*ejpmr, 2019,6(9), 166-171*

SJIF Impact Factor 4.897

EUROPEAN JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.ejpmr.com

Review Article

ISSN 2394-3211

EJPMR

# MOLECULAR BIOLOGICAL AND GENETIC MECHANISMS CARCINOGENESIS OF COLORECTAL CANCER (REVIEW)

**Ten Y. V.***

Republican Specialized Scientific-Practical Medical Center of Oncology and Radiology, Uzbekistan.

***Corresponding Author: Dr. Ten Y. V.**

Republican Specialized Scientific-practical Medical Center of Oncology and Radiology, Uzbekistan.

**Article Received on 09/07/2019** **Article Revised on 30/07/2019** **Article Accepted on 20/08/2019**

Colorectal cancer (CRC) is a malignancy that begins in the colon or rectum. Colon cancer (CC) and rectal cancer (RC) are often grouped together because they have many common features. CC is one of the most common types of malignant neoplasms (MN) in the world (Jemal et al., 2018; http://www.cancer.org). According to the international Agency for research on cancer (IARC), more than a million patients with newly diagnosed colon cancer have been registered in the world since 2016. According to Professor S. Winawer (USA), CRC will take the first place in the world in the next 15-20 years in the future, given the current trend of increasing morbidity in various regions of the globe.[3,11-13] Statistics show that more than 50,000 new cases of CRC disease are diagnosed annually in Russia. There is a certain discrepancy in the statistics: in the US the incidence rate is 33.2; in Sweden - 17.8; in the UK - 25.8; in Japan - 15.7; in Senegal - 2.5; in Russia - 12.6; in Uzbekistan - 4.1. As can be seen from the presented, there is a certain territorial variability of indicators, which may be associated with various endogenous and exogenous factors that contribute to the emergence of the disease. In Uzbekistan, problem of CRC also tends to increase, given the annual increase in the number of patients and the increase in morbidity and mortality. According to State Statistics Committee of the Republic of Uzbekistan and the Cancer registry the cancer research center of the MOH of RUz, the incidence rate of CRC 2016 was - 4,1, rectum cancer (RC) is 2.0, while the mortality rate is 1.5 per 100 thousand population, the ratio of mortality to incidence is 0.75. In the General structure of morbidity in Uzbekistan among all malignant neoplasms (MN) CRC takes the 4th place. The one-year mortality rate is 31.2% for the colon and 28.6% for the rectum. In the first year after the diagnosis of metastatic CRC die more 37тыс. patients [http://globacan.iarc/fr//]. High mortality in this category of patients is primarily due to the biological characteristics of the malignant tumor (active mutations, high proliferative activity, tendency to synchronous metastasis, hidden clinical course, etc.), and the lack of programs for early detection of tumors of this localization. In 30% of primary patients at the time of diagnosis, distant metastases are detected and in 50-60% of patients subjected to radical surgical treatment for early stages, during the first year progression of the disease is revealed [Moiseenko V. M., Orlova R. V., 2000; Tyulyandin S. A., 2018]. As can be seen, the relevance of scientific research in this direction is beyond doubt and requires the introduction of new methods of study in terms of molecular biology and genetics, as is now increasingly confirmed and the importance of such studies are in the specificity and sensitivity in the early diagnosis of CRC.

For a possible presentation of the development of the CRC, it is first necessary to know – how does the CRC begin?

**Polyps in the colon or rectum**

Most CRC begin by growing on the inner lining of the colon or rectum growths called polyps. In this case, some types of polyps can eventually turn into cancer (of course, this requires a long period, usually many years), but not all polyps become cancer. The likelihood of a polyp turning into cancer depends on its type. There are 2 main types of polyps:

Adenomatous polyps (adenomas): these polyps sometimes turn into cancer, which is why adenomas are often called a precancerous condition.

Hyperplastic and inflammatory polyps: these polyps are more common, but in General they are not precancerous. Polyps and polyposes in the gastrointestinal tract are observed quite often. They are characterized by a high risk of malignancy, recurrent course, a significant number of complications in the pre - and postoperative periods.

Polyps and polyposes of CRC are becoming a global problem of the XXI century, due to the increasing number of people suffering from this disease. The essence of this disease is the defeat of the colon mucosa with a variety of polyps with a progressive course, which leads to pronounced metabolic disorders, anemia and almost mandatory (70-100%) cancer degeneration.[3,4,6,8,10]

Diffuse colon polyposis (DCP) is characterized by a large number of polyps (sometimes up to several thousand), the defeat of all parts of the intestine, high frequency of mono-or multicentric malignancy. With endoscopic removal of large polyps with a wide base or a short thick leg, which passes 1-2, and sometimes larger arterial vessels, bleeding and perforation of the intestine may occur.[8,10,14,20]

The frequency of CRC varies widely, it depends on both climatic and geographical factors, lifestyle, and dietary characteristics. a special role is also assigned to the hereditary factor that aggravates the course and prognosis of the disease.[1,5,7,8]

Many literature sources devoted to screening and early diagnosis of tumors, and primarily CRC determine that the timely detection of asymptomatic polyps is the main method of preventing the occurrence of CRC.

It should be noted one of the features, so the incidence of colon adenomas (CA) depends on the age, up to 40 years their frequency is 2.1%; 40-49 years – 11.4%; 50-59 years – 23.6%; 60-69 years – 27.9%; 70-79 years – 34.9% and over 80 years – 47.9% [33,36,39]. In most cases, the age ranges from 40 to 69 years, and with Peitz-Jaegers syndrome (PJS) and juvenile polyposis – up to 45 years.

According to the latest report of the American cancer Association[9,15,18,26,29], 10% of people after 45 years have intestinal polyps, of which 1% goes into cancer. The vast majority of researchers believe that colon adenocarcinoma in the vast majority of cases grows from a benign polyp.

Thus, the conducted excursion on the study of intestinal polyposis has long-standing origins, but despite this, the problem remains relevant today. This is primarily due to the high prevalence of this pathology, the increase in the frequency of the disease as the body ages and the high risk of developing CRC, which determines the need for in-depth study of the etiology, pathogenesis of polyposis, for the subsequent development of pathogenetically justified therapy, taking into account modern knowledge of Oncology.

**Pathogenetic aspects of the development of polyps and colon polyposis**

The process of malignant transformation of the polyp into a tumor is multifactorial and multistage, it develops as a result of the accumulation of various genetic mutations by cells. Thus, there is evidence that changes in at least 6-10 genetic factors are necessary for the development of MN. The main cause of the emergence and progression of MN are disorders in the functioning of proto-oncogenes, tumor suppressor genes (anti-oncogenes). Also, in addition, there is a large group of genes-modulators, which are not included in the process of malignant transformation of cells, but contribute to the spread of tumors in the body.[25,27,29,34]

The first descriptions of the CRC carcinogenesis model appeared in the literature in 1988.[31,33,39] An important role is given to the gene ARS (adenomatous intestinal polyposis), which is responsible for the development of Aden in patients with familial polyposis, so its mutation (loss of allele in the 5th chromosome) leads to hyperproliferation of the normal epithelium. In hereditary CRC loss of allele in the 5th chromosome is not observed, and in sporadic non-investigative CRC it is observed in 30-50% of patients. The second stage in the development of CRC (formation of early adenomas) is associated with the mutated colorectal cancer gene MMS (gene involved in the transmission of signal transduction) and DNA methylation.[10,15,19,20]

DNA methylation is necessary for regulation of gene expression and important for metabolism of cytosine nucleotides, hypomethylation complements cellular genetic instability.[11,17,16] Transformation of early adenomas into "intermediate" is caused by RAS genes, mutations of k-RAS and N-RAS are determined in 45-50% of patients with CRC. With adenomas smaller than 1 cm, gene mutations occur in 10% of patients, more than 1 cm – in 50%. The resulting mutations cause disruption of transduction signals from the cell membrane to the cell nucleus.[11,39,43]

It is known that the epithelial cells of the mucous membrane of the colon are normally intensively updated regularly (physiological apoptosis), which is apparently the prevention of various harmful effects, such as: carcinogenic compounds, the environment, metabolic products of food ingredients (fecal masses in the colon). All these, as well as many other unknown factors are the cause of frequent proliferation of mucosa colon polyps of various shapes, sizes and histological structure.

In recent years, great importance is attached to the genetic predisposition to tumors, polyps and CRC, in particular. Family cancer history, the presence of blood relatives of polyps or other lesions of the colon, past operations are high risk factors for CRC. The establishment of a registry of families with one member who suffers a family colon adenomatosis allows to diagnose the disease with relatives in the early stages of development.[22,27,31] Such an approach can significantly reduce the number of patients with developed at the time of diagnosis of CRC from 70 to 3-5%[38,41], as well as determine the risk groups, which would greatly facilitate the early diagnosis of the disease.

Confirmation of this is the family colon adenomatosis (FCA), leading to CRC. In cases of FCA, the disease is found in approximately 40% of the family members. FCA patients are carriers of germinal mutations in the APC gene (5q21-л22).[26,28,35] The occurrence of somatic mutation in another normal allele leads to their inactivation and the appearance of MN. 95% of people

with mutations in this gene, sooner or later develop cancer, and in 60% of cases there is CRC, and in the rest – breast cancer and rye. A large part of the identified mutations in the gene occurs between 169 and codon 1393. In these cases, there is a phenotype of the classic CA – "carpet" covering the intestinal wall with adenomas. Scattered and less classical forms of FCA are associated with mutations in the last 2-3 codons of the 15th exon.

Research by F. M. Kuzminov et al.[79] it was shown that the classical form of SDP TC corresponds to the intervals between codons 437-1249 and 1465-1596, heavy – between codons 1250-1464, weakened – between codons 0-436 and 1597-2843, i.e. at both ends of the ARS gene. According to the authors, when detecting mutations in the intervals characteristic of severe adenomatosis, it is necessary to carry out surgical treatment up to 20-25 years due to the high risk of developing CRC by this age. In the presence of mutations in the interval of the classical form of adenomatosis, active-wait tactics should be followed, and the question of surgery should be solved after 30 years.

Many researchers believe that the transition from normal epithelium to adenoma and from adenoma to CRC is associated with a number of acquired molecular events.[23,34] It turned out that it is necessary at least 5-7 molecular disorders for normal epithelial cells to become malignant. These changes affect important genes such as ARS (5q), DCC/DPC/JV18 (18q), p53 (17p), and K-Ras oncogen (12P). All this indicates the stage of development of Aden and against their background CRC.

A. P. Kostin et al. by studying the genetic material from biopsies and surgical material of patients with CRC, pathogenic mutations were revealed in 31 patients in the ARS gene, in 5 – in the k-Ras gene and in 14 – in the p53 gene, their absence in the BRAF gene in morphologically altered areas of colon. According to the authors, the mutations are not inherited and are localized exclusively in the pathologically altered mucosa of the colon. At the same time, a number of authors believe that mutations in the p53 gene are more often detected at later stages of oncogenesis.

The model of carcinogenesis of CRC was first described in the literature in 1988.[27,41] The ARS gene is responsible for the development of adenomas in patients with familial polyposis. Mutation of this gene (loss of allele in chromosome 5) leads to hyperproliferation of the normal epithelium. With hereditary CRC, allele loss in the 5th chromosome is never observed, with sporadic non-investigative CRC it is noted in 30-50% of patients.

**Diagnostic and prognostic value of molecular biological markers**

Molecular biological markers of oncogenesis are oncospecific components of human cells and tissues (nucleic acids, proteins). The study of their significance in Oncology is necessary for both early diagnosis of tumor growth and prognosis of metastasis. Detection of circulating tumor cells (CTC), determination of localization of metastases, assessment of tumor prevalence, detection of oncogenesis-associated factors (risk factors), preparation of clinical prognosis of the tumor – all these components can be associated with the diagnosis of CRC.

In order to solve the problem of "family cancers", as well as the study of prognostic markers of the effectiveness of anticancer therapy, molecular biological markers of oncogenesis are studied, which are supplemented by the identification of genes of predisposition to cancer to form groups of cancer risk and solve the problem in order to implement the concept of individual targeted cancer therapy.[44,48,51]

From the point of view of molecular biology, cancer is a heterogeneous group of diseases, the main cause of which is a complex of genetic disorders that cause uncontrolled growth of tumor tissues and activate metastasis. Cancer is a clonal evolution of transformed cells, the mechanism of which is the degeneration of normal cells, due to the large number of mutations, inherited and acquired (somatic), associated with tumors suppressor genes.[22]

Knowledge about the Genesis of cancer has opened up fundamentally new opportunities for the development of molecular biology methods for effective diagnosis and treatment.

Currently, in addition to classical morphological methods, it is recommended to include immunocytochemical and molecular genetic methods in the complex of laboratory studies in Oncology, which contribute to the understanding of the mechanisms of tumor Genesis, as well as its prediction, early diagnosis with the detection of metastases, followed by the determination of treatment tactics taking into account the molecular characteristics of the tumor, providing a high result and a favorable prognosis.[6,11]

Thanks to the latest developments in the field of genetics, molecular biology, immunology, biochemistry, as well as the emergence of new diagnostic techniques, it became possible to determine the content of oncospecific substrates in the samples obtained from the patient, which are called molecular biological markers of oncogenesis, they are divided into three groups:

- Protein-associated markers;
- RNA markers;
- DNA markers.

The development of molecular biological methods made it possible to detect specific molecular markers of tumor growth and to develop tests for early diagnosis of tumors on their basis. Early detection of tumors is most often based on the determination of mutations in the genes ***ras***

and ***p53***, the identification of which allows to determine the stage of the tumor process. The early marker of CRC is ARS gene mutations. A broad range of tumors can be diagnosed using protocols activity teliasoneras. Despite the possibilities associated with the use of tumor growth markers, there are still no absolutely reliable methods for early (pre-symptomatic) diagnosis of tumors. Thus, the methods of molecular diagnostics have undoubted promise and high accuracy and allow to detect specific genetic disorders before the formation of morphologically determined tumor.

4 genomic and epigenomic instabilities are described for the development of CRC. Chromosome instability accounts for 85% of CRC cases, microsatellite instability (MSI), CPG islet methylation phenotype (CIMP), and global DNA hypomethylation.[4]

Advances in understanding colorectal carcinogenesis continue to develop through gene expression research by many research groups. Various colorectal subtypes based on gene expression have been reported. These subtypes do not appear to be similar to each other and may result from the use of different patient groups.

*Conclusion.* Review of the literature shows that the problem of CRC remains one of the most important in clinical Oncology, and also requires the search for new modern biological markers confirming the presence of MN, or the beginning of the process.

Epidemiological analysis shows the current trend of increasing morbidity and mortality from this disease both worldwide and in our country.

The studied literature sources show that CRC is the result of accumulation of both genetic and epigenetic changes that turn normal glandular epithelium into invasive adenocarcinoma. Most of the CRE is developing along two different morphological multistep routes, including the classic sequence of adenoma-carcinoma and serrated neoplasia way.

Over the past 25 years, discoveries in the field of molecular biology and genetics have made it possible to study the molecular basis of the process of carcinogenesis of CRC, which gradually cleared up and contributed to the identification of new markers of MN, including CRC.

**REFERENCES**


1. Ananev, B. S., Tsaryuk, V. F., Cancer of the colon. //Encyclopedia of clinical Oncology. Ed. Davidov M. I. - M., 2004; 305-310.
2. Baranov Vs Genetic passport - the basis of individual and predictive medicine. St. Petersburg: N-L, 2009; 528.
3. Vorobev A.V. General issues of screening // Practical Oncology, 2010; 11(2): 53-59.
4. Glants S. Medico-biological statistics// M.: Publishing house "Practice". 1999-459s.
5. Golovkov D. A., Moshurov I. P. et al. Prognostic significance of nm23 protein content in tumors of colorectal cancer patients // Research and practice in medicine, 2016; 3(2): 31-36
6. Delektorskaya V. V., Molecular-biological markers of metastasis and prognosis in colon cancer: Diss. MD.. Moscow, 2007; 247.
7. Clinical and molecular aspects of colorectal cancer: etiopathogenesis, prevention, individualization of treatment. // Prakt. Onkol, 2005; 6(2): 65-70.
8. Carcinogenesis. (ed. by D. G. Zaridze) // Moscow: Scientific world, 2000t; 420C.
9. Kaprin A.D., starinsky V. V. Petrov G. V. Malignant neoplasms in Russia in 2015 (morbidity and mortality). Moscow: mnioi. P. A. Herzen branch of fgbu "NERC" of Minzdrav of Russia, 2016: 250.
10. Kaprin A.D., starinsky V. V., Petrova G. V. State of cancer care to the population of Russia in 2014 Moscow: mnioi im. P. A. Herzen - branch FGBC "NERC" Russian Ministry of health, 2014; 236.
11. Kit O. I., Burtsev D. V., Maksimov A. Yu. Diagnostic efficiency of serological and epigenetic methods of colon cancer screening. Russian journal of gastroenterology, Hepatology, Coloproctology, 2014; 5: 51-57.
12. Moiseenko V. M., Urmancheyeva A. F., Hanson K. P. Lectures on fundamental Oncology. St. Petersburg: Publisher N-L, 2004.
13. Moiseenko F. V. colon cancer Screening// Practical Oncology, 2010; 11(2): 81-87.
14. Novik A. A., Kamilova T. A., Tsygan V. N. and Shevchenko, Under the editorship of J. L. Introduction to the molecular biology of carcinogenesis. Moscow: GEOTAR-MED, 2004.
15. Fingers M. A., Zaletaev D. V. Systems of genetic and epigenetic markers in the diagnosis of cancer. Moscow: Medicine, 2009. p. 384
16. Pisareva E. E., Lyubchenko L. N., Kovalenko S. P., Shamanin V. A. Analysis of mutations in the genes of KRAS and BRAF in colon and rectum cancer in the Russian population. Siberian journal of Oncology. 2016, Vol. 15, 2, pp. 36-41.
17. Pozharissky K. M., Leenman E. E. Prognostic and predictive value of immunohistochemical markers. //Guide to the immunohistochemical diagnosis of human tumors. Ed. Petrov S. V. and Raikhlin N. T; Kazan. Two thousand four
18. Primak N. V., Grishkov S. M., Tsallagova Z. S., Kotlyarov P. M., SOLODKY V. A. mskt colonography in the diagnosis of cancer and colon polyps. Messenger "RNTSRR" 12 10 2012 http://vestnik.rncrr.ru
19. Sergeeva N. S., Marshutina N. V. General ideas about serological biomarkers and their place in Oncology // Practical Oncology, 2011; 12(4): 147-154.
20. Fedyanin, M. Yu., Chmelikova D. N., Serebrisky T. S., Nikol'skaya T. A., Tyulyandin S. A. tumor Stem cells of colon cancer. Malignant tumor, 2015; 4:

71-81.
21. Zimmerman Ya. S. Colorectal cancer: the current state of the problem. Russian journal of gastroenterology, Hepatology, Coloproctology, 2012; 4: 5-16.
22. The traffic V. I., Taralova S. L. Manual of Oncology. Moscow: Medical news Agency, 2008.
23. Chumakov P. M. Protein p53 and its universal functions in a multicellular organism. Advances in biological chemistry, 2007; 47: 3-52.
24. Ahmed FE, Ahmed NC, et al.: Diagnostic microRNA markers to screen for sporadic human colon cancer in stool: I. Proof of principle. Cancer Genomics Proteomics, 2013; 10: 93-113.
25. Allegra CJ, Jessup JM, Somerfield MR, et al.: American Society of Clinical Oncology provisional clinical opinion: testing for KRAS gene mutations in patients with metastatic colorectal carcinoma to predict response to anti-epidermal growth factor receptor monoclonal antibody therapy. J Clin Oncol, 2009; 27: 2091-2096.
26. Amado RG, Wolf M, Peeters M, et al.: Wild-type KRAS is required for panitumumab efficacy in patients with metastatic colorectal cancer. J Clin Oncol, 2008; 26: 1626–1634.
27. Ashktorab H., Schaffer A.A., et al. Distinct genetic alterations in colorectal cancer. PLoS One, 2010г.: T. 5(1): 8879.
28. Azeem S., Gillani S.W., et al. Diet and Colorectal Cancer Risk in Asia--a Systematic Review. Asian Pacific journal of cancer prevention, 2015г.: T. 16(13): 5389-96.
29. Barrier A., Boelle P.Y., et al. Gene expression profiling of nonneoplastic mucosa may predict clinical outcome of colon cancer patients. Diseases of the colon and rectum, 2005г.: T. 48(12): 2238-48.
30. Barrier A., Boelle P.Y., Lemoine A., Flahault A., Dudoit S., Huguier M. Gene expression profiling in colon cancer. Bulletein de l'Academie nationale de medicine, 2007г.: T. 191(6): 1091-1101.
31. Bartel DP: MicroRNAs: genomics, biogenesis, mechanism, and function. Cell., 2004; 116: 281-297.
32. Bhayani MK, Calin GA, Lai SY: Functional relevance of miRNA sequences in human disease. Mutat Res., 2012; 731: 14-19.
33. Binefa G., Rodriguez-Moranta F., Teule A., Medina-Hayas M. Colorectal cancer: From prevention to personalized medicine. World Journal of Gastroenterology, 2014г.; T. 20, 22: 6786-6808.
34. Bode Z., Dong A. M. Cancer Prevention Research-Then and Now. Nature Reviews Cancer, 2010 г.; T. 9, стр. 508-516.
35. Bohnsack MT, Czaplinski K, Gorlich D: Exportin 5 is a RanGTP-dependent dsRNA-binding protein that mediates nuclear export of pre-miRNAs. RNA, 2004; 10: 185-191.
36. Bosman F.T., Carneiro F., Hruban R.H., Theise N.D. WHO Classification of Tumours of the Digestive System. Lyon: IARC, 2010; 978-92.
37. Brenner B., Geva R., et al. Liebermann N. Impact of the 12-Gene Colon Cancer Assay on Clinical Decision Making for Adjuvant Therapy in Stage II Colon Cancer Patients. Value in health, 2016г.; T. 19(1): 82-7.
38. Breuer-Katschinski B., Nemes K., Rump B., Leiendecker B., Marr A., Breuer N., Goebell H. Long-term use of nonsteroidal antiinflammatory drugs and the risk of colorectal adenomas. The Colorectal Adenoma Study Group. Digestion, 2000; г., T. 61(2): 129-34.
39. Bronte G, Silvestris N, et al.: New findings on primary and acquired resistance to anti-EGFR therapy in metastatic colorectal cancer: Do all roads lead to RAS?. Oncotarget, 2015; 6: 24780-24796.
40. Calin GA, Sevignani C, et al.: Human microRNA genes are frequently located at fragile sites and genomic regions involved in cancers. Proc Natl Acad Sci USA, 2004; 101: 2999-3004.
41. Cancer Genome Atlas Network: Comprehensive molecular characterization of human colon and rectal cancer. Nature, 2012; 487: 330-337.
42. Chan A.T., Giovannucci E.L. Primary Prevention of Colorectal Cancer. Gastroenterology, 2010 г., T. 138(6) 2029-2043.
43. Cheetham S, Tang MJ, Mesak F, Kennecke H, Owen D, Tai IT: SPARC promoter hypermethylation in colorectal cancers can be reversed by 5-aza-2'deoxycytidine to increase SPARC expression and improve therapy response. Br J Cancer, 2008; 98: 1810-1819.
44. Chen DL, Wang ZQ, Zeng ZL, et al.: Identification of microRNA-214 as a negative regulator of colorectal cancer liver metastasis by way of regulation of fibroblast growth factor receptor 1 expression. Hepatology, 2014; 60: 598-609.
45. Chen X, Ba Y, Ma L , et al.: Characterization of microRNAs in serum: a novel class of biomarkers for diagnosis of cancer and other diseases . Cell Res., 2008; 18: 997-1006.
46. Church TR, Wandell M, et al., Presept Clinical Study Steering Committee, Investigators and Study Team: Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. Gut, 2014; 63: 317-325.
47. Colorectal Cancer. Estimated Incidence, Mortality and Prevalence Worldwide in 2012. IARC WHO, 2012 г. http://globocan.iarc.fr
48. Coppedè F, Lopomo A, Spisni R, Migliore L.: Genetic and epigenetic biomarkers for diagnosis, prognosis and treatment of colorectal cancer. World J Gastroenterol, 2014; 20: 943-956.
49. Davies H, Bignell GR, et al.: Mutations of the BRAF gene in human cancer. Nature, 2002; 417: 949-954.
50. De Roock W, Bernasconi D, et al.: Effects of KRAS, BRAF, NRAS and PIK3CA mutations on the efficacy of cetuximab plus chemotherapy in chemotherapy-refractory metastatic colorectal

cancer: a retrospective consortium analysis. Lancet Oncol, 2010; 11: 753-762.
51. Denli AM, Tops BB, Plasterk RH, Ketting RF, Hannon GJ: Processing of primary microRNAs by the Microprocessor complex. Nature, 2004; 432: 231-235.
52. DeVita V.T., Lawrence T.S., Rosenberg S.A. Cancer Principles & Practice of Oncology. Philadelphia: Wolters Kluwer, 2015; 2280.