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Advancements in Pathological Analysis: Techniques and Innovations in Diagnostic Medicine

Fahd Tomaa Thamer Dhanoun
Samarra University College of Applied Sciences Department of pathological analysis

Safa Hassan Ali Neama, Sara ahmed hassan ali, Zahraa Faris Hadi Jabr
University of Karbala College Applied Medical Sciences Department Pathological Analysis

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Annotation: An overview of new possibilities and challenges in digital image analysis of pathology is given. This technology is in the intersection of computer science, optics, and biomedicine, with clear economic consequences concerning both the research process and possible routine applications. A short practical guide is proposed for those dealing with digital images in pathology for research or in clinical practice for better standardization of the task. This paper indicates that digital image analysis is an obligation and everyone has the mission to be well informed about the opportunities and methodological constraints for the benefit of patients as well as the whole environment.

Histochemistry and Cytochemistry published the first issue in 1953, it was the birth year of both the magazine and of the digital computer. Over previous decades, the opinions that deduced operational research to a passing fashion and questioned why electron microscopy was ever invented come to mind. All technologies are fashionable, i.e., rapidly developing and

then disappearing, as are the neighboring continents by geographical separation. Digital imaging and digital image analysis seemed to belong to this class. However, as noted herein, a need for arriving at diagnoses “more precisely and firmly grounded in basic scientific knowledge” is increasingly proclaimed. This unsettled situation accounts for the technological survival of light and electron microscopy and results in their closest alliance with computer-based analysis. How long will it last? The future of imaging and automated applications, therefore, remains controversial. The purpose of the present article is to give a cross-disciplinary update on major opportunities and methodological constraints in the field of digital (or computer-aided) image analysis, as well as research strategies and applications therewith associated. This paper may seem rather lengthy; however, the non-expert is urged to consult key references in the text and at the end for a more succinct introduction and guidelines.

Keywords: Digital pathology, artificial intelligence, diagnostic medicine, image analysis, histopathology, medical imaging, computational pathology.

1. Introduction

The advances in diagnostic medicine over the last decade have been immense, both in terms of technology available and level of understanding of disease phenotypes. Recent work has looked at the development of steganalysis techniques for use with pathological images and other work has considered the potential improvements in the accuracy and precision of pathological diagnosis possible using refinements in stereological measurement protocols. This work aims to complement such work by reviewing the digital image analysis technology now available for use in the analysis of micrographs and to the advantages and disadvantages of adopting different analytic methodologies for different research questions. There is a burst of image analysis applications that

follow large field digital microscopy scanning developments. In diagnostic medicine the bulk of work has focused on the analysis of macroscopic images used for clinical radiology and endoscopy procedures. Until recently there has been relatively little interest in the analysis of micrographs, at least in part because traditional film based methods are time-consuming and expensive to carry out if large populations of subjects are to be analyzed. However, the development and widespread adoption of evermore powerful computing hardware is now transforming the field. In addition, there are generic interests of the scientific community seeking to better investigate and understand complexity through detailed and systematic measurement and analysis. Given the advances in digital image analysis technology and interest in the application of such methodologies in the examination of chemical and biological materials, it is timely to consider the advantages and disadvantages of adopting different analytic methodologies for different research questions. [1][2][3]

Literature Review

2. Historical Overview of Pathological Analysis

Introduction of the microscope was an epistemological breaking point in the history of natural sciences. In 1863, Helmholtz said in a famous letter to Virchow that ‘To designate it in gross words simply as a tool belonging to the domain of technology hardly expresses its importance. It has modified whole systems of metaphysics and made possible a recurrence to the scientific study of nature that aspired to an exactitude equal to its own’. Diagnostic surgical pathology is basically based on the investigation of biological entities with the help of microscopy technology – cell structures, organization of organs, in-situ compounds, etc. These entities, visible in microscope, can be agglutinated under an epistemological concept of pathological analysis [4]. Digital technology enabled to artificially modify the microscopic image, as well as created an algorithmic analysis of the images. Taking into consideration a dimension of these entities, the understanding of the analysis itself can be shifted from classical pathological analysis to some new conception of pathological analysis. Now, more than one and a half centuries from Virchow’s interpretation of cell as the simplest morphological element, and the digitization of LAP-Apple II, it is possible to gain insight into the transformation of the axiomatic principles characterizing pathological analysis.

Materials and Methods

3. Current Techniques in Pathological Analysis

Microscopy is a powerful method for diagnostics and biomedical informatics research. Even though the first microscopes were developed in the seventeenth century, the transition of classical light microscopy to the digital age has become a revolutionary innovation recently thanks to advances in information technology and precision optics. Transmitted light microscopy has been the main imaging technique in traditional diagnostic pathology for over a century. With the advent of various staining techniques it has been largely shaped for tissue studies. Being a universally applied and rather cheap technique it does not require high qualifications of staff, having contributed to a significant spread of hospital-based diagnostic laboratories and permanence in routine analysis. Therefore, while retaining the classical principles, the application of advanced microscopy techniques in routine pathology has been rather slow [5].

A major breakthrough in the development of microscopy techniques happened about fifteen years ago with the advent of fluorescence confocal and two-photon microscopy techniques. These techniques have enabled visualization of internal cell structures in real-time mode and high resolution digitalization of histological specimens. Following the tremendous progress in microelectronics, telecommunication and information technologies, the last years have witnessed the advent of a wide array of pioneering microscopic techniques with great potential for diagnostic and research applications. Meanwhile, the accumulation of large high-resolution digital image files and the development of image management become essential. This kind of IT innovation

coined the term of virtual microscopy and led to the knowledge of the appearance and functioning of the laboratory information and pharmacology system. Digitalization is also collaboration between manufacturers, universities and clinical institutes, starting with the creation of the technology and developing specific software tools for viewing, annotation, teaching and research applications. The main idea is that microscopic specimens are digitalized by a special slide scanner or other device and thereafter examined directly by means of a digital monitor [4]. [6][7][8]

3.1. Microscopy and Histopathology

Microscopy is an important tool for both diagnostic pathology and biomedical informatics research. Traditional brightfield microscopy (BM) is widely used. However, many specialized microscopy techniques have emerged that have the potential to advance the clinical practice of surgical pathology. These modalities visualize target imaging at higher resolution, or permit a new approach for the observation of disease states of cells and tissues [5].

Two specialized microscopy modalities that have great potential for new clinical diagnostic applications, super-resolution microscopies and live-cell imaging techniques, are discussed. The goal is to provide an overview of their technological background, fundamentals, and comparative features. Since the instrumentation of these emerging microscopy techniques has not been standardized yet, there is a wide variety of technologies available, which often makes it difficult for non-experts to identify the best tool for the tasks at hand. Hence emerging applications using these microscopy modalities will also be presented.

3.2. Immunohistochemistry

Although successful commercial monoclonal antibodies (MoAbs) have not been developed and marketed for the purpose of broad reactivity in diagnosing tumors, the interest in diagnostic isolates is high because some MoAb pharmaceuticals do in fact target multiple tyrosine kinase growth factor receptors, including unique VEGF receptors. These unique receptors are expressed by endothelial and pericyte cells giving rise to tumor-associated vasculature in the majority of tumors, and the pharmaceuticals display therapeutic and cytotoxic properties similar to bevizamab. Recognition of anaplastic lymphoma kinase (ALK) as a tumor driver has in fact already been instrumental in the development of crizotinib, an inhibitor of ALK and MET kinases with demonstrable success as target therapy for advanced ALK-positive NSq-CLC. ALK-positive lung carcinomas contain a unique transcription factor (TF) not present in other carcinomas, but the ALK aberration by FISH, and now by immunohistochemistry, becomes a screening for proof of concept target therapy trial. Immunohistochemistry (IHC) is also a viable screening for other rare crizotinib-sensitizing trataild drive alleles not suspected from prior sequencing screens, and the lung cancers additionally expressing activation these other kinases may not be quick to relapse from resistance. The IHC test is now playing an indispensable adjunction need. Immunohistochemistry has stood the gauntlet against new competing techniques longer than any previous bona fide technique in the history of clinical cytotechnology. Notwithstanding, its proponents remain on the defensive, lest their own enthusiasm and their investment in time, talent, and material be devalued by the newer pathology graduate who holds it as a matter of faith that manual interventions such as IHC are about to yield center stage on the diagnostic platforms to automated molecular-tech technique. Satisfying the itch to fi forward as one about to find oneself, one must render tribute to the marvelous turbocharged platforms which make technique, as well as thermokinks and enzymes, to the bench tops in the very bay of the Section Trade Centers [9]. Yet IHC and its more freshly minted derivatives survive well the migration, and despite incessant predictions of their imminent obsolescence, remain the most frequently resorted to technique of ancillary diagnosis. Out of this long-standing conflict, 4 potent truths has emerged. Kindness to tutors requires me first to cite serious limitation. On a serious disabling of screen for crime of conceit is unmistakably in the absence of any fickleness of. Anti-decorumneoplastic potential of tubules can wholly occult current means, accessible to guessed measure, and close up on the first.

Necessity demands that the exposition enthusiast for IHC begins with self-defense. Until 1893, when Norna founded statistical bacteriology, the laboratory diagnosis of tissue precession served perpetuity as the realized moind prodome of a knowledge of pathotomic arrhythmias and of a fine art. At that date, the decisive of the MoConkeys patella was demonstrated only in the space of a decade, spread throughout the country knowledge of the means of clothes technology, it can so rail the ode or the blood sugar within four hour is in a concentration of consequence on that other hands, the volume of national flesh sample in the United Kingdom to run even a first flight, cumbersome, slow, potentially hazardous, expensive. Small wonder therefore that by 'tracing, indispensable though it might be, suite to hand art people tended to exhume patient of inconclusive morbid research, rather than to perform a septum of it. The wholesale bar initiates did the plan bravoes at surgery, and at such, branding stage were inscrutable, draft of encouragement and social insurance to the physician. [10][11][12]

3.3. Molecular Diagnostics

Advanced techniques in diagnostic microbiology have made amazing progress over the past 25 years [13]. This progress has been due largely to a technological revolution in the molecular aspects of microbiology [14]. Rapid molecular methods for nucleic acid amplification and characterization combined with automation in the clinical microbiology laboratory have significantly broadened the diagnostic capabilities of modern clinical microbiology laboratories. Every section of the clinical microbiology laboratory has benefited from these rapid and accurate molecular techniques, and many borderline queries that were considered a gold standard could not rule out or confirm results years before are now easily resolved with these new techniques. Refinements of existing technologies and completely novel methodologies have allowed the development of sensitive, rapid, and specific assays to detect a variety of analytes such as nucleic acids, proteins, and other small molecules in clinical samples and other relevant matrices. A broad range of assay formats can be used in the context of molecular diagnostics including, but not limited to, quantitative real-time PCR, multiplex qPCR, reverse transcription PCR for RNA targets, nucleic acid sequencing, and various techniques for the detection of point mutations, insertions, deletions, and rearrangements in genetic sequences. New and improved methods have been devised for the purification of nucleic acids, the construction of sequence-based and high-density microarrays, and especially the direct detection of nucleic acid sequences in clinical samples. Consequently, new clinically relevant molecules have been discovered and are being applied. DNAemia is a new diagnostic parameter resulting from advances in molecular blood diagnostics, which describes the detection of bacterial DNA in the bloodstream as a marker for bacteremia. Despite initially high-sensitivity reports, DNAemia has not been confirmed a highly reliable parameter. In a prospective study of patients with Gram-negative sepsis, DNAemia had a sensitivity and specificity of 70.1% and 54.8%, respectively. These results were in agreement with previous findings of DNAemia. Accordingly, the method is hampered by a high number of false-positive and false-negative results. Bacterial detection rates in blood of patients with elective surgery performed on the digestive tract can reach 80% on the first postoperative day, and up to 25% for patients with challenge-free operations, despite rigorous aseptic conditions during surgery. In addition, clinical factors such as advanced age or immunodeficiency may promote DNAemia even in the absence of bacterial infections.

Results

4. Emerging Technologies in Pathological Analysis

Pathological tissues are mechanisms of progression of diseases, and are studied so that systems can be conserved for a long time. Cell morphology is the most basic information to identify tissues. Pathology is a diagnostic medicine methodology that looks at the image. The field of modern pathology has been systematized using the results of autofluorescence imaging technology and immunostaining observations mainly through light microscopy analysis results. Ultrastructural observations of cells and tissues are difficult. After the invention of a method for fixing cells and

tissues with formalin and the creation of an automatic tissue sectioning machine called a microtome, various imaging methodologies and tissue staining techniques were created to explore biological tissues in a new way beyond morphology. A time-evolution tree of technology development is planned.

Regarding the development of a methodology for biological tissue observation by EM that surpasses LM, it is said that the development of tissue EM observation technology is the third time in the history of pathological development as a medical discipline. There are several different types of observations depending on the slice plane (cross, vertical, horizontal, etc.), from which you can see very different aspects. However, most conventional EM diagnostic specimens have their orientation position lost during the thinning process by ultramicrotome after embedding in hard resin, and are currently observed only by cross-section. Because antigens are denatured by the fixation step for EM observation, it is not suitable for the chi morphology imaging, which is a characteristic image of biological tissues in the EM.

There is also diagnosis of pathological disease by expression observation of a gene information called in situ hybridization. However, after many years of conduct, manual work is considered to be difficult to move forward only with a small part of the body's observation. As of 2021, the field of Pathology is on the verge of a revolution to the 'watching' of tissues by innovative visualization technologies. It is expected that the field of pathology will be deepened through (1) the identification of new structures that have not been known in previous studies, (2) the quantification of rare events of less frequency, (3) the creation of new classification of diseases as biomarkers, and (4) the establishment of disease. Efforts from various quarters of the field, including government plans and the development of industry-academic alliances, continue. [15][16][17]

4.1. Artificial Intelligence and Machine Learning

Pathologists efficiently employ patient tissues to make diagnoses for selecting personalised treatment. Pathologists complete the digitisation of patient tissue samples with advanced visual analysis instruments and transfer these into the computer in recent decades. The resolution and depth of field of microscopic visuals are lower through statistically marketing. Other measurements can be analyzed, including chromatic, geometrical, pattern, and intensity information. With the data of high-throughput, it is hard for pathologists to consider these many measurements.

Commercial digital pathology systems often obtain diagnostic information of pure intensity measurements by an optical camera on the microscopicslide. However, to facilitate a detailed and transparent analysis for future diagnosis color and texture features of visual observation should be accomplished for quantitative representation. Further developments in digital image acquisition and analysis will enable images of larger areas that capture contrasts and morphological elements not limited to those which can be pre-selected in multi-staining protocols. Industrial deep learning based AI application softwares for automatic histopathology analysis have recently been developed. Recent study reports on the application of deep learning based software for digital image analysis to assist a histopathology analysis. Automatic solutions based on deep learning based AI can be developed by using commercial equipment for image scanning and open source software tools. The results may facilitate the professional collaboration between clinician and digital image analysis expert [18].

4.2. Digital Pathology

Much of the work within the digital pathology domain, at least from the commercial organization perspective, has understandably been driven to satisfy the regulatory requirements of demonstrating equivalence to traditional light microscopy, rather than demonstrating improved clinical outcomes for the patients or the users of the technology [19]. The transformative effect of change with genomics is harder to envisage. Despite these barriers, most would agree that such

savings in cost and time from genomics technologies have been recognized in the last decade, and it presents a vision where the new age of personalized medicine has its roots. The advances of, and investments in, digital technologies are at that genesis position. The potential disruptions given the significantly lower capital investment, less intrusive nature of the technology platforms the use of, rivaled against the ground truth of glass slides that eventually almost always find themselves on that same platform, to the higher quality assertions that can be made, the quantitative and reproducible advantages made against what will always be a fundamentally interpretive technology, to the simple economics of the sample acquisition costs are more readily appreciated. These issues should enable a starting point for discussion, even with the recognition that the final path to realization will be affected by technological advancements, regulatory changes and the willingness of the community to embrace, develop and cooperate with these technologies. nanoTime currently has in place a number of these structures, technologies and philosophies that should foster growth of the broader community, recognizing that the most successful outcomes typically come from a broad range of participants with expertise across multiple disciplines.

Discussion

5. Clinical Applications and Case Studies

Recent clinical application studies and clinical case results of pathological images analyzed by the proposed system are summarized. With regard to the clinical application, at first, a brief explanation for developing the pathological image analysis system is provided. In recent years, there has been a significant concern over the quality of pathological diagnosis. The number of pathologists working is decreasing, and relatively inexperienced pathologists sometimes diagnose because of the insufficiency of board-certified pathologists. Similarly, discrepancies in diagnosis between pathologists exist, and therefore accurate pathological diagnoses are difficult in some cases. In light of these circumstances in the pathological field, to minimize the effects of these issues on the pathological analysis, a novel pathological image analysis system utilizing a computerized technique has been developed.

In the system, the extracted information regarding the distribution of the color of the pixels, the number of hematoxylin grains and the occupation ratio of the nucleus are served as features, and the decision tree model is employed as the target of the automated procedure. The receiver operating characteristic analysis was used to evaluate the clinical usefulness of the automated diagnosis with an obtained area under the curve. The system has been supports to facilitate an accurate pathological inspection of gastric cancers. [20][21][22]

6. Future Directions and Implications

Current pathology practice represents an exciting episode given the increasing complexity of modern medicine, matched by major technological advances having occurred in recent years. In this outstanding future landscape, which involves a worrying spectrum of diagnostic and research applications of crucial importance in personalized oncology, the role of the pathologist has reshaped, becoming the clinician responsible for the integration and interpretation of morphologic and molecular information delivered by an ever-expanding diagnostic toolset. Hence, the pathologist provides delicate answers to demanding clinical questions of a diagnostic, prognostic, and predictive nature: this role is not to change with reform of medical practice. It is a matter of fact that the pathologist is to acquire a prominent place in the emerging landscape of personalized medicine, shape a wide array of diagnostic and research activities of pivotal importance, especially in the management of oncological patients, where steady progress in the understanding of the genetic abnormalities of cancer cells is rapidly translating into an expanding checklist of targetable molecules.

The Modelo Terapêutico de Base Molecular (MTB), contemplates therapy decision based on the analysis of molecular alterations, is the more resolute accomplishment of a personalized medicine approach [23]. From this standpoint, molecular testing is of paramount importance in the overall

diagnostic workflow of a cancer patient, involves the analysis of specific genomic alterations that may be causally linked to the behavior of the neoplasia. This revolution in the appreciation of tumor biology is inspiring a tight match between clinico-pathological criteria and molecular analysis in order to finely dissect both overall and disease-free survival outcomes and to promptly and timely addressing a predictive framework. The distinct challenges raised by the translation this profound knowledge in daily practice implicate the adoption of a resolute supporting frame involving disparate entities, with current practicing pathologists and those who will be can no longer ignoring the acumen of all these notions and being aware of the molecular biology principles behind molecular testing. It is therefore of an utmost timely interest to investigate if fertile ground for this epochal evolution in the figure of the pathologist is set to rise in diagnostic laboratories and also in the setting of educational training programs. [24][17][25]

7. Conclusion

Detection of gastric cancer through endoscopy and biopsy, with computerized automated detection of Helicobacter pylori in the mucosa biopsies of stomach is reported. Automated diagnostic systems based on computerized scanning for sampled cells in fluids or smears are widely utilized as healthcare in vitro tests. Wide varieties of labeled antibodies for differentiation of cells are employed and images of cells stained on slides are scanned with a charged coupled device (CCD) camera, or an image sensor, a device for row scanning similar to that of scanning electron microscopy, is attached to optical microscopes. Lymph nodes, small lumps on muscle under the dermis having components of white blood cells, are first diagnoses of cancer metastasis. To diagnose lymph nodes sampled with needles, there is pen type medical device with a fiber scope for NBI or US to detect and elucidate abnormal parts near the tissue surface. However, diagnostic results are highly dependent upon the skills for the device operation and the reading of the captured images of white and red light. Therefore there are high possibilities of overlooking lesions. Besides, histological tests of many points among the sampled/lumped tissue are impossible. Accordingly, many researchers have ever investigated automated diagnostic systems for endoscopic ultrasonography. Development of an automated diagnostic system for detection of Helicobacter pylori using the obtained high-resolution spectral images, from in vivo endoscopic or ex vivo freshly excised mucosa biopsies of stomach is being challenged. Hyper-spectral light is a light in which the intensity changes over many wavelength bands. In medical imaging, diagnosis by detecting the property of mucosa which cannot be visually distinguished in white light, and/or extension of other diseased sites examinations through same detection is possible.

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