

COLON CANCER SURGERY REGARDING THE DIFFERENCES IN PROGNOSIS OF RIGHT - AND LEFT-SIDED COLON CANCER

Mario Zovak ^{1,2,3}, Dubravka Mužina Mišić ¹

¹Department of Surgery, Sestre milosrdnice University Hospital Center, Zagreb, Croatia;

²School of Medicine, University of Zagreb, Zagreb, Croatia; ³ Faculty of Medicine, Josip Juraj Strossmayer University, Osijek, Croatia

Summary

Human colon is derived from the embryological midgut and hindgut resulting in the development of the right and left colon respectively. Right-sided and left-sided colon cancers are not differentiated only based on the embryological origin, anatomical position and clinical manifestations, but there are also numerous studies which prove that heterogeneous genotype features exist in right and left-sided colon cancers, with distinguishing types of chromosome and microsatellite instability and gene expression patterns. Accumulating evidence suggests that gut microbiota, which differs in right and left colon, also plays an important role in the development of colon cancer. Although the systemic oncologic treatment has changed recently for disseminated left and right colon cancer, the current surgical treatment of both cancer locations for stages I-III follows the same principles of radical surgical oncology and should be executed in the same manner.

Keywords: right- and left-sided colon cancer; microbiota; radical surgical treatment.

INTRODUCTION

From the early 1990's, oncologists have noticed that patients with right colon cancer are diagnosed in a more advanced stage, have lower response rate to chemotherapy and overall have worse prognosis. Bullfill in early 1990's was the first one to propose left/right colon cancer division, believing that, besides

anatomical localization, there were also other differences in tumor biology and pathophysiology (1). Two big studies from 2008. and 2010. have shown that patient with right colon cancer have higher mortality for all stages, independent of age, sex, race, marital status, tumor stage, tumor size, histologic grade, number of lymph nodes examined, and year of diagnosis (2,3). On the other hand a study from Weiss et colleagues, from 2018, did not confirm that (4). The realisation of right-left colon cancer differences lead to multiple research in various fields. Today we can say that right and left colon cancers differ in embryological development, intestinal microbiota composition, chromosomal and molecular characteristics of colon cancer and response to therapy.

EMBRYOLOGY

Although we see colon as a single organ, the embryological origin of right and left colon differs. During the 3rd week of embryological life, the gastrointestinal tract arises initially during the process of gastrulation from the endoderm of the trilaminar embryo and extends from the buccopharyngeal membrane to the cloacal membrane. During the 4th week foregut, midgut and hindgut arise from the endoderm and extend the length of the embryo. Those three distinct parts of primitive gut tube will contribute to different components of the gastrointestinal tract. From midgut, distal part of duodenum, small intestine, caecum, appendix, ascendent colon and two thirds of transverse colon arise, and left colon, rectum and urogenital sustav arise from hindgut (5,6). The embryological margin of the right and the left colon is on the 2/3 of the transverse colon. More research is needed to elucidate if differences in the embryological origin of colonic epithelium of right and left colon determine differences in susceptibility to environmental carcinogens.

CLINICAL AND PATHOHISTOLOGICAL DIFFERENCES

For clinicians, it is a well known fact that right sided tumors are more often diagnosed in more advanced stage, with prevalence in elderly and female population. On the other hand, left-sided tumors are more common in men and in younger population of patients. Patients with right sided colon cancer have higher incidence of recurrence, with lower disease free- survival, and overall survival (7-10). Pathohistologically, right sided tumors are more often poorly differentiated, mucin-producing and with dense lymphocyte infiltrate

and Crohn like reaction, and are more often associated with peritoneal dissemination (7,11,12). There is also a connection between high protein and meat consumption and left-sided tumor, and high fat and carbohydrate consumption with right sided tumors.

MOLECULAR AND CHROMOSOMAL CHARACTERISTICS AND RESPONSE TO THERAPY

Significant differences exist at the molecular level between right-sided and left-sided colon cancer (13): right-sided colon cancer is associated with MMR, KRAS, BRAF and miRNA-31, and left-sided colon cancer is associated with CIN, p53, NRAS, miRNA-146a, miRNA-147b and miRNA-1288. Distinct pathways dominate right- and left-sided colon cancer considering progression to relapse (14). In the treatment of right-sided colon cancer, FOLFIRI chemotherapy gains the same or even better benefit, in comparison with left-sided colon cancer, but inferior to left-sided colon cancer if FOLFOX chemotherapy is applied. In palliative chemotherapy setting, metastatic left-sided colon cancer shows better response and longer survival. For KRAS wild type, left-sided colon cancer benefits more from cetuximab than right-sided, and advanced left-sided colon cancer has a better response to bevacizumab therapy than right-sided. In new ESMO guidelines from 2018., for metastatic colon cancer, there is a different chemotherapy regimen for right- and left-sided colon cancer: Chemotherapy + anti EGFR antibody is the most appropriate treatment choice for the patient with a RAS and BRAF wild type left-sided colon cancer. For right-sided cancer with RAS and BRAF wild type tumors, chemotherapy + bevacizumab may be the best option (15), (Table 1).

Table 1. Common clinical and molecular characteristics of right- and left-sided colon cancer

| RIGHT-SIDED COLON CANCER | LEFT-SIDED COLON CANCER |
|--|-----------------------------------|
| More common in women | More common in men |
| Microsatellite instability | Chromosomal instability |
| Derived from midgut | Derived from hindgut |
| CIMP+, BRAF mutation | APC, DCC, K-ras, p53 mutations |
| MAPK signaling, serrated pathway | EGFR signaling, Wnt signal |
| Mutagenic CYP450 metabolites | HER1, HER2 amplification |
| Hereditary non-polyposis CRC | Familial adenomatous polyposis |
| Higher intake of fat and carbohydrates | Higher intake of protein and meat |

MICROBIOTA

Microbiota represents the entire collection of microorganisms which colonize the human body. Microbiome comprises of all of the genetic material within a microbiota. Human bowel is one of the most dense populated eco-system on our planet, consisting of 100 trillion microorganism. 70% of that number are bacteria, most of them being anaerobes. Reasons for such an abundance in number of bacteria are slow transit in large bowel and lower influence of pancreatic and biliary secretion in large bowel. Intestinal microbiota is a very complex system- there is a difference between mucosal and intraluminal microbiota, and between microbiota in patients with colorectal carcinoma and normal population. There are also differences in bacteria species in right and left colon (16,17). The question is do changes in cancer-induced mucosal changes attract different bacterial species or certain types of bacteria damage the colonic mucosa and act as carcinogens. Mechanism underlying bacterial contribution in development of colorectal cancer are complex and not fully understood, but there are increasing evidence showing a connection between intestinal microbiota and colorectal cancer (18,19). Some of the mechanism involved in that proces are: induction of chronic inflammatory state, synthesis of genotoxins, production of toxic metabolites and heterocyclic amine activation of dietary carcinogenic compounds (20). A lot of research regarding the role of microbiota in development of colorectal cancer is currently underway, so in the near future we can expect some new findings that will help us to understand the connection between microbiota and colorectal carcinoma.

SURGICAL THERAPY

With all of those differences, are right- and left-sided colon cancer the same disease? Should we treat it differently, and do we need to change the approach to the surgical treatment of colon cancer dependable on tumor localization? Today the surgical treatment of both tumor location follow the same principles of surgical oncology- removal of the tumor with adequate proximal and distal margins and local lymphadenectomy. Two big studies, one from Benedix from 2010 (3), and the other from Moritani showed that after radical surgical treatment of patient with stage I-III colon cancer, there was no significant difference in overall survival and disease free survival between right- and left-sided colon cancer (21). In patient with localized and locally advanced disease, no strong evidence exist which would indicate the change in the surgical treatment strategy.

CONCLUSION

Based on current knowledge, we can say that right- and left-sided colon cancer are two different entities, with the same surgical treatment. For disseminates disease, systemic therapy differs, because the different level of response to chemotherapy. Because of the lower response rate in metastatic right colon cancer, the question is, for oligometastatic disease, is the more aggressive surgical approach appropriate, for example extended hepatectomy for liver metastases, peritonectomy for peritoneal dissemination et cetera. Further studies are needed to answer that question.

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Sažetak

Kirurgija raka debelog crijeva s obzirom na razlike u prognozi između desnostranih i lijevostranih tumora

Ljudsko debelo crijevo nastaje iz embriološkog srednjeg i stražnjeg crijeva, odakle se formira desno- i lijevostrano debelo crijevo. Desno- i lijevostrani zloćudni tumori debelog crijeva ne razlikuju se samo prema embrionalnom podrijetlu, anatomskoj lokalizaciji i kliničkim manifestacijama, nego i prema heterogenim genotipskim značajkama, s različitim vrstama kromosomskih i mikrosatelitskih nestabilnosti te različitim uzrocima ekspresije gena, što je i dokazano brojnim studijama. Sve veći broj istraživanja sugerira da i crijevna mikrobiota, koja je različita u desnom i lijevom debelom crijevu, također igra značajnu ulogu u razvoju zloćudnih tumora debelog crijeva. Iako se sistemno onkološko liječenje za metastatski prošireni karcinom debelog crijeva nedavno promijenilo, ovisno da li je primarna lokalizacija desno- ili lijevostrani karcinom debelog crijeva, sadašnje kirurško liječenje za stadije I-III slijedi principe radikalnog onkološkog liječenja i trebalo bi biti isto za obje lokacije karcinoma debelog crijeva.

Ključne riječi: desnostrani i lijevostrani karcinom debelog crijeva; mikrobiota; radikalno kirurško liječenje.

Corresponding author:
Dubravka Mužina Mišić
e-mail: dubi.muzina@gmail.com