REVIEW

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DIGITAL PATHOLOGY AS AN INNOVATIVE TOOL FOR IMPROVING CANCER DIAGNOSIS AND TREATMENT

For more than a century, the "gold" standard for diagnosing malignant neoplasms has been pathohistology. However, the continuous advancement of modern technologies is leading to a radical transformation of this field and the emergence of digital pathology. The main advantages of digital pathology include the convenience of the data storage and transfer, as well as the potential for automating diagnostic processes through the application of artificial intelligence technologies. Integrating digital pathology into clinical practice is expected to accelerate the analysis of histological samples, reduce the costs associated with such procedures, and enable the accumulation of large datasets for future scientific research. At the same time, the development of digital pathology faces certain challenges such as the need for technical upgrades in laboratories, ensuring data cybersecurity, and training qualified personnel.

Keywords: cancer, digital pathology, diagnostics, artificial intelligence.

Cancer is one of the most pressing medical and biological challenges of our time. According to WHO data, cancer is the most prevalent pathology globally among both men and women, significantly surpassing ischemic heart disease and stroke in absolute numbers [1]. In 2022, nearly 20 million new cases of malignancies were diagnosed worldwide, with 9.7 million deaths attributed to tumor progression [2]. The number of cancer cases is expected to rise significantly over the next 50 years due to demographic shifts such as population aging and growth. Additionally, the largest increase in cancer diagnoses is projected in low- and middle-income countries, including Ukraine, which are undergoing significant social and economic transformations [3]. High mortality rates and the limited effectiveness of current medications and treatments highlight early cancer diagnosis as the primary priority in oncology. Implementing screening programs is believed to facilitate the timely detection of cancer, reduce both direct and indirect treatment costs, and minimize national income losses resulting from decreased workforce productivity. Cancer diagnosis typically involves visual examination and manual inspection combined with biomarker analysis. The current most common instrumental methods include X-ray radiography, computed tomography, endoscopy, magnetic resonance imaging, magnetic resonance spectroscopy, positron emission tomography, and ultrasonogra-

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phy [4]. However, these standard approaches are time-consuming and prone to errors [5].

For over a century, histological examination has remained the gold standard for cancer diagnosis and a critical tool for verifying malignancies. During pathological examination, the features of tissue architecture (type of neoplasm, presence of vascular or stromal invasion, etc.) and potential malignancy criteria (abnormal cell morphology, anisocytosis, anisokaryosis, multinucleation, abnormal nuclear structures, and necrosis) are analyzed. Together, these signs provide information about the histogenetic origin, histological type, and differentiation grade, which are crucial prognostic factors [6]. This assessment requires deep knowledge of both clinical and pathological aspects of cancer development, as well as the expertise and experience of the pathologist. The quality of histological evaluations can also be affected by the physical state of the pathologist, as routine slide analysis is an exhausting and time-intensive process, potentially compromising the specialist's health [7]. According to numerous studies [7—9], both retrospective and prospective, non-critical discrepancies in pathologists' conclusions are found in 20%—35% of cases; while a complete discrepancy is observed in 10%—20% of samples. This situation, in addition to the qualification of the specialist, is often due to the pathologist obtaining a "second opinion", additional clinical data that were not taken into account during the previous visit. This emphasizes the importance of a comprehensive approach to assessing the histologic features of the tissue, taking into account the patient's detailed clinical history [10—13].

Meanwhile, the number of qualified histopathologists remains insufficient, which impacts the quality of services [14]. Today, the labor market needs for specialists in this field are poorly met, and employers are often forced to hire workers with minimal experience [15—16]. This also results in the limited collaboration and the infrequent exchange of expertise between physicians for consulting complex cases [17].

In recent years, cancer diagnosis and pathology have undergone significant changes due to advances in computational opportunities. The development of high-throughput imaging tools and image analysis algorithms has facilitated a shift from the traditional "manual" histopathological analyses based on microscopy to digital pathology [18], which involves digitizing histological slides into high-resolution images using scanners or robotic microscopes for subsequent analysis [19].

The use of digital pathology in clinical practice can significantly reduce the time [19]. For instance, digital pathology implementation can save up to 13% of pathologists' time [20], and the effectiveness of remote histological slide evaluation is comparable to traditional microscopy [21]. However, several studies have reported the discrepancies (up to 57%) between traditional and digital pathology in assessing nuclear atypia, classifying dysplasia, determining tumor grades, and identifying small objects (e.g., *Helicobacter pylori* in 16% of cases) [14].

The obvious advantages of implementing digital pathology in clinical practice include centralized organization and storage of large data sets, integration of digital software to optimize and improve the efficiency of diagnostic processes, and convenient image sharing to ensure interdisciplinary remote communication around the world [17]. On the contrary, the traditional histopathology laboratories require significant storage space for archives, with retention periods varying by country and reaching up to 50 years [22—23]. Digital pathology has proven particularly beneficial in regions with low population density or a shortage of qualified pathologists [10].

The evolution of digital pathology has spurred the interest in studying the quantitative histomorphometry attributes derived computationally from histological images, usually after hematoxylin and eosin staining, for cancer diagnosis and prognosis. Currently, the analysis of digital microscopic images is based on the use of several open-source programs that allow them to be "modified" to meet specific needs. TMarker, Orbit, and QuPath, as well as some online tools (Cytomine and Digital Slide Archive), are widely used for personal computers. In the scientific field, ImageJ and FIJI are used to analyze bioimages, and there are a large number of plug-ins for them that significantly expand their functionality. Other tools such as 3D Slicer, CellProfiler, and Icy have also been developed with similar philosophies [24]. However, it is still worth noting that new methods of analyzing digital images described in many publications are not always widely used, and many of them are used only for scientific purposes. This is because the software that implements this or that analysis

method is not available or is too complicated to use. These shortcomings create a gap between the real and the literature-described possibilities of using digital pathology technologies in routine practice [24].

One of the main problems to be solved when analyzing the digital slides is the variation in the image quality caused by the heterogeneous conditions during tissue section preparation or image acquisition, and when working with tumor tissue, by the heterogeneity of tumors. All of this can significantly affect the subsequent segmentation of images and the identification of parameters used to diagnose and predict the course of the disease. In order to reduce such differences, microphoto preprocessing methods are used. In particular, such techniques as the color normalization to minimize color variations, spatial filtering to highlight the main structure of the image, noise reduction, optimization of the contrast between the objects under study and the background, and others are used for this purpose [25]. For example, Huang et al. [26] applied the color normalization and nuclear extraction methods to overcome the differences in the staining technologies, achieving a high accuracy in identifying the specific breast cancer features in hematoxylin and eosin-stained images or those using fluorescent markers.

Significant progress has been made in obtaining clinically relevant quantitative data for the analysis of pathologically altered tissue samples. Beyond assessing various parameters of malignantly transformed cells, substantial attention is directed toward studying the characteristics of cellular and non-cellular elements of the tumor microenvironment (TME) [27]. This interest stems from the understanding that a tumor represents a complex ecosystem that arises and develops under the selective pressure of its microenvironment. These interactions influence its trophic support, metabolism, immune characteristics, and sensitivity to therapy. The relative impact of these biological factors reflects intratumoral heterogeneity, taking into account the quantity, localization, and functional orientation of TME components [27—29].

The use of software for automated analysis of the digital histological images, particularly hematoxylin and eosin-stained tissue, facilitates the evaluation of complex spatial structures. For instance, Acs et al. [30] demonstrated the potential of the automated evaluation of tumor-infiltrating lymphocytes (TILs) as independent prognostic markers for melanoma. In another study, the authors analyzed 21 phenotypic characteristics of TILs, including features such as the regular shape, clear margins, high peak intensity, homogeneous enhancement, and unique textural patterns compared to other cells. The researchers suggest that such an approach could significantly optimize breast cancer diagnostics in the future [31]. According to Xu et al. [32], the neural network-based algorithms for analyzing digital slides provide high accuracy in assessing the histological features of tumor tissues and could serve as a screening tool in the differential diagnosis of colorectal cancer.

Saito et al. [33] demonstrated the possibility of using digital pathology technology and machine learning based on images of hepatocellular adenocarcinoma slides stained with hematoxylin and eosin to predict a risk of tumor recurrence after surgery.

Wang et al. [34] identified 48 unique features of the spatial organization of TME and developed a prognostic model of lung cancer based on the analysis of digital images of histological samples of lung adenocarcinoma stained with hematoxylin and eosin, taking into account the segmentation of tumor cell nuclei, stroma, lymphocytes, macrophages, karyorrhexis, and red blood cells.

At the current stage of digital pathology development, researchers are also focused on investigating the prognostic and predictive significance of the stromal fibrous components of tumors using digital pathology tools. This is supported by the results of our studies, according to which the automation of the assessment of the structural organization of collagen fibers in tumor tissue using the software package CurveAlign v. 4.0. beta and ImageJ software can significantly improve the differential diagnosis of the most common hormone-dependent neoplasms [35, 36] and provide a highly accurate assessment of the aggressiveness of breast and prostate cancer [37].

The study by Li et al. [38] proved the feasibility of using an automated approach to quantifying the orientation of collagen fibers in the stromal component of breast cancer to predict the risk of disease recurrence. Along with this, Gole et al. [39] demonstrated the high efficiency of using some

parameters of the collagen matrix to predict the clinical course of breast cancer of the basal molecular subtype.

According to single studies [40], digital pathology can also be used to assess the response of malignant tumors to anticancer therapy.

Recent advancements in tumor profiling have enabled the identification of the genome, transcriptome, and proteome of malignantly transformed cells as robust sources of diagnostic, prognostic, and predictive markers. Consequently, the spatial gene expression analysis has become a key approach to understanding the localization and complex interactions of DNA, RNA, and proteins in both the parenchymal and stromal components of the TME. This necessitates the development and standardization of methods for an unbiased, objective, rapid, and automated quantitative assessment of tissue-stained sections in terms of the intensity, expression levels, and/or spatial distribution [41].

The digital transformation of histopathology has also facilitated the automation of histological slide analysis using artificial intelligence (AI) technologies. Machine learning (ML) and deep learning (DL) algorithms, including convolutional neural networks (CNNs), enable rapid processing of vast datasets, identifying patterns and anomalies that are difficult for pathologists to detect. Models based on these algorithms (e.g., for tumor histogenesis determination and subsequent histological classification) have been developed for various malignant tumors, including prostate, breast, lung, stomach, and colorectal cancers. Some of these tools have received approval from the U.S. Food and Drug Administration (FDA) and in vitro diagnostic certification from the European Medicines Agency (EMA) [42]. It is worth noting that today the use of AI technology to analyze digital histological slides to diagnose and predict the course of cancer faces several limitations primarily due to the lack of sufficient annotated data for the development and validation of AI systems, the explainability of the "black box" AI models, such as those based on DL, which offer the most promising results, and the difficulty of defining the initial data for training and validation [43].

Several risks are associated with implementing AI technologies in clinical practice, including potential data breaches, high operational costs, and diagnostic inaccuracies [43]. The limitations of the integration of digital pathology into medical information systems are also due to the high cost of the necessary infrastructure and modern equipment. At the same time, the criteria for standardization of the scanner systems, image processing systems, and formats, as well as the interfaces of virtual microscopy with pathological and clinical information systems, such as molecular pathology subsystems, have not been fully developed [6]. It is worth noting that today a number of professional organizations (College of American Pathologists (CAP), Digital Pathology Association, Canadian Association of Pathologists, Royal College of Pathologists, and Bundesverband Deutscher Pathologen (Professional Association of German Pathologists) have already created recommendations for the implementation of digital pathology technology [14].

In summary, the adoption of digital pathology is accelerating in both fundamental oncology research and clinical practice. It has the potential to reduce the workload of pathologists and improve diagnostic efficiency. However, digital pathology is currently viewed as a supplementary tool, with its widespread implementation hindered by high costs and a lack of qualified specialists.

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ЦИФРОВА ПАТОЛОГІЯ ЯК ІННОВАЦІЙНИЙ ІНСТРУМЕНТ ДЛЯ ПОКРАЩЕННЯ ДІАГНОСТИКИ ТА ЛІКУВАННЯ РАКУ

Понад століття «золотим» стандартом діагностики злоякісних новоутворень є патогістологія. Разом з тим невпинний розвиток сучасних технологій приводить до кардинальної трансформації цієї галузі і появи цифрової патології (ЦП). Основними перевагами ЦП є зручність зберігання і передачі даних, можливість автоматизації діагностичних процесів на основі застосування технологій штучного інтелекту. Впровадження ЦП в клінічну практику в перспективі дозволить пришвидшити процес дослідження гістологічних зразків, знизити витрати на їх проведення і накопичити великі масиви даних для подальших наукових досліджень. Водночас розвиток ЦП стикається з певними викликами, зокрема, необхідністю технічного переоснащення лабораторій, забезпечення кібербезпеки даних і підготовки кваліфікованих кадрів.

Ключові слова: рак, цифрова патологія, діагностика, штучний інтелект.