-75.	"attitude," and "combination of actual and planned uptake." Secondary outcomes were "knowledge" and "combination of actual and planned uptake." Knowledge and attitude were assessed after 6 weeks and combination of actual and planned uptake of screening after 6 months.	intervention group made an informed choice, compared with 101/792 (12.8%) in the control group (difference 31.2%, 99% confidence interval 25.7% to 36.7%; P < 0.001). More intervention group participants had "good knowledge" (59.6% (n = 468) v 16.2% (128); difference 43.5%, 37.8% to 49.1%; P < 0.001). A "positive attitude" towards colorectal screening prevailed in both groups but was significantly lower in the intervention group (93.4% (733) v 96.5% (764); difference − 3.1%, −5.9% to −0.3%; P < 0.01). The intervention had no effect on the combination of	and improved knowledge, with little change in attitudes. The intervention did not affect the combination of actual and planned uptake of screening.	

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
								actual and planned uptake (72.4% (568) v 72.9% (577); P = 0.87).		
12	2013	California, United States	RCT. Patients were assigned randomly to 1 of 3 groups.	One group was assigned to fecal immunochemical test (FIT) outreach, consisting of mailed invitation to use and return an enclosed no-cost FIT (n = 1593). A second was assigned to colonoscopy outreach, consisting of mailed invitation to schedule a no-cost colonoscopy (n = 479). These groups also received telephone follow-up to promote test completion.	Usual care; consisting of opportunistic primary care visit–based screening (n = 3898).	Uninsured patients, not up to date with CRC screening, served by the John Peter Smith Health Network, a safety net health system, aged 54 to 64.	Screening participation in any CRC test within 1 year of recruitment.	Mean patient age was 59 years; 64% of patients were women. The sample was 41% white, 24% black, 29% Hispanic, and 7% other race/ethnicity. Screening participation was significantly higher for both FIT (40.7%) and colonoscopy outreach (24.6%) than for usual care (12.1%) (P < .001 for both comparisons with usual care). Screening was significantly higher for FIT than for colonoscopy outreach (P < .001). In stratified analyses, screening was	Among underserved patients whose CRC screening was not up to date, mailed outreach invitations resulted in markedly higher CRC screening compared with usual care. Outreach was more effective with FIT than with colonoscopy invitation.	[39]

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
								higher for FIT and colonoscopy outreach than for usual care, and higher for FIT than for colonoscopy outreach among whites, blacks, and Hispanics ($P < .005$ for all comparisons). Rates of CRC identification and advanced adenoma detection were 0.4% and 0.8% for FIT outreach, 0.4% and 1.3% for colonoscopy outreach, and 0.2% and 0.4% for usual care, respectively ($P < .05$ for colonoscopy vs. usual care advanced adenoma comparison; $P > .05$ for all other comparisons). Eleven of 60 patients with abnormal FIT results did not		

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DOI: http://dx.doi.org/10.5772/intechopen.94396

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
								complete colonoscopy.		
13	2012	Massachusetts, United States	RCT. Participants were randomized to one of two intervention arms and one control group.	Intervention groups received either 1) decision aid plus personalized risk assessment, or 2) decision aid alone. Interventions took place just prior to a routine office visit with their primary care providers.	Controls reviewed a modified online version of "9 Ways to Stay Healthy and Prevent Disease," which discussed generic lifestyle changes other than screening for minimizing risk of preventable diseases.	Population in an urban, academic safety-net hospital and community health center, aged 50-75.	Completion of a CRC screening test within 12 months of the study visit.	Patients in the decision-aid group were more likely to complete a screening test than control patients (43.1% vs. 34.8%, p = 0.046) within 12 months of the study visit; conversely, test uptake for the decision aid and decision aid plus personalized risk assessment arms was similar (43.1% vs. 37.1%, p = 0.15). Assignment to the decision-aid arm (AOR = 1.48, 95% CI = 1.04, 2.10), black race (AOR = 1.52, 95% CI = 1.12, 2.06) and a preference for a patient-dominant decision-making approach (AOR = 1.55, 95%	Decision aid–assisted SDM has a modest impact on CRC screening uptake. A decision aid plus personalized risk assessment tool is no more effective than a decision aid alone.	[40]

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
								CI = 1.02, 2.35) were independent determinants of test completion. Activation of the screening discussion and enhanced screening intentions mediated the intervention effect.		
14	2010	California, United States	RCT. Community based trial.	Intervention groups received either 1) an education session on CRC screening and free fecal occult blood test (FOBT) kits, or 2) an education session but no free FOBT kits	Control group received an education session on the health benefits of physical activity.	Filipino American population, aged 50-75.	Self-reported CRC screening rates during the 6-month follow-up period.	Self-reported CRC screening rates during the 6-month follow-up period were 30%, 25%, and 9% for participants assigned to intervention with FOBT kit, intervention without the kit, and control group, respectively. Participants in either of the 2 intervention groups were significantly more likely to report screening at follow-up than	A multicomponent intervention that includes an educational group session in a community setting can significantly increase CRC screening among Filipino Americans, even when no free FOBT kits are distributed.	[41]

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
								were participants in the control group.		
15	2011	Texas, United States	RCT. Randomized from a baseline survey into one of three groups.	Intervention groups received either 1) a tailored intervention about CRC screening (tailored group), or 2) a public web site about CRC screening (web site group).	Control group; survey-only group.	Patients from Kelsey-Seybold Clinic, overdue for CRC screening, aged 50-70.	Completion of any recommended CRC screening by 6 months.	There was no statistically significant difference in screening by 6 months: 30%, 31%, and 28% of the survey-only, web site, and tailored groups were screened. Exposure to the tailored intervention was associated with increased knowledge and CRC screening self-efficacy at 2 weeks and 6 months. Family history, prior screening, stage of change, and physician recommendation moderated the intervention effects.	A tailored intervention was not more effective at increasing screening than a public web site or only being surveyed.	[42]

No	Year	Country	Design	Intervention	Comparison	Population	Main Outcome Measured	Result	Conclusion	Reference
16	2010	Washington, United States	RCT. A clinic-based individual randomized trial.	Intervention groups received either 1) mailed fecal occult blood test (FOBT) card and instructions on how to complete the test (mailed FOBT only); or 2) mailed FOBT card and instructions on how to complete the test, telephone reminders, and home visits (mailed FOBT and outreach)	Usual care; no formal prompting of colorectal cancer screening, other than what is provided during a physician visit.	Hispanic patients who had been seen in the Seattle-based community clinic, aged 50-79.	Post intervention differences in rates of FOBT screening in intervention and usual care group.	Data analysis occurred between November 2008 and September 2009. Nine-month postintervention screening rates were 26% among patients who received the mailed packet only intervention ($P < .001$ compared with usual care) and 31% in the group that received the mailed packet and outreach intervention ($P < .001$ compared with usual care). This compared with 2% in the group that received usual care. Screening rates in the mailed FOBT only group and in the mailed FOBT and outreach group were not significantly different ($P = .28$).	Culturally appropriate clinic-based interventions may increase colorectal cancer screening among underserved Hispanics.	[43]

Table 1.
Evidence from previous studies on CRC screening and intervention modalities.

promote it. The example from **Table 1** can be part of promoting the CRC screening using FOBT for early detection of cancer.

7. Others prevention strategies

Findings from a systematic review suggest that small media interventions (eg, interventions using mailed materials, text messages, and telephone calls) may be effective in improving screening uptake for breast, cervical, colorectal, and gastric cancer in Asian countries. Therefore, there is a priority need for programs that raise awareness about the warning signs and symptoms of cancer and the benefits of early detection. This form of secondary prevention should be implemented in countries in which resources for population-based screening are lacking, particularly for cancers. Overall, the findings of the evaluation indicate that a culturally adapted, evidence-based mass media intervention appears to impact positively in terms of improving CRC symptom awareness among population; and that impact is more likely when a campaign operates a differentiated approach that matches modes of communication to the ethnic and religious diversity in a population. Research shown that there was a significant improvement in the recognition of all CRC symptoms (prompted) at follow up and a significant improvement in the knowledge of three unprompted symptoms, i.e. 'blood in stool', 'feeling that the bowel does not empty after using the lavatory' and 'unexplained weight loss'.

A recommendation from a physician is the most influential factor in determining whether a patient is screened for colorectal cancer. While the vast majority of primary care physicians report that they screen for colorectal cancer, many patients do not receive the recommendation they need. People with a high risk for CRC should not be included in a routine screening used for the general population. Their screening must be started early in a shorter period, and using various tests. The United States Preventive Task Force recommends CRC screening for the average at-risk population, using an annual fecal occult blood test (FOBT), a periodic flexible sigmoidoscopy (FS), or a colonoscopy [22]. One of the solutions is to engage the primary care doctors and family physician in identifying and recommending high risk patients for colorectal cancer screening. The effectiveness of the family doctor's role has been proven in previous studies and should be the way forward to increase awareness and cancer screening uptake.

Simultaneously, concerted effort is needed to increase numbers of skill operators and availability of the procedure throughout the country. In certain Europe countries, nurses have been trained to perform endoscopy to reduce patient's waiting time. On the other hand, fecal occult blood test can be utilized for mass screening among low risk or asymptomatic patients.

All these barriers could be overcome with the implementation of government-subsidized nationwide population screening, with the provision of more accessible screening times such as having them available during non-working hours or non-working days. However, even if the above-mentioned barriers have been overcome, it would not solve the problem if the people inherently do not wish to participate due to certain psychological barriers that are more difficult to tackle. Among these is the fatalistic belief that their lives are in the hands of fate or God. They believe that if it is destined that they are to have cancer, there is nothing they can do about it and early detection of cancer would not benefit them [23].

A patient's personal awareness of his or her risk level is important. Awareness of the health status of family members is also needed and should be encouraged. Awareness of discrepancies in screening rates for people in racial and ethnic groups can help to reduce these disparities.

8. Conclusions

Public health prevention on CRC screening uptake is very important for reducing the incidence and mortality. Population will benefit more with an early CRC screening uptake. There are multiple barriers that can hinder person from undergoing CRC screening for early prevention, detection and treatment. Majority of these barriers encountered regarding the poor rates of CRC screening are similar across countries in Asia, except for specific barriers that are due to unique circumstances. Lack of knowledge/education is the most critical barrier that is linked to a majority of other barriers. Continuous effort is important to reduce CRC related morbidity and mortality. Previous evidence showed positive effect on promoting CRC screening among community. The increased uptake of CRC screening also needs multicomponent in the intervention such as health communication, employer as well as the commitment from the physician itself. The enhancement of multicomponent screening programme will leads to successful rate of CRC screening uptake among the community.

Conflict of interest

No potential conflict of interest.

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Chapter 2

Colorectal Cancer in Vietnam

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"Policy frameworks for cancer control in general and colorectal cancer in Vietnam are in place, but there is still a lack of proper financing and governing models necessary to support a sustainable program"

Abstract

In this chapter, we focus on the up-to-date status of colorectal cancer occurrence in an Asian country with nearly 100 million in population. Protective and risk factors, time trend of colorectal cancer from 2005 to 2018 will be presented. Perspective of colorectal cancer prevention and research will be highlighted. Data will be derived and based out of current running research projects of prospective cohort study, case-control study, and population-based mortality registration in Vietnam from 2005 to 2020. The association colorectal cancer with lifestyle, diet, cooking methods, demographic factors is taken into analysis. Time trend, colorectal cancer survival, mortality will be presented.

Keywords: colorectal cancer, risk factor, time trend, mortality, incidence

1. Introduction

1.1 Colorectal cancer is an ancient disease

Homo sapiens and other species have suffered from cancer since ancient times. However, while cancer incidences in other animals are very low, human's internal organs tend to be exposed to a lot of risk factors which can develop into cancer [1, 2]. Therefore, the management of risk factors, at community and household levels, becomes the focus in environmental health and oncology.

Both the incidence and mortality rate of all types of cancer in humans have been increasing over time. Determining etiology and causality is difficult and research findings are inconsistent among populations, which lead us to the question of whether scientists' observation was incorrect or risk factors of cancer are different in different populations. Although an estimated 80% of cancer cases, in general, and 98% of colorectal cancer cases, in particular, were associated with environmental factors [3], it is uncertain to determine what the situation will be in a defined population.

1.2 Vietnam country and facilities of cancer research

1.2.1 Improving life expectancy

The culture of Vietnam is a combination between Chinese and French because the country was occupied by China for nearly 1000 years and by France for around

100 years in the past. As colorectal cancer is reported to have connection with Western dietary habits, it is a favorable condition to observe its distribution and etiologies in Vietnam.

Located in Southeast Asia, Vietnam is bordered by China to the north, Laos to the northwest, Cambodia to the southwest, and the East Sea to the east. With a population of approximately 96,491,142 people in 2018 [4], Vietnam is the 13th most populous country in the world. The Socialist Republic of Vietnam has placed a significant emphasis on economic development since the introduction of the "Doi moi" (the economic reform) in 1986. As a result, Vietnam has achieved significantly in a short amount of time. For example, the percentage of the population living on less than a dollar a day has decreased from 58–29% over 10 years, and the life expectancy of Vietnamese people has reached 71 years for men and 75 years for women [5–7]. These progressing economics and urbanizations have changed lifestyles, dietary habits, increasing pollutions in living and working environments, which might be associated with the occurrence of colorectal cancer.

1.2.2 Developing descriptive cancer epidemiology

Regarding the source of data of colorectal cancer, for many countries, civil registration and vital statistics systems are considered the main sources for mortality data [8]. Civil registration was initiated in Vietnam in 1956, and despite the 50 years of collecting data about cancer mortality, limited information was published [9]. However, a recent study assessed the civil registration and vital statistics system in Vietnam and reported that the system had significant restrictions including a lack of data particularly about early neonatal deaths, deaths of temporary residents, and/or migrants [9].

Beyond Vietnam's civil registration and vital statistics system, a national mortality reporting system was introduced in 1992 and periodic updating guidelines to improve the quality of data collecting [10]. Under the auspices of the Ministry of Health (MOH), the A6 mortality reporting system relies on commune-level health officials providing basic demographic data and information on the cause of death, which is recorded in an official book referred to as the A6. The data from the A6 is collated by the district-level health service and the information is then sent to the provincial and central level governments. The community plays a significant role in maintaining the current mortality reporting system, and in turn, can actively use the information to plan commune-level health services. Using the A6 system, mortality data regarding cancer were collected and analyzed [11–14]. Verbal autopsy designed by WHO was applied in the community to determine all causes of death, including cancer [15]. Using the verbal autopsy as a reference, the sensitivity and completeness of the system were observed to be about 80% and 94%, respectively [16]. These findings have suggested that the accuracy and completeness of cancer mortality are feasible, and therefore, it was a source of data for colorectal cancer presented in the present study. The A6 system, with the detailed recordings of deaths in all communes, can easily be conveniently used by health workers. In Vietnam, during the last decade, 7081 (65.1%) medical doctors were working at commune health stations (CHS) [6, 17, 18]. Health workers are trained and work at CHS and they will contribute to the improvement of the mortality data quality and registration completeness gradually soon. Cancer epidemiology and population-based cancer registration were introduced by IARC during the 1980s, focused in the two biggest cities, Hanoi and Ho Chi Minh, representing the north and south of Vietnam, respectively. Cancer incidence during 1988–1997 in the Hanoi city and 1995–1998 in the Ho Chi Minh city was published by IACR [19–21]. Data on

colorectal cancer incidence produced by these two population-based cancer registries include a database of cancer mortality extracted from MOH's national mortality reporting system that was also used to present in the study.

1.2.3 Developing analytical cancer epidemiology

Cancer was observed to be the second most common cause of death nationwide during 2005–2006 (about 16%) [11, 12, 14], after vascular heart diseases (about 25%). Colorectal cancer (ICD-10: C18–20) has occurred at a national level in Vietnam. This study aims to generate a comprehensive picture of the fatal disease in the eight regions of Vietnam, with the hope to facilitate epidemiological studies in our country. For data of risk factors of colorectal cancer, we conducted a molecular epidemiological case–control study on the incident cases of the disease from 2002 to 2011. The study was designed by the leading experts of cancer epidemiologists from Japan and Vietnam. The protocol was approved by the scientific and ethics committees of the MONBUKAGAKUSHO (Japan) and the Ministry of Science and Technology (Vietnam). Initial results and findings were published elsewhere [22–24].

2. Characteristics of colorectal cancer cases in Vietnam

2.1 The occurrence of colorectal cancer at nationwide

From 2005 to 2006, we reported 4646 cases of fatal colorectal cancer among all 93,719 cancer death cases. It was responsible for about 5% of all cancer cases. Colorectal cancer was distributed in all 671 districts within 63 provinces/cities of Vietnam. Among 4646 colorectal cases, there were 2450 men (52.7%). The average age at death was 62 in men and 66 in women [14]. In 2002, the estimated number of death from colorectal cancer was 1730 cases in men and 2401 cases in women, provided that the total number of cases was 4131 [25]. The average reported number per year was 2323 cases in 2005–2006, which was only 56% of the estimated number of 4131 cases. According to GLOBOCAN 2018, colon ranked the fifth in the incidence and mortality among malignant diseases, with 5457 new cases and 3183 deaths per year [4].

2.2 Colorectal cancer caused a premature death

These characteristics suggest that an epidemiological study must be performed:

Colorectal cancer caused thousands of deaths in Vietnam, and it was considered as one of the most important public health problems in our country.

Causality and risk factors of colorectal cancer were presented at nationwide because the cancer was observed in all 671 districts within all 63 provinces/cities. Therefore, we should observe and examine etiology and causality at the household and community levels in identifying and controlling risk factors.

Registration of colorectal cancer mortality nationwide might be underreported for about 40% of total cases. Data on cancer mortality registration will promptly be improved and it will be used for cancer control and prevention in our country.

Using referred data of cancer from China to estimate the cancer incidence and mortality of all sites as well as of colorectal cancer, it might be an overestimated colorectal cancer in 2002 for Vietnam [25].

- Colorectal cancer caused premature death for an average of 7.3 years [18].

3. Colorectal cancer incidence and mortality

3.1 Childhood colorectal cancer

In terms of colorectal cancer in under-18 year-old people, 52 cases (1.13% of 4646 cases) were found [14]. Children and adolescents are not employed and therefore they are not exposed to occupational carcinogens. They are also rarely exposed to tobacco smoking and alcoholic beverages, according to a recent report on student health surveillance by WHO [26], as well as to dioxins in herbicides during the Vietnam War. What were the risk factors that induced colorectal cancer during the 1990s in Vietnam among children and adolescents?

3.2 Incidence of colorectal cancer

Two population-based cancer registrations have been running in the two prominent cities of Hanoi and Ho Chi Minh. The covered population was about 13 million (15% of the country population) in 2008 [6, 19, 21].

Age-standardized incidence rates per 100,000 (ASR) of colorectal cancer was 10.5 in men and 6.5 in women, during 1993–1997, in Hanoi and 12.4 in men and 9.0 in women, during 1995–1998, in Ho Chi Minh City [19, 21]. The incidence rate of colorectal cancer in Vietnam was one fifth of that in the United States (ASR 52.6 in men and 37.0 in women, respectively) [27].

Data on the cancer incidence rate in Vietnam might be deviated by 15–25% since the death certificate was not available at that time. During the 1990s, only 12% of Vietnamese had health insurance (HI). Thus, many cancer patients were not admitted to hospitals, which impacted directly on number of mortality in oncology patients [17]. According to GLOBOCAN 2018, 114,871 cancer patients in Vietnam are deceased in 2018, which takes up more than one third of the prevalent cases [4].

3.3 Mortality from colorectal cancer

In eight regions, ASR colorectal cancer mortality rates were from 4.0 to 11.3 per 100,000 in men and from 3.0 to 7.8 per 100,000 in women (**Table 1**). The highest mortality rates were seen in both men (11.3 per 100,000) and women (7.8 per 100,000) in the region of the Mekong Delta River in the South of Vietnam.

In a specific province population, the colorectal cancer mortality rate per 100,000 person-years during 2005-2018 was 5.8, men 6.9, and women 5.0. Men to

Region	Men			Women		
	Cases	Crude	ASR	Cases	Crude	ASR
Red Delta River	68	5.5	6.9	75	5.8	5.2
Northeast	20	3.1	4.4	34	5.0	5.0
Northwest	7	2.8	4.7	9	3.4	5.0
North central coast	29	3.3	4.0	34	3.7	3.0
South central coast	18	5.4	7.7	13	3.7	4.1
Central highlands	9	3.1	6.0	7	2.3	3.7
Northeast South	34	4.0	6.3	24	2.7	3.4
Mekong Delta River	83	7.5	11.3	78	6.8	7.8

Table 1.
Colorectal cancer mortality rate per 100,000 (ASR) by sex and regions, 2005–2006.

women ratio was 1.4 in the Lang Son province located in North Vietnam, remote areas of the country (**Table 2**).

The age-specific rate per 100,000 sharply increased in the age group of 50–59 with a peak of age group of 80+ at as high as 346.6 and 275.3 per 100,000 in men and women at the region of the Mekong Delta River in the South Vietnam, respectively (**Figure 1**). It supported the mentioned statement of the average age at death of 62 in men and 66 in women.

ASR colorectal cancer mortality rates per 100,000 in men ranged from 4.0 to 11.3 and it was lower than the rate in the developed countries, which was as high as 17.7 (**Figure 2**). Nationwide, it was estimated to be 5.6 per 100,000 (ASR) or it was one third when compared to that of the developed countries [25].

ASR colorectal cancer mortality rates per 100,000 in women ranged from 3.0 to 7.8 and it was lower than the rate in the developed countries, which was as high as 12.3 (**Figure 3**). Nationwide, it was estimated to be 5.2 per 100,000 (ASR) or it was nearly half when compared to that of the developed countries [25].

3.4 Survival of colorectal cancer

Regarding colorectal cancer survival, there was a lack of surveillance data for cases incidence and mortality to estimate the relative survival in Vietnam. Two population-based cancer registries have been running in Vietnam, one in Hanoi

Sex	Year	Total	Crude rate[&]	ASR-Segi[@]	% < 70[#]	ASR-WHO[$]
Men	2005–2018	201	4.4	6.2	66.7	6.9
Women	2005–2018	203	4.5	4.3	55.2	5.0
Both genders	2005–2018	404	4.5	5.1	60.9	5.8

[&]Crude rate per 100,000 person-years.
[@]Age-standardized rate per 100,000 person-years using the SEGI World standard population (in the 1960s).
[#]Proportion of death cases aged under 70 year-olds.
[$]Age-standardized rate per 100,000 person-years using the World Health Organization standard population for 2000-2025. Men to women ratio (ASR-WHO) = 1.4 (6.9/5.0).

Table 2.
Mortality due to colorectal cancer by sex during 2005–2018 in Lang Son province.

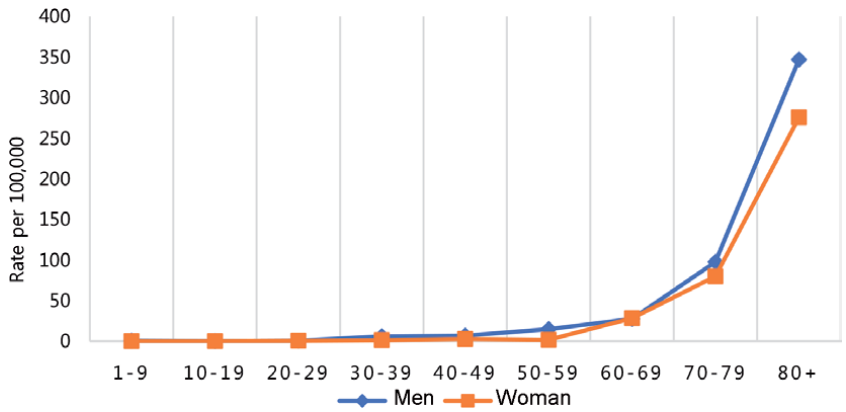

Figure 1.
Age-specific mortality rate per 100,000 in men and women, 2005–2006.

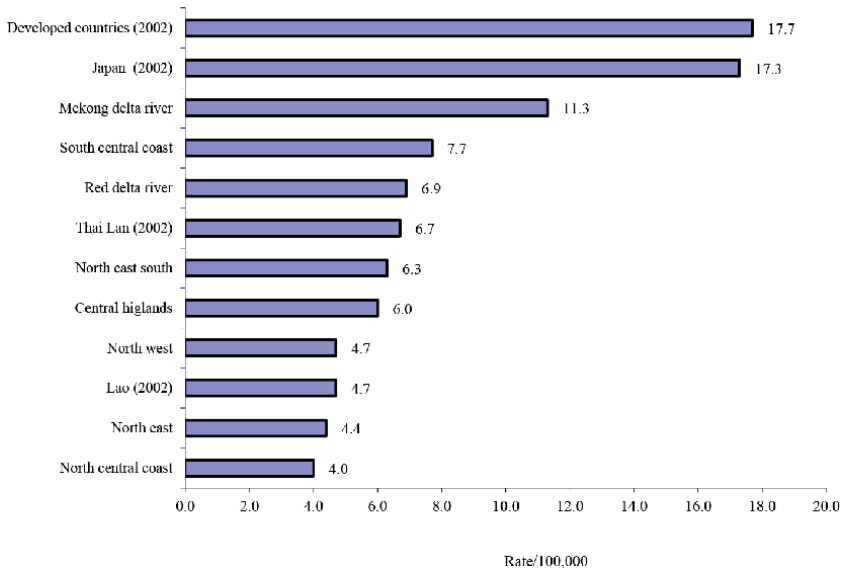

Figure 2.
ASR mortality rates per 100,000 by regions and in Vietnamese men, 2005–2006.

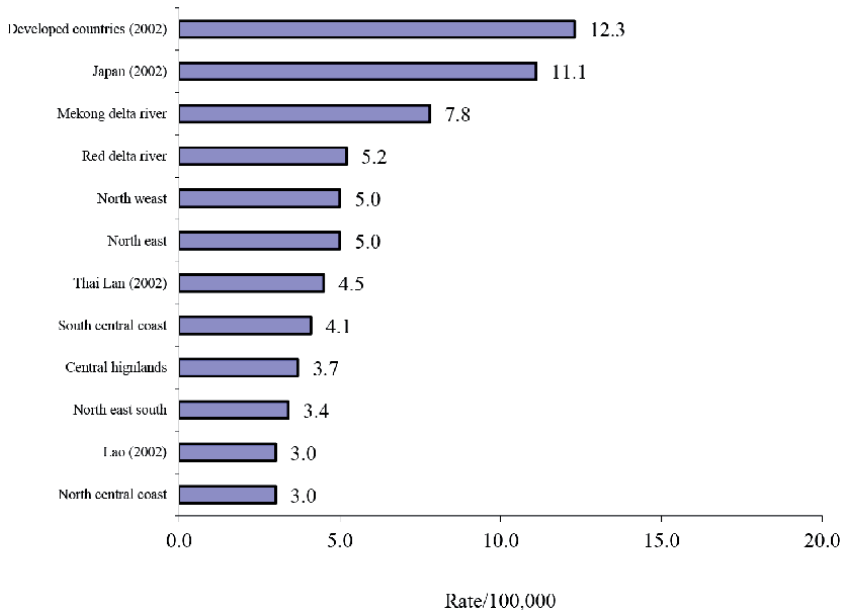

Figure 3.
ASR mortality rates per 100,000 by regions and in Vietnamese women, 2005–2006.

established in 1988, and the other in Ho Chi Minh city established in 1990 [19, 21]. These institutions collected data from medical records only and there was a lack of follow-up data, so the data of incidence rates might be underestimated. We analyzed the survival rate for fatal colorectal cancer cases: 1-year survival was 33.5% and 5-year survival was 4.3%, men and women combined [13].

These data of incidence, mortality, and survival (among fatal cases only) of colorectal cancer cases in Vietnam have suggested that:

- Risk factors-induced colorectal cancer might slightly be related to sex's life-styles, we should examine the risk factors that affect both men and women.

- Prevention of colorectal cancer should be prioritized because the diseases were estimated to be caused by 98% of environmental risk factors [3].

3.5 Time trend of colorectal cancer mortality

Between 2005 and 2018, the age-standardized mortality rate per 100,000 person-years (ASR-WHO) was increased from 3.4 to 9.8 in men and 2.2 to 3.9 in women (**Figure 4**). The significant increase trend was seen in both genders by 3.4% per year (**Table 3**). However, this significant increasing trend was observed in men only (5.2% per year, **Table 4**) but not in women (1.8% per year, **Table 5**).

Figure 4.
The trend of colorectal cancer mortality from 2005 to 2018 by gender in the Lang Son province located in North Vietnam. Missing data in 2009-2010; ASR-WHO: Age-standardized rate per 100,000 person-years using the World Health Organization standard population for 2000-2025.

Year	Case	Crude rate[&]	% < 70[#]	ASR-WHO-[$]	MRR (95% CI)[$$]	p
2005	16	2.2	75.0	2.8	1 (Reference)	
2006	23	3.1	69.6	3.9	1.413 (0.747, 2.675)	0.288
2007	26	3.5	73.1	4.6	1.590 (0.853, 2.964)	0.144
2008	31	4.2	45.2	5.4	1.869 (1.023, 3.418)	0.042
2011	35	4.8	60.0	6.3	2.147 (1.188, 3.879)	0.011
2012	47	6.3	59.6	8.3	2.831 (1.605, 4.992)	<0.001
2013	34	4.6	61.8	5.9	2.073 (1.144, 3.775)	0.016
2014	47	6.0	55.3	8.1	2.706 (1.534, 4.772)	0.001
2015	41	5.2	61.0	6.9	2.343 (1.315, 4.174)	0.004
2016	41	5.2	68.3	6.8	2.349 (1.318, 4.186)	0.004
2017	27	3.4	44.4	4.5	1.527 (0.823, 2.834)	0.180

Year	Case	Crude rate[&]	% < 70[#]	ASR-WHO-[$]	MRR (95% CI)[$$]	p
2018	36	4.6	66.7	6.3	2.065 (1.146, 3.721)	0.016

The estimated proportion of deaths due to colorectal cancer was 0.82% (404 cases of colorectal cancer vs. 49,253 total cases), both genders.[$$]Adjusted for age group (0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80+) and sex. Per year increment MRR (95% CI): 1.034 (1.010, 1.059), p = 0.005.
[&]Crude rate per 100,000 person-years.
[$]Age-standardized rate per 100,000 person-years using the World Health Organization standard population for 2000–2025.
[#]Proportion of death cases aged under 70 years. When combined for all cases from 2005 to 2018, for both genders, WHO-ASR: 5.8 per 100,000 person-years.

Table 3.
Mortality due to colorectal cancer in both genders by year from 2005 to 2018 in Lang Son province.

Year	Case	Crude rate[&]	% < 70[#]	ASR-WHO-[$]	MRR (95% CI)[##]	p
2005	9	2.5	88.9	3.4	1 (reference)	
2006	12	3.3	75.0	4.7	1.311 (0.552, 3.112)	0.539
2007	11	3.0	63.6	4.7	1.196 (0.496, 2.886)	0.691
2008	14	3.8	57.1	5.4	1.501 (0.650, 3.468)	0.342
2011	15	4.1	53.3	6.6	1.636 (0.716, 3.739)	0.243
2012	18	4.8	55.6	7.8	1.928 (0.866, 4.290)	0.108
2013	17	4.6	76.5	6.8	1.843 (0.821, 4.134)	0.138
2014	23	5.9	65.2	9.6	2.354 (1.089, 5.089)	0.029
2015	19	4.9	68.4	7.9	1.930 (0.873, 4.267)	0.104
2016	26	6.7	69.2	10.1	2.649 (1.241, 5.654)	0.012
2017	14	3.5	64.3	5.7	1.408 (0.609, 3.252)	0.424
2018	23	5.9	69.6	9.8	2.346 (1.085, 5.070)	0.030

The estimated proportion of deaths due to colorectal cancer was 0.64% (201 cases of colorectal cancer vs. 31,262 total cases) in men.[##]Adjusted for age group (0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80+). Per year increment MRR (95% CI): 1.052 (1.017, 1.089), p = 0.003.
[&]Crude rate per 100,000 person-years.
[$]Age-standardized rate per 100,000 person-years using the World Health Organization standard population for 2000–2025.
[#]Proportion of death cases aged under 70 years. When combined for all cases from 2005 to 2018 in men, WHO-ASR: 6.9 per 100,000 person-years.

Table 4.
Mortality due to colorectal cancer in men by year from 2005 to 2018 in Lang Son province.

3.6 Screening for colorectal cancer and treatment

Risk factors of colorectal cancer include certain unhealthy dietary regimens, precancerous lesions detected on colonoscopy, and genetic factors. According to the guideline for colorectal cancer diagnosis and treatment released by Vietnam's Ministry of Health in 2018, screening should be conducted on high-risk patients with a history of inflammatory bowel disease (Crohn's disease or ulcerative colitis) or colorectal polyps, or a family history of polyposis syndrome, colorectal polyps, or colorectal cancer. Fecal occult blood test (FOBT) and colonoscopy are pivotal in screening. During 2008–2010, the National Cancer Control Program organized a screening program for five malignant diseases in which 9634 people were screened for oral and colorectal cancer. However, stage I-II colorectal cancers accounted only for 32.2% [28].

Year	Case	Crude rate[&]	% < 70[#]	ASR-WHO[$]	MRR (95% CI)[##]	p
2005	7	1.9	57.1	2.2	1 (reference)	
2006	11	3.0	63.6	3.2	1.545 (0.599, 3.986)	0.368
2007	15	4.1	80.0	4.7	2.097 (0.855, 5.144)	0.106
2008	17	4.5	35.3	4.9	2.344 (0.972, 5.652)	0.058
2011	20	5.4	65.0	6.3	2.805 (1.186, 6.633)	0.019
2012	29	7.7	62.1	8.8	3.994 (1.749, 9.117)	0.001
2013	17	4.6	47.1	5.0	2.369 (0.982, 5.714)	0.055
2014	24	6.1	45.8	7.0	3.159 (1.361, 7.332)	0.007
2015	22	5.6	54.5	6.2	2.874 (1.228, 6.727)	0.015
2016	15	3.8	66.7	4.3	1.965 (0.800, 4.818)	0.140
2017	13	3.3	23.1	3.5	1.681 (0.670, 4.212)	0.268
2018	13	3.3	61.5	3.9	1.704 (0.680, 4.272)	0.255

The estimated proportion of deaths due to colorectal cancer was 1.13% (203 cases of colorectal cancer vs. 17,990 total cases) in women.[##]*Adjusted for age group (0–9, 10–19, 20–29, 30–39, 40–49, 50–59, 60–69, 70–79, and 80+). Per year increment MRR (95% CI): 1.018 (0.985, 1.052), p = 0.294.*
[&]*Crude rate per 100,000 person-years.*
[$]*Age-standardized rate per 100,000 person-years using the World Health Organization standard population for 2000–2025.*
[#]*Proportion of death cases aged under 70 years. When combined for all cases from 2005 to 2018 in women, WHO-ASR: 5.0 per 100,000 person-years.*

Table 5.
Mortality due to colorectal cancer in women by year from 2005 to 2018 in Lang Son province.

Treatment is decided based on multiple factors including staging, tumor location, and histopathology. Available treatment modalities in Vietnam are surgery, radiotherapy, and chemotherapy (systemic and targeted) [29].

In terms of surgery strategy, it depends on the curative/non-curative approaches as well as the operation indication relates to the complications or not. Pham et al. (2020) conducted a study on patients who performed single-port laparoscopic right hemicolectomy. The mean survival time was 67.9 ± 3.3 months and the recurrence rate was 16.7%. The survival rates at 2, 3, and 5 years were 87.5, 79.9, and 66.7%, respectively. Survival was shown to be associated with age, tumor size, and TNM stage at 61.7 ± 3.9 months after treatment [30]. For advanced stages, three main agents were 5-fluoropyrimidines, oxaliplatin, and irinotecan, combined in common regimens including FOLFOX/XELOX, FOLFIRI/XELIRI, or FOLFOXIRI. Trinh et al. followed up with metastatic colon cancer patients treated with FOLFOXIRI. The mean disease-free survival time was 13.37 ± 9 months, with the response after 3 and 6 cycles being 82 and 79.4%, respectively [31]. Radiation therapy is indicated in patients who have metastatic lesions in the liver, bone, or lungs [29].

The surgery method for rectal cancer depends on the extent and location of the tumor [29]. Truong et al. conducted a cohort study during 2009–2016 on patients with low rectal cancer undergoing laparoscopic sphincter-saving resection. The local and distant recurrence rates were 10.4 and 20.8%, respectively. The overall survival was 52.7 ± 3.9 months and the disease-free survival was 38.3 ± 2.9 months [32]. In another study on rectal cancer patients who were treated with surgery, survival was reported to be associated with staging, lymph nodes metastasis, and tumor size. The mean overall survival time was 48.9 ± 52.7 months and the 3-year survival rate was 91.7%. Patients at stage I-II or having lymph nodes <10 mm in diameter had better prognosis [33]. Vi et al. conducted a study on metastatic rectal

cancer patients who were treated with FOLFOX4 and bevacizumab. The median overall survival time was 19 months and the survival rates after 1 and 2 years were 56.9 and 27.6%, respectively. In this population, survival was associated with the CEA level, the number of organs having metastasis, histopathology, and response to bevacizumab [34]. The overall survival time in this study was similar to some studies using similar regimens in the world [35, 36].

3.7 Social health insurance and colorectal cancer control

3.7.1 Health insurance in Vietnam

Health insurance (HI) provides access to health examination and treatment for all patients, including those who cannot cover their medical expenses using out-of-pocket money, ensuring equity and social security. All public health establishments in Vietnam participate in the national health insurance scheme. Private hospitals, especially centers managing chronic diseases, are also encouraged to participate.

After enrolling in the national health insurance program, most of the general populations pay an annual amount of 1,117,000 VND (approximately 48.5 USD). Insurance fees can be waived for some special populations (e.g., poor households and veteran's relatives). In 2018, 86.8% of Vietnamese people are covered with national HI, allowing them to access most health-care services in Vietnam [37].

The mean direct costs for an outpatient and inpatient with colorectal cancer were 13.594 million VND (588 USD) and 63.371 million VND (2741 USD), respectively. This renders a financial burden for people who are not covered by HI and creates a barrier to access to health care [38]. As 80–100% of treatment costs for colorectal cancer are covered by HI in public hospitals and private clinics, patients enrolling in the insurance program can access expensive diagnostics and treatments. However, some targeted drugs and bevacizumab are only covered 30–50% by HI [39]. In Vietnam, the primary care levels are communal health stations and district health centers/hospitals. People who are treated at these facilities are fully covered if they participate in the HI program. If they must be transferred to higher-level (provincial/central) hospitals, patients have to present valid official letters of referral to the insurance agency to maintain maximum insurance coverage. The maximum coverage for a general person who is admitted to a central hospital is 80%; this will be reduced to 40% if they fail to present valid letters of referral [40].

3.7.2 Colorectal cancer control

In Vietnam, a majority of colorectal cancer patients are detected at late stages. In a study in 2015, 67.8% of the patients were diagnosed at stage III/IV [28]. Early detection of colorectal cancer through screening may significantly increase the 5-year survival to 89.9%, compared with 13.8–71.1% in patients with regional and distant colorectal cancer metastasis [41].

Having acknowledged the situation, the Vietnamese Government issued the National Strategy for the Prevention and Control of Non-Communicable Disease (NCD) (2015–2025). One of the objectives of this strategy is to reduce late diagnosis and increase survival for colorectal cancer [42]. Colorectal cancer screening is conducted annually, supported by the National Cancer Control Program, and is accessible in many health-care facilities [28, 43]. For community screening, FOBT is applied in many health-care centers, with the advantage of being a noninvasive, quick, and reliable method. When the patients have positive FOBT, the next step to be performed would be colonoscopy. This strategy helps to screen mass population, especially the people with

risk factors (family history, colon polyp history, or age), as well as save up the human and economic resources. Some preliminary data have shown the effectiveness of this approach in early colorectal cancer; however, the long-term benefits in national screening and management program requires bigger data from multicenters [44, 45].

Efforts have been made to raise the awareness of lifestyle and diet modification, including limiting alcohol consumption and smoking, promoting a healthy diet, and encouraging physical exercises [46–48].

4. Risk factors and benefit factors of colorectal cancer in Vietnam

4.1 Performing case-control study on colorectal cancers

A case-control study was performed for colorectal cancers admitted to Hanoi Cancer Hospital, Viet Duc Surgery Hospital, and Bach Mai General Hospital located in Hanoi. The ratio of case-control is 1:1 with the standards for matching are gender and age (±5). Cases and controls were interviewed to collect data in using demographic and lifestyle questionnaire and semiquantitative food frequency questionnaire. Blood samples were collected in the early morning on the day of operation [23, 24]. Most patients came from the provinces near Hanoi within the Red Delta River. They will be represented as Vietnamese in the north.

4.2 Host factors related to colorectal cancer

4.2.1 Blood ABO group and risk of colorectal cancer

Distribution of blood ABO group in Vietnamese is 45.00, 21.20, 28.30, and 5.50% for types O, A, B, and AB, respectively [49]. In our study, the distribution is different, with 42.97, 23.67, 27.95, and 5.42% for types O, A, B, and AB, respectively [50]. The proportion of type A plus AB is 26.70% while type O plus B is 73.30% in Vietnamese. However, in our study, it is 29.10% and 70.90%, respectively. Distribution of blood ABO group in our study population is similar to that in Vietnamese. Blood ABO group was observed to be associated with cancer risk, whereas blood A was seen to increase the risk of stomach cancer in many studies [51]. Blood A, AB, and B have also increased the risk of pancreatic cancer [52].

In our study, blood type A plus AB was seen to increase the risk of colorectal cancer, with OR = 1.58, 95% CI = 1.05–2.38 [50] (**Table 6**). The mechanism of developing colorectal cancer in patients with blood types A and AB is unknown.

When we separated colon and rectal cancer, the estimated risk was significantly increased for colon cancer, with OR = 3.36, 95% CI = 1.91–5.92, but not significantly increased for rectal cancer, with OR = 0.84, 95% CI = 0.54–1.32.

4.2.2 CYP1A1 genotypes risk of colorectal cancer

The function of CYP1A1 is recognized to be a major chemical carcinogen-induced cancer, in general, and colorectal cancer, in particular, in humans. We found that CYP1A1 (A/G and G/G genotypes) increased the risk of colorectal cancer, with OR = 1.86, 95% CI = 1.16–2.98 (**Table 7**) [50].

4.2.3 Family and personal history of health and risk of colorectal cancer

When parents and close relatives suffered from cancer, the patients are at a higher risk of colorectal cancer, with OR = 3.00, 95% CI = 1.29–6.99, and OR = 3.63,

Blood type	Control	Case	OR	95% CI		P
O and B	187	150	1.00	*Reference*		
A and AB	58	73	1.58	1.05	2.38	0.027

Table 6.
Blood ABO group and risk of colorectal cancer.

CYP1A1 genotypes	Control	Case	OR	95% CI		P
AA	57	32	1.00	*Reference*		
AG and GG	226	237	1.86	1.16	2.98	0.010

Table 7.
CYP1A1 genotypes and the risk of colorectal cancer.

95% CI = 1.31–10.01, respectively. Patients with a past history of colorectal pain and inflammation are also at a higher risk of cancer, with OR = 3.68, 95% CI = 2.01–6.75. Regarding body mass index (BMI), three levels were categorized, including <18.5; 18.5- < 25, and 25- < 30. Patients with body mass index of 25- < 30 are also at a higher risk of cancer, with OR = 2.09, 95% CI = 0.79–5.51, and p for trend <0.05 (**Table 8**) [50]. The Vietnamese households traditionally follow the multigenerational pattern and, therefore, members share living environments as well as similar dietary habits. As a result, all family members might be exposed to the risk of cancer, in general, and the risk of colorectal cancer, in particular. Regarding the body mass index, the mechanism of developing colorectal cancer among the group of obesity was unknown.

4.3 Environmental factors related to colorectal cancer

4.3.1 Drinking habits of alcohol and/or beer and risk of colorectal cancer

Alcoholic beverages have been proven to be a major part of human's diet [53]. Excluding the poisonous effect of heavy intake of alcohol, we considered alcoholic beverages as a promoter of cancer in human. Most carcinogenic chemicals have a higher solubility in alcohol than in water. For example, aflatoxin B is soluble in ethanol but has a limited water solubility [54].

There is sufficient evidence for the carcinogenicity of alcohol beverages in human but inadequate evidence for the carcinogenicity of ethanol and alcoholic beverages in experimental animals [55]. Based on these facts and figures, we hypothesized that alcoholic beverages are promoters for cancer in humans. In this study, three levels of alcoholic drinking were categorized, including not drinking, some drinking per week, and daily drinking. Those who daily consume alcoholic beverages were at a significantly higher risk of colorectal cancer, with OR = 1.91, 95% CI = 0.98–3.72, and p for trend <0.05 (**Table 9**) [50].

4.3.2 The dietary habit of heated foods and risk of colorectal cancer

Referred to earlier statements regarding cancer occurrence in species, only human's internal organs of lung, liver, stomach, and others are seriously exposed to risk factors and can develop cancer. In contrast, animals suffer from cancer with a very rare occurrence in the internal organs [1, 2]. Animals consume natural foods

Factors	Control	Case	OR	95% CI		P
Parent suffered from cancer						
No	303	290	1.00	*Reference*		
Yes	8	21	3.00	1.29	6.99	0.011
Close relative suffered from cancer						
No	305	294	1.00	*Reference*		
Yes	5	17	3.63	1.31	10.01	0.013
History of colorectal pain and inflammation						
No	286	255	1.00	*Reference*		
Yes	15	48	3.68	2.01	6.75	0.000
Body mass index (BMI) (rectal cancer only)						
<18.5	32	17	1.00	*Reference*		
18.5- < 25	108	119	2.03	.12	3.33	0.005
25- < 30	7	8	2.09	.79	5.51	0.135
P for trend = 0.013						

Table 8.
Family and personal history of health and risk of colorectal cancer.

Alcohol and/or beer	Control	Case	OR	95% CI		P
Not drinking	175	145	1.00	*Reference*		
Some drinking per week	29	33	1.61	.90	2.87	0.110
Daily drinking	21	27	1.91	.98	3.72	0.058
P for trend = 0.030						

Table 9.
Drinking habits and risk of colorectal cancer.

without any preparation, while humans consume both natural foods and prepared foods [56, 57]. Also, humans used at least 10,000 chemical additives, which serve as contaminants [58]. Besides, heat-generated carcinogens due to the cooking temperature were reported in many previous studies. One of such carcinogens is acrylamide, which was detected in heated foods. It was evaluated by IARC to be a potential carcinogen to humans (Group 2A) [59].

The concentration of acrylamide was 50 μg/kg in hamburgers prepared at the temperature of 240°C, while it was zero in the control [60]. With this evidence, we hypothesized that the intake of heated foods might be a contributor to the development of colorectal cancer in our study population. Three food items were categorized to be heated food items because they were heated in cooking temperature at 165°C or higher during preparation processing [56, 57]. The concentration of heat-generated carcinogens (acrylamide) was generated and significantly increased when the temperature increased from 100–240°C [60]. Daily and weekly intake of barbecued meats (Usual outside appearance: medium-, well-, and blackened/charred of cooked meats vs. lightly browned of cooked meats), bread, and biscuits significantly increased the risk of colorectal cancer, with OR = 1.70, 95% CI = 1.09–2.63; OR = 2.15, 95% CI = 1.36–3.40; and OR = 2.05, 95% CI = 1.03–4.07, respectively (**Table 10**) [50].

Heated food items and heated levels	Control	Case	OR	95% CI		P
Barbecued meats						
Usual outside appearance: lightly browned of cooked meats	220	194	1.00	Reference		
Usual outside appearance: medium-, well-, and blackened/ charred of cooked meats	43	62	1.70	1.09	2.63	0.019
Bread						
No intake or rare	207	179	1.00	Reference		
Some intake per month	66	67	1.17	0.79	1.74	0.432
Daily or weekly intake	35	65	2.15	1.36	3.40	0.001
P for trend = 0.002						
Biscuits						
No intake or rare	231	206	1.00	Reference		
Some intake per month	68	81	1.34	0.92	1.95	0.125
Daily or weekly intake	14	25	2.05	1.03	4.07	0.040
P for trend = 0.016						

Table 10.
Dietary habits and risk of colorectal cancer.

4.3.3 Cigarette smoking and risk of colorectal cancer

The heating and burning of tobacco products lead to the formation of mainstream smoke and sidestream smoke. Mainstream smoke from cigarettes and cigars is generated during puff-drawing in the burning cone and hot zones; it travels through the tobacco column and exits from the mouthpiece. Sidestream smoke is formed during puff-drawing and is emitted freely from the smoldering tobacco product into the ambient air. A variety of chemical and physical processes occur in the oxygen-deficient, hydrogen-rich environment of the burning cone at temperatures up to 950°C. Tobacco smoke contains more than 3800 constituents and many of them are chemical carcinogens to humans [61]. Tobacco smoking was reported to be responsible for about 25–35% of all cancer in humans [3]. In our study, daily smoking of 11 cigarettes or more increased the risk of colorectal cancer, with OR = 2.08, 95% CI = 0.62–6.91, but it is not significant (**Table 11**) [50].

Both the burning of tobacco and heating of foods leads to the formation of chemical carcinogens, known as "heat-generated carcinogens" or "dietary carcinogens." Thousands of chemicals were reported in the smoke of burning tobacco and heating foods. These chemicals were detected in the user's blood and urine after the intake of these products [60–67]. With this evidence, we should seriously consider the study of heat-generated carcinogens and dietary carcinogens to prevent the development of cancer in humans.

5. Benefit factors preventing colorectal cancer in Vietnam

Humans cannot synthesize micronutrients to meet the body's requirement, so supplement from outside is necessary. Good foods provide good materials for the body's energy metabolism and for activities preventing cancer [68].

Number of cigarettes per day	Controls	Cases	OR	95% CI		P
Nonsmoker	151	140	1.00	*Reference*		
1–10	22	15	0.82	0.37	1.82	0.618
11+	5	9	2.08	0.62	6.91	0.233

Table 11.
Number of cigarettes per day and colorectal cancer.

Refrigerator available at home	Controls	Cases	OR	95% CI		P
No	123	145	1.00	*Reference*		
Yes	121	99	0.69	0.48	0.99	0.045

Table 12.
Refrigerator available at home and risk of colorectal cancer.

The refrigerator is the equipment providing good conditions to keep fresh micronutrients for humans' daily life. An indirect beneficial factor that reduces the risk of colorectal cancer was observed for the refrigerator available at home, with OR = 0.69, 95% CI = 0.48–0.99 (**Table 12**) [50].

5.1 The potential ways to improve the health-care system

With the focus on clinical epidemiology studies on colorectal cancer, the specific risk factors for Vietnamese patients have been identified and they require further investigations to have an instruction on the diet and lifestyle modification. Based on multiple factors in pathological mechanism, the strategy to control this malignancy should have an impact on comprehensive sides: environmental factors, screening strategy, and personalized management. The integration of different diagnostic methods in community, hospital, and individual levels enhanced the improvement in detection of early colorectal cancer and should be invested more. Besides issuing guideline for colorectal cancer from the perspectives of specialists, it is important to have a strategy of prevention and screening in community and to foster educational activities.

5.2 New areas of interest for future research

In the near future, to identify the relationship between risk factors and colorectal cancer in Vietnam as well as to optimize the environmental factors, the microbiome studies in our population should be performed. It is necessary to have a database for healthy people to compare with the colorectal cancer patients, with the collecting of data on diet and lifestyle habits. Furthermore, the studies on health-care cost-effectiveness in this specific field should be performed to support for building up an effective approach in the prevention, screening, and treating of colorectal cancer patients.

6. Perspectives

Based on the observations in Vietnam for colorectal cancer, the distribution of this disease and its causality as well as risk factors were identified. With these findings, some points can be induced:

Colorectal cancer is related to unrecognized heat-generated carcinogens in our foods: we found that tobacco smoking, barbecued meats, bread, and biscuits intake increase the risk of the disease. Tobacco heated at 950oC and smoking carcinogens can generate as much as 3800 types of chemicals [56, 57, 61]. These findings were partly published [24]. Chemical is an independent factor inducing cancer, which was successfully performed and reported for the first time in 1967 by Dr. Sugimura [60, 69]. Our epidemiological observations in humans consisted of these numbers from previous studies.

Control of cooking temperature in both family's kitchen as well as public restaurants in humans' daily life should be a significant consideration to prevent colorectal cancer in particular and all cancer sites in general.

In our study, although alcoholic beverages play an integral role in humans' diets worldwide, alcoholic consumption would be categorized as a promoting factor of colorectal cancer development. Because of the organic solution of chemical carcinogens, similar to tobacco smoking, barbecued meats, bread, and biscuits are promoting colorectal cancer in our body.

- Host factors committed to developing colorectal cancer included blood types A and AB, CYP1A1 genotypes A/G and G/G, family history of cancer, body mass index, history of colorectal pain, and inflammation.

7. Conclusions

Three groups of risk factors were determined to develop colorectal cancer, including tobacco smoking, barbecued meats, bread, and biscuits intake as the first group; alcohol consumption as the second group; and the identified host factors as the third group. Possible management of identified risk factors in preventing colorectal cancer can be refrainment of smoking and reduction of intake of heated foods at unsafe cooking temperatures. A screening for colorectal polyp and cancer for people aged 40+ is highly recommended. Policy frameworks for cancer control in general and colorectal cancer in Vietnam are in place, but there is still a lack of proper financing and governing models necessary to support a sustainable program.

Acknowledgements

The authors deeply appreciate former Prof. Hiroshi Nozawa, Doctor of Laws and Honorary Member of the Institute for Science of Labor, Emeritus Professor of Kanazawa University for the support at the Institute for Science of Labor, Kawasaki, Japan in 1994.

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Section 2

Imaging

Chapter 3

Role of Magnetic Resonance Imaging in Patients with Rectal Cancer

Tsvetelina Teneva, Aleksandar Zlatarov and Rozen Grigorov

Abstract

In a chapter about rectal cancer there is content about rectal anatomy in relation to magnet-resonanse imaging and TME- surgery (total mesorectal excision). Secondly there is content about imaging methods used in diagnosis and follow-up of rectal cancer. Very important topic is concerning the novel imaging strategies in surgical and radiotherapy planning in the era of individual oncologic approach to the patient. At last there is detailed desctiption and metaanalysis of imaging strategies concerning neoadjuvant and adjuvant radiotherapy and chemotherapy for rectal cancer patients. All imaging markers correspond to substantial oncologic parameters such as survival rates. The connecting bridge is magnet-resonance imaging.

Keywords: rectal cancer, imaging, magnet-resonance imaging, tumor response, tumor regression grade, neoadjuvant therapy

1. Introduction

The purpose of this chapter is to provide the reader with detailed information about imaging of rectal cancer in the context of standardized and novel therapy options of rectal cancer. It is essential to put the rectal cancer in the correct stage group based on different imaging markers- local invasion (T-stage), local infiltration of mesorectum, intra- and extravascular invasion, lymph node spreading. Another important imaging biomarker is the tumor regression grade visualized on magnet-resonance imaging after neoadjuvant therapy. All markers correspond to substantial oncologic parameters such as survival rates. The connecting bridge is magnet-resonance imaging.

2. Rectal cancer imaging

Imaging of rectal cancer is more specific than imaging of the other colonic cancers. Rectal cancer staging is based on two principles. The first is an anatomic definition of the tumor and the second is prognostic stage grouping. Both are achieved by magnet-resonance imaging. Additional imaging modalities such as ultrasound US, computed tomography CT and positron emission tomography PET are discussed later on.

2.1 Anatomic definition of rectum

Knowing the anatomy, especially the anatomy on MR studies is the key to the right treatment of rectal cancer. Important anatomical landmarks are sigmoid take-off (transition rectum-sigma), mesorectal fascia MRF and mesorectum, presacral fascia, anterior peritoneal reflection, retrorectal space, anorectal sling (m. levator ani) and anal verge, shown on the pictures below.

The rectum is the most distal part of the gastrointestinal tract, located before the anal canal. There are different definitions of the distal and proximal borders of the rectum – distal border is linea dentata ani, and proximal part is the sigmoid colon and the transitional part called sigmoid take-off. It is a radiological reference point used to identify the connection of the sigmoid mesocolon with the mesorectum and therefore the connection of the sigmoid colon with the rectum (**Figure 1**).

2.1.1 Mesorectum and mesorectal fascia MRF

It is a hypointense line that surrounds the mesorectum. Above this layer it connects with the mesorectal fascia, which lies above the levator muscles and, respectively, connects with the peritoneal reflection forward and with the parietal fascia backward (**Figure 2**).

2.1.2 Anorectal sling (m. levator ani) and anal verge

Anatomically, the anal canal is at the level at which the anorectal sling envelops the rectum and creates the anorectal transition (**Figure 3**).

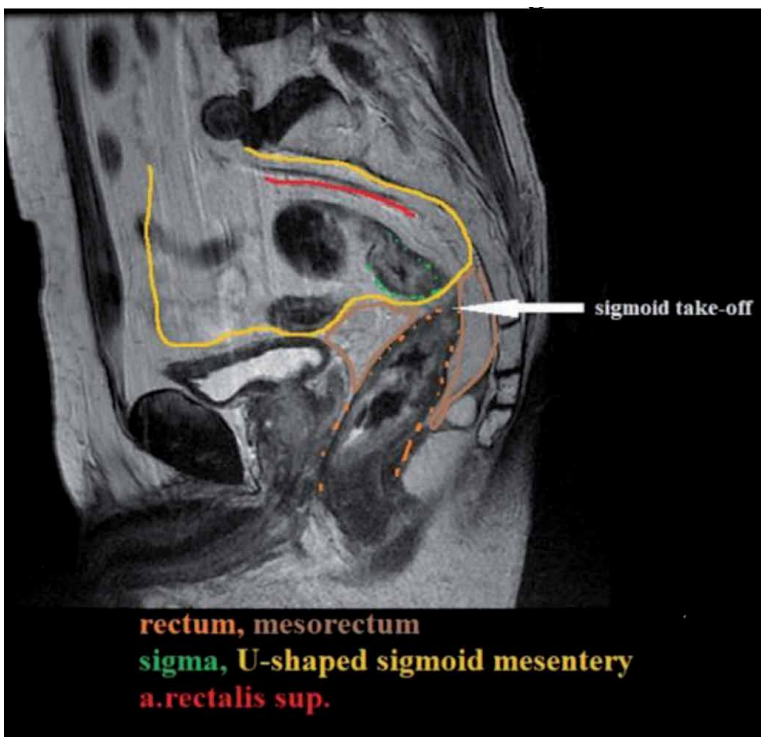


Figure 1.
Anatomical presence of sigmoid take-off (sagittal T2 weighted MR image).

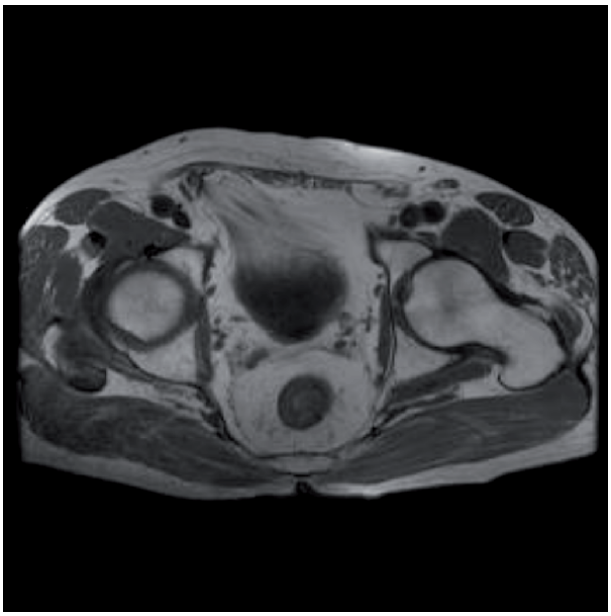


Figure 2.
Mesorectum and mesorectal fascia MRF (axial T2 weighted MR image).

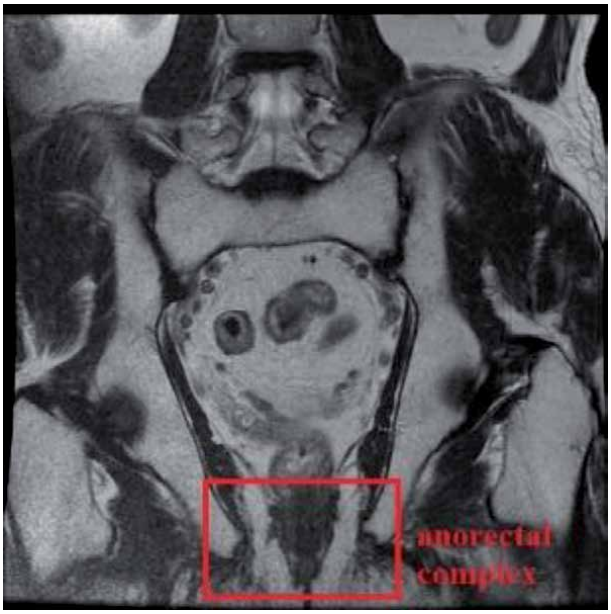


Figure 3.
Anorectal complex (coronal T2 weighted MR image).

2.1.3 Anterior peritoneal reflection

It is a thickened parietal fascia that covers the terminal veins and adipose tissue in the proximal part of rectum.

2.2 Mucosal layers of rectal wall

Another anatomical landmark is differentiating the mucosal layers (**Figure 4**) in relation to the TNM classification of the rectal cancer.

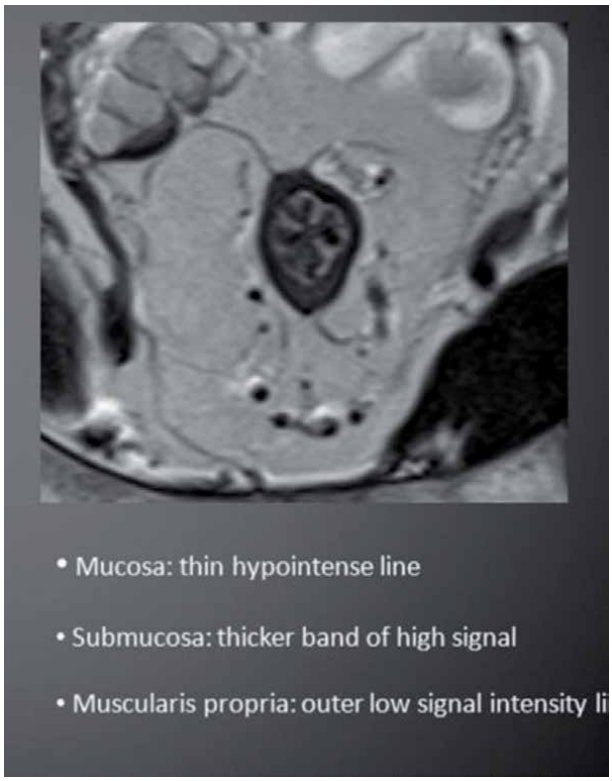


Figure 4.
Mucosal layers of rectal wall (axial T2 weigted MR image).

T1- submucosal invasion.

T2- invasion of muscularis propria.

T3- through the muscularis propria to the submucosa.

T4- perforation of the visceral peritoneum or direct invasion of the peritoneum.

Important fact is that T3 and T4 tumors are associated with extramural invasion. The more pronounced penetration of the mesorectum is associated with a worse prognosis and a higher probability of local recurrence. Many tumors are staged as pT3, but there is actually a heterogeneous T3 group, which is why a subclassification of T3 has been created:

T3a - minimal invasion <1 mm by muscularis propria.

T3b- light-walled invasion 1-5 mm from muscularis propria.

T3c- moderate invasion 5-15 mm from muscularis propria.

T3d- extensive invasion>15 mm by muscularis propria.

T3a and T3b are associated with better outcome for the patient compared with T3c and T3d stages, suggested they are T4 tumors because of worse outcome and poor prognosis [1].

When talking about staging it is important to notice that low rectal cancer is a separate subgroup again due to different anatomical features- the anorectal sling:

Staging of low rectal cancer with MRI (recently validated in the prospective study Mercury II: Low Rectal Cancer study [2].

stage 1 - the tumor is visualized in the rectal wall, but not throughout its thickness (preserved outer muscle layer).

stage 2- the tumor displaces the muscle layer without crossing the intersphincteric line.

stage 3- the tumor invades the intersphincteric line or is 1 mm from the levator ani.

stage 4- the tumor invades the external anal sphincter and infiltrates the levator ani and/or invades neighboring organs.

2.3 Pathways of spreading

For understanding of the neoplastic behavior of rectal cancer it is of great importance to analyze the pathways of spreading of tumorous tissue. They are:

1. direct invasion in the rectal wall,

2. involvement of local lymph vessels and lymph node metastases,

3. venous invasion (intra- and extramural venous invasion- EMVI) and

4. tumor deposits.

Demonstration of any invasion both histologically and by MRI [3] is always associated with a poor prognosis. The detection of EMVI is associated with the presence of synchronous distant metastases. Involvement of extramural venous vessels is more closely associated with poor prognosis, as well as invasion of larger veins. This leads to the conclusion, that detection of EMVI on MRI is of great prognostic importance and it is explained in details below.

2.4 Surgery of rectal cancer

Explaining the anatomy by the radiologists helps the surgeons plan the surgical procedure. Surgeons have 3 options:

1. TEM- Transanal Endoscopic Microsurgery in T1 stage

2. TME- Total Mesorectal Excision is the universally established standard for optimal oncological surgery in rectal cancer [4]. TME is an independent predictor of local recurrence. TME includes excision of the rectum and surrounding adipose tissue, the lymphovascular cuff, the mesorectum, in which the locoregional lymph nodes are located. The outermost border of the mesorectum, the mesorectal fascia, plays the role of an oncological barrier. Thus, if the surgical principles for TME are followed, the prognostic effect of regional lymph nodes may be neglected [5], as they themselves are removed en block in TME.

3. Deferral of surgery or Watch and Wait strategy- novel strategy based on organ preservation if complete clinical response is achieved by neoadjuvant therapy (references on EURECCA (European Registration of Cancer Care [6] and TRIGGER) [7].

4. No surgery and stoma placement in locally advanced and unresectable T4b tumors.

2.5 Treatment options

Before discussing the imaging of rectal cancer one should understand the treatment options for the disease. The ideal prognostic stage allows selection of the

patient according to the risk of local and/or systemic recurrence. This leads to three main treatment options:

- Surgery alone,
- neoadjuvant therapy before surgery and
- palliative pharmacotherapy/radiotherapy alone.

Planning and decision making are listed in the European [8] and Nord-American guidelines [9].

Main goal is to achieve downstaging and downsizing of the tumor and therefore optimal mesorectal excision. This is possible with neoadjuvant therapy and it has a leading role in treatment of rectal cancer. Synchronous to better therapeutical options many imaging markers for response measurement are found out.

In order to objectively measure the rate of tumor response to this therapy, several systems called histopathological tumor regression grades (pTRG) have been developed, the most commonly used being those of Dworak [10] and Mandard [11] Both systems determine the response to treatment based on the residual/residual cells in the fibrous stroma, and the gradation is between "no response" to "complete response". A pathological complete response (pCR) is defined as "no residual tumor cells in the material". A novel radiological method for tumor response has been developed based on pCR - magnetic resonance imaging of the tumor response tumor regression grade (mrTRG) [7] MRI can be used to predict a favorable response and to assess the extent of subsequent treatment.

Therefore we can use some imaging predictors on pretreatment (primary) MRI-scan and on posttreatment (secondary) MRI-scan. This is how we could reach out to the second principle of rectal cancer staging - prognostic stage grouping.

2.6 MRI of rectal cancer

The main imaging modality for local staging of rectal cancer is magnetic resonance imaging (MRI), as it provides the most accurate information about important prognostic markers that could affect the choice of treatment. In addition, there are many new studies on the role of MRI in assessing the response after neoadjuvant radiation therapy.

Technical parameters for MRI: 1,5 T or 3 T, FOV (160 x 160 mm, 256 x 256 matrix), 0.6 x 0.6 x 3 mm, high-resolution image (1 mm 3 voxel size), sequences: first series - T2-weighted sagittal, turbo spin-echo sequences for tumor identification, second series – axial T2 to the whole pelvis, third series - T2-weighted thin-section axial through the neoplasia, and they should be perpendicular to the long axis of the rectum and to the level of the neoplasm (3-mm slices). Addition: for low rectal cancer there is a fourth series - high resolution, coronary images for the levators, the sphincter complex, the intersphincter axis and the relationship to the rectal wall. Follow-up MRI after treatment follows the same protocol.

Diffusion-weighted imaging (DWI) images of magnetic resonance show the random movement of water molecules in the body. The degree of water restriction in biological tissues is directly proportional to the tissue cellularity and integrity of the cell membrane. Therefore, the contrast of tissues at D The apparent diffusion coefficient (ADC) is recalculated by the DWI, using these two techniques to compare different tissue compartments depending on the cell composition. Evaluates the response to treatment. DWI could be useful in the primary detection of rectal cancer and lymph nodes, but not for follow-up assessment or measurement of tumor regression, incl. mrTRG.

Gadolinium-enhanced MRI is not recommended.

MRI has the ability to distinguish each individual layer of mucosa and muscle due to their different signaling characteristics. For this purpose, the T2 sequence is used:

- Mucosa - fine hypointense line
- Submucosa - thicker hyperintense layer
- Muscularis propria - a double layer of inner circular and outer longitudinal layer, the latter having an irregular appearance due to the passing vessels
- Perirectal adipose tissue/mesorectum - high signal tissue
- Mesorectal fascia - a thin hypointense band surrounding all of the above (**Figure 5**)

Patients with rectal cancer will receive a series of MRIs during the course of their treatment:

- the initial (primary) MRI will guide whether neoadjuvant therapy is needed, will guide the operative plan, and factors such as mrEMVI will determine the type of neoadjuvant therapy
- the secondary MRI follows the neoadjuvant therapy, and the response is assessed by mrTRG. In patients with a good mrTRG response [1, 2], it is possible to wait with surgery or reduce the volume of the operation or continue with radical surgery. The first two options potentially lead to the preservation of the integrity of the rectum, but additional MR examinations are needed. In case of a weak response (mrTRG4–5) it is possible to choose surgery or

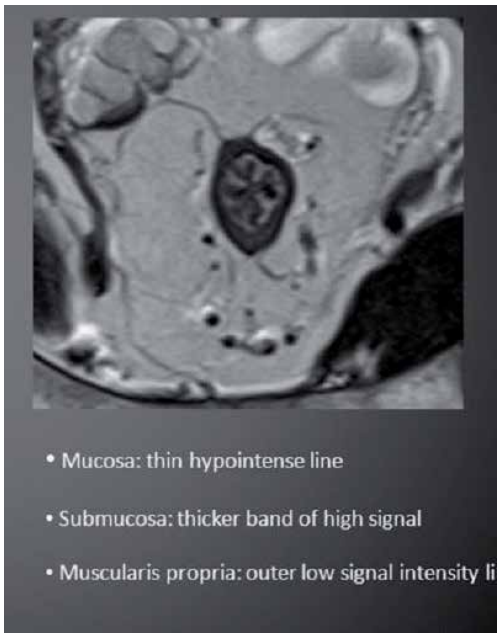


Figure 5.
Mucosal layers of rectal wall (axial T2 weigted MR image).

continuation with chemotherapy with intensification and/or experimental pharmacotherapy and change of mrTRG to a prognostically better group.

- the third MRI is for the group waiting for surgery and MRI is used to monitor recurrence.

As already mentioned, we have to separate some imaging markers on the pre- and posttreatment studies that are essential for predicting response and outcome from the disease.

In the first group is the pretreatment MRI and the imaging features for predicting the tumor response:

- Tumor height - low rectal cancer is more likely to have a bad response;
- T stage- T1, T2, T3a, T3b are more likely to have a good response;
- EMVI - the presence of mrEMVI is associated with a worse prognosis.

In the second groups is the posttreatment MRI and evaluation of the post-therapeutic response (used prefix "y"- after neoadjuvant therapy):

- Tumor height from the intersphincteric line to the distal TME line
- mrTRG (tumor regression)
- EMVI- ymrEMVI
- CRM (circumferential resection margin)
- ymrT (depth of invasion)
- ymrN (nodal status).

2.6.1 Assessing tumor high

Rectal cancer can be divided (**Figure 6**) into:
Low rectal cancer:
Distal border is 0–5 cm from the anorectal angle.
Mid rectal cancer:
Distal border is 5–10 cm from the anorectal angle.
High rectal cancer:
Distal border is 10–15 cm from the anorectal angle.

Involvement of the intersphincteric plane, external sphincter and levator musculature should be assessed. Low cancer localization increases the risk of CRM engagement.

2.6.2 Assessing T-stage

Determination of the T-stage (**Figure 7**) depends on the correct visualization of each individual layer in compliance with the MR-protocol. T category is characterized by the depth of tumor penetration into the rectal wall and extramural spread into the mesorectum and adjacent structures.

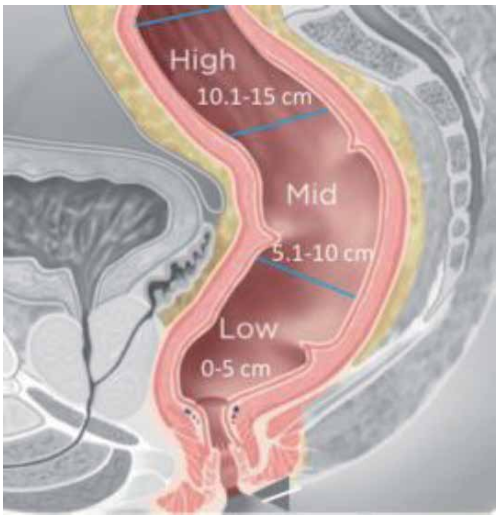


Figure 6.
Rectal tumor high. Source: MRI of Rectal Cancer: Tumor Staging, Imaging Techniques, and Management", Horvat et al. [12].

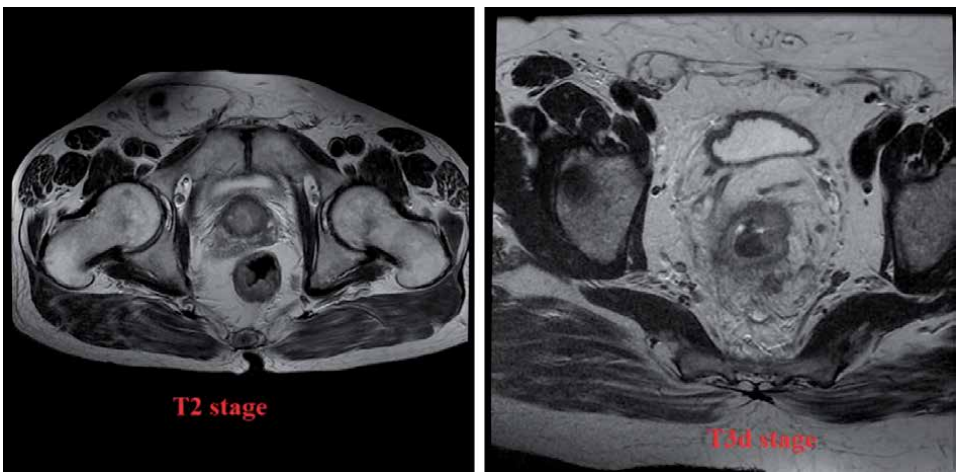


Figure 7.
Different T stages of rectal cancer: T2 rectal cancer (left) and T3d rectal cancer (right) (axial T2 weighted MR images).

in T1 and T2 rectal tumors is an intact external muscularis layer, which is identified as a hypointense thin line surrounding the rectum. T3-tumors grow through the external muscularis into the surrounding mesorectum, important is to classify T3 to T3a, b, c, d.

Consistency between MRI and histopathology in determining the T-stage was initially studied by Brown et al. [3], who found a 94% match between MRI and pT-stage. The MERCURY multicentre study directly compared the extramural depth of invasion as measured by MRI and histopathology.

Numerous histopathological studies have shown the importance of the T-stage. The T3 subclassification was developed because the majority of patients have a T3 tumor, but the heterogeneity in survival values is high:

- pT3 with>5 mm tumor invasion have a worse 5-year survival (disease-free survival (DFS)) than tumors with an invasion below 5 mm (pT3b); and this regardless of the nodal status.
- T3a tumors, with an invasion below 1 mm, have a very good prognosis
- The values for local recurrence and overall survival of T2 and T3a are identical
- The palpable difference in DFS between T3b and T3c shows that their differentiation is of greater clinical significance than the distinction between T2 and T3.

2.6.3 Assessing CRM- circumferential resection margin

CRM is the surface of the nonperitonealized part of the rectum that is resected during surgery. In the description of T3-tumors, the report should include the shortest distance between the tumor margin and the mesorectal fascia MRF because of increased risk for local recurrence. MRF often refers to CRM. CRM > 5 mm measured by MRI is sufficient to predict microscopically clear resection lines (**Figure 8**).

2.6.4 Assessing EMVI: extramural venous/vascular invasion

Extramural vascular invasion is defined as the presence of tumor cells in vessels outside the lamina muscularis propria (**Figure 9**, arrows).

Positive mrEMVI is associated with low survival rates. The 3-year survival in mrEMVI-positive patients was 35% compared to 74% in mrEMVI-negative patients. mrEMVI-positive patients have a fourfold increased risk of developing distant metastases.

The radiological characteristics of EMVI observed on MRI are described in detail -The veins around the rectum are recognized on the T2 sequence as serpiginous or curved linear structures; in the tubular structures considered to be blood vessels, in addition to changes in the contour, there is a weakening of the signal.

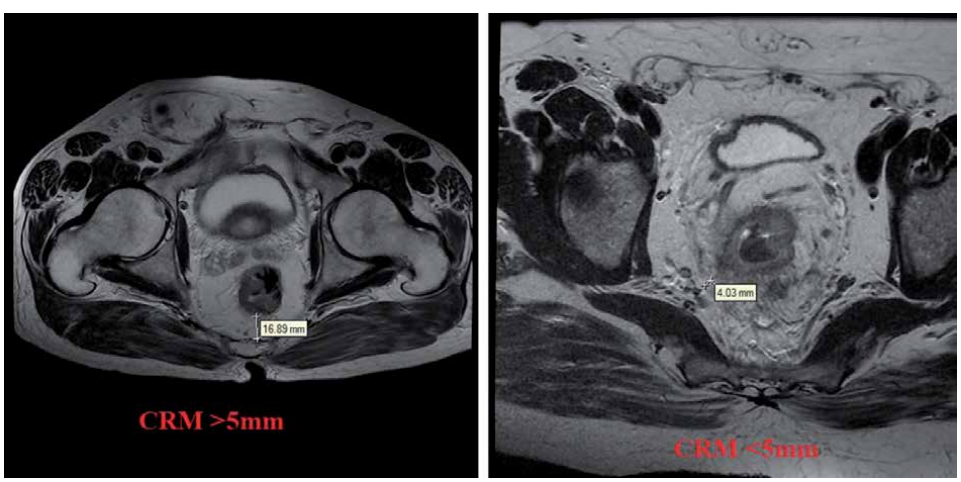


Figure 8.
CRM- circumferential resection margin (axial T2 weighted MR images).

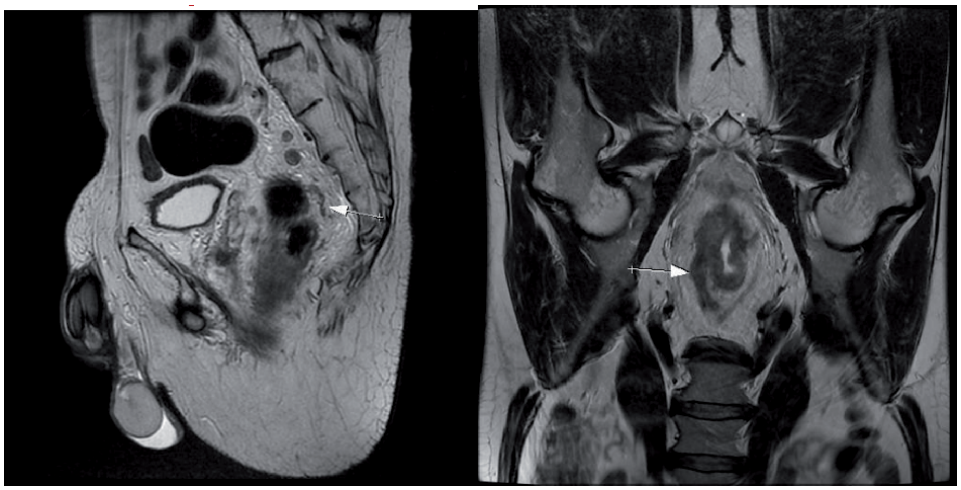


Figure 9.
EMVI- extramural venous/vascular invasion (T2 weighted MR images).

A complete evaluation of mrEMVI should include the following: (entry into small veins may produce a nodular border); location of the tumor relative to the large vessels; vascular caliber (the tumor causes the vessels to dilate and amplify the tumor signal in the lumen) and the vessel boundary.

2.6.5 Assessing N- stage

The N-stage is an important risk factor for local recurrence. The size of the lymph node itself is not indicative, as 15–42% of patients with rectal cancer have small (<5 mm) mesorectal lymph nodes containing tumor cells (**Figure 10**, arrowheads).

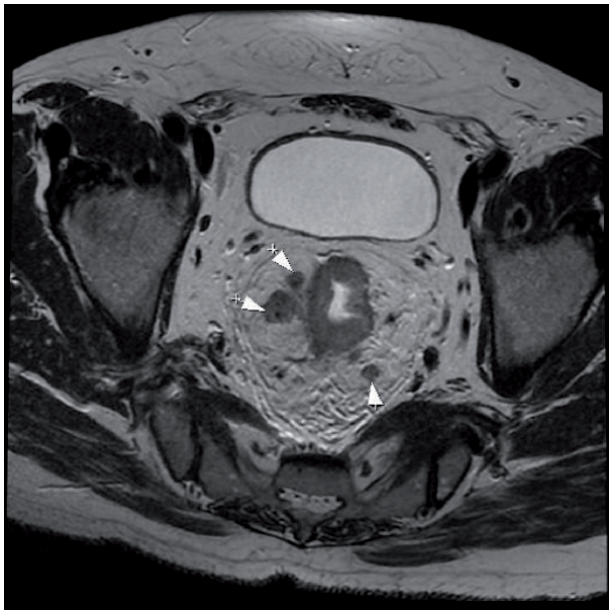


Figure 10.
Lymph nodes (arrowheads).

2.6.6 Assessing mrTRG (special focus)

Tumor regression refers to the effect of neoadjuvant radiotherapy or chemotherapy on the tumor. The degree of tumor regression (TRG) is determined by the amount of residual tumor cells and the degree of fibrosis induced by non-adjuvant therapy. High tumor regression correlates with higher survival and lower rate of local recurrence. Several scales have been developed for TRG, such as Mandard and Dworak, but no consensus has been reached on which to use routinely.

After chemoradiotherapy, a number of tissue changes induced by radiation occur. These include swelling, inflammation, necrosis and fibrosis. mrTRG evaluates the changes on MRI after 12 weeks of neoadjuvant chemo-, radiotherapy.

This mrTRG system uses a 5-point scale. The low points [1–3] correspond to a more significant regression, and the high points [4, 6] mean no regression. The system also divides the categories according to the type of answer (complete, good, moderate, poor, none).

mrTRG1- radiologically complete response- linear, eccentric scar of 1–2 mm, limited in the mucosa or submucosa.

mrTRG2- good response- dense fibrosis without visualizing a residual tumor and without suspecting (**Figure 11**).

mrTRG3- incomplete response - over 50% fibrosis or mucin and visible intermediate signal intensity.

mrTRG4- weak response- small areas of fibrosis or mucin among tumor tissue (**Figure 11**).

mrTRG5- no response- intermediate signal intensity, tumor visualization without tumor dynamics or growth.

(Proposed by Bhoday et al) [13].

Many studies show that mrTRG is a prognostic and predictive biomarker- MERCURY trial, EXPERT-C trial [14], GEMCAD study, CORE study [5]. EXPERT – C study shows significant difference in rates of disease-free survival DFS and overall survival OS: mrTRG 1 & 2 (good response), mrTRG3 (medium response) and mrTRG4–5 (poor response) have a 3-year DFS survival of 82, 72 and 61%, respectively. These independent studies show that mrTRG predicts different groups- mrTRG could distinguish between "good" and "poor" responses to chemotherapy ('good' and 'poor' responders). It could be suggested that mrTRG can be used as a biomarker to stratify the choice of treatment for rectal cancer. Good responses (mrTRG1–2) are similar to good pCR, so surgery rejection and intensive follow-up of these patients can be chosen (watch and wait strategy). Poor responses (mrTRG3–5) could be subject to additional chemotherapy in order to improve mrTRG status to a lower grade. This requires the use of MRI to repeat the assessment of mrTRG.

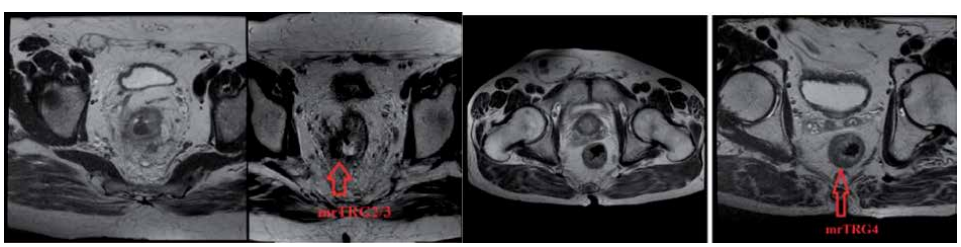


Figure 11.
Tumor regression grade on MRI: First picture T3d rectal cancer before neoadjuvant therapy. Second picture mrTRG 2/3 same patient after neoadjuvant therapy. Third and fourth picture another patient with T3 tumor before (third) and after (fourth) neoadjuvant therapy- mrTRG 4/5.

mrTRG and pTRG were compared in patients with rectal cancer in two clinical trials (EXPERT and EXPERT-C) [14]. The concurrence of the opinions of radiologists and pathologists was assessed with the weighted k test. The Kaplan–Meier method was used to evaluate the results of overall survival. Results: 191 patients were included in the study. The mean time from completion of neoadjuvant treatment to preoperative MRI and surgery was 4.1 weeks (IQR: 3.7–4.7) and 6.6 weeks, respectively (IQR: 5.9–7.6). good agreement was found between mrTRG and pTRG, with regression classified according to standard five-stage systems (kj0.24) or modified three-stage systems (kj0.25). Sensitivity and specificity of mrTRG 1–2 (complete / good radiological regression) for predicting the pathological complete response was 74.4% (95% CI: 58.8–86.5) and 62.8%, respectively (95% CI: 54.5–70.6) Survival outcomes in patients with intermediate pTRG 2 were numerically better if complete/good regression was also observed with mrTRG 1–2, compared with poor regression of mrTRG4–5 (5-year recurrence-free survival 76.9% vs. 65.9%, P00.18; 5-year overall survival 80.6% vs. 68.8%, P0.22).

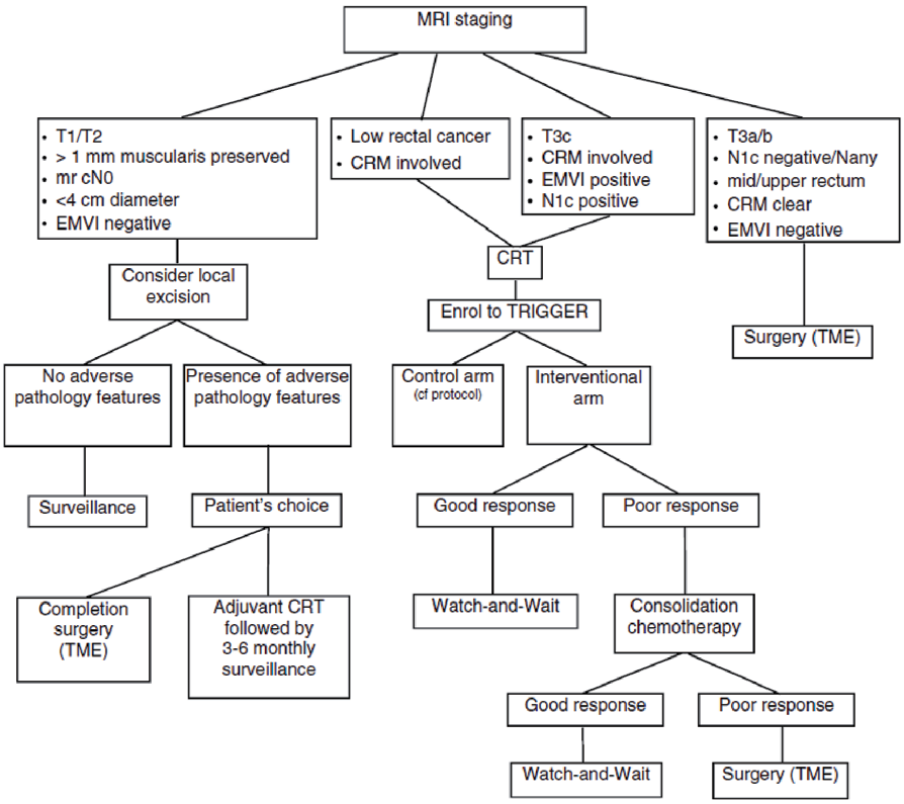
Conclusions: The coherence between mrTRG and pTRG is low and mrTRG cannot be used as a substitute for pTRG. Further studies are needed to assess the ability of mrTRG to detect patients with a complete response to pTRG and to provide additional prognostic information to pTRG for better risk stratification after surgery.

Evaluation of the preoperative response to treatment of rectal cancer by MRI is an area of growing importance both in terms of predicting results and in determining the complete response. Clinical use is currently limited. The MERCURY study [13] shows that tumor regression can be assessed by MRT (mrTRG) after preoperative chemotherapy and radiation, using the differences in signal intensity between tumor and fibrous tissue. In this study, the 5-year overall survival (OS) was 27% for poor response (mrTRG4–5) versus 72% ($p = 0.007$) for good response (mrTRG 1–2), and the 5-year free survival was relapse survival (DFS) resp. 31% vs. 64% ($p = 0.007$). Nougart et al. [15] reported that volume assessment with MRI in patients receiving preoperative therapy was of prognostic significance. In this study, a reduction in tumor volume of at least 70% was associated with a better DFS value (HR 13.7; 95% CI 3.98–31.93).

Another PAN-EX study [16] by the same study group again demonstrated that mrTRG had greater value for prognostic factors such as relapse-free survival (RFS), long-term relapse-free survival (DFS), and overall survival (OS).

The main advantage of mrTRG is that it is not based on evaluation of resection material. The degree of tumor regression with MRI can be assessed before any surgery. This information provides a potential opportunity to consider other preoperative therapies. Previous analyzes of the PAN-EX study showed that patients who achieved mrTRG 1–2 after completion of CLT had a significantly better prognosis than patients who were assessed as mrTRG 3–5. mrTRG can potentially be used as an imaging parameter for the selection of patients with a good prognosis, in whom a non-operative approach after neoadjuvant treatment may be preferred. mrTRG appears as a dynamic, non-invasive, surrogate method for assessing tumor regression after neoadjuvant treatment and before surgical resection.

Be aware that the classification of patients as good and poor responders on the basis of mrTRG makes it possible not only to predict the outcome of the disease, but also to modulate therapeutic behavior. This means that patients may be advised to delay surgery, modulate chemo-, radiotherapy or choose another approach. The TRIGGER study [17] evaluated mrTRG as a new biomarker for stratification of patients with good and poor response to neoadjuvant therapy for rectal cancer and the inclusion of good responders in a new strategy, namely Watch & Wait.



2.7 Additional imaging modalities

Computed tomography, ultrasound and positron-emission tomography are imaging studies that could be complementary to MRI and be incorporated in the management of rectal cancer in some cases. Be aware that MRI is not available imaging tool in some institutions and CT and/or US are the only diagnostic choice for rectal cancer.

2.7.1 Computed tomography CT

Computed tomography CT (**Figure 12**) is not a modality of choice in the staging of rectal cancer due to the low resolution of the method and the inability to distinguish the different layers of the intestinal wall required for T-staging compared to MRI. CT is not applicable for detection of accurate T-stage, CRM- or EMVI involvement, but a method of choice for N- and M-staging and CT is still used in many centers. CT is not recommended for follow-up or for monitoring after therapy.

2.7.2 Ultrasound US

Endorectal ultrasound is effective diagnostic modality in the assessment of rectal cancer. Its accuracy in numerous trials is around 80% for T-staging and 70% for N-staging.

ERUS images of the rectal wall comprise three hyperechoic and two hypoechoic layers, which alternate with each other and correspond to anatomic layers. (**Figure 13**).

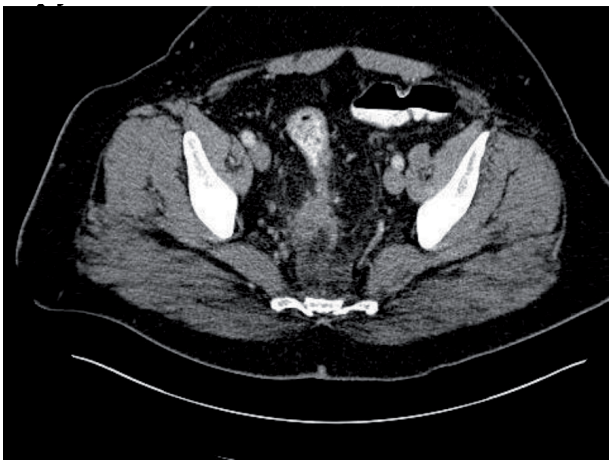


Figure 12.
CECT of rectal cancer, axial view, soft tissue window.

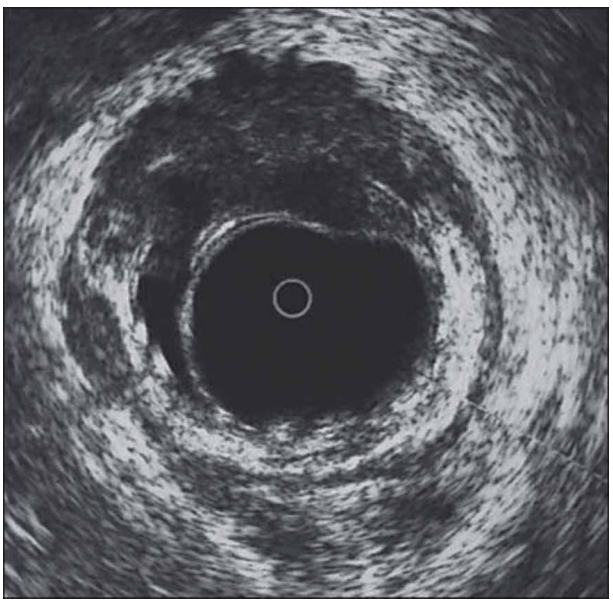


Figure 13.
Endorectal ultrasound illustrating rectal cancer invading beyond the rectal wall into perirectal fat.

On endorectal ultrasound, rectal tumors appear as hypoechoic lesions and are staged according to level of invasion through the rectal wall. Ultrasound stages are labeled with the prefix "u".

ERUS can also be used to monitor for rectal cancer recurrence postoperatively. After surgery, the excision site appears as a pattern of mixed echogenicity, replacing the normal five-layer image.

ERUS is a method of staging rectal cancer which is human dependent. ERUS is less accurate for T staging of stenotic tumors, but the accuracy may still be within acceptable limits. Surgeons use ERUS to adopt a treatment protocol, knowing the risk of under-staging and over-staging of this method. The accuracy of ERUS is higher in diagnosing rectal cancer in stages T1, T2 and with less sensitivity for T3 and T4 tumors.

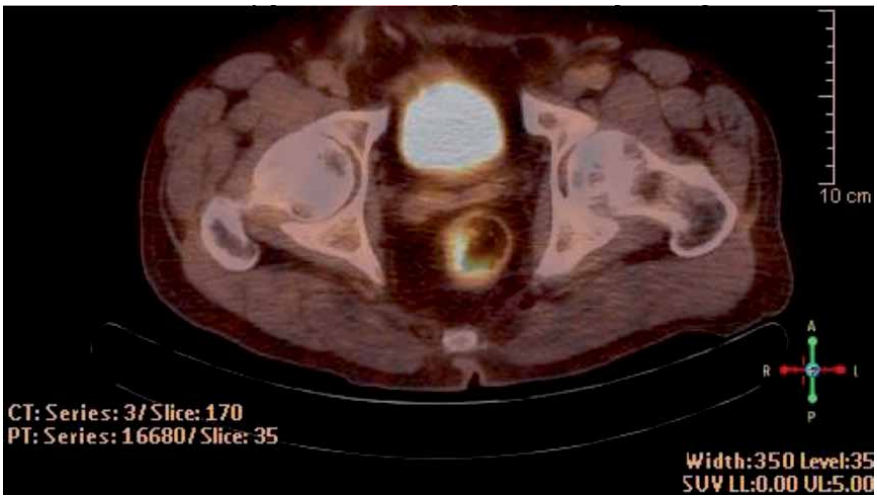


Figure 14.
PET/CT of rectal cancer.

2.7.3 Positron emission tomography PET

Positron emission tomography PET with computed tomography is an additional method for functional staging by imaging in the following cases: [1] in unconvincing computed tomography and magnetic resonance data for primary tumor or distant visceral metastases with elevated values of tumor markers; [2] for N-staging; 3) for M-staging. Disadvantages are the high cost and low availability of the method. Inaccuracies in the differentiation of changes in the mesorectum and pelvic lymph nodes and inaccuracies in the assessment of mucinous tumors are known. It also cannot stratify patients with complete and incomplete response (**Figure 14**).

3. Conclusion

In this chapter about rectal cancer there is content about rectal anatomy in relation to magnet-resonance imaging and TME- surgery (total mesorectal excision). There is a detailed description of imaging strategies concerning neoadjuvant and adjuvant radiotherapy and chemotherapy for rectal cancer patients. The staging and choice of treatment for rectal cancer are the main goal of any national and international organization in choosing guidelines and resp. guideline. The main guidelines are those of the European Society of Medical Oncology (ESMO), the European Rectal Cancer Consensus Conference (EURECCA-CC2) and the National Comprehensive Cancer Network (NCCN), but they also differ in their recommendations in some aspects of rectal cancer management.

Conflict of interest

The authors declare no conflict of interest.

Notes/Thanks/Other declarations

All figures (except **Figure 6**) are provided by Teneva MD from Department of Imaging Diagnostics, University Hospital St. Marina, Varna, Bulgaria.

Abbreviations

MRI	magnet-resonance imaging
DWI	diffusion-weighted imaging
US	ultrasound
CT	computed tomography
PET	positron emission tomography
MRF	mesorectal fascia
EMVI	extramural venous invasion
CRM	circumferential resection margin
pCR	pathological complete response
mrTRG	magnetic resonance imaging of the tumor response tumor regression grade
pTRG	histopathological tumor regression grades
TEM	transanal endoscopic microsurgery
TME	total mesorectal excision
DFS	disease-free survival
OS	overall survival

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Chapter 4

Imaging and Diagnosis for Planning the Surgical Procedure

Ferdinand Bauer

Abstract

The preoperative imaging diagnosis of rectal cancer lies at the heart of oncological staging and has a crucial influence on patient management and therapy planning. Rectal cancer is common, and accurate preoperative staging of tumors using high-resolution magnetic resonance imaging (MRI) is a crucial part of modern multidisciplinary team management (MDT). Indeed, rectal MRI has the ability to accurately evaluate a number of important findings that maBay impact patient management, including distance of the tumor to the mesorectal fascia, presence of lymph nodes, presence of extramural vascular invasion (EMVI), and involvement of the anterior peritoneal reflection/peritoneum and the sphincter complex. Many of these findings are difficult to assess in non-expert hands. In this chapter, we present currently used staging modalities with focus on MRI, including optimization of imaging techniques, tumor staging, interpretation help as well as essentials for reporting.

Keywords: rectal cancer, staging, MRI, protocol, reporting, 3D imaging

1. Introduction

The preoperative imaging diagnosis of rectal cancer lies at the heart of oncological staging and has a crucial influence on patient management and therapy planning. Computer tomography (CT) with intravenous contrast medium is the standard method to exclude metastases in the liver and lungs. However, the current state-of-the-art modality for local staging of the tumor is magnetic resonance imaging (MRI). Its new development, 3D MRI, seems to bring additional valuable possibilities for the surgery planning of rectal cancer.

1.1 Multidisciplinary management team (MDT) in rectal MRI

Due to the multitude of treatment options available today for the treatment of rectal cancer, it became an international standard (e.g. in [1]) that a multidisciplinary team (MDT) discusses each patient situation pre-therapeutically in a tumor conference. This procedure ensures that all therapeutic options are considered as necessary for the patient's benefit. The basis for these discussions and decisions of the MDT is in most cases the imaging findings. Magnetic resonance imaging (MRI) of the pelvis has become of central importance in recent years, as it can best depict the relationship of the tumor to the mesorectal fascia and the other structures of the pelvis.

In order to make good therapeutic decisions, an MRI must not only be carried out in a technically adequate manner, but must also be interpreted and presented accordingly. Moreover, the radiologist should also have a basic understanding of the various available therapy options. In particular, it is important to understand the surgery relevant aspects in order to have a target-oriented interdisciplinary discussion. Similarly, the treatment partners should also have basic knowledge of the findings and interpretation of MRI in order to be able to understand the findings of the radiologist.

2. Magnetic resonance imaging (MRI) basics

2.1 Useful MRI sequences

T1 weighted sequences (T1w) are highly sensitive to fat, marrow and gadolinium contrast media, which are able to detect a high intensity signal, so they appear light in T1w images. On the other hand, water retrieves a low intensity signal, so it appears dark. Therefore, you recognize T1w images by the dark gray representation of water, e.g. urine in the bladder, and by the almost white representation of fat, like in the bone marrow. T1w sequences are important particularly for the examination of the pelvic lymph nodes and the bone marrow.

T2 weighted sequences (T2w) are the most important sequences for MRI pelvic imaging. They provide high-resolution anatomical images that allow an accurate representation of the rectal carcinoma and its relationship to surrounding structures. It depicts the mesorectal fascia (CRM) as a thin line of low T2-signal intensity. You may easily recognize the T2w-images by their parameters: the signal-rich representation of water, e.g. urine in the bladder, and the signal-rich representation of fat. T2-weighted (T2w) sequences are water-sensitive, so water is signal-rich (light), whereas fibrotic tissue with low water content is signal-poor (dark). Paradoxically, fat also appears signal-rich (light) in T2w-images, which makes it difficult to distinguish from water in individual cases. A specific suppression of the fat signal might help here. However, since fat suppression techniques (FS) all lead to a loss of signal and thus either to increased image noise or to limited spatial resolution, they are not recommended for pelvic imaging - only after intravenous administration of gadolinium chelates contrast agent. In addition, FS techniques reduce the contrast between the low-signal rectal carcinoma in the T2 weighting and the signal-rich mesorectal fat tissue, which has a negative impact on the exact spread of the disease.

Diffusion weighted imaging (DWI) is achieved using diffusion-sensitive gradients in fast T2w sequences. DWI, in contrast to T1 and T2 measurement (excellent for morphological properties) is an **in vivo measurement** and shows the mobility of water molecules in different tissues (normal, tumorous, or fibrotic tissue). The limited diffusion in malignant tissue leads to a higher signal (bright) on the DW images. Tumors therefore usually appear bright on DWI images, while their lower diffusivity then leads to a low signal on ADC maps. DW sequences have the lowest spatial resolution of all sequences used in routine clinical protocols due to limitations in the signal-to-noise ratio, and they are susceptible to artifacts and distortion. These distortions are particularly pronounced at air-tissue boundaries (e.g. intestine) and OP clips. Moreover, the DWI technique necessarily requires fat saturation, so that fat presents itself with little or no signal. For spatial orientation, we always take corresponding anatomical images using T2w sequences.

Diffusion-weighted sequences are optional for the primary staging of rectal carcinoma, but we strongly recommend including them into the standard MRI protocol, as they can significantly facilitate the localization of the tumor and lymph

nodes, and later restaging. MRI examinations for restaging of the rectal carcinoma after neoadjuvant therapy should contain a DWI sequence in order to be able to detect or exclude vital tumor remnants.

2.2 Patient preparation

2.2.1 Bad diagnosis always begins with bad patient preparation

Contrary to what is still being claimed, preparation of the bowel by means of enema (clyster or micro clyster) immediately prior to the examination is extremely important. We want to perform a high-precision examination similar to colonoscopy in a clean medium and not in a contaminated organ. The patient will always be informed in detail about the exact procedure of the examination, and this ensures active cooperation in most cases. This way, we minimize restlessness and movement artifacts. After flushing with Microlax Rectal Solution, the rectum is filled with warm tap water. Water is an excellent contrast medium without risking distension of the intestinal wall. In our department, we only use ultrasound gel for MRI defaecography, but not for tumor diagnosis, as the expansion of the rectum due to compression may restrict the assessment of the mesorectal space. Water as contrast medium allows an exact detection of even small flat lesions, which may be the case after RCT. Another advantage is the elimination of air besides stool residues. This procedure also creates perfect conditions for high quality DWI, which plays a particularly important role in restaging. Air is an enemy and real falsificator of DWI measurements! Last but not least, we prepare an infusion for administration of butylscopolamine to reduce intestinal motility, and for administration of contrast agent, if necessary.

Having this done, specially trained medical-technical staff accompanied by doctors trained in rectal MRI perform the actual MRI examination. They always follow a standardized protocol with particular attention to angulation. The main axial layers must always be orthogonal to the tumor. Only in this way can the MRI results correspond with histology in terms of local tumor staging, and measurement of infiltration depth and distance to the mesorectal fascia. Furthermore, it is important to ensure that the restaging examination is always performed with the same equipment as the primary staging examination was done. Our experience has shown that different devices (e.g. Siemens vs. Phillips) deliver different DWI, which can make precise restaging difficult. These organizational challenges can only be overcome if we are all aware of them.

2.3 Examination protocol

Rectal MRI can be performed routinely on a 1.5 T or 3 T system and takes about 25 minutes. However, our surgery department prefers 3 T systems because of their clearly higher resolution, shorter examination time, and the possibility of performing 3D imaging. A limited FOV ("field of view") is recommended, as it allows both accurate local tumor diagnosis, and excellent imaging of the mesorectum and adjacent organs.

We begin with a sagittal T2-weighted turbo spin echo (TSE) sequence, which serves as the planning sequence for the second axial thin-layer (3 mm) T2 TSE sequence and is the decisive sequence of the rectal protocol. Axial in this context always means perpendicular to the carcinoma, so that depending on the extent and location of the tumor, paraaxial, axial or paracorononary layers result!

The mandatory and most important measurements, done in mm, such as tumor infiltration depth into the mesorectum and the tumor distance to the mesorectal fascia, are performed based on these paraaxial images. If the radiological department performs accurately, then the measured values and the tumor staging correspond to

the histological results. Radiologists achieve this performance only after a relatively long learning curve. We always correlate our results with the pathology results during the tumor board.

Tips for the high resolution T2 axial sequence

- Must be angled perpendicular to the tumor. The invasive center (the part of the tumor extending the most within the mesorectal fat) of the tumor must be detected on the sagittal plane. It is at this level where the sequence must be angled perpendicularly to the tumor.

- Sometimes, it may be necessary to obtain more than one sequence angulation for optimal assessment in bulky tumor masses.

- A slice thickness of 3 mm or less is recommended.

As mentioned above, in deep carcinomas (lower third of the rectum) a **coronary** T2w TSE sequence is obligatory in order to detect or exclude infiltration of the muscle levator ani (T4 stage) or to diagnose infiltration of the anal canal. For deep carcinomas, we recommend to perform a Gd-enhanced T1 weighted axial and

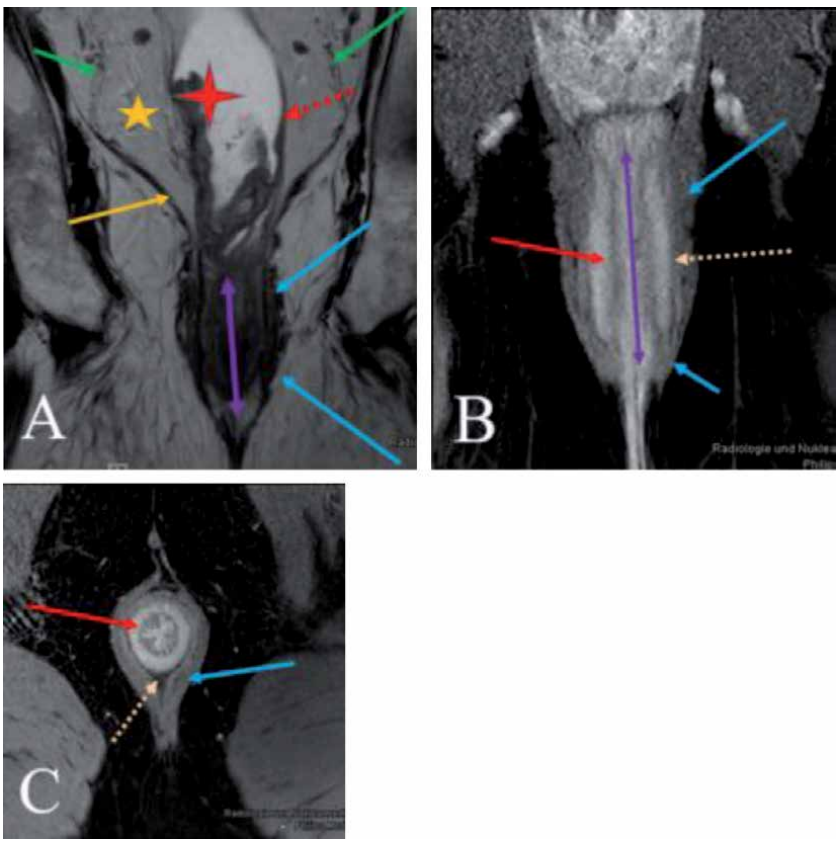


Figure 1.
A. Paracoronal T2WI, no enhancement, shows a lower rectal T2 stage tumor without infiltration of the mesorectum, levator ani or anal canal. B. Gd enhanced paracoronal T1FS, anal canal. C. Gd-enhanced axial T1 FS. Markings: Yellow arrow: Levator ani; Yellow star: end of mesorectum; Green arrow: FMR = CRM; Red star: tumor; Red dashed arrow: muscularis propria; Red plain arrow: internal anal sphincter (IAS); Blue plain arrow: external anal sphincter (EAS)'Purple double arrow: anal canal; and Yellow dashed arrow: intersphincteric plane (ISP). Source: F. Bauer, Radiology Kaufbeuren.

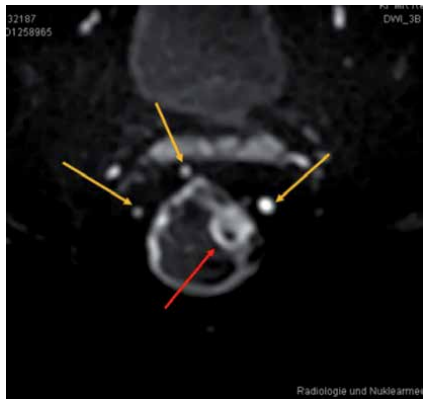


Figure 2.
Axial DWI-T2W image of a rectal cancer. Note the good demarcation of the tumor (red arrow) and of some irregular intramesorectal lymph nodes (yellow arrows) with the same signal intensity as the tumor. DWI is good in nodal detection, but has no value in assessing nodal malignancy. Source: F. Bauer, Radiology Kaufbeuren.

coronal gradient echo sequence with fat saturation (GRE fs) as standard. These sequences depict the infiltration of the anal canal more accurately than with the native T2 sequence alone, **Figure 1A** and **B**.

Another important part of the MRI rectal protocol is the preparation of diffusion-weighted sequences (DWI-MRI) including the quantitative measurement of ADC values (*apparent diffusion coefficient*), which in particular provides valuable additional information for the evaluation of therapy response after neoadjuvant radiochemotherapy. DWI is also very helpful for detection of lymph nodes (**Figure 2**), but it is not suitable for determining their benignity or malignancy, because in both cases the lymph nodes have a high cellularity [2].

Since about 12 months, we included the 3D volume measurement into the standard protocol, when using modern 3 T systems with newest hardware and software. This supplementary measurement takes about 5 minutes.

2.4 Clinically relevant embryology of rectum and anal canal

Rectum and anal canal emerge from the part of the endodermal intestinal tract known as the hindgut. At the ventrocaudal end (approx. 5th week of development) this has a sack-shaped dilatation, cloaca, which is closed to the outside by the cloacal membrane. The cloaca lined with endoderm provides not only the epithelial lining for the rectum and anal canal, but also for the bladder and urethra. Through growth or proliferation of the urorectal septum in the direction of the cloacal membrane (approx. 7th week of development), the cloaca is divided into the ventrally located urogenital sinus and the dorsally located anorectum. The cloacal membrane, which consists of epithelial cell clusters, disappears by apoptosis (rupture of the cloacal membrane), so that the urethral and anal canals are each open to the outside. The tip of the urorectal septum has now reached the body surface and forms the future perineum. Through the use of refined methods it has been disproved for decades that the cloacal membrane is the place where the endoderm and ectoderm meet.

Proliferating epithelial cell clusters, so-called anal membrane, temporarily displace the anal opening. This lies at the level of the linea pectinata, which can already be detected at this point by the different immunohistochemical behavior of the surface epithelia. The epithelial closure disappears in the 8th week of development. In the following 9th week of development, the different epithelia proliferate and differentiate and the columnae and sinus anales are formed, thus not only the linea dentata is clearly

marked, but the epithelial border between high-prismatic (cubic) epithelium and squamous epithelium becomes clear. In the mesenchyme around the anorectum, the smooth inner ring muscle layer differentiated, reaching with a thickened end in the 8th week of development to the level of the Linea pectinata. The outer longitudinal muscle layer differentiates with a time delay in craniocaudal direction [3].

Conclusion: Only the rectum part above the linia anorectalis emerges from the endoderm, similarly to the colon. The anal canal emerges from the ectoderm, and for this reason, some authors do not consider it as belonging to the rectum.

3. Normal anorectal anatomy in MRI and the fasciae

In MRI, we can divide the rectum into three sections based on its three lateral curvatures (in analogy to the Houston valves inside).

The upper two thirds are surrounded anterolaterally (upper third) and anteriorly (middle third) by the visceral peritoneum. This forms the anterior peritoneal fold approximately at the level of the middle curve (in the area of the so-called Kohlrausch's fold) and thus delimits the upper two thirds of the rectum from the extraperitoneally located wide lumen rectal ampulla.

The anterior peritoneal fold has a specific shape in axial stratification, which resembles the appearance of a seagull, hence the name "seagull sign" (**Figure 3C**).

As mentioned in 2.3, T2-weighted sequences optimally depict the individual wall layers of the rectum:

1. Submucosa, represented as an inner layer of high intensity. Appropriate examination parameters (see below), allow even to differentiate between mucosa and submucosa. In this case, the mucosa stands out as a fine low intensity line against both the positively contrasted intestinal lumen and the high intensity submucosa;

2. Muscularis propria, represented as a further adjacent layer of intermediate to low signal intensity.

3. Mesorectal fat, the natural barrier to tumor spread, represented as an outer layer of high intensity.

The mesorectal fascia (MRF) represents an important boundary structure for the description of the tumor extension and is well recognizable in T2-weighted sequences as a thin linear structure of low signal intensity.

The mesorectal fascia encases the perirectal (so-called mesorectal) fat including lymph nodes and vessels and represents an important natural barrier to tumor spread [4]. It corresponds to the so-called circumferential resection margin (CRM), which determines the extent of surgical resection in the context of total mesorectal excision (TME) [5], as seen in **Figure 3A** and **B**. At the level of the anterior peritoneal fold, the MRF fuses with the peritoneum. From this point on, the proportion of mesorectal fat decreases continuously until neither fat nor fascia are visible in imaging at the level of the anorectal transition. Inferiorly, the rectum fuses with the anal sphincter complex (Sphincter ani externus and internus).

The external sphincter consists of striated muscles, can be defined as a hypointense structure in all sequences in the MRI and only slightly accumulates contrast medium after gadolinium administration (a typical feature of striated muscles).

The boundary between the rectum and the anal canal can be easily recognized in MRI by the complex of the muscle levator ani at the upper end of the anal canal, which

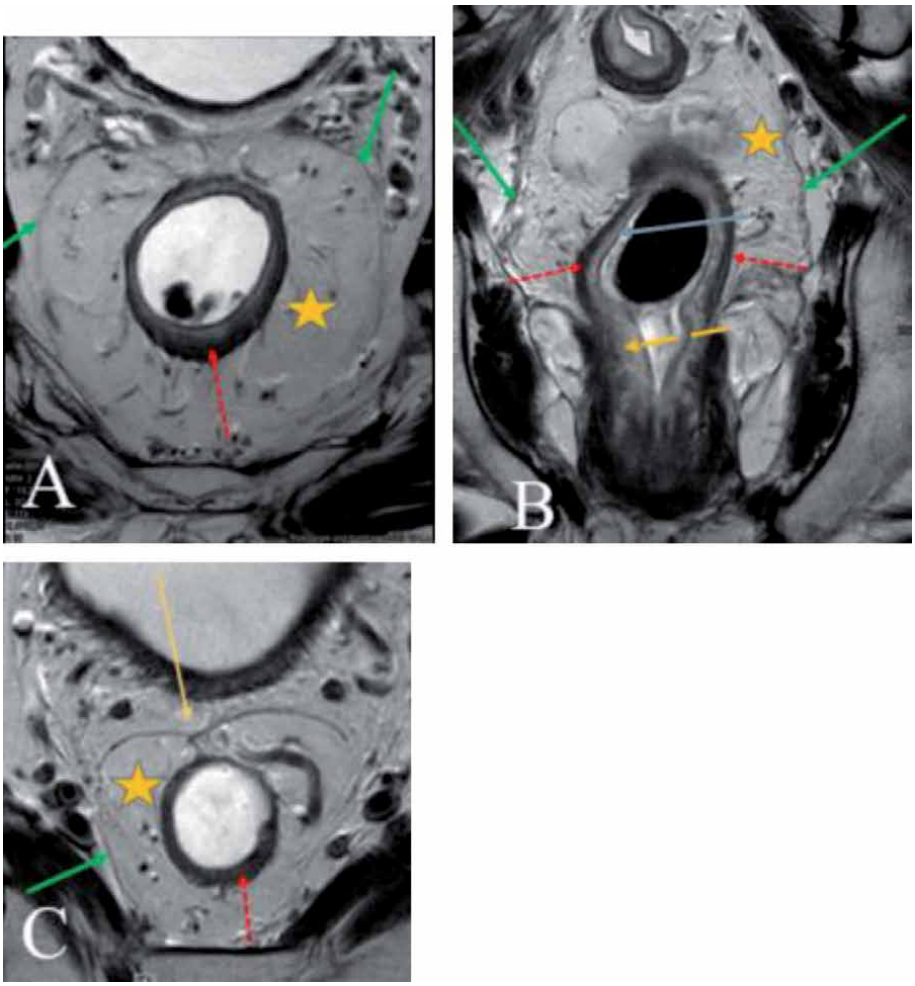


Figure 3.
Normal rectal wall in high-resolution MRI. A. Paraaxial T2WI depicts well layers of the rectal wall around the high-intensity intestinal lumen (filled with water): low intensity muscularis propria (red arrow) and high intensity mesorectal fat (yellow star) including lymph nodes and vessels. MRF (green arrow) is shown as a very thin line of low intensity surrounding the mesorectum. This line is crucial for surgery planning, as it represents the CRM (MRF=CRM). B. Paracoronal T2WI depicts additionally the low intensity mucosa (blue arrow), followed by the high intensity submucosa (yellow arrow) followed by again a low intensity structure, the muscularis propria. C. Paraaxial T2WI depicts the anterior peritoneal fold "Seagull sign" (yellow arrow). Source: F. Bauer, Radiology Kaufbeuren.

fuses with the muscle layer of the inferior rectum [5]. The internal sphincter represents a sort of expansion of the circular muscle layer of the Muscularis propria of the rectum and consists of smooth muscle. In both T1-weighted and T2-weighted sequences it has an intermediate signal intensity. We use Gd-enhanced MRI with i.v. administration of the contrast agent to highlight the internal sphincter, **Figure 1B** and **C**.

4. Tumor morphology with MRI

By far the most common rectal adenocarcinoma, up to 90%, in MRI may appear as solid, polypoid or flat lesions within the intestinal wall, whereas the aspect of an annular or semiannular mass and growing with varying degrees of stenosis is the most frequent image.

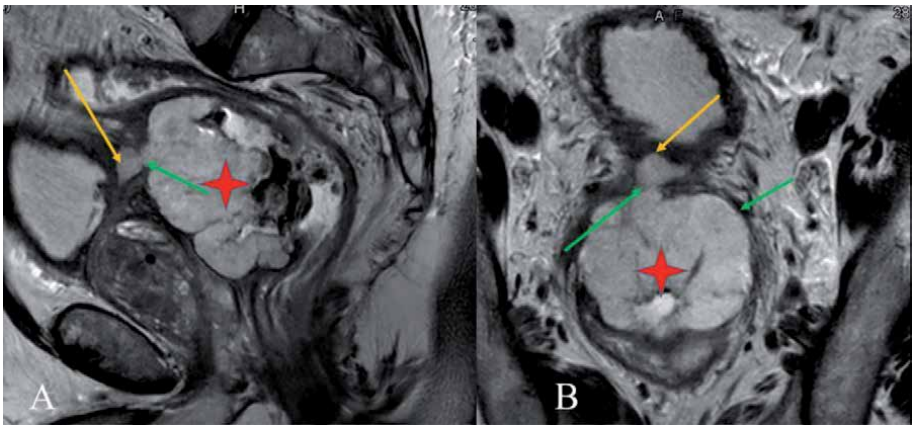


Figure 4.
A. Axial T2w image shows a low-lying mucinous tumor of high signal (red star) disrupting the mesorectal fascia (green arrows) and extending into the dorsal bladder wall (yellow arrow). B. The very large mucinos adenocarcinoma (signet-ring) with a central scar situated in the middle third of the rectum with complete infiltration of the mesorectum, and of the dorsal bladder wall at 12 o'clock. Stage: T4, CRM+, N0, EMVI. Histology confirmed this result. Source: F. Bauer, Radiology Kaufbeuren.

Less rectal tumors, up to 10%, may contain mucin, and mucinous tumors have a poor prognosis and a high risk of spillage during surgery [6]. MRI depicts these tumors well on T2w as well delimited high intensity masses, **Figure 4.**

As described above, T2-weighted sequences under optimal conditions can differentiate the wall layers of the rectum. The vast majority of carcinomas have a higher signal than the hypointense (not always controllable) mucosa, but a lower signal than the clearly hyperintense submucosa. Exceptions to this are, on the one hand, mucinous carcinoma and on the other hand, sigmoid ring cell carcinoma [7].

After administration of contrast medium, the entire rectal wall is clearly hyperintense and the individual wall layers can no longer be differentiated from each other. Therefore, the native T2-weighted sequences should be used for the primary diagnosis of the T category.

5. Local staging with MRI

The assessment of the findings obtained with MRI should be based on the TNM system. However, the MRI also provides other essential information, such as the distance of the tumor to the circumferential resection margin (CRM), and the tumoral invasion of the venous structures beyond the muscularis propria (EMVI). This additional information must be included in the report as well.

Multiple studies have proved the added value of structured reporting in rectal cancer [8–10], and resulted in many proforma available online. The diagnosis is ideally carried out using a structured report (SR) like our Structured Report (see Appendix at end of this chapter) for Primary Staging of Rectal Carcinoma at our Imaging Center (www.radiologie-kaufbeuren.de).

The report should include both the appearance of the tumor (e.g. ulcerative growth), as well as its minimum distance from anus. In addition, the craniocaudal tumor extent and the positional relationship of the tumor to the peritoneal fold should be reported. Furthermore, the radius of the carcinoma in the intestinal wall according to lithotomy position (SSL), whether the muscularis propria is infiltrated or whether extramural growth is already present should be reported.

5.1 T-staging

Rectal cancer staging is based on the TNM (tumor, nodes, and metastases) system. In this context, a **stage T1** disease passes through the mucosa and submucosa but does not infiltrate the muscularis propria.

A **stage T2** (**Figure 5A**) disease infiltrates additionally the muscularis propria.

The more advanced **stage T3** (**Figures 5B, 6,** and 7) disease infiltrates the muscularis propria and goes beyond into the mesorectum. This stage T3 has been further split into substages **a**, **b**, **c**, and **d** to categorize the depth of extramural invasion, as follows: < 1 mm = T3a; 1–5 mm = T3b; > 5–15 mm = T3c, and > 15 mm = T3d (**Figures 6** and 7).

The last stage, **T4**, also divides into two subclasses, **a,** and **b**. Substage **T4a** is diagnosed when the tumor involves visceral peritoneum or anterior peritoneal reflection, while **T4b** is diagnosed when the tumor invades at least one adjacent organ, see **Figure 8**.

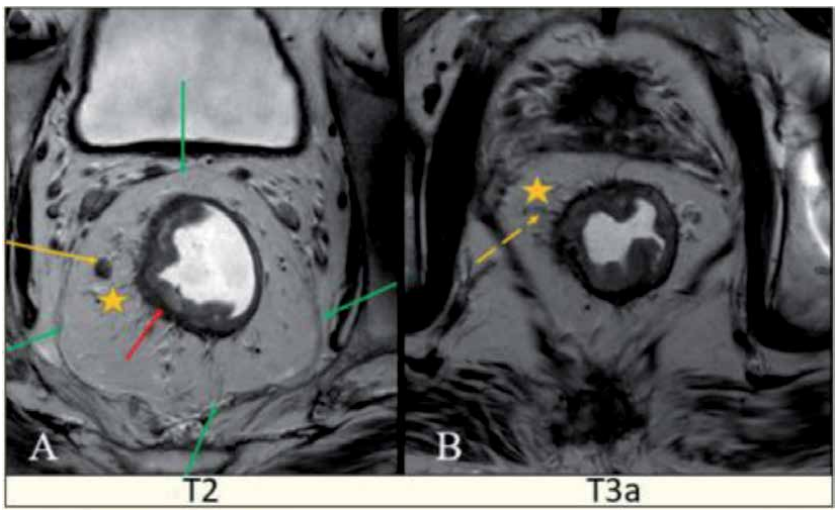


Figure 5.
A. Paraaxial T2w image shows a rectal tumor which invades the muscularis propria (red arrow) but does not penetrate its external margin. Note the fine spiculations towards the mesorectum (yellow star), and the irregular heterogeneous nodes of same signal intensity as the tumor, indicating potential nodal involvement (yellow arrow). Diagnosis: T2, N1, CRM-, EMVI-, which was confirmed by histology (T2 with "desmoplastic reaction" and nodal metastasis). B. Rectal tumor stage T3a. Note the similarity to A: tumor extensions (yellow arrow) into the mesorectal fat (yellow star). Source: F. Bauer, Radiology Kaufbeuren.

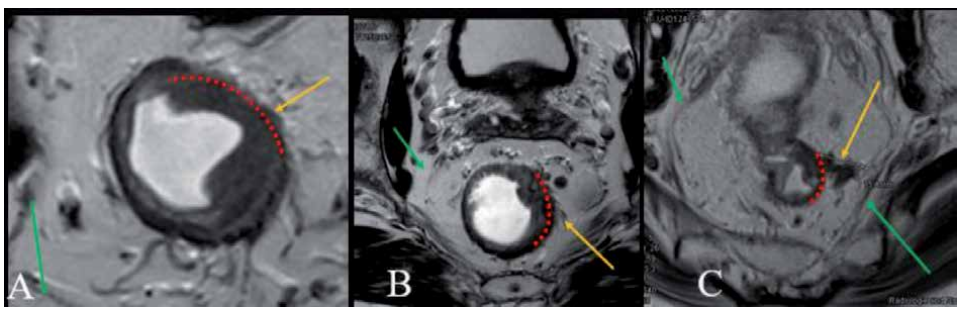


Figure 6.
Short axis axial high-spatial-resolution T2w images of different sub-classifications of T3 tumors with extramural spread (arrow): A. T3a (<1 mm), B. T3b (1-5 mm), C. T3c (>5-15 mm). Markings: mesorectal involvement (yellow arrow), muscularis propria (red dashed line), and CRM = FMR (green arrow). Source: F. Bauer, Radiology Kaufbeuren.

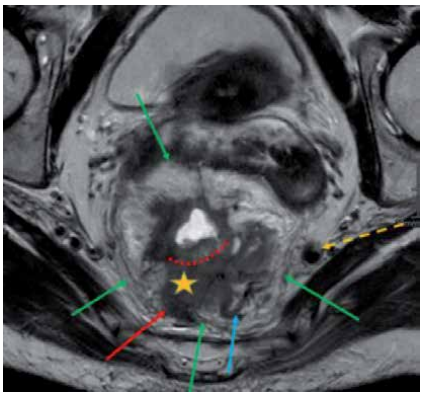


Figure 7.
Axial T2wi shows a rectal tumor (yellow star) staged: T3d (>15 mm), CRM+, EMVI+, N1). The extramural spread is measured from the level of the supposed muscularis propria (red dashed line) to the maximal point of mesorectal involvement (red arrow). Notice also the invasion of the venous structures (EMVI, blue arrow) and the extramesorectal metastatic node (yellow arrow). This node group will not be removed in a regular TME! CRM = FMR (green arrow). Source: F. Bauer, Radiology Kaufbeuren.

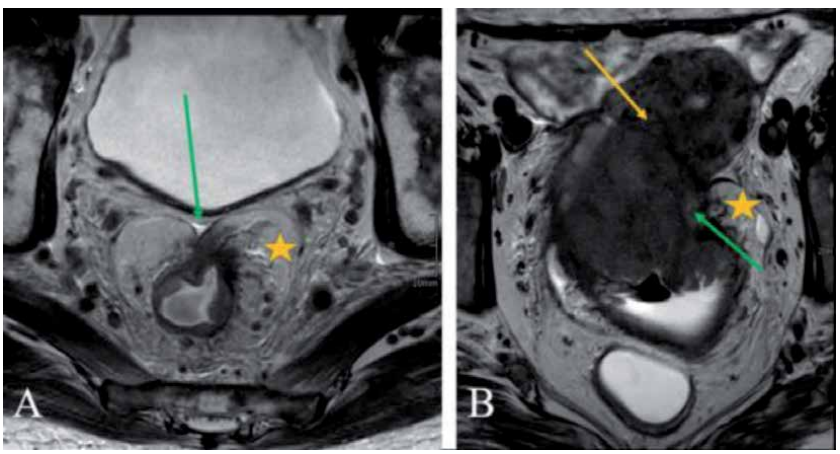


Figure 8.
A. Stage T4a tumor involves visceral peritoneum or anterior peritoneal reflection (green arrow). B. Stage T4b tumor involves an adjacent organ, uterus (yellow arrow), and the mesorectum (yellow star). Source: F. Bauer, Radiology Kaufbeuren.

Several histopathologic studies have shown that T3 tumors with more than 5 mm mesorectal invasion have a cancer-specific 5-year survival rate of approximately 54% [11]. On the other hand, for tumors of 5 mm or less in diameter, the cancer-specific survival exceeds 85% [12, 13]. Therefore, it is crucial to report the depth of extramural spread in detail, with the precise substage **T3a, b, c** or **d**. The overall reported accuracy for T staging using a pelvic phased-array coil ranges from 59% to 95% [12, 13]. Differences in T2 signal intensity between the tumor, submucosa, muscular layer, and mesorectum play the main role while detecting and staging rectal cancers using MRI.

T stage must be assessed on planes strictly perpendicular to the tumor. Incorrect prescription of the acquisition plane leads to blurring of the muscularis propria and may lead to overstaging. When the tumor is not visible on sagittal T2 WI: obtaining high-resolution images of the entire length of the rectum and adding DWI may help localize the mass. The depth of extramural spread must be measured in millimeters beyond the outer edge of the longitudinal muscular layer [13], as depicted in **Figures 5, 6** and **7.**

Al-Sukhni et al. [9] published a meta-analysis (21 studies between 2000 and 2011) on the diagnostic accuracy of MRI and found a high overall accuracy in the assessment of the T-stage with a sensitivity of 87% and a specificity of 75%.

5.1.1 Challenges for T-staging

Differentiation between T2 and borderline T3 lesions is still challenging today. The main issue is to distinguish true mesorectal tumor invasion from desmoplastic reactions [14]. In this case, the inflammatory accompanying reaction in the adjacent mesorectal fat masks the actual tumor spread. In particular, fine spicular extensions in the mesorectum should be evaluated carefully - if these are mistakenly interpreted as a tumor (T3 instead of T2), overstaging and thus overtherapy may occur.

One often error source is the use of thicker sections and lower resolution techniques. Therefore, using fine sections in T2WI should help clarifying such cases. Indeed, desmoplasia associated with ulcerating tumors at the invasive border is typically seen as fine low-signal-intensity spicules on T2WI. These spicules do not show restricted diffusion. Tumor extension into the mesorectum, on the other hand, forms thicker, intermediate signal- intensity nodular bands with restricted diffusion and disruption of muscularis propria [15].

From the therapeutic point of view, the differentiation between T2 and T3a, b stages is not important since the treatment of these lesions is identical: TME alone or short term RCT followed by TME.

5.1.2 Specific issues related to low-lying tumors

Low-rectal tumors are associated with higher rates of positive resection margins, higher local recurrence rates, and poorer survival [16]. This is largely due to anatomic considerations and the fact that the mesorectal envelope tapers and narrows at this level. These rates can be improved by using CRT in locally advanced low-rectal tumors. The results show a good response with higher sphincter preservation rates and disease-free survival [15]. In consequence, a tumor that would have previously required an abdominoperineal excision may instead be treated with ultralow resection and coloanal anastomosis.

Our experience has shown that, particularly in the case of low-lying tumors, the primary surgical concept changed relatively often after CRT and restaging. Consequently, tumors that had required abdominoperineal excision before CRT only needed ultralow resection and coloanal anastomosis after CRT.

All these require a very good quality MRI beforehand, to define the location of the tumor relative to the sphincter complex precisely, so that we select correctly the patients who will profit from preoperative CRT.

For the assessment of the anal canal, T1w lipid-saturated T1FS sequences with contrast medium are superior to T2w-sequences, since m. levator ani and m. sphincter ani externus are reliably separated from m. sphincter ani internus due to their signal and contrast medium behavior.

Rectal carcinoma usually shows low signal intensity compared to the normal intestinal wall and sphincters. **Stage T3** implies the infiltration of the external sphincter. At **stage T4**, the tumor infiltrates also of the m. levator ani. As a matter of fact, as soon as a rectal carcinoma crosses the mesorectal fascia and infiltrates the visceral peritoneum, the diagnosis is T4. Here, it must be differentiated whether adjacent organs (vagina, uterus, ovaries, prostate, seminal vesicles, bladder and ureter) are reached by the tumor (T4b) or whether only the visceral peritoneum (T4a) is infiltrated **(Figure 8A** and **B).** The contact of the tumor with surrounding

organs (without a preserved fat layer adjacent to the organ) automatically requires classification as T4 in the findings report, even if the adhesion later turns out histopathologically to be a peritumorous inflammation.

Tips for T-staging of low-lying tumors with MRI

- Protocol of choice: High-spatial-resolution T2W and T1 FS coronal imaging after i.v. administration of Gd, because it depicts optimally the tumor relationship with the levator and puborectal muscles, sphincter complex, and intersphincteric plane, as depicted in **Figure 1A**, and **B**.

- First focus on the location of the lower edge of the tumor in relation to the puborectalis sling:

  a. If tumor is located above the puborectalis sling: sphincter involvement can be easily excluded.

  b. If the tumor extends below the puborectalis sling, 3 areas have to be evaluated and reported on, **Figure 1B**, and **C** (see Appendix on structured reporting).

     1. The internal sphincter (IAS)

     2. The intersphincteric plane (ISP)

     3. The external sphincter (EAS)

- In case of stage T4: Levator and puborectalis muscles or external sphincter are involved.

5.2 Mesorectal fascia (MRF) = Circumferential resection margin (CRM)

A central component of preoperative local staging is the assessment of the distance of the tumor from the mesorectal fascia (MRF) and thus from to the circumferential resection margin (CRM). CRM infestation is an important prognostic indicator for the occurrence of local recurrences [5].

In the case of MRI-based surgery of the rectum, we deliberately equated fascia mesorectalis (MRF) with Circumferential Resection Margin (CRM) in the MDT conference, which naturally led to a need for clarification at the beginning of the discussions. In the meantime, this discussion has been clarified, if one considers the following anatomical and surgical conditions.

The CRM is the non-peritoneal surgical resection plane that is prepared during surgery and has no direct anatomical correlate in the MRI, as it is de facto only determined by the surgeon during the procedure. In practice, however, the surgeon orients himself or herself on the MRF, so that the MRF serves as the most important anatomical landmark in preoperative staging and is practically equated with the surgical resection plane. Accordingly, the visceral peritoneum or peritoneal flap are not part of the CRM, as they cannot be influenced by the surgeon. Consequently, the CRM is only "circumferential" in the lower third of the rectum and thus strongly dependent on the height of the respective rectal section, since in the middle third, the rectum is already covered anteriorly by peritoneum, and the CRM accordingly only exists laterally and posteriorly. In the upper third of the rectum, the CRM is only present on the dorsal side, since the rectum is predominantly peritoneal at this height. The distance between the rectal carcinoma and the circumferential resection

margin (CRM) is the most important risk factor for a local tumor recurrence, therefore special importance must be attached to the CRM.

The CRM is considered positive (MRI predicted "cut edge positivity") if the distance between the rectal carcinoma and the mesorectal fascia is 1 mm or less (= CRM positivity), see **Figure 7**.

Therefore, we need to document the minimum distance to the MRF in millimeters in the findings. There is no general consensus regarding the evaluation of the lymphatic of extramural vascular infiltration if these are closer to the MRF than the primary tumor. In our clinic, we consider clear lymph node metastases and clear extramural vascular infiltration a CRM positive criteria, when the shortest distance to the MRF is lower than or equals 1 mm.

The lower third of the rectum poses a particular challenge for the assessment of CRM due to its anatomical situation. Therefore, the best possible image quality is essential here, including the exact angulation of the layers with respect to the anal canal. The mesorectal fascia fuses in the lower third of the rectum on the levator ani and ends at the upper edge of the sphincter complex. CRM positivity here depends in particular on the surgical procedure. In this context, the intersphincterian fat lamella is an important anatomical guiding structure in addition to the m. levator ani. If the m. sphincter ani internus is infiltrated, but there is a distance between the tumor and the intersphincterian fat lamella or m. levator ani of more than 1 mm, the CRM for an intersphincterian resection is negative. If, on the other hand, the intersphincterian fat lamella or the m. levator ani is infiltrated, an extended resection must be performed, otherwise CRM positivity would be present.

5.3 Extramural venous invasion (EMVI)

EMVI is defined as tumoral invasion of large vessels, typically veins, in close proximity to the muscularis propria. It represents an important criterion for the individual prognosis, as positive EMVI leads significantly more often to local tumor recurrence and metastases (both local and distant). The probability of metastasis increases with the caliber of the infiltrated vessel, whereas larger vessels with a caliber of ≥3 mm greatly increase the probability of metastasis. On the other hand, smaller vessels are difficult to differentiate from lymph vessels, which have a somewhat better prognosis. This distinction is difficult even for histopathology, where it may be achieved using special staining. EMVI indicates at least stage T3, since EMVI expands per continuitatem and represents a tumor infiltration through the muscularis propria.

MRI has shown an increasing sensitivity for the detection of EMVI with the increasing use of 3 T systems. The infiltration can be detected much easier using a higher resolution, where it is shown as an intravascular substrate having an identical T2w signal intensity as the primary tumor. At the same time, no flow signal can be detected inside the vessel (**Figure 7**).

The MRI-EMVI point score system recommended by Smith and Brown in 2008 was not practical for us, and with the increasing use of 3 T equipment, we are now increasingly successful in directly detecting vascular infiltration.

5.4 Lymph node staging

All radiological imaging procedures, including MRI, have limited sensitivity and specificity in assessing lymph node metastasis, but we can significantly improve this result by consistently applying the DLC system, as depicted in **Figure 9** [2]:

D – Detection using axial DWI (number of lymph nodes), see also **Table 1**;

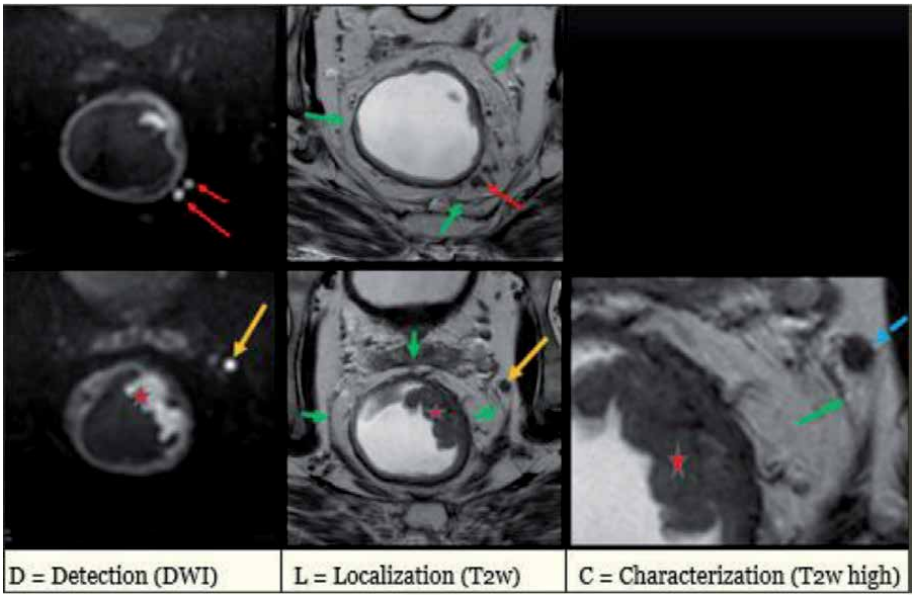


Figure 9.
Nodal staging using the DLC system. D = Detection using DWI, L = Localization using T2w, and C = Characterization using high resolution systems with 3 T. Red arrow: intramesorectal nodes. Yellow arrow: extramesorectal nodes. Green arrow: fascia mesorectalis (CRM). Blue dashed arrow: characterization (inhomogeneity, round-oval with spiculae). Red star: tumor. Source: F. Bauer, Radiology Kaufbeuren.

Class	Interpretation
Nx	Regional lymph nodes cannot be assessed
N0	No involved regional lymph nodes
N1	
a	1 involved regional lymph node
b	2-3 regional lymph nodes involved
c	No involved regional lymph nodes, but tumor deposits in subserosa, mesentery or non-peritonealized pericolic or perirectal/mesorectal tissues
N2	
a	4-6 regional lymph nodes involved
b	> = 7 lymph nodes involved

Table 1.
Extended N-classification for rectal cancer.

L – Localization of lymph nodes (no. of intra and extra mesorectal) using T2w high resolution multiplanar imaging using a 3 T system (axial, coronal, and sagittal planes);

C – Characterization using T2w high resolution imaging using a 3 T system: tumor size in mm and morphological criteria like inhomogeneity, round-oval with spiculae, etc.

We can answer all therapeutically relevant questions using this scheme. In addition, the increase use of 3 T devices has significantly improved the resolution. Our experience shows that many lymph nodes previously considered round and smooth show distinct spiculae in high resolution images, which is a clear criterion for malignancy. We have also previously seen this correlation between focal findings

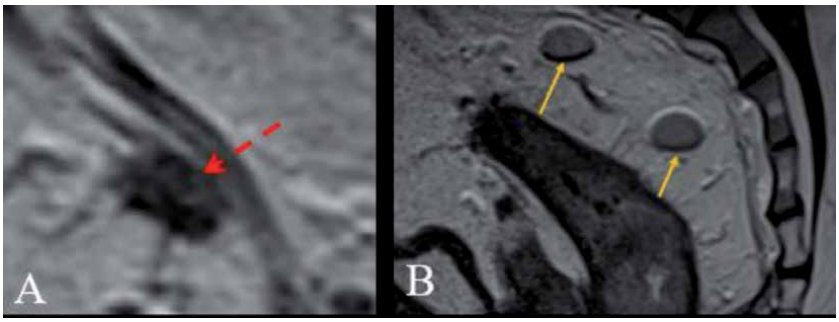


Figure 10.
Lymph nodes of same size (4 mm) but with totally different morphology in MRI. A. Lymph node metastasis in a patient with rectal cancer. Note the typical aspect of malign lymph nodes: inhomogeneous signal; irregular border with spikes (red arrow). B. Benign (reactive) nodes (arrows), characterized by homogeneous signal and well-defined borders on the background of anal fistula (no cancer!). Source: F. Bauer, Radiology Kaufbeuren.

and resolution in mammography. A good resolution is the key to a correct morphological assessment of the lymph nodes. Currently, the morphology of lymph nodes is becoming more important than their size!

The mesorectal fatty tissue offers a unique and excellent opportunity for a very clear demarcation of lymph nodes. In signal-rich fatty tissue (light), the signal-poor lymph nodes (dark) can be excellently demarcated and characterized (see **Figure 10**). Unfortunately, we do not have this unique situation everywhere in the abdomen!

In general, we have no problems with the assessment of the larger lymph nodes over 5 mm near the tumor or proximal to the primarius, which are usually always positive. We only have problems with smaller lymph nodes below 4 mm, which as we know can contain micrometastases. Here, morphology with good resolution and powerful 3 T devices provides a valuable help, as shown in **Figure 10**.

In our tumor conference, we focus on the localization of lymph nodes, because it is crucial to assess the presence of potentially malignant extramesorectal lymph nodes. While intramesorectal lymph nodes are standardly removed in TME, extramesorectal/obturator lymph nodes are usually left out. If the latter ones present malignancy aspects in MRI, the surgical procedure may change to a D3 lymphadenectomy removing extramesorectal lymph nodes (depending on the surgical strategy).

We recommend the consistent use of structured reporting (see template in Appendix) for primary MRI staging of rectal cancer. This report includes all therapeutically and diagnostically important points.

Nodal metastases must be detected and characterized preoperatively, as they are critical for surgical planning, prognosis, and the decision to administer adjuvant/neoadjuvant chemoradiation.

6. MRI and the newer 3D technology

As in all areas of life, knowledge and experience are also the key to success in dealing with technology. One of these new technologies that deserves application and experience is "high resolution 3D imaging". Perhaps, it will even change the way we scan in MRI in the future.

3D imaging does not mean, as the term might suggest, image representation in spatial form, but rather the generation of images by means of 3-dimensional data sets.

3D imaging provides numerous benefits for experienced surgeons, from the facilitated planning of complex operations to the use of realistic models. The latter

provides effective solutions for one of the greatest challenges in any academic surgical department: training young surgeons in practical techniques without the negative impact of the learning curve on the patient.

Since 2019, radiologists working in MRI have been using extremely fast, high-resolution 3D data sets. These make even the smallest lesions visible and allow viewing from a variety of perspectives. The "isotropic resolution" (less than 1 mm) ensures excellent display of the tumor's characteristics and its relation to the surroundings and neighboring organs – and in the shortest possible time. A relevant surgical area can often be measured in only 5 minutes, which saves time and reduces movement artifacts. The "3D high-resolution compressed SENSE pelvic program" converts layered 2D measurements into a single 3D volume scan (**Figure 11**), plane by plane. It allows easily reformatting of isotropic 3D volume data in the range below 0.5 mm in any plane, without gaps, and with the same resolution as the "native" plane. The SNR-rich, ultra-thin 3D volume allows visualization of even subtle lesions without the partial volume averaging effect. Moreover, tissue structures that are best seen in oblique view can be viewed easily.

The new, self-calibrating technique with parallel imaging and compressed scanning significantly speeds up the MRI examination. As a result, scanning times can be reduced by up to 50% compared with those of conventional examination without "compressed SENSE" – all while providing exquisite tissue contrast.

The advantage of 3D imaging in surgical and radiotherapy planning is obvious: multiplanar images with excellent soft tissue contrast. This allows exact delineation of the tumor and healthy tissue, which is of decisive importance for RCT planning.

Furthermore, during follow-up, e.g. after RCT, changes in anatomy and tumor biology can be better visualized, thus permitting improved adaptation of treatment plans.

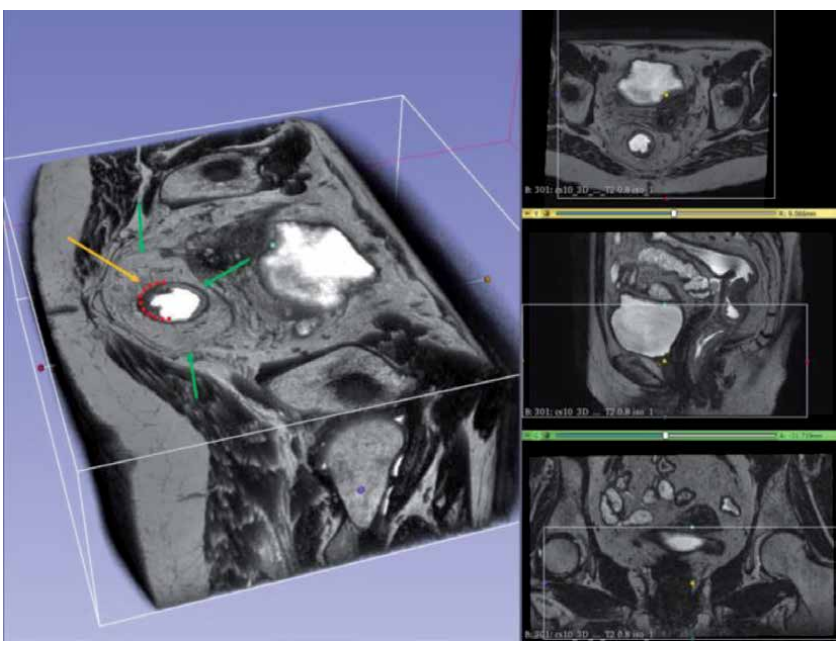


Figure 11.
A 3D volume of pelvis acquires contiguous, sub-millimeter, isotropic 3D data sets that can be easily reformatted into any plane, without losing its resolution. The SNR-rich, ultra-thin slices can provide help to visualize even small and subtle lesions without partial volume averaging effect. This will change the way we scan in the future. Muscularis propria with rectal tumor (red dashed line), mesorectum (yellow arrow), FMR = CRM (green arrow). Source: F. Bauer, Radiology, Kaufbeuren.

Our own experience shows that high resolution in 3D has clear advantages with regard to the assessment of the mesorectal fascia. 3D volume scans allow very clear and seamless visualization of the MRF/CRM at any desired level — even in critical areas, such as ventrally or around the junctional zone, where there is very little to no fat tissue.

Another advantage we see is in the use of arbitrary angulation (adapted to the tumor level) in real time, which permits any possibly unfavorable 2D angulation to be checked quickly and, if necessary, to be corrected accordingly.

Our current results contradict our own older experience as well as the common opinion in the literature regarding the reliability of 3D MRI. The new technology is very stable and can be implemented quickly if given the prerequisite of using 3 T systems with the latest hardware and software technology. **Localization** certainly plays an important role here. In the small pelvis we have no respiratory or pulsation artifacts and the intestinal peristalsis can be exposed very effectively with Buscopan. Of course, we do not have all these unique local conditions in the area of the parenchymatous upper abdominal organs. I can only encourage every user to include this 3D measurement of the pelvis (if 3 T devices are available) in the standard protocol of the rectal examination.

The surgical department has particularly appreciated this 3-dimensional, high quality, multiplanar real-time imaging. We, radiologists, we are especially pleased that the correct orthogonal planning to the tumor can be done very accurately and now in real time, but retrospectively. In the past, incorrect angulation has often produced incorrect readings, resulting in over or underestimation to the distance to the mesorectal fascia. If our measurements are to agree with the histological result, this evaluation must be extremely precise. We see a further advantage in tumors with a strong curvature or in double carcinomas, where multiple angulation is required for precise axial layers. We can now perform all these transformations from one acquired 3D data set. We see no real argument against this 3D volume measurement of the pelvis, which supplements the current standard protocol with an additional 5-minute measurement.

7. Other imaging modalities

7.1 MRI vs. CT

CT cannot be recommended for the local staging of rectal cancer.

The decisive advantage of MRI over CT is that it displays much better the morphology of the tumor and its topographical relationship to the border lamella of the mesorectum and to neighboring structures (prostate, seminal vesicle, vagina, uterus, os sacrum and os coccygeum as well as bladder and sphincter apparatus). As we have shown above, the relationship of the tumor to the neighboring structures is just as important as the TNM classification scheme [17, 18]. In addition, the lymph node prediction accuracy of CT is lower than with MRI.

For the detection of distant metastases, however, contrast-enhanced CT (CECT) is currently the method of choice due to its high availability and supported by current guidelines [19]. In most cases, it consists of a combined examination of the thorax and abdomen, which is a routine protocol both preoperatively for staging and in follow-up.

7.2 MRI vs. PET-CT

We do not routinely use PET-CT in our center for primary staging, nor for restaging after CRT, as complete remission can be evaluated much better with MRI.

In fact, although PET-CT can address the question of tumor response, it cannot determine the presence of complete remission.

However, we do apply PET-CT in particular cases for metastasis detection and evaluation on the background of high CEA values.

7.3 MRI vs. EUS

For the detection, characterization and staging of rectal tumors, MRI is being considered the imaging modality of choice alongside endoscopic ultrasound (EUS), which offers particular advantages for early tumor stages T1 and T2. Without radiation exposure, it enables excellent soft tissue imaging and offers the possibility of multiplanar image acquisition and reconstruction, which is the current standard for the preoperative imaging of rectal tumors [20].

Currently, MRI increasingly being replacing EUS in the local staging for rectal cancer. Both modalities are equivalent for assessment of tumor spread beyond the muscularis propria (i.e., T2 versus T3 status). However, MRI holds several advantages over EUS in case of locally advanced rectal cancers (LARC), because it allows to better characterize lesion size, morphology, tumor margin and other helpful details for surgical planning. In addition, this modality offers a precise characterization of important aspects that may impact therapeutic decisions, such as proximity of the tumor to the mesorectal fascia, presence of extramural vascular invasion (EMVI), presence of extramesorectal pelvic lymph nodes, and involvement of the peritoneum/anterior peritoneal reflection, as well as the assessment of the R0 resectability.

Many of these findings are either difficult to assess, or are beyond the scope of EUS. Because of these advantages, MRI has become the preferred modality in the initial staging of rectal cancer, particularly as part of an interdisciplinary approach [15].

7.4 Endorectal sonography (ERUS) and its evaluation in the MDT tumor conference

At our clinic, our colleagues from gastroenterology apply ERUS routinely for the preoperative local diagnosis of rectal carcinoma and for restaging. The obtained images are then loaded together with colposcopy images into PACS, so that the obtained information is available to all involved personnel, including radiologists. The examination protocol is well defined and observed: clinical examination at first, followed by colposcopy with biopsy, and then by ERUS. After this series of examination, and after delivery of the histological finding, we do MRI. At the end, we discuss the results together with all involved departments in the MDT tumor conference.

ERUS is particularly well suited for the preoperative diagnosis of small tumors T1, T2, T3a, and b. However, ERUS has difficulties with large tumors, especially if they are high-set or stenosing carcinomas; likewise, the limited FOV (field of view) of large T3 and T4 tumors can push ERUS to its limits - MRI is superior here. Most of the misdiagnoses in MRI occur during differentiation between T1 and T2 tumors, mostly because of an inadequate representation of the submucosa. In conclusion, ERUS is slightly better suited for the preoperative diagnosis of small low-lying tumors than MRI.

The assessment of the mesorectal fascia (MRF) remains a domain of MRI; especially after neoadjuvant radiochemotherapy, endosonography can neither assess the distance of the tumor to the potential circumferential resection margin (CRM), nor does it offer sufficient sensitivity/specificity to assess the primarius.

ERUS and MRI should not be considered as competing procedures, but rather as complementary imaging modalities. Additionally, we must consider that, especially for endorectal ultrasound, there is a steep learning curve, which possibly also contributes to the lower overall accuracy of ERUS in large multicenter studies. In the hands of an experienced investigator, however, ERUS has proven to be a cost-effective and reliable method for the preoperative diagnosis of rectal cancer.

8. Imaging modalities for restaging

At our Imaging Center we evaluated in the past 5 years (2015-2020) 135 patients with rectal carcinoma using MRI (4 devices of 1.5 T, 2 devices of 3 T).

In the first 2 years, we almost exclusively performed primary diagnoses, the question of restaging being very low. On the one hand, this was due to our surgeons, who did not want to reconsider their original operation planning after completing CRT; on the other hand, it was due to us, because we were still very busy delivering high quality MRI diagnoses. When our image diagnostic results matched the histology, we finally got an adequate appreciation. This required a long learning curve. Today, restaging is as obligatory in our institute as preoperative MRI diagnostics. Restaging is a very demanding examination and can only work if the primary staging is performed with constant high quality. At this point, at the latest, the standardized examination protocol with DWI pays off.

While restaging, MRI imager after nCRT are correlated with MRI images before nCRT in all elements evaluated in primary staging. This requires post therapeutic image acquisition under nearly identical protocol parameters and levels. Essential points at this stage are position, extent and signal intensity of the tumor. These features are compared in the MRI images before and after nCRT. Care is also taken to ensure that restaging or follow up is always performed with the same device, because of the decisive diffusion-weighted images. As already mentioned, different devices (e.g. Siemens vs. Philips) provide different diffusion values, which are not always comparable.

Restaging is not for beginners and requires a long learning curve, similar to MRI of the mamma or MRI of the prostate. A minimum of 50 histologically confirmed cases/examinations are necessary to achieve a good performance.

The difficulties of restaging are obvious: Neoadjuvant therapy leads to profound changes in tumor tissue and surrounding structures, such as excessive fibrosis, deep stoma aging, wall thickening, characteristic muscle remodeling, tumor necrosis, calcification and inflammatory infiltration. As a result, the diagnostic accuracy of the imaging procedures decreases significantly with respect to restaging. Accordingly, the local tumor extent can be over- or underestimated.

These challenges can best handled using MRI with diffusion images. The accuracy of clinical examinations using endorectal ultrasound (EUS), computed tomography (CT) and 18F-FDG protrusion emission tomography with CT (18F-FDG-PET/CT), is very low both for the assessment of mesorectal invasion and for the evaluation of lymph node metastases and is therefore not used at our clinic for restaging as the sole examination.

Our restaging strategy includes digital rectal examination, endoscopy/EUS, and finally MRT (DWI). Care is always taken to ensure that this examination sequence is followed. This is where the multidisciplinary team meeting between surgeons, gastroenterologists and radiologists plays a special role (**Figure 12**). The decisive images are introduced into the PACS system and are available to everyone. When

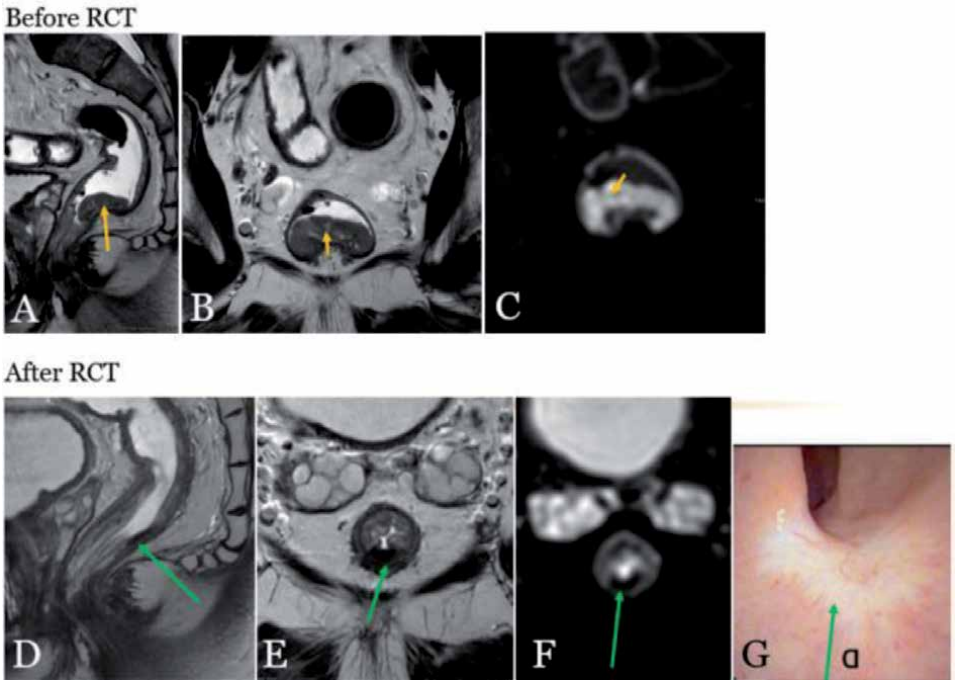


Figure 12.
Response assessment with MRI T2w, DWI, and EUS. Pre RCT imaging shows a rectal cancer stage T2 (yellow arrow) with low to moderate signal in T2w (A, B) and high signal in DWI, C. Reporting: T2, No, EMVI-, CRM-. Post RCT imaging shows complete remission, stage mrTRG-1. Note the tumor has completely regressed and was replaced by fibrosis (green arrows show fibrotic wall thickening with no evidence of tumor remnants) D, E. F. There is no focal high signal in DWI anymore, no diffusion restriction F. G T2wi shows a typical endoluminal white scar. Reporting: yTo, yNo, yEMVI-, CRM-. Therapy strategy: wait-and-see with no tumor recurrence within the following 2.8 years. Source: F. Bauer, Radiology Kaufbeuren.

the radiologist starts restaging, these important staging examinations are already available to everyone.

Almost 90% of our patients have received the internationally recommended standard of care for adenocarcinoma of the lower to middle third of the rectum with a tumor stage T3/4 and/or cN+ and neoadjuvant radiochemotherapy (nRCT).

In addition to the generally known findings such as reduction of the local recurrence rate and improvement of the tumor-free interval, we try to identify the group of patients who would benefit from a non-surgical treatment strategy. The surgical community was initially very reticent towards the watch-and-wait strategy. In fact, it requires a high accuracy MRI examination to identify patients with full remission (CR: ypToN0). Own experience, good interdisciplinary cooperation and evaluation of all diagnostic tests are the prerequisite for reliable diagnostics.

The reference standard for CRT was histopathology or the recurrent free interval of >12 months in watch-and-wait approaches. After a long learning curve, our diagnostic accuracy has improved steadily. In about 24% (33 patients) of the cases we could show a full response, here interestingly also in some patients where chemotherapy had to be discontinued due to cardiac side effects. In almost all CRT cases, the initial stage was a T2 and/or T 3a, b, or c tumor stage. During a follow-up period of 2 years, we could see that almost always a small fibrosis limited to the intestinal wall took place and that this fibrosis was almost always unchanged in the course of the treatment. If a complete remission (CRT) occurred after radiotherapy, a high percentage of patients remained tumor-free.

Restaging remains particularly difficult for initially advanced tumor stages, like T3d with CRM+ or T4. Here, the strong hypointense mass fibrosis of the tumor bed and irregular fibrotic mass or wall thickening with irregular margins and/or spicules makes reliable diagnosis very difficult. In these cases, surgical resection, mostly TME, has always been recommended and performed. In case of low rectal tumors, the anal canal must be assessed.

In fact, our standardized protocol must answer the following questions for surgery:

- Are there vital tumor remnants inside the fibrosis?
- Is the tumor limited to the rectal wall?
- Is the mesorectal fascia (CRM) tumor-free?
- Are there still metastatic lymph nodes?
- Has the tumor withdraws from the anal canal?

In some cases, we have seen that the tumor has actually retreated from the anal canal, thus opening the way for sphincter-preserving surgery and a life without an artificial exit.

The restaging of the lymph nodes often turned out to be surprisingly simple. In the vast majority of cases, where there was a very good or good response to radiochemotherapy, the mesorectum showed complete remission of the lymph nodes. In some cases, the morphological assessment with regard to spicules and inhomogeneity is particularly difficult due to the extensive fibrosis within the lymph nodes. In such cases, we use the significant reduction in size of the lymph nodes for assessment. Consequently, we consider negative small, star-shaped lymph nodes below 3 mm. However, these lymph nodes must be monitored particularly closely during follow-up.

The time interval to restaging was about 6-8 weeks after the end of CRT. In uncertain cases, where we suspected an almost complete remission, a follow-up examination in about 4 weeks was recommended, because persistent inflammatory reactions and/or a short-term reduction in tumor metabolism can cause an inaccurate result.

The key to success in MR diagnostics and especially in restaging is the unique combination of morphological T2 imaging with in vivo functional (diffusion weighted measurements, DWI) imaging. High-resolution T2 imaging can detect very accurately the extent of fibrosis and mucoid degeneration within fibrosis. Only diffusion-weighted images can assess whether vital tumor tissue is still present within the fibrosis and only MRI is able to combine morphology and functional imaging uniformly within one examination in only 25 minutes (**Figure 12**). Perhaps the mnemonic can help: MRI with DW is a kind of "PET- CT" of the poor man. There is another functional MRI imaging and that is DCE-MRI (Dynamic Contrast Enhanced), which we know very well from prostate diagnostics. We are also experimenting with these sequences. Although we apply here our experience from prostate diagnostics, we currently cannot recommend this examination for routine practice.

Recording the size of the tumor must be paid attention to during restaging and in cases of poor response. A reduction in tumor size can be effectively measured by 3-dimensional MR volumetry and shows a good correlation with the ypT stage after neoadjuvant therapy [21].

Grade	Response	MRI Finding
mrTRG-1	Complete response	No tumor signal, nor evidence of relapse.
mrTRG-2	Good response	Dense fibrosis, no detectable tumor signal.
mrTRG-3	Moderate response	>50% fibrosis or mucin lakes; detectable tumor signal.
mrTRG-4	Poor response	Predominance of tumor signal over fibrosis and mucin lakes.
mrTRG-5	No response	No change in tumor signal after therapy.

Table 2.
MRI based tumor regression grading.

Good tumor regression rate in the pathological examination correlates with a tumor volume reduction of more than 70% after nCRT [21, 22] and a higher disease-free survival [21]. Moreover, a volume reduction of more than 75% is significantly associated with pCR [21, 23]. mrTRG can be used to effectively assess the response of rectal carcinomas to CRT. This classification is easy, effective and practice-oriented. According to our experience, a good agreement in histology can be achieved even with minimal training. Again, the focus should be on facilitating the identification of good responders (see **Table 2** for tumor regression stages).

9. Conclusion

Magnetic resonance imaging plays a key role in planning rectal cancer treatment, as it not only accurately depicts the local extent of the cancer and its anatomical positional relationship to the key structures, but can also generate relevant information for prognoses and thus can directly influence the choice of the optimal therapeutic procedure for each individual patient.

To exploit the full potential of MRI, the following must also be reported in addition to the T-stage, including the respective T3 sub-classifications:

- the distance to the circumferential resection margin (CRM),
- presence of extramural vascular infiltration (EMVI), and
- the lymph node status, under consideration of the methodological limitations of MRI.

Endosonography (EUS) is a very important complementary method, especially for determining tumor stage T1 versus T2. A CT thorax/abdomen is routinely used to assess the M status. A PET-CT does not play a significant role in local primary diagnosis and restaging. In this context, the expertise of the radiologist plays an important role, especially in more difficult restaging. We expressly encourage everyone to include 3D volumetry in the standard protocol, because this new technique is already playing an increasingly important role in precise, preoperative surgery planning.

Due to the multitude of therapeutic options available for the treatment of rectal cancer today, it has become an international standard to discuss each patient's findings pre-therapeutically in a tumor board comprising a multidisciplinary team (MDTmeetings). This procedure ensures that all therapeutic options are considered for the benefit of the patient, according to need.

Appendix

STRUCTURED REPORT (PRIMARY STAGE RECTAL CARCINOMA)

Local tumour status

Location ☐ upper rectum ☐ middle rectum ☐ lower rectum ☐ anal canal

Morphology ☐ Solid-polypoid
☐ Solid-(semi)annular: from ..... to ..... o'clock
☐ Mucinous: from ..... to ..... o'clock

Distance from the annorectal junction to the lower pole of the tumour: ..... cm

Tumour length: ..... cm

T-stage ☐ T1-2 → Rectal wall - The tumour is limited at muscularis propria
☐ T3 → ☐ T3 a,b (≤ 5 mm invasion of perirectal fat tissue)
☐ T3 b,c (> 5 mm invasion of perirectal fat tissue)
☐ T4 → ☐ Prostate ☐ Uretra ☐ Uterus ☐ Ureter
☐ Seminal vesicles ☐ Vagina ☐ Sacrum (level) ☐ Others: .....

Sphyncter invasion: ☐ No
☐ Internal sphincter only
☐ + intersphincteric plane ☐ upper ☐ middle ☐ distal 1/3 of anal canal
☐ + external sphincter

Mesorectal fascia (and peritoneal) involvement → Only fill in when stage ≥ T3

Shortest distance between tumour and MRF: ..... mm → CRM - ☐ free (>2 mm)
CRM + ☐ threatened/involved (≤2 mm)

Location of the shortest distance between tumour and MRF: ..... o'clock

Relation to anterior peritoneal reflection: ☐ below (MRF invasion)
☐ at or above

Lymph nodes and tumour deposits

N-stage ☐ N0 ☐ N+

Total number of lymph nodes: .....

Number of suspicious lymph nodes: ..... (..... mesorectal nodes; ..... extramesorectal nodes)
..... nodes with short axis diameter ≥ 9 mm
..... nodes with short axis diameter 5-8 mm AND at least 2 morphologic criteria*
..... nodes with short axis diameter <5 mm AND all 3 morphologic criteria*
*N.B. Morphologic criteria:[1] round shape, [2] irregular border, [3] heterogenous signal

Are there any tumour deposits within the mesorectum: ☐ No
☐ Yes, ... (number of deposits)

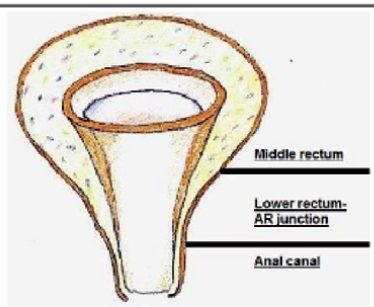
Extramural venous invasion EMVI ☐ No
☐ Yes, from ..... to ..... o'clock

Conclusion

T Stage ☐ T1 ☐ T2
☐ T3a,b ☐ T3c,d
☐ T4a ☐ T4b

N Stage ☐ N0 ☐ N+ no. .....

☐ Free CRM ☐ Involved CRM ☐ Positive EMVI ☐ Negative EMVI



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Section 3

Surgery

Chapter 5

Laparoscopic Right Colectomy. Intracorporeal Anastomosis Is Associated with Better Outcome

Giulio Aniello Santoro, Simone Novello, Ugo Grossi, Martino Zucchella, Andrea Kazemi Nava and Giacomo Zanus

Abstract

Colon cancer is the third most common cancer in man and woman in the developed world. Laparoscopic right colectomy is the standard of care for right colon cancer. Since the first report on laparoscopic approach in 1991, the surgical technique has been improved and currently all procedure is performed intracorporeally. The ileo-colic anastomosis can be performed either intracorporeal and extracorporeal: the differences in clinical outcome, complications rate, hospital stay and quality of life between that two techniques are not still clear and a large number of studies has been published about that. According to most recent meta-analysis, intracorporeal anastomosis have showed better outcome in anastomotic leakage rate, surgical site infection rate, development of incisional hernia, postoperative pain and recovery of gastrointestinal function.

Keywords: right colectomy, laparoscopy, intracorporeal anastomosis, cancer, anastomotic leakage

1. Introduction

Cancer of the colon is the third most common cancer in men and women in the developed world, and resection is the only curative treatment. Traditionally, cancers of the colon were removed through large abdominal incisions. The first report on laparoscopic right colectomy appeared in 1991 [1], since then a large number of studies was performed to define technical and oncological safety of the laparoscopic approach. However, reports of tumor recurrence at the port sites after laparoscopic resection for colon cancer have questioned the oncological safety of mini-invasive approach in patients with bowel cancer. In 2008, the Colon Cancer Laparoscopic or Open Resection Study Group carried out a randomized clinical trial, with the primary end point being disease-free survival at 3 years after laparoscopic and open surgery for colon cancer. The results showed no differences in disease-free survival and overall survival between the two groups; moreover, no differences in tumor recurrence were reported [2].

A large number of subsequent randomized and non-randomized studies confirmed the short-term advantages of laparoscopy as compared to traditional treatment in terms of cosmesis, pain control, bowel function, postoperative morbidity, and hospital stay. Long-term follow-up data provided by the CLASSIC and COLOR

trials showed comparable outcomes between open and laparoscopic surgery in terms of overall survival and disease-free survival [3].

From a technical point of view, various operative factors - such as extent of resection, number of lymph nodes sampled, length of bowel and mesentery resected, and bowel margins – do not differ significantly between patients who underwent laparoscopic surgery and those who underwent open colectomy. With regards to intra-abdominal staging accuracy, laparoscopy allied with solid-organ imaging offers adequate staging information [4].

Laparoscopic right hemicolectomy is currently considered the standard of care in benign and malignant right colon disease [2].

This chapter describes the technique for laparoscopic right colectomy technique, with a focus on ileo-colic anastomosis, highlighting the differences between intra-corporeal and extracorporeal anastomosis fashions in terms of clinical outcome and surgical safety.

2. Surgical technique

With the patient placed supine in neutral position, the surgeon and first assistants stand on left and the laparoscopic tower is situated on the right. Second assistant, if present, stand on the right. It is important that the patient is well secured to the operating table to avoid incidents during bed movement.

After surgical site disinfection, the pneumoperitoneum is established using open technique (our preferred method) or Veress needle. The first trocar is placed next to the navel. Once pneumoperitoneum has reached target pressure (12 mmHg), the exploratory laparoscopy is performed in order to assess the presence of carcino-matosis or metastases to solid organs missed by imaging on pre-operative staging, which may preclude tumor resectability. Two working trocar for surgeon are subsequently placed: one (10 mm) in the left upper quadrant and the other (10 mm) in the left lower quadrant. A fourth trocar (5 mm) can be positioned in right middle quadrant for further assistance (**Figure 1**).

Sliding and left shifting of the patient in Trendelenburg positioning (i.e. head lower than legs) facilitates optimal exposure of the operating field. This leads to a shift of greater omentum over the stomach and small bowel 'descent' towards the left upper quadrant allowing adequate exposure of cecum, ascending colon, right portion of mesocolon, ileocolic vessels and right colic vessels.

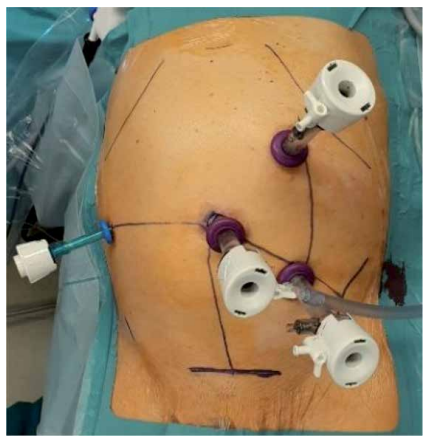

Figure 1.
Trocars position.

Using laparoscopic forceps, the assistant lifts up the ascending colon to expose the right portion of mesocolon that is straightened by the surgeon: this step allows visualization of ileocolic vessels (**Figure 2**).

In case of malignant disease, it is mandatory to performed lymphadenectomy simultaneously with the resection of vascular stem. In order to do that, ileocolic and right colic vessels must be ligated and sectioned at their origin.

Once vascular stem has been sectioned, visceral peritoneum is cut on ileocolic vessels axis in front of duodenum, so the colic dissection can be performed under a "tent" formed by Toldt's fascia and prerenal fascia from medial-to-lateral. The dissection must be continued up to cecum in distal direction and up to hepatic flexure in cranial direction paying attention to avoid to open retroperitoneum and to damage genital vessels or ureter (**Figure 3**).

This procedure is continued until the horizontal part of the duodenum comes into view. The hepatocolic ligament is sectioned to allow separation of the ascending colon from the duodenum. Access into the omental bursa is facilitated by gentle caudal retraction of the transverse colon and incision of the gastrocolic ligament. Partial removal of the mesotranverse colon is performed towards the right colonic angle.

In this way the colon limb can be eviscerated or approached in a tension-free manner. At this point, using laparoscopic stapler, colon and ileum are sectioned (**Figure 4**) and the specimen is extracted using endobag.

Until this moment, surgical procedure is the same for both totally intracorporeal and extracorporeal (i.e. with bowel transection and anastomosis performed out of abdomen).

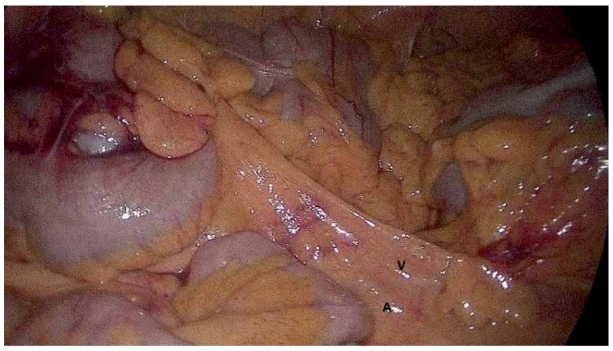

Figure 2.
A-artery, V-vein.

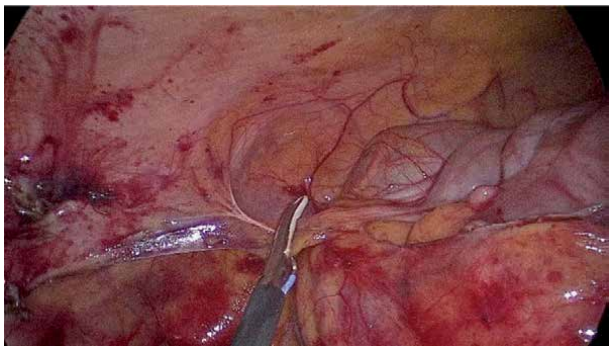

Figure 3.
Dissection of colon from abdominal wall.

2.1 Anastomotic techniques

There are two ways to perform ileocolic anastomosis: extracorporeal anastomosis (EA) and intracorporeal anastomosis (IA). In the EA a Kocher or middle-line or Pfannenstiel incision is made, protected with an Alexis device. The ileum and the colon are extracted, the dissection of the mesocolon is continued and, if necessary, the isolation of the arcade vessels is finished; the transection of ileum and colon is performed with a 60 mm GIA stapler, and the specimen is separated. A side-to-side

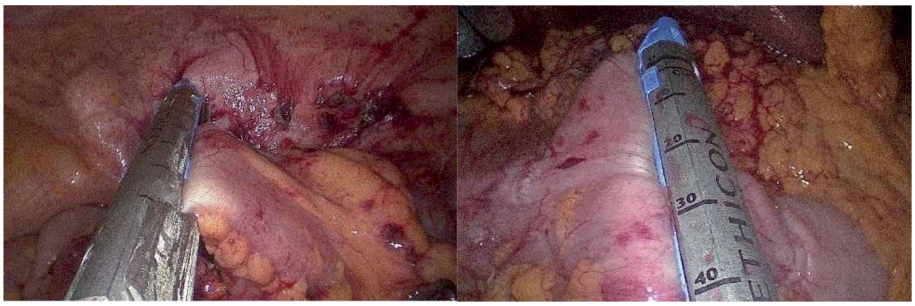

Figure 4.
Section of ileum (left) and colon (right).

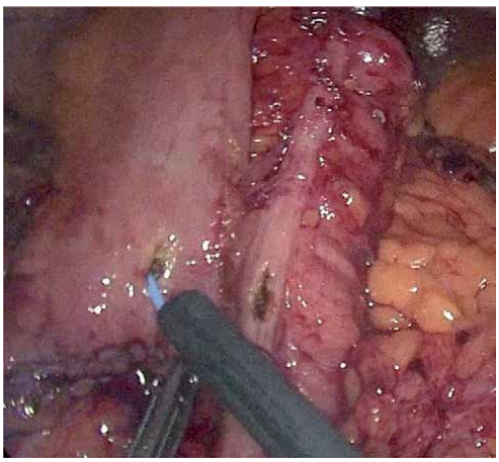

Figure 5.
Enterotomy for insertion of stapling device.

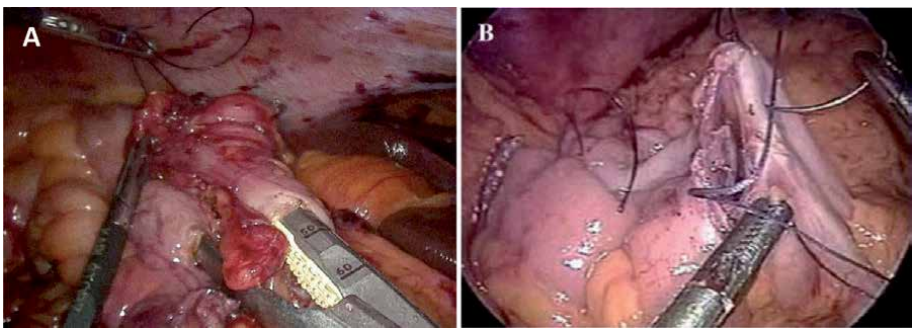

Figure 6.
(A) Stapled ileocolic anastomosis; (B) Hand-sewing of enterotomy after stapler removal.

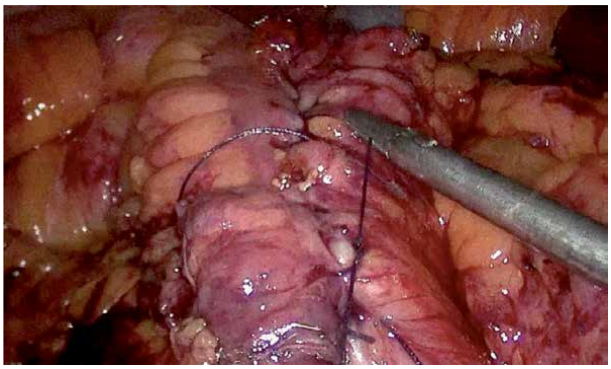

Figure 7.
Completed side-to-side intracorporeal ileocolic anastomosis.

isoperistaltic or antiperistaltic anastomosis is created with a 60 mm GIA stapler and it is reinforced with continuous suture. In IA, the entire procedure (vascular ligation, colon and ileum section and anastomosis) is performed intracorporeally: ileum and the transverse colon are transected using an Endo-GIA stapler and the piece is placed over the liver. Ileum and colon are moved close, an enterotomy is performed (**Figure 5**) to allow insertion of stapler.

A side-to-side isoperistaltic or antiperistaltic anastomosis is created with the 60 mm endostapler; after that, the enterotomy is closed with continuous suture as shown in **Figure 6** (by Stein and Bergamaschi [5]). In this phase, we usually use 2–0 prolene). In **Figure 7** is showed the final result of intracorporeal ileocolic anastomosis.

The specimen is extracted through a Pfannenstiel incision, which is protected with an Alexis device. After performing anastomosis, 2 tubular drainages are placed: one of them near to anastomosis and the other in pelvic cavity. These devices can be removed, if no complications occurred, 3–5 days after surgery [6].

3. Intracorporeal or extracorporeal anastomosis: differences in clinical outcome

When an anastomosis has been performed, the main complication that surgeons try to avoid is anastomotic leakage (AL) which means that bowel content can move from bowel lumen into abdominal space. In EA, despite the entire operation is carried out laparoscopically, the anastomosis is comparable to that performed during open surgery. The IA has been proved safe by several study, showing no statistically significant difference in AL rate between IA and EA [7]. A recent international snapshot audit [8] has identified 3 surgeon-dependent variables significantly associated with AL: duration of surgery, surgical approach, and anastomotic technique. Regarding duration of surgery, operating time varied widely: Magistro et al. [9] reported a significant longer duration of surgery for IA. Although the IA technique is retained faster by some [10], most studies showed no significant difference. However, it has been shown that the learning curve plays a major role in reducing the operative time [11].

Laparoscopic approach decreases morbidity and mortality after colorectal resection [4, 12]. Similarly, a laparoscopic approach is associated also with a lower AL rate compared with an open approach [8]. Considering anastomotic technique, the last Cochrane review [13] concluded that stapled ileocolic anastomosis was associated with fewer leaks than handsewn anastomosis. Two large observational

studies [14, 15] showed that the stapled technique is an independent risk factor for ileocolic anastomotic leak. Future large, randomized controlled trials are needed to identify the best anastomotic technique. To the authors' knowledge in 2018 has been proposed a study protocol for a randomized controlled trial IA versus EA in which primary endpoint is to compare hospital stay and secondary endpoints are intraoperative and postoperative events included AL. The results os this study will be available in 2021, depending on the volume of patients.

Surgical site infection (SSI) is reported in several case series; a meta-analysis by Ricc et al. reported a reduced risk of wound infection in favor of IA. The higher incidence of infection at the extraction site incision in EA anastomosis may be due to wound contamination during exteriorization of the bowel ends and performing the anastomosis through the incision [16].

The length of incision is another factor that influence morbidity after laparoscopic surgery: patients who had an EA were more likely to develop incisional hernia due to the longer incision required for specimen extraction and anastomosis: in EA group the extraction site is about 2.2 cm longer than IA group. Beside its length, the location of the extraction site incision may favor the development of incisional hernia. This was most frequently observed in cases of midline incision in the EC group, as compared to the IC group, where a Pfannenstiel incision was preferred [17]. Moreover, shorter incision is associated to less postoperative pain which result in early recovery after surgery [18].

Gastrointestinal function, demonstrated by time to first flatus and time to bowel movement, resume sooner in IA group than EA.

The technical challenges of EA may explain the earlier recover observed in the IA group. Indeed, delayed recovery of GI function may arise from traction on the bowel ends and mesentery needed to allow complete mobilization of the transverse colon during EA [17]. A recent RCT supports this hypothesis [19] by showing a significantly less surgical stress response after IA. Interleukin-6 and C-reactive protein levels were indeed markedly lower in this group.

Another aspect of intracorporeal ileocolic anastomosis which deserve to be studied is the configuration between ileum and colon. The anastomosis can be carried out in isoperistaltic or antiperistaltic configuration. ISOVANTI randomized clinical trial, performed in 2017 and published in 2018, has compared iso- and antiperistaltic configuration in order to understand if there is any difference in postoperative outcome. The results show that no differences were found in conversion rate, total operative time, and global complication rates after applying Clavien-Dindo's classification. Regarding functional results, the antiperistaltic group showed better results than the isoperistaltic group with less time to first flatus, less time to first stool and shorter time to satisfactory oral intake with statistically significant differences in all cases. However, this fact did not reduce hospital stay and there was no difference between both groups [20].

4. Conclusions

In the last few years a large number of studies was performed to understand if intracorporeal anastomosis were safe and associated with less morbidity and mortality. As we exposed above, IA is now considered safe from surgical and oncological point of view as long as colorectal surgeon had trained on it. Regarding morbidity and mortality, **Table 1** summarizes differences in IA and EA group published by Ricci et al. [16].

Regarding duration of surgery, some studies report that IA is associated with longer operating time but others found no differences between IA and EA group.

Outcome of interest	Intracorporeal	Extracorporeal	P value
Anastomotic leakage (%)	29 (3.4)	39 (4.6)	0.120
Operative time (min)	129 ± 32	121 ± 38	0.460
SSI (%)	39 (4.9)	71 (8.9)	0.030
Internal hernia (%)	0 (0)	3 (2.3)	0.440
First flatus (days)	2 ± 1	2 ± 1	0.110
First defecation (days)	3 ± 1	4 ± 1	0.110
Hospital stay (days)	5 ± 5	5 ± 4	0.004
Overall morbidity	176	231	0.009
Overall mortality	0	5	0.320

Table 1.
Differences in IA and EA group.

This variance could be explained with different level in laparoscopic surgery training in addition to various number of patient treated per year: when anastomosis is performed by trained colorectal surgeon, there is no significant difference in duration of surgery.

IA showed better outcome in anastomotic leakage rate, surgical site infection rate, development of incisional hernia, postoperative pain and recovery of gastrointestinal function. All these aspects can explain the difference in length of hospital stay, that is reported shorter in IA as compared to EA by all most recent meta-analysis and clinical trial [7, 16, 17, 21, 22].

Unfortunately, all currently available data are too uneven to be compared; further randomized controlled trial with homogeneity in surgeons training and large number of patient should be performed to understand the real advantage of IA.

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Section 4

Frontiers in Oncology

Chapter 6

Indocyanine Green Fluorescence in Colorectal Cancer

Elvis Vargas and Cesar Ginesta

Abstract

Fluorescence vision using indocyanine green is a surgical tool with increasing applications in colorectal cancer surgery. This tool has received acceptance in several disciplines as a potential method to improve visualization of the surgical field, improve lymph node resection and decrease the incidence of anastomotic leaks (ALs). In colorectal surgery specifically, some studies have shown that intraoperative fluorescence imaging is a safe and feasible method to evaluate anastomotic perfusion, and its use could affect the incidence of anastomotic leaks. Currently, controlled trials are carried out to validate these conclusions, as well as new indications for indocyanine green such as detection and guidance in the management of hepatic colorectal metastases, visualization of ureters and even as tumor marking and improvement the lymph node harvest of early tumors. These advances could offer great value to surgeons and patients, by improving the accuracy and results of cancer resections.

Keywords: indocyanine green fluorescence, colorectal cancer surgery, anastomotic leaks, tumor marking, lymph node harvest

1. Introduction

Some basic concepts are necessary to define as Fluorescence, which is a form of luminescence, that is, it is a process of light emission, caused by an energy, in this case it is by ultraviolet rays and that said energy is absorbed in form of electromagnetic radiation to later be emitted in the form of wavelengths and thus can be captured by an image system.

And what is the Indocyanine green? (ICG). As it is a colorant that is soluble in water and has a spectral absorption of light of approximately 800 nanometers, this spectrum is capable of binding both oxygenated and reduced hemoglobin and has 5 pharmacological characteristics: one that is not metabolized by therefore it is considered almost inert by binding to plasma proteins. Two, which is eliminated by a concentration gradient, that is, passively. Three, it is eliminated by the hepatocyte into the bile canaliculi. Four, it does not suffer from enterohepatic circulation and fifth, that its use is clearly diagnostic and not curative since its approval by the FDA in 1960 when Fox IJ of Mayo Clinic [1], showed in a work the physical and metabolic properties of this substance and its use diagnosis in liver diseases, ophthalmological, cardiac, neurological, etc.

Colorectal Cancer is the 4th most frequent in the USA, more than 135,000 new cases are diagnosed per year, of which 95,500 are colon and almost 40,000 rectal, with an estimated and unfortunate mortality of more than 50,000 cases, that is,

approximately 35% [2] . In Spain, despite the fact that a little more than 41,000 cases per year of colorectal cancer are diagnosed according to the Spanish society of medical oncology (SEOM), it constitutes the first cancer in incidence in that country, logically due to the demographic density - incidence relationship and with a mortality close to 25% [3].

Another concept we must handle is anastomotic leakage because as we all know the standard care in colon and rectal cancer to date is surgery, before or after neo-adjuvant treatment. And what is an anastomotic leak?. Since a very simple concept is the one proposed in 1991 by the study group of surgical infections in the United Kingdom [4], where it comments that "it is the escape of luminal content from the surgical union between two hollow viscera". Concept that seems very simple, but that generates a lot of controversy at least in the literature where they talk about the subject, because these works are not homogeneous many times at least in the diagnosis of this entity since there may be an anastomotic leak, for example radiological, It is that detected in imaging studies performed routinely, without the patient showing signs or clinical symptoms, but does not require changes in management. To give an example, it is the typical case of the patient who has been left with an ileostomy or protective colostomy and before closing or restoring it, imaging studies are performed and a leak is detected or the patient who is performed due to postoperative leak prevention protocols blood markers such as C-reactive protein, procalcitonin or other acute phase reactants that, despite the patient being asymptomatic, can lead to imaging studies. It can also be an anastomotic leak with a minor clinic where the patient presents intestinal or purulent discharge from the wound or drainage, associated with fever, leukocytes, presence of abscess. And they do not require surgical intervention at least initially, but lengthens the hospital stay, the use of antibiotics, the need for percutaneous drainage, endoscopic procedures, etc. And the anastomotic leak that already presents with greater symptoms, that is, with more spectacular symptoms due to a degree of severe disruption of the anastomosis and that does require surgical intervention.

And how frequent is an anastomotic leak in colorectal surgery? This will depend on the anastomosed segment. And according to this multicenter and prospective study carried out in Europe [5], the leak rate of an ileocolic anastomosis varies between 1 to 18%, of the colo-colonic between 2 to 13%, ileo-rectal between 3 to 11% and colorectal or coloanal between 5 to 21%, although on average the Spanish Rectal Cancer Project carried out in the main colorectal surgery units in Europe showed an average leakage rate for rectal anastomosis of 10% [6]. And well, the anastomotic leak is associated with a large increase in morbidity and mortality, therefore it is the most feared complication by every surgeon and any health system in the world due to expenses that generates that are calculated that they are approximately between 1.6 to 5 million Euros per year or 40,000 € approximately per patient [7].

And what are the risk factors for an anastomotic leak to occur? They are preoperative risk factors that generally depend on the patient and that are many but the most important seem to be obesity, age, sex, tobacco, alcohol, steroids, non-steroidal anti-inflammatory drugs, nutritional status, type of ASA, tumor size, the performance of chemo or radiotherapy previously and intraoperative factors that depend a lot on the surgeon and that perhaps are the ones that we can intervene or modify with some exceptions such as the distance from the anal margin, since the closer the greater the risk, but if we could modify, for example, the duration of the intervention, perioperative sepsis or need for transfusion, the performance of protective stomas that are known not to reduce the incidence of anastomotic leaks, but if the severity of their presence, the intestinal preparation that some studies say that there are no differences with their use, but others who speak that if especially when using them with antibiotics and especially orally, this for a reason perhaps

from the gut microbiota. And another very important factor is the quality of the anastomosis that we perform, because as we all know it must be tension-free and adequately vascularized, regardless of whether it is handsewn or mechanical. In addition to predicting the risk of anastomotic leak, there are many scales in the literature, some that predict morbidity and mortality and indirectly the risk of leak, such as the ASA, APACHE, POSSUM and others more specific such as the Dekker Score or Colorectal Leak Score (CLS) [8], which is perhaps the most used that it consists of 11 items that score the patient between 0 and 41, with a high risk of AL being a score greater than 11; this with a sensitivity of 67% and Specificity of 89%; However, on the internet, very practical and easy scales and calculators are available, such as the www.anastomoticleak.com [9] and the real-score that is specific for rectal cancer [10].

Now, how do we evaluate intraoperatively that our anastomosis is fine and that it will not leak? Well, there is a subjective assessment such as the visualization of the anastomosis, with the fingers we evaluate the caliber, the color of the serosa and the mucosa, which bleeds when cutting the intestine, palpating the pulses of the Riolano arch, etc. But unfortunately demonstrated by many works and corroborated by Karliczek in 2009 [11], the prediction of AL with these methods is very low and he recommends in his work to carry out some other tests to make a more objective assessment and here they enter by for example, the verification of donuts when we use mechanical suture, air leak test or with methylene blue as sometimes used by some bariatric surgeons and or the performance of intraoperative endoscopy. Regarding air leakage, in a systematic review and meta-analysis published in 2016 by a Chinese group [12], they showed that ALs are lower in patients who undergo the test vs. those who do not, but that it is not statistically significant and that when the air test is positive that this occurred according to the review of the multiple works on the subject between 1.5 to 24.7%, the AL is higher 11.4% vs. 4.2% in those that is negative. And this is the reason why it continues to be used because in the cases that are positive, some measure must be taken, be it reinforcement of the anastomosis, performance of protective ostomies or replacement thereof.

The performance of intraoperative endoscopy, this allows us to evaluate the air leak, the staple line, presence of bleeding or areas of ischemia. In fact, there is a classification in degrees proposed by Alessio Pigazzi et al. [13] of the University of Irving, California. Grade I is an anastomosis with the pink mucosa, well perfused through the entire staple line. Grade II there is ischemia or congestion in less than 30% on one side of the anastomosis and Grade III there is ischemia or congestion in more than 30% on one side of the anastomosis or any degree on both sides. In this work with 110 patients with rectal anastomosis who underwent endoscopic evaluation, 96 being Grade I, that is, normal, 10 were Grade II and 4 patients were Grade IIII. Of these 4, all were taken to Grade I, that is, the anastomosis was redone. And the percentage of leakage was 9.78% for the normal ones, that is grade I, that is 9 patients out of 96. Of 40% in Grade II, that is 4 patients out of 10 and 0% in grades III that they took to GI. What this study showed despite being with few patients is that Grade III patients have to have the anastomosis re-done, Grade II have a very high risk of AL, so some other measure would have to be taken and Grade I despite being normal they escape up to almost 10%; therefore, is it possible to have another method that reduces this risk of AL?

And the answer seems to be yes, and already in 2010, 50 years after the FDA approval of Indocyanine Green, a German group made the first publication on the use of green to prevent anastomotic leaks in colorectal surgery. In this work they included 402 patients divided into two groups. A group who underwent perfusion of the anastomosis with green between 2005 and 2008 and whose leak rate was 3.5% and a retrospective group between 1998 and 2003 who did not evaluate perfusion

with green and whose rate of AL was 7.5%, that is, 4% more than the group with green. This work carried out by the disciples of Dr. Christian Tons was a dedication for him who died in 2008 before its publication, this because he is considered the pioneer of the use of this technology in colorectal surgery and inventor of the first system for this, the IC View® from Pulsion Medical Systems [14].

In these almost 10 years, interesting scientific publications on the subject have begun to appear and also private companies have improved the technology, for example a Canadian commercial company called Novadaq® appears, which is leading, already financed and supported several works in this regard with its system called PINPOINT ™ for laparoscopic surgery or the SPY Elite ™ for open surgery [15]. In fact, this company began to be part of Stryker in 2017. And thus also intuitive since 2016 its latest generation Da Vinci Robot Xi, the Firefly system™ for fluorescence use [16]. Companies like Medtronic®, Storz® among others have also entered the market with this technology.

2. Evolution of ICG in colorectal cancer and literature experience

The first prospective, multicenter study with the use of ICG in prospective colorectal surgery was called Pillar II published in 2015 [17]. Here the utility and feasibility of the use of indocyanine green in left colectomy and anterior laparoscopic rectal resections were evaluated using the PINPOINT™ technology from Novadaq®. Among 11 hospitals in the USA, 139 patients were included, 44% operated for diverticulitis, 25% for rectal cancer and 21% for colon cancer. The feasibility of using green was 99% with 1.4% AL and the interesting thing about the work is that the use of this technology allowed 11 patients, that is, 8% to change the area where the colon was cut due to poor perfusion in the site previously chosen by the surgeon before the placement of green, and specify that of these 11 patients when doing this, none had AL.

In 2017, the first systematic summary and metanalysis with what was published up to that date on the use of green to prevent AL in colorectal surgery was published by Espin et al. [18] in this publication after the exclusion of many methodologically weak studies, they include 5 non-randomized studies with 1302 patients of which 555 were operated using ICG and 747 without ICG. The overall rate of AL in this review was 7.4%, demonstrating that ICG reduces the risk of AL in colorectal cancer with a $p = 0.06$. And specifically, it was seen that in rectal cancer the leak rate in the group with ICG was 1.1% vs. 6.1% in the group without ICG. This with a $p = 0.02$. But it also shows that when analyzing the use of green in both malignant and benign diseases, there are no significant differences in the prevention of leakage with its use. The authors in this review conclude that the literature up to that point is very heterogeneous and that new randomized, randomized and multicenter studies should be carried out for what they propose the ICEBerg Trial [19], a study carried out to evaluate the use of ICG vs. not in colorectal surgery.

Morales Conde et al. published in 2019 a prospective, monocentric study [20], that included 192 patients who were divided into 4 groups. Group A consisted of 67 patients undergoing right hemicolectomy, group B 9 patients undergoing segmental resection of the splenic angle, Group C with 81 patients undergoing left hemicolectomy, and group D with 35 patients undergoing anterior rectal resection. There was a change in the area of colon section in 35 patients, that is, 18.2%, and these were distributed in 4 (6%) of Group A of right hemicolectomy 1 (11%) of group B of segmental resection of the splenic angle, 21 (25.9%) from group C for left hemicolectomy and 9 (25.7%) from group D for anterior resection. The leak rate was 2.6% (5 patients), but none of the AL have been those that were able to change the cut site with the evaluation of the ICG.

In January 2019, another systematic review and meta-analysis on anastomotic tests in colorectal surgery in the new millennium was published that included a total of 11 articles with 3844 patients and where direct analyzes were compared between the control group, that is, the one that was not did no intraoperative leak test (No IOLT) with which it was verified with ICG or with ALT (Air Leak Test) and with IOC (Intraoperative Colonoscopy). This meta-analysis concluded that AL are higher in the No IOLT group, that is, no test compared to green with a p = 0.0004 and also that they are higher when compared with ALT (Air Leak Test) and IOC (Intraoperative Colonoscopy), but these data were not statistically significant [21]. In September Wexner et al. [22] recommend the quadruple evaluation of colorectal anastomoses to achieve the greatest possible safety, doing it in the following way: First ICG to decide the level of the proximal colon cut, second air test to the rectal stump, that is, before doing the anastomosis, third confirmation of the donuts from the self-suturing machine when performing the anastomosis and fourth the intraoperative colonoscopy with white light and again with green to evaluate the perfusion of the mucosa. In this reading it is recommended that what should never be lacking is the green test, but that one test does not discriminate against another.

In 2020 the FLAG randomized trial [23], with 377 cases, 187 had ICG and 190 were in the non-ICG group and they demonstrated ICG did not decrease the rate of AL of high anastomoses (9–15 cm from the anal verge), at 1.3% vs. 4.6% in the non-ICG group (P = 0.37). In contrast, a decrease in AL rate was found for low (4–8 cm) colorectal anastomoses (14.4% in ICG vs. 25.7% in the non-ICG group; P = 0.04).

Currently, some large randomized studies are being carried out such as the PILLAR III [24] and two more which are in the recruitment phase [25, 26], that is expected to have soon any results about this. And on the other hand, they are trying to investigate and elucidate a question that many colorectal surgeons ask themselves. How green should green be? so that we can say that the evaluated tissue is well perfused. And this question is the one that many of the detractors of this technique ask themselves that perhaps creates uncertainty when they face a real-time image with green. And for this the experts in conjunction with the companies are trying to find a solution and for that at least Medtronic® with its new technology called Elevisión® [27], have included a system for quantifying green in percentages, where through colors and on a percentage scale that it goes from 0 to 250% we can quantitatively know the irrigation of each area of the colon (**Figure 1**). And this has already been working and published by plastic surgeons. They have shown when performing a skin flap, that when an area of the flap has more than 33% of the most perfused point, it can be ensured that 88% of cases that area will not be necrotic. And when that value is less than 25% in 90% of the cases it will be necrotic [28, 29]. This is being tried to evaluate and agree, that is, what percentage of perfusion we should have in the colon to decide that it is well vascularized.

Now indocyanine green only serves to assess anastomotic perfusion? And well, although perhaps if it is its most important function, it may have others like the ones we show in a video published by Vargas et al. [30], in the Spanish journal of surgery of a clinical case of upper rectum cancer where we use green not only for the evaluation of the anastomotic perfusion but also for marking the tumor and as a guide at the time of lymphadenectomy, these very important points to achieve an ideal oncological or radical surgery. The important difference with the little-published marking is that we have done the marking by rectoscopy 4 hours before surgery (**Figure 2**), diluting the green ampoule in 100 cc of serum and from there we have injected 0.3 cc to 2 cm at the submucosal level distal to the tumor in order to locate the lesion intraoperatively because it is very small (only 3 cm) and to mark the lymph nodes to be resected as a kind of sentinel lymph node (**Figure 3**). What is

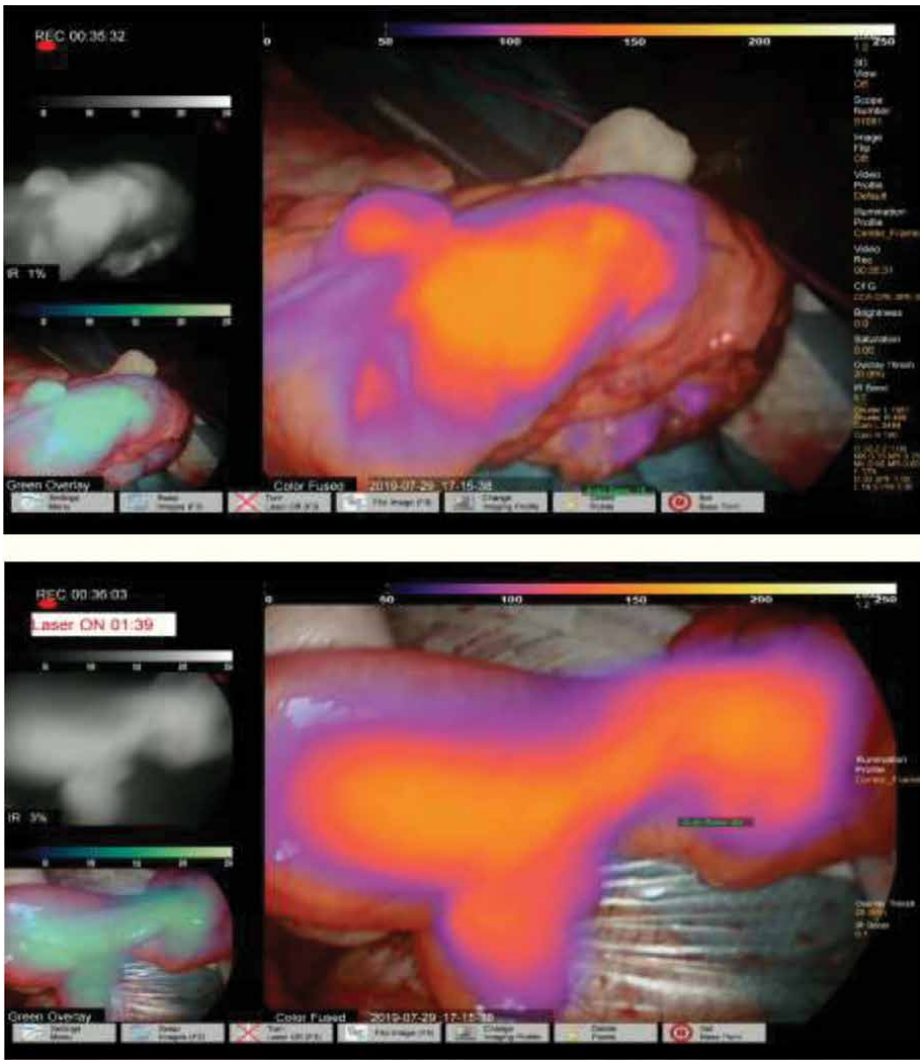

Figure 1.
Quantification of the vascularization of the colon.

published in the literature in this regard are still clinical cases or videos, but there is some experience in the literature regarding lymphadenectomy, especially in right colon tumors with the intention of performing surgery with D3 lymphadenectomy or complete excision of the mesocolon as shown by the work on a clinical case of Complete excision of the mesocolon in a right hemicolectomy using the Firefly fluorescence system of the Da Vinci® robot [31]. Now the injection of green in published cases is performed intraoperative technique of subserosal ICG injection with a fine needle for sentinel lymph node (SLN) [16]. This technique is feasible in very large tumors that can be located without problems via laparoscopy or robotics or that have been previously marked in a conventional way with ink (an important difference with our technique). The studies published to date do not show any statistically significant difference in the number of lymph nodes dissected using marked-oriented lymphadenectomy in advanced tumors but in early colon tumors, that is, T1 or T2. These findings have been demonstrated by Asian groups that have the most experience in this, as shown in a work published in 2015 but using

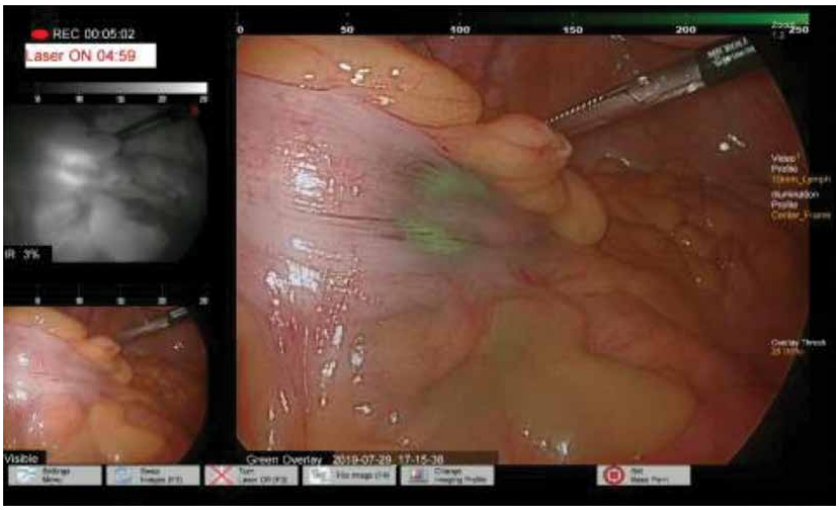

Figure 2.
Location of the tumor marked prior to surgery with ICG.

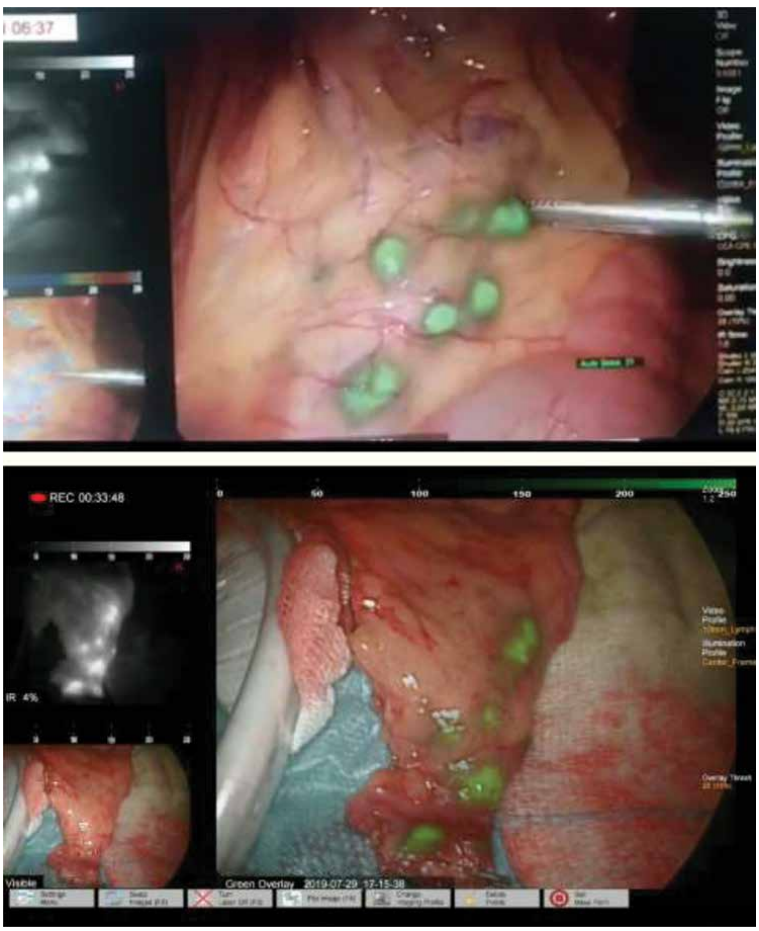

Figure 3.
Lymph node marking with ICG for lymphadenectomy.

conventional ink marking [32] and this other by, which is the only one published to date, used indocyanine green as a marker of the tumor [33]. In middle-low rectal cancer local recurrence greatly affects the treatment efficiency and the survival outcomes for patients with rectal cancer. Lateral pelvic lymph node (LPLN) metastasis (LPNM) is an important factor for local recurrence after surgery in patients with middle-low rectal cancer, and approximately 8.6% to 21.0% of patients with rectal cancer have associated LPNM. As one of the effective treatment methods, laparoscopic LPLN dissection (LPND) can significantly reduce the local recurrence rate compared with simple total mesorectal excision (TME) surgery. In clinical applications, LPND is limited by various complications because the ureters and hypogastric nerves might be damaged without efficient guidance, and for this using ICG improve the dissection increasing the numbers of lymph nodes harvested and decreasing complications [34].

There are also publications of its use in various situations, such as in the Japanese article of August 2019 by et al. [35] where this group devised a Kit that they called IRIS U Kit that allows them to transilluminate the urethra and prostate in transanal total mesorectal excision (TaTME) with the intention of avoiding one of the most feared complications of this technique, which is the injury of the urinary tract. As well as this, there are already published cases of its use, for example, in the transillumination of the ureters in very difficult cases from the surgical point of view, such as big tumors, complicated diverticulitis or pelvic surgery [36]. In 2017, a Belgian Group published a systematic review [37] of the use of green as a guide in the diagnosis and surgical treatment of hepatic or peritoneal metastases of colorectal origin. This work concluded that the use of green facilitates the detection and resection of hepatic and peritoneal metastases of colorectal origin.

3. Conclusions

Anastomotic leaks after colorectal surgery continue to be a serious public health problem; therefore the use of new therapies could minimize this problem.

With regard to standard tests for the prevention of ALs, they continue to be used for the structural evaluation of the anastomosis, but with the knowledge that their efficacy is often insufficient; for this reason the use of fluorescence allows us to evaluate anastomotic perfusion is becoming more and more important every day and gives us greater surgical safety for the benefit of the patient.

In addition, we must remember that the ICG is not only limited to the anastomotic perfusion, new functions begin to emerge, such as its use in tumor marking, lymphadenectomy, location of ureters, urethra, liver and peritoneal metastases, among other functions.

Conflict of interest

The authors declare no conflict of interest.

Appendices and nomenclature

ALS	Anastomotic leaks
ICG	Indocyanine green
SEOM	Spanish Society of Medical Oncology
FDA	Food Drug Administration

ASA	American Society of Anesthesiology
CLS	Colorectal Leak Score
ALT	Air Leak Test
No IOLT	No intraoperative leak test
IOC	Intraoperative Colonoscopy
SLN	sentinel lymph node
LPLN	Lateral pelvic lymph node
LPNM	Lateral pelvic lymph node metastasis
LPND	Laparoscopic lymph node dissection
TME	Total mesorectal excision
TaTME	Transanal total mesorectal excision

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Chapter 7

Landscape of Current Targeted Therapies for Advanced Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is one of the most frequent and lethal cancer types worldwide. While surgery with chemotherapy and radiotherapy remains the only curative approach for localized CRC, for metastatic disease the therapeutic landscape has significantly evolved over the last years. Development and approval of novel targeted therapies, such as monoclonal antibodies against EGFR and VEGF, have significantly increased the median survival of patients with metastatic disease, with some trials reporting a benefit over 40 months. Increasing accessibility of high throughput sequencing has unraveled several new therapeutic targets. Actionable alterations, such as HER2 overexpression, BRAF mutations, and NTRK fusions, are currently available in metastatic disease, providing significant therapeutic opportunities for these patients, while new emerging agents, as immune checkpoint inhibitors, promise better treatment options in the near future. In this chapter, an overview of established and future CRC targeted therapies in the clinical setting is provided, as well as their mechanism of action, limitations, and future applicability.

Keywords: EGFR, immunotherapy, metastatic colorectal cancer, targeted therapy, VEGF

1. Introduction

Colorectal cancer is the third most common cancer worldwide and remains an important cause of death. CRC diagnosis and treatment require a multidisciplinary approach, and in stage IV disease combination chemotherapy (CT) and regional multimodality treatments – like metastasectomy and other local treatments – are increasingly used. Systemic therapy has evolved over the past few decades, with the emergence of combination CT and targeted agents (**Figure 1**).

In the present review, genomic and tumor microenvironment alterations driving treatment selection are discussed.

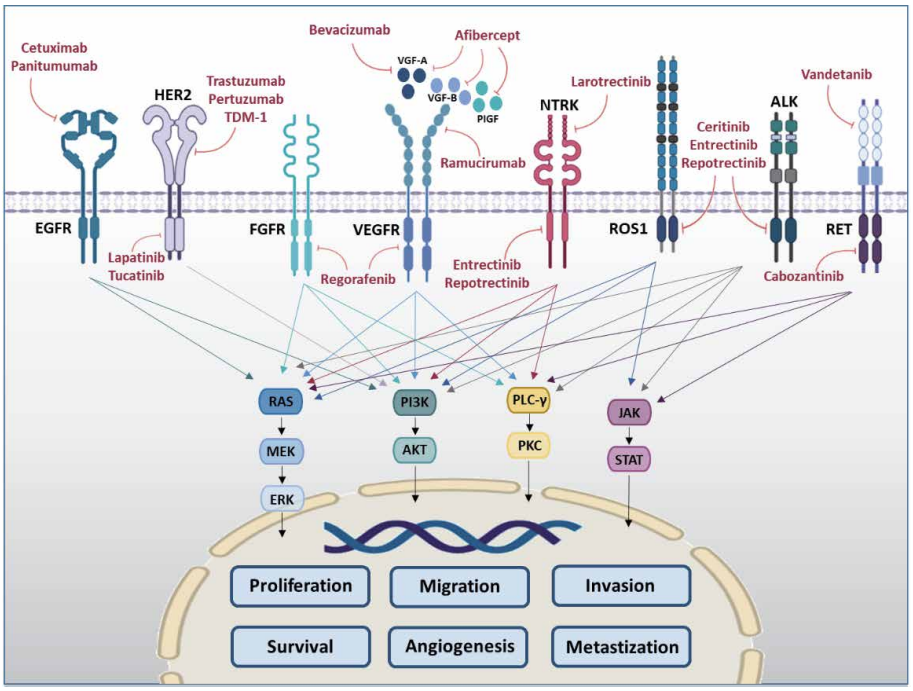

Figure 1.
Targeted therapies that have been approved or are currently under investigation for advanced colorectal cancer.

1.1 Historical background

Metastatic CRC (mCRC) presents with synchronous metastatic disease at initial diagnosis in 20% of cases, with 50–60% of patients developing metachronous metastases. Approximately 56% of patients with CRC will ultimately die from their cancer [1]. The cornerstone of CRC treatment for 20 years has been fluoropyrimidine-based CT doublets, with either irinotecan (FOLFIRI or CAPIRI) or oxaliplatin (FOLFOX or CAPOX) in the first- and second-line settings [2].

In the past two decades, remarkable progress has been achieved in mCRC treatment with the introduction of molecular targeted agents (**Figure 2**). Today, the median overall survival (OS) for these patients in phase III trials is approximately 30 months, more than doubling that of 20 years ago [3]. Simultaneously, mortality has declined, what is attributed to earlier diagnosis (due to screening tests) and improved treatment options, including new systemic CT agents and biologic agents targeting specific pathways [1].

More recently, consensus molecular subtypes (CMS) defined by gene expression profiling have identified biologically different CRC subtypes, which seem to have a prognostic and predictive value. However, CMS subtyping is not a standard test with therapeutic application at present, being more relevant in the research field [2].

2. EGFR pathway

New targeted therapies against the epidermal growth factor receptor (EGFR) had an impressive impact on mCRC prognosis, with an actual median OS over 30 months (varying according to therapeutics options) [4–6].

As part of the ErbB tyrosine kinase family, EGFR is a transmembrane receptor and its activation by extracellular ligands stimulates downstream pathways, such as

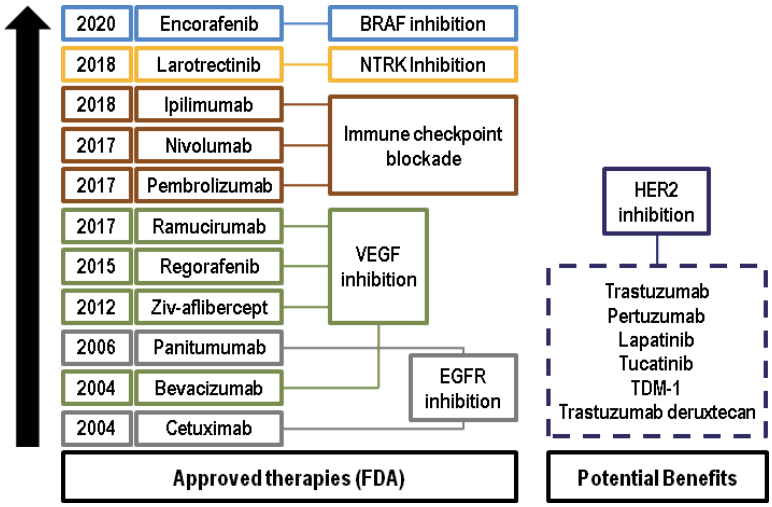

Figure 2.
Timeline of development of targeted therapies in colon cancer.

RAS–RAF–MEK-MAPK, PIK3CA-AKT, the SRC family kinases, PLCγ-PKC, and JAK/STATs, inducing proliferation, migration, invasion, survival, and angiogenesis [6, 7]. Thus, EGFR is an important factor in tumor development and progression, being expressed in various cancers and in 60–80% of CRCs [8].

Target therapy against EGFR is now a standard of care in RAS wild-type mCRC. Two monoclonal antibodies (mAbs) are approved: cetuximab (human-mouse chimeric mAb) and panitumumab (fully human mAb). By recognizing and binding to the extracellular domain of the EGFR receptor, these mAbs prevent binding of other extracellular ligands and subsequent receptor internalization and degradation, thus inhibiting and blocking downstream pathways and signaling [9]. Tumor RAS mutational status predicts efficacy of anti-EGFR agents in mCRC patients, with RAS mutations being a well-established negative predictive biomarker for patient selection [10].

2.1 Clinical trials

Several phase II and III clinical trials have established the efficacy of cetuximab and panitumumab, either in monotherapy or in association with CT, in terms of progression-free survival (PFS), OS, and overall response rate (RR), while maintaining quality of life (**Table 1**) [6, 11–13].

2.1.1 First-line setting

The PRIME trial, a randomized phase III trial investigating the addition of panitumumab to FOLFOX4 as first-line therapy in RAS wild-type mCRC, showed a 2- and 6-month PFS and OS benefit, respectively, with the combination. Regarding safety, known EGFR inhibition adverse events (AE) were more frequently observed with panitumumab, including skin toxicity and diarrhea (36% vs. 2% and 18% vs. 9% in panitumumab and placebo arms, respectively) [11].

The randomized phase II PEAK trial compared the efficacy and safety of mFOLFOX6 plus panitumumab with mFOLFOX plus bevacizumab (an anti- vascular endothelial growth factor [VEGF] mAb) as first-line therapy in RAS wild-type mCRC. The study primary endpoint was met, with panitumumab showing a 3.5-month PFS increase compared with bevacizumab. An OS improvement was also

observed, although not statistically significant [14]. Rivera et al. and Stintzing S et al. also demonstrated that early tumor shrinkage in an important and early predictor of treatment sensitivity and deep tumor response correlates with OS [15, 16].

The open-label phase II PLANET-TTD trial compared panitumumab with two different CT regimens (FOLFOX 4 and FOLFIRI) as first-line treatment of RAS wild-type mCRC, but no significant efficacy differences were observed between the two regimens [17].

The 314 trial, a single-arm phase II study evaluating first-line panitumumab plus FOLFIRI in mCRC patients, confirmed the impact of KRAS exon 2 status in being a negative predictor of efficacy in mutant patients. In a total of 154 patients, 59% had KRAS wild-type tumors. RR and median duration of response (DoR) were higher in the KRAS wild-type group. Additionally, more patients in the wild-type group underwent R0 resection (8% vs. 5%), and a PFS benefit was also observed in this group (8.9 vs. 7.2 months) [18].

In the COIN trial, cetuximab was added to oxaliplatin-containing CT (FOLFOX or CAPOX) in first-line setting of mCRC. In patients with KRAS wild-type tumors, no OS or PFS difference was reported between the two groups, while overall response rate (ORR) was higher with the addition of cetuximab to CT compared to CT alone [19].

Similar ORR results were seen in the OPUS trial. In KRAS wild-type tumors, the addition of cetuximab to FOLFOX-4 was associated with a clinically significant increased chance of response and a lower risk of disease progression. The same results were not seen in the overall population, confirming the relevance of KRAS mutational status [12].

Although the addition of cetuximab to oxaliplatin-containing CT had little survival impact, the CRYSTAL trial showed different results when combining cetuximab to FOLFIRI. A borderline significant PFS increase was seen in the combination arm, although with no OS differences. However, when KRAS mutational status was considered, a significant PFS increase was observed favoring cetuximab [20].

Additionally, in the phase III open-label FIRE-3 trial, cetuximab was compared with bevacizumab, both in combination with FOLFIRI. No differences were observed in the primary endpoint of ORR or in PFS, but the median OS was improved in cetuximab arm [21].

Cetuximab was further compared with bevacizumab, both combined with CT (FOLFOX or FOLFIRI), in the CALGB 80405, with no significant differences in ORR, PFS, or OS [22].

2.1.2 Second- and subsequent-line setting

In the 181 trial, the efficacy and safety of adding panitumumab to FOLFIRI was compared with FOLFIRI alone in RAS wild-type mCRC patients who had failed the initial treatment. Addition of panitumumab to the regimen resulted in a significant PFS improvement, of approximately 2 months. Although not significant, a trend towards an OS benefit was seen with the addition of panitumumab [23].

Conversely, the randomized open-label PICOLLO trial reported no benefit with the addition of panitumumab to irinotecan after progression on fluoropyrimidine, with or without oxaliplatin. However, better PFS and more responses were reported in the panitumumab group [24].

In 2004, Saltz et al. and Cunningham et al. evidenced the role of cetuximab in heavily pretreated patients. Saltz et al. reported a median OS of 6.4 months and a median PFS of 1.4 months in 57 patients receiving cetuximab monotherapy after

progression on irinotecan, and a tumor RR of 8.8% [25]. Cunningham et al. included over 300 patients and investigated the role of cetuximab (with or without irinotecan) after progression on irinotecan. A PFS and ORR benefit was observed, with a numeric but not statistically significant difference also observed in OS (8.6 vs. 6.9 months) [26].

Later, the randomized phase II ASPECCT trial compared panitumumab alone with cetuximab alone as third-line treatment for mCRC patients with RAS wild-type (exon 2) tumors. With OS as primary endpoint, panitumumab was given at a dose of 6 mg/Kg every two weeks and cetuximab at a loading dose of 400 mg/m^2, followed by a weekly dose of 250 mg/m^2. No efficacy differences were observed, with a median OS of 10.4 months for panitumumab and 10.0 months for cetuximab [27].

Setting	Study	Treatment	RR□, %	PFS□, months	OS□, months
1st line	PRIME	PAN+FOLFOX4	59*	10.1*	26.0*
		FOLFOX4	46*	7.9*	20.2*
1st line	PEAK	PAN-mFOLFOX6	64	13.0*	41.3
		mFOLFOX6	61	9.5*	28.9
1st line	PLANET-TTD	PAN-FOLFOX4	74	12.8	39.0
		PAN-FOLFIRI	67	14.8	45.8
1st line	314	PAN-FOLFIRI	RASwt: 56* RASmt: 38*	RASwt: 8.9* RASmt: 7.2*	NR
1st line	COIN	CET-OXAL	64*	8.6	17.9
		OXAL	57*	8.6	17.0
1st line	OPUS	CET-FOLFOX4	61*	8.3*	22.8
		FOLFOX4	37*	7.2*	18.5
1st line	CRYSTAL	CET-FOLFIRI	46.9*	9.9*	24.9
		FOLFIRI	38.7*	8.7*	21.0
1st line	FIRE-3	CET-FOLFIRI	62.0	10.0	28.7*
		BEVA-FOLFIRI	58.0	10.3	25.0*
1st line	CALGB 80405	CET-FOLFOX/FOLFIRI	59.6	10.5	30.0
		BEVA-FOLFOX/ FOLFIRI	55.2	10.6	29.0
2nd or greater	181	PAN-FOLFIRI	36*	5.9*	14.5
		FOLFIRI	10*	3.9*	12.5
2nd or greater	PICOLLO	PAN- CPT-11	34*	HR 0.78*	10.4
		CPT-11	12*		10.9
2nd or greater	Saltz, 2004	CET	8.8	1.4	6.4
2nd or greater	Cunningham, 2014	CET + CPT-11	22.9*	4.1*	8.6
		CET	10.8*	1.5*	6.9
2nd or greater	ASPECCT	PAN	22.5	4.1	10.4
		CET	20	4.4	10.0

BEVA, bevacizumab; CET, cetuximab; CPT-11, irinotecan; mt, mutated; NR, not reported; ORR, overall response rate; OS, overall survival; OXAL, oxaliplatin-containing chemotherapy regimen; PAN, panitumumab; PFS, progression-free survival; wt, wild-type.
□Results for the KRAS wild-type subgroup, except if clearly stated.
**Difference between groups is statistically significant ($p < 0.05$).*

Table 1.
Targeted therapies against EGFR in colorectal cancer.

2.1.3 Maintenance/treatment intensification

Regarding maintenance and treatment intensification, three clinical trials are worth mentioning: VOLFI, VALENTINO, and SAPPHIRE.

VOLFI was a randomized open-label phase II trial comparing the addition of panitumumab to FOLFOXIRI CT regimen. An ORR of 87,3% was seen in the FOLFOXIRI plus panitumumab arm, which was higher compared with FOLFOXIRI alone. PFS was similar in both arms, whereas OS showed a trend in favor of panitumumab [28]. This was the highest ORR reported in mCRC, suggesting that these protocols can be considered to obtain maximum cytoreduction in selected patients.

The VALENTINO trial, an open-label phase II trial, investigated maintenance therapy with panitumumab (induction therapy with FOLFOX-4 + panitumumab followed by maintenance with panitumumab ±5FU/LV). The study hypothesis that panitumumab alone was not inferior to the combination as maintenance therapy could not be proven. ORR and OS results did not differ between the two arms [29].

In the SAPPHIRE trial, patients received six cycles of mFOLFOX6 plus panitumumab as induction therapy. Patients who completed induction therapy without progression were then randomized to mFOLFOX6 plus panitumumab (group A) or 5-FU/LV plus panitumumab (group B). PFS, RR, OS, and time to treatment failure were similar between groups, adding to the concept that planned discontinuation of oxaliplatin after six cycles of mFOLFOX6 is a potential treatment option for mCRC patients, achieving similar efficacy while reducing oxaliplatin-associated peripheral neuropathy compared with mFOLFOX6 plus panitumumab [30].

2.2 Resistance mechanisms

Although anti-EGFR therapy has shown benefit in a particular subgroup of CRC patients, primary or innate resistance is high among unselected patients. Furthermore, even patients that initially respond to cetuximab and panitumumab, eventually develop resistance and relapse under these therapies (secondary resistance). Knowledge of the resistance mechanisms associated with the EGFR pathway is crucial to improve therapy efficacy.

2.2.1 RAS-RAF *mutations*

RAS–RAF-MAPK is an EGFR direct downstream signaling pathway, highly deregulated in CRC. Mutations frequently found in these family members generally lead to protein constitutive activation independently of the upstream signaling cascade. Over the last decade, analysis of retrospective clinical trial data (in particular of the OPUS, CRISTAL, and PRIME trials) led to the discovery that patients harboring *RAS* (*KRAS* and *NRAS*) and *BRAF* (specially V600E) activating mutations do not benefit from cetuximab and panitumumab treatment, and that it could even be detrimental for them [31]. These results have led the European Medicines Agency (EMA) and Food and Drug Administration (FDA) to recommend against the use of EGFR-targeted therapies in patients harboring *RAS* and *BRAF* mutations. These mutations are currently the only clinically validated predictive marker of resistance to anti-EGFR therapies in CRC.

2.2.2 PIK3CA *gene and PTEN expression*

Although *RAS* and *RAF* mutations are effective in predicting resistance, not all wild-type patients respond to cetuximab and panitumumab. The EGFR receptor also signals through the PI3K-AKT pathway, resulting in tumor cell proliferation

and survival [32]. Retrospective studies of cetuximab treatment in chemorefractory metastatic CRC patients revealed that *KRAS* wild-type patients with *PIK3CA* mutations in exon 20 (but not in exon 9) have lower response rates compared to unmutated patients (0.0% vs. 36.8%; 95% confidence interval [CI] 0.00–0.89; p = 0.029) [33]. PTEN is another potential marker of response to anti-EGFR therapy, given its inhibitory role on PI3K-AKT signaling pathway. Although PTEN studies are scarce and inconclusive, some works suggest that loss of PTEN expression (measured by immunohistochemistry [IHC]) is associated with decreased RR, PFS, and OS in metastatic CRC patients treated with anti-EGFR therapy [34, 35].

2.2.3 Other resistance pathways

Evidence from cellular studies has suggested that constitutive activation of other EGFR downstream pathways, such as those including the JAK–STAT family, are implicated in resistance to the anti-EGFR gefitinib [36, 37].

Additionally, amplification of other receptor tyrosine kinases (RTKs) has been proposed as a resistance mechanism to anti-EGFR therapies. Expression of VEGF-1 or its receptor (VEGFR) has been associated with cetuximab resistance in both preclinical models and metastatic CRC patients [38]. Bertotti et al. reported that human epidermal growth factor receptor 2 (HER2) gene amplification correlated with cetuximab resistance in a patient-derived xenograft mouse model [39]. Besides HER2, also HER3 has been described to have a role in resistance mechanism to EGFR-targeted therapies. In a cohort of metastatic CRC patients treated with irinotecan and cetuximab, HER3 overexpression was associated with lower PFS and OS [40].

Finally, growing evidence implicates the MET pathway in both primary and secondary resistance mechanisms to mAbs in *KRAS* wild-type patients, through MET amplification or hepatocyte growth factor (HGF) increased expression [41]. In a randomized phase II clinical trial of chemorefractory *KRAS* wild-type anti-EGFR-naïve patients, the combination of anti-HGF mAbs and panitumumab led to higher RR and a trend towards better outcomes in the population with MET overexpression [42].

2.3 BRAF

Although RAS mutations are negative predictors of efficacy in cetuximab and panitumumab treatment, it is acknowledged that not all RAS wild-type patients respond to these agents. To investigate this, research efforts were driven downwards in the MAPK pathway, putting the spotlight on BRAF. This is the main effector in EGFR pathway and is usually mutated in 5–10% of mCRC patients. BRAF and KRAS are usually mutually exclusive, with BRAF V600E mutation (class I) accounting for most alterations found and conferring worse prognosis to these patients.

Regardless of EGFR blockade, BRAF mutations can keep the downstream signaling persistently activated, suggesting that they can confer EGFR blockade resistance. In fact, in a retrospective trial, De Roock et al. showed that chemorefractory mCRC patients with *BRAF* V600E mutations have significantly lower RR to cetuximab than patients with wild-type tumors (8.3% vs. 38.0%; odds ratio 0.15; p = 0.0012) [43]. Several multicentre trials and meta-analyses have subsequently confirmed that *BRAF* V600E mutation results in shorter PFS and OS compared to the wild-type phenotype, emphasizing its role in resistance to anti-EGFRs in patients with chemorefractory mCRC.

Multiple combinations with drugs targeting the MAPK pathway have been tested in BRAF-mutant CRC. Monotherapy results were disappointing when compared to the clinical activity seen in melanoma. In contrast to melanoma, CRC expresses high levels of activated EGFR, which reactivate the MAPK pathway after

single BRAF inhibition [44, 45]. In view of the possibility of therapy resistance via EGFR signaling feedback activation, the trial was amended to include safety and efficacy assessment of vemurafenib combined with cetuximab in a heavily pretreated population, with positive results (median PFS of 3.7 months and median OS of 7.1 months). Similar results were observed when combining dabrafenib with panitumumab (median PFS of 3.5 months) and encorafenib with cetuximab (RR of 23.1%, median PFS of 3.7 months), with phase II results of the latter showing a median PFS of 4.2 months and an ORR of 22% [46].

CT was also combined with BRAF and EGFR inhibition in a phase II trial of irinotecan, cetuximab, and vemurafenib. A total of 106 patients were enrolled, with the study reporting a PFS benefit of 4.3 months with the addition of vemurafenib compared to 2.0 months in the control arm [47].

BRAF inhibition can also induce EGFR overactivation or PI3K modulation, and triplet combos targeting EGFR, MAPK, and PI3K have shown positive results. The MEK116833 trial included 24 patients receiving full-dose combination of panitumumab, trametinib, and dabrafenib and reported an ORR of 21%, a median PFS of 4.1 months, and an OS of 9.1 months. Additionally, a randomized phase II trial combining encorafenib, cetuximab, and the PI3K inhibitor alpelisib reported a median PFS of 5.4 months and an ORR of 27% in interim analysis [48–51].

More recently, the phase 3 BEACON trial investigated the doublet of encorafenib plus cetuximab and the triplet of encorafenib plus cetuximab plus binimetinib in patients with *BRAF*-mutant CRC after one or two prior regimens. The updated analysis confirmed an ORR of 27% with the triplet versus 20% with the doublet versus 2% in the control arm. Median OS was 9.3 months with the duplet and 5.9 months in the control group (hazard ratio [HR] 0.61). The benefit was seen across all subgroups. Numerically identical median OS was observed when comparing the triplet and doublet, with higher toxicity for the triplet (mainly gastrointestinal toxicity and anemia). Subgroup analysis suggested survival benefits in some subgroups, such as those with ECOG 1, three or more organs affected, and higher levels of C-reactive protein and with unresected primary tumors, suggesting that patients with higher disease burden and inflammatory drive could benefit from triple therapy. PFS was also comparable between doublet and triplet and clearly superior to the control arm [52, 53].

2.4 HER2-amplified CRC

HER2 is a growth factor receptor involved in CRC development and progression. HER2 amplification is relatively uncommon, reported in only 3–5% of metastatic CRC patients with wild-type KRAS and wild-type BRAF [54].

Trastuzumab is a monoclonal antibody targeting HER2. The phase II HERACLES trial included mCRC patients with KRAS wild-type, HER2-positive (defined as 2+/ 3+ HER2 score in >50% of cells by IHC or HER2:CEP17 ratio > 2 in >50% of cells by fluorescent *in situ* hybridization [FISH]) tumors who were refractory to standard therapy with EGFR inhibitors and were treated with trastuzumab and lapatinib. ORR was 30%, with one complete response, and median OS was 46 weeks [55]. The most common AEs were diarrhea, rash, and fatigue (78%, 48%, and 48%, respectively). These findings suggested that HER2 positivity was an important driver in CRC. In the phase IIa multi-basket MYPATHWAY trial, patients with HER2-amplified tumors (including CRC) received dual blockade therapy with pertuzumab and trastuzumab. Preliminary results showed promising response, with an ORR of 37.5%, and suggested durable responses with HER2-targeting agents, with a median DoR of 11 months [56].

Both the TRIUMPH (trastuzumab and pertuzumab) and MOUNTAINEER (trastuzumab and tucatinib) trials reported high response rates (35% and 52%,

respectively) and encouraging median PFS (4.0 and 8.1 months, respectively), supporting dual HER2 blockade in patients with HER2-amplified metastatic CRC [57, 58]. Conversely, the combination of pertuzumab and TDM-1 did not show an enhanced objective response in the HERACLES-B trial, although achieving a similar disease control to the HERACLES-A trial (ORR of 10% and median PFS of 4.8 months at cut-off) [59].

Regarding new antibody-drug conjugates, the phase 2 DESTINY-CRC01 trial, of trastuzumab deruxtecan (T-DXd; DS-8201) and also in patients with metastatic HER2-amplified CRC, reported significant responses (ORR of 45.3%, disease control rate [DCR] of 83%), including in patients previously submitted to HER2 blockade [60].

3. VEGF pathway

Tumor angiogenesis is one of the hallmarks of cancer and a key process in tumor development [61, 62]. One of the most relevant pathways involved in angiogenesis is the vascular endothelial growth factor/vascular endothelial growth factor receptor (VEGF/VEGFR) signaling pathway. VEGF-A is a heparin-binding glycoprotein with potent angiogenic activity. VEGF is produced by different cell types, such as immune cells, fibroblasts, and cancer cells, in response to tumor hypoxia via hypoxia-inducible factor (HIF)-1a pathway, inducing an angiogenic switch [63]. Overproduction of pro-angiogenic growth factors leads to formation of chaotic blood vessels in the tumor, with a leaky endothelial wall [64].

3.1 VEGF inhibition in mCRC

In CRC, primary tumor growth and distant metastases development are highly dependent on new vessel formation, making VEGF signaling pathway an attractive therapeutic target. Inhibition of VEGF signaling pathway can be achieved through neutralizing antibodies binding VEGF ligands or blocking VEGFR, or tyrosine kinase inhibitors (TKIs) blocking intracellular VEGFR-dependent signaling [65].

Bevacizumab. The first angiogenesis inhibitor approved for mCRC was bevacizumab, an immunoglobulin G (IgG)1 monoclonal antibody with affinity to VEGF-A. Several trials have evaluated the benefit of adding bevacizumab to cytotoxic regimens as first-line treatment of patients with mCRC, with inconsistent PFS and OS results (**Table 2**).

A phase III trial conducted by Hurwitz et al. compared the efficacy of irinotecan, bolus fluorouracil, and leucovorin (IFL) plus bevacizumab versus IFL plus placebo in untreated mCRC patients. Bevacizumab was intravenously administered at a dose of 5 mg/kg every two weeks along with CT. Bevacizumab arm showed a meaningful improvement in OS (20.3 versus 15.6 months in placebo arm) and PFS (10.6 versus 6.2 months in placebo arm) [66]. Saltz et al. assigned mCRC patients in a 2x2 factorial design to receive CAPOX or FOLFOX4 followed by bevacizumab or placebo as first-line treatment. Median PFS was higher in the bevacizumab group compared with placebo (9.4 versus 8.0 months). OS differences did not reach statistical significance, but only 29% of bevacizumab recipients were treated until disease progression or toxicity [67]. For elderly patients with untreated and unresectable mCRC not candidates for oxaliplatin- or irinotecan-based therapies, the phase III AVEX trial compared the efficacy and safety of capecitabine combined with bevacizumab versus capecitabine alone. Capecitabine was given at a dose of 1000 mg/m^2 orally twice a day on days 1–14 and bevacizumab was administered intravenously at a dose of 7.5 mg/kg on day 1, every 21 days. Longer PFS was

documented in the bevacizumab arm (9.1 versus 5.1 months for capecitabine alone), with acceptable tolerance. Grade ≥ 3 adverse events reported in the combination arm included hand-foot syndrome (16%), diarrhea (7%), and venous thromboembolic events (8%) [68].

Despite these results, the 2015 phase III ITACa trial reported no statistically significant PFS and OS differences when bevacizumab was added to standard first-line CT (FOLFIRI or FOLFOX4) [69]. Other previous trials reported the same negative results. Considering these discrepancies, a 2017 meta-analysis based on 9 studies examined the survival impact of bevacizumab plus CT in first-line treatment of mCRC patients, showing that the combination significantly prolonged PFS (HR 0.66; $p < 0.0001$) and OS (HR 0.84; $p = 0.0001$) compared with CT alone. Subgroup analyses suggested that irinotecan-based regimens might be a better partner for bevacizumab than oxaliplatin-based regimens, with superior PFS and OS benefit [70].

Sidedness of the primary tumor is known to be an important prognostic factor in metastatic setting of CRC, with worst survival outcomes for right-sided tumors. Several clinical trials investigated the prognostic role of bevacizumab in the treatment of patients with right-sided and left-sided CRC. A post-hoc analysis of 16 randomized trials including PEAK, FIRE-3, and CALGB/SWOG trials showed that right-sided tumors have impaired CT sensitivity, while addition of bevacizumab to cytotoxic regimens can be an optimal first-line treatment for RAS-wild-type right-sided mCRC [71].

Although continuing bevacizumab with second-line chemotherapy showed benefit after disease progression, other anti-VEGF drugs should be considered for fast progressors (PFS <3–4 months) [72].

In patients with unresectable mCRC who are not candidates for intensive therapy, the ongoing phase III SOLSTICE trial is currently comparing trifluridine/tipiracil (TAS-102) plus bevacizumab versus capecitabine plus bevacizumab as first-line treatment [73].

Aflibercept. Aflibercept is a recombinant fusion protein composed by VEGF-binding portions from VEGFR-1 and -2 extracellular domains fused to the Fc portion of human IgG1. It acts by blocking the activity of VEGF-A and -B, preventing their binding to VEGFR on endothelial and tumor cells [74].

The role of aflibercept was evaluated in the phase III VELOUR trial, of mCRC patients previously treated with oxaliplatin-based regimens in first line, including with bevacizumab. Second-line FOLFIRI was intravenously administered with placebo or aflibercept at the dose of 4 mg/kg every two weeks. Aflibercept improved the median OS (13.50 vs. 12.06 months) and median PFS (6.90 versus 4.67 months) compared to placebo [74]. These results lead to approval of the drug in combination with FOLFIRI as second-line treatment for patients pretreated with oxaliplatin-based doublet with bevacizumab. The most common grade ≥ 3 AEs reported in the VELOUR trial included neutropenia, diarrhea, stomatitis, hypertension, and fatigue. Additionally, there was no evidence of greater toxicity in patients previously treated with bevacizumab [74].

More recently, the phase II AFFIRM trial investigated the addition of aflibercept to first-line oxaliplatin-based regimens in mCRC patients. Patients received mFOLFOX6 plus aflibercept or mFOLFOX6 alone. Despite VELOUR results, this study did not reach the primary endpoint of PFS. Adding aflibercept to first-line mFOLFOX6 did not increase efficacy and was associated with higher toxicity [75].

Ramucirumab. Ramucirumab is a human IgG1 monoclonal antibody against VEGFR-2. Efficacy and safety of ramucirumab in combination with second-line FOLFIRI was evaluated in the phase III RAISE trial. Patients with progressive mCRC during or after first-line treatment with bevacizumab, oxaliplatin, and

fluoropyrimidine were randomized to receive intravenous ramucirumab 8 mg/kg plus FOLFIRI or placebo plus FOLFIRI every 2 weeks. Ramucirumab significantly improved survival in this subpopulation, reaching a median OS of 13.3 months, against 11.7 months in the placebo arm. Grade ≥ 3 AEs included neutropenia (38%), hypertension (11%), diarrhea (11%), and fatigue (12%). Febrile neutropenia was only reported in 3% of patients and most toxicities reported were manageable [76]. This trial lead to the approval of ramucirumab in combination with FOLFIRI in the second-line setting of mCRC previously treated with bevacizumab, oxaliplatin, and fluoropyrimidine in first line.

Regorafenib. The only TKI approved for mCRC treatment is regorafenib, a multi-kinase inhibitor of angiogenic pathway members, including VEGFR-1 and -2, platelet-derived growth factor receptor (PDGFR)-β, and tyrosine kinase with immunoglobulin-like and EGF-like domains 2 (TIE2) [77].

Several phase III trials evaluated the role and efficacy of regorafenib as single-agent in mCRC patients progressing after several standard lines of treatment (**Table 2**). The CORRECT trial was the first to compare treatment with regorafenib 160 mg daily for 21 days, every 28-day cycle, versus placebo. Final study results reported a quality of life (QoL) and OS (6.4 vs. 5.0 months in placebo arm) improvement in favor of regorafenib [78]. The phase III CONCOUR trial was similar to the CORRECT trial but exclusively recruited Asian patients, holding similar OS results [79]. The CONSIGN trial was designed to specifically evaluate regorafenib safety. In a total of 2864 patients (median age of 62 years), the most common grade ≥ 3 AEs were hypertension (15%), hand-foot syndrome (14%), fatigue (13%) and diarrhea (5%). Grade ≥ 3 laboratory toxicities included elevated alanine aminotransferase (6%), aspartate aminotransferase (7%), and bilirubin (13%) [80].

3.2 Resistance to anti-VEGF drugs

Despite the outcome benefits seen with anti-VEGF agents in CRC, these are usually transient and followed by relapse and tumor growth [81]. Several resistance mechanisms to anti-VEGF therapies have been described, including VEGF axis-dependent alterations, non-VEGF axis-dependent upregulation, and stromal cell interactions [82].

3.2.1 VEGF-dependent pathways

Upregulation of alternative VEGFR-2 angiogenic ligands, such as VEGF-C, −D, and placental growth factor (PIGF), can bypass VEGF-A inhibition and elicit bevacizumab resistance [82]. In a phase II trial, Kopetz et al. showed that PlGF, VEGF-C, and VEGF-D plasma levels in mCRC patients receiving FOLFIRI plus bevacizumab were elevated prior to and at the time of disease progression [83].

3.2.2 Non-VEGF-dependent pathways

Complementary angiogenic pathways other than VEGF/VEGFR signaling exert control on tumor angiogenesis and may explain acquired resistance to anti-VEGF therapies. These pathways involve members of the platelet-derived growth factor (PDGF) family, HIF, members of the fibroblast growth factor (FGF) family, angiopoietin (Ang), and Notch [84, 85].

The PDGF family consists of five ligands that bind to tyrosine kinases PDGFR-α and -β, activating downstream signal transduction pathways, as PI3K/Akt and PLCγ. PDGF-C was shown to be upregulated in cancer-associated fibroblasts (CAFs) of anti-VEGF-resistant tumors in vivo [86], making it a possible resistance mediator.

Study	Treatment	PFS, months	OS, months	HR (p-value)
Hurwitz et al. (III)	BEVA-ILF PLACEBO-IFL	10.6* 6.2*	20.3 15.6	PFS - 0.54 (<0.001) OS - 0.66 (>0.001)
Saltz et al. (III)	XELOX BEVA-FOLFOX PLACEBO	9.4* 8.0* -	23.3 19.9 -	PFS - 0.83 (0.002) OS - 0.89 (0.077)
AVEX (III)	BEVA-CAP CAP	9.1* 5.1*	—	PFS - 0.53 (<0.001)
ITACa (III)	BEVA-FOLFIRI/FOLFOX PLACEBO-FOLFIRI/ FOLFOX	9.6 8.4	—	PFS - 0.86 (0.182)
SOLSTICE (III)	BEVA-Trifluridine/tipiracil BEVA-CAP	—	—	Ongoing
VELOUR (III)	Aflibercept-FOLFIRI PLACEBO-FOLFIRI	6.90* 4.67*	13.50* 12.06*	PFS - 0.758 (<0.001) OS - 0.817 (0.003)
AFFIRM (II)	Aflibercept-FOLFOX PLACEBO-FOLFOX	8.48 8.77	—	PFS - 1.00
RAISE (III)	Ramucirumab-FOLFIRI PLACEBO-FOLFIRI	—	13.3* 11.7*	OS - 0.844 (0.022)
CORRECT (III)	Regorafenib PLACEBO	—	6.4* 5.0*	OS - 0.77 (0.005)
CONCOUR (III)	Regorafenib PLACEBO	—	8.8* 6.3*	OS - 0.55 (<0.001)
CONSIGN (III)	Regorafenib	AEs: hypertension (15%), hand-foot skin reaction (14%), fatigue (13%), diarrhea (5%), and elevated aminotransferase (6%), aspartate aminotransferase (7%), and bilirubin (13%).		

AEs, adverse events; BEVA, bevacizumab; CAP, capecitabine; HR, hazard ratio; OS, overall survival; PFS, progression-free survival.
**Difference between groups is statistically significant ($p < 0.05$).*

Table 2.
Targeted therapies against VEGF in colorectal cancer.

HIF-1 is a transcription factor with a key role in cellular response to reduced oxygen levels. Among its multiple downstream effects is induction of VEGF-A, VEGFR, PIGF, and PDGF expression [85].

Growth factors of the FGF family are potent mediators of tumor angiogenesis. Binding of FGF to fibroblast growth factor receptor (FGFR) tyrosine kinase activates downstream pathways such as MAPK/ERK, PI3K/Akt, and STAT [86], acting synergistically with VEGFA to induce angiogenesis via endothelial cell proliferation, survival, and migration [87]. FGF-2 upregulation is observed in anti-VEGF-resistant tumors, especially in tumors exposed to a hypoxic environment, [86] while FGF-2 blockade results in decreased tumor growth in *in vivo* models [88].

Ang-Tie signaling is a vascular-specific pathway essential for blood vessel development and vascular permeability regulation. Ang-2 acts as an antagonist of the Tie2 receptor, leading to development of vascular sprouts in the context of VEGF exposure [86]. mCRC patients with poor bevacizumab response showed high serum Ang2 levels, suggesting its relevance in resistance to anti-angiogenic therapy [89].

Delta-like ligand 4 (DII4) is a Notch ligand overexpressed in several solid malignancies, including CRC. DII4 upregulation is thought to contribute to

bevacizumab resistance, which can be overcome by Notch inhibition with a γ-secretase inhibitor [90].

TGF-β is a ligand for type II TGF-β receptors and endoglin (CD105). It has important regulatory functions in angiogenesis, either directly, or indirectly by activating fibroblasts to produce extracellular matrix and stimulating the tube formation in endothelial cells [91]. Anti-VEGF therapy-resistant tumors can exhibit high levels of TGF-β1 expression. Additionally, in preclinical models VEGF pathway blockade led to increased CD105 levels, suggesting a role for CD105 in anti-VEGF therapy resistance [92].

3.2.3 Stromal cell interactions

It has been recently suggested that tumor stromal cells and bone marrow-derived cells (BMDCs) recruited to the tumor microenvironment by secreted cytokines play an important role in acquired resistance to anti-VEGF therapies [81].

CAFs entail a large portion of stromal cells present in the tumor environment. These cells secrete a number of pro-angiogenic mediators, including IGF, FGF, EGF, cytokines, and chemokines, and are capable of recruiting endothelial progenitor cells (EPCs) to the tumor site [93, 94]. Interestingly, Kinugasa et al. showed that CAFs from anti-VEGF-resistant tumors express high levels of CD44, a marker for cancer stem cells and cytotoxic resistance. CAFs can hence be considered a promising target for overcoming resistance to anti-angiogenic agents [95].

BMDCs are comprised of endothelial and pericyte progenitors, macrophages, and myeloid-derived suppressor cells (MDSCs) [96]. Preclinical models suggest that EPCs in the tumor microenvironment are able to secrete different proangiogenic factors and accelerate angiogenesis [97]. More importantly, endothelial precursor cells can differentiate into endothelial cells and participate in new vessel formation [98, 99].

Tumor-associated macrophages (TAMs) are also involved in angiogenesis. VEGF blockade by bevacizumab seems to promote TAM proliferation and reprogramming to pro-angiogenic macrophages [81]. This type of macrophages can secrete VEGF-A, TNFα, and IL-8, all of which affect different stages of angiogenesis by modifying the local extracellular matrix, promoting proliferation and migration of endothelial cells, and inhibiting development of differentiated capillaries [81].

A study by Shojaei et al. demonstrated that MDSCs were present in higher levels in anti-VEGF-resistant tumors and were functionally different from those in anti-VEGF-sensitive tumors. This population was able to sustain tumor growth even in presence of anti-VEGF inhibitors, although the exact mechanism behind this is not been fully established [100].

CD4+ T-helper cells mediate anti-VEGF resistance through IL-17 production in the tumor microenvironment and BMDC recruitment. These cells have been shown to regulate secretion of several proangiogenic factors from CAFs and other stromal cells. Additionally, Numasaki et al. reported that tumor microvessel density correlates with levels of infiltrating IL-17-producing CD4 T-cells [25, 42, 81, 101].

3.3 Anti-EGFR and -VEGF safety profile

The main side effects of the anti-EGFR therapies cetuximab and panitumumab are dermatological toxicities, reported in 85–96% of patients (**Table 3**) [102]. The most common AE is papulopustular skin rash, generally developing over a period of 6 weeks after starting treatment and potentially impacting quality of life and therapy adherence. General prevention and management principles include the use of skin moisturizer, sunscreen, hydrocortisone cream, and oral tetracycline. The STEPP trial compared pre-emptive with reactive skin treatment and showed an

over 50% reduction in grade ≥ 2 skin toxicities and less QoL impairment with the pre-emptive compared with reactive treatment [103]. In cases of grade 3 rash, treatment should be delayed until toxicity has resolved to grade 2 or less and dose should be reduced in a second occurrence. In grade 1 or 2 rash, dose reduction is not indicated. Other dermatological symptoms, including hair growth, periungual and nail plate abnormalities, xerosis, telangiectasias, and pruritus can occur at lower rates [102].

Infusion reactions commonly occur with cetuximab and should be prevented with premedication, antihistamines, and corticosteroids. Other adverse effects, like hypomagnesemia, ocular toxicities as conjunctivitis and blepharitis, and less commonly diarrhea, can also occur [104]. Toxicity management is grade-depend and, in some cases, should be addressed by a multidisciplinary team.

The main anti-VEGF side effects are cardiovascular and kidney problems (**Table 3**). Hypertension has been observed at high rates in all phase III studies of anti-VEGF drugs and is normally manageable with standard antihypertensive medications, but this treatment should not be initiated in patients with uncontrolled hypertension. Proteinuria is another side effect, defined as protein content in the urine >300 mg/dL. No standard treatment is established, but anti-angiogenic drugs should be disused if protein content in the urine is >2 g/24 h, and evaluation by a nephrologist should be considered. Hand-foot syndrome is also common with this class of drugs [105].

Bevacizumab has also been associated with other side effects, like thromboembolic events (8%), delayed wound healing, bleeding, fistulae, and gastrointestinal

Target	Effect	Drug-incidence	Prevention/treatment	Dose reduction/delay treatment
EGFR	Rash	C 52–89% P 20–50%	Skin moisturizer, sunscreen, hydrocortisone cream, and oral tetracycline	Reduction in 2nd G3 occurrence, delay until ≤ G2
	Infusion reactions	C 14–21% P-3%	Antihistamines and corticosteroids Low rate, gradual titration	Grade dependent
	Hypomagnesemia	C 4–38% P 27%	Magnesium replacement	Some G3/4 toxicity delay until recovery
	Diarrhea	2% G3/4	Loperamide, hydration, electrolyte replacement, hospitalization	Reduction in 1st G3 or 2nd G2 occurrence
VEGF	Hypertension	B 25% A 42.4% Reg 15% Ram 11%	Blood pressure monitoring, antihypertensive drugs	Cease if G4 or persisting G3 toxicity
	Proteinuria	18.7%	Screening for proteinuria angiotensin receptor blockers	Discontinue if nephrotic syndrome
	Hand-foot syndrome	B 16% Reg 14%	Emollient, analgesia	Reduction in 1st G3 or 2nd G2 occurrence, delay until ≤ G1
	Thromboembolic events	B 8%	Anticoagulation therapy	Cease bevacizumab

A, aflibercept; B bevacizumab; C cetuximab; EGFR, epidermal growth factor receptor; G grade; P, panitumumab; Ram, ramucirumab; Reg, regorafenib, VEGF, vascular endothelial growth factor.

Table 3.
Adverse effects of any severity with anti-EGFR and -VEGF therapies.

perforation (1.7%). Bevacizumab treatment should be ceased in cases of hemorrhagic events ≥grade 3, pulmonary embolism, cerebrovascular events or arterial insufficiency, arterial thromboembolic events, grade 4 or persistent grade 3 hypertension, nephrotic syndrome, or gastrointestinal perforation [106]. Potentially life-threatening events have occurred only in a small number of patients, with bevacizumab being well tolerated by the majority.

4. Other targets

4.1 NTRK fusions

The constitutive activation of RTKs promoted by genomic translocations play an important role in tumorigenesis across different malignancies, including CRC. Examples include ALK, ROS1, and NTRK1–2-3 (NTRK), which altogether occur in 0.2–2.4% of CRCs and may represent new therapeutic targets (**Table 4**) [107].

The NTRK (neurotrophic tropomyosin receptor kinase) 1, 2, and 3 genes encode three tropomyosin receptor kinase (TRK) receptors —TrkA, TrkB, and TrkC— which are transmembrane proteins [2, 108, 109]. Gene fusions involving those genes lead to constitutively activated NTRK proteins and, consequently, tumorigenesis [107]. The prevalence of NTRK fusions in mCRC is estimated to be 0.5–2.0% [110], but increases to 4% in microsatellite instability-high (MSI-H) mCRC [2].

NTRK gene rearrangements are more commonly detected in non-Lynch syndrome MSI-H/ deficient mismatch repair (dMMR) tumors with MLH1 promoter hypermethylation and wild-type BRAF/KRAS/NRAS, and define a molecular subgroup associated with poor prognosis [111]. They are also more frequent in elderly females with right-sided tumors [107, 109, 112].

Fusion-detection options include targeted DNA and RNA panels, RNA sequencing, FISH, and IHQ [2]. Recent ESMO recommendations for NTRK fusion detection state that, in tumors with low NTRK fusion frequency, as mCRC, detection can be done via one-step next-generation sequencing (NGS) or via IHQ followed by NGS (if IHQ positive) [113].

Larotrectinib and entrectinib are TRK inhibitors approved by the FDA and EMA in more than 10 tumor types. Larotrectinib, a small-molecule inhibitor targeting all three TRK proteins, has been tested in the multicenter single-arm LOXO-TRK-14001, SCOUT, and NAVIGATE clinical trials [111]. Larotrectinib at the dose of 100 mg twice daily showed a good safety profile and good responses (75% of ORR, 1-year PFS of 55%) [114]. In November 2018, the FDA granted accelerated tissue-agnostic approval to larotrectinib for solid tumors with NTRK gene fusions [2, 111, 112] Entrectinib is an oral pan-TRK, -ROS1, and -ALK inhibitor that is clinically active in patients with NTRK-rearranged tumors and is able to penetrate the blood–brain barrier [107]. Three clinical trials (ALKA-372-001, STARTRK-1, and STARTRK-2) have investigated this agent [107]. Pooled analyses of the three trials presented at the ESMO 2018 Congress and ASCO 2019 Meeting showed that entrectinib induced clinically meaningful durable responses in patients with solid tumors with or without metastatic central nervous systemic disease harboring NTRK fusions [111].

The second-generation TRK inhibitor BAY2731954 (formerly known as Loxo-195) and the next-generation ROS1, pan-TRK, and ALK inhibitor repotrectinib are being tested, with promising results [111].

As already shown with BRAF V600E mutations, patients with ALK-, ROS-, and NTRK-rearranged tumors seem to derive no benefit from treatment with anti-

EGFR monoclonal antibodies [107]. Additionally, the high prevalence of MSI-H status in rearranged tumors opens the way for evaluation of new combination approaches including targeted (ALK, ROS1, TrkA-B-C) and immunotherapy agents [107].

Regarding resistance mechanisms, a dose-dependent effect seems to affect mutation emergence. Two mutations have been associated with entrectinib resistance: NTRK1 p. G667C and NTRK1 p.G595R [108]. For larotrectinib, three different mutational categories have been described: solvent front mutations (NTRK1 p. G595R, NTRK3 p.G623R); gatekeeper mutations (NTRK1 p.F589L); and xDFG mutations (NTRK1 p.G667S, NTRK3 p.G696A). Novel agents under development intend to overcome NTRK1 p.G595R-mediated resistance to TRK inhibitors [115].

4.2 MET alterations

The mesenchymal-epithelial transition (MET) protooncogene (also known as N-methyl-N′-nitroso-guanidine human osteosarcoma transforming gene) encodes for c-MET, a receptor with tyrosine kinase activity targeting HGF. Activation of this pathway has been implicated in CRC metastatic progression [2].

MET receptor tyrosine kinase can be overexpressed in 50–60%, amplified in 10%, and mutated in 5% of CRCs [2]. In a study by Lee et al., c-MET overexpression showed no correlation with primary tumor site, histological type, or molecular aberrations, but correlated with shorter OS and was a predictive biomarker of shorter PFS in bevacizumab-treated patients [3].

EGFR and MET are co-expressed in CRC and MET activation has been implicated in resistance to the anti-EGFR therapy [2, 116]. Inhibition of the HGF/c-Met pathway may improve response to EGFR inhibitors in CRC and combination therapy should be further investigated [116]. This supports the hypothesis that anti-EGFR therapy selects MET-amplified (cetuximab- and panitumumab-resistant) preexisting clones, eventually limiting the efficacy of further anti-EGFR therapies [117].

Multiple clinical trials have evaluated MET inhibition, but several of those conducted in mCRC have been unsuccessful [2]. Treatment strategies targeting HGF and c-Met include HGF antagonists, c-Met and HGF-blocking antibodies, and small-molecule c-Met inhibitors [118].

Although MET genomic aberrations are commonly observed in mCRC, these remain in the research setting [2].

4.3 Other rearrangements

4.3.1 ALK/ROS1 translocations

The EML4-ALK fusion gene is produced by inversion in the short arm of chromosome 2, where anaplastic large-cell lymphoma kinase (ALK) joins echinoderm microtubule-associated protein-like 4 (EML4), resulting in a chimeric protein with constitutive ALK activity. ROS1 is an orphan receptor tyrosine kinase phylogenetically related to ALK [110].

ALK and ROS1 gene rearrangements have not been extensively studied in CRC. Around 0.8–2.5% of patients with mCRC have been reported to have either ALK or ROS1 rearrangements [110]. ALK, ROS1, and NTRK fusions occur more frequently in elderly patients with right-sided, RAS wild-type, MSI-H mCRC, and are associated with shorter OS and poor prognosis [107, 110]. The small patient numbers make it challenging to develop a clinical trial of targeted therapies for this patient population [110]. As no FDA-approved agents targeting these genomic alterations

Target	Frequency	Clinicopathological features	Testing methods	Agent	Mechanism of action	Current status
NTRK genes (NTRK 1, NTRK 2, NTRK 3) fusions	0.5–2.0% in mCRC (4% in MSI-H)	Associated with MSI-H/dMMR; wt BRAF/RAS, elderly females and right sided tumors; associated with poor prognosis; resistance to anti-EGFR monoclonal antibodies	IHC and NGS	Larotrectinib Entrectinib	Small molecule inhibitor targeting TRK proteins	Approved by the FDA and EMA
ALK/ROS1	0.8–2.5%	Associated with MSI-H/dMMR; wt BRAF/RAS, elderly females and right-sided tumors; associated with poor prognosis; resistance to anti-EGFR monoclonal antibodies	FISH, RT-PCR, NGS	Clinical trials; Ceritinib	Small-molecule inhibitor targeting ALK/ROS1	Under investigation
FGFR	3–5%	FGFR3 related with worse prognosis	NGS plus FISH	Regorafenib and newly developing FGFR-specific TKIs	Small-molecule inhibitor targeting FGFR signaling	Under investigation
c-Met overexpression	Overexpressed in 50–60%, amplified in 10% and mutated in 5% of CRCs	Shorter OS, shorter PFS with bevacizumab treatment; poor prognosis; resistance to anti-EGFR monoclonal antibodies	IHC	Clinical trials	Under investigation	Under investigation
RET fusions	0.2%	Worse prognosis, poor treatment response, and reduced OS	IHC and FISH	Vandetanib, cabozantinib	Under investigation	Under investigation

dMMR, deficient mismatch repair; FGFR, fibroblast growth factor receptor; FISH, fluorescent in situ *hybridization; IHC, immunohistochemistry; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; NGS, next-generation sequencing; OS, overall survival; PFS, progression-free survival; RT-PCR, reverse transcription polymerase chain reaction; TKI, tyrosine kinase inhibitor; wt, wild-type.*

Table 4.
Summary of new targeted therapies in mCRC.

exist for CRC patients, basket trials (as the TAPUR trial) may give valuable insights in this setting [112].

4.3.2 RET fusions

RET is a proto-oncogene encoding a transmembrane tyrosine kinase receptor for the glial-derived neurotrophic factor family [110].

RET fusions occur in 0.2% of solid tumors, being very typical in specific tumor types, such as thyroid carcinomas [119]. The effect of RET activation is less clear in CRC, but several studies suggest that it might be associated with worse prognosis, poor treatment response, and reduced OS. Due to rarity of this aberration, clinical trials in CRC are not easy to conduct, with data derived mainly from early trials or case reports [110]. Clinicopathological factors associated with RET fusions include right colon location, older age, RAS and BRAF wild-type status, and MSI-H status [119].

4.3.3 FGFR

Fibroblast growth factor receptors (FGFRs) are a subfamily of RTKs occurring in approximately 3–5% of CRC patients [112]. Initial evidence shows poor outcomes associated with FGFR3 alterations [120]. There is no evidence of clinicopathological characteristics related to these alterations [120].

Regorafenib, a multi-kinase inhibitor also targeting FGFR, is currently approved by the FDA for metastatic CRC patients who progressed on frontline therapies. This agent can be considered in CRC patients with FGFR alterations while novel FGFR inhibitors are not available [121]. Newly developed, more potent FGFR inhibitors are currently being investigated in multiple solid tumors [112].

5. Microsatellite instability and immune checkpoints inhibitors

Microsatellite instability (MSI) is currently a key biomarker in CRC, with diagnostic, prognostic, and therapeutic implications. For these reasons, MSI analysis is becoming increasingly important and testing for deficient mismatch repair (d-MMR)/MSI is recommended, both for hereditary syndrome screening and due to prognostic and treatment implications [122].

Inactivation of a DNA mismatch repair (MMR) gene (MLH1, MSH2, MSH6, or PMS2) by mutation or transcriptional silencing results in deficient function of the MMR system, responsible for excising DNA mismatches introduced by DNA polymerase during cell division. This activity loss translates in an accumulation of DNA replication errors and mismatches in repeated sequences, leading to hypermutated tumors [123]. In most cases, d-MMR and MSI arise due to sporadic somatic hypermethylation of MLH1 and other genes, but they can also result from germline mutations in MMR genes and from Lynch syndrome in approximately 3% of all CRCs [124].

The MMR system can be assessed through different approaches, as IHC, polymerase chain reaction (PCR)-based assays, and more recently NGS. IHC looks at MLH1, MSH2, MSH6, and PMS2 staining in tumor samples to identify the protein expression loss that characterizes d-MMR [125]. PCR amplification requires both tumor and matched normal samples. Five microsatellite loci have been PCR-amplified and analyzed by capillary electrophoresis. Instability at more than one locus was defined as MSI-high (MSI-H), at a single locus as MSI-low (MSI-L), and absence of instability at any locus as microsatellite stable (MSS), proficient MMR

(p-MMR) [126]. NGS detection directly targets certain genes, which are genome sequenced to retrieve information on MSI and MMR and tumor mutational burden (TMB), integrating all information in the same test. NGS requires a smaller sample and is more accurate than PCR. Ethical issues may arise with the use of this technique regarding counseling and consent for additional genetic testing [127]. In CRC, MSI varies according to tumor stage, with higher incidence reported in early stages (20% in stages I-II, 12% in stage III) and lower incidence reported in the metastatic setting (4–5%) [128].

5.1 Immune checkpoint inhibitors

The success of immune checkpoint inhibitors (ICI) in d-MMR over the last years has disclosed a new therapeutic scenario. Endogenous peptides are processed and presented on major histocompatibility complex (MHC) class I molecules on the surface of all cells, being recognized by T cell receptors (TCRs). TCR–MHC signaling pathways are modulated by co-stimulatory or co-inhibitory signals. ICI target co-inhibitory receptors, like cytotoxic T lymphocyte antigen 4 (CTLA-4) and programmed cell death 1 (PD-1) on T cells, or their ligands, as programmed cell death ligand 1 (PDL-1), on tumor and various immune cells [129]. ICI are approved in several malignancies. In mCRC, phase I trials reported response to immune checkpoint therapy in a subgroup of patients with MSI-H, d-MMR, or high TMB [130].

Pembrolizumab is a humanized IgG4 antibody and was the first anti-PD-1 to show efficacy in d-MMR mCRC (**Table 5**). In the phase II KEYNOTE-016 trial, patients with d-MMR tumors responded better to pembrolizumab (RR of 40%, 20-week PFS of 78%) than MSS tumors (RR of 0%, 20-week PFS of 11%) [131]. In the updated analysis, an ORR of 52%, 2-year PFS of 59%, and OS of 72% was reported for MSI-H CRC [132]. The phase II KEYNOTE-164 trial confirmed the efficacy of pembrolizumab in second-line setting of MSI-H CRC, with an ORR of 33%, median PFS of 2.3 months, and median OS of 31.4 months [133]. Based on these results, pembrolizumab was approved by the FDA for MSI-H/d-MMR unresectable or metastatic CRC after progression on CT. In the phase III KEYNOTE-177 trial, first-line treatment with pembrolizumab in monotherapy significantly reduced the risk of disease progression or death by 40% (HR 0.60; 95% CI 0.45–0.80; p = 0.0004), with a median PFS of 16.5 months versus 8.2 months with CT in MSI-H CRC. The study is ongoing, and OS data will be presented later this year [134]. This led to FDA approval of pembrolizumab in first-line treatment of unresectable or metastatic MSI-H/dMMR CRC.

Nivolumab, a humanized monoclonal IgG4-based PD-1 antibody, showed activity in MSI-H/d-MMR refractory CRC in the phase II CheckMate-142 trial, with an ORR of 31.1% regardless of tumor PD-L1 expression, 1-year PFS of 50%, and OS of 73% [135]. This trial included a cohort of nivolumab in combination with the CTLA-4 inhibitor ipilimumab, which showed a 55% ORR, 71% PFS, and 85% OS. Both nivolumab and the combination of nivolumab plus ipilimumab were approved by the FDA for CT-refractory MSI-H/dMMR mCRC. The immunotherapy doublet was also evaluated in first line in the CheckMate-142 trial, with 1-year PFS and OS of 77% and 83%, respectively, ORR of 60%, and DCR of 84% [136].

Following these studies, MSI status has become a crucial biomarker to define therapeutic options for patients in the metastatic setting.

Other PD-1/PD-L1 inhibitors are under investigation, like atezolizumab, avelumab, and durvalumab, and new immune checkpoint targets are in phase I trials, such as tumor-overexpressed T cell Ig and mucin domain-containing protein 3 (TIM-3), T cell Ig, and T cell-derived lymphocyte activation gene 3 (LAG-3). [137].

Setting	Study	Treatment	RR	PFS	OS	Approval
CT-refractory MSI-H/d-MMR mCRC	Phase II Keynote 164	Pembrolizumab	33%	2.1 m	31.4 m	FDA (1st line, CT-refractory)
1st line MSI-H/d-MMR mCRC	Phase III Keynote 177	Pembrolizumab	43.8%	16.5 m	NR	
CT-refractory MSI-H/d-MMR mCRC	Phase II CheckMate-142	Nivolumab	31%	50%	73%	FDA (CT-refractory)
	Phase II CheckMate-142	Nivolumab + ipilimumab	55%	71%	85%	
1st line MSI-H/d-MMR mCRC	Phase II CheckMate-142	Nivolumab + ipilimumab	60%	77%	83%	Not approved

CT, chemotherapy; dMMR, deficient mismatch repair, FDA, Food and Drug Administration; mCRC, metastatic colorectal cancer; MSI-H, microsatellite instability-high; NR, not reached; OS, overall survival; PFS, progression-free survival; RR, response rate.

Table 5.
Immune checkpoint inhibitors in mCRC.

5.2 Immunotherapy resistance

Most mCRC patients are MSS/p-MMR and results with ICI have been unsatisfactory, with immune resistance mechanisms not clearly elucidated yet. Several trials have been developed exploring ways to overcome this resistance, including by modulating tumor microenvironment, reducing tumor-specific antigen expression, altering immunosuppressive pathways, and activating other immune checkpoint pathways, immune regulatory cells, and cytokines [138]. Combining immunotherapy with CT, radiotherapy, bispecific antibody therapy, other immune checkpoint modulators, and other targeted agents are among strategies explored. The rationale behind this multimodal approach is the potential synergistic effect of targeting different immune escape pathways, resulting in improved response to ICI and patient outcomes [139].

CT has anti-tumor activity due to the direct cytotoxic effect on cancer cells and to stimulating host immune response, and several clinical trials are ongoing investigating the combination of immunotherapy with CT and targeted agents [140]. Radiotherapy can activate the host immune response by upregulating expression of tumor-specific neoantigens through cell damage and increasing membrane MHC class I expression, and several studies are ongoing in CRC combining radiotherapy with ICI. Another combined strategy is ICI and MEK blockers, considering that MEK blockade seems to increase T cell response via upregulation of PD-L1 expression [141]. Following a phase Ib trial of atezolizumab and the MEK inhibitor cobimetinib in MSS CRC, other trials were conducted, with no significant survival improvement [142]. The CEA CD3 TCB (RG7802, RO6958688) is a novel T-cell bispecific antibody targeting the carcinoembryonic antigen (CEA) on tumor cells and CD3 on T cells, which displays anti-tumor activity, leading to increased intra-tumoral T cell infiltration and activation and PD-1/PD-L1 upregulation. CEA-TCB antibody was tested in phase I trials of MSS CRC plus atezolizumab, showing antitumor activity with acceptable toxicity [143].

5.3 Biomarkers

Considering immune side effects associated with ICI and their variable efficacy, it is important to identify biomarkers that help predict response to ICI and select potentially sensitive patients that can be candidates for these agents.

PD-L1 expression level is an established biomarker in some malignancies, but the relationship between PD-L1 positivity and response has not been proven in CRC [144]. TMB has emerged as a marker of response to immunotherapy in some tumors, suggesting that tumor cells with high mutational burden generate and present more peptide neoantigens on their MHC class I molecules, increasing T cell infiltration [145]. In CRC, dMMR/MSI-H tumors have a high mutational burden, as well as some pMMR/MSS, which may present an ultramutated phenotype as DNA polymerase epsilon (POLE) mutations, found in ~1–2% of pMMR CRC. POLE mutations cause an increased immunogenicity and upregulation of immune checkpoint genes, such as PD-1/PD-L1 and CTLA-4, which result in similar clinical responses to dMMR tumors and may predict response to anti-PD-1 therapy [146]. Some case reports link POLE mutations with efficacy to PD-1 blockade, and phase II studies are ongoing in this setting.

The interaction between tumor and microenvironment led to the development of an immunoscore based on calculation of two lymphocytic populations (CD3/CD45-CD8 or CD8/CD45) in the centre and invasive margins of the tumor, which may predict ICI response [147]. Other lines of investigation are being explored, including the study of factors that indicate cytotoxic T cell activity, such as granzymes, perforins, and IFN-γ levels.

CRC is one of the tumor types for which immunotherapy has been less effective. Better knowledge of the molecular immune mechanisms is required to develop predictive biomarkers and effective therapeutic combination strategies, converting "cold" tumors, immune-desert and immunotherapy-resistant, in "hot" tumors, inflamed, infiltrated by the immune system, and immunotherapy responsive.

6. Conclusions

CRC treatment has changed over the last decades, not only by including different chemotherapy agents and combinations, but mainly because new targeted agents have emerged.

In metastatic setting, anti-EGFR and anti-VEGF drugs are widely used and have shown gains in survival and response rate, an important marker in CRC potentially resectable liver metastases. In contrast, several trials with targeted agents have been conducted in the adjuvant setting, without survival benefit. Immunotherapy emerged as a new treatment option with survival benefit, but at the moment it is only effective in a small portion of patients. Several other agents targeting other pathways are emerging, such as NTRK, c-MET, ALK, ROS1, and FGFR inhibitors, with promising results.

In conclusion, patients with CRC are living longer with targeted treatments, but more information about resistance mechanisms and biomarkers is necessary to extend even more their survival gains.

Acknowledgements

The authors gracefully acknowledge Joana Cavaco-Silva (jo.cvsilva@gmail.com) for manuscript English language revision and Inês Gomes (ines.gomes@medicina.ulisboa.pt) for **Figure 1** graphic drawing.

Conflict of interest

L. Costa performed consulting activities for Amgen, Novartis and Servier outside the scope of this manuscript. The remaining authors declare no conflicts of interest.

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Chapter 8

Adjuvant Therapies in Colon Cancer

Thiru Prasanna and Desmond Yip

Abstract

Most of the patients with localized colon cancer undergo curative resection. However, significant number of patients will recur with metastatic disease, especially those with node positive cancer. Adjuvant chemotherapy has shown to improve cure rate and survival by eradicating micrometastases. The benefit of adjuvant therapy is well established in node-positive cancers, while their role in stage II cancer is not well defined. A number of molecular markers have been identified that are prognostic and/or predictive in colon cancer. Such molecular markers, and other clinicopathological features play an important role in selection of appropriate therapy and duration of treatment. Emerging evidence for the utility of genomic profiling or detection of circulating tumor DNA (ctDNA) are promising which may further facilitate decision making in the future. This chapter reviews the evolution of adjuvant therapy for resected colon cancer, the current evidence and the factors influence the choice of therapy.

Keywords: colon cancer, adjuvant therapy, mismatch repair, BRAF, RAS

1. Introduction

Colon cancer is a major cause of morbidity in the world and the second most common cause of cancer death. Most patients undergo curative resection of the primary colon cancer and removal of regional lymph nodes. Colon cancer mortality rates have improved over the years with the advancement of surgical techniques, diagnostic modalities and systemic therapy (**Figure 1**). Most important prognostic determinant is the stage of the cancer. The original pathological staging system used for colon cancer was the Dukes staging system which was based on the extent of penetration of the cancer through the bowel wall and whether there was involvement of regional lymph nodes (**Table 1**). It was originally described for rectal cancer but applied to colon cancer as well [2].

Staging of colon cancer has been further refined in detail and standardized according to the AJCC (American Joint Committee for Cancer)/UICC (Union for International Cancer Control) TNM staging system of which the latest version is the eighth edition which was adopted in 2018 [3]. The tumor and node definitions are shown in **Table 2**. Primary tumor and nodal factors define the stages as shown in **Table 3**.

The risk of recurrence increases with the stage, especially when there are nodal metastases. Postoperative adjuvant chemotherapy is utilized to eradicate the micrometastases which reduce the risk of recurrence and improve the cure rate. The role of adjuvant chemotherapy is well defined I stage III colon cancer; however, it

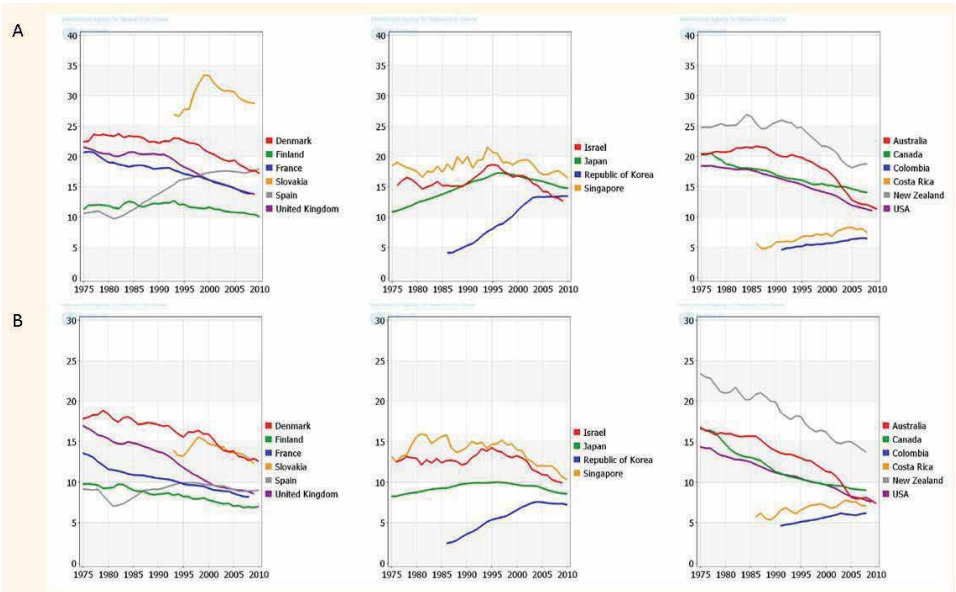

Figure 1.
Colon cancer related mortality from 1975 to 2010, (A) in males and (B) in females. Figures are from International Agency for Research on Cancer, global cancer observatory website [1].

Stage	Description
Dukes A	Tumor confined to within submucosa
Dukes B1	Tumor penetrates muscularis propria but not through bowel wall
Dukes B2	Tumor penetrates through bowel wall
Dukes C1	Tumor not through bowel wall with lymph node metastases
Dukes C2	Tumor through bowel wall with lymph node metastases

Table 1.
Dukes staging system for colorectal cancer.

T—Primary tumor	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intramucosal (involvement of lamina propria with no extension through muscularis mucosae)
T1	Tumor invades submucosa (through muscularis mucosae but not into the muscularis propria)
T2	Tumor invades muscularis propria
T3	Tumor invades through muscularis propria into pericolorectalic (subserosal) tissues
T4	Tumor invades the visceral peritoneum or invades or adheres to adjacent organ or structure
T4a	Tumor penetrates to the surface of the visceral peritoneum (including gross perforation of the bowel through areas of inflammation to the surface of the visceral peritoneum)
T4b	Tumor directly invades or adheres to other organs or structures
N - Regional lymph node	
NX	Regional lymph nodes cannot be assessed
NO	No regional lymph nodes metastases

N1	One to three regional nodes are positive (tumor in lymph nodes measuring >0.2 mm), or any number of tumor deposits are present and all identifiable lymph nodes are negative
N1a	One regional lymph node is positive
N1b	Two or three regional lymph nodes are positive
N1c	No regional lymph nodes are positive, but there are tumor deposits in the • subserosa • mesentery • or non-peritonised pericolic or perirectal/mesorectal tissues
N2	Four or more regional lymph nodes are positive
N2a	Four to six regional lymph nodes are positive
N2b	Seven or more regional lymph nodes are positive
M - Distant metastasis	
Mo	No distant metastasis by imaging, etc.; no evidence of tumor in distant sites or organs
M1	Metastasis to one or more distant sites or organs or peritoneal metastasis is identified

Table 2.
The tumor, node, metastasis (TNM) staging system.

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0

Table 3.
Prognostic stage groups.

remains controversial in stage II. This chapter reviews the role of adjuvant therapies in resected colon cancer.

2. Primary treatment of colon cancer

About 70–80% of patients diagnosed with localized non-metastatic colorectal cancer undergo curative resection which is the main modality of treatment for those

with good performance status and acceptable comorbidities. This is achieved by surgical resection of the primary tumor, anastomosis of the bowel and removal of 12 or more regional lymph nodes. The aim of oncological resection is the complete removal of the tumor and potential lymphovascular spread with a clear margin of at least 5 cm proximally and distally for colon cancer, and minimal proximal margin of 5 cm and distal of 2 cm for rectal carcinoma. Circumferential/radial margin clearance of at least 1 mm is considered optimal. Endoscopic resection involves complete tumor resection and adjacent tissue in one block. This may be acceptable for those accept vigorous close surveillance and potential need for further surgical resection or those who are non-surgical candidates.

3. Adjuvant therapies

3.1 Drugs used: 5FU, capecitabine, oxaliplatin

3.1.1 5-Fluorouracil (5-FU)

5FU is an antimetabolite drug that inhibits DNA and RNA synthesis by acting as a false substrate in purine and pyrimidine synthesis thereby interfering in the S phase of the tumor cell cycle. It is metabolized by the rate limiting enzyme dihydropyrimidine dehydrogenase. The main toxicities are related to mucosal inflammation and this presents clinically as mucositis, stomatitis and diarrhea. It can also cause nausea and myelosuppression. Rarely, it can cause cardiotoxicity presumably by inducing coronary artery spasm.

3.1.2 Capecitabine

Capecitabine is an oral fluropyrimidine prodrug which is taken up inside the tumor cells and metabolized to the active 5FU product by thymidine phosphorylase. Repeated oral administration mimicks the pharmacokinetics of protracted infusional 5FU. The side effects are similar to 5FU in term of mucositis and diarrhea but hand-foot syndrome or palmar-plantar erythrodysesthesia with redness, tenderness and swelling of these areas is a common toxicity experienced.

3.1.3 Oxaliplatin

Oxaliplatin is a third-generation platinum drug which acts as an alkylating agent in causing DNA damage by intrastrand crosslinks. The drug is not nephrotoxic or ototoxic but the main side effect is cold related dysesthesia which can lead to cumulative sensory neuropathy. It is moderately emetogenic and myelosuppressive. It exhibits synergy with fluoropyrimidines and so is normally used in combination with this class of cytotoxics.

3.2 Historic data; levamisole, folinic acid

3.2.1 Levamisole

Levamisole is an anti-helminthic drug that is used in veterinary medicine. It was found to have effects on phagocytosis and chemotactic responses of neutrophils as well as on stimulation of lymphocyte proliferation, differentiation and cytotoxicity suggesting an immunomodulatory effect. Preclinical studies suggested an antimetastatic effect in tumor xenograft models.

The initial Leicester trial randomized patients after curative surgery either to observation, 5FU, or 5FU plus levamisole. 5FU was administered intravenously for # days following surgery, and then orally once weekly for 6 months; levamisole was administered for only three postoperative days. After 5 years of follow-up, the survival of patients randomized to 5FU plus levamisole was significantly prolonged compared with 5FU alone ($p = 0.02$) or observation ($p = 0.045$).

Levamisole alone, given intermittently for 1 year, did not produce a survival benefit in an EORTC trial with Dukes C colon cancer patients [4]. In the NCCTG trial levamisole was inferior to the combination with 5FU [5].

Two trials the US Intergroup 0035 and the Netherlands Adjuvant Colorectal Cancer Project (NACCP) study both found a significant benefit of 5FU and levamisole in the adjuvant therapy of resected colon cancer compared to observation [6]. A subsequent meta-analysis of these two studies found that after adjustment for the total planned 5FU dose the effect of levamisole became non-significant. Subsequent trials disproved the benefit of levamisole in adjuvant therapy of colon cancer [7, 8].

3.2.2 Leucovorin (folinic acid)

Leucovorin is an active metabolite of folic acid which works by enhancing enzymatic binding of 5FU onto thymidylate synthetase to prolong the half-life of 5 U and therefore potentiates the 5FU. It is not a cytotoxic agent on its own. Rarely, it can cause rash or itch.

Clinical trials compared 5FU-leucovorin regimens to 5FU-levamisole regimens and disproved the benefit of levamisole. The INT-0089 and QUASAR studies have demonstrated that there is no difference in outcome between the use of high dose or low dose leucovorin [7, 8].

3.3 Stage I colon cancer

Stage 1 colon cancer is often an incidental finding in those patients undergoing polypectomy. Therefore, pedunculated polyps should be resected with excision of the stalk down to the base. When stage 1 colon cancer is found in a polyp that was completely excised with clear margin of more than 2 mm, further surgical excision may not be required, provided there are no high risk features such as lymphovascular invasion, poor cell differentiation, and malignant invasion beyond stalk. Such patients with high risk features should undergo further excision like segmental resection for complete staging. Sessile polyps with invasive cancers also can be managed with segmental colon resection unless they can be removed in one piece [9]. An estimated 5% of resected polyps and 20% of unresectable polyps contain invasive cancer [10]. Five-year survival rate for stage 1 colon cancer is more than 95%, and adjuvant therapy is not indicated [11].

3.4 Stage II colon cancer

The role of adjuvant chemotherapy in stage II is not clearly defined. 5-year disease free survival for these patients is more than 80%. Because of this relatively good prognosis, benefit from adjuvant 5FU-based chemotherapy is small and remains questionable given many of the trials are underpowered. In order to demonstrate a larger benefit or to unravel small differences with statistical significance, a highly efficacious therapy or trials with larger samples are needed. To detect an absolute improvement in survival at 5 years by 4% with more than 90% power, 4700 patients with stage II colon cancer would be required. A retrospective study based on SEER-Medicare linked database explored the outcome of more

than 3000 patients without any adverse features depending whether they received chemotherapy within 3 months after surgery or not. Interestingly, 27% of patients received adjuvant therapy in this group without much evidence to support it [12]. They reported a 5-year survival of 75% for those who did not receive chemotherapy versus 78% in those who received therapy. High grade, younger age, low comorbidities and white race were more likely to receive chemotherapy. After adjusting for known variables there was no difference in survival (HR 0.91, 95% CI 0.77–1.09).

A number of trials have tried to address the role of adjuvant therapy in stage II colon cancer with conflicting results. QUASAR (Quick and Simple and Reliable), a large UK study investigated the role of adjuvant 5FU in this randomized controlled trial [13]. This study enrolled more than 3000 patients with (91%) stage II cancers (node-negative) which also included 30% rectal cancer. After a median follow up of 5.5 years, there was about 20% reduction in the relative risk of death (any cause mortality HR 0.82; 95% CI 0.70–0.95; $p < 0.008$) in those treated with chemotherapy compared to placebo controlled arm which translated into small but significant absolute survival benefit of 3.6% (95% CI 1.0–6.0). Despite significant results, number of pitfalls in this trial has raised questions with regard to the benefit seen. The median number of lymph nodes removed in this study was 6 (in more than 60% of patients <12 lymph nodes were removed) which is well below current standards. In addition, there was a group of patients who received radiation therapy (14%) and another proportion received portal vein infusion therapy (6%), which are not standard practice.

There were a number of meta-analyses which support the use of adjuvant therapy in stage II colon cancer including NSABP, NCCTG and IMPACT. International Multicenter Pooled Analysis of Colon Cancer Trial (IMPACT) was a pooled analysis of randomized trials, showed a 2% improvement in 5-year overall survival. In another analysis of more than 150,000 patients with stage II colon cancer from National Cancer Database reported survival advantage of adjuvant therapy (HR 0.76; $p < 0.001$) [14]. Gill et al. analyzed pooled individual patient data of 3302 patients with stage II and stage III colon cancers. Although there was a statistically significant improvement in disease free survival (by 4%), overall survival difference (absolute benefit of 5%) was not significant [15]. The Adjuvant Colon Cancer End Points (ACCENT) collaboration analyzed individual patient data with regard to long term outcome after adjuvant therapy. Among 6900 patients with stage II cancers, there was 5% improvement survival at 8 years [16].

Given the conflicting data, adjuvant therapy in stage II colon cancer remains controversial. Several clinicopathological features and molecular markers are associated with poor prognosis in stage II colon cancers. These include T4 primary, bowel obstruction of peroration, poorly differentiated phenotype (including signet ring cells and mucinous) high pre-operative carcinoembryonic antigen (CEA), inadequate lymph node sampling (<13 nodes), lymphovascular space invasion and perineural invasion [17, 18]. Although most expert groups consider these factors as high risk features in stage II colon cancer, some discrepancy exist among their definition for high risk stage colon cancer [19–21]. While most expert groups recommend to consider these adverse factors when considering adjuvant therapy, there is limited evidence to suggest that the presence of one or risk factors are more likely to benefit from adjuvant therapy. In the landmark MOSAIQ trial, 434 patients were considered high risk stage II colon cancer. Although there was trend towards better disease-free survival in the FOLFOX arm compared to 5FU arm, overall survival was essentially similar [22]. The decision regarding adjuvant therapy in this setting will need to be individualized and take into account the patient's preferences regarding therapy.

3.4.1 Role of oxaliplatin

Two large phase III trials explored the role of oxaliplatin in stage II colon cancer; MOSAIC and NSABP C-07 which have virtually shown the lack of benefit of oxaliplatin in stage II colon cancer [22, 23]. Forty percent and 27% of patients were stage II in MOSAIC and NSABP C07 trials, respectively. An updated 10-year follow up report of MOSAIC confirmed the lack of benefit from oxaliplatin in stage II colon cancer. In fact there was a trend towards adverse outcome in low-risk stage II in MOSAIC, while there is a non-significant trend of improvement in disease free survival (7%) and overall survival (2%) [22]. No disease-free survival or overall survival benefit was seen in NSABP C-07 trial in patients with stage II colon cancer [23]. Therefore oxaliplatin is unlikely to benefit most patients with stage II colon cancer; however, it may be appropriate to discuss oxaliplatin in those with extremely high risk features, given the findings from MOSAIC.

3.5 Stage III colon cancer

Patients with node positive colon cancer are at higher risk of recurrence with a 5-year overall survival estimate of 40–60%. Adjuvant therapy is indicated for most patients with stage III disease to eliminate micro metastases and to improve disease free survival and overall survival. Combination 5FU/leucovorin and oxaliplatin regimen is the standard of care unless they are medically unfit to receive intensive chemotherapy where single agent 5FU/Leucovorin may be appropriate.

A landmark study in the 1990s established the benefit of adjuvant therapy in resected stage III colon cancer where 5FU/levamisole for 12 months decreased recurrence and improved survival [5]. Results remained significant at 5 years with a 41% reduction in recurrence and 33% reduction in death [24]. However subsequently leucovorin has emerged as an effective potentiator of anti-tumor activity of 5FU, whereas levamisole lacked significant biological activity. 5-FU is metabolized in cancer cells to 5-fluorouridine 5′-monophosphate (FUMP), by uridine monophosphate synthetase, with a resultant active form, 5-fluoro-2′-deoxyuridine 5′-monophosphate (FdUMP). FdUMP then forms a ternary complex with thymidylate synthase in the presence of reduced tetrahydro folate (5,10-CH_2-THF) which eventually inhibit DNA replication. Leucovorin is metabolized into 5,10-CH_2-THF and enhance formation of thymidylate synthase/5FU ternary complex and anti-tumor activity. Subsequent studies confirmed the lack of utility of levamisole and efficacy of leucovorin in combination with 5FU in adjuvant therapy of colon cancer [25].

Two large randomized studies established the role of oxaliplatin in the adjuvant treatment of stage III colon cancer. Multicentre International Study of Oxaliplatin/5FU/Leucovorin in the Adjuvant Treatment of Colon Cancer (MOSAIQ) utilized a 2 hour bolus infusional 5FU followed by 22 hours 5FU infusion along with oxaliplatin in a 2 weekly cycle (FOLFOX4) for 6 months in resected colon cancer patients (60% stage III and 40% stage II). A total of 2246 patients were randomized to receive either FOLFOX4 or 5FU/leucovorin. In the intention to treat population FOLFOX4 significantly improved 5-year disease free survival (73.3% 67.4%) compared to 5FU/leucovorin (HR 0.80, 95% CI 0.68–0.93; p = 0.003). Overall survival at 6 years was 78.5% versus 76.0% (HR 0.84; 95% CI, 0.71–1.00; p = 0.04). In a subgroup analysis, there was 4.2% improvement by the addition of oxaliplatin in 6-year overall survival in stage III disease (72.9% versus 68.7%, HR =0.80; 95% CI =0.65–0.97; p = 0.023), however, no overall survival benefit was evident by the addition of oxaliplatin in stage II cancer (85% versus 83.3%, p = 0.65). In a 10-year updated analysis, results essentially remained consistent. Oxaliplatin was approved for adjuvant treatment of colon cancer and is the standard of care for most patients

with stage III colon cancer. The FOLFOX4 regimen is associated with more toxicity compared to 5FU/leucovorin, notably grade 3/4 neutropenia was 41% in FOLFOX4 compared to 5% in 5FU/leucovorin and grade 3/4 diarrhea was 11% versus 7%. Oxaliplatin was associated with cold related dysesthesia and mostly reversible peripheral sensory neuropathy. Grade 3 neuropathy was reported in 12% of patients who received FOLFOX4. Although considered reversible, minority of patients may suffer long term or permanent sensory loss. About 30% of patients still had residual numbness at 12 months (5.9% grade 2/3) with another 24% experiencing some degree of neuropathy at 18 months from the end of treatment (3.9% grade 2/3).

A large second study confirmed the efficacy of oxaliplatin in adjuvant therapy for stage III colon cancer. NSABP C-07 enrolled 2409 patients with stage III (71%) and stage II (29%) colon cancer. They were randomized to receive either combination 5FU/leucovorin/oxaliplatin (FLOX) or 5FU/leucovorin. A weekly bolus 5FU Roswell Park regimen was used here instead of infusional 5FU. FLOX regimen improved disease-free survival compared to control arm (69.4% versus 64.2%; HR 0.82; 95% CI 0.72–0.93; p = 0.002), however overall survival differences were not statistically different. (HR 0.88; 95% CI 0.72–1.02; P = 0.08) No interaction was seen between treatment on the stage, however treatment effect did vary by age overall survival significantly improved in patients younger than 70 (HR 0.80; 95% CI 0.68–0.95; p = 0.01) with no effect seen in older patients [23]. However, FLOX regimen was associated with high incidence of grade 3/4 diarrhea (38% versus 32%) and hospitalization (5.5% versus 3%). Given the lack of survival benefit and toxicity with bolus 5FU regimen, infusional 5FU regimens like FOLFOX have become standard of care.

The XELOXA trial supported the benefit of oxaliplatin in combination with capecitabine. In this randomized trial, 1866 patients with stage III colon cancer were either treated with capecitabine/oxaliplatin or bolus 5FU/leucovorin regimen (Mayo clinic or Roswell Park) for 6 months. After a median follow up of 7 years disease free survival (63% versus 56%, HR 0.80; 95% CI; 0.69–0.93; p = 0.004) and overall survival (73% versus 67%, HR 0.83; 95% CI 0.70–0.93; p = 0.04) improved significantly compared to 5FU/leucovorin.

In all three trials oxaliplatin was associated with significant neurotoxicity which can be acute or chronic. Acute cold related neurotoxicity present as paresthesia or dysesthesia of hands and feet or muscular cramps including laryngospasm. This is often reversible but tends to recur with each treatment. On the other hand chronic neuropathy causes primarily a sensory neuropathy in limbs is thought to be due to accumulation of platinum products in dorsal root ganglia in a dose -dependent manner. About 10–15% of patients experience severe neuropathy after cumulative dose of 780–850 mg/m^2. Other clinical factors are implicated in the onset of neuropathy, but none shows strong association. Patents with existing other comorbidities such as diabetes, hypertension and smoking may be associated with higher incidence of neuropathy from oxaliplatin, these results were not statistically significant. But patients with diabetes seem to develop neuropathy at lower cumulative dose [26]. Another report suggests that incidence neuropathy may be less XELOX 3-wekely (130 mg/m^2) regimen than FOLFOX 2-weekly (85 mg/m^2) regimen [27]. Therefore, choice of oxaliplatin in the adjuvant treatment of colon cancer should be based on individual assessment of risk of recurrence and other clinical factors.

3.5.1 Role of radiation

Adjuvant and neoadjuvant radiotherapy is routinely used in the treatment of rectal cancer and has an impact on reducing the local recurrence rate and

therefore improving local control. However, the use of this modality in non-rectal colon cancer is controversial and not supported by randomized controlled trials. It is however considered in the situation of T4 tumor which invades surrounding structures such as the bladder or the abdominal wall where there is a perceived high risk of local recurrence of the tumor. A retrospective analysis of 21,789 patients with T4 colon cancer using the US SEER (Surveillance, Epidemiology and End Results) database found 1001 patient who received radiotherapy [28]. After adjustment for sex, age, N stage and tumor grade the relative risk of death from cancer at 5-years was 0.88 (95CI 0.8008–0.9779, p = 0.0165) in patients who received radiotherapy.

3.6 Role of adjuvant therapy for resected colorectal cancer metastases

Liver is the commonest site of metastases in colon cancer. Unlike many other solid organ cancers, metastasectomy improves survival in colorectal cancer, where 5-year overall survival may reach 50%. The best postoperative management strategy is not well defined, however, often perioperative chemotherapy is utilized in the form of FOLFOX or CAPOX with agents like irinotecan, anti-EGFR, or anti-VEFG therapy often added for eligible patients in the neoadjuvant setting if downstaging was necessary. In the EORTC 40983 trial, perioperative chemotherapy was associated with 7.3% absolute increase in 3-year progression-free survival, however there was no difference in overall survival [29, 30]. Another Japanese study also did not show overall survival benefit with adjuvant chemotherapy [31]. Given the established role of adjuvant therapy in stage III colon cancer, despite lack of strong evidence many expert groups support perioperative or postoperative chemotherapy for resectable colorectal cancer metastases.

4. Molecular markers

4.1 Mismatch repair enzyme deficiency

Colon cancers that lack mismatch repair enzyme (dMMR) exhibit high microsatellite instability (MSI-High) and are associated with better prognosis compared to those with proficient mismatch repair enzymes (pMMR). Consistently, frequency of dMMR is higher in stage II colon cancer (20%) compared stage III (12%) and stage IV (4%) [32]. In a seminal study by Ribic et al., reported the prognostic differences between dMMR and pMMR in 570 patients from 5 different trials of 5FU based adjuvant chemotherapy (stage II and III) [33]. Five-year overall survival was significantly better in dMMR compared to pMMR(HR 0.31; 95% CI, 0.14–0.72;p = 0.004). Furthermore, there was no survival difference between dMMR and pMMR among those who received adjuvant chemotherapy (HR 1.07; 95% CI, 0.62–1.86; p = 0.80). The benefit of adjuvant chemotherapy was restricted to those with pMMR only. Although not all studies are consistent, a systemic review of 32 trials supported the above finding [34]. The key enzyme involved 5FU metabolism in cancer cells, thymidylate synthase, is found to be overexpressed in dMMR colon cancers which confer resistance to 5FU based therapy. Therefore, most patients with stage II colon cancer would not benefit from 5FU (only) based adjuvant therapy. Nevertheless, the role of dMMR in adjuvant therapy for stage III colon cancer is less clear. Despite lack of prospective data, retrospective studies support the use of oxaliplatin based adjuvant therapy, although Sinicrope et al. reported reduced distant recurrence in stage III cancers after treatment with 5FU [35, 36].

4.2 Other molecular markers

Lack of CDX2 was associated with lower 5-year survival rate compared to CDX2-positive tumors, especially in stage II tumors (49% versus 87%, p = 0.003). CDX2 was also predictive of treatment benefit with higher disease-free survival in CDX2-negative tumors in both stage II and III tumors. This need to be further validated in prospective studies. The presence of BRAF V600E mutation confers a poor prognosis in colon cancer; however, concomitant loss of one or more MMR enzymes (dMMR) seems to improve the survival. In an analysis of three adjuvant chemotherapy trials of stage II and III colon cancer, BRAF mutation was not prognostic, however overall survival was poor among those with pMMR [32]. While another study of 2299 patients from two NSABP trials showed similar results, where BRAF mutation was not predictive of oxaliplatin benefit [37]. The presence of RAS (KRAS and NRAS) mutation is associated with resistance to EGFR targeted therapy in metastatic colon cancer. Although the presence of KRAS mutation seems to confer poor prognosis, not all studies are consistent [32, 37–39]. Number of other molecular markers such as DCC, TP53, thymidylate synthase and POL-E are also found to have prognostic significance [40–43]. Despite emerging evidence of these molecular markers, their predictive value is still not validated in clinical practice and they are not routinely considered in decision making regarding adjuvant therapy, except for MMR status.

Gene expression profiling has been utilized to characterize colon cancers and to identify gene signatures that could be predictive and prognostic. A number of commercial assays are developed in the recent past (OncoDefender-CRC, ColonPRS, ColoPrint colon cancer recurrence assay, GeneFx colon) but none have been approved for routine use in clinical practice. The Oncotype-DX colon cancer assay is perhaps the most validated tool which is a 12-gene assay developed to predict the recurrence score in stage II colon cancer. It was validated using prospective data from large studies including QUASAR, CALGB9581 and SUNRISE [44–46]. Despite the ability in predicting the risk of recurrence with confidence, it is unclear whether patients in higher risk category will benefit from adjuvant chemotherapy. A treatment score was developed using the data from QUASAR, but it was not predictive of the treatment effect. At this stage the data are insufficient to recommend routine use of multi-gene assays when deciding adjuvant therapy for stage II colon cancer.

4.3 Circulating tumor DNA (ctDNA)

Gene sequencing of colorectal cancer have identified number of common somatic mutations and these tumor-specific mutations can be utilized to detect the tumor DNA (ctDNA) in the cell free component of peripheral blood. Detectable ctDNA after surgical resection or after completion of adjuvant chemotherapy seem to be associated with high risk of recurrence. In a study of 230 patients with resected stage II colon cancer, 14 patients out of 178 who did not receive adjuvant chemotherapy had detectable ctDNA. Eleven of the 14 (79%) developed recurrence at a median follow up of 27 months. Among those who received chemotherapy 3/44 had detectable ctDNA and all of them have relapsed within 11 months [47]. In metastatic setting, changes in ctDNA correlate with radiological responses [48]. Consistently in the early stage colon cancer, patients who clear ctDNA after adjuvant therapy have favorable prognosis [49]. Currently available data suggest that ctDNA is robust marker of minimal residual disease after surgery or after adjuvant chemotherapy with good prognostic and predictive value. Although current assays used to detect ctDNA have high specificity and positive predictive value, the sensitivity of these assays need optimization. In addition, a consensus on the methodology and larger number of prospective trials are needed before their routine use in clinical practice.

5. Timing of chemotherapy

Adjuvant therapy should be initiated as soon as patient has recovered from surgery with complete healing of surgical wounds which usually takes about 2–4 weeks. A meta-analysis in 2019 which included 34 comparative studies of resected colon cancer reported that delay in treatment beyond 6–8 weeks was associated with inferior survival (HR 1.27,95% CI 1.21–1.33; $p < 0.001$) [50]. Another review which included more than 15,000 patients concluded that a 4-week increase in time to initiate adjuvant chemotherapy was associated with a 14% relative decrease in disease free survival and overall survival [51]. A number of other studies have consistent findings suggesting inferior outcomes when chemotherapy was initiated more than 6–8 weeks. However, most of these studies are retrospective in nature and potentially biased by confounding factors such as comorbidities, post-operative complications, and emergency resections which are all likely to delay the recovery.

6. Duration of therapy

The recommendations for duration of adjuvant therapy for colon cancer are evolving. Early adjuvant trials treated patients for 12 months with 5FU/levamisole which was the standard of care in 1990s. Subsequent studies revealed 6 months of therapy was at least comparable to 12 months which became the standard of care in late 1990s [25, 52]. MOSAIQ an NSABP C-07 trials utilized 6 months of oxaliplatin and 5FU based regimen which remained as standard practice until recently the IDEA (International Duration Evaluation of Adjuvant Chemotherapy) collaboration study explored non-inferiority of 3 months of adjuvant therapy versus 6 months. IDEA collaboration study was a prespecified exploratory combined analysis of six separate international randomized trials of 6 versus 3 months of oxaliplatin based adjuvant therapy. Although non-inferiority of 3-months was not proven in the intention to treat population, sub-group analysis revealed patients those who received capecitabine and oxaliplatin (CAPOX) for 3 months, 5-year disease free survival was non-inferior to 6 months, however 3 months of 5FU and oxaliplatin FOLFOX did not meet the non-inferiority margin [53, 54]. Among low risk patients (T1–3,N1) the 5-year overall survival benefit between 3 versus 6 months therapy was 89.6% versus 88.9% (absolute difference of 0.7%) whereas the absolute difference was 2.7 among higher risk patients (T4N2 and above). Therefore, in lower risk patients, 3 months of therapy is acceptable if CAPOX regimen was chosen, while 6 months of therapy should be offered with FOLFOX regimen for others with stage III disease with clear discussion with patients regarding the small added benefit and risk of long-term neuropathy. 5FU/Leucovorin without oxaliplatin is offered as adjuvant therapy in stage III colon cancer sometimes, when patients are medically unfit or elderly. Six months adjuvant therapy is the standard recommendation in this situation, given absence of prospective data comparing 3 months versus 6 months. Similarly, 6 months of 5FU based adjuvant therapy is standard in stage II colon cancer. However, patients with high risk stage II disease are sometimes treated with oxaliplatin based regimen. TOSCA trial investigated 3 months versus 6 months of adjuvant therapy in stage II and III colon cancer where one-third of them were stage II [55]. In the overall population, 6 months was superior to 3 months, however, 3 months of CAPOX regimen was non-inferior to 6 months. There were 1254 patients with high risk stage II disease in the IDEA collaborative study (including TOSCA study) which investigated the optimal duration of adjuvant therapy [56]. Investigators concluded that 3 months of CAPOX may be non-inferior to 6 months

in high risk stage II cancers, reflecting the finding in stage III disease. Consistently 3 months of FOLFOX was not non-inferior to 6 months.

7. Adjuvant therapy in elderly

Systemic chemotherapy in older adults may possess unique challenges due to comorbidities, and age-related organ dysfunction which may limit their life expectancy. In addition the impact on quality of life from chemotherapy may be more prominent in older adults. Benefit of adjuvant chemotherapy in older adults is well established. A pooled analysis of seven randomized trials of adjuvant chemotherapy (5FU/levamisole or 5FU/leucovorin) in stage II and III found comparable overall survival and disease free survival benefit in patients of over 70 compared to those less than 70 [57]. Similar outcomes were seen in another analysis of prospective data from 85,934 patients [58]. Although it is not clearly determined whether older patients experience more toxicities from chemotherapy, an analysis of 37,568 patients from ACCENT database (Clinical Trials From the Adjuvant Colon Cancer Endpoints Database) reported early mortality was significantly higher among those who are >70 compared to younger patients [59]. A pooled analysis suggested no difference in toxicity from 5FU based therapy in older adults; however, it is important to consider that toxicity from 5FU may vary depending on the schedule, specially gastrointestinal side effects in older adults may be more frequent with bolus regimens compared to short term infusional regimens [60]. In addition capecitabine may be associated with more severe toxicities in older adults, especially in those with diminished renal function. In a phase 3 trial of stage III colon cancer, particular toxicities like diarrhea were higher among patients over 65 with capecitabine [61]. Similarly, in X-ACT trial which examined capecitabine versus bolus 5FU (Mayo clinic), treatment-related toxicity was higher in patients above 70 (51%) compared to those less than 70 (39%) [62].

Although oxaliplatin based adjuvant chemotherapy improves survival in stage III colon cancer, its role in older adults above 70 is debatable. Subset analysis of three large randomized trials failed to demonstrate survival advantage in older patients. In an updated analysis of the MOSAIQ study, addition of oxaliplatin did not improve survival in 315 patients above 70 years (HR 1.16; 95% CI, 0.83–1.7) [22]. NSABP C-07 study enrolled 396 patients over 70 years, and no added benefit was seen with oxaliplatin in either in disease free survival (HR 1.03; 95% CI 0.77–1.36) or overall survival (HR 1.18; 95% CI 0.68–1.62) [23]. Consistently XELOXA study failed to demonstrate benefit of oxaliplatin over capecitabine alone in patients above 70 years (Disease free survival: HR 0.86; 95% CI, 0.64–1.16 and overall survival: HR 0.98; 95% CI, 0.62–1.56) [63]. A pooled analysis of seven randomized trials from ACCENT database with more than 14,500 patients (including 2575 patients over 70 years) suggested no survival advantage of oxaliplatin in those above 70 years (Disease free survival: HR 0.94; 95% CI, 0.78–1.13; Overall Survival: HR, 1.04; 95% CI, 0.85–1.27) [64]. However, it is unclear as to why addition of oxaliplatin was beneficial in metastatic setting and not in early cancer setting. Therefore, with currently available data, oxaliplatin is not recommended for routine use in patients above 70 who need adjuvant therapy, however, in those with high risk cancer and medical fit with good life expectancy, the benefit and risk of oxaliplatin should be discussed.

8. Drugs that are not routinely indicated as adjuvant therapy

Irinotecan, via its active metabolite SN-38 inhibits topoisomerase 1 enzyme, causing inhibition of DNA replication and cell death. Irinotecan has well

established activity in metastatic colorectal cancer in combination with 5FU/leucovorin and as single agent. However, three phase III randomized controlled trials have failed to show any benefit of irinotecan based regimens [65–67]. Bevacizumab and cetuximab have shown survival advantage in metastatic colon cancer when added to irinotecan or oxaliplatin based regimens. Bevacizumab is a vascular endothelial growth factor inhibitor, failed to show benefit when added to FOLFOX or capecitabine [68–70]. The NCCTG-N0147 trial examined the utility of cetuximab which is a mouse/human chimeric monoclonal antibody that targets the epidermal growth factor receptor, with FOLFOX compared to FOLFOX alone in resected colon cancer [71]. The trial was closed prematurely after the interim analysis showed no benefit of cetuximab. This was confirmed in another European PETACC8 trial which enrolled RAS wild-type patients [72]. Edrecolomab is a murine monoclonal antibody against EpCam antigen. Addition of edrecolomab to standard 5FU based adjuvant therapy did not improve disease-free survival or overall survival in stage III colon cancer [73]. Raltitrexed is a quinazoline folate analogue that acts as a direct and specific thymidylate synthase inhibitor which is often utilized in patients who experience cardiac toxicity with 5FU based therapy. PETACC1 trial examined the role of adjuvant raltitrexed in stage III colon cancer compared to 5FU/leucovorin. This trial was closed prematurely due to high rate of treatment related toxicity and death. However, an independent review found multiple incidences of protocol violations in relation to dose adjustment for renal function. Therefore, it may be appropriate to consider raltitrexed as an alternative to 5FU in patients with high risk stage III colon cancer who experience significant cardiac toxicity. Appropriate discussion about the evidence and potential toxicity is key in such instances [74, 75].

Non-steroidal anti-inflammatory (NSAID) drugs like aspirin or celecoxib have been examined as adjunctive therapies, however large randomized trial data are lacking. Most of the evidence supporting the use of aspirin in secondary prevention of colon cancer recurrence are from observational studies, though not all studies are consistent. Subset analysis of number of such studies have identified potential link to PIK3CA status, prostaglandin-endoperoxidase synthase 2 expression, and BRAF mutations. Although these data are interesting, they need to be confirmed in prospective trials. A large randomized controlled study examined the benefit of celecoxib in more than 2500 patients and there was no disease-free survival or overall survival benefit from the addition of celecoxib. Therefore updated 2013 American Society for Clinical Oncology (ASCO) guidelines did not endorse routine use of aspirin in this setting [76, 77]. Therefore, routine use of NSAIDs is not recommended currently until further studies are available. An association between serum vitamin D levels and resected colon cancer has been postulated; however, there is no high-quality evidence to support the routine use of vitamin D for this indication. Given the adverse of effect of vitamin D deficiency in skeletal system, it is not unreasonable to replace vitamin D in those who are deficient.

9. Surveillance

Aim of surveillance after curative resection of primary colorectal cancer is to identify asymptomatic recurrences who may be a potential candidate for curative resection. Although most randomized trials suggest modest survival benefit, not all trials are consistent. The benefit Intensive versus less intensive follow up strategies is still debated. Accordingly, surveillance strategies vary among different expert groups. Multiple meta-analyses have been conducted in an attempt to rationalize the surveillance plan, the latest being Cochrane analysis 2019, which examined the data from 13,216 patients from 19 randomized trials and found there was no

overall survival benefit from intensive surveillance. Intensive follow up resulted in higher rates of salvage surgeries with curative intent; however, this did not result in improved survival. Furthermore, these results were confounded by heterogeneity of the trials included in the meta-analyses. For example, definition of intensive versus less intensive follow up varied among the trials in terms of frequency of follow up [78]. In addition some trials included patents with stage I disease who have low rates of recurrence. Despite inconsistencies in the data, and the fact that curative metastasectomy improves survival in colorectal cancer patients, intensity of follow up should be tailored according to patient and cancer characteristics. Surveillance modalities include physical examination, carcino-embryonic antigen (CEA) and computerized tomography (CT) for surveillance. Follow up guidelines varies between the expert groups [79, 80]. A relatively intense follow up is reasonable for the first 3 years after the curative surgery, with 3–6 monthly physical examination and measurement of CEA. A 12 monthly CT scan is appropriate for the first 3 years and CT scans should be performed on any clinical suspicion thereafter. A colonoscopy is indicated after adjuvant therapy, if a complete colonoscopy was not performed at the time of surgery. Otherwise a routine colonoscopy should be performed at 12 months and then 5-yearly unless an adenomatous polyp is found which should prompt an earlier follow up colonoscopy.

10. Conclusion

Colon cancer is one of the leading cause or morbidity and mortality in the world with incidence increasing, especially in younger population. Advances in systemic chemotherapeutic options have improved the survival. Adjuvant chemotherapy has been shown to reduce the risk of recurrence after resection of primary colon cancer; however, it is associated with chemotherapy related morbidity and mortality. Clinicopathological features and molecular characteristics of the tumor need to be carefully assessed and adjuvant therapy should be tailored accordingly in order to avoid futile treatment and serious toxicities. Advances in genomic profiling and evolution of detection of circulating tumor DNA are promising and may guide the choice and intensity of treatment in the future.

Conflict of interest

The authors declare no conflicts of interests.

DOI: http://dx.doi.org/10.5772/intechopen.93874

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Chapter 9

Retinoids in Treatment of Colorectal Cancer

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Abstract

Retinoids are vitamin A metabolites best known for their role in embryonic development. Indeed, retinoid acid (RA) signaling plays a key role in regulating the development of the embryo body-plan by controlling embryonic stem cells (SCs). Retinoids function through their ability to induce cellular differentiation. Mutations in RA signaling pathway genes occur in most human cancers. The classic example is the chromosomal translocation involving RA receptor alpha in acute promyelocytic leukemia (APL). Because all-trans retinoic acid (ATRA) is a highly effective and often curative treatment for APL patients, determining if retinoids are efficacious for other cancer types is imperative. We review the current research on retinoids in colorectal cancer (CRC) and provide bioinformatics analyses of RA signaling. Our results show that most RA pathway genes are overexpressed and often mutated in CRC. Moreover, aberrant expression of many RA signaling proteins predicts decreased CRC patient survival. We also review aldehyde dehydrogenase (ALDH) expression in CRC because ALDH is a key enzyme in RA signaling, which regulates colonic SCs. Further investigation of RA signaling mechanisms that regulate colon SCs and how dysregulation contributes to the SC overpopulation that drives CRC growth should provide insight into strategies for designing new SC-targeted therapies for CRC.

Keywords: retinoic acid, stem cells, colon cancer, adenomatous polyposis coli, aldehyde dehydrogenase

1. Introduction

Our goal herein is to review current research findings on retinoids in colorectal cancer (CRC), and to provide an update from our bioinformatics analysis of RA signaling components in CRC. Retinoic acid (RA) is currently being used in the treatment of specific types of human cancers [1]. The classic example is use of ATRA as first line treatment for acute promyelocytic leukemia (APL). RA therapy has also been shown to improve survival in patients with neuroblastoma [2–4]. Additionally, RA-based agents have been evaluated for clinical anti-cancer activity in breast cancer and in lung cancer [5]. In this review, we discuss the anti-cancer activity of retinoids using *in vitro* and *in vivo* models of CRC, and the use of ATRA as a differentiation agent in SC research [4, 6–8].

A strong rationale to investigate RA signaling in oncology research is that ATRA is an effective drug used to treat APL patients. Indeed, ATRA effectively induces APL cells to terminally differentiate into neutrophils [9–11]. Current treatment regimens for APL also include arsenic in combination with ATRA because the combination provides a synergic drug response that cures the majority of APL patients, who

would otherwise be facing a highly fatal illness. The precise mechanism involved in triggering APL cells have been extensively studied with the hope of understanding how it can be applied to trigger differentiation in other cancer types. What appears to be the basis for clinical success in treating APL is that the RA/arsenic combination not only induces terminal differentiation, but it also abrogates self-renewal of APL SCs [12]. Thus, future retinoid-based treatments for other cancers will likely necessitate drug combinations that incorporate a RA signaling differentiation therapy and a SC-targeting therapy that inhibits cancer SC self-renewal.

2. Key components of the retinoic acid signaling pathway

To understand how the RA signaling pathway is altered in cancer and to provide a basis for designing retinoid-based treatment approaches to cancer, we provide a brief description of the key components in the RA signaling pathway. The reader is referred to Das et al. [13] for more detailed information. Listed below are the main proteins essential to proper functioning of the RA signaling pathway. A simplified schematic of the RA signaling pathway is illustrated in **Figure 1**.

2.1 STRA6 (stimulated by retinoic acid 6)

STRA6 is a cell surface protein that functions as a receptor to accept all-trans retinol from the extracellular retinol-binding protein RBP4 and to transport retinol across the cell membrane. STRA6 removes the retinol from RBP4 and transfers it to RBP1 in the cytoplasm. STRA6 does not transport RA.

2.2 LRAT (lecithin retinol acyltransferase)

LRAT is an enzyme that converts retinol to all-trans retinyl esters, which is a storage form of vitamin A. LRAT also functions to enhance cellular uptake of retinol by STRA6, which contributes to the activation of the RA signaling cascade.

2.3 RDHs (retinol dehydrogenases)

RDHs are a family of dehydrogenase enzymes involved in the conversion of retinol to retinaldehyde by catalyzing the oxidation of cis-isomers of retinol, including 11-cis-, 9-cis-, and 13-cis-retinol in an NAD-dependent manner. This family of short-chain dehydrogenases/reductases functions to catalyze the final step in the biosynthesis of 11-cis retinaldehyde.

2.4 DHRS3 (retinaldehyde reductase-3)

DHRS3 is an oxidoreductase that catalyzes the oxidation/reduction of all-trans-retinal to all-trans-retinol in the presence of NADPH. DHRS3 is essential for preventing the formation of excess RA during embryonic development.

2.5 ADHs (alcohol dehydrogenases)

ADHs are a family of alcohol dehydrogenases involved in retinoid metabolism via conversion of retinol to retinaldehyde by catalyzing the NAD-dependent oxidation of all-trans-retinol and its derivatives such as all-trans-4-hydroxyretinol. These enzymes metabolize a wide variety of substrates, including ethanol, retinol,

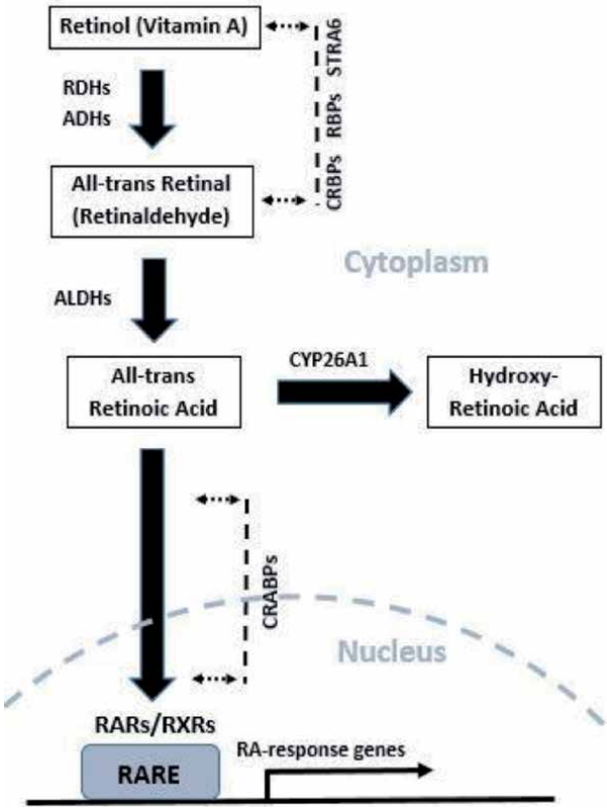

Figure 1.
This figure illustrates a simplified schematic of the RA signaling pathway, which plays a key role in embryogenesis and adult tissue homeostasis. The cell surface protein STRA6 accepts all-trans retinol from the extracellular milieu to transfer it across the cell membrane into the cytoplasm. STRA6 does not transport retinoic acid. After transfer or diffusion into cytoplasm, the internalized free retinol is bound to CRBP or is oxidized to retinal by retinol dehydrogenases (RDH) or alcohol dehydrogenases (ADH) and eventually to form all-trans retinoic acid (ATRA) by aldehyde dehydrogenases (ALDHs). ATRA then binds to cellular retinoic acid-binding proteins (CRABPs), which transfers ATRA to the nucleus. Once localized in the nucleus, ATRA serves as a ligand for binding to retinoid X receptors (RXRs) and retinoic acid receptors (RARs). Once ATRA travels to the nucleus, it binds RARs to induce the transcription of retinoid-responsive genes. Specifically, bound ATRA (or other ligands such as 9-cis) induces formation of a heterodimer (RA:RAR:RXR) in a complex at retinoic acid receptor elements on DNA, which then is able to induce transcription of RA-response genes. Thus, the RAR:RXR heterodimer acts as the main transcription factor in the classical RA signaling pathway. Nonetheless, the rate of formation of the RA:RAR:RXR complex, is still affected by other intracellular RA binding proteins such as CRABPs, which can sequester RA in the cytosol and limit the amount of RA available for binding to RARs. CRABPs can also facilitate RA degradation by directing RA to CYP26A1 RA-degrading enzymes. STRA6 = stimulated by retinoic acid 6, RDHs = retinol dehydrogenases, ADHs = alcohol dehydrogenases, RBPs = retinol binding proteins, ALDHs = aldehyde dehydrogenases, CRABPs = cellular retinoic acid binding proteins, CYP26A1 = cytochrome p450 family 26 subfamily a member 1, RARE = retinoic acid response element; RXRs = retinoid X receptors, RARs = retinoic acid receptors.

aliphatic alcohols, hydroxysteroids, and products of lipid peroxidation. ADHs consist of several homo- and heterodimers of alpha, beta, and gamma subunits, which plays major roles in ethanol catabolism. For example, three genes encoding alpha, beta, and gamma subunits of ADH1 are tandemly organized in a genomic segment as a gene cluster.

2.6 RBPs (retinol-binding proteins)

RBP1 (Retinol Binding Protein 1) and RBP2 (Retinol Binding Protein 2) are cytoplasmic retinol-binding proteins, which contribute to retinol uptake, storage,

and retinoid homeostasis. Specifically, RBP1 is the carrier protein for transport of retinol from the liver storage site to peripheral tissue. RBP2 also plays an important role in the uptake and intracellular transport of retinol, which is necessary for intracellular metabolism of vitamin A.

2.7 ALDHs (aldehyde dehydrogenases)

ALDHs are cytoplasmic enzymes that convert/oxidize retinaldehyde to RA. ALDHs are the enzymes that function after the alcohol dehydrogenase step in the RA signaling pathway. Nineteen ALDH isoforms encoded by 19 different genes exist in humans with as many orthologs in the mouse plus some alternatively spliced transcriptional variants. Through its role in retinol metabolism, ALDHs play a major role in the regulation of responses to RA.

2.8 CRABPs (cellular retinoic acid-binding proteins)

CRABP1 (Cellular Retinoic Acid Binding Protein 1) and CRABP2 (Cellular Retinoic Acid Binding Protein 2) are paralogous genes that encode cellular RA binding proteins. These proteins transport RA to the nucleus and function to regulate the access of RA to the nuclear RA receptors. Specifically, CRABPs are cytosol-to-nuclear shuttling proteins, which facilitate RA binding to its cognate receptor complex and nuclear transfer. These activities in the retinoid signaling pathway play an important role in RA-mediated differentiation and proliferation processes. CRABPs are structurally similar to the cellular retinol-binding proteins, but CRABPs only bind RA, which contributes to RA-directed differentiation in epithelial tissue. Diseases associated with CRABPs include embryonal carcinomas.

2.9 CYP26A1 (cytochrome P450 family 26 subfamily A member 1)

CYP26A1 is a cytochrome P450 monooxygenase that plays a key role in the metabolism of ATRA. The cytochrome P450 superfamily contains 57 members that are monooxygenase enzymes which catalyze many processes including drug metabolism and synthesis of cholesterol, steroids, and various lipids. CYP26A1 acts on ATRA by catalyzing the hydroxylation of carbon hydrogen bonds of ATRA. This includes both 4-hydroxylation and 18-hydroxylation activities. It has little activity toward 9-cis and 13-cis RA ligands. By regulating intracellular concentrations of RA, CYP26A1 can control RA signaling mediated gene expression in both embryonic and adult tissues. There are two alternatively spliced transcript variants of CYP26A1 that encode the different isoforms. This enzyme regulates the cellular level of RA which in turn regulates gene expression in both embryonic and adult tissues. Diseases associated with CYP26A1 include embryonal carcinoma and APL.

2.10 Retinoid X receptors (RXRs) and retinoic acid receptors (RARs)

The proteins encoded by RARs (*RARA, RARB, RARG*) and RXR (*RXRA, RXRB, RXRG*) genes are classified as members of the steroid and thyroid hormone receptor superfamily of transcriptional regulators. Various receptor isoforms can result from differential splicing of RA receptor genes and alternate promoter usage. RXRs and RARs are nuclear receptors that are central to retinoid acid (RA) signaling through their role in RA-mediated gene activation in response to their ligands ATRA or 9-cis retinoic acid. The 9-cis RA ligand has a high affinity for RXRs. These receptors are localized to cytoplasm and sub-nuclear compartments where they can bind RA to activate cellular signaling by forming homodimers or heterodimers. These dimers

primarily act as transcription factors via binding to the retinoic acid response elements (RARE) made of tandem 5'-AGGTCA-3′ sites known as DR1-DR5. When the ligand is absent, RXRA/RARB forms a multiprotein complex containing transcription co-repressors that can induce histone deacetylation, chromatin condensation and transcriptional suppression. When the ligand is present, it induces the co-repressors to dissociate from the receptors and co-activators are recruited which leads to transcriptional activation. Moreover, depending on the RARE DNA element condition, the heterodimer can act as a transcriptional repressor or transcriptional activator. For example, the heterodimer can act as a repressor on the DR1 element and as an activator on the DR5 element. RA receptors can also dimerize with thyroid hormone, and vitamin D receptors, which increases their DNA binding and transcriptional effects on their respective response elements. RA signaling regulates gene expression in various biological processes such as embryonic morphogenesis, granulocytopoiesis, and skeletal growth. It also plays an essential role in mediating the antiproliferative effects of RA by inducing cellular differentiation and apoptosis. In oncology, translocations between RARA and other loci are associated with the development of APL.

Now that we have briefly covered the key components in the RA signaling pathway that are critical to its proper function, we will discuss alterations of this pathway that occur in CRC.

3. Studies on alterations of retinoic acid signaling in CRC

Many studies have been done to identify mechanisms that explain how RA resistance occurs in solid tumors. Indeed, CRCs have been shown to lose the ability to produce ATRA and fail to growth inhibit or differentiate in response to treatment with ATRA [14–16]. Retinoic acid resistance appears to arise spontaneously in human cancers. To assess how alterations in RA signaling components effect response to RA ligands, we performed a literature search. Most of the published studies discussed below used *in vitro* experiments on CRC cell lines and analysis of human CRC tissues.

In a study by Jette et al. [16], seven CRC cell lines were evaluated for retinol dehydrogenase (RDH) enzymatic activity. They found CRC cells have decreased conversion of retinol into RA compared to normal cells. This inhibition of RDH expression appeared to be due to loss of adenomatous polyposis coli (APC) function. Interestingly, reintroduction of *wild-type APC* into an *APC*-mutant CRC cell line (HT29) increased expression of DHRS9 (RDHL) but not RDH5. Transfection of *wild-type APC* also increased production of RA. This study indicates intracellular crosstalk occurs between WNT signaling and RA signaling pathways.

Another study by Park et al. [14] examined the ability of retinol to inhibit the growth of CRC cell lines. They observed that some CRC cells are ATRA-sensitive (HCT-15) and other cells are ATRA-resistant (HCT-116, SW620, and WiDR). They also found that retinol inhibited the growth of both ATRA-sensitive and ATRA-resistant CRC cells through a RA receptor-independent mechanism.

Other studies by Shelton et al. [17] evaluated for over-expression of CYP26A1 enzymes that could lead to increased ATRA degradation. Indeed, CYP26A1 was upregulated in *APC*–deficient CRC tissues which provides a mechanism that might explain how increased WNT-signaling might be tied to impaired RA-signaling function in ATRA-resistant cells.

Lecithin retinol acyltransferase (LRAT), which esterifies retinol to retinyl esters, has also been evaluated by Cheng et al. [18]. Indeed, the LRAT gene promoter was hypermethylated in CRC cell lines and neoplasms compared to normal tissue [18]. A decrease in LRAT expression due to hypermethylation could lower availability of retinoids and reduce intracellular storage of retinol.

Additionally, several studies have investigated whether RA receptors are intact in CRC cells [19]. We discuss below a few studies that reported loss of RAR in CRC cells. In one study by Moison et al. [20], epigenetic changes appeared to lead to loss of RARB expression in HCT116 cells from DNA hypermethylation [20]. Interestingly, a DNA methylation inhibitor is able to restore RARB expression [21]. In a second study by Nicke et al. [22], the RA-resistant LoVo CRC line was induced to over-express RARB, which produced responsiveness to ATRA resulting in growth inhibition. A third study by Lee et al. [23] had similar results. They observed that ATRA treatment of RA-sensitive and RA-resistant CRC lines induced *RARA* expression in all cell lines, but ATRA only increased RARB expression in lines that were sensitive to RA. The DLD-1 RA resistant cells acquired sensitivity to ATRA when RARB was over-expressed. Additional studies that examine RA resistance due to alterations in RARs have also been reported [23, 24].

Finally, a recent study by Kropotova et al. [15] used RT-PCR to measure expression patterns of genes involved in ATRA biosynthesis. They evaluated normal human colorectal tissues, primary carcinomas, and cancer cell lines. Expression of most genes involved in ATRA synthesis was altered in CRC tumors and colorectal cell lines. Moreover, the expression of several genes, particularly ADH isoforms ADH2 and ADH3, showed decreased gene expression in adenomas when compared to more advanced carcinomas.

Overall, the studies on CRC discussed above show that RA signaling components become altered at many levels along the pathway. This includes: (i) loss of RAR expression that impairs RA response and gene transcription; (ii) decreased ability to enzymatically synthesize ATRA; (iii) LRAT alterations that impair retinoid storage; (iv) enhanced degradation of ATRA via CYP26A1. Many of these alterations appear to be a consequence of the mutations, such as *APC*, that drive CRC development [1, 25]. Thus, as CRC progresses, tumor cells develop resistance to ATRA by losing their ability to produce and respond to it, as well as, by causing its degradation.

4. Animal model studies

In addition to the studies on RA signaling in cell lines and CRC tissues discussed above, other important investigations have been done using animal models. Many of these studies were done using azoxymethane (AOM) or 1,2-dimethylhydrazine (DMH) to induce colonic neoplasms in rats to investigate the anti-tumor effects of retinoids [26]. An early study by Stopera and Bird [27] found that ATRA treatment reduced the number of AOM-induced aberrant crypt foci (ACF), a precursor to CRCs. Two studies [28, 29] using the DMH-induced colon carcinogenesis model indicated that vitamin A dietary supplementation may diminish ACF formation. Other studies by Wargovich et al. [30, 31] reported that 13-cis-retinoic acid (13-cRA), 9-cis-retinoic acid, and the synthetic Vitamin A derivative 4-hydroxy-phenretinamide (4-HPR) diminished AOM-induced ACF in rats. An interesting study by Zheng et al. [32] screened thirteen retinoids for prevention of ACF. They found that two retinoids, 9-cis-retinoic acid and 4-HPR, reduced both colonic ACF and tumor formation. In another study by Zheng et al. [33], 2-(carboxyphenyl)retinamide (2-CPR) was evaluated because it prevents ACF. However, they found that this synthetic retinoid analogue increased the number of colon tumors. Thus, these studies on rats show that ATRA, retinol, 9-cis-retinoic acid, 4-HPR, 13-cRA, and 2-CPR can inhibit the formation of carcinogen-induced ACF. However, only 9-cis-retinoic acid and 4-HPR were

shown to reduce colonic tumor formation, and 2-CPR actually increased the number of colon tumors in this rat model.

Several other animal studies to evaluate the effect of retinoids have employed the *Apc*$^{Min/+}$ mouse model. Experiments using this model are important because these mice develop intestinal tumors due to *Apc* mutations and *APC* is a driver mutation for CRC growth in humans.

A study of *Apc*$^{Min/+}$ mice by Volate et al. [34] showed that retinoic receptors including *Rara, Rarb, Rxrb, Rxrg* were all expressed in *Apc*$^{Min/+}$ adenomas. However, in AOM-treated *Apc*$^{Min/+}$ mice, *Rxra* was selectively downregulated in intestinal tumors. Therefore, these findings indicate that *Rxra* downregulation occurs early in CRC carcinogenesis and is not dependent on *Apc* mutations and beta-catenin.

Another study by Mollersen et al. [35] administered ATRA to *Apc*$^{Min/+}$ mice and discovered that ATRA treatment failed to prevent tumor formation. Three studies were then performed that gave results which provide mechanisms that helps explain this unexpected ATRA resistance.

One line of investigation focused on C-Terminal Binding Protein 1 (CTBP1), which has been reported to inactivate retinoid dehydrogenase RDH [36]. Examination of adenomas from *Apc*$^{Min/+}$ mice and familial adenomatous polyposis coli (FAP) patients showed an increased expression of CTBP1. Because CTBP1 decreases RDH levels, upregulated CTBP1 will lead to lower ATRA levels in tumors [37].

In another study on *Apc*$^{Min/+}$ mice, Shelton et al. [17] analyzed expression levels of CYP26A1, the major RA catabolic enzyme. They found that CYP26A1 expression was increased in tumors from *Apc*$^{Min/+}$ mice, and in tumors from FAP patients. They also determined that CYP26A1 is a TCF4 target gene which explains why CYP26A1 expression is increased due to upregulated WNT signaling in *APC* mutant tissues. An increase in CYP26A1 would lead to increased ATRA degradation, which provides a mechanism that helps explain why ATRA treatment failed to prevent tumor development in *Apc*$^{Min/+}$ mice.

A recent innovative study by Penny et al. [38] involved treating *Apc*$^{Min/+}$ mice with the CYP26a inhibitor Liarozole. Administration of Liarozole to *Apc*$^{Min/+}$ mice increased endogenous RA signaling (presumably by blocking ATRA metabolism) and effectively reduced intestinal adenoma numbers in these *Apc* mutant mice. We also found that treatment of human CRC cells with Liarozole decreased proliferation, sphere formation and size of the ALDH+ stem cell population [39]. This suggests that Liarozole might decrease tumor stem cell numbers in *APC* mutant tissues.

Thus, the above discussed animal model studies have provided valuable information on how the retinoid pathway might be targeted in designing treatment approaches for human CRC patients. The studies using chemical carcinogen models show that different retinoid drugs have different activities against colon tumors. The studies using the *Apc*$^{Min/+}$ model reveal it might be an effective screen for other retinoid drugs that have anti-tumor activity against *APC* mutant tissues. Perhaps a reasonable place to start would be to screen other agents for their ability to inhibit specific cellular processes upregulated in tumors that lower endogenous ATRA levels and decrease RA signaling.

5. Clinical studies

There have been an increasing number of clinical trials done on solid tumors using retinoids. However, our search of trials listed www.clinicaltrials.gov does not show any trials on CRCs using retinoids, Tretinoin or Liarozole. There were several

trials listed for breast, lung, prostate, pancreatic, renal, cervical, brain, skin, and several hematologic malignancies. Given the pre-clinical data discussed above, it seems like it would be reasonable to develop a retinoid-based trial for CRC.

6. Prospect for retinoid-based, stem cell-targeted therapies for CRC

We have been interested in the role of RA signaling in regulation of colonic SCs and how dysregulation of RA signaling may contribute to CRC development for several reasons: (i) RA regulates embryonic SCs during development [40] and WNT signaling, another key developmental pathway, has an opposing effect on embryonic SCs [41]. The idea that the mechanisms that regulate embryonic SCs are the same mechanisms that become dysregulated in the SC etiology of cancer [42] is intriguing because some scientists view cancer as aberrant organogenesis [43] and metastases as aberrant morphogenesis [44]. (ii) *APC* mutations occur in most CRCs (nearly 90%) during CRC development and *APC* mutation leads to constitutively activated WNT signaling. (iii) *APC* mutations that drive CRC development appear to do so by causing SC overpopulation [45]. (iv) ALDH, a key component in RA signaling, marks colonic SCs and tracks SC overpopulation during CRC development.

Indeed, our research team [39, 46–49] and others [50–52] have been using ALDH as a marker to identify and isolate SCs from patient tissues for several years. ALDH not only marks colonic SCs, but ALDH+ cells also have SC properties of self-renewal, drug resistance, and cell differentiation potential [53]. For example, ALDH+ cells possess self-renewing ability as shown by sphere-forming ability *in vitro* and tumor-initiating ability in mice [46, 51, 52, 54]. The drug resistance property of ALDH+ SCs comes from aldehyde dehydrogenase's enzymatic function, which is the cell's natural detoxification mechanism [50, 55, 56]. The ability of ALDH+ cells to differentiate comes from ALDH's functional role in the RA signaling pathway [5, 13, 57–59]. Moreover, we examined ALDH+ cells from colon tissues and observed that retinoid receptors RXR and RAR are selectively expressed in ALDH+ cells [39], which indicates that RA signaling mainly occurs via ALDH+ SCs. That RA signaling primarily occurs in ALDH+ stem cells provides a mechanism for selective treatment of SCs using RA analogues.

ATRA is commonly used as a differentiating agent in SC research. For example, we found that treatment of ALDH+ cancer SCs (CSCs) with ATRA inhibits cell proliferation, reduces SC proliferation, sphere formation, and SC population size, as well as enhances SC differentiation [39, 47]. Others have shown that retinoids decrease proliferation of ALDH+ SCs and, conversely, that inhibitors of ALDH increase proliferation of ALDH+ SCs [4, 6–8]. Because ALDH is key to retinoid acid (RA) signaling and retinoids are well known to promote differentiation of SCs [4], it follows that having ALDH in a SC provides the capacity for it to differentiate in response to retinoids.

Since *APC* mutations are known to increase WNT signaling in CRC, this raises the question: does increased WNT signaling lead to decreased retinoid signaling? Indeed, previous studies have implicated a role for APC in regulating RA biosynthesis and that *APC* mutations may lead to aberrant RA signaling [16, 36]. Notably, studies show that appropriately regulated WNT signaling is necessary for RA to induce neuronal differentiation of embryonic SCs [60]. Furthermore, not only does WNT suppress retinoid signaling, but conversely, increased RA signaling diminishes the ability of WNT signaling to block retinoid induction of the neural differentiation of SCs [61, 62]. That WNT signaling must be downregulated for neural differentiation to be inducible by RA treatment helps explain how *APC* mutation and increased WNT signaling might prevent maturation of ALDH+ colonic SCs in CRC development. Thus, it appears that *APC* mutations may alter the ability of

ALDH+ SCs to differentiate in response to retinoids, which would lead to expansion of the ALDH+ SC population size in CRC [39, 46].

7. Bioinformatics analysis of retinoid signaling components in CRC

We extended our study of RA signaling in CRC herein by using bioinformatics to analyze expression and mutation of RA signaling genes in CRCs and identify RA pathway genes that predict CRC patient survival. We found that most genes in the RA pathway are overexpressed and many are mutated in CRC (**Figure 2**). This is consonant with our previous result showing that RAR, RXR and other RA signaling proteins are overexpressed in CRC, which parallels overpopulation of ALDH-positive SCs that occurs during CRC tumorigenesis [39, 46]. Moreover, we found that aberrant expression of many RA signaling proteins (10 of 27) predicted ($p < 0.05$) decreased survival of CRC patients (**Figure 3**). We refer the reader to the meta-analysis by Chen et al. [63] which reveals that increased ALDH also indicates a poor prognosis in CRC patients. These updated findings provide insight into the complexity of RA signaling mechanisms and how RA signaling, when dysregulated, contributes to the development of CRC.

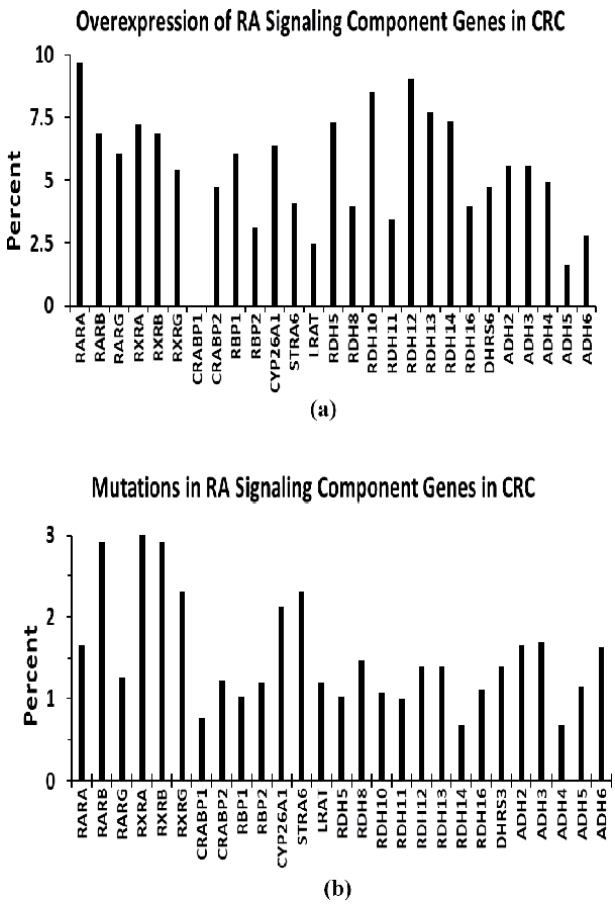

Figure 2.
Bioinformatics analyses of RA signaling genes in CRC, including overexpression (a) and mutations (b). Bioinformatics data derived from cosmic catalog of somatic mutations in cancer (https://cancer.sanger.ac.uk/cosmic).

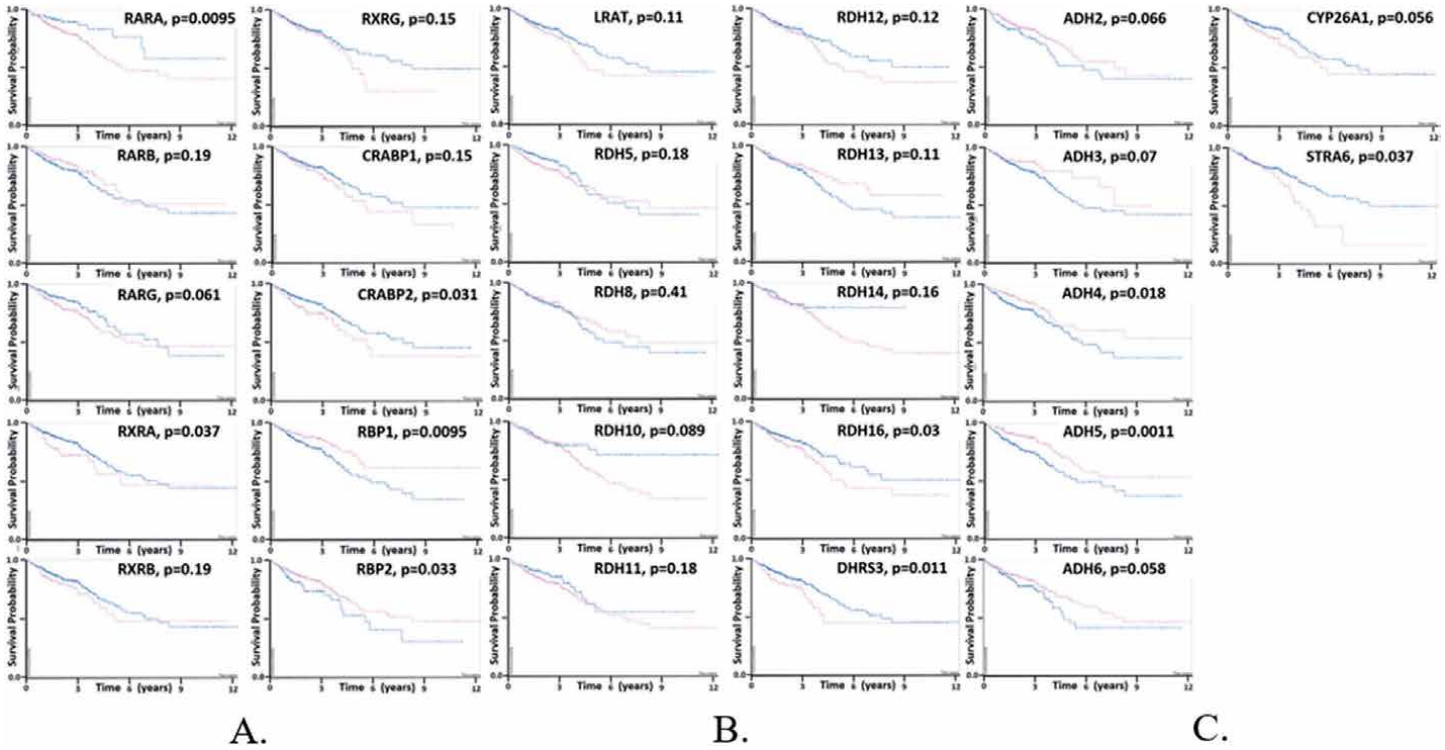

Figure 3.
Kaplan-Meier survival analysis of RA signaling genes that predict ($p < 0.05$) CRC patient survival. (A) shows survival curves for RARs (retinoic acid receptors), RXRs (retinoid X receptors), CRABPs (cellular retinoic acid binding proteins), and RBPs (retinol binding proteins). (B) shows survival curves for LRAT (lecithin retinol acyltransferase), RDHs (retinol dehydrogenases), and DHRS3 (retinaldehyde reductase-3). (B) shows survival curves for CYP26A1 (cytochrome P450 family 26 subfamily A member 1), STRA6 (stimulated by retinoic acid 6), and ADHs (alcohol dehydrogenases). Curves reflect low (blue) and high (red) gene expression. Y axis = survival probability (0.0–1.0). X axis = time (years 0–12). Bioinformatics data derived from the human protein atlas (https://www.proteinatlas.org).

CRC Cell line	APC mutation	Microsatellite instability	Beta-catenin mutation	RARA mutation	RARB mutation	RARG mutation	RXRA mutation	RXRB mutation	RXRG mutation
HT-29	Yes	Stable	No	No	No	No	No	No	No
SW480	Yes	Stabe	No	Yes	No	No	No	No	Yes
HCT116	Yes	High	Yes	Yes	No	No	No	No	No
LoVo	Yes	Low	Yes	No	No	No	Yes	No	No
DiFi	Yes	Stabe	Yes	No	No	No	No	No	No
SW48	Yes	High	Yes	Yes	No	No	No	No	No
SW1116	Yes	Stabe	No	No	No	No	Yes	No	No
COLO320	Yes	Stabe	No	No	No	No	No	No	No
LIM1863	Yes	Stabe	Yes	?	?	?	?	?	?
DLD-1	Yes	Stabe	No	?	?	?	?	?	?
RKO	No	High	No	No	No	No	Yes	No	Yes

Analysis done using the COSMIC database on human somatic mutations in cancer (https://cancer.sanger.ac.uk/cosmic).

Table 1.
Bioinformatics results on RXR and RAR mutations in CRC cell lines.

8. Conclusion and future perspectives

Our results indicate that RA signaling, when dysregulated, plays a major role in the SC origin of CRC. Overall, our review provides a strong rationale for future exploration of retinoid therapies for CRC in precision oncology. A few clues gleaned from our review are as follows: (i) drug screens using CRC cell lines (**Table 1**) and knockout of RA-signaling genes in human CRC cells might identify which retinoid drugs are active against cells with specific mutations; (ii) $Apc^{Min/+}$ mice may be useful to identify additional retinoid agents that are active against *Apc* mutant tissues; (iii) strategies for designing retinoid-based CRC therapies will likely need to incorporate retinoids into drug combination regimens; (4) CRCs will likely need to be genotyped to determine the status of RA signaling genes when administering RA-based treatments to CRC patients. Finally, continued discovery of the mechanisms that explain how RA signaling regulate normal colon SCs and how dysregulation of RA signaling in cancer SCs drive CRC growth should provide insight into how new SC-targeted therapies might be designed for CRC.

8.1 Materials and methods

The bioinformatics analysis on overexpression and mutation of RA signaling component genes in CRCs was done through the COSMIC website (cancer.sanger.ac.uk/cosmic). Bioinformatics analysis to identify RA signaling genes that predict CRC patient survival was done through The Human Protein Atlas (https://www.proteinatlas.org).

Conflict of interest

The authors do not have any conflicts of interest.

Funding

This study was supported in part by the Lisa Dean Moseley Foundation (BB), Cancer B*Ware Foundation (BB), and Cawley Center for Translational Cancer Research Fund (BB, CF).

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Section 5

Best Supportive Care

Chapter 10

Palliative Care in Colorectal Cancer

Ricardo Caponero

Abstract

Approximately 25% of patients present with liver metastases at the time of the first diagnosis and up to 50% will further develop recurrence in the liver during their disease course. Traditionally approached surgically, by resection of the primitive tumor or stoma, the management to incurable stage IV colorectal cancer patients has significantly changed over the last three decades and is nowadays multidisciplinary, with a pivotal role played by chemotherapy. Most patients with stage IV colorectal cancer have a poor prognosis, but numerous palliative modalities are available today. When a cure is no longer possible, treatment is directed toward providing symptomatic relief. Good symptom management in oncology is associated with improved patient and family quality of life, greater treatment compliance, and may even offer survival advantages.

Keywords: palliative care, supportive measures, symptom control

1. Introduction

Cancer is a major public health problem worldwide, and colorectal cancer is the third most diagnosed cancer among both men and women in the United States [1], Brazil [2] and, overall, it is the third more frequent malignant disease around the world (1.85 million of new cases/years; 10.2% of total malignancies), with a 2.27% cumulative risk of onset between 0 and 74 years [3].

The mortality from colorectal cancer varies with several factors from the genetic variations of disease to the developmental status of a nation. Tumor staging remains the main prognostic factor.

The last two decades have seen substantial progress in the treatments to metastatic disease offering significant improvements in survival. According to SEER, the 5-year relative survival rate for patients diagnosed from 2008 to 2012 was about 64% for all stages taken together, and it was 14% for patients with metastatic disease [4].

At the time of first diagnosis, approximately 25% of patients present stage IV, with liver metastases, and up to 50% will develop recurrence in the liver during the disease course [5]. Most of these patients have liver metastasis considered unresectable at presentation [6], but about 20–30% of patients have a resectable disease that is confined to the liver [3], and despite a metastatic diagnosis, a half these of patients may benefit from the surgical resection of liver metastasis with curative intent, with improvements in a 5-year survival [7].

Colorectal cancer survival disparities are largely driven by socioeconomic inequalities that result in differences in access to early detection tests, refinements in molecular diagnosis, and the receipt of timely, high-quality treatment [8].

Today, the median overall survival for patients with metastatic colorectal cancer being treated both in phase III trials and in large observational series or registries is about 30 months and is more than double that of 20 years ago [9]. These patients with unresectable disease remain incurable and the treatments are mainly palliative.

We performed a non-systematic literature review of the results of a search in PubMed® with terms "palliative care" and "colorectal cancer" published in the last 5 years without restrictions of language. We found 304 articles that were manually selected for reading and synthesis of this work.

2. Palliative care

Palliative care has appropriately been receiving increased attention in recent years, due to better comprehension of this field of action and due to incremental costs of antineoplastic therapy disproportionated with clinical results.

From practical standpoint, therapy is considered palliative when resection of all known tumor sites is no longer possible or advisable and chemotherapy have limited benefit rate. Since a cure, as commonly defined, is not possible, the goal of treatment and eventually the success of therapy become judged by the control of symptoms and alleviation of suffering, not more by survival advantages or longer disease-free intervals [10].

Providing optimal palliative care for the patient with advanced colorectal cancer is a complex and challenging process. The success rate depends on proactive multidisciplinary interventions, taken early in metastatic disease [11].

Palliative care can improve all phases of the disease, it allows better decisions in the end-of-life care and potentially reduces health-care expenditures, but the exact understanding of commonly used terms such as "supportive care," "symptom control" "palliative care," and "hospice care" was rarely and inconsistently defined in the palliative oncology literature [12].

The roots of palliative medicine may be traced since Hippocrates through medieval medicine until a more recent approach of Cicely Saunders and to a new concept of modern palliative care. It has evolved from a philosophy of care for the dying to an interprofessional discipline that addresses mainly the quality of life for patients and their families throughout the disease trajectory [13].

The best palliative care will ever require a multidisciplinary approach where treatment plans will be made in accordance with the wishes of the patient and his family with a goal of decreasing morbidity and focus on improving quality of life by addressing their physical, emotional, and spiritual needs, and on supporting their families [14].

The provision of optimal palliative care for these patients is a compound and demanding process and becomes more challenging when an incurable and asymptomatic primary progress to advanced metastatic colorectal disease [15].

Surgical resection may provide good palliation of symptoms and prevent future tumor-related complications as we saw before [15].

Better than dividing patients into strict treatment protocols and different models of care, this new concept supports the provision of patient care by a single discipline comprised of a team of health-care professionals with expertise in symptom management, psychosocial care, spiritual support, caregiver care, communication, complex decision-making skills, and end-of-life care [16].

The need for incorporating palliative care into routine oncology practice is still enormous, but the benefits of doing so are even more significant. Outside United States and some places in Europe, financially strained health systems will need cost-effective models of palliative care delivery. As the aging population increases, the

number of people diagnosed with cancer, and degenerative disease will increase, raising the need for this kind of approach.

As we see in the United States, as the cancer population grows, an already limited oncology workforce will be further strained. Cost- and resource-effective models of palliative care delivery will be required.

Volunteer work fills a large part of these gaps and can be the way out to overcome difficulties in access and funding [17], but adequate training of volunteers is essential to obtain the appropriate level of performance [16].

Community involvement needs to go beyond resource mobilization. In the current context of health systems, reaching higher levels of participation, involving the community as a partner in the implementation and support of these projects is something more complex and more difficult to achieve. Common barriers include the lack of mandatory preparatory work to understand the community's social and political dynamics, the facilitators' values and agenda [18].

Public expectations will rise and require that expectations will rise and require that palliative care be well integrated into all oncology care settings. All these factors will serve to promote the integration of expectations of a new way of oncology care.

The most important goals of palliative care are stablishing a good communication and offer an outstanding symptom control. Without adequate symptom control, no psycho-emotional measures can be adequately developed.

3. Symptoms of advanced disease

Initial symptoms vary from mild anemia to bowel obstruction. In extremis, two main situations are considered, asymptomatic (or minimally symptomatic) and severely symptomatic patients needing aggressive management, including emergency cases [9].

For a significantly part of symptoms or complications, the main treatment approach is surgery, by resection of the primitive tumor or stoma, eventually resection of liver metastasis, combined with radiotherapy (for rectal cancer) and chemotherapy (adjuvant or for metastatic disease).

Beyond surgery, the management of metastatic disease has significantly changed over the last three decades with the incorporation of antiangiogenics (bevacizumab and panitumumab) and anti EGFR1 agent (cetuximab), and more recently, immunomodulation with anti-PD1 and Anti PD-L1 agents. Nowadays the multidisciplinary approach is essential [19].

Emergency management of colorectal cancer patients still represents a major issue and is associated to high morbidity/mortality, and where there was often no time for patient directives to be established. The two major situations are obstruction and massive bleeding. Perforation is a rare presentation [20]. For these situations, palliative surgery may be the most appropriate approach.

Obstruction is traditionally approached surgically by colonic resection, stoma, or internal by-pass or a stenting [21].

Bleeding may be managed by surgery or less invasive approaches, including radiotherapy, laser therapy and other transanal procedures [12].

Perforation is associated with the highest mortality and remains mostly matter for surgeons, by abdominal lavage/drainage, colonic resection and/or stoma [11].

In cases of more advanced disease, patients may present with jaundice (due to liver metastasis or biliary tract obstruction) or malignant ascites. As the number of patients with malignant distal biliary obstruction who will undergo curative surgery is limited, endoscopy has a crucial role in palliation [22].

Biliary obstruction was most common cause of jaundice, and standard techniques of biliary cannulation by endoscopic retrograde cholangio-pancreatography are the main treatment option. When it fails, endoscopic ultrasound-guided biliary drainage is a better option compared to percutaneous drainage [23].

Biliary obstruction can be the presentation of an advanced stage of disease. Median overall survival after onset of jaundice was 1.5 months but may improved to 9.6 months in patients submitted to a biliary decompression who were able to receive further chemotherapy. Jaundice due to metastatic colorectal cancer is often an ominous finding, representing aggressive tumor biology or exhaustion of therapies [14].

Jaundice represents a major concern for patients, from the unpleasant feeling of itching and to the limitations of social interaction because the change in color of the skin.

Malignant ascites accompanies a variety of abdominal and extra-abdominal metastasis and mainly peritoneal dissemination of disease. It is a cause of high morbidity, major discomfort, and several other symptoms, leading to a significant reduction in the patient's quality of life. This situation raises several treatment challenges where treatment options include a multitude of different procedures but with limited efficacy, new clinical problems as loss of proteins and electrolyte disorders that may cause diffuse edema, and some degree of risk [24].

Patients with anasarca usually present with great discomfort, with cold, thin skin and with skin transudate. These are situations that may require palliative sedation and suspension of parenteral hydration since excess of fluids worsens symptoms [25].

The treatment of malignant ascites primarily includes paracentesis and diuretics, as first-line treatments. Diuretic therapy is effective at the very beginning of the disease but efficacy declines with tumor progression and was associated with dry mouth and orthostatic hypotension [15].

Paracentesis is widely adopted but it is associated with significant patient discomfort, risks of bleeding or bowel perforation, and loss of significant amount of albumin, with worsening of peripheral edema.

Intraperitoneal chemotherapy, targeted therapy, immunotherapy, and radioisotopes are rarely an option in this situation [13].

Some symptoms of advanced disease may be less specific for colorectal carcinoma and represent a systemic impairment by neoplastic disease, like cachexia/sarcopenia.

Cachexia is a multifactorial syndrome characterized by loss of appetite, weight, and skeletal muscle (sarcopenia) [26], leading to a cluster of symptoms like fatigue, functional impairment, increased treatment-related toxicity, poor quality of life, and reduced survival. Across malignancies, cachexia becomes more prevalent as the disease progresses, impacting approximately half of patients with advanced cancer [27].

Cachexia is a situation where preventive treatment is the most efficient. Once severe sarcopenia is established, the condition is rarely reversible. The nutritional approach should start with the development of anorexia, before weight loss begins [28].

Dietary counseling and physical activities must be offered with the goals of providing patients some advice for the preemptive management of cachexia. Enteral feeding tubes and parenteral nutrition should not be used routinely due to the discomfort, increment of costs and social life limitations.

No specific pharmacological intervention can be recommended as the standard of care, but progesterone analogs and short-term corticosteroids. It may be choose wisely because is associated with thromboembolic risk and gain of more fat gain than muscle mass [16].

Among other nonspecific symptoms of colorectal carcinoma, but often associated with advanced neoplasia, 35–96% of patients experience pain, 32–90% experience fatigue, and 10–70% experience breathlessness [25]. The broad ranges of incidence arise from the forms and time of assessment.

Symptom assessment in patients with advanced disease shows a progressive clustering of cascading events. Patients typically experience more than one symptom at any one time [29]. Grond et al. [16] found that 94% of those referred to a cancer pain clinic experienced additional symptoms, with 15% reporting at least five.

Symptoms may be a result of the interactions of conditions not only caused by the cancer itself, but as indirect consequences of the cancer, early or late adverse effects of treatment, and/or comorbid conditions [30].

Most patients with stage IV colorectal cancer have a poor prognosis, but numerous palliative modalities, as seem, are available today. When a cure is no longer possible, treatment is directed toward providing symptomatic relief, and a better quality of life [31].

It is difficult to draw the line between the usefulness of chemotherapy and therapeutic futility. As more drug options become available, the greater the tendency to prolong antineoplastic treatment.

Functional activity indexes can correctly evaluate disability but need to be combined and integrated with other parameters to assess prognosis.[15 Poor] performance status values are the main point to assess the possibility of the usefulness of chemotherapy.

Chemotherapy administration near death, showed that this approach did not improve quality of life for patients with poor performance status, and can be detrimental also for patients with good performance status [13]. Third line and beyond treatments prolonged overall survival versus palliative care, in high selected [32].

Aggressive care near the end of life as a sign of poor-quality cancer services [33] but, although numerous studies have measured these indicators, different criteria were used to define populations of interest make a comparison of results difficult [34].

Despite the frequency of symptoms and the limitations of antineoplastic therapy, oncologists did not systematically refer patients to a palliative care specialist, but only requested their intervention for pain and symptom management [35].

We need to change reality and dispel myths and prejudices in relation to palliative care to improve the quality of life between cancer diagnosis and death. It is necessary to change the role of the physician in navigating this course [36], or create referral programs regardless of the physician.

4. Time of palliative care in colorectal cancer

When a cure is no longer possible, treatment is directed toward providing symptomatic relief. The data available today leave little doubt that surgical resection, when feasible, may provide good palliation for some patients with metastatic disease. Although palliative surgery has been the mainstay of palliative care, an individualized multidisciplinary approach, which may involve both surgical and nonsurgical modalities, is probably the best current option [31].

In the last decade major changes in health-care delivery, changing demographics, and new treatment options have significantly changed the cancer patients' trajectory [37]. Now is the time to adapt the current models of palliative care to achieve the strongest dissemination to all cancer care settings. Implementation of palliative care can be achieved through recognition of emerging best practices and financial support to afford this model of care [38].

The difference between curative and palliative care lies in defining the main goal of treatment, since palliative treatments can extend life [39]. Palliative care is incorrectly associated with the suspension of all forms of antineoplastic therapy, but the persistence of inappropriate antitumor treatments in non-responding patients and overly aggressive care often affects a patient's quality of life [40].

A report from a retrospective cohort study including all patients who died of colorectal cancer between 2004 and 2012 in Manitoba, Canada, provides the better evidence that early palliative care involvement is associated with decreased odds of dying in hospital and lower health-care utilization and costs in patients with colorectal cancer [41].

5. Expected results

The goal of palliative care is improvement of quality of life. Good communication skills and flawless symptom control is associated with improved patient and family quality of life, greater treatment compliance, and may even offer survival advantages [42].

A 2016 meta-analysis evaluated 40 palliative care trials and concluded that this care was associated with improved patient quality of life and control of symptom burden [43].

The American Society of Clinical Oncology (ASCO) recommends the integration of palliative care into oncology practice [23], but despite the increasing evidence of the benefits of palliative care there is little consensus regarding strategies for integrating palliative care into the routine practice of oncology [44]. The lack of qualified professionals, the difficulties of access and the remuneration of professionals are still the biggest obstacles, especially in underdeveloped countries.

Palliative care has emphasized support for family caregivers. Although the family caregiver literature is even more limited than patient-focused studies, there is growing evidence of the benefits of palliative for family caregivers [15], but our current models of remuneration are insufficient to cover the care of the patient's family members, and especially in the assistance to bereavement.

For palliative care to be truly integrated into oncology care, it will need to take on new forms, expanding for greater use in outpatient and community settings, survivorship clinics, and the most important, primary practice of oncology [45].

In an era of limited resources and incremental costs of health care, expanding palliative care capacity to meet clinical guidelines and population health needs seems to save costs. The major problem is a significant variance in estimates of the effects of treatment on costs, depending on the timing of intervention, the primary diagnosis, and the overall illness burden.

Because ASCO guidelines state that palliative care should be provided concurrently with other treatment from the point of diagnosis onward for all metastatic cancer, a broad evaluation is required to evaluate the cost effects of palliative care across the entire disease trajectory [46].

6. Conclusion

Colorectal carcinoma is a frequent entity, with many patients being diagnosed with metastatic disease "de novo" or having recurrences of the disease after primary treatment.

Although a fraction of patients may undergo resection of metastases with curative intent, the vast majority will remain eligible only for palliative treatment modalities, which may include surgery or systemic antineoplastic therapy.

Fundamentally, the practice of palliative care includes an impeccable control of symptoms, good communication, and psycho-emotional support for patients and their families.

The demand for palliative care to be integrated throughout the cancer trajectory, combined with a limited palliative care workforce, means that new models of care are needed.

Palliative care began in academic centers with specialty consultation services, and its value to patients, families, and health systems has been evident.

Volunteering can help fill most of the gaps in palliative care, but its implementation is still difficult and restricted to some more developed centers.

This chapter discusses evidence regarding the need for integration of palliative care into routine oncology care and describes the best practices recognized for dissemination of palliative care. The available evidence suggests that palliative care be widely adopted by clinicians in all oncology settings to benefit the patients with cancer and their families. Efforts are needed to adapt and integrate palliative care into community practice.

The benefits of palliative care can only be realized through effective dissemination of these principles of care, with more primary palliative care delivered by oncology clinicians.

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Edited by Alberto Vannelli

Colorectal cancer is the third most common cancer diagnosed in both men and women worldwide. This book examines state-of-the-art research relating to the etiology, diagnosis, prevention and treatment of colorectal cancer. It emphasizes the importance of a multidisciplinary approach involving multiple specialties, including surgery, gastroenterology, radiology, biology, oncology, radiotherapy, nuclear medicine, and physiotherapy.

Published in London, UK

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ISBN 978-1-83881-117-4