Colorectal cancer (CRC) is the third most common cancer and the fourth cause of cancer-related mortality worldwide (1). In an attempt to raise awareness on this situation, and to implement preventive measures, March 31st has been established as international colorectal cancer awareness day. Our country, with the Spanish "Alianza para la Prevención del Cáncer de Colon," pioneered in 2008 an institution that brought together scientific and civil societies to pursue this goal (2). A stabilization, even a decrease in the incidence and mortality of this condition has been reported in western countries for the last few years (1), which may be attributed to a number of highly relevant factors. First, a progressive implementation of CRC screening programs, which in our country went from 6 autonomous communities (ACs) and a coverage of 4% of the total population in 2009, to all ACs and a coverage of 38% in 2016 (3,4). Secondly, we are now witnessing advances in the diagnosis and endoscopic management of polyloid lesions because of improved endoscopic equipments, a better understanding of the factors involved in detection (5,6), and the development of clinical practice guidelines establishing quality standards (7-9). Lastly, improvements in surgical procedures (with a widespread use of laparoscopic surgery as opposed to open surgery) and cancer therapies (with the development of new agents for the treatment of CRC) have had a major impact on cure rates and survival (10,11).

However, a focus of concern remains in this encouraging outlook regarding right colon cancer (RCC), whose distinct molecular, clinical, and pathological characteristics may involve a prognosis at variance with that of left colon cancer (LCC).

CRC is thought of as a heterogeneous group of diseases with different genetic and epigenetic changes. Such changes entail a loss or gain of function in the suppressor genes and oncogenes, respectively, which regulate the adenoma-carcinoma sequence. This sequence may develop from 3 molecular pathways: microsatellite instability (MSI), chromosomal instability (CIN), and CpG island methylator phenotype (CIMP). Based on the different embryonic origin of the right colon as compared to the left one, and on their different gene expression, immune activity, and microbiota characteristics, a distinct tumor behavior between these two segments is to be expected (12). RCCs more commonly exhibit a MSI pattern, BRAF mutations, and CIMP, whereas LCCs have CIN, KRAS mutations, and higher EGFR expression. However, these molecular differences are not discriminatory but show a gradual pattern from the rectum to the ascending colon (12,13).

RCCs are more common in women and older individuals, exhibit simmering symptoms such as anemia and weight loss, and have a more advanced stage at diagnosis when compared to LCCs. Furthermore, they are less differentiated, with greater infiltration by lymphocytes, more vascular invasion and affected nodes, and a mucinous pattern more commonly (13).

RCC is also challenging as regards screening and endoscopic diagnosis. The fecal immunological test (FIT), the primary tool for screening programs, is less sensitive for the identification of lesions in the right colon (14,15). The right colon is a difficult-to-clean organ with low visibility areas and higher numbers of flat and serrated lesions, which are more challenging to identify and to treat (16).

All these characteristics may be of prognostic significance, and survival was reported to be shorter for RCC versus LCC in stages III and IV; also, a recent meta-analysis revealed that LCC is associated with a 19% reduction in mortality risk, regardless of disease stage (13,17).

In the present issue of Revista Española de Enfermedades Digestivas (The Spanish Journal of Gastroenterology) A. Cienfuegos et al. analyze the clinical, histopathological, and oncological differences between RCC and LCC in a cohort of patients with stages I, II and III who were managed in one institution (18). RCC was more common in women and older adults, and most commonly presented with anemia. While no differences in preoperative morbidity were reported according to the ASA, POSSUM, and P-POSSUM scales, postoperative complications (28.5% vs. 21%; p = 0.004) and mortality (1.2% vs. 0.2, p = 0.07) were more common for RCC.

RCCs were diagnosed in more advanced stages (stage I 28.3% vs. 34.5%, p = 0.002), with a higher frequency of mucinous phenotype and signet-ring cells, and lower differentiation grade.

Survival was similar in both groups but stage-III LCCs showed a greater tendency to longer disease-free survival at 5 and 10 years (65.6% and 64.4% vs. 73.9% and 70.1%, p = 0.06). Similarly, among patients receiving chemotherapy, those who had LCC tended to have longer disease-free survival times.
This paper highlights the tendency shown by RCCs towards poorer prognoses in stages with loco-regional involvement (stage III). Several factors, reported by authors, may impact prognosis: older age, larvate presentation with anemia, pathological characteristics with poorer prognosis (which may reflect the activation of more aggressive molecular pathways), and greater percentage of postsurgical complications. The fact that this is a single-center study, with homogeneous management, provides plausibility for a biological difference between RCC and LCC; nonetheless, such differing prognoses are likely not the result of location but of varying genetic and epigenetic mechanisms activated by hereditary and environmental factors.

With these characteristics in mind, there is some room for improvement regarding the prognosis of RCC – non-invasive screening, diagnostic, and therapeutic techniques involving the right colon, as well as improved surgical and oncologic management.

Several noninvasive tests have proven more sensitive than FIT for the detection of lesion in the right colon. The identification of fecal ADN (Cologuard) showed a sensitivity of 90% for RCC, as compared to 66% for FIT (19). This test is now available in the US, but high cost is a major barrier for widespread use ($649, www.cologuardtest.com), and increased false-positive results imply increased numbers of screening colonoscopies. Testing for blood biomarkers may also be helpful here. The combination of sCD26 testing and FIT may increase detection rates for proximal advanced adenoma from 7% (FIT) to 35-50% (20). The usefulness of these tests should be verified in larger series, and their primary limitation is, again, an increase in false-positive results.

From an endoscopic perspective it is crucial that endoscopy quality programs be implemented, which should include improvements in colonic cleansing, endoscopist training, and routines (positioning, cecal retroversion, double right colon examination) (21,22). Furthermore, improved resection techniques for precancerous lesions may bring about a reduction in the incidence of RCC.

RCC is diagnosed in older patients, and is more commonly associated with anemia. Therefore, greater attention should be paid to patient optimization during the preoperative period in order to improve surgery outcomes (23).

Finally, improved understanding of the molecular pathways responsible for the development of CRC in general, and of RCC in particular, may result in better therapeutic algorithms and the development of novel anitneoplastic agents. In this respect, the National Comprehensive Cancer Network establishes differences in the treatments of some LCCs and RCCs (24), and the effectiveness of combined immune therapy was recently reported in the management of metastatic CRC with dMMR/MSI-H phenotype (25).

RCC represents a challenge in the management of CRC, currently the subject of extensive research efforts undertaken to improve its screening and therapy, on the way towards individualized, tumor molecular profile-directed medicine, which will have a major impact on the condition in the near future.

REFERENCES


