ANNOTATION
on PhD thesis of Ainakulova Akmaral Serikovna entitled
"Modern radiology methods in the early diagnosis of breast cancer " presented as an application for the PhD degree on the specialty 6D110100 – «Medicine»

The relevance of research

Breast cancer (BC) is the most common malignant neoplasm, both worldwide and in Kazakhstan (Sung H., 2021).

According to GLOBOCAN (2020), the incidence of breast cancer in the world has reached more than 2.2 million new cases per year, which is 11.7% of all new cases of cancer among both sexes, the death rate is more than 680 thousand women per year (Sung H., 2021).

In Kazakhstan, about 4,000 new cases and 1,400 deaths from breast cancer are registered annually (Kaidarova D.R., 2019). In the structure of oncological morbidity and mortality among women, breast cancer ranks first (Kaidarova D.R., 2019).

For early diagnosis of breast cancer, since 1977, many countries (USA, Canada, Great Britain, Sweden, Germany, France, etc.) have introduced mammographic screening programs (Tabar L., 2019; Duffy S., 2020; Zielonke N., 2020; Tabar L., 2021).

In Kazakhstan, since 2008, target groups have been approved for screening studies for the early detection of malignant tumors, including target groups for early diagnosis of breast cancer. As in many developed countries, screening in the Republic of Kazakhstan is carried out using the mammographic method of research using additional methods of radiology diagnostics in complex differential diagnostic cases (Order of the Ministry of Health of the Republic of Kazakhstan No. 685 dated November 10, 2009).

Despite the improvement in five-year survival rates for breast cancer, the detection rate of early stages is 31.7%, and the rates of detection of breast cancer in the later stages remain stable (DeSantis C., 2015; Berumen A., 2018; Ginsburg O., 2020; Mutebi M., 2020). With timely diagnosis of breast cancer at an early stage, the complete recovery of patients is up to 95% (Ilbawi A., 2018; McCormack V., 2020; Rositch A., 2020; Stoltenberg M., 2020). The detection of breast cancer in the later stages is influenced by a number of factors: the participation of women in the screening program and the difficulties in the differential diagnosis of breast cancer.

In the diagnosis of breast cancer, radiology research methods are important: mammography, ultrasound, magnetic resonance imaging (Fallenberg E., 2017; Monticciolo D., 2017; Katzen J., 2018; Sorin V., 2018; Emami L., 2021; Zielonke N., 2021).

Mammography has some limitations in the diagnosis of pathological changes in dense breast (Melnikow J., 2016; Geisel J., 2018; Bakker M.F., 2019). According to statistics, breast cancer is most common in women aged 40 to 60 years (Melnikow J., 2016). At this age, women have a predominance of fibroglandular tissue in the mammary gland over adipose tissue, which makes it difficult to diagnose breast diseases (Melnikow J., 2016).

The sensitivity of mammography depends on the age of the woman, the density of the mammary glands, the quality of the study, and, according to different authors, ranges from 60% to 95% (Mandelson M., 2000; Kolb T., 2002; Nikolova N., 2007; Checka C., 2012; Friedewald S., 2018). Up to 35% of all invasive malignant tumors are not detected by mammography at the age of 40–49 years, compared with 10% at 50–59 years of age (Hubbard R., 2011; Moss S., 2015; Duffy S., 2020).

Ultrasound is an informative, non-invasive, affordable research method for diagnosing breast pathology. The sensitivity of ultrasound in the diagnosis of breast cancer is 73-93%, the specificity is 62-88% (Brem R., 2015; Guo R., 2018; Ding Z., 2021). However, the method has limitations: the subjectivity of image interpretation, low information content in fatty involution of the mammary glands, the difficulty in assessing intraductal tumors and in retromammary localization of lesions (Scoggins M., 2015; Weigert J., 2017; Liu G.2019).

Magnetic resonance imaging is an informative method for diagnosing breast cancer, the sensitivity of which, according to different authors, is 75-100%, and the specificity is 53-98% (Sung J., 2016; Mann R., 2019; Partovi S., 2020). Along with the advantages of the method, MR mammography is a relatively expensive and less accessible method for routine use in the diagnosis of breast cancer (Mann R., 2020).

Scientific and technological progress contributes to the continuous development of new medical technologies. In recent years, modern methods of medical imaging of the mammary glands have been introduced into clinical practice.

One of these methods is contrast enhanced spectral mammography. Since 2011, more than 50 scientific studies have been conducted to research the possibilities of contrast enhanced spectral mammography in the diagnosis of breast cancer (Suter M., 2020).

In the published literature, there are data on the sensitivity and specificity of contrast enhanced spectral mammography in the diagnosis of breast cancer, which amounted to a sensitivity of 85% (62-96%) and a specificity of 66% (50-83%) (Diekmann F., 2011; Dromain C., 2012; Brandan M., 2016; Luczyńska E., 2016; Tohamey Y., 2018; Xing D., 2019; Clauser P., 2020; Sogani J.,2021). All studies were conducted with the participation of a different number of patients from 18 to 235.

Moreover, in the available literature there are the results of studies devoted to a comparative analysis of the possibilities of contrast enhanced spectral mammography with other radiology methods for diagnosing the mammary glands, such as mammography, ultrasound diagnostics, and magnetic resonance mammography.

To date, the issues of using contrast enhanced spectral mammography in the diagnosis of breast cancer in women with dense breast are being discussed (Jochelson M., 2013; Badr S., 2014; Fallenberg E., 2014; Li L., 2017; Mori M., 2017).

However, there is no consensus decision on the use of this method in the diagnosis of breast cancer, due to the lack of multicenter randomized controlled trials.

Contrast enhanced spectral mammography is one of the new methods of radiology diagnostics, the study of the possibilities of which must be continued due to the ambiguous results on the sensitivity and specificity of the method in the diagnosis of breast cancer according to different authors. The place of this method in

the early, clarifying and differential diagnosis of breast cancer has not been fully determined.

Further research on the possibilities of contrast enhanced spectral mammography is needed to optimize the diagnosis of breast cancer.

The aim of the study is the improvement of early diagnosis of breast cancer with the use of contrast enhanced spectral mammography.

Object of the study: for 2018-2021 in the Department of Radiation Diagnostics of the Kazakh Research Institute of Oncology and Radiology, a mammographic study was conducted in 1968 women according to clinical indications. According to the results of a mammographic study, 374 patients revealed changes in the breast that require differential and clarifying diagnostics. All 374 patients underwent contrast spectral enhanced mammography with delayed image.

Subject of the study: correlation between the data of mammography, standard contrast enhanced spectral mammography and contrast spectral mammography with delayed image in the diagnosis of breast cancer in comparison with the results of a pathological study.

Research methods: radiological (contrast enhanced spectral mammography); morphological (histological examination); statistical analysis.

The research objectives are:

1. To develop a method for diagnosing breast cancer using contrast enhanced spectral mammography.

2. To study radiology semiotics of breast pathological changes with the determination of pathognomonic signs of breast cancer on contrast enhanced spectral mammography with delayed image.

3. To evaluate the possibilities of contrast enhanced spectral mammography with delayed image in the diagnosis of breast cancer.

4. To optimize the algorithm for early diagnosis of breast cancer using contrast enhanced spectral mammography.

Scientific novelty:

For the first time, a method for diagnosing breast cancer using delayed image with contrast enhanced spectral mammography has been optimized (**patent RK, Eurasian patent**).

For the first time, the dynamic characteristics of breast cancer were determined using contrast enhanced spectral mammography (**article in the journal Web of science Core Collection and Scopus Q2**).

For the first time, the diagnostic capabilities of contrast enhanced spectral mammography with delayed image in the diagnosis of breast cancer were determined (**article in the journal Web of science Core Collection and Scopus Q2**).

The main provisions to be defended:

The developed method using contrast enhanced spectral mammography with delayed image improves the diagnosis of breast cancer.

Contrast enhanced spectral mammography with delayed image can detect pathognomonic signs of breast cancer.

Contrast enhanced spectral mammography with delayed image is a highly sensitive and specific method for diagnosing breast cancer, which reduces the number of invasive examinations.

The practical significance of the research:

The use of contrast enhanced spectral mammography with delayed image will improve the diagnosis of breast cancer.

Contrast enhanced spectral mammography with delayed image will allow to assess the multifocality, multicentricity, synchrony of breast cancer, which is important in the timely choice of an adequate treatment method.

Conclusions:

1. Contrast enhanced spectral mammography with delayed image allows assessment of the degree of accumulation (2091 (P25=2061; P75=2138)), quantitative characteristics (-16.0 (P25=-31.5; P75=-3.0)), the type of contrasting of malignant breast lesions, which statistically significantly prevails over the capabilities of standard contrast enhanced spectral mammography in the diagnosis of breast cancer (U=1029.0; Z=-9.515; p<0.001).

2. Contrast enhanced spectral mammography with delayed image revealed pathognomonic signs of breast cancer, characterized by mass lesion (64.2%); irregular shape (76%) and spiculated contours (56%) against the background of A and B breast density; accumulation of the contrast agent (100%) followed by washout into the delayed phase (80%) (p<0.001).

3. Contrast enhanced spectral mammography with delayed image has a high sensitivity of 96%, specificity of 91.6% and an accuracy of 95.5% in the diagnosis of breast cancer, which is statistically significantly higher than standard contrast enhanced spectral mammography by 3.2%, 23.7%, 14 .6% and mammography by 7.5%, 40.3%, 31.9% - respectively (p<0.001).

4. The developed algorithm for diagnosing breast cancer using contrast enhanced spectral mammography with delayed imaging will improve early and clarifying diagnosis with the exclusion of breast cancer (33.2%) with a decrease in the number of invasive interventions (p<0.001).

Practical recommendations:

1. Contrast enhanced spectral mammography with delayed image should be performed when pathological changes in the mammary glands are detected due to mass lesion, a architectonics disturbance, asymmetry, requiring differential diagnosis, which will reduce the number of unreasonable invasive examinations.

2. With established breast cancer, contrast enhanced spectral mammography should be performed to assess multifocality, multicentricity, and synchrony of the process, which is important in choosing treatment tactics.

Personal contribution of the doctoral candidate: all the results presented in the dissertation work and having scientific novelty were obtained by the author personally. The author personally carried out the technique of contrast spectral mammography, as well as a complete statistical analysis of the data. The method of contrast spectral mammography has been introduced into the Department of Radiaology Diagnostics at the Multidisciplinary Center for Oncology and Surgery East Kazakhstan region (implementation act No. 33-2019). The author received a

patent of the Republic of Kazakhstan for an innovative invention "Method for diagnosing breast cancer" No. 33709, which was introduced into the practice of the radiology department of JSC "Kazakh Research Institute of Oncology and Radiology" (implementation act No. 56-2019, No. 23 -2021). The author received a Eurasian patent for the invention "Method for diagnosing breast cancer" No. 036245.

Approbation of the research:

The main provisions and results of the dissertation are reported on:

1.   International Congress of Radiologists. Bishkek, Kyrgyzstan, March 2019.

2.   VIII Eurasian Radiological Forum. Nur-Sultan, Kazakhstan, July 2019.

3.   Korean Congress of Radiology and Annual Delegate Meeting of the Korean Society of Radiology. Seoul, South Korea, September 2019.

4.   European Congress of Radiology. Vienna, Austria, July 2020.

5.   Korean Congress of Radiology and Annual Delegate Meeting of the Korean Society of Radiology. Seoul, South Korea, September 2020.

6.   Competition of young scientists within the framework of the extraordinary XII Congress of oncologists and radiologists of the CIS and Eurasian countries named N.N. Trapeznikov, dedicated to the 25th anniversary of the 1st Congress, Russia, April 2021 (2nd place diploma).

7.   At the extended meeting of the department "Visual Diagnostics", protocol No. 4, dated 29.10.2021.

Publications:

The author published a total of 21 scientific articles, of which 8 are on the topic of the dissertation, 6 are in the List of Publications, in an international peer-reviewed scientific journal that has an impact factor according to JCR (indexed in the Web of science Core Collection database, science Citation Index Expanded , CiteScore percentile indicator of at least 25 in the Scopus database) - 1, in the materials of foreign international conferences - 3, in other scientific publications - 1, patents - 2.

1.   Ainakulova A., Zholdybay Zh., Kaidarova D., Inozemtceva N., Gabdullina M., Zhakenova Zh, Panina A., Toleshbayev D., Amankulov J. Contrast-enhanced spectral mammography without and with a delayed image for diagnosing malignancy among mass lesions in dense breast // Contemporary Oncology/Współczesna Onkologia. – 2021. – Vol.25, No. 1. – P. 17-22, (percentile 54, Q2 - WoS, Scopus);

2.   Ainakulova A.S., Kaidarova D.R., Zholdybay Zh.Zh., Inozemtseva N.I., Gabdullina M.O., Karibaev I.M. The role of modern imaging techniques in additional visualization of breast cancer screening: a literary review // Siberian journal of oncology. – 2021. – No. 4. – P. 99-107 (percentile 12, Q4 - Scopus);

3.   Ainakulova A.S., Zholdybay Zh.Zh., Saktaganov M.I., Amankulova Zh.B., Suleimenova D.M., Gabdullina M.O. The role of contrast enhanced spectral mammography in the diagnosis of breast cancer (literature review) // Vestnik UDP RK. – 2020. – No. 3 (80). – P. 65-69;

4.   Ainakulova A.S., Kaidarova D.R., Zholdybay Zh.Zh., Zhakenova Zh.K., Inozemtseva N.I., Suleimenova D.M., Gabdullina M.O., Gunyasheva E.M., Musakhanova A .S., Moldazhanova S.B. Comparative analysis of contrast enhanced mammography and breast MRI (literature review) // Bulletin of KazNMU. – 2020. – No. 2. – P. 135-139;

5.   Ainakulova A.S., Zholdybay Zh.Zh., Zhakenova Zh.K., Inozemtseva N.I. Diagnostic value of contrast enhanced spectral mammography in "BI-RADS IV" mammographic lesions // Bulletin of KazNMU. – 2019. – No. 4. – P. 90-93;

6.   Suleimenova D.M., Zholdybay Zh.Zh., Ainakulova A.S., Amankulova Zh.B., Isaeva A.M. Breast cancer in young women: adapted imaging recommendations // International Journal of Applied and Fundamental Research. – 2021. – No. 3. – P. 46-52;

7.   Pat. 33709 Republic of Kazakhstan, IPC A61B 6/00 (2006.01), A61K 49/04 (2006.01), G01N 33/574 (2006.01). A method for diagnosing breast cancer / Ainakulova A.S., Zholdybai Zh.Zh., Zhakenova Zh.K., Inozemtseva N.I.; applicant and patentee Kazakh Research Institute of Oncology and Radiology, Ainakulova A.S., Zholdybay Zh.Zh., Zhakenova Zh.K., Inozemtseva N.I.; dec. 2017/0979.1; publ. 21.10.2019.

8.   Pat. 036245 Eurasian Patent Organization, IPC A61B 6/00 (2006.01), A61K 49/04 (2006.01). A method for diagnosing breast cancer / Ainakulova A.S., Zholdybai Zh.Zh., Zhakenova Zh.K., Inozemtseva N.I.; applicant and patentee Kazakh Research Institute of Oncology and Radiology, Ainakulova A.S., Zholdybay Zh.Zh., Zhakenova Zh.K., Inozemtseva N.I.; dec. 201800379; publ. 16.10.2020.

Structure and scope of the dissertation work

The dissertation work is presented on 112 pages of a computer text, consists of an introduction, a literature review, a description of the material and research methods, own research results, a discussion of the results, conclusions, a list of references from 202 sources. The work is illustrated with 37 figures and 10 tables.