# ANNOTATION

on PhD thesis of Zhandos Amankulov entitled «Optimization of modern radiological methods in diagnosis of colorectal cancer» presented as an application for PhD degree on the specialty «6D110100–Medicine»

**The relevance of research**

According to the International Agency for Research on Cancer (IARC), there is an increase of incidence and mortality rates from colorectal cancer (CRC) worldwide. CRC is the third most frequently diagnosed malignant neoplasm in the world and the fourth leading cause of death of cancer patients, accounting for about 1.4 million new cases per year and about 700,000 deaths (Bray F., 2018), including Asia-Pacific region (Onyoh E.F., 2019).

According to GLOBOCAN 2018 Kazakhstan has the highest rates of incidence and mortality from CRC among the countries of Central Asia and is among the top ten Asian countries with the highest incidence (Bray F., 2018). In Kazakhstan, CRC ranks fourth in the structure of malignant neoplasms and is the third most common cause of cancer death. The incidence of CRC in the country has increased in recent years, while the mortality rates from CRC remain at a high level.

In Kazakhstan, CRC screening has been organized and conducted since 2011 with the use of fecal immunochemical test (FIT). The analysis of the effectiveness of CRC screening in Kazakhstan showed that there is a low level of screening with FIT and a low coverage of endoscopic examination of FIT positives. The main reason for the low endoscopic coverage is the refusal of FIT positive subjects from follow-up colonoscopy (Kaidarova D., 2019). At the same time, endoscopic colonoscopy is the gold standard in the diagnosis of colon neoplasms and endoscopic screening reduces CRC mortality by 68% (Brenner H., 2014). The disadvantages of endoscopic colonoscopy are the invasiveness of the method and the risk of complications, the main of which are hemorrhage and perforation.

An alternative to endoscopic examination of the colon is computed tomographic colonography (CT colonography). Randomized, multicenter studies and meta-analyses have shown that CT colonography diagnoses CRC and colonic polyps with the same high accuracy as endoscopic colonoscopy (De Haan M.C., 2011; Pickhardt P.J., 2012; Shirley L., 2013). The effectiveness of CRC screening using CT colonography depends on many factors, such as participation rate of population, adenoma detection rate, and the low probability of developing severe complications. The behavior of asymptomatic population to screening programs and screening methods has a high geographical and socio-cultural difference. To date, there is no published data on the effectiveness of CT colonography as a primary screening tool in asymptomatic population of Central Asian region.

In recent years, the methods of assessing the risk of developing cancer in CRC screenings programs have been widely discussed. Of particular interest is the test for

natural killer (NK) cells activity in assessing the risk of developing CRC (Tang Y.P., 2020). To date, there are no published data in the literature on the predictive value of this test in the diagnosis of CRC in medium risk asymptomatic population.

The choice of the most effective treatment option of rectal cancer (RC) is based on the results of preoperative radiological visualization. Over the past decade, it has been proven that magnetic resonance imaging (MRI) is the most accurate method for determining the stage of primary RC (São Julião G. P., 2017). Most of the studies conducted to assess the diagnostic accuracy of MRI in determining the stage of RC were carried out on the high-field MRI devices with a magnetic field strength of up to 1.5 Tesla (T). MRI at a higher magnetic field (3T and higher) can improve the diagnostic accuracy of MRI in staging of RC, since 3T MRI, theoretically, has at least a twofold increase in the signal-to-noise ratio compared to MRI devices with a lower magnetic field.

It follows from the above that conducting a study on using modern radiological methods and new predictive laboratory test in the diagnosis of CRC will give new results that will optimize the National CRC screening program.

**The aim of the study** is to improve the diagnosis of colorectal cancer using modern radiological methods.

**Research objectives:**

1. To study the incidence and mortality rates from colorectal cancer in Kazakhstan in a ten-year period covering 5 years before and 5 years after the introduction of the National CRC screening Program with the identification of geographical regions and age groups with high incidence and mortality rates.

2. To evaluate the diagnostic value of computed tomography colonography in the early diagnosis of colorectal cancer in geographical region of Kazakhstan with high rates of incidence and mortality from colon cancer.

3. To determine the diagnostic value of natural killer cells activity test as a tool for forming the high-risk group for developing colorectal cancer in asymptomatic population.

4. To study the diagnostic value of very high-field magnetic resonance imaging in loco-regional staging of rectal cancer and prognostic capabilities of the method in detection of histological type.

**Objects of study:**

- 26,422 registered cases of colorectal cancer and 15,835 deaths from colon cancer taken from the database of the Electronic Register of Cancer Patients and the Statistics Committee of the Ministry of National Economy of the Republic of Kazakhstan;

- 593 study participants who underwent CT colonography as a primary method of screening for colorectal cancer;

- blood samples of 354 participants in colorectal cancer screening for enzyme immunoassay to determine the activity of NK cells;

- data of high-field multiparametric magnetic resonance imaging of 86 patients

with rectal cancer.

**Subjects of the study:**

- the changes of standardized incidence and mortality rates from colorectal cancer over a ten-year period;

- the frequency of detection of colorectal cancer and advanced adenoma in asymptomatic population during CT Colonography screening for CRC;

- the level of interferon-gamma (IFN-$\gamma$) produced by NK cells;

- correlation between the data of high-field magnetic resonance imaging and morphological examination.

**Study methods:**

- radiological (CT colonography, high-field magnetic resonance imaging); endoscopic (colonoscopy); laboratory (stimulation of NK cells with subsequent ELISA analysis); morphological (histological examination); statistical analysis.

**Scientific novelty:**

The epidemiological aspects of incidence and mortality from colorectal cancer in Kazakhstan were studied for a ten-year period covering 5 years before and 5 years after the implementation of the CRC screening program.

For the first time, screening of asymptomatic population for early diagnosis of colorectal cancer using computed tomography colonography was carried out in the region of Kazakhstan with high rates of incidence and mortality from colon cancer.

For the first time, the association between the activity of natural killer cells and the risk of developing colorectal cancer in an asymptomatic population was studied.

The diagnostic significance of 3 Tesla magnetic resonance imaging in loco-regional staging of rectal cancer and predicting the histological type of tumor is determined.

**The main points for defense:**

Standardized incidence rates for colorectal cancer for the period 2006-2015 increased with a decrease in mortality rates, with the highest rates in the Northern regions of Kazakhstan and Almaty city, with a prevalence in the age group over 50 years.

Computed tomography colonography is a highly informative method for diagnosis of colorectal cancer with high diagnostic accuracy in the detection of colorectal neoplasia, with high rates of voluntary participation of asymptomatic population in the primary screening and follow up.

Natural killer cells activity has a high predictive value in colorectal neoplasia with the possibility of forming the high-risk group for developing colorectal cancer in asymptomatic population.

3 Tesla magnetic resonance imaging is a highly informative method in loco-regional staging of rectal cancer with the ability to determine the histological type of tumor.

**Practical significance of the work:**

The use of CT colonography as a primary method for early detection of colon

cancer improves the diagnosis of colorectal cancer and colonic advanced adenomas.

Determination of natural killer cells activity allows forming a group of high risk of colorectal cancer and progressive adenomas in asymptomatic population.

High-field magnetic resonance imaging allows determining the loco-regional spread of rectal cancer with high diagnostic accuracy with the determination of the histological type of tumor, which is important in the choice of treatment.

**Conclusions:**

1. From 2006 to 2015, the incidence of CRC in Kazakhstan increased by 14.2%, with a decrease in mortality rates by 12.2% ($p=0.001$) with a tendency to improve rates after the introduction of National colorectal cancer screening program, with the detection of high rates in the Northern regions of Kazakhstan and in Almaty city and the prevalence of incidence in population over 50 years of age (88% of all registered cases of CRC).

2. CT colonography has high specificity (97.4%), negative predictive value (99.7%) and accuracy (97.1%) in the diagnosis of colorectal cancer. The use of CT colonography improves the diagnosis of colorectal cancer (3.0%, 18/593) and advanced adenomas (7.1%, 42/593) in the asymptomatic population of a geographic region with high rates of incidence and mortality from colon cancer.

3. Natural killer activity is statistically significantly lower in patients with CRC (140 pg/ml, $p<0.05$) and progressive adenomas (392.0 pg/ml), with a high negative predictive value (96.4%) and 73.4 % diagnostic accuracy in diagnosis of colorectal neoplasia, which allows the method to be used to form a high-risk group for developing colorectal cancer for subsequent in-depth diagnosis.

4. High-field multiparametric magnetic resonance imaging is a highly informative method for assessing the local prevalence of rectal cancer with high specificity (94.1%) and sensitivity (87.9%) in assessing the T stage of rectal cancer, with high sensitivity (83.4%) and specificity (80.4%) in the assessment of stage N and the possibility of predicting the histological types of the tumor ($p\leq0.05$).

**The personal contribution of the doctoral candidate:**

All the results presented in this dissertation and have a scientific novelty were obtained by the author personally. The author personally conducted all radiological methods, including CT colonography and magnetic resonance imaging, as well as statistical analysis of data.

**Approbation of the research:**

The main provisions and results of the dissertation were reported at:

1. VI Congress of Oncologists and Radiologists of Kazakhstan. Almaty, Kazakhstan, April 27-28, 2017.

2. XV Conference of Young Medical Scientists of the CIS countries «Modern problems of theoretical and clinical medicine». Almaty, Kazakhstan, May 19, 2017.

3. XII Scientific and Annual Meeting of the European Society of Coloproctology. Berlin, Germany, September 20-22, 2017.

4. 101st Congress of the Russian Society of Radiologists and Roentgenologists. Moscow, Russia, November 8-10, 2017.

5. XIV International Scientific and Practical Conference of Students, undergraduates, postgraduates, doctoral students and young scientists «Youth, science and Innovation», Aktobe, Kazakhstan, 2018.

6. 5th International Scientific and Practical conference of Young scientists «Science and Medicine: a modern view of youth» within the framework of the International Conference «Akanov readings: topical issues of medicine and healthcare». Almaty, Kazakhstan, April 19, 2018.

7. X Congress of Oncologists and Radiologists of the CIS and Eurasia countries. Sochi, Russia, April 23, 2018.

8. II Scientific and Practical conference of specialists in computed and magnetic resonance imaging: «The role of CT and MRI research in oncology and pediatrics». Almaty, Kazakhstan, June 23-24, 2018.

9. XI All-Russian National Congress of Radiologists and Radiation Therapists «Radiology-2017». Moscow, Russia, May 23-25, 2017.

10. Korean Congress of Radiology. Seoul, Korea, September 12-15, 2018.

11. European Congress of Radiology. Vienna, Austria. February 27 – March 3, 2019.

12. 2nd International Scientific Congress of Russian and Foreign Scientists «Modern research in the humanities and natural sciences». Taganrog, Russia, October 18, 2019.

13. International Scientific and Practical Conference «Oncology of Kazakhstan: yesterday, today, tomorrow», Almaty, Kazakhstan, December 10-11, 2020.

14. Extraordinary Congress of oncologists and radiologists of the CIS and Eurasian countries named N.N. Trapeznikov, dedicated to the 25th anniversary of ADIOR. Moscow, Russia, April 6-9, 2021.

15. VIII Congress of Oncologists and Radiologists of Kazakhstan with international participation. Turkestan, Kazakhstan, October 14-16, 2021.

16. Expanded Meeting of the Department «Visual diagnostics» of Kazakh National Medical University named after S.D. Asfendiyarov. Protocol No. 2 from September 7, 2021.

**Information about the implementation:**

Methods of virtual colonoscopy using a low-dose protocol, and high-field magnetic resonance imaging have been introduced into the clinical practice of the Department of Radiology and Nuclear Medicine at Kazakh Institute of Oncology and Radiology, as well as in the Zhambyl and Atyrau regional cancer dispensaries.

**Publications:**

The author has published a total of 27 scientific articles, including 16 scientific papers on the topic of the dissertation:

- in journals recommended by the Committee for Quality Assurance in the

Field of Education and Science of the Ministry of Education and Science of the Republic of Kazakhstan - 4; in the international peer-reviewed scientific journals indexed in the Web of Science Core Collection, Science Citation Index Expanded database or in the Scopus database - 3; in the materials of international conferences - 7; in other scientific publications - 2.

«Method for diagnosing colon cancer» patent for an innovative invention was obtained: Innovation patent number: 30740 from 25.12.2015.

Methodological recommendations have been developed and published: «Virtual colonoscopy» //Almaty, 2020.

**Structure and scope of the dissertation work**

The dissertation is presented on 138 pages of computer text, consists of an introduction, a review of the literature, materials and methods, own results, discussion, conclusion, and a list of references from 253 sources, appendices. The work is illustrated with 25 figures and 21 tables.