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RADIOMICS AND RADIOGENOMICS OF PROSTATE CANCER (LITERATURE REVIEW)

Imaging plays an important role in the detection, diagnosis and staging of cancer, as well as in treatment planning and therapeutic response assessment. In recent years, there has been considerable interest in the extraction of quantitative information from images in order to obtain more complete information about the phenotype of the neoplasm image. Research has demonstrated that deeper analysis can reveal new imaging features that can provide useful diagnostic and prognostic information as well as data on tumor size and volume. In addition, imaging phenotypes can be associated with genomic data, which contributes to understanding their biological basis, improving the accuracy of predicting clinical outcomes. The aim of this review is to provide an update on the application of radiomics-based approaches and to discuss the potential role of radiogenomics in prostate cancer.

Keywords: prostate cancer, radiomics, radiogenomics.

Epidemiology of prostate cancer. Death from cancer is the second leading cause of death in the world. In 2018, 9.6 million people died for this reason. Cancer is the cause of almost one in six deaths in the world.

Prostate cancer (PCa) is one of the most common malignant diseases in men. About 1.6 million cases of prostate cancer are registered annually in the world, and 366 thousand men die annually from this pathology. In connection with these data, more and more attention has recently been paid to the diagnosis and treatment of this pathology, both in the Russian Federation and abroad. High incidence rates of prostate cancer are noted in the USA, Canada and in a number of European countries, where it comes out on top in the structure of cancer in men. According to the National Cancer Institute of the USA, from 1986 to 1992. the incidence of prostate cancer among the white population increased by 108% and by 102% - for African Americans [1]. The global incidence of prostate cancer has increased in most countries, and this increase has been most pronounced in Asia, Northern and Western Europe [13]. In the Russian Federation, the incidence of prostate cancer is constantly increasing. In the structure of the incidence of malignant neoplasms in the male population of Russia, prostate cancer takes the second place, which corresponds to 14.5% of all diagnosed neoplasms in men.

In the last decade, an increase in life expectancy has been observed throughout the world [3]. From 2000 to 2015, male life expectancy increased from 64.1 years to 69.1 years worldwide [37]. This poses serious problems for global health, as some diseases, such as cancer, tend to develop with age [36]. It was found that 5% of men under the age of 30 and 59% of men over 79 years of age had PCa at autopsy [21]. It is a common and serious medical condition that poses serious challenges to the health care system.

Genetic predisposition, genomics and epigenomes in prostate cancer. Numerous studies, especially epidemiological studies, twin studies and large-scale genome-wide association studies (GWA study, GWAS) have demonstrated the genetic component of the etiology of prostate cancer [34]. In particular, epidemiological studies have found that a family history of prostate cancer significantly increases the risk of developing prostate cancer [33]; twin studies have shown that prostate cancer is one of the most inherited cancers [8]; GWAS identified locus of susceptibility to prostate cancer [11], such as the single nucleotide polymorphism (SNP) rs339331, which increases the expression of the RFX6 gene, which promotes the development of cancer, through functional interaction with the HOXB13 gene, the role of which is the normal development of prostate tissue, and changes in its structure, indicate a predisposition to malignant cell changes in the prostate) [4]; genomic studies have identified family mutations in *HOXB13* [5] and DNA repair genes such as *BRCA2, ATM, CHEK2, BRCA1, RAD51D*, and *PALB2* [14]. Moreover, differences in the incidence and outcomes of prostate cancer were observed in men from different racial / ethnic groups. Men of African descent had the highest rates of morbidity and mortality [6], which may be due in part to genetic factors [9].

Cataloging the genetic factors of PCa underlies the definition of disease subtypes and associated therapeutic strategies. Several large-scale genomic studies of primary prostate tumors and metastatic castration-resistant prostate cancer have revealed repetitive changes in DNA copy numbers, mutations, rearrangements and gene fusion [10], [35]. Primary tumors of the prostate gland and metastatic castration-resistant prostate cancer are characterized by an increase in the altered copy number across the entire genome, but show only a small increase in the number of mutations [15]. Genetic changes target the AR, PI3K - PTEN, WNT pathways, as well as the repair of DNA and cell cycle components in almost all metastatic prostate tumors and in a high proportion of primary prostate cancer [16].

Radiomics and radiogenomics of prostate cancer. Imaging plays an important role in the diagnosis and staging of cancer, as well as in patient treatment planning and therapeutic response assessment. Recently, there has been considerable interest in extracting quantitative information from images that conform to the standard of clinical care, i.e. radiomics, in order to provide a more complete characterization of tumor image phenotypes. Several studies have demonstrated that

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deeper radiome analysis can reveal new imaging features that can provide useful diagnostic and prognostic information beyond standard data on tumor size and volume. In addition, imaging phenotypes can be linked to genomic data, that is, radiogenomics, to understand their biological basis or further improve the accuracy of predicting clinical outcomes.

The purpose of this article is to provide a brief overview of the progressive changes in the application of approaches to radiomics and to discuss the potential role of radiogenomics in PCa.

The shift of interest from qualitative interpretation of medical imaging with a bias towards obtaining quantitative information to medical imaging (radiomics) is due to the hypothesis that macroscopic heterogeneity in the image reflects the biological diversity of the underlying disease [25, 29]. The use of radiomics in localized prostate cancer is particularly interesting given the widespread but underutilized use of imaging. Currently, the main method of risk stratification in men is the diagnosis of localized prostate cancer. A "diagnosis of prostate cancer" is made after evaluating the biopsy material, serum PSA levels and clinical staging [12]. However, the complex anatomical structure and incomplete tissue sampling leads to spatial sampling bias when using standard biopsy methods. This high level of misclassification is thought to be due to spatial heterogeneity.

In addition to morphological variability, there is growing evidence of the existence of genetic heterogeneity in prostate cancer in the same patient [32]. An insufficient assessment of biological heterogeneity can lead to an underestimation of the risk in localized PCa.

Thus, prognostic tests are needed that can provide a complete model or complement current therapies for prostate cancer.

Multiparameter magnetic resonance imaging is the standard imaging technique for detecting localized disease and demonstrates high sensitivity in identifying and localizing lesions in the prostate gland [20]. Despite its high sensitivity, multivariate MRI (mpMRI) is limited to false positives.

Radiomics refers to a method for extracting higher order objects from images. There are several functions of radiomics - this is extraction from medical images based on the research task or research goal (Fig. 1). Scoring and scoring has remained a highly controversial topic in recent years due to the large number of functions available to use and changing implementation methods. The technical description and implementation of radiomic analysis is outside the scope of this review; however, brief descriptions of the features of radiomics relevant to study evaluation are listed below. From a methodological point of view, most can be classified as describing the intensity, texture, or shape of an area of interest.

The scheme of operation of the radiomics process consists of four main stages [2]:

- receiving and collecting images,
- image segmentation (the process of dividing a digital image into multiple segments (superpixels); accurate segmentation of the prostate is important for many applications, including radiation therapy planning, biopsy preparation, PSA assessment, and tumor localization. Ultrasound is most commonly used to visualize the prostate from because of its real-time implementation and low cost [30]. Because of this, many researchers have attempted to create semi-automatic and automatic segmentation algorithms to reduce workload and standardize results [19]. Recently, a number of studies have been segmentation of zonal structures prostate [38],
- extraction of features, their statistical processing (actually radiomics);
- 3D visualization and model creation [24] (Fig. 1)

1. Standard mpMRI analysis of the prostate includes T2-weighted images (imaging) (T2W), diffusion-weighted images (b2000) and calculated diffusion coefficient maps (ADC), dynamic contrast-enhanced imaging sequence (DCE) MRI.

2. Areas of interest are identified and the prostate is segmented. In the prostate gland, the areas of interest are its peripheral zone and then the transition zone, the urethra, tissues with normal structure, tumor focus or foci. Extracts the quantitative characteristics of the image associated with volume / shape

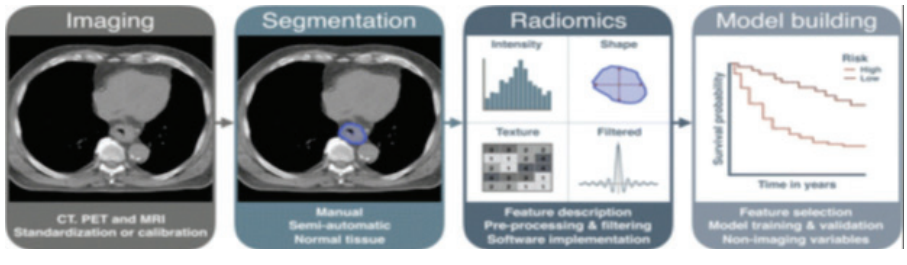

Fig. 1. Stages of the radiomic process using positron emission tomography (PET)

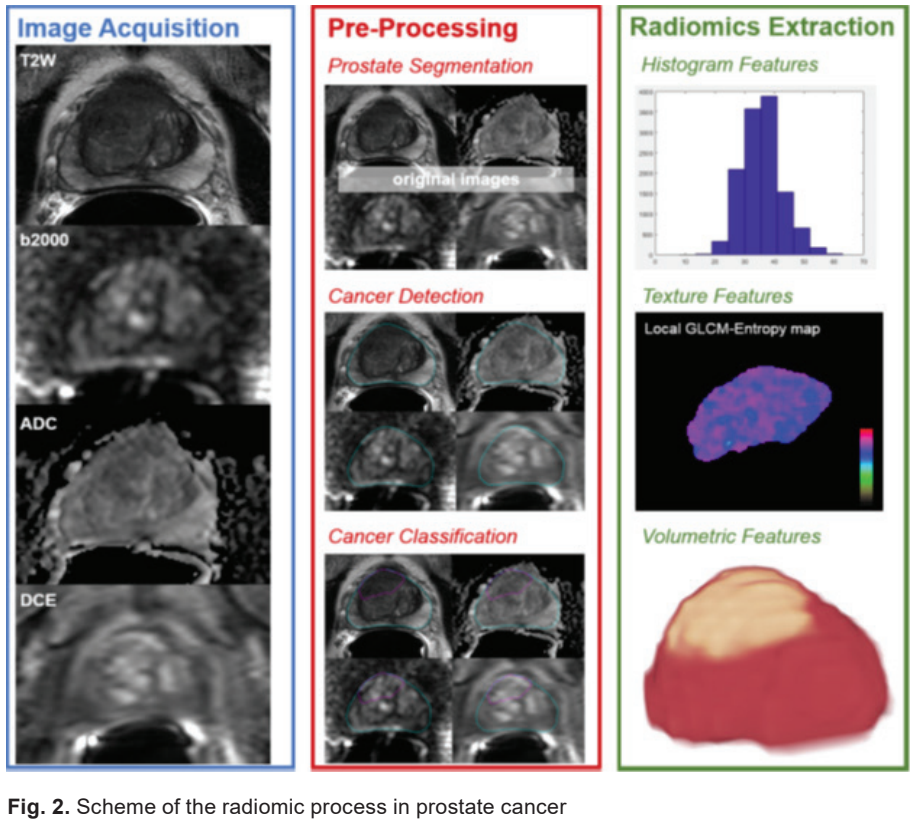

Fig. 2. Scheme of the radiomic process in prostate cancer

(shown in blue) or lesion volume (shown in pink), intensity volume histogram (first order functions), texture function (second order functions) and transformation analysis functions. Extraction of radiomic features can be performed on a voxel (voxel is a volumetric image element containing the value of a raster element in three-dimensional space) or a volumetric basis, depending on the method.

3. The data obtained through radiomic analysis is combined with clinical, genomic, proteomic and metabolic data.

4. The Scanning Diffusion Coefficient Map (ADC) is calculated on the MRI console.

The resulting images are transferred to an image processing station. There are many platforms for medical imaging. The choice of volumes for analysis affects the entire further analysis process.

Thus, radiomic analysis can become a "virtual biopsy", providing additional information about the disease, but not replacing the standard biopsy, which at the moment remains necessary for a more detailed analysis of the pathological process.

Radiogenomics in the diagnosis of prostate cancer/. In recent years, more and more articles have been published on radiomics in prostate cancer. The terms radiomics and radiogenomics are easily confused and are often used interchangeably. But both terms describe different areas of imaging. Radiogenomics was originally described as a method of linking pretreatment diagnostic imaging with genomic profiles that are associated with various toxic reactions to radiation therapy. The concept of radiogenomics has changed quite recently [31, 27]. The term “radiogenomics” is a combination of the morphemes “radiomics” and “genomics”. Radiomics is a technique for extracting visual cues from diagnostic images [28]. The data obtained can be used as non-invasive biomarkers for the detection [17], as well as for assessing the aggressiveness of prostate cancer [22]. Genomics provides a different approach to personalized medicine and correlates genomic profiles obtained from biopsy samples with clinical outcomes [26]. New technologies such as microarrays [23] and next generation sequencing (NGS) [7] are emerging, and genomic analysis is becoming widely available. Radiogenomic methods rely on information obtained from radiomic analysis to determine imaging biomarkers in order to predict genomic profiles [18].

Radiogenomics is an interesting new approach that can take oncology to a new level, from detecting cancer to predicting genomic systems that are associated with different clinical outcomes. The existing data on the diagnosis of prostate cancer are promising, but further research is needed in this direction.

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MICROARRAYS IN CLINICAL DIAGNOSTICS AND PROSPECTS FOR THEIR APPLICATION AS A SCREENING TOOL

Abstract. In this paper diagnostic microarrays and its application in various fields of clinical medicine are reviewed. The use of DNA microarray based diagnostics for carrying out the genetic carrier screening has been proposed.

Keywords: hereditary diseases, molecular genetic screening, biological microchips, practical medicine

Introduction. A series of outstanding discoveries: DNA and the genetic code gave a big impact to the development of genetics and methods in molecular biology. In 1977, Frederick Sanger developed the first in the modern sense of the method of DNA sequencing, which at that time was called the "chain termination method". Soon in 2001Human genome project were completed. In parallel with sequencing, after the discovery of the polymerase chain reaction in 1983, another method rapidly began to gain popularity and develop, which combines the developments of several areas from biology to electronics - microarray technology. Biological microchips are microarrays with various kinds of biopolymers deposited on a solid substrate as probes, and the biological material under investigation as targets.

There are two types of microchips, high and low density, which are widely used in basic research and in various fields of clinical medicine. High density microarray fabrication is characterized by the synthesis of probes directly on the substrate. For example, the GeneChip microchip photolithography technology developed by Affimetrix is designed to analyze large DNA fragments and the entire genome of an organism. Such types of microchips require expensive equipment and specially trained bioinformatics specialists to interpret a huge amount of information [21].

A slightly different approach is used in the manufacture of low-density microchips, in which the probes are applied to the prepared substrate surfaces. In clinical medicine, low-density microarrays are gaining more and more popularity due to their low cost and specificity of the studied DNA fragments.

Application of biological microchips in practical medicine. A significant part of ongoing genetic medical research is currently aimed at diagnose monogenic and multifactorial diseases caused by point mutations in the genome - single nucleotide polymorphisms. DNA microarrays are used to identify mutations and genetic polymorphisms to detect hereditary diseases, hereditary predisposition to various widespread diseases, for example, diabetes, cardiovascular diseases, oncology, ophthalmology, as well as for the diagnosis of infectious diseases. Table 1 presents a list of diagnostic microchips developed for use in clinical medicine.

Gene expression profiling using DNA microarrays provides information on the relative differences in gene expression between two different cell populations, for example, in a comparative analysis of certain drugs tested on cultured cells, or a comparison of gene expression in cancer cells with normal cells. The human genome is made up of 3.2 billion nucleotides. According to some estimates, it contains about 10 million nucleotide substitutions - the so-called single nucleotide polymorphisms (SNPs). SNPs are distributed throughout the genome and can be used as genomic markers to find links between genes and diseases. SNP is essentially the replacement of one nitrogenous base in DNA with another. For example, guanine is replaced by cytosine, while all other bases located nearby remain unchanged. Since SNP can be located within one gene, or in several at once, therefore, the probe for the microchip must be designed in such a way that the entire genome is covered. This can be a serious obstacle to genome-wide analysis [34]

Microchips for the biomarker detection in multifactorial disease diagnostics. The discovery of new specific biomarkers associated with a specific disease is very important for making an accurate diagnosis and drug development. The search for a biomarker using a DNA microarray is carried out by analyzing a large amount of data on expression levels under various genotypic, phenomical, and environmental conditions, which makes it possible to identify a larger number of candidates. It allows the simultaneous identification of candidate biomarkers by analyzing differentially expressed genes in comparison with normal and pathological conditions. By carefully applying clinical specimens at different stages or conditions to the DNA microarray, it is possible to identify those

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