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EDITORIAL

Digital pathology in urology: The new frontier?

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Summary ***Systems of digital pathology are used to enhance diagnostic consistency and reduce workload. They cannot replace pathologists but can serve as tireless and intelligent assistants. Artificial intelligence (AI) excels at high-volume and repetitive tasks, freeing pathologists to focus on complex cases and final diagnostic decisions. The other advantages of digitization include reducing interobserver variability, use as second reader tools and for triage negative biopsies. Digital images can be used for remote consultation, external quality assessment, and education. Despite these favorable results, it must be kept in mind that AI is merely a tool to assist in pathological diagnosis and treatment that cannot replace human expertise. Ethical and legal implications must be considered in order to establish legal frameworks and ensure transparency and ethical use of AI-based tools.***

Key words: *Digital pathology; Artificial intelligence; Whole-slide imaging; Prostate cancer; Urinary cytology.*

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Digital pathology has rapidly evolved in recent years, moving from an experimental context to being a validated tool integrating modern diagnostic practice. This progress is due to the widespread use of *whole-slide imaging* (WSI), which is based on a complete scanning of the slide, capturing many small, high-resolution images that are then montaged to create a high-resolution full image of a histological section for computer-aided analysis, with diagnostic performance comparable to conventional light microscopy. These results have been possible thanks to improvements in scanner speed and resolution, standardized color calibration, and image management systems. The digitization of pathological images has seen significant development in the field of urology, particularly for the diagnosis of prostate, bladder, and kidney cancers, which are diseases characterized by high case volumes, some degree of interobserver variability, and the need for standardized quantitative assessment.

In prostate cancer, *artificial intelligence* (AI)-assisted algorithms have been validated for cancer diagnosis, Gleason grading, and quantification of tumor burden (1-3).

A systematic review included 80 studies (2), mostly dealing with biopsy specimens, showing that algorithms achieved good results about cancer detection and grading in association with reduction of times for evaluation. AI-identified histologic features of biopsies were also used to predict surgical pathological findings (extraprostatic extension, perineural invasion) and disease-free survival. Another review (3) pointed out that "*machine learning algorithms will not replace human pathologists in the near future*" although they can be used as tools "*to decrease the work burden and increase the accuracy of practicing pathologists*." The Authors listed s number of currently available softwares for detecting and grading prostatic carcinoma as well providing other quantifiable measurements.

In bladder cancer, digital tools have been developed to support the identification of carcinoma in situ, assessment of muscle invasion, and quantification of immune biomarkers relevant to immunotherapy.

A systematic review (4) of studies that used computational pathology in bladder cancer, found that algorhytms showed a high accuracy in distinguishing normal vs tumor tissue and in segmenting tissue compartments (urothelium, stroma, muscle, etc.). Models trained on regions of interest can classify low vs high grade tumors and identify stage-relevant structures (e.g., invasion into lamina propria or muscle) with > 80% accuracy and models based on quantitative nuclear features achieved > 80% accuracy for recurrence/survival prediction. It was concluded that computational pathology "*holds the potential to improve diagnosis and prediction of prognosis of bladder cancer*", although its implementation in clinical practice still requires addressing several challenges, including "*standardization of data collection*" and "*analysis and interpretation of AI models*".

In renal tumors, computational models were used for subtype classification, grading, and prognostic stratification (5, 6).

A systematic review (5) about potential applications of computational pathology in *renal cell carcinoma* (RCC) found that AI models based on deep learning *achieved area under the curve* (AUC) of over 0.93 in subtype classification, 0.89-0.96 in grading of clear cell RCC, 0.70-0.89 in molecular prediction, and over 0.78 in survival prediction. Another systematic review concluded that, despite the progress in research activity, "*computational pathology is not yet ready for widespread routine use*."

The use of digitized images can further evolve with the identification of morphometric, textural, and spatial features ("*morphomics*") not discernible to the human eye

that can be used for predicting recurrence, progression, and therapeutic response. Furthermore, digital images could be integrated with spatial transcriptomic technologies enabling measurement of gene expression levels throughout tissue space.

Similarly, digital cytology has rapidly evolved through the adoption of whole slide imaging and artificial intelligence (7). Modern scanners now reliably digitize with sufficient quality ThinPrep, SurePath, and conventional smears that are used for cervical cancer screening and can also be successfully employed for digitizing urinary cytology slides which can be evaluated by AI based systems to classify urothelial cells and to estimate the risk of high-grade urothelial cancer on the basis of quantitative features aligned with cytomorphologic criteria defined by the Paris System. Digital urinary cytology primarily aims to the detection of *high grade urothelial carcinoma* (HGUC) although digital scoring also improves reproducibility for the most challenging categories as *Atypical Urothelial Cells* (AUC) and Suspicious for HGUC categories. Digital cytology can be integrated with ancillary tests such as FISH, DNA ploidy, and urinary molecular biomarkers. Limitations still exist, such as the persistent difficulty in identifying low-grade tumors and the need for thorough standardization of staining and slide preparation procedures.

In this issue of the *Archives of Italian Urology and Andrology* (AIUA), two papers propose the application of digital tools to facilitate histopathological and cytological diagnosis in urology.

The paper by *Noviardi et al.* (8) evaluated the use of an automated urine analyzer (Sysmex UF 4000/5000) to facilitate and accelerate the search for tumor cells in urine. The Sysmex UF series (UF 4000/5000) are based on fluorescence flow cytometry to provide quantitative counts of *red blood cells* (RBCs), *white blood cells* (WBCs), epithelial cells, bacteria, and casts. These automated analyzers are excellent for infection screening, sediment triage, and workflow optimization, although they are not designed for cancer cell detection. The analyzer during automated urine sediment analysis can also generate a flag for *Atypical Cells* (Atyp.C) parameter (for research purpose) that measures the flow cytometric signal pattern suggesting the presence of cells with abnormal scatter/fluorescence characteristics. *Forward scatter* (FSC) is related to cell size, *side scatter* (SSC) to internal complexity of the cell and *fluorescence intensity* (FL) to nucleic acid content (DNA/RNA). However, the measurement of the Atyp.C parameter is not a morphological diagnosis of atypia and it is not equivalent to cytological *atypical urothelial cells* (AUC) in The Paris System.

On the contrary, use of *whole slide imaging* (WSI) of urine cytology preparations and application of deep learning models for detecting atypical and malignant urothelial cells have been used for automated *high grade urothelial cancer* (HGUC) prediction.

Tsuji et al. (9) trained a deep learning model to predict histologically confirmed HGUC obtaining a performance comparable to expert cytopathologists with an AUC ≈ 0.78 for HGUC prediction with a more rapid slide level assessment. The AIxURO platform (10), an artificial intelligence-based tool, has also been used to support cytopathologists for bladder cancer management. The platform is a specialized deep learning-based instance segmentation model that do not independently render a diagnosis but identifies and localizes cells indicative of high-cancer risk urothelial cells (suspicious cancer cells) and those linked to lower risk (atypical cells) presenting these cells for further examination by a cytopathologist. It has shown the potential to improve both sensitivity and efficiency of cytopathologists in bladder cancer diagnostics by urine cytology and to markedly decrease screening times. Limitations of this approach are the low performance for low grade tumors (as for classic cytology) and dependance on high quality slide preparation. These technologies could become a powerful adjunct to traditional cytology, especially in surveillance and high volume settings, although they are not yet replacements for expert cytopathology.

Pepe et al. (11) evaluated the use of the software QuPath for tumor-burden reporting, including the measure of the Greatest Percentage of Cancer in the evaluation of repeat biopsies in patients undergoing active surveillance for prostate cancer. QuPath is an open-source software platform designed specifically for digital pathology and whole-slide image analysis. It is engineered for whole-slide processing and cell segmentation, being compatible with multiplex imaging techniques to analyze different biomarkers on a single tissue section. For analyzing prostate biopsy whole slide images, the software, after importing the slides and detecting the tissue cores, can automatically segment glands and nuclei, helping distinguish benign from malignant areas. Users can annotate tumor regions, quantify tumor burden (including tumor length and percentage of core involvement), and extract detailed morphometric features.

In conclusion, systems of digital pathology are used to enhance diagnostic consistency and reduce workload. They cannot replace pathologists but can serve as a tireless and intelligent assistant. In fact, AI excels at high-volume and repetitive tasks, freeing pathologists to focus on complex cases and final diagnostic decisions. The other advantages of digitization include reducing interobserver variability, use as second reader tools and for triage negative biopsies.

Furthermore, digital images can be used for remote consultation, external quality assessment, and education.

Despite these favorable results, it must be kept in mind that AI is merely a tool to assist in pathological diagnosis and treatment that cannot replace human expertise.

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Finally, ethical and legal implications must be considered in order to establish legal frameworks and ensure transparency and ethical use of AI-based tools.
The FAIR (*Fairness of Artificial Intelligence Recommendations in healthcare*) statement (12) was recently proposed to "*provide a foundation for discussing the responsible and equitable implementation and deployment of AI in healthcare*".

Comment by Prof. Rodolfo Montironi

The paper by *Pepe et al.* (11) can be considered of great interest to histopathologists and clinicians for adopting a whole-slide imaging technique and QuPath, an open-source software for digital pathology image analysis, in the objective detection of architectural and cytological changes, including malignant transformation, in histological slides. The development of such an approach was started several years ago at the *Optical Sciences Center of the University of Arizona* (*Tucson, AZ*) by *Peter H. Bartels* and his group. The approach led to the development of machine vision-based histometry of premalignant and malignant prostatic lesions and automated analysis and interpretation of tissue abnormalities (13) as well as of automated reasoning system in histopathologic diagnosis and prognosis of prostate cancer and its precursors (14).
The paper by *Noviardi et al.* (8) can be considered of great interest to cytopathologists and clinicians for the investigation of atypical urothelial cells with automated urinalysis and expert review of microscopic sediment as early parameter for suspected bladder cancer patients. It is worth mentioning here the work by *Bartels* and his group. Years ago, they developed an automated system for the detection of subvisual changes in chromatin organization state detected by karyometry in the histologically normal urothelium in patients with synchronous papillary carcinoma (15). In the years that followed the original investigations by Bartels and his group, great steps have been taken in the field of digital pathology and image analysis, thanks also to the use of artificial intelligence. Currently, the major advantages associated with tissue digitalization have become evident in terms of consultation and remote interpretation, including image analysis, but also in the direct integration with data derived, for instance, from surgery and other imaging techniques, such as multiparametric Magnetic Resonance Imaging. All of this has required combining and integrating our knowledge of pathology and oncology with engineering and informatics (16).
The papers by *Pepe et al.* (11) and by *Noviardi et al.* (8), published in the current issue of journal, have both taken full and successfully advantage of the previous developments in the field of digital pathology image analysis. And this makes both papers of great interest to pathologists, clinicians and patient advocates.

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