Coordinated by Robert Benamouzig
& Gabriel Rahmi

CRC HORIZON 2030

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SUMMARY

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COLORECTAL CANCER, WHAT VISION FOR 2030 ?

FOREWORD

Robert Benamouzig [1], Gabriel Rahmi [2]
[1] *Service of gastroenterology and digestive oncology, Hospital Avicenna, Bobigny*
[2] *Service of gastroenterology and digestive endoscopy, Hospital George Pompidou, Paris*

« *Our knowledge of dynamic processes is necessarily inferior to our ability to describe stationary conditions.* »
Oskar Morgenstern

The authors of this book, which is based on colorectal cancer in 2030, that are all recognized experts in their field, approached this unusual writing exercise with humility. From accepted scientific facts, how can we talk about the medicine of tomorrow, instead of medicine of today? We can easily recognize in this legitimate apprehension from the authors, a sign of their competence.

Several difficulties inherent in this projection into the future have been identified. A discussion about colorectal cancer requires a discussion about its epidemiological progression. Current data require dynamic reading and sometimes contradictory trend analysis, that are evolving over time and affect space in different ways. Colorectal cancer is not only a disease of the human body but also a disease of the social body, and as such it is subject to external dynamics. Lifestyles and demographic variations will determine future prevalence, while at the same time our understanding of the genetic factors and factors that influence the exposome will grow. Current prevention policies, based on the level of established proof, are also social phenomena and thus subject to change according to current sociological and economic concerns. The year 2020 is a striking example of the intricacy of the political and medical spheres and it would be naive to think that the year 2030 would be different...

The nosological framework of "colorectal cancer" is going to evolve. Will the term "colorectal cancer" exist in 2030? The question seems provocative but it is not impossible that in the future nomenclature there will not be one but many colorectal cancers, classified according to their molecular and cellular characterization.

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A better understanding of tumor development and a more refined characterisation of its microenvironment could thus radically change our approach to this pathology.

The last thirty years have seen the deployment of screening and prevention strategies, that have mobilized both translational and clinical research, clinical management and public activism. This model of healthcare, centered on the identification of at-risk populations and identification of early forms, follows an undeniable medical and economic rationale. How likely is it to evolve? The advent of artificial intelligence and big data seem to complete the existing strategies rather than upset them. Nevertheless, the unprecedented possibility of a machine carrying out fine-grain correlations, identifying at-risk profiles by cross-checking data, such as closely modeling the intra-individual evolution, will certainly have an impact.

What will be the role of *in silico* studies in developing treatments in the years to come? What control and validation protocols should be put in place, when the size of the studies does not allow classical procedures and comparisons with a control group? This evolution of our disciplines is difficult to anticipate and it will require a lot of creativity, with the physician occupying a role in the design of future research at the junction of institutional and industrial actors.

Moreover, the study of colorectal cancer comes up against a difficulty formulated by the economist and philosopher Oskar Morgenstern in the 1920s: the very act of predicting can affect the future prediction. The authors of this book (and the readers) will therefore likely contribute through their representation and affect the future to come.

Of course, these stumbling blocks are a justification for this enterprise. Because the future is not fixed and because our predictions directly influence them, often our foresight has a practical value: formulating hypotheses, setting up scenarios and questioning the inevitable gap between our forecasts and the reality as it happens, creates a task that is not only stimulating, but also necessary for anyone wanting to master their fate. Also, because our most entrenched conceptions are likely to undergo great upheavals, it is important to preserve our "sense of the possible", our ability to think outside of the present realities, to step aside from short-term pragmatic approaches which may soon become outdated. Finally, because innovation is already influencing our methods and our representations, it is important to understand what is already from the future in our society, to preserve it, make it grow, and finally let it take over.

The reader should not expect a work of science-fiction in this book. The perspectives provided in the following pages are based on rigorous scientific data.

The contributors to this book have attempted to define the developments, to see how they may contribute, and what opportunities, what uncertainties, and even what tensions could result from them. We have not attempted to homogenize

or to propose an artificially coherent chart: any disagreements or differences of point of view make sense. We have not even corrected the authors when they have attributed the quote "*It's difficult to make predictions, especially about the future*" to different personalities, from Niels Bohr to Pierre Dac... Nevertheless, the reader will also find many common points and many echoes between disciplinary fields. The idea is not to offer a static picture but a preview of a moving panorama under perpetual recomposition.

We would like to express our gratitude to the authors that have undertaken an unsusal writing exercise, that they have recognized as interesting and original. A big thank you also goes to Mast diagnostic laboratories who's support has rendered the realization of this book possible. Under the current circumstances of mistrust toward progress, the biomedical industry as well as medicine, reflections about the future will not only stimulate us, they will also federate us.

NUTRITION & LIFESTYLE

A KEY ROLE IN THE INCIDENCE OF COLORECTAL CANCER

David Deutsch [1], Mélanie Deschasaux-Tanguy [2,3], Julie Ginhac [3], Juliette Bigey [3], Robert Benamouzig [1], Mathilde Touvier [2,3], Bernard Srour [2],
[1] *Department of Gastroenterology and Digestive Oncology, AP-HP, Avicenne Hospital, Sorbonne Paris Nord University, Bobigny, France*
[2] *Nutritional epidemiology research team (CRESS-EREN), U1153 Inserm, U1125 Inrae, Cnam, Sorbonne Paris Nord University, Bobigny, France*
[3] *NACRe network, Jouy-en-Josas, France* *

« *Progress imposes not only new possibilities for the future, but new restrictions.* »
Norbert WIENER

Colorectal cancer (CRC) is a major public health problem, accounting for 10% of all cancer cases worldwide. With 48,061 new cases and 20,453 deaths in 2020, it is the second most common cancer in women (after breast cancer), the third in men (after prostate and lung cancers), and irrespective of sex, the second cause of death by cancer in France [1].

One of the prevention strategies for CRC in France today is based on fecal screening every two years by immunological testing, and it is proposed to all individuals between the ages of 50 to 74 who are asymptomatic with no personal or family history of colorectal adenoma or cancer. If the test is positive, a colonoscopy is performed with the aim of detecting colorectal adenomas or CRC at an early stage. Indeed, complete resection of adenomatous precancerous lesions is associated with a decrease in the incidence and specific mortality related to CRC [2,3], and the diagnosis of early CRC is associated with good prognosis and high survival rates (89% survival at 5-years in stage I) [4]. According to « Public Health France » (Santé publique France, SpF), during the period between 2018-2019, only 30.5% of the targeted population in France took part in this CRC screening program [5].

Furthermore, it was estimated that in France in 2015, approximately 56% of incident cases of CRC in men and 40% in women were attributable to modifiable risk factors, among which nutritional factors [6].

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It is therefore urgent to explore and promote the factors that are associated with the risk of CRC to patients and citizens, to initiate a preventive medical approach.

DIETARY FACTORS ASSOCIATED WITH THE RISK OF CRC

Nutritional risk factors: red and processed meats

Beef (including veal), lamb, pork, goat and horse meat are considered to be "red meats". According to the latest report from the WCRF (World Cancer Research Fund) 7, red meat consumption is associated with an increased risk of CRC with a «probable» level of evidence, equivalent to group 2A of the International Agency for Research on Cancer (IARC) 6. The increased risk of CRC is 12% for the consumption of 100 g of red meat per day (relative risk (RR): 1.12 [95% CI: 1.00-1.25]). This increase is 22% for colon cancer (RR: 1.22 [95% CI: 1.06-1.39]), but it is not significant for rectal cancer 7. Red meat is therefore considered a probable carcinogen.

«Processed meats» include deli meats (including cooked ham), salted, dried or smoked meats (including canned meats). In their latest report, the WCRF attributes a convincing level of evidence to the association between processed meats and the risk of CRC, with a 16% increased risk per 50g serving per day (RR: 1.16 [CI 95 %: 1.08-1.26]), which is significant for colon cancer but borderline significant for rectal cancer 7. The IARC also classifies processed meats as group 1 carcinogen (established carcinogen) 6.

In practice, it is estimated that 4.3% and 9.8% of new CRC cases in France can be attributed to red and processed meat consumption, respectively 6.

Public Health France, through the National Nutrition and Health Program (PNNS), therefore recommends limiting the consumption of red meat to 500 g per week, and charcuterie to 150 g per week, and favoring cooked ham and poultry. The consumption of poultry, fish, eggs, as well as dry vegetables (a source of vegetable proteins) allows to compensate for protein intake 8.

The pathophysiological hypotheses to explain the link between red and processed meat consumption and CRC are multiple. Cooking at high temperatures leads to the formation of heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH), i.e. mutagenic chemicals that are able to form DNA adducts 9. Red meats are also rich in hemoglobin and heme iron, which stimulate the formation of N-nitroso compounds with an effect on the transport of oxygen, oxidative phosphorylation, DNA synthesis and cell growth 10,11. Oxydative phosphorylation is an important source of reactive oxygen species, that are genotoxic and that stimulate lipid peroxidation. Regarding processed meats, the role of nitrite salts (used as preservatives) has been mentioned as potentially genotoxic 11. Finally, red meats and processed meats are rich in saturated fats, leading to the formation of potentially carcinogenic secondary bile acids.

Protective nutritional factors

Foods with high fiber content

Dietary fibers are complex carbohydrates that are non-digestible in the small intestine. They include cellulose, pectin, mucilages, lignin, etc. They are present in foods of plant origin, mainly in whole grain products (whole grain or cereal breads, pasta, semolina, brown rice, etc.), legumes (lentils, peas, dried beans, etc.) as well as in fruits and vegetables. According to the WCRF, the level of evidence for the association between the consumption of dietary fiber and the risk of CRC is considered probable. A meta-analysis of the dose-response association showed a risk reduction of 7% for a consumption of 10 g of dietary fiber per day (RR: 0.93 [95 % CI: 0.87-1.00]) 7. Consumption of whole grains has also been independently studied, with a 17% reduction in the risk of CRC for a 90 g serving per day (RR: 0.83 [95% CI: 0.78-0.89]), statistically-significant for colon cancer but not for rectal cancer.

Public Health France therefore currently recommends consuming at least 30 g of fiber per day, which can be achieved by consuming legumes at least twice a week, whole grain products at least once a day, and at least 5 servings of fruits and vegetables per day (about 400 g per day) 8.

Several mechanisms seem to potentially explain the protective effects of dietary fiber and whole grains on the risk of CRC 12. Fibers are fermented in the intestinal lumen by the microbiota, resulting in the formation of short-chain fatty acids (butyrate being the main one) with anti-inflammatory and anti-proliferative properties. Fibers also accelerate intestinal transit and increase the volume of stools, thus reducing the contact between the colonic mucosa and the carcinogens that could be present in the colonic lumen, as well as reducing the production of secondary bile acids 13,14.

A high-fiber diet limits insulin-resistance and inflammation, and it reduces the blood concentrations of steroid hormones and growth factors, thus limiting cell proliferation 15. Whole grains are rich in vitamin E, selenium, copper, zinc, lignans, phytoestrogens and other phenolic compounds with possible anti-tumor and anti-oxidant effects 13,16. Finally, they may also have anti-tumor activity by binding carcinogens and regulating the glycemic responses.

Dairy products and calcium

Dairy products include milk of animal origin, milk-based beverages, yogurts, fresh or ripened cheeses. According to the latest WCRF report, the level of evidence for the association between the consumption of dairy products and the risk of CRC is considered probable, with a reduction in the risk of colon cancer of 13% per consumption of 400 g per day (RR: 0.87 [95% CI: 0.81-0.94]), and it is not statistically-significant for rectal cancer 7. This association is also observed for a consumption of 200 g of milk per day (RR: 0.94 [95 % CI : 0.92-0.96]) or 200 mg of dietary calcium per day (RR: 0.94 [95 % CI: 0.93-0.96]) 7.

Current recommendations for adults are to consume two servings of dairy products per day. A portion corresponds for example to approximately 150 ml of milk, 125 mg of yogurt or 30 g of cheese. It is also recommended to favor cheeses that contain the highest calcium levels and with less fat, and to vary the dairy products [8].

Most of the protective effects of dairy products on colorectal cancer risk seem to be related to calcium, whose bioavailability is increased by casein and lactose through several mechanisms [17]. Calcium acts by binding toxic substances, limiting the occurrence of KRAS mutations in colonocytes and preventing the effects of heme iron on colon carcinogenesis [18,19]. It acts directly on cells via different signaling pathways, decreasing cell proliferation while promoting cell differentiation and apoptosis of cancer cells [20]. It exerts a negative feedback control on the Parathyroid hormone and therefore regulates cell proliferation [21]. Finally, it also has an indirect mode of action by binding to unconjugated secondary biliary acids and free fatty acids, thereby limiting their toxicity on the colorectal mucosa [22]. Other elements that can be found in dairy products, such as lactic acid bacteria, butyrate, lactoferrin and vitamin D may also play a role [23].

Other nutritional factors may have beneficial effects in preventing CRC but the data remain insufficient at this stage to reach a good level of evidence and allow clear recommendations (*table 1*).

It should be noted that the Nutri-Score, an official 5-letter/5-colour logo displayed on food packaging, orients food consumers towards healthier foods (low in calories, saturated fats, salt, sugar while rich in fruits and vegetables, legumes, nuts, proteins and fibres), thus helping to tend towards more effective prevention of colorectal cancer and other chronic diseases on a daily basis. It is therefore important to educate patients and their families regarding its use [24].

NON-DIETARY NUTRITIONAL, ENVIRONMENTAL AND LIFESTYLE PARAMETERS ASSOCIATED WITH CRC RISK

Tobacco

Smoking is associated with an increased risk of CRC, with a long latency period and an increased risk that remains for about 25 years after smoking cessation in former smokers [25-27]. Around 6.6% of CRC cases are estimated to be attributed to smoking in France [28]. Patients must therefore be encouraged to quit smoking and they should be supported to achieve complete and prolonged abstinence.

Alcool

Alcohol consumption is a risk factor for colorectal cancer with a «convincing» level of evidence as determined by WCRF, for all types of alcohol (wine, beer, spirits, etc.). It is considered responsible for 16.1% of incident cases of CRC in France [7].

Given its impact on the development of other cancers, as well as other health problems, Public Health France recommends limiting alcohol consumption to a maximum of two standard drinks per day (i.e. 20 g) and not consuming alcohol every day (a maximum of 10 glasses per week) [8]. One should however note that the risk of cancer increases with as little as one glass per day on average for breast cancer [29]

There are several hypotheses to explain the effect of alcohol on colorectal carcinogenesis. The main hypothesis is based on acetaldehyde, a toxic metabolite produced by ethanol oxidation that has a carcinogenic effect on colonocytes. Heavy alcohol consumption can also lead to oxidative stress and the production of genotoxic reactive oxygen species (ROS). Alcohol can also promote the entry of food carcinogens into cells, from tobacco or of environmental origin, through its solvent effect. It also leads to a hormonal imbalance, interferes with the metabolism of vitamin A and with DNA repair mechanisms. Folate deficiency (vitamin B9) may promote the genotoxic effects of alcohol and disrupt DNA methylation, thereby modifying the expression of the genes involved in carcinogenesis [30].

Overweight and obesity

Overweight and obesity represent major concerns for public health. Nearly half of adults in France are considered overweight, and the prevalence of overweight increases in a disadvantaged social context [31].

The WCRF carried out a dose-response meta-analysis that assigned a «convincing» level of evidence for the association between overweight and the risk of CRC, both in men and women. For each increase of 5 kg/m² in body mass index (BMI), this analysis found a 7% increase in colon cancer risk (RR: 1.07 [95 % CI : 1.05-1.09]) and a 2% increase for rectal cancer risk (RR: 1.02 [95 % CI % : CI 1.01-1.04]). This association was even greater above a BMI of 27 kg/m². Considering waist circumference, that reflects abdominal obesity each 10 cm increase was associated with a relative risk of 1.04 (95% CI : 1.02-1.06) for colon cancer, but not for rectal cancer.

In France in 2015, 13.6% and 7.1% of incident cases of colon and rectal cancer were considered attributable to overweight, respectively.

Several mechanisms could explain the increased risk of CRC associated with overweight, the main one being insulin resistance leading to increased secretion of insulin by the pancreas. This chronic hyperinsulinism stimulates cell proliferation via the production of IGF-1 and it inhibits apoptosis [32-36]. An overweight status also contributes to the establishment of a chronic inflammatory state, with increased serum levels of pro-inflammatory factors (TNF-α, IL-6, CRP, leptin), promoting oxidative stress and lipid peroxidation with genotoxic consequences [37,38].

In order to limit overweight, Public Health France and the French National Cancer Institute (INCa) therefore recommend:

- limiting the consumption of energy-dense foods, rich in fats and/or sugars;
- favoring foods with low energy density (fruits and vegetables);

TABLE 1. Level of evidence of the association between nutritional parameters and the risk of colorectal cancer according to the WCRF (World Cancer Research Fund) 7.

Level of evidence		Decreases risk	Increases risk
High	Convincing	Physical activity[1,2]	Processed meats[3] Alcohol consumption[4] Overweight/obesity[5] Adult height[6]
	Probable	Whole grain cereals Food rich in fibers [7] Dairy products[8] Calcium intake[9]	Red meat[10]
	Limited (favorable)	Vitamin C-rich food[11] Fish Vitamin D[12] Multivitamin supplements[13]	Low intake of non-starch vegetables[14] Low fruit intake[14] Foods containing heme iron[15]
Limited	Limited (no conclusions possible with the current level of knowledge)	Cereals and derivatives; potatoes; animal fat; poultry; sea food; fatty acids; cholesterol; omega-3 fatty acids (fish oil); legumes; garlic; non-food sources of calcium; foods with added sugar; sugar (sucrose); coffee; tea; caffeine; carbohydrates; fat; starch; glycemic load; glycemic index; folate; vitamin A; vitamin B6; vitamin E; selenium; low-fat foods; methionine; β-carotene; α-carotene; lycopene; retinol; caloric intake; meal frequency; eating habits	

1. Any type of physical activity: habitual, household, transport, leisure.
2. Convincing for colon cancer, without any possible conclusions for rectal cancer.
3. Charcuteries, salted, dried, smoked meats, or meats with preservatives.
4. Based on a consumption of approximately 30 g/day (2 glasses per day).
5. Overweight assessed by body mass index (BMI), abdominal circumference, abdominal adiposity (waist circumference/hip circumference ratio).
6. Height in adulthood does not directly influence the risk of cancer but is a marker of environmental, hormonal and nutritional growth factors.
7. Includes both foods naturally rich in fibers and foods with added fiber.
8. Including dairy products in general, milk, cheese, and dietary calcium.
9. Based on calcium intake > 200 mg per day.
10. Includes beef, pork, lamb and goat.
11. Limited level of evidence for colon cancer, no conclusion possible for rectal cancer.
12. Foods that contain vitamin D, serum vitamin D concentration, vitamin D supplements;
13. Non-standardized definition.
14. Increased risk observed for intake < 100 g per day.
15. Including any processed meat, fish and poultry.

- consuming foods that contain dietary fibre;
- limiting the consumption of sugary drinks;
- maintaining a healthy body weight, notably through a regular self-monitoring (at least once a month) 8;
- practicing at least 30 minutes of physical activity per day and reducing sedentary lifestyle, these two factors being themselves risk factors of CRC (see below).

Physical activity

There is a significant association between the level of physical activity and the risk of colon cancer, and this association is not found for rectal cancer. The level of evidence is considered convincing for both total physical activity and activity related to sport practice and leisure 7.

In the WCRF meta-analysis, a reduction in the risk of CRC for the highest level of physical activity regarding total physical activity, was at 19% (RR: 0.81 [95% CI: 0.69-0.95]) and regarding physical activity related to sports and leisure at 16% (RR: 0.84 [95% CI: 0.78-0.91]) 7. It is estimated that 3.6% of colon cancers can be attributed to a lack of physical activity 6.

Among the mechanisms that could explain the preventive effect of physical activity, the acceleration of intestinal transit reduces the exposure of the colonic mucosa to luminal carcinogens 39. Physical activity can also indirectly reduce insulin resistance and inflammation by preventing overweight and obesity. The existence of an independent effect remains to be clearly demonstrated 32–38.

CONCLUSION

It is becoming clear that a number of nutritional and lifestyle-related parameters can have a positive or negative impact on the risk of CRC. Since CRC is emerging as a preventable cancer, it is important to widely disseminate the recommendations for primary and secondary prevention established by national and international societies, for example by increasing the communication channels using new digital tools and field campaigns. It is also important to promote epidemiological and experimental research in order to identify new risk factors and to understand the underlying mechanisms. Establishing preventive medicine departments, which are key elements for future healthcare would, with the application ofpersonalized follow-up approaches, lead to a significant reduction in the incidence of CRC and therefore cancer mortality.

REFERENCES

1. Sung H, Ferlay J, Siegel RL, *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA *Cancer J Clin*. mai 2021 ; 71 : 209-49.
2. Zauber AG, Winawer SJ, O'Brien MJ, *et al.* Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012 ; 366 : 687-96.
3. Nishihara R, Wu K, Lochhead P, *et al.* Long-term colorectal-cancer incidence and mortality after lower endoscopy. *N Engl J Med* 2013 ; 369 : 1095-105.
4. Drouillard A, Bouvier A-M, Rollot F, Faivre J, Jooste V, Lepage C. Conditional net survival: Relevant prognostic information for colorectal cancer survivors. A French population-based study. *Dig Liver Dis* 2015 ; 47 : 597-601.
5. Santé publique France. *Taux de participation au programme de dépistage organisé du cancer colorectal 2018-2019*, 2020. www.santepubliquefrance.fr/maladies-et-traumatismes/cancers/cancer-du-colon-rectum/articles/taux-de-participation-au-programme-de-depistage-organise-du-cancer-colorectal-2018-2019
6. International Agency for Research on Cancer. *Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine*, 2018 https://gco.iarc.fr/includes/PAF/PAF_FR_report.pdf.
7. Diet, Nutrition, Physical Activity and Colorectal Cancer. *World Cancer Res Fund Am Inst Cancer Res* 2017 ; 111.
8. Santé publique France. *Recommandations relatives à l'alimentation, à l'activité physique et à la sédentarité pour les adultes*, 2019. www.santepubliquefrance.fr
9. Cross AJ, Sinha R. Meat-related mutagens/carcinogens in the etiology of colorectal cancer. *Environ Mol Mutagen* 2004 ; 44 : 44-55.
10. Cross AJ, Pollock JRA, Bingham SA. Haem, not protein or inorganic iron, is responsible for endogenous intestinal N-nitrosation arising from red meat. *Cancer Res* 2003 ; 63 : 2358-60.
11. Santarelli RL, Pierre F, Corpet DE. Processed meat and colorectal cancer: a review of epidemiologic and experimental evidence. *Nutr Cancer* 2008; 60: 131-44.
12. Réseau NACRe. Fibres alimentaires et risque de cancer, les principales données, 2020. www6.inrae.fr/nacre/Prevention-primaire/Facteurs-nutritionnels/Fibres-alimentaires-et-cancer
13. Slavin JL. Mechanisms for the impact of whole grain foods on cancer risk. *J Am Coll Nutr* 2000 ; 19 :300S-307S.
14. Bingham SA. Mechanisms and experimental and epidemiological evidence relating dietary fibre (non-starch polysaccharides) and starch to protection against large bowel cancer. *Proc Nutr Soc* 1990 ; 49 : 153-71.

15. Pi-Sunyer X. Do glycemic index, glycemic load, and fiber play a role in insulin sensitivity, disposition index, and type 2 diabetes? *Diabetes Care* 2005 ; 28 : 2978-9.
16. Kim K-H, Tsao R, Yang R, Cui SW. Phenolic acid profiles and antioxidant activities of wheat bran extracts and the effect of hydrolysis conditions. *Food Chem* 2006 ; 95 : 466-73.
17. Guéguen L, Pointillart A. The bioavailability of dietary calcium. *J Am Coll Nutr* 2000;19 : 119S-136S.
18. Llor X, Jacoby RF, Teng BB, Davidson NO, Sitrin MD, Brasitus TA. K-ras mutations in 1,2-dimethylhydrazine-induced colonic tumors: effects of supplemental dietary calcium and vitamin D deficiency. *Cancer Res* 1991;51 : 4305-9.
19. Pierre FHF, Martin OCB, Santarelli RL, *et al.* Calcium and α-tocopherol suppress cured-meat promotion of chemically induced colon carcinogenesis in rats and reduce associated biomarkers in human volunteers. *Am J Clin Nutr* 2013 ; 98 : 1255-62.
20. Fedirko V, Bostick RM, Flanders WD, *et al.* Effects of Vitamin D and Calcium on Proliferation and Differentiation in Normal Colon Mucosa: A Randomized Clinical Trial. *Cancer Epidemiol Biomark Prev* 2009 ; 18 : 2933-41.
21. Fedirko V, Riboli E, Bueno-de-Mesquita HB, *et al.* Pre-diagnostic Circulating Parathyroid Hormone Concentration and Colorectal Cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. *Cancer Epidemiol Biomark Prev* 2011 ; 20 : 767-78.
22. Newmark HL, Wargovich MJ, Bruce WR. Colon cancer and dietary fat, phosphate, and calcium: a hypothesis. *J Natl Cancer Inst* 1984 ; 72 : 1323-5.
23. Norat T, Riboli E. Dairy products and colorectal cancer. A review of possible mechanisms and epidemiological evidence. *Eur J Clin Nutr* j2003 ; 57 : 1-17.
24. Santé publique France. *Nutri-Score,* 2021. www.santepubliquefrance.fr/determinants-de-sante/nutrition-et-activite-physique/articles/nutri-score.
25. Tsoi KKF, Pau CYY, Wu WKK, Chan FKL, Griffiths S, Sung JJY. Cigarette smoking and the risk of colorectal cancer: a meta-analysis of prospective cohort studies. *Clin Gastroenterol Hepatol* 2009 ; 7 : 682-8.e1-5.
26. Liang PS, Chen T-Y, Giovannucci E. Cigarette smoking and colorectal cancer incidence and mortality: systematic review and meta-analysis. *Int J Cancer* 2009 ; 124 : 2406-15.
27. Gong J, Hutter C, Baron JA, *et al.* A pooled analysis of smoking and colorectal cancer: timing of exposure and interactions with environmental factors. *Cancer Epidemiol Biomark Prev* 2012 ; 21 : 1974-85.
28. Cao B, Hill C, Bonaldi C, *et al.* Cancers attributable to tobacco smoking in France in 2015. *Eur J Public Health* 2018 ; 28 : 707-12.
29. World Cancer Research Fund/American Institute for Cancer Research. *Diet, nutrition, physical activity and breast cancer*, 2018. www.wcrf.org/wp-content/uploads/2021/02/Breast-cancer-report.pdf
30. Boffetta P, Hashibe M. Alcohol and cancer. *Lancet Oncol* 2006 Feb; 7 : 149-56. doi : 10.1016/S1470-2045(06)70577-0.
31. Santé publique France/Équipe de surveillance et d'épidémiologie. Activité physique et sédentarité. In: *Étude de santé sur l'environnement, la biosurveillance, l'activité physique et la nutrition (Esteban), 2014-2016 Volet Nutrition*. Deuxième édition. Saint-Maurice : Santé publique France, 2020. www.santepubliquefrance.fr
32. Murphy N, Cross AJ, Abubakar M, *et al.* A Nested Case-Control Study of Metabolically Defined Body Size Phenotypes and Risk of Colorectal Cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). *PLoS Med* 2016 ; 13 : e1001988.
33. Ma J, Giovannucci E, Pollak M, *et al.* A prospective study of plasma C-peptide and colorectal cancer risk in men. J Natl Cancer Inst. 7 avr 2004;96(7):546-53.
34. Jenab M, Riboli E, Cleveland RJ, *et al.* Serum C-peptide, IGFBP-1 and IGFBP-2 and risk of colon and rectal cancers in the European Prospective Investigation into Cancer and Nutrition. *Int J Cancer* 2007 ; 121 : 368-76.
35. Koohestani N, Tran TT, Lee W, Wolever TM, Bruce WR. Insulin resistance and promotion of aberrant crypt foci in the colons of rats on a high-fat diet. *Nutr Cancer* 1997 ; 29 : 69-76.
36. Tran TT, Naigamwalla D, Oprescu AI, *et al.* Hyperinsulinemia, but not other factors associated with insulin resistance, acutely enhances colorectal epithelial proliferation in vivo. *Endocrinology* 2006 ; 147 : 1830-7.
37. Ho GYF, Wang T, Gunter MJ, *et al.* Adipokines linking obesity with colorectal cancer risk in postmenopausal women. *Cancer Res* 2012 ; 72 : 3029-37.
38. Zhou B, Shu B, Yang J, Liu J, Xi T, Xing Y. C-reactive protein, interleukin-6 and the risk of colorectal cancer: a meta-analysis. *Cancer Causes Control CCC* 2014 ; 25 : 1397-405.
39. Song BK, Cho KO, Jo Y, Oh JW, Kim YS. Colon transit time according to physical activity level in adults. *J Neurogastroenterol Motil* 2012 ; 18: 64-9.

COLORECTAL CANCER SCREENING IN 2030

Antoni Castells [1],
[1] *Gastroenterology Department, Hospital Clinic of Barcelona, University of Barcelona, Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Centro de Investigación Biomédica en Red en Enfermedades Hepáticas y Digestivas (CIBERehd), Barcelona, Catalonia, Spain*

« *The art of progress is to preserve order amid change and to preserve change amid order.* »
Alfred North WHITEHEAD

Colorectal cancer (CRC) is a major worldwide public health issue ranked among the top 10 diseases for health burden by the World Bank. Although there is wide geographic variation in CRC incidence, with higher incidence in developed than developing countries, it is increasing in countries with growing wealth. It is predicted that by 2040 the number of cases will have risen from 1.8 million today to 3.1 million [1]. This huge burden remains a challenge despite the expert consensus view that CRC is one of the most preventable cancers.

Five decades ago, the World Health Organization developed criteria for a public health approach to screening if evidence and health burden justified it and it was feasible. In the last twenty years, such evidence has appeared. Indeed, fecal occult blood testing has been proven to reduce CRC mortality, while colonoscopy was also shown to decrease both incidence and mortality. As a consequence, the coverage of CRC screening has increased across the globe. By 2018, more than 50 countries had initiated population-based, organized screening programs, the vast majority following a two-step approach with detection of blood in feces (i.e. fecal immunochemical testing [FIT]) as the first step. Only Italy and the UK now include flexible sigmoidoscopy as an initial screening test, and few have adopted colonoscopy as a first-line test 1. The lack of evidence from randomized comparative trials has contributed to this heterogeneous scenario, in which no unique screening strategy is universally accepted.

"*Prediction is very difficult, especially if it's about the future*!" said Niels Bohr, Nobel laureate in Physics and father of the atomic model. Predicting what CRC screening

[1] http://gco.iarc.fr/tomorrow/home

will be like in the year 2030 is not an exception to such a difficulty. However, there is no doubt that the extraordinary effort of scientific societies and international organizations involved in this field, with special mention to the World Endoscopy Organization Colorectal Cancer Screening Committee [2], will continue contributing to "define" the future. In this chapter, I will try to identify some of the most relevant unmet needs and anticipate potential solutions.

PARTICIPATION IN PROGRAMMATIC COLORECTAL CANCER SCREENING

The aim of population-based screening is to discover latent disease in the population in order to detect it in its early stages and to enable adequate treatment. In order to maximize its impact and ensure high coverage and equity of access, it is highly recommended to implement organized screening programs, as opposed to case-finding or opportunistic approaches, since they include an administrative structure responsible for service delivery, quality assurance and evaluation [3].

Participation in programmatic CRC screening continues to be a major issue, with figures around 40-65% in most European countries [1]. To overcome this limitation, several strategies have been proposed: reminders to non-responders, educational information, advertising, simplification of screening tests, training of personnel involved, and removing administrative, economic and/or geographic barriers, among others [4].

One of the most appealing strategies to increase participation is offering different screening alternatives to the invited population and, in my modest opinion, we should continue advancing in this direction. The multiple-option approach allows the participants to choose the test after discussing the benefits and risks of each available option. Recently, a pragmatic randomized trial demonstrated that screening strategies that combine FIT and colonoscopy can result in 60-70% higher participation rates compared to offering primary colonoscopy screening alone [5]. In the sequential strategy, most participants completed primary screening colonoscopy, whereas in the choice strategy, the majority performed the FIT test. In absolute terms, the increase in participation rates were only 8-10% points higher, thus indicating the need to continue improving this multiple-option approach [5].

PRESENT AND FUTURE OF SCREENING TESTS

Evidence from several studies has shown that CRC screening is effective6 and cost-effective [7] in an average-risk population. Recommended CRC screening strategies fall into two broad categories: stool tests, which include detection of occult blood and, more recently, exfoliated nucleic acids (i.e. DNA and miRNA); and structural exams, which include flexible sigmoidoscopy, colonoscopy, CT colonography and capsule endoscopy [6,8,9]. Fecal occult blood testing and flexible sigmoidoscopy are predominantly implemented in Europe and Australia, where screening is mainly programmatic, whereas colonoscopy is the dominant screening modality in the US, where screening is mostly opportunistic [3].

Colonoscopy

Colonoscopy is considered to be the most precise approach for early detection and prevention of CRC [6,8]. Although results from randomized clinical trials evaluating its effect on CRC mortality are still lacking, it is recommended as a first-line screening modality based on indirect data and observational studies. In fact, population-based case-control studies have suggested that colonoscopy decreases CRC incidence [10] and mortality [11], whereas there is evidence indicating that patients with a previous negative colonoscopy have markedly reduced CRC risk [12,13]. A meta-analysis of 6 observational studies evaluating the efficacy of screening colonoscopy in average-risk individuals concluded that this strategy was associated with a reduction in CRC incidence and mortality of 69% and 68%, respectively [14]. Finally, cohort studies of patients with adenomas suggested that polypectomy could prevent up to 80% of CRC [15].

While colonoscopy plays a key role in all CRC screening modalities, not only in the average-risk population but also in high-risk individuals [16], it has some limitations and lesions can be missed at variable rates. In that sense, the adenoma detection rate (ADR) has become the most important indicator of the quality of colonoscopy [17] because it is directly related to key outcome parameters, such as interval cancer, and indirectly reflects other surrogate markers including quality of preparation, colonoscopy completeness, withdrawal time, as well as dedication and experience of the endoscopist [18].

In the last few years, it has been suggested that automatic polyp detection systems based on artificial intelligence (AI) may contribute to increased ADR. Indeed, in an open, non-blinded trial, this approach resulted in a significant increase in the number of hyperplastic polyps and diminutive adenomas detected, although there was no difference in the detection of larger adenomas [19]. These results were very similar to those obtained in a randomized trial, in which computer-aided detection significantly increased identification of adenomas smaller than 6 mm, as well as those between 6 and 9 mm in size, without increasing withdrawal time [20]. The usefulness of AI-based algorithms to increase ADR has been subsequently confirmed in a recent meta-analysis [21], along with their capacity to differentiate diminutive adenomas from hyperplastic polyps with high accuracy [22].

Concerns about the use of colonoscopy as a first-line screening method in a population-based scenario include the resources needed and potential complications. Indeed, it is estimated that the cost of screening the whole target average-risk population in Europe (i.e. 146 million people, approximately) will exceed 3,650 million Euros annually. Moreover, in this setting, although the rate of serious gastrointestinal side

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effects of colonoscopy (i.e. perforation and bleeding) is relatively small (2.4‰) [23], the absolute number cannot be neglected from a public health perspective. Taking into account all these considerations and, more importantly, the fact that the prevalence of advanced neoplasm –the main target lesion of CRC screening– in the average-risk population does not exceed 10% [24], the most rational approach seems to be to limit the use of colonoscopy to subjects with the highest likelihood of presenting such lesions.

The above-mentioned selection of individuals who may benefit the most from colonoscopy screening relies on the concept of risk stratification, which can be established with different strategies. First, the use of mathematical scores to estimate the likelihood of detecting advanced neoplasms during colonoscopy. Indeed, several models derived from regression analyses of large series of individuals undergoing colonoscopy have been proposed [25-27]. With minor differences, most of them include age, gender, family history of CRC, cigarette smoking and the body mass index. This approach can be useful in opportunistic screening, in which this information is easily available, but it may be more difficult to implement it in an organized program. Second, it has recently been proposed to use genetic or genomic profiling to select the subjects with the greatest predisposition for developing colorectal neoplasms. In fact, common genetic variants (i.e. single nucleotide polymorphisms) identified in large whole-genome association studies seem to play a critical role in CRC development [28], but its potential utility in risk stratification for screening purposes has not yet been demonstrated. Finally, the most common approach employed in programmatic screening is the use of non- or less-invasive methods to select individuals with a higher probability of presenting advanced neoplasms. In this scenario, FIT is the most used strategy1, whereas the detection of molecular biomarkers of colorectal neoplasia in either blood or feces is emerging as an appealing alternative.

Fecal occult blood testing

In the context of programmatic screening, the vast majority of countries have chosen a two-step approach with FIT as the first step [1]. Fecal occult blood testing was demonstrated to reduce CRC mortality [29-31] in randomized controlled trials. On the other hand, several trials have confirmed the superiority of FIT over the guaiac-based tests, which is especially noteworthy with respect to uptake and detection rate of advanced neoplasms [32, 33]. Moreover, the quantitative nature of FIT allows the selection of an optimal cut-off for a specific target population, thus adjusting the positivity rate to local resources1, as well as the identification of the individuals with the highest risk of developing advanced colorectal neoplasms in order to prioritize them in centers with a large colonoscopy demand [34].

On the other hand, it has been suggested that FIT may be more effective than other screening strategies in a population-based scenario because of higher acceptability. Indeed, the baseline analysis of the COLONPREV study, a multicenter, randomized controlled trial performed in Spain, indicated that one-time screening with FIT was equivalent to colonoscopy in the detection of CRC in terms of diagnostic yield, detection rate and tumor staging. Interestingly, FIT was better accepted than colonoscopy, needed to scope 5 times fewer individuals to detect one advanced neoplasm, and had fewer complications [24]. The long-term results of this study and others – the SCREESCO [35] and the CONFIRM [36] studies – , also comparing colonoscopy and FIT on average-risk CRC screening, will definitively establish the impact of these strategies on CRC mortality.

Molecular biomarkers

Although the highest level of evidence supports the implementation of FIT-based screening, this strategy is limited by a low sensitivity for advanced adenomas, a high false-positive rate resulting in unnecessary colonoscopies, and a still insufficient compliance. The use of biomarkers, other than blood in feces, may overcome these limitations.

In the last few decades, many molecular events participating in the initiation and progression of CRC have been elucidated. In that regard, genetic and epigenetic changes may constitute non-invasive biomarkers if they are measurable in different biological fluids. In fact, exfoliation of neoplastic cells in feces is a continuum process in patients with CRC, whereas cancer cells and tumor-associated markers may reach systemic circulation favored by the angiogenic process.

Initial studies evaluating the use of stool-based DNA tests showed a disappointing sensitivity for the detection of colorectal neoplasms. However, in the last few years, great technical advances have been introduced, including better stabilizing buffers, more discriminating markers and more sensitive analytic methods, NDRG4 and BMP3 methylation, and β-actin, plus a hemoglobin immunoassay, detected more neoplastic lesions than FIT, at the expense of more false-positive results [37].

More recently, we have which have resulted in higher sensitivity for the detection of both cancer and precancerous lesions. Indeed, a multitarget stool DNA test (Cologuard®, Exact Sciences, Madison, WI), which includes quantitative molecular assays for KRAS mutations, aberrant technically and clinically validated a predictive algorithm based on a fecal miRNA signature – the miRFec test, a gradient boosting machine-generated algorithm that includes two fecal miRNAs (miR-421 and miR-27a-3p) and fecal hemoglobin concentration, along with age and gender, – able to identify patients with advanced colorectal neoplasms more accurately than hemoglobin concentration in FIT-positive individuals [38,39]. A large, prospective clinical trial comparing the effectiveness and cost-effectiveness of the miRFec test compared to FIT is being planned.

The use of blood-derived biomarkers has also been advocated because it may favor screening uptake. For this purpose, two different strategies have been evaluated.

On the one hand, detection of aberrant DNA methylation patterns, which have been found in plasma and serum samples of CRC patients [40]. Unfortunately, following this approach, most studies have demonstrated a relatively high sensitivity for CRC detection, but still quite poor sensitivity for adenoma detection. Indeed, results of the PRESEPT study, the largest multicenter trial evaluating Septin 9 methylation, the only commercially available blood-based CRC screening test, were somehow disappointing, showing a sensitivity for CRC and advanced adenoma detection of 48% and 11%, respectively [41].

On the other hand, it has been demonstrated that miRNAs can also be detected in serum and plasma [40]. In a recent study, we have identified a panel of 6 miRNAs (i.e. miR18a, miR19a, miR19b, miR15b, miR29a, and miR335) which are significantly up-regulated in patients with CRC [42]. In a validation study using an independent cohort of patients, this signature had a sensitivity of 85% and specificity of 90% in distinguishing patients with advanced colorectal neoplasms from healthy individuals [43]. These results reinforce the use of miRNA as biomarkers for CRC screening, although large comparative studies are needed to validate this alternative.

REFERENCES

1. Young GP, Rabeneck L, Winawer SJ. The Global Paradigm Shift in Screening for Colorectal Cancer. *Gastroenterology* 2019 ; 156 : 843-51.
2. Rutter MD, Beintaris I, Valori R, *et al.* World Endoscopy Organization Consensus Statements on Post-Colonoscopy and Post-Imaging Colorectal Cancer. *Gastroenterology* 2018;155:909-925.
3. Segnan N, Patnick J, von Karsa L. European guidelines for quality assurance in colorectal cancer screening and diagnosis. Luxembourg : Publications Office of the European Union, 2010.
4. Camilloni L, Ferroni E, Cendales BJ, *et al.* Methods to increase participation in organised screening programs: a systematic review. *BMC Public Health* 2013;13:464.
5. Pilonis ND, Bugajski M, Wieszczy P, et al. Participation in Competing Strategies for Colorectal Cancer Screening: A Randomized Health Services Study (PICCOLINO Study). Gastroenterology 2021 ; 160 : 1097-105.
6. Levin B, Lieberman DA, McFarland B, *et al.* Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008;134:1570-95.
7. Heitman SJ, Hilsden RJ, Au F, Dowden S, Manns BJ. Colorectal cancer screening for average-risk North Americans: an economic evaluation. *PLoS Med* 2010 ; 7 : e1000370. doi : 10.1371/journal.pmed.1000370
8. Winawer S, Fletcher R, Rex D, *et al.* Colorectal cancer screening and surveillance: clinical guidelines and rationale-Update based on new evidence. G*astroenterology* 2003 ; 124 : 544-60.
9. Gonzalez-Suarez B, Pages M, Araujo IK, *et al.* Colon capsule endoscopy versus CT colonography in FIT-positive colorectal cancer screening subjects: a prospective randomised trial-the VICOCA study. *BMC Med* 2020 ; 18 : 255.
10. Brenner H, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection from colorectal cancer after coloscopie: a population-based, case-control study. *Ann Intern Med* 2011 ; 154 : 22-30.
11. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of coloscopie and death from colorectal cancer. *Ann Intern Med* 2009 ; 150 : 1-8.
12. Imperiale TF, Glowinski EA, Lin-Cooper C, Larkin GN, Rogge JD, Ransohoff DF. Five-year risk of colorectal neoplasia after negative screening coloscopie. *N Engl J Med* 2008 ; 359 : 1218-24.

Castells A, *in :*
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13. Brenner H, Chang-Claude J, Seiler CM, Hoffmeister M. Interval cancers after negative coloscopie: population-based case-control study. *Gut* 2011 ; 61 : 1576-82.
14. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening coloscopie on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. *BMJ* 2014 ; 348 : g2467.
15. Zauber AG, Winawer SJ, O'Brien MJ, *et al.* Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012; 366 : 687-96.
16. Castells A, Castellvi-Bel S, Balaguer F. Concepts in familial colorectal cancer: where do we stand and what is the future? *Gastroenterology* 2009 ; 137 : 404-9.
17. Kaminski MF, Regula J, Kraszewska E, *et al.* Quality indicators for coloscopie and the risk of interval cancer. *N Engl J Med* 2010 ; 362 : 1795-803.
18. Jover R, Zapater P, Polania E, *et al.* Modifiable endoscopic factors that influence the adenoma detection rate in colorectal cancer screening colonoscopies. *Gastrointest Endosc* 2013 ; 77 : 381-9.
19. Wang P, Berzin TM, Glissen Brown JR, *et al.* Real-time automatic detection system increases colonoscopic polyp and adenoma detection rates: a prospective randomised controlled study. *Gut* 2019 ; 68 : 1813-9.
20. Repici A, Badalamenti M, Maselli R, *et al.* Efficacy of Real-Time Computer-IAded Detection of Colorectal Neoplasia in a Randomized Trial. *Gastroenterology* 2020 ; 159 : 512-20.
21. Hassan C, Spadaccini M, Iannone A, *et al.* Performance of artificial intelligence in coloscopie for adenoma and polyp detection: a systematic review and meta-analysis. *Gastrointest Endosc* 2021 ; 93 : 77-85.
22. Byrne MF, Chapados N, Soudan F, *et al.* Real-time differentiation of adenomatous and hyperplastic diminutive colorectal polyps during analysis of unaltered videos of standard coloscopie using a deep learning model. *Gut* 2019 ; 68:94-100.
23. Warren JL, Klabunde CN, Mariotto AB, *et al.* Adverse events after outpatient coloscopie in the Medicare population. *Ann Intern Med* 2009 ; 150 : 849-57.
24. Quintero E*, Castells A*, Bujanda L, *et al.* Coloscopie versus fecal immunochemical testing in colorectal-cancer screening. *N Engl J Med* 2012 ; 366 : 697-706. *Premiers auteurs.
25. Kaminski MF, Polkowski M, Kraszewska E, Rupinski M, Butruk E, Regula J. A score to estimate the likelihood of detecting advanced colorectal neoplasia at coloscopie. *Gut* 2014 ; 63 : 1112-9.
26. Wong MC, Lam TY, Tsoi KK, *et al.* Predictors of advanced colorectal neoplasia for colorectal cancer screening. *Am J Prev Med* 2014 ; 46 : 433-9.

27. Ma GK, Ladabaum U. Personalizing colorectal cancer screening: a systematic review of models to predict risk of colorectal neoplasia. *Clin Gastroenterol Hepatol* 2014 ; 12 : 1624-34.
28. Huyghe JR, Bien SA, Harrison TA, *et al.* Discovery of common and rare genetic risk variants for colorectal cancer. *Nat Genet* 2019 ; 51 : 76-87.
29. Hardcastle JD, ChamberlIAn JO, Robinson MH, *et al.* Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996 ; 348 : 1472-7.
30. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996 ; 348 : 1467-71.
31. Mandel JS, Bond JH, Church TR, *et al.* Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993 ; 328 : 1365-71.
32. Guittet L, Bouvier V, Mariotte N, *et al.* Comparison of a guIAac based and an immunochemical faecal occult blood test in screening for colorectal cancer in a general average risk population. *Gut* 2007 ; 56 : 210-4.
33. van Rossum LG, van Rijn AF, Laheij RJ, *et al.* Random comparison of guIAac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. *Gastroenterology* 2008 ; 135 : 82-90.
34. Auge JM, Pellise M, Escudero JM, *et al.* Risk stratification for advanced colorectal neoplasia according to fecal hemoglobin concentration in a colorectal cancer screening program. *Gastroenterology* 2014 ; 147 : 628-36.
35. Wangmar J, Jervaeus A, Fritzell K, Wangdahl J, Hultcrantz R, Wengstrom Y. Health literacy levels and views about being invited to a colorectal cancer screening program. *Acta Oncol* 2018 ; 57 : 743-9.
36. Dominitz JA, Robertson DJ, Ahnen DJ, *et al.* Coloscopie vs. Fecal Immunochemical Test in Reducing Mortality From Colorectal Cancer (CONFIRM): Rationale for Study Design. *Am J Gastroenterol* 2017 ; 112 : 1736-46.
37. Imperiale TF, Ransohoff DF, Itzkowitz SH, *et al.* Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med* 2014; 370 : 1287-97.
38. Duran-Sanchon S, Moreno L, Auge JM, *et al.* Identification and Validation of MicroRNA Profiles in Fecal Samples for Detection of Colorectal Cancer. *Gastroenterology* 2020 ; 158 : 947-57.
39. Duran-Sanchon S, Moreno L, Gomez-Matas J, *et al.* Fecal MicroRNA-Based Algorithm Increases Effectiveness of Fecal Immunochemical Test-Based Screening for Colorectal Cancer. *Clin Gastroenterol Hepatol* 2021 ; 19 : 323-30.
40. Mitchell PS, Parkin RK, Kroh EM, *et al.* Circulating microRNAs as stable blood-based markers for cancer detection. *Proc Natl Acad Sci U S A* 2008 ; 105 : 10513-8.

41. Church TR, Wandell M, Lofton-Day C, *et al.* Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. *Gut* 2014 ; 63 : 317-25.
42. Giraldez MD, Lozano JJ, Ramirez G, *et al.* Circulating microRNAs as biomarkers of colorectal cancer: results from a genome-wide profiling and validation study. *Clin Gastroenterol Hepatol* 2013 ; 11 : 681-8.
43. Herreros-Villanueva M, Duran-Sanchon S, Martin AC, *et al.* Plasma MicroRNA Signature Validation for Early Detection of Colorectal Cancer. *Clin Transl Gastroenterol* 2019 ; 10 : e00003.

WHAT WILL BE THE ROLE OF DIAGNOSTIC COLONOSCOPY ON THE 2030 HORIZON?

Guillaume Perrod [1], Mehdi Cadi [2], Emmanuel Coron [3], Gabriel Rahmi [1]
[1]*Department of Hepatogastroenterology, European Hospital George Pompidou, APHP, University of Paris, France*
[2]*Department of Radiology, European Hospital Georges Pompidou, APHP. University of Paris, France*
[3] *Department of Internal Medicine, Geneva, Switzerland*

« Engineering, medicine, business, architecture and painting are concerned not with the necessary but with the contingent – not with how things are but with how they might be – in short, with design.
Herbert Simon

Optical colonoscopy is the main endoscopic exam available in 2022 to perfectly explore the lumen of the colon. It allows the diagnosis of precancerous lesions as well as cancers. In France, it is mostly performed under general anesthesia (GA) after an orally-administred preparation that often leaves an unpleasant memory for the patients.

It is difficult to predict what role this medical examination will have in 2030, but it is almost certain that new techniques suited for diagnosis will represent possible alternatives and might even become preferred choices over colonoscopy, at least in some situations. The diagnostic technique that will be acceptable to all patients, and that will be preferred, will need to have a number of characteristics in addition to being efficient for the detection of colorectal neoplastic lesions and at a low cost. First of all, it should be safe and without complications, which is not entirely the case with optical colonoscopy, even if bleeding and perforations are rare and even exceptional events. Ideally, it should be an examination that does not require the oral administration of colonic preparation, which is always uncomfortable. Finally, the possibility of performing this examination without general anesthesia would be advantageous, considering its limited availability, high cost, and the occurrence of intrinsic anesthetic complications.

Among the techniques that could more or less completely fulfill this list of criteria, the colonic capsule, radiological examinations for virtual colonoscopy and Posi-

tron-Emission Tomography (PET-scan) are candidates (*figure 1*). In this chapter, we will not discuss the possible role of "liquid biopsies" or biological markers, that still require validation.

WHAT WILL BE THE ALTERNATIVES FOR DIAGNOSIS IN 2030?

Colonoscopy in 2030 will not be the same as in 2022

This point must be underlined before comparing the possible alternatives available for colonic exploration. It is highly probable that artificial intelligence (AI) will arrive and it has already even started. AI is gradually entering medicine; it is a valuable aid for patient management, and its importance will not be restricted to digestive endoscopy, and it will likely also enter into other disciplines, especially radiology.

AI uses «machine learning» and problem-solving methods called «algorithms». The most immediate application of AI in medicine relates to image processing. Real-time image processing systems have been developed for colonoscopy, providing major assistance to operators in the detection and characterization of colonic lesions.

Currently, the adenoma detection rate (ADR) is defined by the detection of at least one adenoma during colonoscopy. This is one of the major quality criteria for colonoscopy because it is directly related to the risk of occurrence of interval colorectal cancers 1. Some studies have shown an inverse relationship between the ADR and the rate of interval colorectal cancer 2. Unfortunately however, there is a great inter-operator variability in the ADR and tandem studies have shown that the rate of missed adenoma also varies widely, from 6 to 41% 3. Among the missed lesions, it is possible to distinguish between lesions related to a limited visual field (mucosal folds, presence of residues, etc.) and those that are missed by the operator. For the former, endoscopic tools fixed at the extremity of the endoscope (cap, balloon system, etc.) or those that increase the visual field have shown an improvement in the ADR 3. Conversely, many solutions have been proposed for the lesions missed by the operator, but convincing evidence is still lacking 4.

With the progress of AI, Computer-Assisted Detection Devices (CADe) have been developed for colonoscopy. These easy-to-use systems have shown very promising results when compared to high definition (HD) white light. Indeed, data from a first meta-analysis that included five randomized controlled trials (4,354 patients) have shown a significantly higher ADR in the CADe group compared to the HD group (36.6% vs 25.2%; p<0.01) 5. This help in the detection of adenomas appears to be a real technological advancement, because it also seems to be superior to techniques that rely on chromoendoscopy, in particular for lesions <5 mm. Recent results from another meta-analysis based on the results of 50 randomized controlled trials (34,445 colonoscopies) confirmed the superiority of CADe

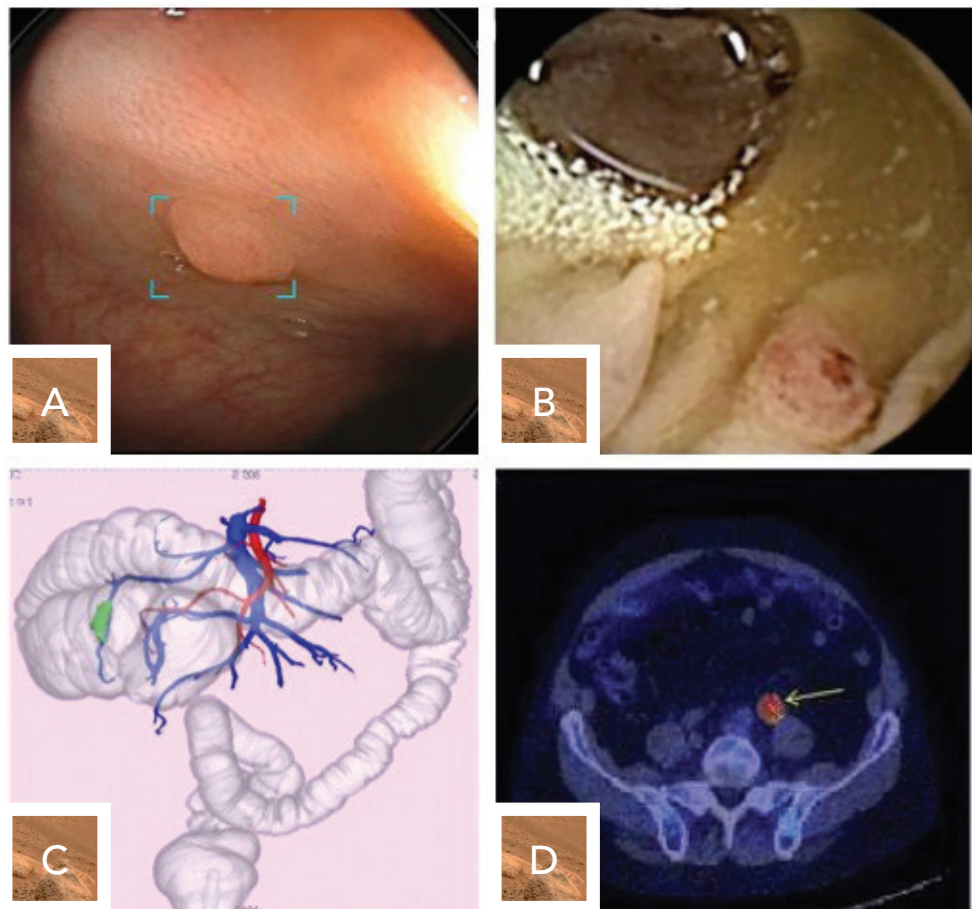

FIGURE 1. Different methods for the exploration of the colorectal lumen. A) Automatic detection with an artificial intelligence system (System CADEYE, Fujifilm ®) of a colonic polyp (White light, the polyp is surrounded by blue marking); B) small colonic polyp visualized using a video-capsule (Pill-Cam VCC2, Medtronic ®) in the lower-right quadrant; C) virtual colonoscopy with injection of an iodine contrast reagent and three-dimensional spatial reconstruction (3D-angiocolonoscanner [3D ACS]) of an adenocarcinoma of the right colon (in green); D) positron emission computed tomography (PET) coupled to a scanner (PET-scan) showing an increased uptake area (arrow), revealed the presence of an invasive adenocarcinoma of the rectum.

for the detection of colonic adenomatous lesions [6]. In this study that compared different assistance methods for detection to the gold standard (HD), the ADR was 7.4% higher in the CADe group (OR 1.78 [95% CI: 1.44–2.18]) vs 4.4% higher in the chromoendoscopy group (1.22 [1.08–1.39]). Interestingly, the comparison of the ADR between these two groups (cross comparison) was also in favor of the CADe group (OR 1.45 [1.14-1.85]), confirming the superiority of AI.

The same is true for the characterization of colonic polyps. Currently it is recommended to resect all polyps that are detected during colonoscopy, which represents a high economic cost and considerable societal cost. An American medico-economic study estimated the cost of endoscopic polypectomies at $179 per person, with the cost of a pathological analysis at $46 per person [7]. In this context, a number of teams have proposed the strategy known as "predict-and-leave", which consists of only resecting small adenomatous polyps and leaving the small polyps that are likely to be hyperplastic. Others have also suggested the possibility of resecting and directly discarding small polyps without further histological analysis (a strategy known as "predict-resect-and-discard") [8]. Therefore, a major challenge is to distinguish adenomatous polyps from hyperplastic polyps, as a way to determine whether polypectomy and histological analyses are required. The American Gastroenterological Association recommends using a highly reliable method for the diagnosis of adenomatous polyps (with a negative predictive value [NPV]) >90%) before the so-called "predict-resect-and-discard" strategy can be applied [9]. Currently, HD colonoscopy and virtual chromoendoscopy cannot be proposed as a substitution to histological analysis [10].

The use of AI for the detection and the prediction of polyp histology during colonoscopy would in theory replace histological analysis (optical biopsy). An evaluation of the corresponding CAD is ongoing. Early studies performed on frozen images of adenomas suggested that AI can have a diagnostic performance that is similar to that of experts (sensitivity, specificity and precision of 92.9%, 90.6% and 91.7%, respectively) [11,12]. These results are promising but they still need to be validated in a prospective manner, especially in order to confirm their high NPV. Furthermore, this characterization system can only predict two types of polyps, i.e. hyperplastic and neoplastic, without being able to distinguish high grade dysplasia from superficial or infiltrating cancers.

The colonic video-capsule

Capsule endoscopy has undergone a technological revolution over the last twenty years. The main advantage of the colon capsule is the non-invasive nature of this medical examination, and the fact that it does not require general anesthesia. After swallowing a camera within a capsule, images of the colon are stored and sent to a recorder and a movie of the entire colon is created. This exam is usually performed out of the hospital, and a nurse is usually in charged of explaining its practical realization to the patient, and could even be in charge of the initial selection of images of interest.

The main limitation of the capsule, besides the fact that this examination is strictly diagnostic and not therapeutic, is the need for a reinforced initial oral preparation. A good preparation is mandatory in order to get reliable results. The colonic capsule is composed of two heads that allow an almost total analysis of the colonic mucosa. The time required to read the movie can also be considered as a limitation, because it takes one hour on average. However, reading is simple for a trained operator.

Many prospective controlled studies have validated the sensitivity and the specificity of second generation colon capsules for colorectal cancer screening [13-18]. On the basis of these data, the French HAS (Haute Autorité de Santé) has authorized the use of the colonic capsule in France in 2016 "*to search for polyps and cancers in adult patients, in a context of incomplete optical colonoscopy not accounted for by poor colonic preparation or the presence of digestive stenosis*".

In the future, the colonic capsule could become the preferred examination for diagnostic endoscopy of the colon. One could imagine that a medical prescription could allow the patients to receive their capsule at home, followed by self-administration of the preparation, and the recording would be done without having to go to the hospital. The company Medtronic has already launched such a program by partnering with Amazon in the United States during the SARS-Cov-2 crisis. Images could be transmitted via a cloud (a remote storage solution) to an automated reading center that would generate a report for the gastroenterologist. In the future, automated interpretation will very likely be the rule, thanks to the development of AI.

Virtual colonoscopy

Virtual colonoscopy (VC), also known as CT colonography is a non-invasive imaging strategy for the colon. VC was developed 20 years ago, and its performance allowed it to irreversibly replace conventional imaging methods that are now outdated (barium enema). Despite this, it is still not well-known to the doctors and the public, and it is therefore rarely prescribed. It does not only allow the detection of precancerous colonic lesions and colonic cancers, but also the exploration of the extra-digestive organs when searching for any significant clinical abnormalities [19,20].

This cross-sectional digestive imaging technique differs from the conventional abdominal and pelvic scanner because of the need to administer a colonic preparation the day before the examination, which is based on the oral administration of a laxative (magnesium citrate) with two oral contrast agents to distinguish stool from polyps by "tagging" the remaining stool. Another step, performed with an automatic

insufflator, consists of the distension of the lumen of the colon with low pressure carbon dioxyde (CO_2). This step is performed under the control of a radiology operator with specific training, which makes him/her entirely autonomous. The interpretation of images is possible using dedicated software, leading to the acquisition of a 3D view of the colonic lumen and to perform an endoluminal anterograde and retrograde navigation from the rectum to the cecum. VC is an examination that is performed without any intravenous injection of contrast reagents and iodine. When a colonic tumor is suspected, intravenous injection of iodine allows the concomitant performance of distant tumor staging (by performing a thoracoabdominal scan) and local tumor staging (by 3D angio-CT-colonoscan, 3D ACS) allowing a complete preoperative assessment. VC is a minimally-invasive method and the perforation rate described in asymptomatic patients in a screening setting is about 0.003 %.

VC plays an important role in the prevention of CRC and early stage diagnosis. The performance of VC in the detection of CRCs and large adenomas (>10 mm) has been the topic of randomized clinical trials [21,22], multicenter [23] and single-center trials [24] and meta-analyses [25]. All data confirm that the diagnostic performances of VC are similar to those of optical colonoscopy, irrespective of the symptomatic or asympatomatic presentation of the patients (95%). Conversely, optical colonoscopy appears to be more sensitive for the detection of polyps of intermediate size (6-9 mm). According to the recommendations from European societies for endoscopy and digestive imaging, an endoscopic polypectomy is recommended when a polyp is identified by VC [26].

VC also plays a role in staging upstream of laparoscopic surgery for endoscopically unresectable tumours. The preoperative assessment of colon cancer is based on optical colonoscopy and contrast-enhanced thoracoabdominopelvian scanner. Optical colonoscopy allows the histological diagnosis of the tumor, defines its topography and reports the presence of synchronous colonic lesions (2-11%). However, in case of a tumor that cannot be cleared, or when the tumor is present in the transverse or the left colon, particularly in the case of a dolichocolon, optical colonoscopy has its limits. In these situations, VC with an injection of iodinated contrast reagent and a spatial reconstruction (3D ACS) allows an estimation of the colonic morphology in 3D, and it also establishes the precise location of the tumour. The fusion of colonic images with CT-angioscanner images allows precise vascular, arterial and venous mapping at the same time for the whole colon and to determine the precise segment where the tumor is located. It also allows the search for synchronous colon tumors in case of incomplete colonoscopy and a better definition of the T stage by evaluating the degree of penetration of the tumor with respect to the digestive wall and the mesocolon. Locally-advanced tumors could then benefit from preoperative chemotherapy. 3D ACS makes it possible to produce, in a single step, the preoperative locoregional tumor staging and in addition, if necessary, perform a thoraco-abdomino-pelvic scanning for the assessment of distant tumor locations. VC is also indicated in case of incomplete optical colonoscopies: the presence of a dolichocolon, inflammatory stenosis, post-operative strictures producing a fixed sigmoid, or a tumor that blocks the progression of the endoscope.

This radiological technique is minimally-invasive, requires a less aggressive preparation than optical colonoscopy and results in very little radiation exposure. In the future, it could become a useful tool for the diagnosis of premalignant lesions and early stage colorectal cancer.

Positron Emission Tomography and Computed tomography (PET-CT) scan

Positron Emission Tomography and Computed tomography (PET-CT) scan is a metabolic imaging method suited for whole body analysis. It is mostly used in digestive oncology in order to detect metastases. However, recent technological progress and improvement in the injection of radioisotopes raise the question of its effectiveness for the detection of early lesions of colorectal cancer, and even precancerous lesions.

Kim *et al.* [27] reported the results of a Korean study in 345 patients that underwent a PET-scan for stenosing colon cancer that prevented the exploration of the upstream colon by colonoscopy, who were finally operated. Fourteen patients had focal hyperfixation of fluoro-desoxyglucose (FDG), a radiopharmaceutical analogue of glucose (n=39 areas with suspicion of focal uptake). Per patient, the performances of the PET-scan for the detection of synchronous upstream cancer were: sensitivity (Se) 100%, specificity (Sp) 94%, positive predictive value (PPV) 41%, negative predictive value (NPV) 100%. Per lesion, the performances were: Se 100%, Sp 93%, PPV 36%, NPV 100%. On the other hand, Se and Sp of the PET-scan were clearly not as good for advanced adenomas (46% and 93%, respectively).

The detection of focal uptake of 18-FDG was the topic of a retrospective study examining 41,538 PET-scans performed over 10 years at the Mayo Clinic [28]. In this study, the majority of the examinations were performed for tumor extension assessment (74% solid, 26% haematological). A focal colonic uptake was noted in 0.7% of cases, and was associated with precancerous or cancerous colonic lesions in 32% and 14% of cases, respectively. The right colon location was often associated with colonic lesions (42%), while the sigmoid location was more often associated with unspecific hyper-uptake. Finally, among the precancerous lesions that were highlighted, tubular adenomas (n=36) or tubulovilleus (n=27) with low-grade dysplasia, and festonated lesions (n=4) were found, an observation that highlights the continuous progress of metabolic imaging.

A Japanese study [29] performed on a more limited number of patients (n=48), while more recent, questioned these performances. The retrospective review of 51 areas of focal hyperuptake of 18-FDG showed than only half of these areas matched with cancerous lesions (n=14) or adenomas (n=16). The rest corresponded to hyperplastic polyps,

colonic erosions, diverticles and one lymphoma. Interestingly, the authors reported an index for the uptake (early and delayed) that was higher in cancerous lesions and adenomas, which could better distinguish the lesions worth exploring by endoscopy. However, endoscopic explorations showed that 4 lesions had been missed by the PET scan, 2 of which were advanced adenomas (<10 mm) and 2 tumors with lateral extension (TLE) with intramucosal adenocarcinoma.

Another Japanese study [30] brings complementary information regarding the performances of the PET-scan according to the size of adenomas. The examination was proposed for the purpose of exploring the upper colon, with a colonoscopy performed before or during the year following surgery. In 83 patients, the authors determined that the Se and PPV of PET-scan were 25% and 78%, respectively. Se was better for larger lesions: 3% for those <5 mm, 30% for 6-10 mm, 45% for 11-20 mm, 71% for >21 mm. Se was also better for more advanced histological lesions: 15% in case of low grade dysplasia, 38% with high grade dysplasia, 67% with superficial carcinomas, 100% with invasive carcinomas. Interestingly, the lesions that were rounder in shape on the PET-scan were predictive of neoplastic lesions.

In summary, PET-scan offers the advantage of a non-invasive method and it is feasible in ambulatory practice, without the need for preparation or general anesthesia. However, its diagnostic performances remain clearly lower, at least with the current state of development of the technique, than other diagnostic methods: colonoscopy, videocapsule and virtual colonoscopy. Another problem is the possibility to access this examination, especially considering the frequency of morphological examination of the colon.

SPOILED FOR CHOICE: TOWARD MORE PERSONALIZED INDICATIONS IN 2030?

In a context of increasing and more efficient possibilities adapted for the morphological examination of the colon, it is probably appropriate to move towards a more personalized approach, and this dictates an immediate prospective reflection.

Table 1 summarizes the advantages and limitations of the four morphological examinations that we have presented above. We can safely argue that in 2030 none of these examinations will match all characteristics and demands, one of the major remaining limitations being the need for preparation (except for PET-scan). Cost uncertainties are important because it is difficult to estimate how they will influence the decisions of public health agencies, in a time when those agencies must take into account environmental, economic, societal, political as well as medical demographic parameters. Finally, it is highly desirable to avoid the emergence of interdisciplinary competition (gastroenterology vs. radiology vs. nuclear medicine), and instead, the advantages and limitations of each type of examination should be considered and adapted to individual patient and his/her enviroment.

Table 1. Advantages and limitations of exams used to assess colon morphology on the 2030 horizon.

	Colonoscopy	Videocapsule	Virtual colonoscopy	PET-scan
Preparation	++++	+++	+++	0
	0 if under GA	0 or +	+	0
Diagnostic performance	++++	+++	+++	+
Access to the exam	+++	++++	+++	Limited
Therapeutic intervention at the same time	Yes	No	No	No
Cost *	+++ (GA)	+++	++	?
Risk	+	0 (if not CI)	+ (Rx)	0

* Based on the actual rates, that are likely to change; real costs still to be determined.

GA: general anesthesia ; CI:contraindications ; Rx:irradiation.

Figure 2 represents an attempt to schematically position each examination by trying to take into account several decisive parameters, in addition to the diagnostic performance, such as:

- the diagnostic indication (irritable bowel symptoms vs. family history of CRC for example)
- tolerance to preparation and previous experience with the examinations ;
- the desire to avoid GA, to perform the examination at home, accessibility of the technique, the likelihood of having to perform a therapeutic procedure at the same time (a colonoscopy would be the choice if a polypectomy is likely to be necessary), the presence of contraindications (comorbidities, signs of occlusion that would contraindicate the use of capsule)…

Moreover, society will likely become less and less tolerant of any risks, even if minimal, which will likely lead to the preference of safe examinations (for the patient as well as for the doctor). Modeling based on approaches with different levels of complexity will likely gain importance, here again with the help of AI-powered protocols. Such models may produce complex scenarios alternatively using different types of medical examinations for the follow-up of patients, for example with alternative use of capsule and colonoscopy.

CONCLUSION

On the 2030 horizon, colonoscopy will surely remain important for the diagnosis of colorectal cancers. Fast technological improvements will allow this examination to become even more efficient, as illustrated in particular by the application of AI to improve the ADR and reduce the risk of interval cancers.

One of the major challenges will be to increase the acceptability of examinations aiming to diagnose precancerous or superficial colorectal cancers. This acceptability requires an easier logistics (sending the capsule to the patient's home after a simple internet order, for example, without the need for anesthesia or colonic preparation, without complications or irradiation…) and techniques that are as minimally-invasive as possible. With this in mind, non-invasive techniques that do not require hospitalization will probably prevail, without even considering the context of the sanitary crisis that strongly influences the organization of healthcare.

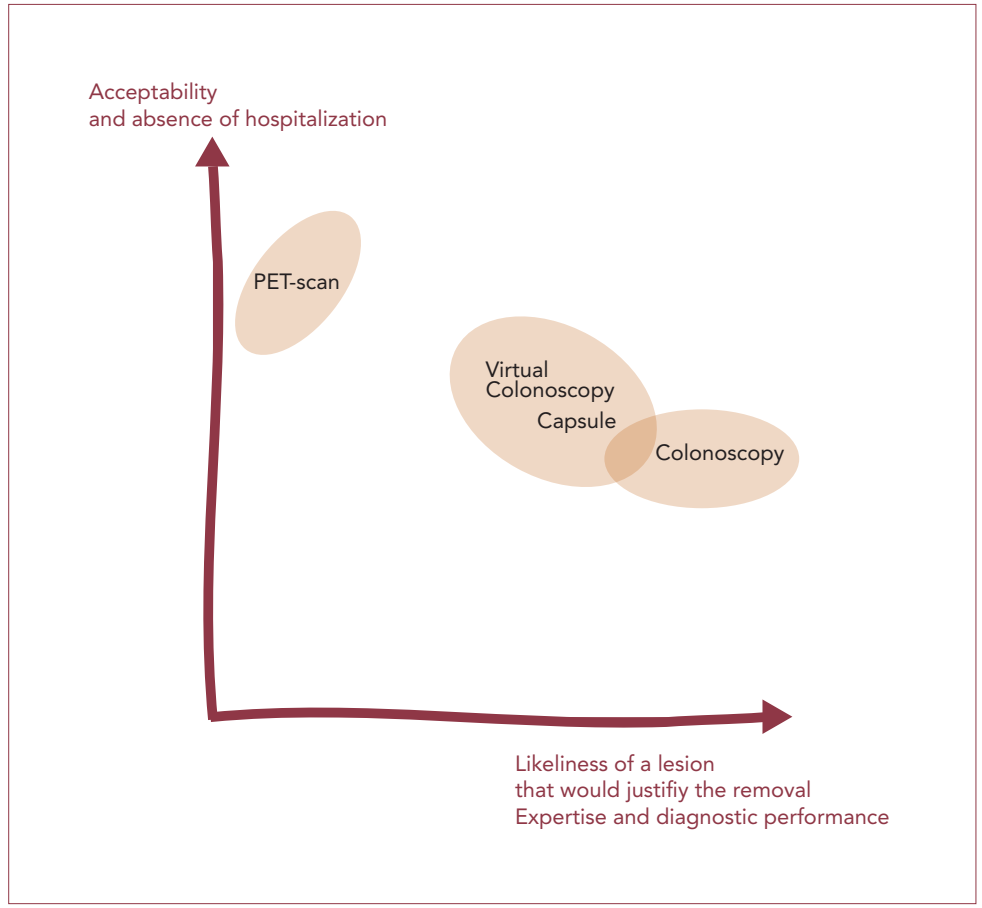

FIGURE 2. An attempt to position the different morphological examinations of the colon for the diagnosis of colorectal cancer or precancerous lesions. Brown circles show the indications of each technique. As can be seen, the indications of virtual colonoscopy, capsule and colonoscopy, partially overlap.

Perrod G, Cadi M, Coron E, Rahmi G, *in :*
CRC 2030

REFERENCES

1. Bressler B, Paszat LF, Chen Z, Rothwell DM, Vinden C, Rabeneck L. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. *Gastroenterology* 2007 ; 132 : 96-102.
2. Corley DA, Jensen CD, Marks AR, *et al.* Adenoma detection rate and risk of colorectal cancer and death. *N Engl J Med* 2014 ; 370 : 1298-306.
3. Ahn SB, Han DS, Bae JH, Byun TJ, Kim JP, Eun CS. The Miss Rate for Colorectal Adenoma Determined by Quality-Adjusted, Back-to-Back Colonoscopies. *Gut Liver* 2012 ; 6 : 64-70.
4. Ngu WS, Bevan R, Tsiamoulos ZP, *et al.* Improved adenoma detection with Endocuff Vision: the ADENOMA randomised controlled trial. *Gut* 2019 ; 68 : 280-8.
5. Wang P, Berzin TM, Brown JRG, *et al.* Real-time automatic detection system increases colonoscopic polyp and adenoma detection rates: a prospective randomised controlled study. *Gut* 2019 ; 68 : 1813-9.
6. Hassan C, Spadaccini M, Iannone A, *et al.* Performance of artificial intelligence in colonoscopy for adenoma and polyp detection: a systematic review and meta-analysis. *Gastrointest Endosc* 2021 ; 93 : 77-85.e6.
7. Spadaccini M, Iannone A, Maselli R, *et al.* Computer-aided detection versus advanced imaging for detection of colorectal neoplasia: a systematic review and network meta-analysis. *Lancet Gastroenterol Hepatol* 2021 ; 6 : 793-802.
8. Hassan C, Pickhardt PJ, Rex DK. A resect and discard strategy would improve cost-effectiveness of colorectal cancer screening. *Clin Gastroenterol Hepatol* 2010 ; 8 : 865-9, 869.e1-3.
9. Rex DK, Kahi C, O'Brien M, *et al.* The American Society for Gastrointestinal Endoscopy PIVI (Preservation and Incorporation of Valuable Endoscopic Innovations) on real-time endoscopic assessment of the histology of diminutive colorectal polyps. *Gastrointest Endosc* 2011 ; 73 : 419-22.
10. Rees CJ, Rajasekhar PT, Wilson A, *et al.* Narrow band imaging optical diagnosis of small colorectal polyps in routine clinical practice: the Detect Inspect Characterise Resect and Discard 2 (DISCARD 2) study. Gut. 2017;66(5):887-95.
11. Sakamoto T, Nakashima H, Nakamura K, Nagahama R, Saito Y. Performance of Computer-Aided Detection and Diagnosis of Colorectal Polyps Compares to That of Experienced Endoscopists. *Dig Dis Sci* 2021; epub. doi : 10.1007/s10620-021-07217-6.
12. Hann A, Troya J, Fitting D. Current status and limitations of artificial intelligence in colonoscopy. *United European Gastroenterol J* 2021 ;9 : 527-33.
13. Spada C, Hassan C, Munoz-Navas M, *et al.* Second-generation colon capsule endoscopy compared with colonoscopy. *Gastrointest Endosc* 2011 ; 74 :581-589 e1.
14. Eliakim R, Yassin K, Niv Y, *et al.* Prospective multicenter performance evaluation of the second-generation colon capsule compared with colonoscopy. *Endoscopy* 2009 ; 41 : 1026-31.
15. Sacher-Huvelin S, Coron E, Gaudric M, *et al.* Colon capsule endoscopy vs. colonoscopy in patients at average or increased risk of colorectal cancer. *Aliment Pharmacol Ther* 2010 ; 32 : 1145-53. doi: 10.1111/j.1365-2036.2010.04458.x
16. Van Gossum A, Munoz-Navas M, Fernandez-Urien I, *et al.* Capsule endoscopy versus colonoscopy for the detection of polyps and cancer. *N Engl J Med* 2009 ; 361 : 264-70.
17. Spada C, Pasha SF, Gross SA, *et al.* Accuracy of First- and Second-Generation Colon Capsules in Endoscopic Detection of Colorectal Polyps: A Systematic Review and Meta-analysis. *Clin Gastroenterol Hepatol* 2016 ; 14 : 1533-43 e8.
18. Spada C, Hassan C, Barbaro B, *et al.* Colon capsule versus CT colonography in patients with incomplete colonoscopy: a prospective, comparative trial. *Gut* 64 : 272-81.
19. Pickhardt PJ, Graffy PM, Perez Alberto A *et al.* Screening at abdominal CT : use of automated body composition biomarkers for added cardiometabolic value. *Radiographics* 2021 ; 41 : 524-42.
20. Pickhardt PJ, Graffy PM, Zea R, *et al.* Automated CT biomarkers for opportunistic prediction of future cardiovascular events and mortality in an asymptomatic screening population: a retrospective cohort study. *Lancet Digit Health* 2020 ; 2 : e192-e200.
21. Atkin W, Dadswell E, Wooldrage K, *et al.* SIGGAR investigators. Computed tomographic colonography versus colonoscopy for investigation of patients with symptoms suggestive of colorectal cancer (SIGGAR): a multicentre randomised trial. *Lancet* 2013 ; 381 : 1194-202.
22. Stoop EM, de Haan MC, de Wijkerslooth TR, *et al.* Participation and yield of colonoscopy versus non-cathartic CT colonography in population-based screening for colorectal cancer: a randomised controlled trial. *Lancet Oncol* 2012 ; 13 : 55–64.
23. Johnson CD, Chen M-H, Toledano AY, *et al.* Accuracy of CT colonography for detection of large adenomas and cancers. *N Engl J Med* 2008 ; 359 : 1207-17.
24. Pickhardt PJ, Choi JR, Hwang I, *et al.* Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med* 2003 ; 349 : 2191-200.
25. de Haan MC, van Gelder RE, Graser A, *et al.* Diagnostic value of CT-colonography as compared to colonoscopy in an asymptomatic screening population: a meta-analysis. *Eur Radiol* 2011 ; 21 : 1747–63.

26. Spada C, Hassan C, Bellini D, *et al.* Imaging alternatives to colonoscopy: CT colonography and colon capsule. European Society of Gastrointestinal Endoscopy (ESGE) and European Society of Gastrointestinal and Abdominal Radiology (ESGAR) Guideline - Update 2020. *Eur Radiol* 2020 ; 52 : 1127-41. doi : 10.1055/a-1258-4819.
27. Kim WS, Lee HS, Lee JM, *et al.* Fluoro-2-deoxy-d-glucose positron emission tomography/computed tomography for the detection of proximal synchronous lesions in patients with obstructive colorectal cancer. *J Gastroenterol Hepatol* 2017 ; 32 : 401-8. doi : 10.1111/jgh.13486.
28. Shmidt E, Nehra V, Lowe V, *et al.* Clinical significance of incidental [18 F] FDG uptake in the gastrointestinal tract on PET/CT imaging: a retrospective cohort study. *BMC Gastroenterol* 2016 ; 16 : 125. doi : 10.1186/s12876-016-0545-x.
29. Kashiwagi K, Nakazato Y, Arai M, *et al.* Limited Identification of Dual-time-point Positron Emission Tomography/Computed Tomography in Advanced Colorectal Neoplasms. *Intern Med* 2017 ; 56 : 1287-92. doi : 10.2169/internalmedicine.56.8037.
30. Hojo D, Tanaka T, Takahashi M, *et al.* Efficacy of 18-fluoro deoxy glucose-positron emission tomography computed tomography for the detection of colonic neoplasia proximal to obstructing colorectal cancer. *Medicine (Baltimore)* 2018 ; 97 : e11655. doi : 10.1097/MD.0000000000011655

WHAT ARE THE NEEDS FOR THERAPEUTIC COLONOSCOPY ON THE 2030 HORIZON?

Mathieu Pioche [1],
[1] *Hepatogastroenterology department, Édouard Herriot Hospital, Hospices Civils de Lyon*

« Tomorrow will not be like yesterday. It will be new and it will depend on us. It is less about discovery than it is about invention. »
Gaston BERGER

We are writing this chapter in October 2021. Who's clever enough to say what technological advances will change our discipline in 2030, considering how fast things are changing? What is likely is that minimally-invasive treatments of colorectal cancer will become even more common than today, that their indication will expand to more invasive lesions, adjuvant non-surgical treatments will be more frequent and the quality of surgical resections will improve with the aim of systematically achieving R0. Indeed, it seems unlikely that the uncertainty that accompanies fragmented resection will be acceptable for much longer, considering that it represents a procedure that is imprecise, and non-personalized, and because it leads to heavy monitoring in order to detect recurrence, which is becoming more and more uncommon. The only thing that could again increase the validity of fragmented mucosectomy would be progress in endoscopic characterization via for example AI, approaching perfection to the point that no cancer would be missed within any lesion. Personally, I believe much more strongly in the simplification of R0 resection technology, its systematic application and the obtention of R0 in the vast majority of cases. Unless it becomes possible one day to analyse the whole volume of a tumor (to achieve the equivalent of microscopic examination at any level), there is little probability that the analysis of tumor surface can lead to a perfect diagnosis. Indeed, some tumors degenerate in depth without their surface being altered. As long as the characterization is not perfect, the gold standard, although still to be improved, will remain the histological analysis of the R0 resected lesion. There is also an unmet need for our pathologists to perform homogeneous analyses of high quality, in order to obtain pathological analysis of the most pejorative areas within a

lesion. Immunohistochemistry and digital slide analysis could improve this, especially considering that artificial intelligence will likely outperform experts in this setting and allow all centers to offer analyses of identical quality, irrespective of the experts..

I am proposing an experimental journey into the future to the year 2030, based on the presentation of our national congress and the progress reported regarding colonoscopy and the management of patients with colorectal lesions.

The 2030 JFHOD will probably be mainly digital and we could imagine that the programs will be even more personalized, with automatic pathways oriented by artificial intelligence according to our centers of interest and our desires of the moment. Here are some examples of sessions that may be hot in 2030 at our National Convention.

PREPARING WILL BE MORE SIMPLE IN THE FUTURE

The therapeutic management of our patients coming from far could be significantly simplified by a new generation preparation based on a single tablet allowing colic preparation of good quality in less than 3 hours after taking it. This would shorten the care of the patient for colonoscopy into a single day, and thus simplify the problems raised by the transfer of patients, and the necessity of overnight hospitalization of frail patients.

MODERN DETECTION, A CHALLENGE STRONGLY SUPPORTED BY DIGITAL APPROACHES

The rate of detection of adenomas, which has long been considered the quality criterion allowing to differentiate between good and bad endoscopists, will possibly become less significant when AI systems, such as the EndoAngel [1], will be used to highlight polyps in real time, and most importantly the potential blind spots that are missed during the descent, by orienting the area worth exploring more carefully using arrows. It will be important to demonstrate that high detection rates (>55%) have a real positive impact on patients by reducing interval cancers. An active debate took place in 2021 regarding the clinical relevance of finding small adenomas of less than 5 mm. However, one of the key issues to solve are the false-negative results from colonoscopy asssisted by AI regarding Laterally Spreading Tumors (LST), non-granular serrated sessile lesions [2]. Going even further, the first prototypes of semi-autonomous coloscopes could help the gastroenterologist to maneuver and to better examine these blind areas. The added human value and motivation could one day be supplanted by quasi-autonomous systems. If this turns out to be the case, a major change will be required regarding quotations, in order to enhance the quality over the quantity of examinations. It will be important to value more greatly the detection and removal of lesions than increasing the number of “blank” examinations.

A tremendous benefit of these systems will be to standardize the practice and quality, thus equalizing the care proposed all over the territory, irrespective of the level of expertise or specialization of the local endoscopist.

COLORECTAL CHARACTERIZATION OF THE TUMOR VOLUME USING THE COMBINED TECHNIQUE (ENDOSCOPY AND TOMOGRAPHY)

A current limitation of endoscopic characterization is the inability to scan the whole tumor volume, since currently it is only possible to consider the visible surface. Tumor characterization will therefore remain fragmentary, until new technical approaches, such as for example optical coherence tomography, permit the acquisition of images of the whole tumor volume, and not exclusively its visible surface. Some tumors present as deep degenerative lesions, a particularity that explains the existence of discordances between endoscopic predictions (even with the CONECCT classification [3]) and the final histological evaluation. Thus, a characterization supported by artificial intelligence, based on complex algorithms of machine learning/ deep learning could help to combine the benefits of these two techniques, approaching perfect characterization and precise prediction of the nature of polyps. This might help to offer treatments à la carte.

THE R0 REVOLUTION: PIECEMEAL RESECTION WILL LIKELY BE LESS FREQUENT

Even if predictions improve, fragmented resections will likely disappear in the future, thanks to the simplification of techniques used to achieve R0 resection in most cases. Future randomized studies should measure the loss of information caused by piecemeal procedures (number of emboli missed, inacurrate depth of invasion), and if this loss of information is significant, piecemeal will likely become unacceptable. In fact, achieving a resection of oncologic quality for degenerative lesions should become indispensable for our patients, to ensure the curative nature of our resections without any hazard that would be secondary to piecemeal resection.

TRIANGULATION IN ENDOSCOPY: THE NEED FOR INDEPENDENT TRIANGULATION

Traction devices (magnetic or not) will probably dominate our daily practice regarding submucosal dissection and other endoscopic techniques: better catheterization of the biliary tree, better access to the small intestine... In fact, a reversible «extra-hand» (magnetic power) seems to be one of the currently unmet needs in therapeutic endoscopy. Recently introduced medical devices (elastic traction, magnetic traction, shape memory nitinol alloy) are bound to become more efficient and more popular.

One could also imagine digital assistance to guide operations, for example by helping the operator identify the structures of the submucosa (vessels or muscular layers) with augmented reality, in order to prevent complications.

PERFORATION WILL NOT BE SCARY ANYMORE

Although the current data are already reassuring (more than 97% success with the endoscopic closure of small perforations of <5 mm), attitudes have not yet really changed and perforation is still considered scary. However, based on these good performances, we should progressively move toward simpler 12-hours surveillance for successfully-closed perforations, without systematic CT scan or antibiotic therapy. After overnight monitoring, endoscopic clip closure of perforation without symptoms should no longer justify imaging or surgery. In the future, it is likely that perforations will not be referred for surgery without an initial attempt at endoscopic closure, and also as long as the patient remains asymptomatic after this closure.

THE AMBULATORY MANAGEMENT OF COLONIC INJURIES SHOULD BE EXPANDED

The vast majority of submucosal dissections of the colon are performed under general anesthesia with intubation. The very low morbidity reported in late 2021 in the RESECT Colon protocol could change the practice with, on one hand, a reversal to sedation without systematic intubation, and on the other hand, the generalization of ambulatory management of lesions with an access to hospital beds in order to monitor the patient for the first 12 hours in case of a perforation. Indeed, therapeutic endoscopic procedures are less invasive than many surgical procedures performed in an ambulatory setting, making the whole procedure more flexible.

EXPANDING SINGLE OR COMBINED ENDOSCOPIC RESECTIONS WITH ADJUVANT TREATMENTS

A current trend is to downscale the risk of nodal metastasis in a context of T1 lesion in the absence of budding or lymphovascular infiltration. Simple monitoring might become the first choice for these lesions, once they are endoscopically R0 resected, regardless of the depth of submucosal invasion. One step further, large transmural resections could become possible (Full Thickness Resection Device), such as those that already exist for small lesions. This would allow organ conservation with the use of perioperative chemotherapy to prevent local and distant metastases for T1b or T2 lesions. It is likely that combined treatments based on endoscopic resection and chemotherapy will become standard therapy to avoid the current paradox of T1b tumors with pejorative criteria referred for surgery (gold standard according to the French 'Thesaurus

National de Cancérologie Digestive'), while T2 tumors of the rectum that respond to chemoradiotherapy can be treated conservatively with a watch and see attitude.

HISTOLOGY MUST ALSO EVOLVE TO REDUCE ITS BIAS

Today, endoscopic resection specimens are cut every 2 mm, and a single section of a few micrometers (5-10 µm) is therefore examined every 2 mm, i.e. about 0.5% of the tumor volume is explored. This represents a considerable sampling bias and it explains why the conclusions will not necessarily reflect the most unfavorable histology at the points of deep invasion. Histology, largely considered as the gold standard, remains unfortunately the best option to analyze the tumor volume, but it could dramatically improve if one could find ways to determine the position of the deepest point of invasion of the tumor. If one day tumor scanners will be able to spot the tumor invasion front with 3D-vision of the tumor volume, it would be interesting to compare conventional pathology with 3D-optimized pathology. An artificial intelligence algorithm could also probably detect the point of deepest invasion on digital slides, as well as spot budding or lymphovascular invasion, thus allowing for pathologists to focus their examination on the most advanced lesions instead of the dozens of slides that reflect a small portion of the tumor and present a major sampling bias.

ECOLOENDOSCOPY: THE NEED FOR SUSTAINABLE DEVELOPMENT!

Finally, and this is perhaps the most important for future generations, the zero carbon impact of colonoscopy should be our goal for 2030. Indeed, we pollute a lot, in particular with our disposable devices. The evolution of European regulations for medical waste should lead to the recycling of the majority of our waste, which is essential for reducing our environmental impact. Despite a stammering start [4,5], ecology is now firmly considered within the walls of endoscopy services, while these services represented in 2020 the third largest polluter of the British health system [6]. The new generations now consider having such a high impact on the environment as impossible and endoscopy of 2030 has no other future than to be green.

THE TRAINING IN 2030

More and more conferences will probably become virtual, in an ecological-responsible perspective, while trying to preserve some conviviality. While automated colonoscopy devices without an operator currently do not seem possible in the near future, better simulators are coming, equiped with force feedback or correctors that limit unwanted movements of beginners, and could become effective assistance for endoscopy learners.

CONCLUSION

There is no doubt that the nine years to come will be rich in innovations, and that minimally-invasive endoscopic techniques will gain ground (except if one day, a drug becomes available to destroy polyps without having to remove them). In 2030, I think that the therapeutic colonoscopy will be simpler, perfomed in an ambulatory setting, without intubation, faster but still performed with the aim of achieving R0, with lesser and controlled morbidity. Tomorrow's endoscopy will be green, concerned and involved in sustainable development, keeping in mind that our carbon footprint today is unacceptable with 3 kg of waste per patient per day, most of it sent for incineration 6.

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REFERENCES

1. Gong D, Wu L, Zhang J, *et al.* Detection of colorectal adenomas with a real-time computer-aided system (ENDOANGEL): a randomised controlled study. *Lancet Gastroenterol Hepatol* 2020 ; 5: 352-61. doi:10.1016/S2468-1253(19)30413-3
2. Lafeuille P, Lambin T, Yzet C, *et al.* Flat colorectal sessile serrated polyp: an example of what artificial intelligence does not easily detect. *Endoscopy* 2021; epub. doi :10.1055/a-1486-6220
3. Fabritius M, Gonzalez J-M, Becq A, *et al.* A simplified table mixing validated diagnostic criteria is effective to improve characterization of colorectal polyps: the CONECCT teaching program. *Endoscopy International Open* 2019 ; 7 : e1197-206. doi: 10.1055/a-0962-9737
4. Leddin D, Omary MB, Veitch A, *et al.* Uniting the Global Gastroenterology Community to Meet the Challenge of Climate Change and Non-Recyclable Waste. *Gastroenterology* 2021 ; 161 : 1354-60. doi:10.1053/j.gastro.2021.08.001
5. Leddin D, Omary MB, Veitch A, *et al.* Uniting the global gastroenterology community to meet the challenge of climate change and non-recyclable waste. *Gut* 2021 ; 70 : 2025-9. doi : 10.1136/gutjnl-2021-325789
6. Vaccari M, Tudor T, Perteghella A. Costs associated with the management of waste from healthcare facilities: An analysis at national and site level. *Waste Manag Res* 2018 ; 36 : 39-47. doi : 10.1177/0734242X17739968

THE ROLE OF SURGERY FOR THE TREATMENT OF COLORECTAL CANCER ON THE 2030 HORIZON

Mehdi Karoui [1],
[1] *Université de Paris, Assistance Publique–Hôpitaux de Paris, Department of Digestive and Oncological Surgery, Georges Pompidou European Hospital, Paris*

« *The roads of science are narrow, so that they who travel them, must wither follow or meet one another.* »
Samuel Johnson

Over the past thirty years, colorectal cancer surgery has undergone a revolution with the advent of minimally-invasive surgery, either laparoscopic or robotic. Minimally-invasive surgery consists of performing an operation after creating a pneumoperitoneum with CO_2 insufflated through a short incision, allowing the introduction of a camera and microinstruments, thus reducing abdominal trauma, postoperative pain and morbidity, while respecting the fundamental principles of open surgery (laparotomy). Minimally-invasive surgery, coupled with optimized perioperative care (prehabilitation, enhanced recovery after surgery [ERAS], ambulatory surgery) makes it possible to reduce the length of hospitalization, improve the quality of life of operated patients and start adjuvant chemotherapy earlier if necessary. Progress in the field of computing and robotics with the development of artificial intelligence (AI), progress in the field of radiology and gastrointestinal endoscopy, the development of targeted treatments in oncology with the advent of immunotherapy, the evolution of radiotherapy and new effective neoadjuvant treatments with chemotherapy and/or radiotherapy will profoundly modify the technique and the role of surgery in colorectal cancer care in the next 10 years.

TECHNICAL DEVELOPMENTS

By 2030, surgery will become increasingly minimally-invasive, computer-assisted, guided by images, robotics and AI. It will be hybrid, combining radiology and inter-

ventional endoscopy, inevitably leading to a transformation of operating theaters. The use of virtual reality will make it possible to develop a virtual 3D model of the patient («avatar») from cross-sectional images, offering new possibilities for surgical planning and for the simulation of the intervention before operating the «real» patient [1]. This model will also be superimposable over the real images of the patient at the time of the operation, with augmented reality allowing the surgeon to better visualize and identify anatomical structures, thus improving the surgical procedure. The introduction of AI in the operating room could similarly assist the surgical procedure by providing access to the large number of similar previously recorded interventions, facilitating the automatic adaptation to anatomical variations [2]. The concept of computer-assisted surgery combining robotic automation and image guidance will facilitate the procedure and optimize the surgeon's performance. The performances of AI could also be used to promote communication between the different actors present in the operating room: surgeons, anesthesiologists and nurses, to coordinate their activity and also give an alert in case of deviation of the procedure from the standards [2]. These recordings could also be used *a posteriori* to analyze the causes of complications and thus improve the safety of interventions through the feedback of experience. Image capture technologies and cameras fixed on the operator's head, filming what the surgeon is looking at, will not only allow a retrospective analysis of the surgical procedure, but will also produce a new video-expertise, well-suited for training and for "computer vision" and the identification of the different phases of surgery, thus helping in operative decision-making [1]. An operative voice assistant (chatbot) will allow the surgeon to receive information regarding the patient, and possibly, to obtain "advice" from AI through visual identification of the different surgical phases [1]. The use of "cobots" (an agile version of the current surgical robots with 3-4 articulated arms with instruments and a camera) will make it possible for the surgeon to be assisted during the procedure (fluidity of movement, stabilization of the movements, practical assistance….) [1].

Improvement of the minimally-invasive approach, and in particular NOTES surgery (Natural Orificial Trans Endoscopic Surgery), will push the current limits of minimally-invasive surgery. NOTES surgery, which consists of a planned incision through the wall of natural orifices to access the peritoneal cavity and perform a surgical intervention without skin incision, will require the surgeon to acquire skills and expertise in interventional endoscopy. This hybrid minimally-invasive surgery (surgical endoscopy) will be based on a close collaboration between surgeons and interventional endoscopists and will revolutionize the management of colorectal cancer, which will lead to a reorganization of the operating room for the integration of one or more imaging and endoscopy systems.

EVOLUTION OF CONCEPT

To date, the standard of care for the treatment of colorectal cancer is based on radical excision surgery (colectomy or proctectomy) with systematic lymph node dissection. The rise of personalized medicine, with in particular the identification of molecular tumor markers – microsatellite instability status (MSI), KRAS/BRAF mutations – prognostic and predictive of treatment response, will have a major impact on defining the role of surgery in the curative treatment of colorectal cancer. The proven efficacy of immunotherapy in non-metastatic colorectal cancer with microsatellite instability (MSI or dMMR, Mismatch Repair deficient), leading to high rates of complete histological responses will in the years to come raise the question of the necessity to operate on these patients or not [3]. The encouraging data from neoadjuvant chemotherapy trials on localized colorectal cancer [4] and anti-BRAF treatments associated with anti-EGFR (Epidermal Growth Factor Receptor) and anti-MEK in metastatic situations [5] will also lead to the evaluation of the efficacy of these treatments in BRAF-mutated non-metastatic patients. In addition, the results of induction chemotherapy trials and consolidation with radiotherapy (TNT, Total Neoadjuvant Treatment) in rectal cancer, leading to high rates of complete response, will lead to the possibility of rectal sparing [6]. These data, coupled with the development of modern imaging, in particular metabolic imaging, adapted for the prediction of treatment responses (PET-MRI for example) will gradually lead to a shift from systematic radical organ excision to strategies of organ preservation, with the objective of reducing morbidity and mortality and improving the quality of life of patients without having a negative impact on oncological results [7]. This trend will also benefit from the progress in diagnostic endoscopy (prediction of the complete response) and therapeutic endoscopy (endoscopic submucosal resection techniques for the histological analysis of previously treated areas). The evolution of targeted radiotherapy – contact radiotherapy, brachytherapy – and the intensification of neoadjuvant treatments will make it possible to propose organ preservation strategies to a growing number of patients.

CONCLUSION

By 2030, colorectal cancer surgery will be minimally-invasive and it will be based on the combined use of computer-assisted techniques, image building and robotics with the aim of improving surgical results. Advances in surgery, interventional endoscopy and radiology will make it possible to propose a new hybrid approach for the curative treatment of colorectal cancer. This new hybrid therapeutic approach of «surgical endoscopy» justifies specific endoscopic and surgical training for young surgeons and endoscopists, and it will require changes in the operating room to integrate the necessary imaging and endoscopy tools. Finally, the effectiveness of neoadjuvant treatments and the possibility of proposing targeted treatments, based on the molecular status of tumors, will make it possible to no longer propose systematic radical excision surgery and instead favor strategies of organ preservation in colorectal cancer patients.

REFERENCES

1. Vibert E. Surgery: An old profession with an expanding future. *J Visc Surg* 2021 ; 158 : S1-3. doi : 10.1016/j.jviscsurg.2021.01.006.
2. Nordlinger B. Surgery and artificial intelligence: Just around the corner? *J Visc Surg* 2021 ; 158 : S4-S5. doi : 10.1016/j.jviscsurg.2021.01.007.
3. Chalabi M, Fanchi LF, Dijkstra KK, *et al.* Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. *Nat Med* 2020 ; 26 : 566-76. doi: 10.1038/s41591-020-0805-8.
4. Arredondo J, Pastor E, Simó V, *et al.* Neoadjuvant chemotherapy in locally advanced colon cancer: a systematic review. *Tech Coloproctol* 2020 ; 24 : 1001-15. doi : 10.1007/s10151-020-02289-4.
5. Kopetz S, Grothey A, Yaeger R, *et al.* Encorafenib, Binimetinib, and Cetuximab in BRAF V600E-Mutated Colorectal Cancer. *N Engl J Med* 2019 ; 381 : 1632-43. doi : 10.1056/NEJMoa1908075.
6. Kong JC, Soucisse M, Michael M, *et al.* Total Neoadjuvant Therapy in Locally Advanced Rectal Cancer: A Systematic Review and Metaanalysis of Oncological and Operative Outcomes. *Ann Surg Oncol* 2021 ; 28 : 7476-86. doi : 10.1245/s10434-021-09837-8.
7. Rullier E, Vendrely V, Asselineau J, *et al.* Organ preservation with chemoradiotherapy plus local excision for rectal cancer: 5-year results of the GRECCAR 2 randomised trial. *Lancet Gastroenterol Hepatol* 2020 ; 5 : 465-74. doi : 10.1016/S2468-1253(19)30410-8

WHAT WILL BE THE TARGETS AND THE MODALITIES OF FUTURE CHEMOTHERAPIES AND TARGETED THERAPIES?

Cindy Neuzillet [1]
[1] *Department of medical oncology, Institut Curie, Saint-Cloud, France*

« *The present is nothing but a hypothesis that has not yet been surmounted.* »
Robert Musil

A BRIEF HISTORY OF CHEMOTHERAPIES AND TARGETED THERAPIES BEFORE 2022

The management of metastatic colorectal cancer (CRC) has known a series of revolutions over the past 30 years (*figure 1*). Until the 1990s, CRC was regarded as particularly chemoresistant, with limited anti-tumor activity of 5-fluorouracil (5-FU). In the year 1990, the optimization of the administration of 5-FU with the modulation of its activity using folinic acid (LV5FU2 scheme) has helped to increase its efficacy 1. Then in the 2000s, bi-chemotherapy regimen combining 5-FU (or its oral form, capecitabine) with oxaliplatin (FOLFOX) and irinotecan (FOLFIRI), followed by tri-chemotherapy (FOLFIRINOX) have been developed 1. The trifluridine-tipiracile came later to increase the chemotherapeutic arsenal.

The years 2000 and 2010 witnessed the arrival of the first targeted therapies against EGFR (Epidermal Growth Factor Receptor) - cetuximab, panitumumab - and angiogenesis - bevacizumab, aflibercept, regorafenib – most often assessed in association with these chemotherapies 2. Overexpression of HER2 (2% of metastatic CRC) has also emerged as a target for antibodies – trastuzumab, pertuzumab - and multikinase inhibitors – lapatinib, tucatinib – 2, and more recently, for a new therapeutic class, i.e. conjugated antibodies – trastuzumab deruxtecan. Moreover, the *BRAFV*^{600E} mutation (8-10 %), that was originally identified in malignant melanoma, was reported as a prognostic marker in metastatic CRC, with a markedly reduced overall survival (OS) (2-3 times lower than for the non-mutated tumors) and was found to be associated with a specific phenotype (tumors of the right colon, often mucinous, more frequently found in elderly women with nodal and peritoneal metastases). It has become a

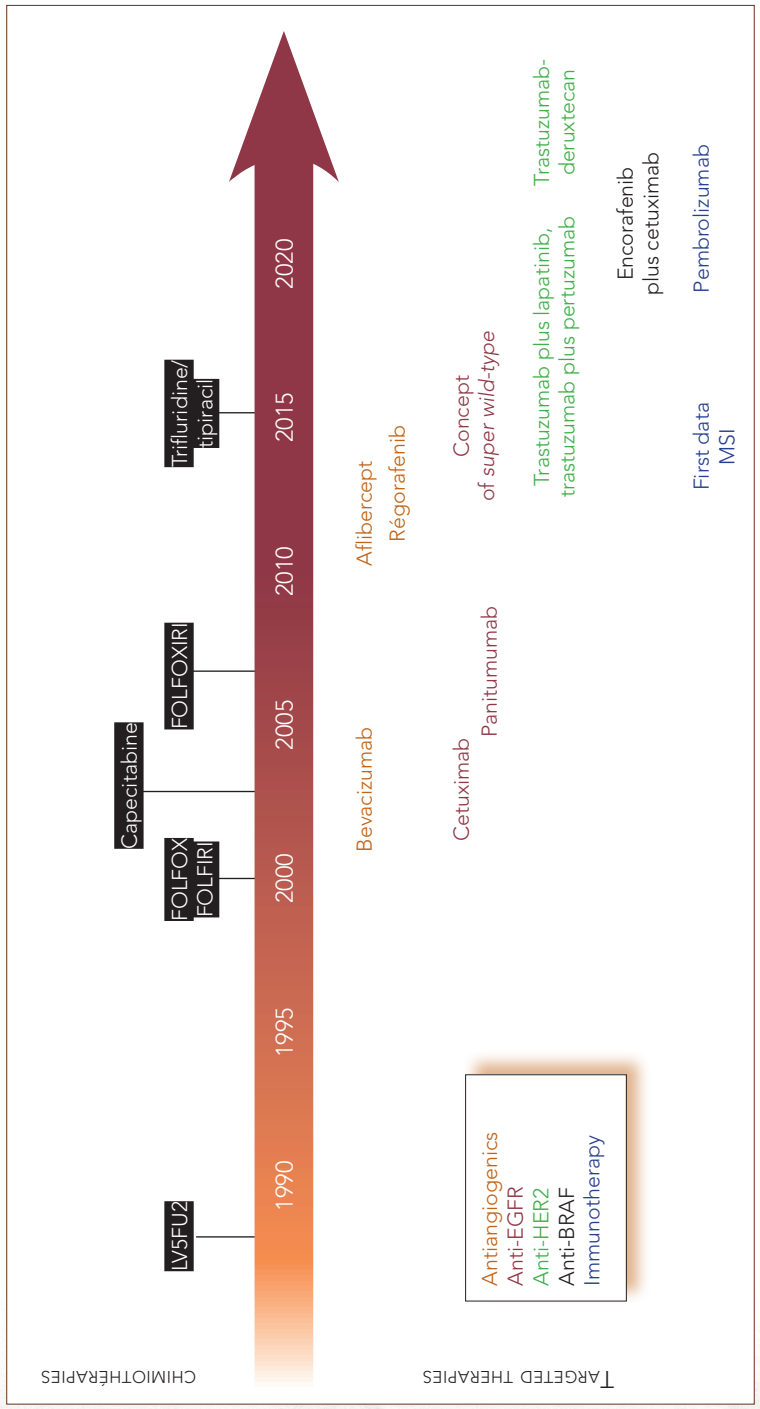

FIGURE 1. History of the main advances in the treatment of colorectal cancer since the 1990s. MSI: microsatellite instability.

target for the association of anti-BRAF and anti-EGFR molecules (encorafenib plus cetuximab) 3. Finally, as discussed in the next chapter, CRC with microsatellite instability (MSI: 4-5%) have seen their management revolutionized by immunotherapies (pembrolizumab, nivolumab plus ipilimumab) 4 .Thus, CRC has been stratified into multiple molecular subentities accessible with specific therapeutic strategies 5.

The clinical development of antiangiogenics has followed a different path from anti-EGFR, anti-HER2 or anti-BRAF agents 2:

- antiangiogenics were developed on the basis of a concept that was once believed to be universal (the existence of an angiogenic switch), and tested as early-line anti-metastatic agents without any companion biomarkers, and the issue of biomarkers able to predict the response to these agents is still not resolved to this day;
- anti-EGFR agents were developed as late-line anti-metastatic agents, with companion biomarkers being progressively identified. After the initial erroneous assumption that the response to anti-EGFR would be correlated to EGFR expression by immunohistochemistry (IHC), later studies identified the predictive role of *KRAS* mutations. The spectrum of sensitive tumors was further narrowed to those without mutations in exons 2, 3, 4 of *KRAS* and *NRAS* (i.e. around 40% of metastatic CRCs), with the recent demonstration of the impact of colonic location (a greater sensitivity of tumors of the left colon);
- anti-HER2 agents were initially tested only in HER2-positive tumors (IHC 3+ or 2 +/positive ISH) on the basis of proof of concept obtained from breast and stomach cancers;
- targeting *BRAF* alone, following the model of melanoma, was initially unsuccessful, and it took basic studies to understand the role of EGFR-mediated feedback in order to develop effective combinations against CRC.

These improvements have resulted in a steady increase in the rate of tumor response and the OS of patients increased from a median of about 12 months in the 1990s to more than 30 months today 5.

In this chapter, we will present some leads for progress in the years to come in the treatment of metastatic CRC with chemotherapy and targeted therapies.

TUMOR CELL TARGETING

5-FU-based chemotherapy remains the cornerstone of the treatment of metastatic CRC and the basis for most combinations with targeted therapies, but today we are witnessing the development of targeted strategies without chemotherapy, as is the case for pembrolizumab or the combination of encorafenib + cetuximab, at least for defined subsets of tumors with precise molecular alterations.

The identification of actionable subtypes of CRC (*table 1*) has been a source of progress in terms of survival, and this strategy is continuing with the identification

of new entities, some of them rare [6]. For example, CRC bearing fusion transcripts (*NTRK, RET, ALK*...), are extremely rare in the general population (<1%), but specific inhibitors are available (eg. larotrectinib against *NTRK*). The rare occurrence of these alterations raises the problem of demonstrating the efficacy of these therapeutic agents, considering that randomized phase III studies are not the most suitable in this situation of precision medicine, but they still remain the reference for authorities in charge of regulation. Thus, larotrectinib obtained the European marketing authorization but its reimbursement for adult patients with a tumor bearing a *NTRK* fusion has not been validated in France, based on the absence of a control group of patients. However, the low frequency of this molecular alteration (0.1-0.5%) would not reasonably permit this. This raises the question of alternative criteria for judging the clinical benefit for these patients with orphan subentities of CRC (the response rate?). Another issue is the benefit of the diagnostic tests if they are perfomed in unselected patients. Indeed, the search for fusion transcripts does not rely on DNA analysis, as is the case when looking for *RAS* or *BRAF* mutations, but on RNA, and it uses specific panels of New Generation Sequencing (NGS), that are costly, and it is therefore not feasible to perform systematic testing for all patients. However, better molecular understanding of CRC has revealed that these rare alterations can be enriched in certain groups of patients: fusion transcripts are more frequent in MSI (5%) and even more so if they are *RAS*/*BRAF* wild-type (going as high as 50% or more) [7]. This echoes a broader concept in digestive oncology, that when a strong driver oncogenic mutation is present, for example in *KRAS* or *BRAF*, there is very little likelihood of identifying another potentially targetable alteration. For example, in pancreatic cancers that carry a KRAS-activating somatic mutation in more than 90% of the cases, fusion transcripts are almost exclusively detected in patients without *KRAS* mutation. This allows the restriction of the search for fusion transcripts using an NGS RNA panel to *RAS* wild-type patients [8]. A similar two step-strategy could be proposed for CRC, starting with the search for *RAS*/*BRAF* mutations and the MSI and HER2 status, to select the patients that are the most likely to benefit from broad molecular DNA panels and RNA panels (reserved for *RAS*/*BRAF* non-mutated), even if the cost of these analyses is bound to decrease in the coming years.

A further unresolved issue to date is the possibility of targeting *KRAS* mutations that were long considered to be inaccessible to targeted therapies. In the recent years, new inhibitors have been developed that target the *KRAS G12C* mutation (adagrasib, sotorasib), based on the physicochemical characteristics of the cysteine amino-acid in G12C [9]. The targeting of this mutation was first developed against bronchial cancers, where it is common (14 %), and where the inhibition of *KRAS* with an anti-G12C molecule alone proved efficient (a response rate of around 40%). In contrast, similarly to *BRAF* targeting, the anti-G12C monotherapy had lower results in CRC (a response

TABLE 1. Main targetable alterations in colorectal cancer according to the ESMO Scale for Clinical Actionability of molecular Targets (ESCAT) [24].

MOLECULAR ALTERATION	FREQUENCY (%)	MOLECULES	ESCAT CATEGORY	SIGNIFICANCE
KRAS mutation *NRAS* mutation	44 4	Cetuximab, panitumumab	Non applicable	
BRAF ^{v600e} mutation	8.5	Encorafenib plus cetuximab	IA	Targeted treatment administered to patients with the molecular alteration showed an improvement in clinical results in prospective clinical trials. **Access to treatment should be considered as the reference therapy.**
Microsatellite instability	4-5	Pembrolizumab	IA	
NTRK fusions	0.5	Larotrectinib, entrectinib	IC	
ERBB2 (HER2) amplification	2	Trastuzumab plus pertuzumab, trastuzumab plus lapatinib	IIB	Targeted treatment administered to patients defined through molecular analysis and is likely to improve the clinical results in one type of tumor, but additional data are required. **Treatment to be evaluated prospectively (register or clinical trial).**

ESMO : European Society for Medical Oncology.

rate of 10-20%), and co-targeting EGFR significantly increased their effect (40%), forming the rationale for the current Phase III trial (KRYSTAL-10, NCT04793958) [9]. Nevertheless, G12C mutations are rare (4%) in CRC, and no effective inhibitors against the most common mutations of *KRAS* (*G12D*, *G12V*) exist to date, however several molecules are in the process of pharmacological development.

An alternative solution to directly targeting KRAS is to instead target the cellular vulnerabilities that this mutation induces, for example due to the replicative stress associated with it, especially when a TP53 mutation is also present. Cell cycle checkpoint inhibitors (anti-WEE1) showed activity against CRC with *KRAS* and *TP53* mutations (FOCUS-4C study) according to the concept of synthetic lethality, and other molecules are in development (anti-ATR, anti-CHK) [10].

Finally, an evaluation of the molecular status of a tumor with liquid biopsies is not yet validated in the context of routine clinical practice, but prospective data are accumulating and the sensitivity of the technologies used to detect mutations in circulating tumor DNA (ctDNA) is increasing, which could in the near future help in the analysis of the tumor *RAS*/*BRAF* status without tumour material [11]. These techniques could also be useful as tools for therapeutic monitoring by giving access to the load of ctDNA and the detection of the emergence of resistance mutations. Nevertheless, the clinical interest of these therapeutic strategies remains to be demonstrated with dedicated studies.

TARGETING THE MICROENVIRONMENT

Models of oncogenesis have evolved from being more cancer cell-centered to a more global vision that integrates the tumor microenvironment [12]. This led to the development of antiangiogenics and more recently to immunotherapy.

Tumor cells should not be considered separately, but only in the context of their microenvironment or stroma, a complex structure composed of extracellular matrix and endothelial, immune, nerve and fibroblast cells. These cellular partners interact with cancer cells and with each other via multiple mediators (intercellular contacts, physical constraints, soluble factors, extracellular vesicles, metabolites ...) and modulate the proliferation, invasion and the resistance to treatments of cancer cells (12). It is therefore essential to take them into consideration to better understand therapeutic failures and to explore new therapeutic avenues.

CRC are heterogeneous entities both in terms of molecular alterations, and in terms of the composition of their microenvironment, which can be fibrotic, vascularized or inflammatory to various degrees. This characteristic appeared in the Consensus Molecular Subtypes (CMS) classification proposed in 2015, where the CMS1 subtype corresponds to a subtype with a lymphocytic infiltrate, and CMS4 is a mesenchymal subtype with an abundant stroma, dense vascularization and inflammation related to the activation of the TGF -pathway [13].

Just as there are multiple subpopulations of immune cells (for example, M1 macrophages in tumors with an antitumor phenotype, or M2 with a protumor phenotype), different types of fibroblasts have been described with pro- or anti-tumor effects [14]. Refining the classifications of these cells and achieving a better understanding of their function is necessary in order to develop new therapeutic strategies designed to specifically target the «bad» fibroblasts or possibly also reprogram them into «good» fibroblasts.

Finally, a new partner has been identified in the tumor microenvironment in recent year: the intratumoral microbiota. In addition to the bacteria that are present in the digestive lumen (intestinal microbiota), bacteria can also be present within tumors. Most often, intracellular bacteria are present within cancer cells or immune cells, and are involved in the process of carcinogenesis (mutagenic action of some bacterial toxins [15]), in the recruitment of inflammatory cells, and they can also modulate tumor response to treatments [16]. Among them, *Fusobacterium nucleatum* is associated with colonic tumors mainly of the right colon and it is linked to poor prognosis. It has been shown that when this bacterium is detected in the primary tumor, it is also commonly found in the metastases, thus forming an ecosystem with the tumor and its stroma [17]. These bacteria are emerging as a new source of biomarkers and therapeutic targets.

The tumor microenvironment is overall rich in biological information and therapeutic potential. One of the major obstacles to its clinical analysis lies in the difficult access to tumor material and the intratumoral and the interlesional heterogeneity in each patient. Progress in the analysis of CT scans and MRI images, in particular with the contribution of artificial intelligence (radiomics), and their coupling to functional imaging - PET FDG, new probes and tracers (e.g., anti-FAP for fibroblasts) - and their correlation with the pathological examination, should enable a better capture of this heterogeneity in the cancer patient [18].

TARGETING THE HOST

Finally, advances in the treatment of metastatic CRC will also come from the improvement of supportive care. More than 10 years ago, it was demonstrated in lung cancer that the patients with the longest survival are not those who received the most chemotherapies, but those who received supportive care early on [19].

Supportive care covers all multidisciplinary interventions aimed at controlling the symptoms related to the tumor or the treatments, in order to optimize their tolerance and the patient's quality of life. They include pain control, caring for secondary effects of chemotherapy (nausea, bowel dysfunction, mucositis, neuropathy...), fatigue, anxiety, thromboembolic complications, frailty in geriatrics and accompanying the entourage.

Nutritional support and physical activity are two major pillars of supportive care of CRC. A chapter of the French national Thesaurus on gastrointestinal cancer was

recently added in order to emphasize their importance [20]. The majority of metastatic CRC patients are malnourished at diagnosis, and this malnutrition has a negative impact on all facets of the patient's life: survival, quality of life, risk of treatment complications, infections, hospitalization; and it is also associated with less effective treatment. It can therefore be considered as a real loss of opportunity for the patients.

Undernutrition is reversible with therapeutic interventions at early stages but it becomes refractory at later stages. Therefore, it is crucial to detect malnutrition as early as possible (criteria of the French HAS, High Authority of Health, proposed in 2019 for patients under 70 years of age [21] and in 2021 for those above 70 [22], and to reassess it at each consultation and implement dietary interventions - dietary advice, oral nutritional supplements, enteral nutrition, parenteral nutrition - and activity - endurance exercises and muscle building - to overcome it [23].

These measures do not only improve the quality of life of patients by counteracting malnutrition and fatigue, but they also play a role after the treatment of CRC. Physical activity reduces the risk of recurrence, the overall mortality and CRC-related mortality in observational studies for patients with adjuvant treatment. A large randomized trial (CHALLENGE, NCT00819208) is in progress.

CONCLUSION : THE IMPORTANCE OF MOLECULAR STUDIES AND MULTIDISCIPLINARITY

Considerable progress has been made in recent decades in the management of metastatic CRC. The progress was based on the advent of molecular analyses and the development of targeted therapeutic strategies matching the alterations. Prospects for the future rely on the rationalization of these tools, the promise of liquid biopsies for non-invasive analyses, and the development of new inhibitors, in particular to target the "untargetable" KRAS.

It is also essential to leverage on ancillary studies using clinical trials to understand the mechanisms that allow tumors to escape these new therapies, in order to develop new «catch-up» strategies. The second key word is the integration of the tumor in its microenvironment (immune cells, fibroblasts, bacteria, as new leads for therapeutic targets), and the need to achieve multidisciplinary care with supportive care occupying a place that is as important as specific treatments.

REFERENCES

1. Gustavsson B, Carlsson G, Machover D, *et al.* A review of the evolution of systemic chemotherapy in the management of colorectal cancer. *Clin Colorectal Cancer* 2015 ; 14 : 1-10.
2. Neuzillet C, Rousseau B, Kocher H, *et al.* Unravelling the pharmacologic opportunities and future directions for targeted therapies in gastro-intestinal cancers Part 1: GI carcinomas. *Pharmacol Ther* 2017 ; 174 : 145-72.
3. Kopetz S, Grothey A, Yaeger R, *et al.* Encorafenib, Binimetinib, and Cetuximab in BRAFV600E-Mutated Colorectal Cancer. *N Engl J Med* 2019 ; 381: 1632-43.
4. Andre T, Shiu KK, Kim TW, *et al.* Pembrolizumab in Microsatellite-Instability-High Advanced Colorectal Cancer. N Engl J Med 2020; 383: 2207-18.
5. Dekker E, Tanis PJ, Vleugels JLA et al. Colorectal cancer. *Lancet* 2019; 394: 1467-80.
6. Mosele F, Remon J, Mateo J, *et al.* Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. *Ann Oncol* 2020. doi : 10.1016/j.annonc.2020.07.014
7. Wang J, Li R, Li J, *et al.* Comprehensive analysis of oncogenic fusions in mismatch repair deficient colorectal carcinomas by sequential DNA and RNA next generation sequencing. *J Transl Med* 2021 ; 19 : 433. doi : 10.1186/s12967-021-03108-6
8. Singhi AD, George B, Greenbowe JR, *et al.* Real-Time Targeted Genome Profile Analysis of Pancreatic Ductal Adenocarcinomas Identifies Genetic Alterations That Might Be Targeted With Existing Drugs or Used as Biomarkers. *Gastroenterology* 2019 ; 156 : 2242-53.
9. Pfeiffer P, Qvortrup C. KRAS(G12C) inhibition in colorectal cancer. *Lancet Oncol* 2021 ; epub. doi : 10.1016/S1470-2045(21)00652-5
10. Seligmann JF, Fisher DJ, Brown LC, *et al.* Inhibition of WEE1 Is Effective in TP53- and RAS-Mutant Metastatic Colorectal Cancer: A Randomized Trial (FOCUS4-C) Comparing Adavosertib (AZD1775) With Active Monitoring. *J Clin Oncol* 2021 ; 39 : 3705-15.
11. Dasari A, Morris VK, Allegra CJ, *et al.* ctDNA applications and integration in colorectal cancer: an NCI Colon and Rectal-Anal Task Forces whitepaper. *Nat Rev Clin Oncol* 2020 ; 17 : 757-70.
12. Hanahan D, Weinberg RA. Hallmarks of cancer: the next generation. *Cell* 2011 ; 144 : 646-74.
13. Guinney J, Dienstmann R, Wang X, *et al.* The consensus molecular subtypes of colorectal cancer. *Nat Med* 2015 ; 21 : 1350-6.

14. Kalluri R. The biology and function of fibroblasts in cancer. *Nat Rev Cancer* 2016 ; 16 : 582-98.
15. Berger H, Meyer TF. Mechanistic dissection unmasks colibactin as a prevalent mutagenic driver of cancer. *Cancer Cell* 2021 ; 39 : 1439-41.
16. Nejman D, Livyatan I, Fuks G, *et al.* The human tumor microbiome is composed of tumor type-specific intracellular bacteria. Science 2020 ; 368 : 973-80.
17. Bullman S, Pedamallu CS, Sicinska E, *et al.* Analysis of Fusobacterium persistence and antibiotic response in colorectal cancer. *Science* 2017 ; 358 : 1443-8.
18. Maclean D, Tsakok M, Gleeson F, *et al.* Comprehensive Imaging Characterization of Colorectal Liver Metastases. *Front Onco*l 2021 ; 11 : 730854.
19. Temel JS, Greer JA, Muzikansky A et al. Early palliative care for patients with metastatic non-small-cell lung cancer. *N Engl J Med* 2010 ; 363 : 733-42.
20. Neuzillet C, Anota A, Foucaut AM, *et al.* Nutrition and physical activity: French intergroup clinical practice guidelines for diagnosis, treatment and follow-up (SNFGE, FFCD, GERCOR, UNICANCER, SFCD, SFED, SFRO, ACHBT, AFC, SFP-APA, SFNCM, AFSOS). *BMJ Support Palliat Care* 2020. doi : 10.1136/bmjspcare-2020-002751
21. HAS, Fédération française de nutrition. *Diagnostic de la dénutrition de l'enfant et de l'adulte*. Recommandation de bonne pratique. HAS, 2019. www.has-sante.fr/upload/docs/application/pdf/2019-11/reco277_recommandations_rbp_denutrition_cd_2019_11_13_v0.pdf.
22. HAS, Fédération française de nutrition. *Diagnostic de la dénutrition chez la personne de 70 ans et plus. Recommander les bonnes pratiques*. HAS, 2021. www.has-sante.fr/upload/docs/application/pdf/2021-11/reco368_recommandations_denutrition_pa_cd_20211110_v1.pdf.
23. Muscaritoli M, Arends J, Bachmann P, *et al.* ESPEN practical guideline: Clinical Nutrition in cancer. *Clin Nutr* 2021 ; 40 : 2898-913.
24. Mosele F, Remon J, Mateo J, *et al.* Recommendations for the use of next-generation sequencing (NGS) for patients with metastatic cancers: a report from the ESMO Precision Medicine Working Group. *Ann Oncol* 2020 ; 31 : 1491-505.

NANOMEDICINE FOR THE MANAGEMENT OF COLORECTAL CANCER ON THE 2030 HORIZON?

Anna C Sebbagh [1], Giovanna Lollo [2], Nicolas Tsapis [3], Florence Gazeau [1], Nathalie Mignet [4], Amanda K A Silva [1]

[1] *Université de Paris, CNRS (UMR 7057), Laboratoire Matière et Systèmes complexes (MSC), Paris, France*

[2] *Université Claude Bernard Lyon 1, CNRS, LAGEPP UMR 5007, Villeurbanne, France*

[3] *Université Paris-Saclay, CNRS, Institute Galien Paris-Saclay, Châtenay-Malabry, France*

[4] *Université de Paris, CNRS, Inserm, Unit of chemical and biological Technologies applied to health (UTCBS), Paris, France*

« *The idea of the future is more fruitful than the future itself.* »
Henri Bergson

Nanomedicines are particles of nanometric size that can encapsulate one or more active substances for their delivery to the pathological site of interest, increasing their benefit/risk ratio. Nanomedicines can also amplify the activity of other therapies, such as radiotherapy. Advances in this field have led to the emergence of nanomedicines with multiple properties and advantages (*figure 1*) conferred by the variety of their composition, their architecture and surface properties. The surface of these particles can be modified chemically, giving them specific targeting properties. All these properties allow them to be good imaging agents that can be used as diagnostic, therapeutic or theranostic agents by combining these two aspects within the same system.

To date, the most marketed nanodrugs are lipid-based formulations, either with liposomes incorporating anticancer drugs, such as Doxil(r), or vaccines against Covid-19 from Pfizer or Moderna, which are lipid particles that deliver mRNA.

In the context of colorectal cancer, several clinical trials are currently underway (*tables 1 and 2*) to test liposome-based therapy or other nano-objects in order to address the issues of personalized medicine, especially in terms of targeting, drug

administration and imaging. This chapter, written by members of the French Society of Nanomedicine and the "Controlled Release Society BeNeLux & France Local Chapter", is devoted to these aspects and shows how nanomedicine could contribute to the management of colorectal cancer by 2030.

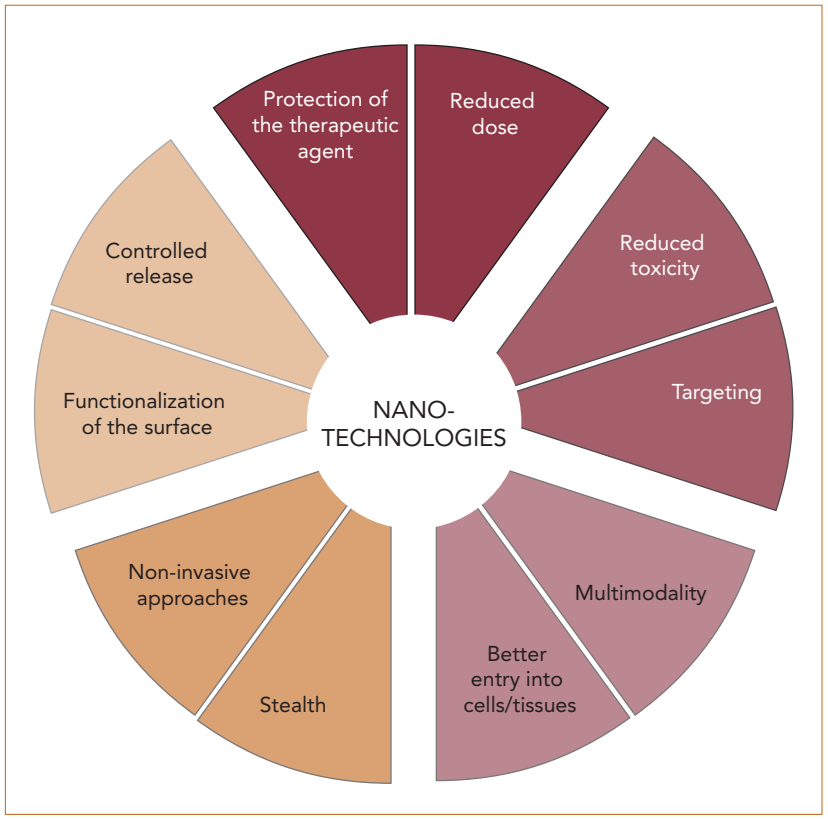

FIGURE 1. The advantages of nanodrugs that could improve the management of colorectal cancer on the 2030 horizon.

NANOMEDICINE FOR TARGETING

One of main interests of nanomedicine in the treatment of colorectal carcinomas is the possibility to target, either passively or actively, the tumor tissue to promote better efficacy of drugs and limit their side effects on healthy tissues.

Passive targeting, also called EPR effect (Enhanced Permeability and Retention effect) describes the preferential accumulation of macromolecules within the tumor via its vascular abnormalities. This principle is widely used by the liposome formulations that are marketed for antineoplastic treatments. In particular, the phase II PEPCOL study (No. NCT01375816) (*table 1*) [1] has compared the FOLFIRI regimen to 5-fluorouracil/leucovorin administration combined with PEP02 - a liposomal nanoparticle formulation of irinotecan [2] – as second line for the treatment of metastatic colorectal cancer resistant to oxaliplatine. The safety profile was similar in both groups, and the efficacy of the experimental treatment was superior to the FOLFIRI-1 regimen, and comparable to the mFOLFIRI-3 regimen. Other nanoparticles, more concentrated in active substances, such as nanocrystals, could in the future boost this strategy of passive accumulation of antineoplastic treatment in tumors [3].

However, the EPR effect strongly depends on the tumor characteristics (size, location, primary tumor versus metastases, etc.). To overcome this drawback, strategies of active targeting of tumor cells have been proposed in preclinical studies in mouse models of cancer based on colon cancer xenografts and/or *in vitro* models. These include functionalizing nanodrugs with addressing molecules, such as monoclonal antibodies directed against the VEGFR2 receptor [4] or aptamers (synthetic oligonucleotides that interact with a specific ligand) directed against the mucin MUC1 [5].

These approaches of passive or active targeting could be used in addition to strategies for local delivery [6,7], to improve the management of metastases, for example in peritoneal carcinosis, compared to intraperitoneal hyperthermic chemotherapy [8]. For example, it has been proposed in the literature to induce per-operative hyperthermia during cytoreductive surgery by photoactivating gold nanoparticles combined with 5-fluorouracil, to restrict the chemohyperthermic treatment to the cells that have internalized the nanoparticles [9]. In a mouse model of peritoneal carcinomatosis, the preferential accumulation of gold nanoparticles in the tumor nodules led to reduced toxicity and better efficacy with greater tumor necrosis compared to 5-fluorouracil alone. The same model was used to study the interest of delivering a therapeutic agent in extracellular vesicles produced by mesenchymal stromal cells [10]. Extracellular vesicles are subcellular-scale bodies (40-5 000 nm) delineated by a lipid membrane, containing proteins and nucleic acids, that are secreted by cells as vectors for intercellular communication. The principle is to take advantage of the inherent tropism of the extracellular vesicles produced by mesenchymal stromal cells for tumors. Vectorization of the temoporfin photosensitizer in extracellular vesicles led to better targeting of tumor nodules and improved efficacy compared to temoporfin alone or its liposomal formulation, with a significant increase in the infiltration of tumor nodules by CD8+ T-lymphocytes [10].

NANOMEDICINE FACING THE CHALLENGE OF ORAL ADMINISTRATION

Oral administration of drugs, when possible, should be favored because of its ease of use, good acceptance and non-invasive character. In addition, the gastrointestinal tract represents a large absorption surface (300-400 m^2). However, several barriers limit the absorption of macromolecules: pH, lytic enzymes, the

Table 1. Examples of clinical trials using nanomedicine for colorectal cancer - completed clinical trials. and/or with unpublished results, and trials not yet identified by a NCT reference are excluded. Trials that included pathologies other than colorectal cancer, not-completed trials

Numéro NCT	Phase	Context	Intervention	Number	Tumor Response Rate				Survival	Security	Web link
					CR (complete response)	PR (partial response)	Stabilization	Progression			
NCT01375816	II	2nd line treatment of metastatic colorectal cancer after oxaliplatin	PEP02 (nanoliposomal irinotecan) + leucovorin + 5-fluorouracil; IV	28	0	4		7	5-month median progression-free survival; median overall survival 14.6 months	10 severe side effects including 6 related to PEP02	doi : 10.1002/ cam4.635
			Irinotecan + leucovorin + 5-fluorouracil; IV	27	0	3		6	Median progression-free survival 6.8 months; median overall survival 10.5 months	13 severe side effects	doi : 10.1007/ s00280-006-0235-4
NCT00043199	II	Treatment of metastatic colorectal cancer, unresectable or locally recurrent and resistant to 5-fluorouracil/ leucovorin or to capecitabine and irinotecan	L-NDDP (aroplatin incorporated into multilamellar liposomes); IV	20	0	1	3	14	N/A	17 side effects, grade 3/4 related to treat-ment	doi : 10.1016/j. nano.2019.02.021
NCT0201056	Ib/II	Neoadjuvant therapy for locally-advanced colorectal cancer	CRLX101 (nanoparticles containing camptothecin) IV in combination with a standard regimen of neoadjuvant radio-chemotherapy (capecitabine p.o.)	32	6 (pCR)	17 moderate responses (histology)	7 minimal responses (histology)		N/A	13 side effects, grade 3/4	doi : 10.1007/ s10637-020-00897-3
NCT0170500	Ia/Ib	Treatment of advanced colorectal cancer refractory to chemotherapy	Prodrug of mitomycin C encapsulated in pegylated liposomes +/- capecitabine +/- bevacizumab; IV	53	0	0	15	21	Median overall survival 6.4 months	50 severe side effects, including two possibly related to treatment	doi. org/10.1007/ s10637-020-00897-
NCT00361842	II	Treatment of advanced colorectal cancer in second line after oxaliplatin and/or irinotecan	CPX-1 (liposome with irinote-can-HCl and floxuridine); IV	59	0	2	23	19	Mean progression-free survival 4.69 months in irinotecan-naive patients and 3.48 months in patients previously exposed to irinotecan	24 severe side effects	www.clinicaltrials. gov/ ct2/show/ results/NC-T00361842? term= Liposomes&cond= Colon+Cancer&- draw=2&rank=4

Table 2. Examples of clinical trials using nanomedicine for colorectal cancer – ongoing clinical trials. trials and those not yet identified by a NCT reference are excluded

Trials that included pathologies other than colorectal cancer, already completed

Numéro NCT	Status	Phase	Context	Estimated number	Intervention	Primary objective(s)	Secondary objective(s)
NCT03774680	Recruiting	I	Treatment of colorectal cancer	30	Ethylcellulose polymer nanoparticles coated with octreotide encapsulating Cetuximab	Study of the pharmacokinetics, biodistribution, and therapeutic window of nanoparticles of Cetuximab after oral or IV administration	N/A
NCT04759820	Recruiting	II/III	Intraoperative detection of lymph nodes	298	Carbon nanoparticle suspension Indocyanine green	Number of lymph nodes detected, number of positive lymph nodes detected depending on tumor T status, ratio of positive lymph nodes	Relapse-free survival at 1 year
NCT03350945	Unknown (latest update November 2017)	N/A	Detection of tumor and lymph nodes	150	Endoscopic implantation of preoperative clips Intraoperative endoscopy Intraoperative injection of carbon nanoparticles	Time required for tumor localization	Relapse-free survival and overall survival at 5 years, rates of post-operative complications, distance to the margins, number of dissected lymph nodes, length of hospitalization, total duration of the operation, blood loss
NCT03563157	In progress (recruitment completed)	I/II	Treatment of metastatic or recurrent colorectal cancer after treatment with fluoropyrimidine, oxaliplatin, irinotecan, anti-VEGF +/- anti-EGFR according to RAS status	332	Anti-colorectal cancer vaccine NANT (combination of many treatments including paclitaxel bound to albumin nanoparticles) Regorafenib	Side effects and severe side effects under treatment, progression-free survival, overall response rate	Overall survival, duration of response, disease control rate, quality of life

presence of mucus... Active Pharmaceutical Ingredients (APIs) generally have a limited water solubility, stability and their ability to cross biological barriers is often limited (classes 2 and 4 of the Biopharmaceutical Classification System 11). In this context, nanodrugs represent a promising strategy to encapsulate APIs, to protect them from degradation in the gastrointestinal tract, to allow their oral administration. While no nanomedicines compatible with oral intake have reached the market yet for the treatment of colorectal cancer, this application is widely described in the literature 12.

Nanoparticles comprised of self-assembling squalene complexes - a lipid intermediate of cholesterol biosynthesis – have been developed to encapsulate cisplatin 13. *In vitro*, these nanoparticles were compared to non-encapsulated API, showing more internalization of API by HT-29 cells and greater induction of apoptosis. After oral administration in a mouse model of intestinal carcinogenesis, a greater reduction in the tumor mass and an increase in the maximum tolerated dose were observed compared to free cisplatin.

Another interesting example of an application of nanomedicine for the oral treatment of colorectal cancer is the development of redox nanoparticles, consisting of a core of nitroxide radicals with amphiphilic copolymer coating 14. Following *in vivo* oral administration, these nanoparticles preferentially accumulate in the colon without any systemic distribution, preventing any side effects of the nitroxide radicals. The redox and anti-inflammatory activities were combined with conventional irinotecan therapy. This approach led to a reduction in tumor volume by suppressing inflammation around the tumor microenvironment and the side effects of irinotecan.

In order to improve the active targeting of tumor cells, nanoparticles based on polylactic-co-glycolic acid adorned with a Fab'-siCD98 and encapsulating camptothecin, have also been developed 15. These nanoparticles were included in a chitosan/alginate hydrogel degraded in the gastrointestinal tract. siRNAs are non-coding RNAs that destroy target mRNAs and prevent their translation into proteins. The functionalization with the Fab-siRNA has been developed to reduce the expression of CD98, a glycoprotein overexpressed in colon cancer cells. *In vivo* studies in an orthotopic tumor model indicate that the Fab'-siCD98/camptothecin-nanoparticles/hydrogel system is able to induce the specific release of nanoparticles in the colonic lumen and facilitates the internalization of both APIs (siCD98 and camptothecin) in target cells, demonstrating significant potential for clinical applications of combination therapies.

Finally, a formulation of siRNA encapsulated in lipid nanoparticles and suitable for oral administration has been reported 16 recently.

Oral delivery is therefore an active field for the development of nanotechnology and the management of digestive cancers.

NANOMEDICINE FOR DIAGNOSTIC AND THERANOSTIC APPROACHES

Besides their therapeutic potential, nanoparticles are also used for diagnostic applications in medical imaging. These nanoparticles are often injected intravenously and serve as contrast agents for the detection of solid tumors, metastases or lymph nodes. Sometimes, the detection is directly followed by a surgical procedure. The type of nanoparticular contrast agent used depends on the imaging method (MRI, ultrasound, fluorescence-based imaging).

Many iron oxide nanoparticles obtained authorization for use in humans as contrast agents for MRI. Depending on their size and the nature of the polymer covering their surface, their distribution in the body is specific. The larger ones (>50 nm) have been used for the detection of liver tumors, while the smaller ones (3-50 nm) are used for imaging of the lymphatic system or for angiography (blood vessel imaging). Nuclei other than protons, such as fluorine, can be detected by MRI, and fluorinated contrast agents have been evaluated at the preclinical level for the detection of solid tumors, for example in a mouse model of colon cancer through CT26 cell transplantation 17. The company Celsense [1] is also developing fluorinated contrast agents for stem cell detection and their follow-up after administration.

Ultrasound can be used to visualize organs in real time. Suitable contrast agents consist essentially of fluorinated gas microbubbles that are not strictly speaking nanoparticles. However, these microbubbles can be condensed into nanodroplets with improved stability, which prolongs their circulation 18. The nanodroplets can be vaporized again under the effect of ultrasound. This vaporization can cause sonoporation of the cells that are located close to the nanodroplets, an event that could promote the entry of therapeutic molecules co-administered or co-encapsulated in the nanodroplets 19.

Another technique, near-infrared fluorescence imaging (700-900 nm) is frequently used in interventional surgery. Several fluorescent probes have been synthesized for this region of the fluorescence spectrum. Indocyanine green (IG) is the most commonly used, either in free form or encapsulated in nanoparticles. In the context of colorectal cancer surgery, IG is used for the localization of tumors and lymph nodes and intraoperative angiography 20. Clinical trials comparing free IG to carbon nanoparticles as an assistance to laparoscopic surgery for colorectal cancer are underway (No. NCT04759820 and NCT03350945) (*table 2*).

Finally, over the past fifteen years, several studies have examined the possibility of combining contrast agents with nanodrugs for theranostic applications (based on the contraction of the words therapy and diagnosis). Theranostic systems are designed

1 www.celsense.com

to track the biodistribution of nanodrugs to assess the extent of pathology, to deliver the treatment and follow its effectiveness in time real. For example, paramagnetic liposomes encapsulating combretastatin CA4P were used to target the tumor vasculature using an external magnet 21. The efficacy of targeting and the impact of treatment on the tumor vasculature were thus evaluated by MRI.

CONCLUSION

Although it is not possible to predict which nanotherapies will be used in the clinics for colorectal cancer by 2030, a few promising options, as discussed in earlier sections, are emerging. Several clinical trials, mainly phase I and II, have been carried out or are currently underway (*tables 1 and 2*). Upstream of human studies, the aim of current research is to develop nanodrugs that could, alone or in combination, allow:

1. active or passive targeting of primary tumors or their metastases;
2. approaches of personalized medicine and precision medicine;
3. oral administration of antineoplastic treatments;
4. reduction of the doses of treatments administered and the associated side effects;
5. better detection of tumors using contrast agents combined with their theraputic use;
6. the development of theranostic systems to improve the treatment monitoring efficacy.

All these possibilities opened up by nanomedicine should encourage the pursuit of research towards the clinical adaptation of nanomedicines in the years to come.

CONFLICTS OF INTEREST

Amanda K A Silva is the co-founder of the start-up Everzom.
Amanda K A Silva and Florence Gazeau are co-founders of the start-up Evora Biosciences.
Nicolas Tsapis is co-founder of the start-up Imescia.

REFERENCES

1. Chibaudel B, Maindrault-Gœbel F, Bachet J-B, *et al.* PEPCOL: a GERCOR randomized phase II study of nanoliposomal irinotecan PEP02 (MM-398) or irinotecan with leucovorin/5-fluorouracil as second-line therapy in metastatic colorectal cancer. *Cancer Medicine* 2016 ; 5 : 676-83. doi : 10.1002/cam4.635
2. Drummond DC, Noble CO, Guo Z, *et al.* Development of a highly active nanoliposomal irinotecan using a novel intraliposomal stabilization strategy. *Cancer Research* 2006 ; 66 : 3271-7. doi : 10.1158/0008-5472.CAN-05-4007
3. Martin B, Seguin J, Annereau M, *et al.* Preparation of parenteral nanocrystal suspensions of etoposide from the excipient free dry state of the drug to enhance in vivo antitumoral properties. *Scientific Reports* 2020 ; 10 : 18059. doi : 10.1038/s41598-020-74809-z
4. Charalambous A, Mico V, McVeigh LE, *et al.* Targeted microbubbles carrying lipid-oil-nanodroplets for ultrasound-triggered delivery of the hydrophobic drug, Combretastatin A4. *Nanomedicine: Nanotechnology, Biology and Medicine* 2021 ; 36 : 102401. doi : 10.1016/j.nano.2021.102401
5. Azhdarzadeh M, Atyabi F, Saei AA, *et al.* Theranostic MUC-1 aptamer targeted gold coated superparamagnetic iron oxide nanoparticles for magnetic resonance imaging and photothermal therapy of colon cancer. *Colloids and Surfaces. B, Biointerfaces* 2016 ; 143 : 224-32. doi : 10.1016/j.colsurfb.2016.02.058
6. Al Sabbagh C, Seguin J, Agapova E, *et al.* Thermosensitive hydrogels for local delivery of 5-fluorouracil as neoadjuvant or adjuvant therapy in colorectal cancer. *European Journal of Pharmaceutics and Biopharmaceutics* 2020 ; 157 : 154-64. doi : 10.1016/j.ejpb.2020.10.011
7. Lemdani K, Mignet N, Boudy V, *et al.* Local immunomodulation combined to radiofrequency ablation results in a complete cure of local and distant colorectal carcinoma. *Oncoimmunology* 2019 ; 8 : 1550342. doi : 10.1080/2162402X.2018.1550342
8. Roy P, Mignet N, Pocard M, *et al.* Drug delivery systems to prevent peritoneal metastasis after surgery of digestives or ovarian carcinoma: A review. *International Journal of Pharmaceutics* 2021 ; 592 : 120041. doi : 10.1016/j.ijpharm.2020.120041
9. Mulens-Arias V, Nicolás-Boluda A, Pinto A, *et al.* Tumor-Selective Immune-Active Mild Hyperthermia Associated with Chemotherapy in Colon Peritoneal Metastasis by Photoactivation of Fluorouracil-Gold Nanoparticle Complexes. *ACS Nano* 2021 ; 15 : 3330-48. doi : 10.1021/acsnano.0c10276
10. Pinto A, Marangon I, Méreaux J, *et al.* Immune Reprogramming Precision Photodynamic Therapy of Peritoneal Metastasis by Scalable Stem-Cell-De-

rived Extracellular Vesicles. *ACS Nano* 2021 ; 15 : 3251-63. doi : 10.1021/acsnano.0c09938

11. Durán-Lobato M, Niu Z, Alonso MJ. Oral Delivery of Biologics for Precision Medicine. *Advanced Materials* 2020 ; 32 : 1901935. doi : 10.1002/adma.201901935
12. Ying K, Bai B, Gao X, *et al.* Orally Administrable Therapeutic Nanoparticles for the Treatment of Colorectal Cancer. *Frontiers in Bioengineering and Biotechnology* 2021 ; 9 : 670124. doi : 10.3389/fbioe.2021.670124
13. Kotelevets L, Chastre E, Caron J, *et al.* A Squalene-Based Nanomedicine for Oral Treatment of Colon Cancer. *Cancer Research* 2017 ; 77 : 2964-75. doi : 10.1158/0008-5472.CAN-16-1741
14. Vong LB, Yoshitomi T, Matsui H, *et al.* Development of an oral nanotherapeutics using redox nanoparticles for treatment of colitis-associated colon cancer. *Biomaterials* 2015 ; 55 : 54–63. doi : 10.1016/j.biomaterials.2015.03.037
15. Xiao B, Viennois E, Chen Q, *et al.* Silencing of Intestinal Glycoprotein CD98 by Orally Targeted Nanoparticles Enhances Chemosensitization of Colon Cancer. *ACS Nano* 2018 ; 12 : 5253-65. doi : 10.1021/acsnano.7b08499
16. Busignies V, Arruda DC, Charrueau C, *et al.* Compression of Vectors for Small Interfering RNAs Delivery: Toward Oral Administration of siRNA Lipoplexes in Tablet Forms. *Molecular Pharmaceutics* 2020 ; 17 : 1159-69. doi : 10.1021/acs.molpharmaceut.9b01190
17. Diou O, Tsapis N, Giraudeau C, *et al.* Long-circulating perfluorooctyl bromide nanocapsules for tumor imaging by 19FMRI. *Biomaterials* 2012 ; 33 : 5593–5602. doi : 10.1016/j.biomaterials.2012.04.037
18. Sheeran PS, Luois SH, Mullin LB, *et al.* Design of ultrasonically-activatable nanoparticles using low boiling point perfluorocarbons. *Biomaterials* 2012 ; 33 : 3262-9. doi : 10.1016/j.biomaterials.2012.01.021
19. Nittayacharn P, Yuan H-X, Hernandez C, *et al.* Enhancing Tumor Drug Distribution With Ultrasound-Triggered Nanobubbles. *Journal of Pharmaceutical Sciences* 2019 ; 108 : 3091-8. doi : 10.1016/j.xphs.2019.05.004
20. Son GM, Ahn H, Lee IY, *et al.* Multifunctional Indocyanine Green Applications for Fluorescence-Guided Laparoscopic Colorectal Surgery. *Annals of Coloproctology* 2021 ; 37 : 133-40. doi : 10.3393/ac.2021.05.07
21. Thébault CJ, Ramniceanu G, Boumati S, *et al.* Theranostic MRI liposomes for magnetic targeting and ultrasound triggered release of the antivascular CA4P. *Journal of Controlled Release* 2020 ; 322 : 137-48. doi : 10.1016/j.jconrel.2020.03.003

WHAT IS THE FUTURE OF BIOTHERAPIES?

IMMUNE THERAPIES AND CELLULAR THERAPIES

Jaafar Bennouna [1],
[1] *Service of medical oncology, Hospital Foch, Suresnes*

« *All failures of* [biological] *life attract and have attracted attention to life. The current knowledge stems from the study of life failures* »
Georges CANGUILHEM, in *The Normal and the Pathological*

MICROSATELLITE INSTABILITY AND COLORECTAL CANCER

Colorectal cancers (CRC) with microsatellite instability (MSI) are the product of defective activity of the MMR (MisMatch Repair) system, a system that corrects DNA mismatches. They are a source of Hereditary Non Polyposis Colon Cancer (HNPCC) and occur when a germline mutation is present in one of four genes: MLH1, MSH2, MSH6 or PMS2. They occur in a sporadic manner when MLH1 expression becomes silent through promoter methylation. Association with a BRAF mutation excludes a germline origin (approximately 30% of MSI+ CRC). The incidence of MSI+ CRC is around 15-20% at early, local stages, and only around 5% at the metastatic stage. Their prognosis depends on the stage at diagnosis. Compared to microsatellite stable (MSS) tumors, MSI status is associated with a favorable prognosis at early, localized stages. At advanced stages, it is an element of poor prognosis, mainly due to the association with BRAF mutation. MSI CRC are often found in the right colon, and they often present poor cellular differentiation, mucinous, with sometimes isolated cells. Sporadic forms are frequently diagnosed in elderly women.

MICROSATELLITE INSTABILITY PREDICTS TUMOR RESPONSE TO IMMUNOTHERAPY

The Nobel prize for Medicine in 2018 was awarded to James Allison and Tasuku Honjo, two immunologists, for their study on the immune molecules CTLA-4 (cytotoxic T-lymphocyte-associated protein 4) and PD-1 (Programmed cell Death Protein 1), respectively. During lymphocyte maturation in lymphoid organs, CTLA-

4 competes with CD28, a costimulatory molecule for the binding of CD80 and CD86 on the surface of antigen-presenting cells. As a result, T cells become inactive and they are unable to exert their cytotoxic activity. PD-1 is present on the surface of activated T lymphocytes that infiltrate the tumor microenvironment and interacts with its ligand PD-L1 that is expressed on the surface of cancer cells. Here, a negative signal is transmitted that induces T lymphocyte anergy (*figure 1*).

The pan-tumor use of immunotherapy is based on the use of anti-PD-1 or anti-PD-L1 antibodies, eventually associated with anti-CTLA-4 antibodies.

The KEYNOTE-177 study, a randomized phase 3 study comparing pembrolizumab, an anti-PD-1 antibody, to standard 5FU-based chemotherapy has established the efficacy of immunotherapy in advanced MSI+ve colorectal cancers as first line [1]. 307 patients were included, and the median progression-free survival (PFS) was 16.5 months and 8.2 months [HR=0.60; confidence interval (CI) 95%: 0.45-0.80; p=0.0002] with pembrolizumab vs standard chemotherapy, respectively. The median duration of response was not reached in the experimental arm, while it was 10.6 months in the standard arm. Overall, 60% of patients treated with chemotherapy later received an anti-PD-1 or anti-PD-L1 antibody, explaining why no significant difference was observed in terms of overall survival (OS) [HR=0.74 ; CI 95%: 0.53-1.03; p= 0.0359].

Analysis of the PFS curve with pembrolizumab demonstrates the existence of two subgroups of patients:

1. patients with primary resistance to immunotherapy; 29.4% of patients progressed at 9 weeks;
2. patients with acquired resistance to immunotherapy, as can be estimated from the differential % of patients without progression at 12 months (55%) and at 36 months (42%).

This already represents a revolution for CRC treatment. A third group can be qualified as long responders, i.e. patients who remain progression-free at 36 months (42%) and are sometimes cured.

The CheckMate 142, a non-randomized phase 2 study, demonstrated the efficacy of nivolumab (anti-PD-1) + ipilimumab (anti-CTLA-4) in metastatic CRC patients after chemotherapy failure, with a 74% PFS at 24 months [2]. The CheckMate 8HW (NCT 04008030), randomized phase 3 trial has now completed its recruitment, and it will answer the question regarding the possible benefit of adding an anti-CTLA-4 antibody (ipilimumab) to anti-PD-1 antibody (nivolumab) in this immunotherapy-sensitive population.

The existence of a strong response to immunotherapy in CRC with microsatellite instability is the consequence of a high mutational burden generating multiple tumor neo-antigens, because of poorly-repaired DNA mismatches. The corresponding tumors belong to the molecular subgroup CMS1 (Consensus Molecular Subtype) and they are characterized by the presence of an inflammatory microenvironment enriched in

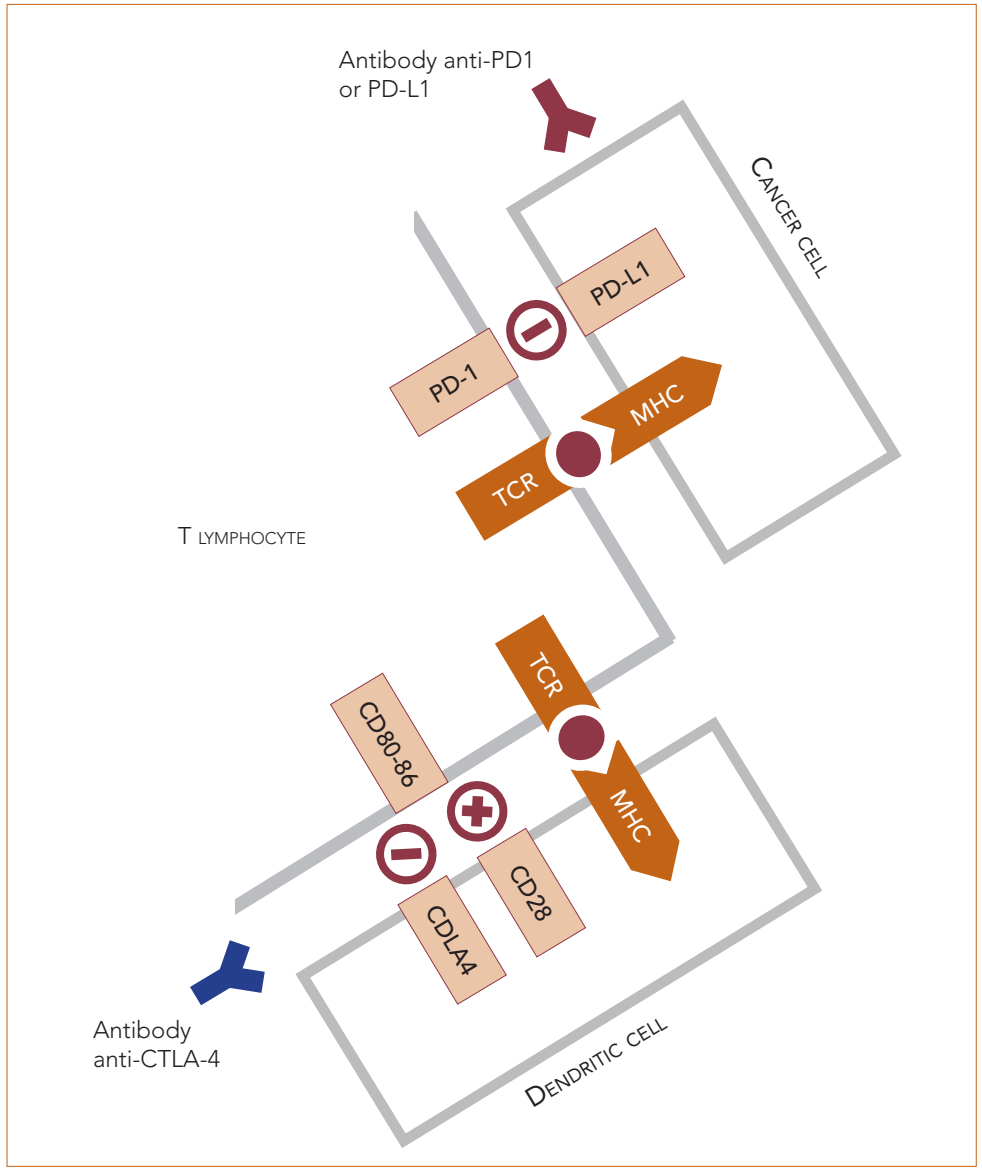

FIGURE 1. The local anti-tumor immune response in the tumor tissue (T lymphocyte and cancer cell) and in lymphoid tissues (lymphocyte and dendritic cell). MHC: Major Histocompatibility Complex; TCR: T Cell Receptor.

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cytotoxic T lymphocytes and NK (Natural Killer) cells. They have a high immunoscore, a test that quantifies the infiltrate of cytotoxic T lymphocytes and memory cells within the tumor and its invasion front [3]. The immunoscore ranges from 0 to 4 (low to high density for these two lymphocyte populations). It predicts higher PFS at the local stage, independently of the TNM.

Exhaustion of the immune response can nevertheless occur, for example via the loss of expression of class I HLA (Human Leukocyte Antigen) molecules as is observed with mutations in the b2 microglobulin gene. This can be observed in 30% of MSI tumors and it occurs less frequently in microsatellite stable tumors [4].

IMMUNOTHERAPY IN COLORECTAL CANCER: FAILURES AND OPPORTUNITIES

Besides tumors with MSI, 80 to 85% of all CRC emerge in a context of chromosomal instability. From an immunological point of view, these tumors correspond to «cold tumors», i.e. with a reduced tumor mutational burden. Their immune phenotype is characterized by the predominance of Th2 (anti-inflammatory) lymphocytes over Th1 (pro-inflammatory) lymphocytes [5]. The studies that were conducted with anti-PD-1 antibodies in metastatic CRC with stable microsatellites (MSS) have given disappointing results. For example, the KEYNOTE 028 study tested pembrolizumab in 137 patients with metastatic CRC after the failure of chemotherapy. A single partial response was reported, corresponding to the one patient with a tumor with microsatellite instability [6].

As previously mentioned, the immunoscore reflects the peritumoral immune infiltration. It is elevated in 21% of MSS CRC [3]. It is possible that only a subset of MSS CRC may be sensitive to immunotherapy or therapeutic combinations including immune therapies. A Canadian randomized study compared durvalumab (anti-PD-L1) + tremelimumab (anti-CTLA-4) with best supportive care in metastatic CRC patients after multiple lines of treatment. Patients with an MSS tumor and a high tumor mutational burden (≥28 mutations per megabase) benefited the most in terms of OS (HR=0.34; CI 90% : 0.18-0.63; p=0.004) [7].

Another study examining neoadjuvant indication found evidence for potential efficacy of immunotherapy in MSS tumors [8]. Nivolumab and ipilimumab were administered before primary surgery. A histological response was observed in 100% of patients (20/20) with MSI tumours. The rate of major histological responses (≤10% viable residual tumour) was 95% (19/20) and complete histological responses were observed in 60% (12/19) of tumors. 27% of MSS tumors (4/15) had histological tumor regression. The intensity of the CD8+ PD-1+ T lymphocyte infiltrate was predictive of the response in MSS tumors.

Other combinations and immunotherapy protocols are currently in early testing, with new immune checkpoint inhibitors. A phase 1 study combined an anti-LAG-3 antibody (favezelimab) with pembrolizumab in previously-treated metastatic CRC. Four partial responses and one complete response occured in a total population of 89 patients. The median duration of response was 10.6 months [9].

Chemotherapy has immunostimulant effects. Oxaliplatin induces an immunogenic form of cancer cell death, which could facilitate the response of the immune system toward the tumor cells and their antigens [10]. Bevacizumab, an antibody that binds to VEGF-A (Vascular Endothelial Growth Factor) normalizes the tumor vasculature and might facilitate the access of T lymphocytes to the tumor, while also promoting the maturation of dendritic cells that present tumor antigens to effector cells of the adaptive immune system [11].

The results of a randomized phase 2 study were recently published. Patients with metastatic CRC were treated with FOLFOXIRI + bevacizumab in the control group, and compared to an experimental arm with added atezolizumab (anti-PD-L1) [12]. As expected, the MSI subgroup (n=13) benefited greatly from the addition of atezolizumab, with a median PFS not reached in the experimental arm vs 6.6 months in the control group [HR=0.11, 80% CI: 0.04-0.35]. For Patients with MSS tumors (n=183), the median PFS was 11.4 months in the FOLFOXIRI + bevacizumab vs 12.9 months in the FOLFOXIRI + bevacizumab + atezolizumab arm [HR=0.78 ; CI 80%: 0.62-0.90].

The LEAP-005 trial is a phase 2 study combining lenvantinib, a multi-tyrosine kinase inhibitor with an anti-angiogenic effect with pembrolizumab. In a population of 32 patients with advanced MSS CRC that received multiple lines of treatment, the rate of objective response was 22% [13].

Beyond the analysis of efficacy, a major objective of these studies has been to identify predictive biomarkers that would identify patients with the greatest benefit and major responses to immune therapies. In addition to the biomarkers that we have already mentioned (tumor mutational burden, infiltration with T cells, immunoscore), experimental data demonstrate the role played by the intestinal microbiota in the antitumor immune response. In malignant melanomas, patients that respond to anti-PD-1 antibodies have a bacterial population that differs from that of non-responders, characterized by an enrichment in *Bifidobacterium longum*, *Collinsella aerofaciens* and *Enterococcus faecium*, as determined from stool samples. This beneficial intestinal microbiota promotes the migration of a dense CD8+ cytotoxic T lymphocyte infiltrate in the microenvironment [14].

NEW IMMUNOTHERAPIES AND PERSPECTIVES

One of the new strategies is based on the modification of the immune system, with the aim of effectively directing it against the tumor, for example via the infusion of allogeneic or autologous T cells. The CAR-T cell technology consists of modifying T cells with a Chimeric Antigen Receptor (CAR) constructed with an antibody frag-

ment (scFV) that recognizes a membrane antigen present on the surface of tumor cells, and with an intracellular domain from a signaling protein of T cells. A costimulation domain (CD28) was fused to CD3ζ in the second generation of CAR-T cells.

The third generation of CAR-T cells includes two costimulation domains fused to CD3ζ.

In colorectal cancer, CAR-T therapies that are being examined target for example the ACE, MUC-1, guanylyl cyclase C (GUCY2C), TAG72 (tumor-associated glycoprotein), HER2, EpCAM (Epithelial-cell adhesion molecule), as well as other antigens expressed on the surface of colonic cancer cells [15].

Bispecific antibodies are currently under development. By targeting two epitopes or antigens, for example CD3 and ACE, they can bridge T lymphocytes and tumor cells. Many phase 1/2 trials examining the possibility of targeting different antigens are underway.

The other approaches in immunotherapy consist of using vaccines that directly stimulate the host immune response via the injection of antigenic peptides or dendritic cells loaded with antigens. For the moment, the results are disappointing. The possibility of combining these strategies with anti-PD-1 and anti-CTLA-4 to bypass the effect of the immunosuppressive tumor microenvironment is actively being considered.

CONCLUSION

Immunotherapy has an established efficacity against MSI CRC, which constitute a therapeutic niche. Today's challenge is to address MSS CRC, that represent the vast majority of tumors and that are naturally resistant to immunotherapy. Strategies to increase the efficacy of immunotherapy include double combinations of immunotherapy (anti-CTLA4 and anti-PD1), combinations with chemotherapies, with anti-angiogenics or inhibitors of tyrosine kinases, such as *MEK* inhibitors. CAR-T cells, bispecific antibodies or vaccines represent a new generation of immune therapies for which clinical results are still lacking. Certainly, progress will depend on the identification of new biomarkers. Biomarkers are essential because the variability of the response to immunotherapy is linked to the existence of an intra-tumor heterogeneity present at different levels, i.e. the genome, the epigenome, the transcriptome and the tumor microenvironment (*figure 2*). Extrinsic causes that constitute the exposome and reflect our lifestyle, such as the exposure to dietary or chemical agents, psychosocial stress, may also have a biological impact [16].

FIGURE 2. Immune therapies, possible combinations and biomarkers: intrinsic factors and the exposome. MSI: Microsatellite Instability.

REFERENCES

1. André T, Shiu KK, Kim TW, *et al.* Pembrolizumab in Microsatellite- Instability-High Advanced Colorectal Cancer. *N Engl J Med* 2020 ; 383 : 2207-18.
2. Lenz HJ, Van Cutsem E, Limon ML, *et al.* First-Line Nivolumab Plus Low-Dose Ipilimumab for Microsatellite Instability-High/Mismatch Repair-Deficient Metastatic Colorectal Cancer: The Phase II CheckMate 142 Study. *J Clin Oncol* 2021 ; epub. doi : 10.1200/JCO.21.01015.
3. Pagès F, Mlecnik B, Marliot F, *et al.* International validation of the consensus Immunoscore for the classification of colon cancer: a prognostic and accuracy study. *Lancet* 2018 ; 391 : 2128-39.
4. Kloor M, Michel S, Buckowitz B, *et al.* Beta2-microglobulin mutations in microsatellite unstable colorectal tumors. *Int J Cancer* 2007 ; 121 : 454-8.
5. Thorsson V, Gibbs DL, Brown SD, *et al.* The Immune Landscape of Cancer. *Immunity* 2018 ; 48 : 812-30.
6. O'Neil BH, Wallmark JM, Lorente D, *et al.* Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with advanced colorectal carcinoma. *PLoS One* 2017 ; 12 : e0189848.
7. Chen EX, Jonker DJ, Loree JM, *et al.* Effect of Combined Immune Checkpoint Inhibition vs Best Supportive Care Alone in Patients With Advanced Colorectal Cancer: The Canadian Cancer Trials Group CO.26 Study. *JAMA Oncol* ; 6 : 831-8.
8. Chalabi M, Fanchi LF, Dijkstra KK, *et al.* Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. *Nat Med* 2020 ; 26 : 566-76.
9. Garralda E, Sukari An Lakhani N, *et al.* A phase 1 first-in-human study of the anti-LAG-3 antibody MK4280 (favezelimab) plus pembrolizumab in previously treated, advanced microsatellite stable colorectal cancer. *J Clin Oncol* 2021 ; 39 : 15_suppl, 3584 (abstract)
10. Wang W, Wu L, Zhang J, *et al.* Chemoimmunotherapy by combining oxaliplatin with immune checkpoint blockades reduced tumor burden in colorectal cancer animal model. *Biochem Biophys Res Commun* 2016 ; 487 : 1-7.
11. Limagne E, Euvrard R, Thibaudin M, *et al.* Accumulation of MDSC and Th17 Cells in Patients with Metastatic Colorectal Cancer Predicts the Efficacy of a FOLFOX-Bevacizumab Drug Treatment Regimen. *Cancer Res* 2016 ; 76 : 5241-52.
12. Cremolini C, Rossini D, Antoniotti C, *et al.* FOLFOXIRI plus bevacizumab (bev) plus atezolizumab (atezo) versus FOLFOXIRI plus bev as first-line treatment of unresectable metastatic colorectal cancer (mCRC) patients: Results of the phase II randomized AtezoTRIBE study by GONO. *Ann Oncol* 2021 ; 32 : S1294-S5 (abstract).
13. Gomez-Roca C, Yanez E, Im SA, *et al.* EAP-005: A phase II multicohort study of lenvatinib plus pembrolizumab in patients with previously treated selected solid tumors—Results from the colorectal cancer cohort. *J Clin Oncol* 2021 ; 39 : 3_suppl, 94 (abstract).
14. Matson V, Fessler J, Bao R, *et al.* The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. *Science* 2018 ; 359 : 104-8.
15. Aparicio C, Belver M, Enríquez L, *et al.* Cell Therapy for Colorectal Cancer: The Promise of Chimeric Antigen Receptor (CAR)-T Cells. *Int J Mol Sci* 2021 ; 22 : 11781.
16. Morad G, Helmink BA, Sharma P, *et al.* Hallmarks of response, resistance, and toxicity to immune checkpoint blockade. *Cell* 2021 ; 184 : 5309-37.

PREVENTION, SCREENING AND THERAPEUTIC INNOVATION IN COLORECTAL CANCER IN FRANCE

WHAT STRATEGIES FOR 2030?

Daniel Benamouzig [1], Jean-Marc Sabaté [2], Robert Benamouzig [2],
[1] *Sciences Po, Center for Sociology of Organizations & Health Chair, CNRS Paris*
[2] *Department of gastroenterology and digestive oncology, Avicenne Hospital, Bobigny*

« *The future is only the present that needs to be put in order.* »
Antoine de Saint-Exupery

In France, nearly 3.3 million people were treated for cancer in 2019, either considered as "active" disease or "under surveillance", and more than 160,000 people died from it (29% of all deaths). Between 2015 and 2019, the number of cancer patients treated incHealth expenditure related to cancer represents 12% of total health expenditure, i.e. 20.1 billion euros in 2019 1. Cancer represents a dynamic item of health expenditure with an increase of 20% between 2015 and 2019. This increase is not only linked to the number of patients, it can also be explained by the increase in the average cost of treatment. Average health expenditure per patient treated for cancer increased by 11.4% between 2015 and 2019. This increase is directly related to the cost of anticancer drugs and in particular to the development of immunotherapies, whose annual cost is close to 100,000 euros per year, per patient.

Colorectal cancer is the third most common cancer in France and the second in terms of mortality. Each year, it afflicts around 1% of insured people for a global cost of care, as estimated by health insurance, of around 1.7 billion euros in 2019. The costs of the medical care of colorectal cancer are mainly related to the cost of hospitalization and treatment.

Prior to 2004, the average cost for the first year of care varied from 17,000 euros for stage I cancers to 36,000 euros for stage IV cancers 2. Compared to this period, during which inexpensive chemotherapies based on 5-FU were mainly used, current treatments increase survival by several months or even several years in some patients.

The estimated cost of «old» treatments (5-FU alone or combined) was around 500 euros per semester. It is currently sometimes higher than 50,000 euros per semester, i.e. multiplied by a factor of 100.

Between 2015 and 2019, health expenditures for colorectal cancers have evolved differently depending on the status of the cancer as being «active» or «under surveillance». Healthcare expenditures for active colorectal cancer have only increased by 2.5%, compared to the increase in the number of people treated (+10% over the period). This situation may be linked to a higher representation of early stage cancers, the treatment of which is less costly. Healthcare expenditures for colorectal cancers under surveillance have increased by 20% over the same period. Most of the costs are seen during the initial phase of treatment, but they are also significant in the final stages of the disease. A study carried out in 2015 on 15,361 patients with colorectal cancer who died during the same year reported that cancer was the cause of death in 84% of cases with estimated expenditure of around 48,000 euros during the last year, a large part of which was devoted to the last month of life [3].

In order to control these costs, two complementary levers are potentially actionable: more effective prevention and better economic regulation of therapeutic innovations.

DEVELOPPING AND ORGANIZING PRECISE PREVENTION

As with other cancers, prevention and screening are major strategic elements to reduce the burden. Screening has long been the preferred, if not exclusive, public action tool in the prevention of colorectal cancer. Within a few years, it could evolve toward greater personalization, while various preventive actions are expected to have increasing importance in addition to screening.

Towards better, targeted-screening

Screening is a major lever in the prevention of colorectal cancers. It should remain so because screening allows for the detection of early cancerous lesions in a context where the stage at diagnosis is a key element of prognosis: for early-stage cancer, either stage I or II, patient survival is as high as 90% at 5 years, whereas it is only 11% when the cancer is diagnosed at a metastatic stage.

However, for the past decades, organized screening for colorectal cancer has been difficult to implement in France and it only reaches part of the target population. Screening actions come up against organisational, social and behavioral obstacles. The participation of the population in the different screening actions varies depending on the region considered, the specificities of the population considered (lower participation in men compared to women, population in economic precarity or geographic isolation). Even when subjects participate in screening, a phenomenon known as fatigue occurs after several negative tests that reduces the participation rate in screening in later years. In 2018-2019, participation in organized colorectal cancer screening reached only 30.5% of the target population in France. However, this rate does not include the part of the population already covered by a colonoscopy performed over the last five to ten years, a proportion that probably varies between 10 and 25% of the target population depending on the territory. Overall, the rate is clearly below the target of 65%, leaving France well behind leading European countries, such as the Netherlands and the United Kingdom.

The actions that are currently being evaluated mobilize two types of strategies: one-step strategies, with an upfront colonoscopy, and two-step strategies, starting with the search for occult blood in the stool, with or without molecular testing, rectosigmoidoscopy, a blood test or other procedures, colonoscopy being performed as a second step. According to a recent evaluation, the two-stage strategy with initial fecal occult blood testing is the most cost-effective in France and should remain so. The search for fecal DNA abnormalities associated with the search for occult blood or upfront colonoscopy improves the efficiency of screening, but does not reach the cost-effectiveness threshold that would be required in the general population in the French context. The role of fecal bacterial signatures for the screening of colorectal cancer still needs to be assessed.

In the years to come, improving adherence, the effectiveness of screening and its efficiency could be attained by more precise targeting of the population and by directing actions toward precarious or geographically-isolated populations. The current age limits could be revised, whether it be the lower limit of 50 years or the upper limit of 75 years. Digital awareness tools as well as the mobilization of social networks could be used to increase the participation in screening [4]. Incentives can also be imagined. In North-America, some health insurers aim to increase participation in screening by giving financial incentives, such as gift certificates of 20 Euros for those who perform a fecal test and 100 euros for a colonoscopy [5]. While doing this in France might not be possible, a deeper and up-to-date reflection on the behavioral restraint and the motivations that favor the adherence of individuals to testing and examinations could increase participation in screening.

Organized screening programs will likely undergo changes toward more personalized screening for colorectal cancer. While maintaining the principles of organized screening in the general population, the aim would be to move from mass screening to targeted screening, paying more attention to at risk populations. This should not lead to the renouncement of organized screening, for the benefit, for example, of individual or opportunistic diagnoses.

Regarding organized screening, the increasing use of big data in health and organizational simplifications are to be implemented. The optimized use of big data, such as for example the National Health Data System (Système National des données de Santé, SNDS) could help to improve prevention. Linking data from routine biological examinations, which are not yet integrated with other health

data, will make it possible to identify the developments in exposure to risk factors in some patients and it may then be possible to provide them with targeted information, promoting earlier diagnosis.

Finally, it should be possible to access tests without having to first consult a general practitioner, the access to which is sometimes difficult. Accessing tests through other health professionals, even those who are not at all or little involved today, could also improve participation. The involvement of biologists, pharmacists or nurses deserves to be evaluated.

Screening for colorectal cancer should take place in a health system with better-coordinated health professionals, with better coordination between outpatient and hospital care. The rapid access to ambulatory examinations and in particular colonoscopy, and if necessary to a healthcare pathway, will require a reinforcement of the collaborations between private medical practice and hospitals, which are sometimes precarious in certain areas.

Prevention that is less medicated

Screening is now the preferred strategy for colorectal cancer. Even though it leads to earlier diagnosis and a better prognosis, it occurs relatively late, once preneoplastic lesions have evolved. In the rationale of public health, prevention that is less directly associated with medical care and more with the life context will significantly improve the health benefits for individuals. Protective factors / risk factors have been better defined and their specific contribution has been measured in recent years [6]. This knowledge should allow upstream interventions and hopefully behavioral changes.

The diversification of prevention strategies will allow a move from predominantly medical prevention, oriented toward the diagnosis and early management of the disease, towards a broader approach that promotes a «healthy lifestyle» and the maintenance of a good health status. The two approaches are complementary. This diversification of actions will make it possible to involve new actors, new knowledge and new instruments for prevention, leading to multi-professional prevention and going beyond the scope of the health professions alone. These challenges were recently clarified within the framework of the ten-year cancer control strategy for the decade to come [7].

Decrease in smoking and alcohol consumption as well as the promotion of protective nutritional factors and physical activity are considered major levers for the prevention of colorectal cancer. Changes in lifestyle and diet in a context of rapid changes in eating habits (the quest for healthier diets) will likely lead to a reduction in overweight and obesity of around 20% by 2030. The role of the intestinal microbiota seems important and is currently being investigated [8]. This trajectory requires the voluntarism of many actors involved in different sectors, starting from food consumers themselves, who are likely the only ones in a position to really influence the strategy of the food industry.

The role of environmental factors other than nutritional factors was recently better defined thanks to research that aimed to explore the effects of exposure to multiple agents (i.e. the so called "cocktails"). Precise prevention based on better knowledge of the exposome and individual exposure factors could make it possible to identify the risk profiles of almost any individual, according to their former exposures. Better detection of cancer clusters could permit the identification of new carcinogenic agents.

Accordingly, the role of public authorities is also bound to evolve. Today, it is limited to the organization of screening, but tomorrow its intervention tools and regulation are likely to become more diverse. New public action tools, such as the nutritional recommendations of the National Nutrition and Health Program (Programme National Nutrition et Santé, PNNS) or the Nutriscore, are already changing the food industry, the way it designs and produces food. Regulations that apply to risky products, such as ultra-processed foods, and advertising, in particular intended for the youngest people, will need to be reinforced. Regarding the environment, the enforcement of European regulations on chemical products is going to lead to a better control of chemical risks. Whether it be actions related to the environment or food, they should be based on better research organization, relying on labelling of dedicated prevention research centers as well as specific actions that would rely on already-established networks, such as those that already exist in the field of nutrition.

The role of health insurance is likely to evolve from the historical organization that contributes to reimbursement and shift toward an organizer of coordinated prevention, the support of public and administrative authorities for personalized prevention.

The expected effects will go beyond only the prevention of colorectal cancer, and will be part of a broader attempt to prevent cancers and other lifestyle-related pathologies, such as diabetes or cardiovascular diseases. Alliances with other medical specialties will therefore be possible and should be favored with the rationale of «multi-pathology» prevention, by adjusting prevention toward the interest of the public rather than the capacity of detection of the healthcare system.

Communication to the general public will require both positive actions, promoting the appropriation of messages and people's empowerment, and negative actions to fight "fake news" conveyed by social networks. The mobilization of the French educational apparatus, including public schools, will also be developed. Quantified objectives have been issued with an expected reduction in the number of preventable colorectal cancers by about a third by 2040. This national plan will be enforced at the European level by a "European cancer beating plan".

COPING WITH THE INCREASING COSTS OF TREATMENT

The management of colorectal cancer benefits from several therapeutic innovations, which illustrates the dynamism of research and responsiveness of pharmaceu-

tical companies in terms of development. Targeted therapies, immune therapies, biotherapies, gene or cell therapies and possibly mRNA vaccines will offer real therapeutic advances to patients. Nevertheless, the cost of these innovations raises the question of their financial sustainability, considering the legitimate demand of patients, professionals and manufacturers and the principles of universal health insurance. Furthermore, the corresponding pharmaceutical costs come in addition to those of other innovations, including new devices necessary for surgery, such as laparoscopic instruments or surgical robots.

The legal system that organizes the financing of French social security (Lois de financement de la sécurité sociale, LFSS) makes budget constraints explicit and may lead to fear that new expensive molecules might be financed to the detriment of other items, and ultimately to the detriment of other treatments/other diseases. These issues have been recognized for about ten years and are the subject of public debates, including during parliamentary meetings devoted to cancer. They are also perceived by the general population, as shown in the Viavoice survey in 2017, in which 89% of respondents said they were attached to the current social model, and 42% feared that it could no longer guarantee universal access to innovative treatments to all in the future [9].

A system under pressure

These tensions have been taken into account since the first 2009-2013 cancer plan. In 2009, the Economic Committee for Health Products, responsible for setting drug prices, estimated that the acceptable cost of innovative treatments should be capped at 50,000 euros per product, per patient and per year. The decision to cover the cost of new molecules is based on the clinical benefit assessed in terms of survival or median duration of progression-free survival, the response rate and/or relative risk of toxicity, or even the number of years of life gained expressed as quality-adjusted life year, QALY. In the context of negotiation with manufacturers, decisions to set prices also take into account possible savings made on specific medical consumptions after the implementation of particular treatments and, in a less obvious manner, the calculation of the efficiency, expressed as an incremental cost-effectiveness ratio (ICER) calculated by the French High Authority for Health.

Pharmaceutical innovation interacts with the organization of medical care at different levels. At the beginning of the healthcare pathway, public health insurance pointed out in 2018 that the implementation of new screening tests from 2015 had enabled a 10% increase in the number of patients treated. At the other end of the trajectory, the effectiveness of the therapies prolongs the lifespan of the treated patients by several months or years, and therefore the duration of use of therapeutics, sometimes to the point that their use could become chronic. New molecules can also reduce the impact of healthcare management, as was for example shown with Hepatitis C, whose costs of care initially rose sharply, before decreasing. The mRNA vaccine technologies that have been successfully implemented for SARS-CoV-2 are now being explored in the field of cancer and could possibly have an impact within a few years.

Irrespective of these innovations, financial sustainability requires verifying that the use of available resources is optimized. Good practice still needs to be reinforced, for example with a virtuous follow-up of national recommendations, such as those from the Thesaurus National de Cancérologie Digestive (TNCD), that are proposed by the various multidisciplinary meetings. Compared to these recommendations, some patients are still undertreated, while other patients are treated and followed in a questionable way. This represents a small percentage of patients, but it could represent a source for cost optimization.

Faced with the increasing costs of pharmaceutical treatments, several other options can be considered. Certain orientations are the continuation of the existing evolutions initiated over the past twenty years. Other options may introduce major changes, beyond the case of colorectal cancer or cancers in terms of drug regulation. These issues are not specific to France and they apply to at least the whole of Europe. Whatever the options considered, they do not only require new institutional arrangements, which are necessarily political, but also the involvement of stakeholders and patient representatives. Discussions with public authorities and companies also require the involvement of professionals. Regarding colorectal cancer, the discussions could be organized within the framework of a professional organisation, at least at the national level, and ideally in the European context.

Contractual regulation and optimization according to efficiency

The first option is to promote collective choices on the basis of effectiveness of the therapies assessed. A possible approach would be to differentiate priorities according to efficiency, leading to collectively covering only real therapeutic progress. For this, a reference threshold, implicit or explicit, could be defined with the calculation of the cost per year of life gained with an acceptable quality of life. With the creation of the NICE (National Institute for Health and Care Excellence) in 1999, the British proceeded in this direction for different types of diseases. In terms of cancer therapy, however, this scenario remains fairly virtual: the British have given up on it by considering other dedicated funding systems, thus avoiding the often highly publicized social and human dilemmas. The French "Haute Autorité de Santé" gradually acquired economic power from 2004, and this type of arbitration has never been seriously implemented in France. It would only allow marginal regulation of the prices without supporting significant innovations. Along this line, it should be noted that data on the efficacy of colorectal cancer treatments are still relatively scarce.

The second option would be to strengthen contractual arrangements linking private firms and public authorities, as payers for certain particularly expensive drugs. Price-volume negotiations between public authorities and private companies place

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France in a contractual system reputed to be relatively efficient compared to other countries, but this approach remains global and it is not the most transparent [10]. Another contractual avenue is that of performance-based payment via agreements between payers and hospitals for highly-expensive drugs that are not used systematically. A pay-for-performance strategy in digestive oncology led by Medicare in the US has not demonstrated its benefit in terms of cost reduction, eventhough a reduction in the use of the emergency department was initially observed [11]. However, in this American experiment, it led to an increase in the relevance and the quality of care. It is not certain that such freedom is possible in the French system, which is more regulated. In general, this type of agreement runs in the long-term and it is generally more beneficial for manufacturers than for funders.

Shifting property rights and regulating the two types of manufacturers

A third, more radical option can also be considered. It would aim to shift the boundary of property rights regarding innovation. While this border is well established, the distribution between public and private actors is not intangible. On the one hand, innovation must be rewarded with appropriate financing, guaranteeing the continuation of the private investments necessary for future progress. Private actors are also essential for ensuring the development, the industrial process and marketing of innovative products. On the other hand, public actors are also very present during initial research, during clinical research and they contribute to the solvency of the management of innovations. In recent years, large pharmaceutical companies have increasingly outsourced the initial development of innovative therapies to small startups, that often arise from public research. This leads to an inflation of costs which are no longer only related to the «true» costs of development and clinical research, and instead take into account the valuations of intermediary companies that generate large profits. Thus the collective investment in public research appears to be at least partially exploited for the benefit of private companies, in a sector whose overall profitability exceeds that of all the other economic sectors. One could imagine a displacement of the boundaries between public and private spheres, especially over time: a significant part of the profit would go to the industry, until payoff and investment return, then other industrial actors would take over. These actors would not necessarily be state-based. They could be private and would work under guaranteed conditions within the framework of agreements defined by public authorities. Two types of manufacturers would exist: innovation manufacturers, that will be able to count on significant, attractive and rapid gains, but only for a limited period of time (which would encourage them to pursue their search for other innovations); and generalization industries, whose prospects for gains would be lower but for a longer time and guaranteed by public contracts. For a number of innovations, France would probably have a good position on this second type of market. The main tool of action here would be regulatory: allowing sovereign industrial players to find their place by limiting the exclusive rights of exploitation of industrial innovators. The exact boundaries of this new system remain to be defined, in particular the transition from one sector to another. The experience acquired in terms of contractual regulation could favor the implementation of this type of orientation, which may be less radical in practice than it appears in principle.

CONCLUSION

The explosion of costs linked to therapeutic progress requires a revision of actions and established dogmas. Prevention is a major lever for action, but it is still underexploited. Inequalities linked to social status or geography should be the subject of corrective actions, both in terms of prevention and management, because the current universalist systems (high reimbursement and little remaining cost) does not guarantee equivalent support for all. The role of patients has gradually increased in recent years, and it will need to be further strengthened. The dissemination of erroneous information can limit the benefits of progress by restricting the use of healthcare. Past developments reveal the need for new professional and interprofessional connections. In addition to the requirement of collective organization, it is important to confront new knowledge and professional practices and achieve the necessary changes. These links will need to be strengthened through new collegial, pluralistic and open organizations.

The relationship with manufacturers needs to be revisited, including at the professional level. Manufacturers can be allies but their positions should not determine the strategic orientations. The emergence of two classes of industries with different roles should be encouraged within the framework of new regulation, adapted to the specific rationale of innovation.

REFERENCES

1. Assurance maladie. *Améliorer la qualité du système de santé et maîtriser les dépenses : les propositions de l'Assurance Maladie pour 2022*. Études et données, 2021. https://assurance-maladie.ameli.fr/etudes-et-donnees/2021-rapport-propositions-pour-2022-charges-produits
2. Clerc L, Jooste V, Lejeune C, *et al.* Cost of care of colorectal cancers according to health care patterns and stage at diagnosis in France. *Eur J Health Econ* 2008 ; 9 : 361-7.
3. Tanguy-Melac A, Aguade AS, Fagot-Campagna A, *et al.* Management and intensity of medical end-of-life care in people with colorectal cancer during the year before their death in 2015: A French national observational study. *Cancer Med* 2019 ; 8 : 6671-83.
4. Koïvogui A, Levi S, Finkler M, *et al*. Feasibility of encouraging participation in colorectal cancer screening campaigns by motivating people through the social network, Facebook. *Colorectal Dis* 2020 ; 22 : 1325-35.
5. Bone RH, Cross JD, Dwyer AJ, *et al*. A path to improve colorectal cancer screening outcomes: faculty roundtable evaluation of cost-effectiveness and utility. *Am J Manag Care* 2020 ; 26 : S123-S43.
6. Ubago-Guisado E, Rodríguez-Barranco M, Ching-López A, *et al.* Evidence Update on the Relationship between Diet and the Most Common Cancers from the European Prospective Investigation into Cancer and Nutrition (EPIC) Study: A Systematic Review. *Nutrients* 2021 ; 13 : 3582.
7. Institut national du cancer. *La stratégie décennale de lutte contre les cancers 2021-2030*. Document de référence, 2021. www.e-cancer.fr/Institut-national-du-cancer/Strategie-de-lutte-contre-les-cancers-en-France/La-strategie-decennale-de-lutte-contre-les-cancers-2021-2030
8. Mori G, Pasca MR. Gut Microbial Signatures in Sporadic and Hereditary Colorectal Cancer. *Int J Mol Sci* 2021 ; 22 : 1312.
9. Observatoire du cancer. *Coûts des traitements innovants en cancérologie*. Dossier de presse, 2017. https://curie.fr/page/observatoire-cancer-2017-couts-des-traitements-innovants-en-cancerologie
10. Megerlin F. Médicaments innovants et prix conditionnels : le contrat de performance, à l'opposé du partage de risques. *Ann Pharm Fr* 2013 ; 71 : 291-301.
11. Dopp AR, Kerns SEU, Panattoni L, *et al.* Translating economic evaluations into financing strategies for implementing evidence-based practices. *Implement Sci* 2021 ; 16 : 66.

THE ROLE OF THE GASTROENTEROLOGIST IN THE MEDICAL CARE OF COLORECTAL CANCER IN RELATION TO OTHER SPECIALTIES

Pierre Michel [1],
[1] *Gastroenterology Service, Hospital Charles Nicolle Hospital, Rouen, France*

« *The future cannot be predicted. It is prepared.* »
Maurice BLONDEL

The issue of the contribution of the gastroenterologist in the medical care of colorectal cancer should be contextualized. Why is this question relevant today?

To answer this question, it is necessary to remember the recent history of medical specialties. Until recently, which corresponds to the end of the 20th century, the degree of medical doctor gave the right to exert the entire field of medicine, i.e. the physician was an omni-practitioner. This model was suited to the development of medicine in the first half of the 20th century, but it became progressively obsolete because of the fast pace of evolution of knowledge, the diversity and the complexity of the technical procedures and the quality requirements. The scientific development of medicine led to a virtuous circle of quality with its key steps of evaluation, certification and specialization. A form of industrialization of medicine has led to the current model that we know today at the beginning of the 21th century, with its organization and financial compensation. Medicine is now sectored, specialized and divided into a series of tasks and acts, according to the industrial methodology, as initially theorized by the American engineer F-W Taylor at the end of the 19th century 1.

In France, the practical implementation of this approach has been acted by the law of the 23rd of December 1982, that was implemented in 1985. This evolution has profoundly changed the organization of the medical world with the creation of medical specialty degrees (Diplômes d'études spécialisées, DES) that define the competence of doctors within a specialty 2. Since 1985, at the end of their third cycle of medical studies, traditionally called "internship", students receive a degree with a field of compe-

tence that is limited to their specialty. A medical doctor that specialized in hepatogastroenterology who graduated after 1989 (at that time, after a 4 year DES) is different from his elders who were omniphysicians, with an additional specialization. The 2017 law further accentuated the burst of medical activity with 44 different DES [3].

On a technical ground, the goal of improving the medical service provided to the population has been reached. However, this evolution also had a number of adverse consequences. The creation of specialties with limited skill fields has created edge effects, with competence limits that are often artificially defined. The existence of borders between specialties can be a source of conflict of jurisdiction. These conflicts are facilitated by the rigid borders that are sometimes artificially defined in a world in constant evolution.

Colorectal cancer is a good example of this situation. How many medical specialties (DES) can claim all or part of the management of the pathological spectrum of colorectal cancer?

1. The general practitioner, for the detection and monitoring of patients with colorectal cancer and palliative care.
2. The radiologist, who participates in the evaluation of tumor staging and advocates a possible non-invasive diagnosis, for example by virtual colonoscopy.
3. The digestive surgeon, claiming the right to perform endoscopy based on the rationale that endoscopy is performed by surgeons in other countries in the world.
4. The oncologist, defending the idea that cancer treatment is too specialized to be performed by someone else.
5. The palliative care doctor, whose early intervention is justified by the potentially fatal outcome of the disease.
6. The hepatogastroenterologist, who claims the medical care of all diseases of the digestive system and defends a global and long-term vision of the disease, including the diagnosis of the disease as well as its prevention and screening.

Moreover, the process of Taylorism influences the scale of income and the recognition by putting the technical act and reasoning at the top of the pyramid to the detriment of the human relationship. A direct consequence of this is a divestment of a large portion of the medical world for human relationships, with less listening to the patient and family. The relational field that is abandoned by the doctor is provided by other professionals, such as nurses and psychologists, or even new self-invested disciplines (coaches with various expertises, naturopaths, ...) who, over time, can become key actors, especially if technical expertise and reasoning become even more dehumanized by the explosion of artificial intelligence.

The quote by the philosopher Maurice Blondel "*The future cannot be predicted. It is prepared.*" offers a perspective for the years to come. To prepare for the coming years, we need to anticipate the changes to come regarding prevention, screening and organization of care. We need to anticipate the available technologies to extrapolate complex personalized strategies and question the role of the gastroenterologists and their training.

"*Forecasts are difficult, especially regarding the future*" said Pierre Dac. However, in a 2030 perspective, it is possible to anticipate a likely positioning of the main specialties involved in colorectal cancer, including radiologists, surgeons and oncologists.

GASTROENTEROLOGISTS *VERSUS* RADIOLOGISTS

Regarding radiologists, technological competition exists between two methods for the exploration of the colonic mucosa. These two technologies are colonoscopy, performed under general anesthesia, which allows the precise exploration of the entire colonic mucosa, and virtual colonoscopy (CT colonography), which allows for colonic exploration without anesthesia. Colonoscopy has the advantage of directly examining the mucosa, increasing the precision of the characterization of mucosal abnormalities, and of course allowing for an eventual excision. CT colonography offers greater acceptability and sensitivity for the detection of mucosal lesions of significant size (>6 mm, or more certainly >10 mm). The most recent data in the literature suggest a possible economic advantage of virtual colonoscopy, mainly because of its superior acceptability [4]. Despite several publications that advocate virtual colonoscopy published in the last 10 years, this technology has not yet been established in France. The need for non-invasive examination might be covered by the endoscopy unit, a possible competitor to virtual colonoscopy [5,6]. Therefore, on the 2030 horizon, the imaging technologies should likely not directly compete with the technologies that are mastered by the gastroenterologists for the screening and the diagnosis of neoplastic colorectal lesions, i.e. colonoscopy and the colonic capsule.

GASTROENTEROLOGISTS *VERSUS* SURGEONS

Regarding surgeons, a key issue is the exclusive technical mastery. The technique of digestive endoscopy was developed in France solely by gastroenterologists. In other countries, such as in Italy or Germany, surgeons have also contributed to the development of endoscopy. Before the revision of the rules that apply to the third cycle of medical studies in 2016, endoscopy teaching was only mentioned during the training of gastroenterologists. Therefore, the only specialists allowed to perform endoscopic procedures were gastroenterologists.

However, a well-organized campaign of lobbying led to the appearance of a new option of surgical endoscopy in the training model of digestive surgeons in 2016. This novelty was based on the alignment with other countries, in particular European countries and the evolution of surgery. This evolution was indeed marked by the development of celioscopic surgery using rigid optics. The existence of a continuum between

celioscopic surgery guided with optics and the endoscopy techniques was presented to non-expert decision makers. The resemblance between the two techniques seemed consistent to the authorities, that have retained the concept of a possible endoscopic training for surgeons. The underlying reality is probably even more prosaic. Digestive surgery suffers from a lack of attractiveness, being ranked at the 27th position in 2021 in the choice of specialties at the beginning of the third cycle of medical studies, while hepatogastroenterology was ranked 13th. Over the past 10 years, the indications of digestive surgery have been regularly discussed and their relevance has often been questioned [7,8]. Efficient medical treatments have reduced the indications of digestive surgery, for example in the context of gastroesophageal reflux disease or sigmoid diverticulitis. The number of digestive surgeons might be too high regarding the indications for some procedures. For the people in charge of this discipline, it seemed urgent to develop new activities for practitioners. Therefore, an open conflict exists that the medical authorities will need to handle in the coming years. The image of the surgeon remains strong in the public imagination, while that of the hepatogastroenterologist is likely too vague to impose itself naturally when confronted with a simple but effective argument. The gastroenterologists however master the training and thus the quality assessment of endoscopy, therefore a limited impact on the discipline can be anticipated on the 2030 horizon..

GASTROENTEROLOGISTS *VERSUS* ONCOLOGISTS

Regarding oncologists, the problem consists in the existence of a shared expertise. The treatment of digestive cancers, which are diseases of the digestive apparatus, enters by definition in the field of competence of hepatogastroenterology. Likewise, digestive cancers are cancerous diseases, the management of which falls within the field of competence of oncologists. There is an intersection between these two specialties. This intersection underlines the fact that not all hepatogastroenterologists are competent to handle all digestive cancers, and conversely, that not all oncologists are competent to take care of all digestive cancers. This medical evidence however collides with current regulations. It is easy to define a hepatogastroenterologist that is competent in digestive oncology, by the existence of a degree called transversal training (FST) in oncology, but there is no reciprocal recognition of hepatogastroenterological competence for general oncologists. This simple observation is already considered politically incorrect… except for the patients!

Even more surprisingly, the French National Cancer Institute (INCa) broadcasts incomplete information regarding cancer figures in France, by restricting the number of doctors taking care of cancer patients to general oncologists [9]. This presentation masks the fact that there are more organ specialists that practice oncology than there are general oncologists. A study carried out in 2012 and endorsed by INCa showed that 79% of hepatogastroenterologists practiced oncology within the context of their digestive expertise, and that 32% were involved in the primary prescription of chemotherapy [10]. Currently, 30 to 40% of students in DES of gastroenterology specialize in oncology. The clinical research activity is usually organized in the frame of multidisciplinary coopoerative groups in which hepatogastroenterologists represent the majority. In medical practice, in tertiary centers, specialists are often either hepatogastroenterologists specialized in oncology or oncologists who became competent in gastroenterology. It is desirable that this situation continues because the organ specialties have gained a lot from their interaction with the culture of cancer, and oncology has not lost anything from these close contacts with gastroenterologists. The access to transversal specialized training (FST) is regulated by specialty, with around 30% for gastroenterology, but with some fluctuations depending on the local pilot of the FST, who is an oncology professor. The establishment of the oncology FST poses a number of problems that are highlighted by intern unions and medical professors of the different specialties (pneumologists, dermatologists, hepatogastroenterologists). Certain aspects of the regulatory texts are a source of suboptimal situations and should be revised. The coordination of FST should be collegially ensured by both oncologists and organ specialists. This delicate situation is currently a source of tension and will likely be detrimental to the quality of the care of patients with digestive cancer, if it is not corrected by the 2030 horizon.

CONCLUSION

The current organization makes us consider our activities in a competitive world. The best way to maintain our activities is to clearly define our values and the fields of competence of our discipline. Applying a strong requirement for the quality of the initial training and maintaining continuous training will allow us to contemplate the future with confidence.

Michel P, *in :*
CRC 2030

REFERENCES

1. https://fr.wikipedia.org/wiki/Frederick_Winslow_Taylor
2. Loi du 23 décembre 1982 ayant réformé les études médicales et mis en place le concours de l'internat qualifiant et les diplômes d'études spécialisées (DES).
3. Décret n° 2016-1597 du 25 novembre 2016 relatif à l'organisation du troisième cycle des études de médecine et modifiant le code de l'éducation. *Journal officiel* 2016 ; (276). www.legifrance.gouv.fr/loda/id/JORFTEXT000033479390/
4. van der Meulen MP, Lansdorp-Vogelaar I, Goede SL. Colorectal Cancer: Cost-effectiveness of Colonoscopy versus CT Colonography Screening with Participation Rates and Costs. *Radiology* 2018 ; 287 : 901-11. doi : 10.1148/radiol.2017162359
5. González-Suárez, Pagés M, IAraujo IK, *et al. BMC Medicine* 2020 ; 18 : epub (255). doi : 10.1186/s12916-020-01717-4
6. Kaalby L, Deding U, Kobaek-Larsen M, *et al.* Colon capsule endoscopy in colorectal cancer screening: a randomised controlled trial. *BMJ Open Gastro* 2020 ; 7 : e000411
7. Igas. *Situation de la chirurgie de l'obésité*. Rapport (tome 1), 2018. www.igas.gouv.fr/IMG/pdf/2017-059R_Tome_I_.pdf
8. HAS. *Note de problématique pertinence Cholécystectomie*, 2012. www.has-sante.fr/upload/docs/application/pdf/2013-03/points-cle_solution_-_problematique_cholecystectomie.pdf
9. *Les Cancers en France - L'essentiel des faits et chiffres*. Collection Les Données / Epidémiologie. Paris : e-Cancer, 2019. www.e-cancer.fr/Expertises-et-publications/Catalogue-des-publications/Les-cancers-en-France-en-2018-L-essentiel-des-faits-et-chiffres-edition-2019
10. Rougier P, Legoux JL, Lepage C, Michel P. Hepato-gastroenterologists and oncologists are complementary in the management of digestive cancers. *Dig Liv Dis* 2011 ; 43 : 583-4.

MANAGING COLORECTAL CANCER ON THE 2040 HORIZON

Is a long term vision possible?

Michel Robaszkiewicz [1], Lucille Quénéhervé [1]
[1] *Service of Gastroenterology, CHU de Brest, France*

« *A book about the future can interest us only if its prophecies look as though they might conceivably come true.* »
Aldous Huxley, foreword of *A Brave New World*

Considerable progress has been achieved in recent years regarding the management of colorectal cancer (CRC). The next twenty years will see the convergence of genetics, multi-omic analyses, digital technology, imaging, robotics and nanotechnology that will increase our understanding of how these cancers arise, how to detect them at an earlier stage and propose effective treatments that are well tolerated and adapted to each patient. In order to plan health policies and orient research and its financing, it is necessary to understand the epidemiological trends regarding CRC in the years to come.

CRC EPIDEMIOLOGY IN THE YEAR 2040

By 2040, substantial changes in cancer incidence and mortality will occur. In the US, the most common tumors will be breast cancer, melanoma, lung cancer, followed by CRC. According to the estimations, lung cancer will remain the leading cause of cancer death followed by pancreatic cancer, liver cancer; CRC and breast cancer will become the fourth and fifth most common causes of cancer-related death 1.

In 2020, WHO recorded 19.3 million new cases of cancer in the world, and it is expected that the number will reach 28.4 millions by 2040. An increase of almost 50% of cancer cases is expected in the coming two decades if the current trends are confirmed 2.

The increase in the number of new cases will be greater in countries with low or intermediate income, where the survival rates are the lowest, due to the lack of resources devoted to prevention. According to WHO, this is largely due to the limited

sanitary resources of these countries, that have been mainly devoted to the fight against infectious diseases and improving the health of the mother and child.

The trend is also relevant to CRC. Globally, the number of new cases of CRC was 1.88 million in 2020 and it is expected to reach 3.07 millions by 2040 [3]; mortality is expected to increase from 0.92 to 1.59 million deaths during the same period (*figure 1*). The number of new cases is expected to increase the most in Asia and Europe, with +700,000 cases and +130,000 cases, followed by Latin America and North America, with +96,000 and +60,000 cases, respectively. The increase in the number of cases will then be at 71% in Asia, 74% in Latin America, 25% in Europe and 35% in North America. Africa will likely experience a doubling of the number of new cases (60,000 in 2020, and 117,000 in 2040) (*figure 2*). The same trends will likely be observed with CRC mortality.

Globalization, economic and social development of emerging countries, the adoption of lifestyles and food-related behaviors inspired by high-income countries, explain the increased incidence and mortality related to CRC that will be observed in some parts of the world in the two decades to come. A study that examined the human development index (HDI, a composite indicator of a country's socio-economic development) and related it to geographical and time-trends regarding cancer incidence and mortality showed that the incidence of CRC will be stable or in decline in several populations with very high HDI, but that it will increase in countries with high or medium HDI, due to the westernization and the social development and economic life of the populations living in these countries [4].

In 2018, the International Agency for Research on Cancer (IARC) reported a study aiming to estimate the proportion of new cancer cases attributable to lifestyle or environment-related risk factors [5]. Among the CRC cases diagnosed in adults aged >30 in France, 56% were attributable to exogenous risk factors in men and 40% in women. The lifestyle determinants that had the highest impact on the risk of CRC were food and alcohol, followed by overweight and obesity, smoking, a sedentary lifestyle and reduced physical activity.

Among the challenges ahead, it will be important to favor primary prevention in order to reduce these risk factors, considering that these measures also have multiple other beneficial effects on public health beyond the prevention of CRC [6]. Health education, especially among young people, will be of major importance. Emphasis should be put on the development of psycho-social skills to make individuals, in particular children, active learners and vectors of positive prevention messages. It has been shown that risky behaviors regarding health are more frequent when individuals have poorly developed psycho-social skills. It will also be necessary to tackle inequalities between rich and poor countries, otherwise the difference in terms of mortality among high-income countries that have adopted prevention and screening programs and low-income countries will increase.

FIGURE 1. Evolution of the incidence and mortality from colorectal cancer in the world between 2020 and 2040. Source: WHO IARC. *Cancer Tomorrow*, 2020 [3]. https://gco.iarc.fr/tomorrow/en/dataviz/isotype

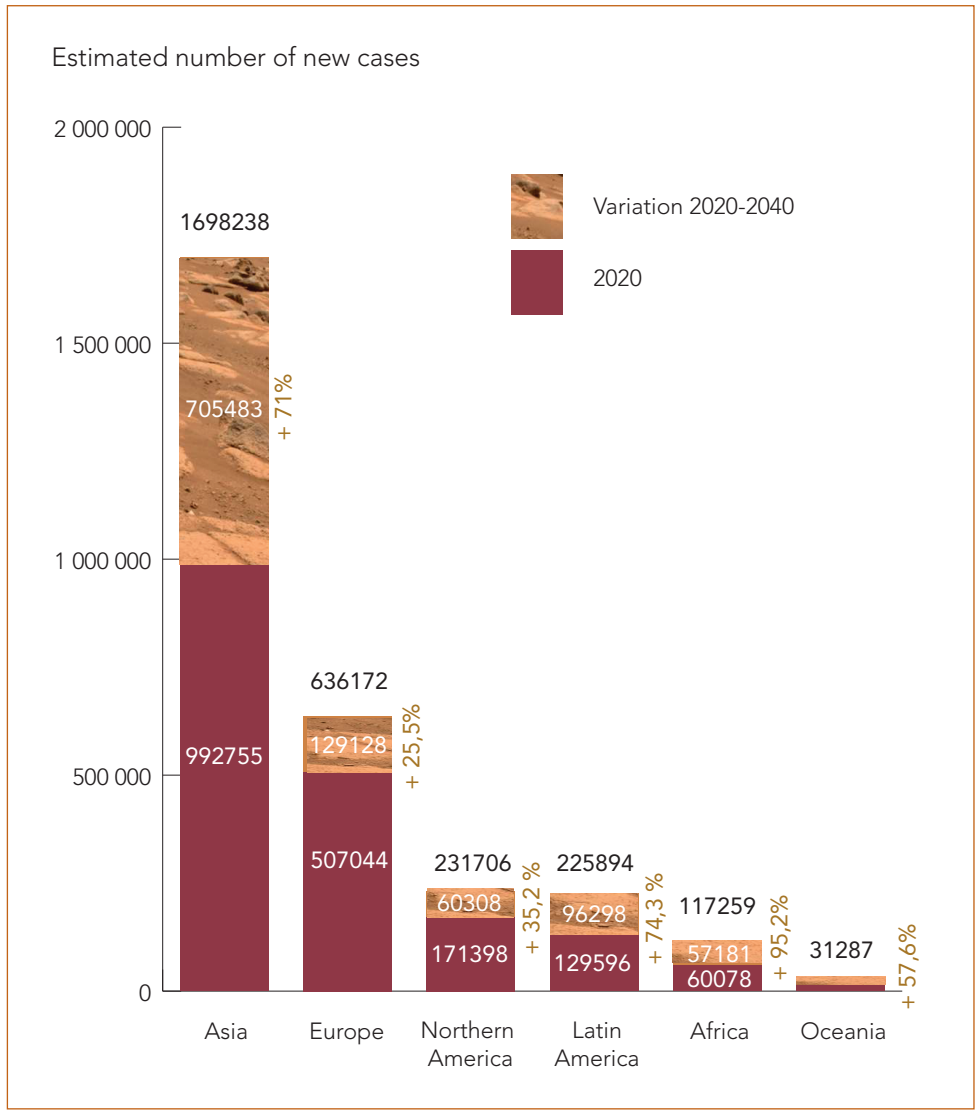

FIGURE 2. Evolution of the incidence of colorectal cancer by continent between 2020 and 2040. Source: WHO IARC. *Cancer Tomorrow,* 2020. [3] https://gco.iarc.fr/tomorrow/en/dataviz/isotype

CANCER COLORECTAL IN YOUNG PEOPLE

An increase in early-onset CRCs is expected in the coming years. Epidemiological studies in several western countries, in particular in the US, show a very significant increase in the incidence of CRC in young individuals [7], projected to grow by over 90% between 2020 and 2030, and even above 120% for rectal cancer in subjects between 20-30 years old. These cancers, defined by an occurrence before the age of 50, are diagnosed outside of the CRC screening programs. They are usually diagnosed at advanced stages and are therefore of poor prognosis. They are more often located in the distal colon, with poor cell differentiation and signet-ring cells during histological examination, likely accounted for by specific risk factors in these individuals [8]. Epidemiological studies have contributed to the identification of some of the environmental parameters related to early-onset CRC, but the knowledge of the mechanisms remains limited for this particular form of CRC. The non-modifiable risk factors include male gender, Caucasian ethnicity, chronic inflammatory bowel disease and family antecedents of CRC [9]. The majority of cases of early onset CRC occur sporadically and are related to environmental or lifestyle factors. They can affect people who are obese as well as non-obese. A number of behaviors may increase the probability of early-onset CRC, such as western eating habits including red and processed meats, monosodium glutamate consumption, titanium dioxide, high fructose-corn syrup, and synthetic dyes [10]. Lack of physical activity and/or alcohol consumption, a sedentary lifestyle, the use of antibiotics, in particular during the first years of life, have also been identified as risk factors. A recent hypothesis is that during pregnancy, stress factors and sleep disorders in the mother may not only have consequences on the fetus but may also induce epigenetic changes in children, by shaping the immune system as well as the gut microbiome [11]. The gut microbiome seems to be a central risk factor for early-onset CRC. Longitudinal studies that address the hypothesis of a link between microbial dysbiosis in early life and subsequent occurrence of CRC are required.

THE INTESTINAL MICROBIOME AND CRC

Recent discoveries pave the way to research on environmental factors acting on the host and on the gut microbiome, as well as on the host-microbiome interactions and their contribution to the onset and progression of CRC. Overweight, obesity, reduced physical activity and the consumption of dietary fiber, sugar, red and processed meat, as well as alcohol consumption influence the composition of the gut microbiome [12]. These factors are a source of dysbiosis that interferes with the intermediate metabolism of intestinal epithelial cells and allow microbial metabolites to enter the circulation. This promotes the recognition of bacterial components by the innate and adaptive immune system and results in the pro-

duction of pro-inflammatory cytokines. In patients with CRC, there is a lower abundance of butyrate-producing bacteria, known to play a role in maintaining intestinal homeostasis and immune tolerance (*Firmicutes* and *Actinobacteria*) and an increased abundance in pro-carcinogenic taxa (such as *Bacteroides*, *Escherichia*, *Fusobacterium* and *Porphyromonas*).

The gut microbiome could be modified as part of strategies to prevent CRC. It is known that the modifications of the intestinal microbiome occur during the early stages of colorectal carcinogenesis, and this may be used to identify individuals at risk for colorectal adenoma. Changes in the microbiome could be used as a biomarker for early detection of CRC in the future and as a way to improve screening strategies. The gut microbiome may also influence the effectiveness or toxicity of therapeutic agents, including immunotherapies.

One goal of future research will be to better understand the complex interactions established between the environment, tumor cells, the immune system and the gut microbiome during colorectal carcinogenesis. This will require the integration of epidemiological, microbiological and multi-omic data (genomic, metagenomic, epigenetic, proteomic and metabolomic analyses). This approach will allow the examination of the impact of lifestyle-related factors, medications and environmental exposure on the gut microbiome and the development and progression of cancer.

CRC MANAGEMENT IN THE YEAR 2040

The coming decades will witness progress in the fields of genetics, epigenetics, genomics and immunotherapy, which will open up new avenues for the diagnosis and treatment of CRC. Understanding the link between the genotype and phenotype will mark the beginning of an era of personalized medicine. In parallel with the development of pharmacogenetics, we will witness the rise of pharmacoepigenetics [13]. The main goal will be to take into account the patient's particularities. The healthcare pathways will gradually transform into personalized pathways, adapted to each individual. This personalization of treatment will pave the way to precision medicine. Every patient will have a digital avatar to integrate medical data in order to offer the most suited treatment. Computer-assisted biosimulation will increase our understanding of how molecules behave in the body of a patient, even before they are introduced, and therefore allow the comparison of the responses of organisms to different medical approaches [14]. The *in silico* trials will not replace *in vivo* and *in vitro* testing, but they will accelerate the development of treatments. Clinical research will benefit from the potential of numerical simulation, by improving the design of trials, the early identification of potential problems raised by a molecule and by reducing their cost. The use of targeted therapies could involve 50% of patients in the years to come, instead of the current 10 to 20%; this will require the reexamination of the requirements for clinical trials. The challenge will also involve the processes of marketing and reimbursement, that will need to be adapted to the fast pace of therapeutic innovation. Genomics will provide new avenues for the development of immunotherapies, including monoclonal antibodies, immune checkpoint inhibitors (ICI), adoptive transfer of cells and anti-cancer vaccines. ICI have proved effective in patients with microsatellite instability; however the majority of patients with CRC do not respond to ICI due to insufficient activation of the immune system. New research will help to design vaccines against cancer and associate these vaccines with other therapies designed to strengthen antitumor immunity. The study of tumor cell composition and tumor heterogeneity will be facilitated by the progress of microfluidics and bioinformatics, allowing individual analysis of thousands of cells. Single-cell analyses will allow the multidimensional study of the genomic, transcriptomic, epigenomic and proteomic characteristics of tumor cells and their microenvironment [15].

They will increase our understanding of the complex interactions between cancer cells and immune/stromal cells, in order to track the molecular mechanisms involved in the response or resistance to immunotherapy. These techniques will be essential for the conception of targeted treatments that will be adapted to the individual situations of patients. Strategies combining nanotechnologies and immunotherapy will also be an important area of research [16]. Nanoparticles can be used as vectors to deliver an immune cargo to stimulate an immune response directed against tumors. They could be used to bypass the immunosuppression induced by the presence of cancer, and even to deliver antigens and adjuvants to memory immune cells. In addition, multifunctional nanoparticles offer the possibility of targeted delivery that can improve the efficacy of immunotherapy and reduce side effects caused by non-specific administration. The specific targeting of immune cells, in combination with real-time bio-imaging of the tumor tissue, opens a new field of nanotechnology-based immunotheranostics. Nanoparticle-based carriers will offer the possibility of modulating the microbiome by delivering live bacteria to the digestive tract. However, several key challenges must be addressed; the systems used for the administration of nanoparticles will have to be biocompatible, biodegradable and have low toxicity.

CONCLUSION

All these projects will require significant investments in high performance technological platforms. They will raise new challenges regarding archiving of biological material, the storage of big data and the analysis of sensitive data. Another challenge will be to establish fruitful collaboration, on the one hand, between academic researchers and private company employees to favor the emergence of new therapies and, on the other hand, physicians. Translational research in cancerology will be fostered by research consortia at the national and international levels. The creation of computer platforms for health data, such as the Health Data Hub in

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France, will permit the storage and the use of medical and molecular data from multiple sources, by providing project leaders an easy, unified and secure access to these data. The complexity of the analysis and interpretation of the results will require active collaboration with computer scientists and mathematicians to extract the relevant information. The conception of systems operating with large computing capacity, artificial intelligence and algorithms of machine learning (deep learning) will allow the synthesis and modeling of the big data to better understand the tumor microenvironment and colorectal carcinogenesis, helping to make better medical decisions. In this context, ethical criteria will become critical in the evaluation and the dissemination of innovative therapeutics.

REFERENCES

1. Rahib L, Wehner MR, Matrisian LM, Nead KT. Estimated Projection of US Cancer Incidence and Death to 2040. *JAMA Netw Open* 2021 ; 4 : e214708. doi : 10.1001/jamanetworkopen.2021.4708
2. Sung H, Ferlay J, Siegel RL, *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021 ; 71 : 209-49. doi :10.3322/caac.21660
3. WHO IARC. *Cancer Tomorrow*, 2020. https://gco.iarc.fr/tomorrow/en/dataviz/isotype
4. Wong MCS, Huang J, Lok V, *et al.* Differences in Incidence and Mortality Trends of Colorectal Cancer Worldwide Based on Sex, Age, and Anatomic Location. *Clin Gastroenterol Hepatol* 2021 ; 19 : 955-66.e61. doi :10.1016/j.cgh.2020.02.026
5. IARC. *Les cancers attribuables au mode de vie et à l'environnement en France métropolitaine*. https://www.cancer-environnement.fr/Portals/0/Documents%20PDF/Rapport/CIRC/PAF_FR_report.pdf
6. Brenner H, Chen C. The colorectal cancer epidemic: challenges and opportunities for primary, secondary and tertiary prevention. *Br J Cancer* 2018 ; 119 : 785-92. doi : 10.1038/s41416-018-0264-x
7. Sung H, Siegel RL, Rosenberg PS, Jemal A. Emerging cancer trends among young adults in the USA: analysis of a population-based cancer registry. *Lancet Public Health* 2019 ; 4 : e137-47. doi : 10.1016/S2468-2667(18)30267-6
8. Mauri G, Sartore-Bianchi A, Russo A, Marsoni S, Bardelli A, Siena S. Early-onset colorectal cancer in young individuals. *Mol Oncol* 2019 ; 13 : 109-31. doi :10.1002/1878-0261.12417
9. Gausman V, Dornblaser D, Anand S, *et al.* Risk Factors Associated With Early-Onset Colorectal Cancer. *Clin Gastroenterol Hepatol* 2020 ; 18 : 2752-9.e2. doi : 10.1016/j.cgh.2019.10.009
10. Hofseth LJ, Hebert JR, Chanda A, *et al.* Early-onset colorectal cancer: initial clues and current views. *Nat Rev Gastroenterol Hepatol* 2020 ; 17 : 352-64. doi: 10.1038/s41575-019-0253-4
11. Zhang Q, Berger FG, Love B, Banister CE, Murphy EA, Hofseth LJ. Maternal stress and early-onset colorectal cancer. *Med Hypotheses* 2018;121:152-159. doi : 10.1016/j.mehy.2018.09.035
12. Song M, Chan AT, Sun J. Influence of the Gut Microbiome, Diet, and Environment on Risk of Colorectal Cancer. *Gastroenterology* 2020 ; 158 : 322-40. doi :10.1053/j.gastro.2019.06.048
13. Miranda Furtado CL, Dos Santos Luciano MC, *et al*. Epidrugs: targeting

epigenetic marks in cancer treatment. *Epigenetics* 2019; 14: 1164-76. doi : 10.1080/15592294.2019.1640546

14. Björnsson B, Borrebaeck C, *et al* (on behalf of the Swedish Digital Twin Consortium). Digital twins to personalize medicine. *Genome Med* 2020 ; 12 : 4. doi : 10.1186/s13073-019-0701-3

15. Davis-Marcisak EF, Deshpande A, Stein-O'Brien GL, *et al.* From bench to bedside: Single-cell analysis for cancer immunotherapy. *Cancer Cell* 2021 ; 39 : 1062-80. doi : 10.1016/j.ccell.2021.07.004

16. Xiong Y, Wang Y, Tiruthani K. Tumor immune microenvironment and nano-immunotherapeutics in colorectal cancer. *Nanomedicine Nanotechnol Biol Med* 2019 ; 21 : 102034. doi :10.1016/j.nano.2019.102034

PRIORITIES FOR RESEARCH

QUESTIONS TO ERIC VAN CUTSEM

Eric Van Cutsem is a head of Digestive Oncology and Professor at the University of Leuven, Belgium

How can translational research be promoted?

Great progress has been made in the knowledge and research on colorectal cancer, leading to many therapeutic advances and to an improved outcome for patients with colorectal cancer.

An important condition for progress is acquiring more integrated knowledge on all factors that influence the pathogenesis, molecular biology, diagnosis and treatment of colorectal cancer. In depth knowledge can only be acquired via fundamental and clinical research projects. Crucial here is the link between fundamental and clinical research via translational research.

Many aspects/conditions are important to fulfill : in depth knowledge of biology of colorectal cancer ; multidisciplinary & multimodal approaches are needed ; improved diagnostic techniques (pathology, molecular biology, endoscopy, radiology) ; personalization and individualization of patient management.

New innovative research projects and developments are needed. Here integration of translational research is important so that the link between clinical and fundamental research can be made.

The starting point for these translational research projects are clinically-oriented questions starting from the clinical needs and questions in relation to the patient and the disease.

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What is the role of the doctor-researcher partnership in translational research?

The physician involved in new innovative developments should have a creative and innovative way of thinking on evidence-based guidelines and should be able to integrate open scientific questions with a direct impact on the diagnosis and therapy of patients with colorectal cancer.
A '"partnership" between physician-researcher has therefore major advantages to more concretely define the needs for research questions and to define these questions more concretely.
He/she is very well placed to integrate and implement the research questions into the clinical management and can work out the feasibility of these clinical/translational questions in the flow of patients with colorectal cancer.
In this process the evaluation of the impact of diagnostic and therapeutic strategies in subgroups of colorectal cancer is very important. Indeed, it is more and more clear that colorectal cancer is a heterogeneous disease, with different pathways involved in the pathogenesis of colorectal cancer, with different genetic backgrounds, with different age groups, with different molecular characteristics and molecular subgroups and with different immuno-phenotypes.
In order to understand these different aspects and patterns and to integrate the different dimensions, translational research projects are crucial.

What is the best way to assess the effectiveness of medical devices in oncology and promote their use in clinical practice?

New developments and trial ideas should be evaluated and measured within the clinical & translational trial by using adequate endpoints and should also be evaluated in clinical practice. Confirmation of the impact in Real World Projects/Trials is equally important.
In order to understand the impact of clinical and translational research projects, adequate evidence-based and innovative endpoints should be developed and used.
These trials and Real World Endpoints include evident endpoints, such as measuring the impact on survival, progression free survival (disease control), response rate (tumour regression) and patient reported endpoints (quality of life), as well as more innovative research endpoints involved in translational research, such as biomarker driven endpoints and pharmacodynamic endpoints, based on repetitive tumour biopsies, liquid biopsies looking at circulating DNA and serum proteins.

What will be the place of *in silico* clinical research in the development of new therapeutic indications?

In silico experiments are experiments performed using computers or via computer simulation. In the future *in silico* experiments will probably be hypothesis generating in colorectal cancer and may be used in further research and screening for diagnostic characteristics and for molecular & immunologic characteristics and patterns, but will need validation in the real world clinical situations.
Indeed, the integration of Artificial Intelligence in pathology, endoscopy, radiology and molecular biology of colorectal cancer is an emerging additional tool and is a very promising method to detect patterns and to discover new pathways involved in cancer development and growth.

What is the best way to develop strategic, industrial or academic trials?

Both academic research and industrial research have specific goals and may therefore have different requirements and designs. Both types of trials are very important and should have the goal of improving our knowledge & understanding of colorectal pathogenesis, diagnostic tools and therapeutic modalities. But collaboration between academia and the industry is very important in every aspect in view of the specific background, knowledge, research capacities and expertise of academia and industry and it is therefore clear that collaboration is crucial.

How should academic trials be developed when it comes to evaluating a drug that is already on the market?

The initial goal of industry is to bring a new anticancer drug to the market.
Even if this is initially successful, further knowledge should be retrieved to demonstrate the real impact in real world situations, and to understand the effect and activity in specific subgroups (clinical and molecular subgroups) and also in other indications (other lines of treatment and other tumour types).
These projects may be driven and led by industry or by academia or in an ideal world by a collaboration between the two. The final goal should indeed be improved outcome and maximal benefit to patients with colorectal cancer or other cancers.
The art, as well as a great challenge, is therefore to find a model in which we can collaborate and can trust the knowledge of academic AND industry trials and not the knowledge of academic OR industry trials through a collaboration which leads to a win-win scenario for everyone, and especially for patients with colorectal cancer.

What about the development of academic trials for niches that involve few patients?

Trials on small subgroups of more frequent cancers and in rare cancers are challenging, because of the increasing complexity, the increasing costs of research trials and the difficulty of making clear, sound and solid assumptions that lead to strong conclusions in trials.
Therefore, the development of these research trials should be done in a collaborative manner between academia and industry, in which the scientific and operational knowledge of the different partners should be respected. The financial limitations

and prospects for the potential financial impact of the trials should also be shared in a transparent way.
Upfront and transparent information sharing is therefore important and developing the trials in real collaborative steering committees is crucial for successful studies with great impact on the outcome of patients with colorectal cancer and other cancers.

How can we reconcile the slow progress in clinical research and the necessity to rapidly assess new «breakthrough» drugs in Europe?

Since research projects are time- and money-consuming and since the fast evolution of the progress in our scientific knowledge requires rapid and intense interactions, dynamic models and fast implementation of clinical and translational research is absolutely necessary in order to avoid that the trials become outdated and the results obsolete while the trials are ongoing, even before the results become available.
Therefore, dynamic steering committees need to work on accurate implementation and follow-up plans of the trials.

How to integrate academic clinical research from different European countries in a context of different and complex national regulatory authorities?

The EU Clinical Trials Directives aim to facilitate the internal market in medicinal products within the European Union, while at the same time maintaining an appropriate level of protection for public health. It seeks to simplify and harmonize the administrative provisions governing clinical trials in the European Community, by establishing a clear, transparent procedure. However, they add an important layer of complexity and extra bureaucratic requirements and conditions on the trials, which have the risk of slowing down the project.
Therefore, professionalization of the academic trial organization is needed, as well as structured interactions with the various partners in trials and research projects.

And finally, what are the current priorities in terms of research and the organization of health care?

It is crucial to structure health care around expertise and high volume and it is essential to integrate in these clinical structures clinical and translational research groups, which have both a clinical and a research task. Key players are certainly the experienced clinicians/researchers who can also fall back and rely on fundamental research teams and who are able to implement innovation in clinical & translational research.

Questions prepared by Robert Benamouzig and Gabriel Rahmi.

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