Hot Topics in Acute Care Surgery and Trauma

Nicola de'Angelis
Salomone Di Saverio
Francesco Brunetti *Editors*

Emergency Surgical Management of Colorectal Cancer

Springer

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Nicola de'Angelis • Salomone Di Saverio
Francesco Brunetti
Editors

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Editors
Nicola de'Angelis
Department of General Surgery
Unit of Digestive, Minimally Invasive and Robotic Surgery,
Henri Mondor Hospital
Créteil
France

Francesco Brunetti
Department of General Surgery
Unit of Digestive, Minimally Invasive and Robotic Surgery,
Henri Mondor Hospital
Créteil
France

Salomone Di Saverio
Cambridge Colorectal Unit, Cambridge Biomedical Campus
Cambridge University Hospitals NHS Foundation Trust, Addenbrooke's Hospital
Cambridge
UK

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To my family, who makes my dreams real by supporting me every single day of my life.
Nicola de'Angelis

To the memory of my Dad "Paito," to my mother Gabriella who is inspiring and missing me, and to the patience and dedication of my beloved wife Omeshnie
Salomone Di Saverio

To my mother Anna and my hometown Napoli
Francesco Brunetti

Preface

This book is part of the series "Hot Topics in Acute Care Surgery," as a result of a successful collaboration between Springer and the World Society of Emergency Surgery (WSES). The WSES is an "open access" society funded in 2009. In less than 10 years, WSES has expanded worldwide, accounting delegates in every continent who share and endorse its aim: promoting emergency surgery training and education through scientific communications, international consensus, academic exchanges, and surgical fellowship.

In the same perspective, this book is addressed to general surgeons, emergency specialists, fellow surgeons, and residents to provide them an extensive and updated overview on the emergency surgical management of colorectal cancer. The increasing prevalence of colorectal cancer, especially in industrialized countries, makes this malignant pathology as one of the most commonly encountered in daily practice and more and more often in the emergency setting. Indeed, the whole book is dedicated to develop the multiple aspects related to the challenging management of colorectal cancer as an emergency, including imaging and interventional radiology strategies, endoscopy, and surgery for both primary tumor and metastases. Novel strategies and techniques, such as the implementation of enhanced recovery program or minimally invasive surgery, are discussed in detail. Particular interest is assigned to specific categories of patients presenting with colorectal cancer emergencies, such as elderly patients, transplanted patients, or patients with hemostatic disorders or receiving immunotherapy or chemoradiation therapy. The postoperative cares and the difficult decision-making process in emergency settings are discussed in dedicated chapters with the aim of providing the reader with detailed descriptions of these important issues. Finally, three chapters focusing on surgical training curriculum, technical aspects, and documented clinical cases have been written specifically for residents and trainees who can find a rapid source of practical and technical information to improve their knowledge and skills in the field.

As editors, we are very satisfied of this work, which emphasizes the international and multidisciplinary collaboration of more than 50 authors from all over the world. Their scientific contribution allowed treating an exhaustive range of pertinent topics and has ensured a perceptive and balanced approach to the complex field of colorectal cancer emergencies.

In this rapidly evolving medical and surgical domain, there remains a shortage of specialists specifically trained to deal with colorectal cancer emergencies.

Those learning more about this field will discover that a successful management is dependent on a consolidated multidisciplinary approach and a straightforward decision-making process in the emergency setting, which relies upon evidence-based knowledge, experience, and pragmatism.

Créteil, France — Nicola de'Angelis
Cambridge, UK — Salomone Di Saverio
Créteil, France — Francesco Brunetti

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Colorectal Cancer Research: A State of the Art

1

Nicola de'Angelis

1.1 Introduction

Research in colorectal cancer is vast and multitudinous, spreading from genetics to surgical techniques. The increasing amount of publications in the last two decades discloses the enormous progress made in the screening, diagnosis, and treatment of this common malignant pathology. Nowadays, colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females [1]. The worldwide CRC incidence varies over a tenfold extent; in developing countries, the incidence amounts to 1–5 patients per 100,000 inhabitants, while it can increase to 20–60 patients per 100,000 inhabitants in industrialized regions, a difference that is likely attributable to lifestyle habits, socioeconomic status, and environmental exposures over distinct genetic susceptibility. Overall, CRC incidence has been steadily decreasing in the last 15 years, thanks to the improvements in diagnostic techniques and the implementation of screening programs. Conversely, the incidence rates of CRC in adolescents and young adults have been progressively increasing; this may be partially explained by a lack of routine screening and emerging lifestyle issues such as obesity, poor physical exercise, and dietary factors, but it seems to have a distinctive molecular profile in this specific young patient population, very different to late-onset CRC cases [2]. Thus, the overall global burden of CRC is expected to rise, with 2.2 million predicted new cases and 1.1 million deaths by 2030 [3], and an estimated global economic burden approaching $100 billion [4].

Although it remains strictly dependent upon the stage of disease at diagnosis, CRC prognosis and related survival have significantly improved. An early-detected localized CRC is associated with a 90% survival at 5 years, whereas a distant metastatic cancer has a much lower chance of survival (10%) [1, 5]. Thus, despite the

N. de'Angelis (✉)
Unit of Digestive, Hepato-Pancreato-Biliary Surgery and Liver Transplantation, Henri Mondor Hospital, AP-HP, University of Paris Est, UPEC, Créteil, France

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great progress made, researchers must continue to search for enhancing the accuracy of the available screening methods and the implementation of prevention programs, as well as identifying the best treatment protocols for CRC in order to impact on cancer incidence and mortality. What should not exist in 2019 is a considerable variation in CRC prognosis that is attributable to global and regional disparities in access to diagnostic and treatment services. Unfortunately, mortality rates are still higher in countries with more limited resources and health infrastructures [6], as well as for socioeconomically deprived neighborhoods in developed countries [7–9]. Moreover, due the growth and aging of the population and the adoption of westernized lifestyle worldwide, the global burden of CRC is expecting to further increase supporting any single effort in CRC research.

1.2 Colorectal Cancer Research: A State of the Art

1.2.1 Advances in Colorectal Cancer Research

In the timeline of colorectal cancer research, several milestones can be found [10] concerning the identification of causes and risk factors, the development of diagnostic and screening tools, the discovery of effective drugs. and the advancements in surgical techniques.

Understanding the basic biology of colorectal cancer development, growth and spread, as well as the environmental risk factors and genetic alterations that contribute to CRC occurrence has been essential for the advancements in CRC prevention and treatments [11]. Indeed, it is well established nowadays that the most important risk factors are age, gender, race, and positive family history, which are related to the genetic component in CRC etiology. Other acquired risk factors include lifestyle (e.g., smoking, lack of physical exercise), dietary habits, and geographic areas [12]. Primary and tertiary preventions of CRC focus on these acquired risk factors, whose modification can contribute to lower the risk of cancer development and recurrence [13–15].

Since the first publication in 1927 by Lockhart-Mummery JP and Dukes C in surgery, gynecology, and obstetrics, research has clearly demonstrated that CRC does not arise de novo from the colon mucosa but from a preexisting lesion that can be early detected and treated to the benefit of the patient's cure and survival. This raised the important issue of screening tests with a high sensitivity for detecting early-stage CRC, but even more importantly, for advanced adenomas and high-grade dysplasia, which are the bridge to invasive cancers [16].

Thus, the screening paradigm has shifted; in 2017, the American Cancer Society recommends to screen for CRC in people at average risk aged between 50 and 75 years with a screening strategy that is able to identify polyps and cancer (i.e., by sigmoidoscopy every 5 years, colonoscopy every 10 years, or CT colonoscopy every 5 years). This is preferred over alternative tools that mainly find cancer (i.e., take-home gFOBT yearly, take-home FIT yearly, or a stool-DNA test every 3 years) [17]. It is noteworthy that the widespread implementation of those screening

methods that can accurately identify premalignant polyps or early-stage cancers allowing for the treatment of curable lesions led to an up to 50% reduction in cancer-related mortality [16, 18, 19].

The twenty-first century has been characterized by the introduction of new agents for CRC chemotherapy, modified therapeutic protocols (adjuvant vs. neoadjuvant chemotherapy), and targeted therapies [10, 20–23], which all contributed to improve survival outcomes also in advanced stages of disease. From the sole active agent available until the year 2000, namely, the fluorouracil, molecules such as irinotecan, oxaliplatin, and humanized monoclonal antibodies (bevacizumab, ramucirumab, cetuximab, and panitumumab) were approved for the treatment of CRC. Moreover, the introduction of an orally active drug, the capecitabine, signed another milestone in the CRC chemotherapeutic protocol.

In the era of personalized medicine and with the effort of predicting or improving drug responses in CRC patients, gene expression-based subtyping and molecular CRC classifications were developed as valuable approaches for patient stratification [24, 25]. Most of the molecular mechanisms involved in colorectal carcinogenesis have been characterized, and 16% of CRCs were found to be hypermutated: three-quarters of these had the expected high microsatellite instability, which is known as predictor of a favorable response to immunotherapy in patients with advanced-stage CRC [26, 27].

In the particular case of locally advanced rectal cancer, the administration of neoadjuvant radiotherapy in combination with total mesorectal excision was proved to decrease the local recurrence rate, and it is nowadays considered as the gold standard protocol [28–30]. Going forward, some authors suggested a true paradigm shift in 2004 in case of a complete response to neoadjuvant chemoradiation therapy: the "wait and watch" approach aiming at sparing organs and tissues and avoiding radical, invasive, and morbid surgery with a tremendous impact on the patient's quality of life [31–35]. Although promising, the oncological safety of this treatment strategy in rectal cancer is currently under investigations.

1.2.2 Critical Issues and Research Gaps in Colorectal Cancer Research

Many critical issues remain unsolved or under investigation in the field of CRC biology, prevention, and treatment [36]. A better understanding of the molecular and cellular interplay between CRC and its macro- and microenvironment would represent a key step forward. In the near future, we expect to have deciphered the roles of gut microbiome in the regulation of the host immune-inflammatory responses and the genesis of neoplastic lesions and, consequently, the possibility of using colorectal microbiota biomarkers to improve treatment outcomes in CRC patients [37].

Definitely, we are still facing an incomplete picture in the etiology of CRC; the absolute risk attributable to inherited, environmental, or lifestyle factors and their synergic interactions remain unclear. To apply precision medicine and tailored

interventions, the risk assessment and patient stratification must become as precise as possible, and this represents the main pathway to undermine the global burden of CRC [38].

Improvements are awaited at any step of CRC cares: in the prevention and screening processes, at the diagnostic level, in the prognostic evaluation, and finally in the application of curative treatments. In general, research advancement should aim to optimize current strategies, fill the gaps, and correct inadequacy while searching for new treatments and novel technologies. Most importantly, there is a real need for more studies focusing on strategies to improve health-related quality of life in patients living with and beyond CRC [36]. Prolonging patient's survival could not be the only objective of modern CRC therapies; research must find a way to weight and counteract the psychological, emotional, and social impact of CRC treatment sequelae, which may include disabling and embarrassing symptoms such as fecal incontinence or sexual dysfunction (observed in up to 35% of patients with rectal cancer) [39–41].

Finally, CRC research in the last decades emphasized the importance of a multidisciplinary team approach to CRC cares, which promoted the creation of national and international networks of colorectal cancer centers of excellence that apply evidenced-based medicine for the standardization of best practices [42]. However, this must be implemented involving not only clinicians and surgeons but also biologists and physical scientists whose expertise is highly required to further advance in CRC research. Moreover, the widespread formation of CRC research networks will assure effective communications between healthcare professionals and optimal knowledge transfer toward healthcare policy-makers, research funders, and CRC patients [36].

1.3 Colorectal Cancer Surgery

1.3.1 Milestones in Colorectal Cancer Surgery

Among all therapeutic options, surgery remains the best chance of cure for CRC when a curative-intent surgery is still possible.

Colon cancer can be safely and efficacy treated by surgery. During the last two centuries, extensive debates have followed about the best technique of colon cancer resection. These concerned the critical issue of high ligation of the lymphovascular pedicle before or after manipulating the tumor, wide or restricted excisions, and the interest of no-touch isolation technique (i.e., early isolation of the lymphovascular pedicle with minimal manipulation).

In general, the type of colectomy is based on tumor location and vascular lymphatic drainage. Although it remains controversial, the high ligation of the lymphovascular pedicle and the no-touch technique seem to confer no additional oncological benefit; however, recent evidence supports the principle of complete mesocolic excision (CME) as the optimal approach that should be applied to all colon cancer. CME includes three essential components: firstly, the dissection between the

mesenteric plane and parietal fascia and the removal of the mesentery within a complete envelope of mesenteric fascia and visceral peritoneum that contains all lymph nodes draining the tumor area. The second component is the central vascular ligation that potentially removes lymph node metastases, vascular and neural invasion in the whole regional draining area. Then, the third component is represented by the resection of an adequate length of bowel to remove all the involved pericolic lymph nodes [43, 44].

Supported by several randomized clinical trials and in order to preserve at best patient's quality of life, the general tendency today is to opt for more conservative and organ-sparing surgical techniques rather than extended resection. Indeed, segmental resections appear as safe as extended ones in case of colon cancer, even located in the transverse colon or at the splenic flexure [45–47].

Rectal cancer was considered incurable until the eighteenth century, when surgery was applied to remove the rectum. However, prior to the introduction of anesthesia, asepsis, and blood transfusions, rectal surgery was highly invasive, aggressive, disabling, and associated with extremely high mortality rates [48]. Early in the twentieth century, Sir Miles described the radical abdominoperineal resection (APR) with permanent colostomy recommending an extensive mesenteric lymphadenectomy to prevent recurrence. To counteract the extreme invasiveness of the radical APR, some surgeons proposed an anastomosis between the rectum and sigmoid colon, which, however, was associated with poor oncological outcomes at that time. The introduction of the Hartmann's procedure with the construction of an end colostomy leaving the distal rectum in place signed a real milestone in rectal cancer management. Since then, the tendency has shifted toward less radical and more sphincter-sparing surgical procedures including anterior resection, low anterior resection (LAR), and pouch reconstructions. The cornerstone in rectal cancer surgery is definitely represented by the concept of total mesorectal excision (TME), proposed by Richard Heald in 1982 [49]. Heald's TME was based on the embryologic development of the hindgut, and it included the excision of the rectal cancer together with the en bloc excision of the mesorectum. By applying this technique, he decreased the rates of positive lateral margins and local recurrence as low as 3.6% and improved the disease-free survival up to 80% at 5 years and 78% at 10 years [49]. Over the years, TME was proved to improve oncologic outcomes and patients' survival over non-TME approaches, and thus, it is currently considered as the gold standard approach in rectal cancer surgery [50, 51].

Parallel to the evolution of surgical principles and surgical techniques, the introduction of new surgical materials and devices allowed for fatal advancements. Particularly, the routinely use of mechanical staplers since the 1970s has revolutionized colorectal surgery and made many challenging or tedious procedures much easier and expeditious [48].

The current debate in CRC surgery concerns the application of minimally invasive approaches, such as laparoscopy, robotics, and transanal endoscopic microsurgery [52]. Laparoscopy in general has refashioned surgery of the last three decades transforming completely the operative and postoperative courses of the operated patients.

Laparoscopic colectomy was first introduced in 1991, and it becomes successively the gold standard approach. Indeed, patients operated on by laparoscopy show faster recovery, shorter hospital stay, lesser pain, and improved cosmetic outcomes compared to open surgery [53–55]. The short-term advantages of laparoscopy are doubtless in both colon and rectal cancer resection, but its oncological safety in case of rectal cancer has been recently questioned [56–59]. Indeed, the adaption of laparoscopy for colon cancer has improved recovery outcomes and patient's acceptation of surgery at no expense to survival [55, 60], whereas laparoscopic rectal cancer surgery has been associated with significantly lower rates of complete mesorectal excision with free resection margins, threating the oncological principles of TME [57]. However, long-term results are lacking, and they will be necessary to finally assess the role of laparoscopy in rectal cancer treatment.

Despite the widespread enthusiasm toward laparoscopy and the encouraging results of randomized controlled trials, especially for colon cancer, it must be noted that the adaption of laparoscopy for CRC surgery remains relatively low. In the USA, a bit more than one patient over two with colon cancer undergoes elective laparoscopic colectomy, whereas only 10% of rectal cancer surgeries are performed by laparoscopy, with significant disparity between urban and rural areas and in high-volume compared with low-volume centers [61, 62]. In France, up to 29% of patients with CRC receive an elective laparoscopic resection [63], with higher rates in high-volume, tertiary, referral hospitals. The hesitation toward laparoscopy, which after more than 20 years from its introduction is still reserved to a minority of patients, may be explained by its complex use in CRC surgery compared to other abdominal operations, leading to long operative times, high conversion rates, steep learning curve, and thus necessary specialized training periods.

To overcome laparoscopic pitfalls, robotic surgery was proposed as high technological approach that allows for a three-dimensional view of the operating field, a 7-degree-of-freedom motion with wristed instruments, and a great surgical ergonomics. The literature is expanding, and several studies have been published on the comparison between robotic and laparoscopic colorectal surgery [45, 64–66]. Despite good surgical outcomes that are most of time comparable to those obtained by laparoscopy, the main drawback of robotic surgery appears to be the costs/benefits ratio that is still unfavorable limiting the indications and spreading of robotics at approximately 1–3% of CRC surgeries [67, 68].

Alternative techniques include natural-orifice transluminal endoscopic surgery (NOTES) and transanal TME (TaTME), which are seen as promising approaches to treat rectal especially located in the low rectum, or in male patients, narrow pelvis or in case of obesity. Still, there is a need for well-designed and executed randomized, controlled trials to define the safety and indications of NOTES or TaTME, as well as their superiority over laparoscopy [52].

Overall, the evolution of CRC surgery is characterized by the progressive shift from radical to organ-sparing procedures and from aggressive to minimally invasive approaches. The pattern of this evolutionary process has definitely accelerated in the last decades reflecting the accelerated rate of technology development in general as

in the medical fields. The development and application of minimally invasive surgical techniques in CRC management must continue because it is supported by a huge clinical impact on patient-centered outcomes as well as on the healthcare systems. In the modern era, it is imperative to optimize the standard of cares in order to reduce the costs of colorectal surgery; this may be pursued by applying the surgical approach with the highest efficiency, the less morbidity rate, and the best oncological outcomes.

1.3.2 The Body of Evidence in Emergency Colorectal Cancer Surgery

Despite increased screening efforts, it is estimated that up to 33% of patients with CRC will present with symptoms requiring acute or emergent surgical interventions. While treating in an emergency setting, the rate of associated morbidity, mortality, and stoma formation is significantly higher compared to elective CRC management. Thus, specific considerations should be made for emergency CRC management and particularly emergency CRC surgery.

The present book is entirely dedicated to the current knowledge and actual issues in the emergency surgical management of colorectal cancer. Each chapter has been written by clinicians and surgeons highly expert in the field with the objective of summarizing the up-to-date literature and merging it with their personal experience. This is one of the fundamental principles of evidence-based medicine, for which any therapeutic choice should be based upon the best available scientific evidence combined with the surgeon's clinical experience and the patient's demand. However, it must be noted that in the specific domain of emergency colorectal cancer surgery, the amount and quality of evidence is limited and mainly supported by retrospective studies. Obviously, practical and ethical issues curtail the feasibility of randomized controlled trails (RCTs), and due to the heterogeneous presentation of CRC in emergency, this latter type of cancer has often represented an exclusion criterion.

It is worth noting that the surgical field in general is not awarded by a high amount of well-conducted RCTs. Indeed, RCTs account for less than 4% of all publications in the leading surgical journals, and their number showed a tendency to decline over time. Hence, most of the available evidence surgery, in both elective and emergency settings, may be considered of poor quality on the evidence-based medicine scale whether it comes from non-RCTs (case-control or cohort studies), retrospective case series, or qualitative reviews [69].

Despite this, systematic reviews and meta-analyses were conducted to summarize the results of emergency vs. elective surgery in CRC patients and compare the outcomes of different surgical approaches [70–73].

In general, a worse prognosis is associated with CRC presenting as a surgical emergency; worse outcomes are related on one side to the patient's specific conditions when admitted in emergency settings (e.g., dehydration, poor nutrition, neglected comorbidities) and, on the other side, to the characteristics of tumors

resected emergently. Indeed, CRC requiring an emergency surgery is typically of a more advanced T stage, of higher histologic grade, or already involving regional lymph nodes or adjacent organs.

Laparoscopy for the emergency surgical management of CRC is gaining popularity, although there is little guidance in the literature about the preoperative evaluation and risk stratification upon which select the type of the operative approach. Moreover, the surgeon's experience and proficiency in laparoscopy play a major role in the adoption of this minimally invasive technique into emergency clinical practice [71].

Finally, in the emergency setting, the individualization of surgical management is even of a greater importance than in elective surgery. However, the emergency colorectal surgeon will face several problems, such as incomplete or unavailable information about diagnosis and staging, complex risk assessment and stratification, and sometimes even the impossibility to gather the patient's consent for surgery. Thus, the decision-making process may be challenging. The available international guidelines and consensus agree that the literature concerning the emergency surgical management of CRC is relatively poor and the existing RCTs are often not sufficiently robust in design and sample size to the point that only few recommendations may be considered as having a strong evidence base (i.e., Grade A). Despite this, the oncologic principles that should be met even in case of CRC requiring an emergency surgery are clear. The Clinical Practice Guidelines Committee of the American Society of Colon and Rectal Surgeons listed the following goals in the treatment of CRC-related emergencies: (1) avert the immediate negative impact of the complication, (2) achieve the best possible tumor control, and (3) ensure timely recovery to permit initiation of appropriate adjuvant or systemic treatment [73]. Surgical principles include wide radial, proximal, and distal margins and a high ligation of the lymphovascular pedicle to obtain an extended lymphadenectomy (>12 lymph nodes) as for CRC resection performed in elective settings.

1.4 Conclusion: Being an Emergency Colorectal Surgeon

With wide disparities among countries and regions, most of colorectal emergencies are still managed by general surgeons, but a greater body of evidence highlights the impact of specialization to reduce morbidity and mortality [74, 75]. Indeed, being a specialized colorectal surgeon seems to be associated with improved surgical outcomes and increased chances for the patient of receiving the best treatment option. Thus, Chap. 26 of this book will discuss the importance of advanced surgical training, revised curriculum, and specialization in colorectal surgery. In parallel, there is a need to progressively shift, especially in tertiary referral hospitals, toward clinical and surgical units that are organized on specialized clinical interest or professional activity to the benefit of the patients' cares and management.

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Epidemiology of Colorectal Cancer: Incidence, Survival, and Risk Factors

2

Florence Canouï-Poitrine, Claudia Martinez-Tapia, Lydia Guittet, and Anne-Marie Bouvier

2.1 Introduction

Colorectal cancer is still a major challenge in oncology. Population-based studies, which accurately record all cases diagnosed in a well-defined population and thus provide unbiased measurements, are the best way to assess changes in colorectal cancer frequency or survival. Worldwide incidence data are available from cancer registries, in particular through the successive volumes of Cancer Incidence in Five Continents covering registration up to 2012 [1–3]. For meaningful survival

F. Canouï-Poitrine (✉)
Public Health Department, University Henri-Mondor Hospital, Créteil, France

Paris Est Creteil University (UPEC), A-TVB DHU, CEpiA (Clinical Epidemiology And Ageing) Unit EA4393, Créteil, France
e-mail: florence.canoui-poitrine@aphp.fr

C. Martinez-Tapia
Paris Est Creteil University (UPEC), A-TVB DHU, CEpiA (Clinical Epidemiology And Ageing) Unit EA4393, Créteil, France
e-mail: claudia.tapia@aphp.fr

L. Guittet
U1086 INSERM-UCBN, ANTICIPE, Caen, France

University Hospital of Caen, Caen, France
e-mail: guittet-l@chu-caen.fr

A.-M. Bouvier
Digestive Cancer Registry of Burgundy, Dijon, France

EPICAD INSERM LNC-UMR 1231, Dijon, France

University Bourgogne Franche-Comté, Dijon, France

Dijon University Hospital, Dijon, France
e-mail: anne-marie.bouvier@u-bourgogne.fr

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comparisons between countries or time periods, net survival is used. Net survival from cancer is the survival that would be observed if cancer were the only cause of death. This major epidemiological indicator allows thus comparisons without interference from other causes of death. Reliable survival rates are regularly published through international (CONCORD) [4–6] and European (EUROCARE) [7, 8] programs and using the French population-based cancer registries network (FRANCIM) [9–11] data. The aim of the present study was to provide updated temporal trends in colorectal cancer incidence and prognosis over the past decades.

2.2 Incidence

Last available worldwide data showed that colorectal cancer was the third most common cancer in men (746,000 cases, 10.0% of the total) and the second in women (614,000 cases, 9.2% of the total) in 2012 [12]. Differences in the incidence of colorectal cancers over the world are striking, with a tenfold variation between highest and lowest area, and geographical patterns are very similar in men and women (Fig. 2.1). Historically, the highest incidence rates have been reported in more developed countries. North America; Australia; New Zealand; Western Europe, including France; and Japan were considered high-risk incidence countries. Colorectal cancer was scarce in South America, China, or Africa. Other countries, mainly Northern, Southern, and Eastern Europe, were considered as middle-risk area. Starting from the mid-1990s, incidence rates declined for both sexes (Fig. 2.2) in the high-risk countries whereas slightly increased in most middle-risk ones (Denmark, Italy, Spain, or the Netherlands) and remained relatively stable in

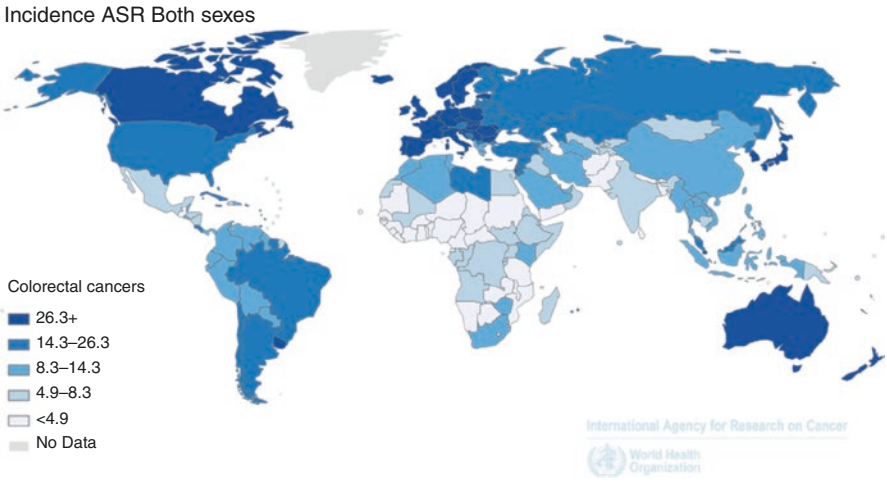

Fig. 2.1 Worldwide colorectal cancer incidence—*GLOBOCAN 2012, International Agency for Research on Cancer IARC*

Switzerland and the UK. In contrast, increasing trends have been seen in developing countries. In the last worldwide published monography covering the 2008–2012 time period, European countries exhibited similar incidence rates as the USA and North America, whereas Eastern Europe and Japan had the highest rates. In France, incidence slightly decreased from the early 2000s with a mean annual decreased of −0.3% in men and in women between 2005 and 2012. The cumulative risk decreased from 2.0% for men born around 1920 to 0.9% for those born around 1950, a more than twofold increase. The corresponding values in women were 0.1% and 0.2%.

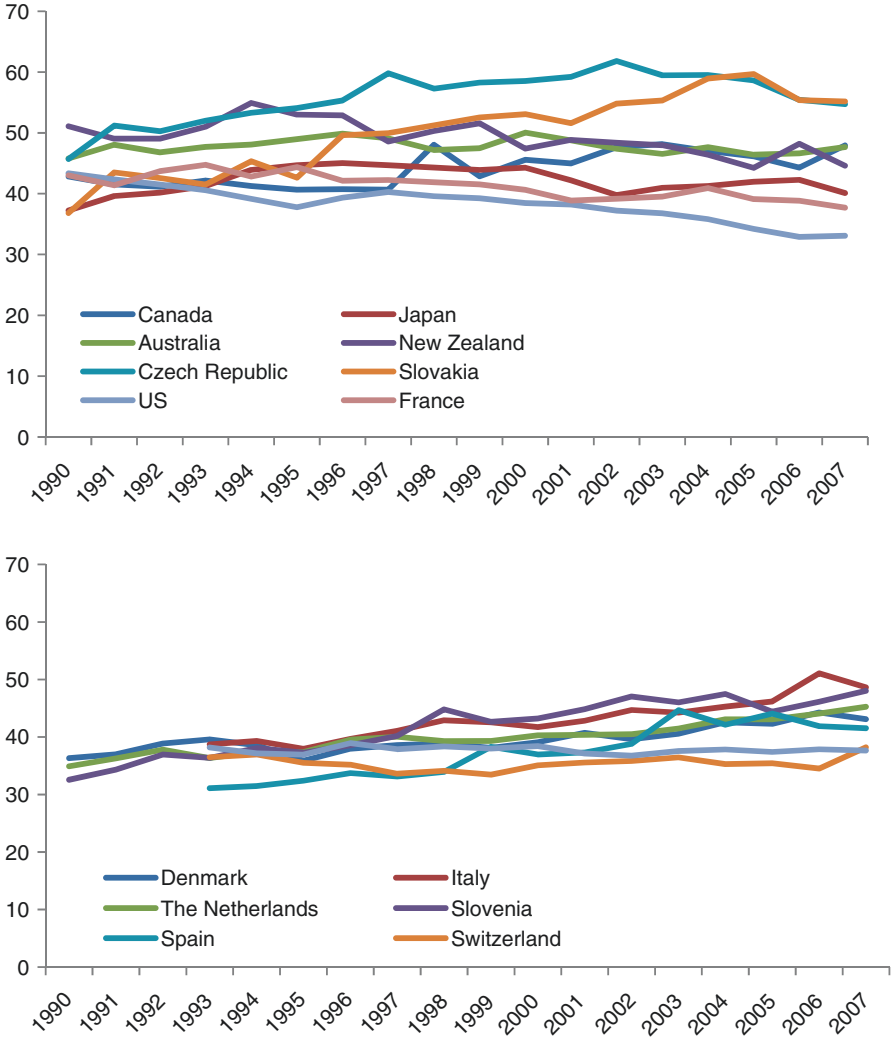

Fig. 2.2 Time trends in incidence of colorectal cancer *(International Agency for Research on Cancer (IARC). Cancer Incidence in Five Continents monographies)*

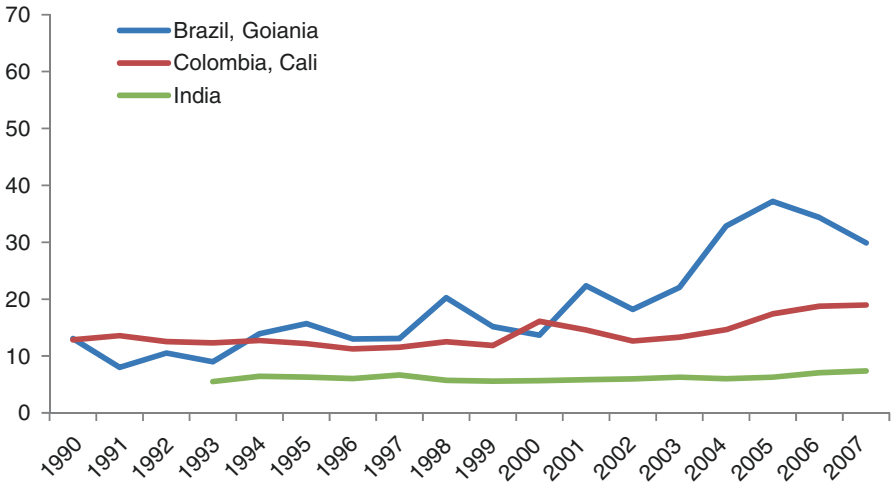

Fig. 2.2 (continued)

Estimated world standardized incidence rates in 2015 are 37.0 per 100,000 inhabitants in men 23.6 per 100,000 in women. Through the GLOBOCAN database, the effects of demographic changes on the expected number of new cancer cases in different regions can be estimated (Fig. 2.3). Overall, nearly 1,700,000 new cases are predicted worldwide in 2020.

In contrast to this overall decreasing trend, the incidence of colorectal cancer has appeared to be increasing in male and female young adults under age 50 years in the USA, Canada, Australia, and New Zealand [13–16]. This trend is not described in European data. Reasons for explaining this trend are unclear or speculative. The measure of the role of established risk factors such as smoking, sedentary lifestyle, and diet in this population required dedicated epidemiologic research.

2.3 Survival

Results from the 65 countries involved in the CONCORD program comparing data from population-based registries show wide variations in survival from colorectal cancer (Fig. 2.4). For patients diagnosed with colon or rectal cancer during 2010–2014, 5-year net survival was higher than 60% in Australia, Canada, the USA, Japan, and New Zealand. In Europe, survival was as high in Northern (Denmark, Finland, Iceland, Ireland, Norway, Sweden, the UK), Southern (Italy, Portugal, Slovenia, Spain), and Western countries (Belgium, France, Germany, the Netherlands, Switzerland). For colon cancer, survival ranged from 50% to 60% in Central and South America, in China, and in Eastern Europe such as Estonia, Lithuania, the Czech Republic, Poland, and Slovakia. Survival was less than 50% in Colombia and India. For rectal cancer, survival ranged from 50% to 60% in Central

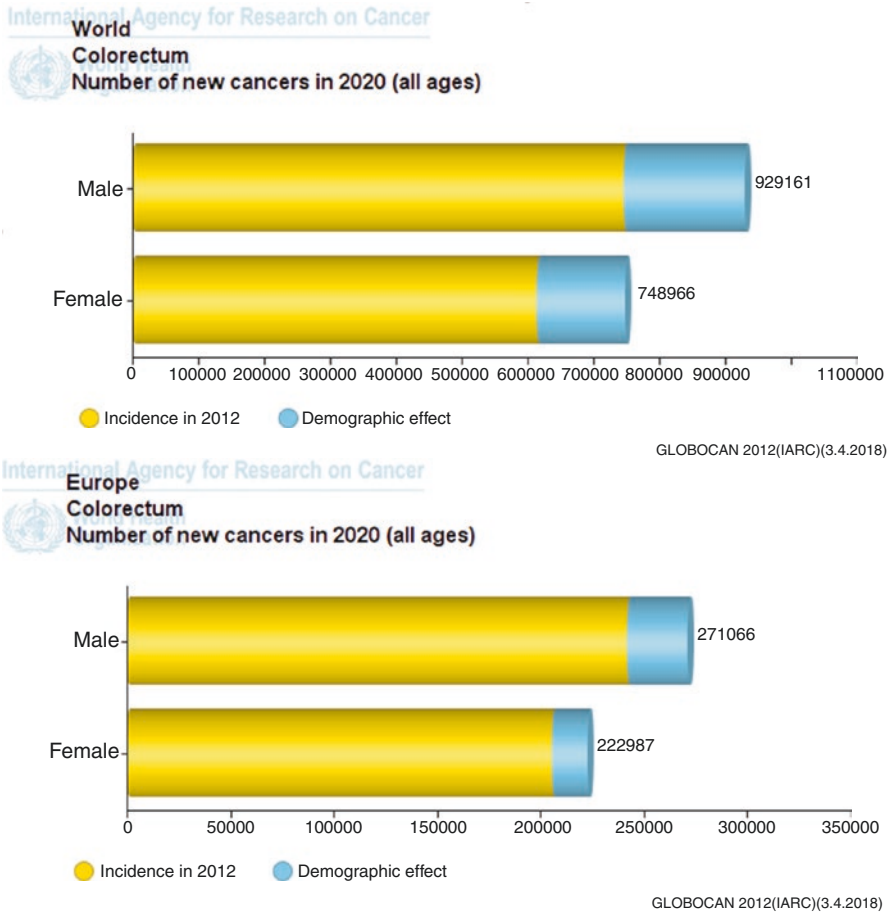

Fig. 2.3 Expected changes in incidence of colorectal cancer between 2012 and 2020, due to demographic changes in Europe and in the World. *GLOBOCAN 2012, International Agency for Research on Cancer IARC. Numbers are computed using age-specific rates and corresponding populations for ten age-groups*

and South America, in China, in Estonia, and in the Czech Republic and was less than 50% in Slovakia, Poland, Croatia, and India.

Through the CONCORD program, a high-resolution study was set up among colorectal cancer cases diagnosed during 1996–1998, in order to explain the difference in 5-year net survival observed between the USA and Europe [4]. Age-standardized survival was quite similar in the USA and Northern and Western Europe (around 54–58%) while lowest in Southern Europe (49%) and in Eastern Europe (42%). The transatlantic difference in survival was attributed to an earlier stage at diagnosis, a higher frequency of surgery, and use of adjuvant treatments in the USA.

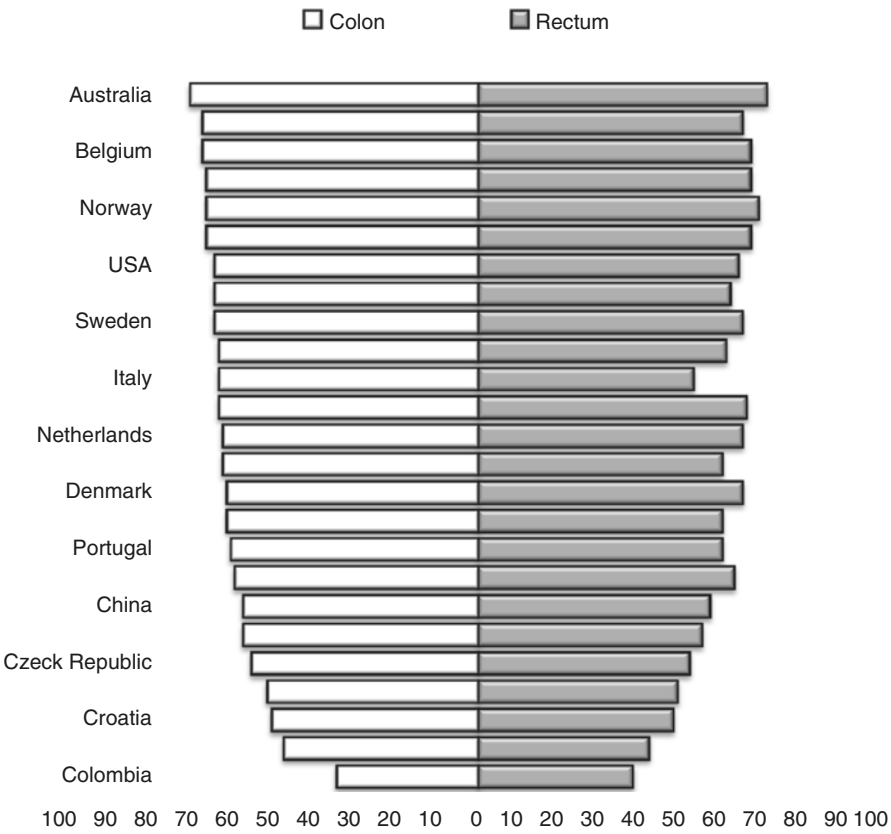

Fig. 2.4 Five-year net survival of colorectal cancer. *Cancer survival 2000–2014, CONCORD-3 program*

Taking into account bowel location, European mean age-standardized 5-year relative survival was 57% after colon cancer and 56% after rectal cancer [8]. There were negligible differences between the sexes for colon cancer, but survival was higher for women than for men for rectal cancer. In all European regions, survival was best for patients aged 15–44 years, roughly constant for those aged 45–64 years, and decreased thereafter for colon cancer, whereas there were smooth age differences up to 74 years with a substantial drop thereafter in rectal cancer.

According to time period, survival varied little between 1995 and 1999 and 2000–2014 [6]. For colon cancer, it mostly flatted, with an increase less than 10% in Canada, Australia, Japan, Estonia, Finland, Lithuania, Sweden, Italy, France, and the Netherlands. It was more than 10% in China, Denmark, Norway, the UK, Portugal, Slovenia, Spain, the Czech Republic, Poland, and Switzerland. For rectal