LUPINE PUBLISHERS

Open Access Journal of Oncology and Medicine

DOI: 10.32474/OAJOM.2021.04.000199

ISSN: 2638-5945

Review Article

The Contribution of Liquid Biopsy in Diagnosis and Prognosis of Colorectal Cancer

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Received: August 16, 2021 **Published:** August 24, 2021

Abstract

Colorectal cancer is one of the most leading causes of death worldwide. Furthermore, early-onset colorectal cancer increased the last decades, affecting both males and females below the age of 50, and has lower survival rates. Prevention and detection at early stages contributes to reduced mortality rates. Liquid biopsy is a powerful tool in prevention and prediction of the disease. Liquid biopsy refers to collection of blood and then, detection and study of circulating tumor cells, circulating-tumor DNA as well as exosomes. This review reports major and recent issues of liquid biopsy and the contribution as diagnostic tool in colorectal cancer.

Introduction

Colorectal cancer (CRC) is a malignant neoplasm that develops in tissues of the colon or the rectum. Due to common features present in both types, colon cancer and rectal cancer are often grouped together. CRC is a significant healthcare challenge that affects millions of people worldwide per year. According to the Global Cancer Observatory (GCO), there were over 1.9 million new cases in 2020 [1]. CRC incidence is higher in men for which the age-standardized rate per 100,000 is at 23.4 while the same rate is at 16.2 for women [1]. In Europe, CRC is the third most diagnosed cancer in men after prostate and lung cancer and the second one in women after breast cancer. In fact, there were 191 thousand new cases diagnosed in men and 150 thousand new cases in women for the year 2020 [2]. It is estimated that in Europe, CRC accounted for 12.7% of all new cancer diagnoses [2]. Deaths caused by colorectal cancer reached 935 thousand in 2020 across the world. Among all cancer types, CRC had the second highest number of deaths behind lung cancer [1]. The mortality rate is directly influenced by the existence of an established screening program. Countries that have a long-standing CRC screening program have observed a decline in colorectal cancer incidence over the years. On the opposite, countries that do not provide large-scale screening observe a continuous increase in CRC incidence [3]. Therefore, prevention and early detection is the key to reduce mortality from CRC. It is estimated that 64.7% of the people diagnosed with CRC will survive for 5 years or more. However, if the cancer is diagnosed early enough, while it is still localized, that percentage rises to 90.6% [4]. A concerning issue associated with CRC is that over the last decades there is a rising incidence of early-onset colorectal cancer (EOCRC). EOCRC, which occurs in people below 50 years of age, has been increasing in both men and women across the globe. Patients diagnosed with EOCRC have a higher prevalence of late-stage disease, which has significantly lower survival rate [5]. The driving force behind the increase of EOCRC incidence is not yet fully elucidated but there are potential risk factors that contribute to EOCRC development. Genetic predisposition is not the sole contributor to the development of EOCRC but factors that the individual has been exposed to during their life play integral roles. Obesity, stress, western diet, consumption of red and processed meat and the overuse of antibiotics are among the highest contributors [6].

The development of CRC is slow and 'silent', meaning it does not produce any symptoms during the early stages of the disease. A CRC tumor establishes through a series of histological and genetic changes that accumulate over time. Generally, CRC begins when a polyp in the bowel develops malignant characteristics. Polyps are abnormal tissue growths that are common and benign in nature. As genetic alterations accumulate in the diving cells of the polyps, they can become cancerous [7]. Studies have shown that three main pathways lead to carcinogenesis: chromosomal instability, microsatellite instability and CpG island hypermethylation [8]. From a morphological standpoint, as the genetic alterations accumulate and the polyp grows in size, severe dysplasia turns

into adenocarcinoma. If the malignant tumor is able to undergo neovascularization, cancer cells may be able to migrate and cause metastasis [7]. The first choice of treatment for a patient that has been diagnosed with CRC is surgical removal of the tumor. However, for CRC that has been diagnosed at advanced stages it is more difficult to remove all malignant tissue, especially in the case of metastases. For those who cannot fully benefit through surgery, radiotherapy and chemotherapy are used to suppress cancer cell proliferation and invasion. If chemotherapy is used, the main options include fluorouracil (5-FU) and leucovorin, oxaliplatin or capecitabine. Radiation therapy might be recommended to reduce the size of the tumor so it can be removed surgically later on [9]. Immunotherapy has also found success in treating CRC. The FDA has approved two anti-PD1 antibodies, pembrolizumab and nivolumab, that have shown efficacy in patients with metastatic CRC [10].

Liquid Biopsy in Colorectal Cancer

In recent years, liquid biopsy has become a valuable tool of clinical oncology. This technique entails the collection of a sample of blood or other biological fluids from the individual and subsequent testing to isolate tumor-derived components. It is a powerful technology that enables analyses that can assist with the detection and characterization of the tumor. However, liquid biopsy aids not only in the detection of cancer but can also be used to monitor the response to a given treatment and for the prediction of relapse and metastasis[11]. As a technique, it is an easy, safe and non-invasive alternative to the standard tissue biopsy and has the potential to become a standard tool in oncology. The peripheral blood of a cancer patient contains cells and other components that shed from the primary tumor and have entered the circulation. Thus, liquid biopsy is used to detect and isolate circulating tumor cells (CTCs), circulating free DNA (cfDNA) and circulating tumor DNA (ctDNA) as well as cancer-related exosomes. Furthermore, cancer stem cells (CSCs) constitute a sub-population of CTCs with self-renewal properties [12]. CTCs are cells that have detached from the primary tumor and circulate in the bloodstream. In CRC patients and especially those that are in the early stages of the disease, the number of CTCs is generally low. Thus, detection of CTCs during screening and an early diagnosis might be difficult. However, technological breakthroughs and a novel CTC assay had recent success by demonstrating an 88% accuracy in detecting early-stage CRC [13]. The detection of CTC presence is associated with disease progression and a poor prognosis. Thus, CTC detection can help select CRC patients that are in need of adjuvant chemotherapy after surgical removal of the tumor. In addition, CTC count can provide an estimation of the risk to develop metastasis in the year following curative surgery [14]. In the case of metastatic CRC, the number of CTCs during chemotherapy could predict the clinical outcome and is also indicative of patient survival time [15]. Moreover, it has been demonstrated that the number of CTCs can help predict the response to treatment. A study revealed that CRC patients with high CTC count have a higher risk of progressive disease. This translates to at least 20 percent growth in the size of the tumor and requires adjustment of the chemotherapy regime [16]. Another component that can be detected through liquid biopsy is cfDNA and more specifically the DNA that is released from necrotic or apoptotic tumor cells, ctDNA. The concentration of cfDNA is much higher in CRC patients compared to healthy individuals. The fragments of cfDNA in circulation are usually 180 to 200 base pairs in length and they are metabolized within a few hours. Therefore, detection of cfDNA provides an accurate measure of disease burden [17]. Advanced technologies, such as next-generation sequencing and quantitative PCR, allow for the identification of genetic alterations in ctDNA. Any variations detected in ctDNA are identical to those in the primary tumor and include point mutations, short indels, copy number variations, and gene fusions. Consequently, ctDNA reveals the mutation profile of the tumor and guides the clinician towards providing a personalized treatment [18]. For example, a study has shown that ctDNA that contains mutated KRAS, detected before surgery in CRC patients could be used to predict recurrence. In those patients, adjuvant chemotherapy may be administered after the surgery to reduce the risk of recurrence [19].

Liquid biopsy can also exploit information carried by exosomes. Exosomes are extracellular vesicles, 100 nm in diameter on average, that contain proteins, lipids and nucleic acids. In addition, exosomes are components of the tumor microenvironment and play a signaling role by communicating with the surrounding cancer-associated fibroblasts, mesenchymal stromal cells and cancer stem cells [20]. Cancer-related exosomes have been shown to be involved in the proliferation, invasion and metastasis of cancer cells. For example, exosomes from cancer-associated fibroblast have been shown to promote epithelial-mesenchymal transition in CRC [21]. The detection of certain exosomal noncoding RNAs, such as miRNAs and lncRNAs, has proven to be useful in the diagnosis and prognosis of CRC. A study has shown that high expression of miR-17-5p and miR-92a-3p is detected in the circulating exosomes of CRC patients. The up-regulation of these two miRNAs is correlated with the pathological stage of CRC and they serve as biomarkers of prognostic value [22]. Further examples that highlight the usefulness of miRNAs is that of miR-4772-3p and miR-6803-5p. Downregulation of miR-4772-3p in CRC patients is associated with recurrence, whereas increased expression of miR-6803-5p is a predictor of poor overall survival [23,24].

Cancer Stem Cells in Colorectal Cancer

Cancer stem cells (CSCs) are a subpopulation of tumor cells that are capable of self-renewal and infinite proliferation. CSCs are implicated in tumor initiation, metastasis, resistance to treatment and recurrence [25]. Consequently, CSCs have been extensively studied in a range of cancers, including CRC. Migrating colorectal CSCs play integral roles in metastasis to the liver, which is the most common metastasis in CRC [26]. In addition, colorectal CSCs have demonstrated resistance to chemotherapy and radiotherapy. The mechanisms that drive resistance are unclear but CSC quiescence, enhanced DNA damage repair and high levels of anti-apoptotic proteins could be the main contributors [27]. The colorectal CSCs that have escaped treatment may remain dormant for very long time intervals and their awakening leads to cancer recurrence [28].

Conclusion

The use of appropriate diagnostic tools could be used to reduce the mortality rates of both CRC and EOCRC. Liquid biopsy provides all the appropriate information needed for screening purposes, prediction of treatment response or progress of the disease.

Competing Interests

The authors declare that they have no competing interests.

References

1. Global Cancer Observatory (2020) Colorectal Cancer Fact Sheet.
2. ECIS - European Cancer Information System (2021) Colorectal cancer factsheet in 2020 for EU-27 countries.
3. Cardoso R, Guo F, Heisser T, Hackl M, Ihle P, et al. (2021) Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. The Lancet Oncology 22(7): 1002-1013.
4. Surveillance Epidemiology and End Results (SEER) Program (nd.), Cancer Stat Facts: Colorectal Cancer.
5. Akimoto N, Ugai T, Zhong R, Hamada T, Fujiyoshi K, et al. (2021) Rising incidence of early-onset colorectal cancer-a call to action. Nature Reviews Clinical Oncology 18(4): 230-243.
6. Hofseth LJ, Hebert JR, Chanda A, Chen H, Love BL, et al. (2020) Early-onset colorectal cancer: initial clues and current views. Nature Reviews Gastroenterology & Hepatology 17(6): 352-364.
7. Balchen V, Simon K (2016) Colorectal cancer development and advances in screening. Clinical Interventions in Aging 11: 967-976.
8. Bosman FT, Yan P (2014) Molecular pathology of colorectal cancer. Polish Journal of Pathology 65(4): 257-266.
9. Xie YH, Chen YX, Fang JY (2020) Comprehensive review of targeted therapy for colorectal cancer. Signal Transduction and Targeted Therapy 5(1): 22
10. Ganesh K, Stadler ZK, Cercek A, Mendelsohn RB, Shia J, et al. (2019) Immunotherapy in colorectal cancer: rationale, challenges and potential. Nature Reviews. Gastroenterology & Hepatology 16(6): 361-375.
11. Palmirotta R, Lovero D, Cafforio P, Felici C, Mannavola F, et al. (2018) Liquid biopsy of cancer: a multimodal diagnostic tool in clinical oncology. Therapeutic Advances in Medical Oncology PP.
12. Poulet G, Massias J, Taly V (2019) Liquid Biopsy: General Concepts. Acta Cytologica 63(6).
13. Tsai WS, Nimgaonkar A, Segurado O, Chang Y, Hsieh B, et al. (2018) Prospective clinical study of circulating tumor cells for colorectal cancer screening. Journal of Clinical Oncology 36: (4_suppl).
14. Vacante M, Ciuni R, Basile F, Biondi A (2020) The Liquid Biopsy in the Management of Colorectal Cancer: An Overview. Biomedicines 8(9): 308.
15. Cohen SJ, Punt CJA, Iannotti N, Saidman BH, Sabbath KD, et al. (2008) Relationship of Circulating Tumor Cells to Tumor Response, Progression-Free Survival, and Overall Survival in Patients with Metastatic Colorectal Cancer. Journal of Clinical Oncology 26(19): 3213-3221.
16. Huang X, Gao P, Song Y, Sun J, Chen X, et al. (2014). Relationship between circulating tumor cells and tumor response in colorectal cancer patients treated with chemotherapy: a meta-analysis. BMC Cancer 14(1).
17. Osumi H, Shinozaki E, Yamaguchi K, Zembutsu H (2019) Clinical utility of circulating tumor DNA for colorectal cancer. Cancer Science 110(4): 1148-1155.
18. Shu Y, Wu X, Tong X, Wang X, Chang Z, et al. (2017) Circulating Tumor DNA Mutation Profiling by Targeted Next Generation Sequencing Provides Guidance for Personalized Treatments in Multiple Cancer Types. Scientific Reports 7(1): 583.
19. Nakamura Y, Yokoyama S, Matsuda K, Tamura K, Mitani Y, et al. (2021) Preoperative detection of KRAS mutated circulating tumor DNA is an independent risk factor for recurrence in colorectal cancer. Scientific Reports 11(1): 441.
20. Dai J, Su Y, Zhong S, Cong L, Liu B, et al. (2020) Exosomes: key players in cancer and potential therapeutic strategy. Signal Transduction and Targeted Therapy 5(1): 145.
21. Hu JL, Wang W, Lan XL, Zeng ZC, Liang YS, et al. (2019) CAFs secreted exosomes promote metastasis and chemotherapy resistance by enhancing cell stemness and epithelial-mesenchymal transition in colorectal cancer. Molecular Cancer 18(1): 91.
22. Fu F, Jiang W, Zhou L, Chen Z (2018) Circulating Exosomal miR-17-5p and miR-92a-3p Predict Pathologic Stage and Grade of Colorectal Cancer. Translational Oncology 11(2): 221-232.
23. Liu C, Eng C, Shen J, Lu Y, Takata Y, et al. (2016) Serum exosomal miR-4772-3p is a predictor of tumor recurrence in stage II and III colon cancer. Oncotarget 7(46): 76250-76260.
24. Yan, S, Jiang Y, Liang C, Cheng M, Jin C, et al. (2018) Exosomal miR-6803-5p as potential diagnostic and prognostic marker in colorectal cancer. Journal of Cellular Biochemistry 119(5): 4113-4119.
25. Capp JP (2019) Cancer Stem Cells: From Historical Roots to a New Perspective. Journal of Oncology.
26. Gonzalez-Villarreal CA, Quiroz-Reyes AG, Islas JF, Garza-Treviño EN (2020) Colorectal Cancer Stem Cells in the Progression to Liver Metastasis. Frontiers in Oncology 10: 1511.
27. Zhou Y, Xia L, Wang H, Oyang L, Su M, et al. (2018) Cancer stem cells in progression of colorectal cancer. Oncotarget 9(70): 33403-33415.
28. Chen W, Dong J, Haiech J, Kilhoffer MC, Zeniou M (2016) Cancer Stem Cell Quiescence and Plasticity as Major Challenges in Cancer Therapy. Stem Cells International 1740936.

DOI: 10.32474/OAJOM.2021.04.000199