

Applications of Artificial Intelligence for Pathological Diagnosis of Bladder Cancer

Rebecca Reese¹, Augustine Miller¹, Anil V Parwani^{2, #}

¹ Wright State University Boonshoft School of Medicine, Dayton, Ohio 45435, USA

² Department of Pathology, The Ohio State University, Columbus, Ohio 43210, USA

Abstract: The introduction and advancements of digital and computational pathology have made integration of Artificial Intelligence (AI) diagnostic algorithms into the clinical laboratory a reality. In the case of bladder cancer, a malignancy which places high burden both on patients and providers, AI has the potential to increase diagnostic sensitivity and improve diagnostic predictive performance. This review aims to synthesize current research and knowledge of the applications of AI in bladder cancer diagnostics. Overall, deep learning and convolutional neural network algorithms have successfully been applied to the diagnosis, grading, and differentiation of both non-muscle invasive and muscle-invasive bladder cancers. Additionally, AI shows great promise to improve treatment prediction and promotion of personalized medicine, including through integration of molecular signatures of bladder cancer. AI has also successfully been applied to cytopathology diagnostics, enabling quantitative and interactive identification of atypical cells. In order to promote clinical adaptation of these AI algorithms for the diagnosis of bladder cancer, key limitations must be addressed. This includes increasing interpretability of AI systems to address the black box effect, generation and collection of adequate and variable data sets, and proper consideration of realistic and safe integration into clinical practice. While AI has also been applied to areas of bladder cancer diagnosis such as cystoscopy and medical imaging, this is outside the scope of pathological diagnostics and is not discussed in this review.

Keywords: Bladder cancer; Artificial intelligence; Digital pathology; Histopathology; Cytology.

Introduction

Overview of bladder cancer

As of 2024, bladder cancer is the 10th most common cancer worldwide and poses a significant financial and administrative burden on patients and healthcare systems, ranking among the top ten most expensive cancers to treat over a patient's lifetime in the USA^[1,2]. Bladder cancer is three-to-four-times more likely to occur in men than women and the strongest risk factors are increasing age and tobacco smoking history^[1,3,4]. Urothelial cell carcinoma, also called transitional cell carcinoma, accounts for 90% of cases^[5]. Common histological subtypes are micropapillary, squamous differentiation, and glandular differentiation^[1,3]. Furthermore, bladder cancer can be classified as muscle-invasive bladder cancer (MIBC), which has invaded the muscularis propria, or non-muscle-invasive (NMIBC), which is less aggressive^[2,3,6]. Bladder cancer also has a strong association with upper tract urothelial carcinoma (UTUC), a rare cancer of the kidney or ureter. Up to 50% of patients with UTUC will develop bladder cancer and have a high risk of intravesical recurrence^[7,8].

Classically, management of bladder cancer involves combina-

tions of surgery, chemotherapy, immunotherapy, and radiation treatment. However, these treatments have heterogeneous outcomes^[9]. Treatment strategy differs dramatically depending on diagnosis of NMIBC or MIBC, as well as incorporation of low- or high-grade diagnosis, as well as presence of other high-risk features such as positive lymph nodes or margins^[9]. While MIBC typically requires a cystectomy with pelvic lymph node dissection, NMIBC may be treated with transurethral resection of bladder tumor (TURBT)^[1,3,9]. Treatment may also include surveillance coupled with intravesical therapy post-TURBT, such as cisplatin-based chemotherapy or immunotherapy with Bacillus Calmette-Guerin vaccine^[6,9]. However, cisplatin use is limited in patients with renal insufficiency, especially those of older age, meaning up to 50% of patients with bladder cancer may be ineligible to receive this first-line therapy^[9,10].

Treatment of bladder cancer relies heavily on diagnostic accuracy, as errors in diagnostic testing carry significant risks for patients with bladder cancer. For example, false positives lead to additional tests and treatments, increasing patient anxiety and cost, whereas false negatives delay treatment and allow for disease progression during vital windows of intervention, during which less aggressive options can lead to improved outcomes. Even cystoscopy, a common follow-up procedure, is invasive and carries risks of infection and inflammation^[1,11]. Additionally, patients with multiple TURBT surgeries have an increased risk of bladder wall perforation during cystoscopy due to fibrosis and weakening of the bladder wall^[12]. While bladder cancers have distinct molecular subtype profiles which can be used to predict

Correspondence: Anil V Parwani. E-mail: Anil.Parwani@osumc.edu. Address: Department of Pathology, The Ohio State University, E409 Doan Hall, 410 West 10th Ave, Columbus, OH 43210, USA.

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prognosis and treatment response, this testing remains costly even when accounting for recent progress in next generation sequencing and is not readily available worldwide^[3,5]. Therefore, due to the challenging and subjective nature of pathological evaluation of bladder cancer, artificial intelligence (AI) has the potential to be a promising source of technology for the future of bladder cancer diagnostics.

An introduction to digital pathology

Digital pathology has revolutionized the field of pathology and overall access is increasing in diagnostic laboratories^[13,14]. Routine digitization enables access to previous slides for review and comparison during follow-up, enabling an increased ease in tracking patient progress^[15,16]. Additionally, digitization can increase the ease of consultation and sharing of challenging cases, potentially helping to reduce health care disparities for underserved areas^[15]. Currently, tissue samples are scanned and stored as whole-slide images (WSIs) with high resolution for interpretation by pathologists^[14,17].

Digitization also opens the door to computational pathology (CPATH), which uses computational IT-assisted methods to aid diagnosis of disease via analysis of digital pathology images^[13,18,19]. Digital pathology allows for computer-assisted diagnostics in the format of AI, which can make predictions from these images, with the overall goal of improving patient care^[17,18]. However, differences in digital pathology workflow, such as scanner type, can influence image quality or color normalization, impacting AI algorithm accuracy^[20]. Thus, digital pathology workflow must be closely monitored prior to validation of AI tools for pathology diagnostics.

AI in pathology diagnostics

AI describes the use of advanced computer systems which can mimic human cognitive processes, such as reasoning and executive functions, via utilization of algorithms. Specifically, CPATH describes the combination of AI with pathology to analyze, interpret, and make predictions of medical data based on microscopic analysis^[13,19,21]. Collaboration between pathologists and AI methodologies increases diagnostic accuracy and reproducibility compared to pathologists alone^[16]. Additionally, AI can detect subtle sub-visual image features that may not be recognized by human eyes^[14,22].

Integration of AI relies on the foundation of a solid digital pathology workflow with direct overview by laboratory staff and pathologists. Generally, an AI-integrated workflow consists of generating digital WSIs from glass slides to enable analysis with AI CPATH algorithms, which are then reviewed and validated by a pathologist prior to incorporation into a final diagnostic report^[16]. Importantly, AI-tools should not and will not replace pathologists, but their existence and creation can improve diagnostic quality, which is recognized in a term called "computer-assisted diagnostics"^[18].

Briefly, applications of AI within pathology include, and are not limited to, detection of neoplasms, tissue segmentation, counting of mitotic figures, grading tumors, measuring tumor size or nucleus:cytoplasm ratios, prediction of gene expression and mutations, detection of lymph node metastases, and prediction of treatment response^[18,19,23,24]. Further, by integrating multiple data sources, including clinical, genomic, and histopathological and imaging data, it is possible to create comprehensive AI-based models which could dramatically improve predictive performance^[21,23].

Brief overview of AI systems

As mentioned, AI involves programming computers to operate autonomously via algorithms. Machine learning is a sub-division of AI which utilizes statistical algorithms to identify patterns in data and make predictions. This technique is called pathomic analysis when using digitized histopathological images. One subset of machine learning is deep learning, which utilizes algorithms resembling human neural networks to incorporate and interconnect complex data to make predictions and generate interpretations (Fig. 1). Convolutional neural networks (CNNs) are specifically useful in diagnostic pathology as they specialize in pattern recognition and visual data (Fig. 2). CNNs use convolutional layers to automatically extract features from images, including histopathological data^[17,18,24–26]. One subtype of a CNN, known as Visual Geometry Group (VGG), is known for its strength in image classification as it has a simple and uniform architecture^[27]. Further, a machine learning algorithm known as random forests enables use of ensemble learning, which combines multiple decision trees, as opposed to simple majority voting, to create an even more objective and accurate diagnostic tool^[20].

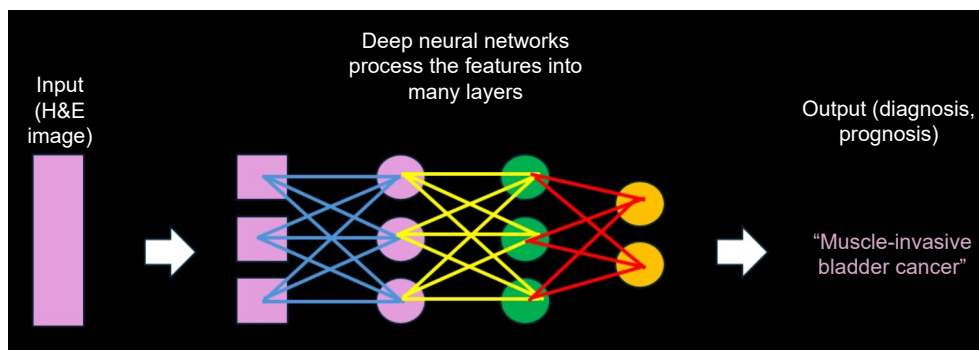


Fig. 1. How deep neural networks work: An H&E slide is scanned into WSI. Deep neural networks analyze the pixels of the image and interconnect them with previous images that the AI system has seen in training. Deep neural networks process these features into many layers, similar to how the human brain works. The system then generates an interpretation of the image.

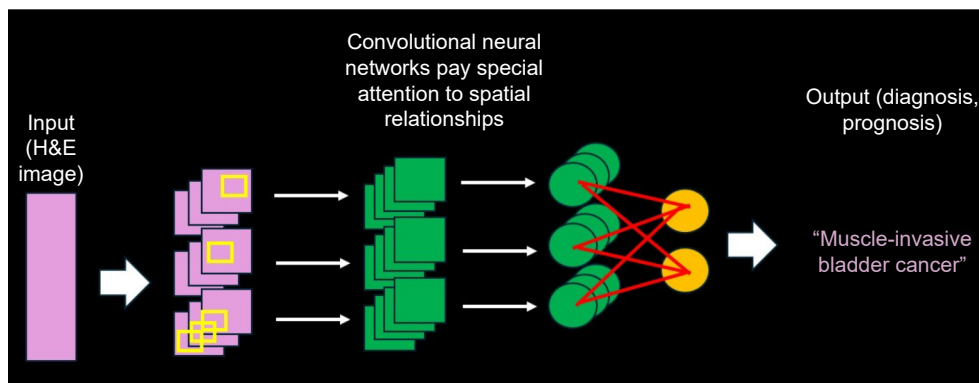


Fig. 2. How convolutional neural networks work: CNNs are a type of deep neural network that pay special attention to spatial relationships and automatically extract features such as edges, colors, and textures, requiring fewer parameters than traditional neural networks.

AI models can be trained with various levels of supervision and annotations. Supervised learning requires provision of human-made pre-labelled datasets, such as pixel-level annotations and labels of regions within histopathological images. For example, these labels may designate benign and malignant areas. While full annotation enables use of all information in a digital pathologic image, this requires extensive work by expert pathologists^[13,18,22,24]. In contrast, unsupervised learning does not require complete annotations. Rather, the model identifies and clusters image patterns and applies them to biologically meaningful groups^[13,18]. Integration of partial annotations or weak supervision can thus reduce time consumption per training image^[22]. Lastly, clustering techniques are often used to train AI to identify and remove redundant features^[23].

AI in urological pathology

Within urological pathology, AI has shown promise in areas of diagnosis, prognosis, and treatment prediction, including for bladder cancer^[26,28]. The use of AI within pathology can improve diagnostic efficiency and treatment quality by reducing the number of repeated procedures, including cystoscopies^[16,23]. One global bibliometric analysis showed that AI-driven urological tumor pathology research has continued to increase, with a surge between 2020–2023, with the greatest contribution coming from the United States^[29]. Compared to other urological cancers such as prostate and renal, which have seen the most advancements in AI diagnostics, bladder cancer is limited by fewer large-scale datasets^[16,26,29].

Machine learning and deep learning techniques have primarily been utilized in the creation of prediction tools for bladder cancer, which is especially of use due to a shortage of global expert pathologists^[26,30]. Within this review, we will focus on the current applications of AI for pathologic diagnosis for bladder cancer. While outside the scope of this review, AI has also been applied to steps in the diagnosis and treatment of bladder cancer outside of pathology. These advancements include AI-guided white and blue-light cystoscopy, bioinformatics, AI-guided radiation therapy, and integration of AI into imaging detection, including CT, MRI, and ultrasound^[24,26,31,32]. AI-incorporated research has also focused on the diagnosis of non-malignant bladder pathology, including bladder outlet obstruction, neurogenic bladder, interstitial cystitis/bladder pain syndrome, overactive bladder, and urinary incontinence^[33]. These non-malignant entities are also outside the scope of this review.

Analysis of AI in Pathological Bladder Cancer Diagnostics

Literature evaluation

This article was constructed via completion of a thorough review of current literature discussing the applications of AI in pathology-based diagnosis of bladder cancer. References were obtained and evaluated from Wright State University Libraries, Google Scholar, and PubMed using a systematic keyword search system. These keywords included words/phrases such as *artificial intelligence* and *bladder cancer*, *AI*, *histopathology*, *cytopathology*, and *pathology diagnostics*. The conclusions described in this article were formed via consensus achieved from the referenced articles in this review and are summarized in [Table 1](#)^[16,17,19–22,30,34–51]. While AI techniques are described thoroughly in this article, no form of AI was used in its creation.

Grading of bladder cancers

Grading is the histopathological examination of tissue that uses tumor cell structure to determine aggressiveness and prognosis, and to guide future treatments^[22,34]. Grading of bladder cancers is currently guided by the 5th edition of the World Health Organization Classification of Urinary and Male Genital Tumors^[22,34,52]. High-grade NMIBC tumors are more likely to progress to MIBC, making accurate grading integral to treatment plans and follow-up^[20]. However, due to the complexity of tumors and variation among pathologists, bladder cancer grading may be improved by the integration of AI diagnostics^[34,52].

One group utilized deep neural network architectures to form five distinct AI for Bladder Cancer (ABC) Grading Systems with the goal to use WSIs to accurately grade bladder cancers. Instead of the current grade values of 1, 2, or 3, the ABC models produce a decimal value for each WSI, improving the granularity of bladder cancer grading^[34]. However, future studies are needed to determine correlation with patient outcomes. All models accurately graded cancerous tissues, but with some variation. Specifically, the ABCInceptionResNet and ABC-Xception versions had the highest accuracy and fastest training stage in 100 epochs, compared to ABC-CNN, ABC-VGG, and ABC-Inception. The authors also described that the ABC system can be utilized to detect discrepancies between projected and originally documented grades, enabling the system to provide feedback to pathologists, especially those still in training^[34].

Table 1. Summary of key findings of current uses of AI in bladder cancer pathology diagnostics.

Focus	Key Findings
Grading of Bladder Cancer	Deep learning and CNNs have been utilized to accurately aid grading of bladder cancer, including through use of random forest algorithms. Grading can be further quantified to the decimal via an ABC Grading System. PAIDM was useful in patch-level recognition, which may be useful in fragmented specimens ^[20,22,34] .
NMIBC and MIBC Diagnostics	AI has shown success in differentiating NMIBC from MIBC. Deep learning showed promising predictive performance of recurrence of NMIBC. There were more relevant studies for applications in MIBC, with successful work in areas including prediction of MIBC prognostic subgroups, molecular subtypes, lymph node metastases, survival prediction, and detection of lymphovascular invasion ^[17,22,30,35–39] .
Prediction of Treatment Response	Deep learning models were successful and may be of use to predict bladder cancer treatment response to BCG, FGFR3 inhibitors, and immunotherapies such as PD-L1 checkpoint inhibitors ^[40–43] .
Genomics and Molecular Integration	Integration of genomic and molecular features via deep learning models can improve treatment prediction and may advance genomic and biomarker studies. Deep learning models have also successfully predicted luminal and basal-squamous molecular subtypes from H&E WSIs ^[30,37,44] .
Cytopathology Diagnostics	Cytology AI programs have aided quantitative identification of AUCS and HGUC and successfully predicted muscle invasion, including for UTUC. Integrated AI and immunocytochemistry algorithms have also shown improved diagnostic accuracy ^[45–51] .
Current Limitations to Adaptation	Key limitations to AI adaptation include the black box, which describes the limited interpretability of AI models, lack of adequate bladder cancer data training sets, and barriers to integration into clinical practice, such as proper data protection, effective digital pathology workflows, and cost effectiveness ^[16,19,21,35,36,45,50] .

AI, artificial intelligence; CNN, Convolutional neural network; ABC, AI for Bladder Cancer; PAIDM, pathological AI diagnostic model; NMIBC, non-muscle-invasive bladder cancer; MIBC, muscle-invasive bladder cancer; BCG, Bacillus Calmette-Guerin; FGFR3, fibroblast growth factor receptor 3; PD-L1, programmed cell death ligand-1; H&E, hematoxylin & eosin; WSI, whole slide image; AUCS, atypical urothelial cells; HGUC, high-grade urothelial carcinoma; UTUC, upper tract urothelial carcinoma.

Further, a single-institutional study developed a multi-scale pyramidal CNN which utilized three levels of patches, from 128×128 to 512×512 , to better predict the grade of NMIBCs. The various patch levels were fused via a random forest algorithm, which enabled increased accuracy, sensitivity, and specificity as compared to more traditional ResNet-18 models^[20]. This system specifically highlights the possible benefits of ensemble machine learning algorithms, which can increase accuracy through fusion of CNN outputs. While currently only applied to low vs high grade NMIBC, it will be interesting to see if it can be applied to other atypical subtypes or even carcinoma in situ in the future^[20].

Another group was able to utilize a pathological AI diagnostic model (PAIDM) to assess histologic grade and invasion depth of bladder cancer specimens^[22]. PAIDM was developed using ScanNet, a deep learning algorithm, and was trained with fully annotated slides. PAIDM especially showed success in patch-level recognition with an AUC of 0.878 (95% CI: 0.875–0.881), which could prove useful in fragmented specimens. Additionally, PAIDM highlighted prediction masks in the image via heatmaps to direct pathologists’ attention to suspicious regions, increasing its interpretability. However, PAIDM was unable to effectively classify carcinoma in situ, though future optimization hopes to include this type of data^[22].

NMIBC and MIBC diagnostics

As mentioned, bladder cancer has classically been divided into two main categories based on depth of invasion: NMIBC and MIBC^[23]. One review found that overall, AI techniques have shown high diagnostic performance in the prediction of MIBC from imaging studies, but application to clinical use will require higher quality studies with increased sample sizes^[53]. Briefly, NMIBC includes the early stages of CIS, Ta, and T1^[6,23]. While MIBC has a higher risk of metastasis, NMIBC has a higher recurrence rate at 70–80% and can progress to MIBC, thus requiring

frequent monitoring^[6,23]. As of 2025, the European Association of Urology Guidelines on NMIBC recommend a first cystoscopy after TURBT at 3 months, followed by a risk-stratified follow-up. For instance, in intermediate-risk NMIBC, if the first cystoscopy 3-months post-TURBT is negative, patients are advised to undergo cystoscopy every 6 months for 2 years followed by yearly cystoscopies up to ten years^[54]. Even when adjusting for risk stratification, this follow-up can impose a high cost to the healthcare system and a significant burden to the patient^[23].

AI algorithms have shown success in differentiating NMIBC from MIBC. As briefly discussed in section 2.2, PAIDM is a deep learning algorithm which showed success in accurately identifying invasion depth of bladder cancer specimens from WSIs with an accuracy of 0.850 and specificity of 0.941^[22]. Further, through incorporation of a spatial proximity factor between muscularis propria and tumor, a CNN-based algorithm was able to identify almost all cases of MIBC from TURBT specimens in a clinical validation cohort. The one missed case was a rarer subtype of nested urothelial carcinoma, which highlights the need for increased variability of training data sets. The algorithm also detailed where areas of muscularis propria invasion were identified, which could be utilized to improve diagnostic efficiency by quickly directing pathologists’ attention to the invasive portion^[35].

Within NMIBC specifically, AI has been applied to predict recurrence of the uroepithelial carcinoma subtype of NMIBC within one year of TURBT. A retrospective multi-center study showed that a deep learning pathomics model was able to achieve an AUC of 0.860 (95% CI: 0.752–0.969), indicating promising performance to predict recurrence within one-year. A heat map was utilized to show which fields had stronger recurrence labels by the program, improving interpretation of the model by clinicians. However, this model was only trained on the uroepithelial carcinoma subtype due to concerns of other variant subtypes affecting the model’s prediction status^[36].

Overall, more relevant studies were found for cases of MIBC. For example, a deep learning procedure was able to successfully classify patients into three distinct MIBC molecular subtypes through integration of hematoxylin and eosin (H&E) WSIs and genomic characteristics. This predicted clinical outcomes with an AUC of nearly 1. Specifically, each of these three subgroups were predicted to respond well to utilization of cytokine/chemokine antagonists, immunotherapy and anti-angiogenic therapies, or chemotherapy depending on the molecular subtype identified by the AI software. This was especially useful for cancers with immune-hot tumor microenvironments, the non-cancerous cells and cellular components within a tumor. This includes immune cells which can serve as targets for therapies that boost immune response^[55]. This opportunity to utilize precision medicine directly from H&E slides would be an economical and efficient stratification system^[38].

Another study identified two distinct prognostic subgroups within MIBC via use of a weakly-supervised learning and neural architecture search (NAS) algorithm from H&E WSIs^[37]. This suggests that histopathological patterns of MIBC are associated with multi-omics profiles. This can be used for cost-effective risk stratification, selection for molecular characterization, and treatment planning^[37]. Multi-omics profiles are further described in section 2.5.

Further, approximately 25% of patients with MIBC have lymph node metastases at the time of diagnosis, indicating a worse prognosis^[39,56]. One group developed the lymph node metastases diagnostic model (LNMDM) to aid detection^[39]. Through a retrospective multicenter study, LNMDM successfully predicted MIBC-associated lymph node metastases, including micro-metastases, from WSIs. Notably, LNMDM detected micro-metastases in 13 patients that had not been noted by pathologists, proving its ability to increase sensitivity, particularly to these micro-metastases^[39].

Additionally, the presence of tumor cells within lymphatic vessels, known as lymphovascular invasion (LVI), is linked to poor prognosis in patients with MIBC^[17,57]. Classically, costly IHC is utilized to distinguish lymphatic versus blood vessels to determine LVI status. The slide-based lymphovascular invasion predictor (SBLVIP) is a deep learning model which successfully identified LVI invasion status, achieving an AUC of 0.77 (95% CI: 0.63–0.84)^[17]. This study also showed that LVI status as predicted by SBLVIP had a high significant independent prognostic value of $P = 1 \times 10^{-6}$, indicating that AI can be utilized to highlight and further determine important prognostic factors for patients with MIBC^[17].

Finally, overall survival prediction for patients with MIBC via incorporation of deep learning has shown promise. Zheng's group has developed both diagnostic and predictive models known as BlcaMIL and MibcMLP, respectively^[30]. Interestingly, the risk score predicted by MibcMLP showed strong survival prediction as compared to pre-existing clinical or histopathologic indicators via both univariate (hazard ratio = 2.390, $P < 0.001$) and multivariate (hazard ratio = 2.414, $P < 0.001$) Cox analyses, which could be used to predict patient outcomes and guide treatment decisions. Tumor areas which had high attention scores were also highlighted via a divergence colormap, which displayed areas most relevant to diagnosis, significantly increasing the interpretability of the model by uropathologists^[30].

Prediction of treatment response and immunotherapies

AI has the potential to play an essential role in treatment prediction and promotion of personalized medicine, including in immuno-oncology and directing the use of immunotherapies^[38,58]. As shown in Jiang et al's study regarding prediction of MIBC molecular subtypes, stratification of suspected treatment response during diagnosis is possible and is highly promising^[38].

Bacillus Calmette-Guérin (BCG) is an immunotherapy which stimulates the body's own immune cells to target bladder cancer cells in NMIBC^[1,59]. However, there have been recent BCG shortages and cases of BCG-unresponsive disease. Fortunately, AI has the potential to predict these treatment failures and thus be utilized in counseling and treatment selection^[6,40]. Specifically, a deep-learning AI model known as the Computational Histology AI (CHAI) platform was successfully validated to analyze WSIs from pre-treatment TURBT specimens of high risk-NMIBC^[40]. The CHAI model has been reported to identify patients at increased risk of post-BCG recurrence, development of BCG-unresponsive disease, and eventual risk of cystectomy. By identifying patients who are less likely to benefit from BCG, CHAI may be used to better allocate resources and guide personalized and higher quality treatment plans^[40].

Further, one deep learning AI system was able to successfully predict fibroblast growth factor receptor 3 (FGFR3) mutational status of bladder cancer patients directly from H&E slides, with acceptable Area Under the Receiver Operating Characteristic Curves (AUROCs) of 0.701 ($P < 0.0001$) and 0.725 ($P < 0.0001$). Currently, FGFR inhibitor treatment is used in advanced MIBC with pT2-4 tumors but traditionally requires molecular testing prior to use which can be costly. While at this time FGFR3 mutational status should still be confirmed molecularly, this AI system could serve as an inexpensive tool to assist in pre-selection of patients for molecular testing^[41].

Immunotherapy checkpoint blockade via targeting of programmed cell death protein-1 (PD-1) or the ligand (PD-L1) has revolutionized the treatment of several cancer types, including bladder cancer. IHC expression is evaluated both on tumor and immune cells, but manual interpretation of IHC is difficult and shows significant intra- and inter-observer variability^[42,60]. PD-L1 immunotherapy is second line for unresectable or metastatic tumors and is first-line for patients who are ineligible for the standard first-line cisplatin-based chemotherapy, usually due to renal insufficiency or age^[10,42,43].

While a relatively small sample size ($n = 43$) was used, one group utilized the free, community-driven QuPath software and compared two AI protocols for PD-L1 IHC scoring^[42]. These protocols included Selected Area Interpretation (AI-SAI), which utilized custom selection of representative areas and was compared to WSI (AI-WSI). Interestingly, AI-SAI displayed stronger agreement with manual assessment, especially in cases with high PD-L1 positive tumor cell content. Unfortunately, immune cell PD-L1 expressions were found to be too complex to assess with these AI models due to confounding factors such as prior transurethral resection lesions, which often results in the infiltration by giant multinucleated cells^[42].

Tumor microenvironments, which contain tumor-infiltrating lymphocytes (TILs) such as CD8 + T cells, show promise for predicting response to immune checkpoint inhibitors. Interestingly, some patients who stain negative for PD-L1 status may still re-

spond to these treatments^[43,61]. UC-TIL is an AI-based model that can quantify spatial features, rather than density, of TILs from H&E stained-slides. UC-TIL achieved strong predictive performance with an AUC of 0.757 and showcased an ability to identify non-responders to immune checkpoint inhibitors with a specificity of 91%. While the study utilized a small retrospective cohort and will require an increased sample size in future studies, UC-TIL may guide and personalize immunotherapy for patients with MIBC in the future^[43].

Genomic and molecular integration and prediction

As briefly discussed, the integration of genomic and multi-omics data features with WSIs can provide a deeper understanding of the tumor sub-set, facilitating precise treatment prediction in bladder cancer based on molecular subtypes^[37,38,62]. Additionally, deep learning models have been able to identify genes related to heightened risk scores within MIBC, potentially advancing biomarker discoveries^[30].

Based on the neural architecture search (NAS) algorithm, which stratified risk levels of MIBC via use of cancer-specific death, one group investigated multi-omic subtypes including variants in molecular regulatory profiles, such as microRNA and DNA methylation levels, from H&E WSIs. Specifically, they found the high-risk MIBC group had molecular subtypes associated with lymphocyte infiltration including CD274 (PD-L1) and PDCD1 (PD-1). These findings suggested that the high-risk group may be more likely to benefit from immune checkpoint inhibitors, such as anti-PD-1 or PD-L1, or from epigenetic therapy. On the other hand, the low-risk MIBC group had a favorable multi-omics profile with high FGFR3 mutations and low CD274 and PDCD1^[37]. By predicting these molecular patterns directly from histopathological images, AI has the potential to stratify patients to promote cost-effective treatment planning.

Bladder cancer has also been sub-typed molecularly into luminal and basal-squamous subtypes, which have distinct molecular expression signatures and response to treatment. Basal-squamous is considered more aggressive and has a worse prognosis, lower survival rate, and higher proliferation rates, but appears to have increased receptivity to treatment with immune checkpoint inhibitors^[44,62,63].

One group developed a deep learning-based model that was able to successfully predict the molecular subtype, either luminal or basal-squamous, from H&E histopathological images^[44]. With the incorporation of the N and M stage, the model achieved relatively high accuracy with an AUC of 0.877 (95% CI: 0.834–0.920) and 0.794 (95% CI: 0.701–0.887) in the training and validation cohort, respectively. While findings are limited without the use of an external validation cohort, this study shows promising potential to enhance treatment prediction directly from H&E slides without the need for expensive molecular mRNA analysis and subjective immunohistochemical analyses^[44].

Finally, one group was also able to predict basal or luminal subtypes via a deep learning model that extracted its own tumor patches via a RetCCL model. Specifically, RetCCL, a specialized version of a Resnet50-based model, obtained its own precise tumor regions prior to analysis of molecular subtypes. This permitted integration of automatic tumor region annotation, reducing the time needed for manual annotation. The additional integ-

ration of support vector machine, random forest, and logistic regression also resulted in an AUC of 0.85, accuracy of 0.80, sensitivity of 0.64, and specificity of 0.96 for prediction of basal vs luminal subtypes. This promising model has plausible scalability for large healthcare centers due to the automatic extraction features. However, work remains to address additional subtypes such as stromal-rich or neuroendocrine-like which may have additional clinical relevance^[62].

Cytopathology diagnostics

Deep learning and CNN-based models have also been applied to urine-based cytological specimens, a non-invasive diagnostic method, to improve detection and surveillance of bladder cancer^[25,31,45]. In 2016, urine cytology adopted The Paris System (TPS), a standardized reporting system that improved classification of high-grade urothelial carcinoma (HGUC) and decreased the reporting of atypical urothelial cells (AUCS), a previously broad category that included cells both with and without signs of malignancy^[24,48,64,65]. The Paris System was updated to the second edition in 2022 and eliminated the diagnosis of low-grade urothelial neoplasm due to the low sensitivity of detection. Overall, TPS has focused on improving the detection of the more aggressive HGUC^[64–66].

While cytology is extremely valuable in bladder cancer management, its sensitivity is limited by reliance on cellular yield and inter-observer variability based on cytopathologist experience^[45]. Compared to traditional digital pathology, use of AI in cytology has lagged due to the difficulty of scanning 3D structures and haphazard distribution of cells in cytology specimens, but use of z-stacking or volumetric scanning in digital cytology systems has helped address these challenges^[64]. Overall, one review showed that the main application of AI within cytopathology is identification and characterization of cytologically abnormal cells, with additional applications including prediction of histopathological results, prediction of recurrence, and risk stratification of abnormal cells^[45].

One primary example of the use of AI in cytology is AIxURO, a deep learning-based model which utilizes a segmentation algorithm and applies TPS criteria to possibly malignant cells to provide quantitative identification of AUCS. Importantly, AIxURO also utilizes a viewing interface software which displays quantitative data on target cells, allowing cytology staff to interact with and learn from the inference results^[47,48]. This interface includes a gallery of images of abnormal cells, along with N/C ratio and nuclear size of each cell. The reviewer can also select the thumbnail to the WSI field, which allows for comparison of the cell to nearby cells and background^[47]. Due to this ability, through data generated by AIxURO, one study suggested decreasing the N/C ratio of cells suspicious for HGUC to 0.66, from the current TPS cut-off of > 0.7 ^[24].

AIxURO has also been shown to increase sensitivity and negative predictive value of cytology for AUCS cases^[47]. It also reduced screening time spent on WSI review. However, despite an enhanced ability to detect positive cases, a lower specificity and positive predictive value indicates that more false positives may be detected, emphasizing the importance of careful integration of AI systems into clinical workflow^[47].

Further, a retrospective study in Taiwan also utilized AIxURO's

instance segmentation to distinguish high-risk cells vs low-risk atypical cells for patients who were undergoing post-nephroureterectomy follow-up for UTUC^[48]. This model significantly improved postoperative urine cytology reporting confidence. Also, despite having a sample size of only 204 cytology slide samples, AIXURO was able to identify two additional cases of early intravesical recurrence, indicating a possible increase in the sensitivity of cytology detection for recurrence of UTUC^[48].

Another AI system known as EffcientNet from Google Brain[®] utilized a semi-supervised machine learning method to detect HGUC from cytology specimens^[49]. This is a fully automated AI system which achieved a superior sensitivity for detection of HGUC compared to pathologists (63% vs 46%, respectively). Pathologists were also able to retrospectively review cells labeled as HGUC, enabling provision and analysis of diagnostic evidence of the AI's decision making^[49].

Additionally, a novel-liquid based immunocytochemistry method was integrated with machine learning to create the Cyto-Bay/Techcyte platform to detect urothelial carcinoma from urine-based samples^[50]. This non-invasive analysis method focused on specimen processing to ensure preservation of cellular integrity during immunocytochemical staining of key biomarkers, including CK17, GATA-3, and hTERT, along with traditional assessment of nuclear: cytoplasmic ratio, chromatin, and nuclear membranes. The workflow-oriented approach with multi-marker analysis enabled achievement of a diagnostic performance of 100% sensitivity and specificity depending on their combined use. This study especially highlights the importance of prioritizing clinical workflow during the integration of AI systems to enhance outcomes^[50].

Finally, AI has also been utilized in cytological specimens to attempt prediction of muscle invasion in urothelial carcinoma from cytology specimens^[51]. Specifically, through integration of cellular-level and contextual features, the precision urine cytology AI solution for muscle invasion (PUCAS-M) was able to effectively predict muscle invasion in urine cytology images with an AUROC of 0.857 (95% CI: 0.820–0.895). This was especially improved through integration and incorporation of clinical and radiological data when making predictions. Specifically, PUCAS-M displayed particularly notable accuracy in neoadjuvant therapy subgroups with a sensitivity of 0.828 (95% CI: 0.642–0.942) and a specificity of 0.868 (95% CI: 0.719–0.956). Further, as UTUCs experience underestimated pathological stages from ureteroscopy, incorporation of PUCAS-M could assist with increasing precision of pre-operative identification of muscle invasion and assist in guidance of neoadjuvant therapy for this subgroup of patients^[51].

Current Limitations of AI in Pathology Bladder Cancer Diagnostics

AI shows much promise in improving laboratory diagnostic performance for patients with bladder cancer. However, these algorithms have yet to be widely adopted by healthcare systems due to three key limitations: interpretability of AI systems, data availability, and clinical practice integration. These must be addressed to ensure successful adoption.

Interpretability of Decision Making and the Black-Box

The black box effect is a common difficulty among deep learning algorithms in which the AI model fails to provide transparency to the reviewer of its decision-making process. This makes it difficult for clinicians to understand how a diagnosis was reached by the model, causing limited trust and acceptance of AI programs^[21,29,36,45]. Models which explain their reasoning are needed to overcome this black box effect^[21,23].

Heatmaps serve as an opportunity to begin addressing this black box effect. As employed by PAIDM, use of heatmaps or highlighting of prediction masks in images can assist with visualization of prediction results and assist in direction to suspicious areas of a sample, thus increasing understanding of the AI decision-making process^[22]. A similar heatmap and divergence colormap approach was used by both Wang's and Zheng's groups to help make the predictions made by their model more understandable to clinicians and uropathologists, which could increase acceptance of AI systems^[30,36].

Additionally, within urine cytology, the black box effect has been addressed specifically by enabling pathologists the opportunity to retrospectively review cells labeled as atypical or high grade by the AI algorithms^[47–49]. For example, the deep learning platform AIXURO provided a viewing interface which highlighted abnormal cells. Cytology staff are also able to interact with inference results on key quantitative data obtained by AIXURO on the selected cells, including N/C ratio and nucleus area, further helping to combat this black-box effect in cytology^[47,48].

The Need for Large Center Studies with Adequate and Diverse Data Sets

In order to create trustworthy AI programs, large, multi-institutional, high-quality datasets for bladder carcinoma are required to ensure generalizability, reliability, and to promote effective and accurate training for AI programs^[16,24,31]. Unfortunately, one review found that many studies they investigated utilized fewer than 30 WSIs in their research, which emphasizes a true need for larger, more thorough data sets^[16]. This is especially important for rarer subtypes of bladder cancer, which if not included in training sets, may lead to misdiagnosis from AI algorithms^[35].

Additionally, diverse training data sets are needed to prevent exacerbation of disparities in healthcare outcomes and healthcare inequalities, due to the risk of misdiagnosis if not included in a training set^[45]. Single institution datasets also pre-dispose AI systems to a phenomenon known as domain shift, in which there are significant feature differences between the training and target data sets. This difference predisposes AI systems to performance degradation^[49,67].

One review proposed a strategy consisting of data-sharing frameworks based on Findable, Accessible, Interoperable, and Reusable (FAIR) principles and establishment of trans-national urological AI pathology research consortia to address key resource sharing and promote collaboration, especially for developing countries^[29]. Among the calls for better quality data sets and sample size, reviewers have also noted the need for higher quality of studies overall, including additional data such as "prediction explanation, failure analysis, and sensitivity analysis"^[53]. As digital pathology continues to evolve, routine digitization of slides can also assist in development of larger, heterogenous training sets for future AI models^[15].

Integration into Clinical Practice

While AI-digital pathology research has flourished, true integration of these AI algorithms into practice still remains limited. As the ultimate goal is, and must always be, to utilize AI to improve patient outcomes, key barriers to protect patients must be in place^[19].

Firstly, integration requires assurance that patient data is protected via data security and safeguards, including ensuring compliance with regulatory frameworks such as the Health Insurance Portability and Accountability Act (HIPAA)^[23,31,45]. Transfer of information from electronic health records is also costly, time-consuming, and must be safely regulated^[28]. Further, integration into clinical practice requires consideration of ethical and legal implications, with reviewers calling for AI-based tools to promote transparency and ethical use^[15,16,21,24]. For instance, there must be standardization of clinical follow-up with patients with bladder cancer who have AI-based results. Additionally, transparency of this information and the use of AI must also promote trust within the laboratory system^[21].

As AI programs rely on digital pathology, thorough planning for implementation of a digital workflow is also essential. Introduction of digital pathology requires consideration of various aspects including technical challenges such as system compatibility, availability of data storage and logistical expertise, and start-up and maintenance costs^[15]. Implementation into clinical settings also requires focus on scalability and infrastructure that matches the speed and intricacy necessary to implement these technologies into health systems^[14,23,31].

A workflow-oriented approach to employment of AI algorithms can also assist with "ensuring practical clinical utility"^[50]. This includes addressing specimen collection, quality, and processing prior to utilization of AI-assisted diagnostics, as well as consideration of implementation of digital pathology workflows. It is essential to ensure that workflow is optimized prior to incorporation of AI technological implementation^[50].

Cost effectiveness and timeliness of the AI technology must also be considered to improve clinical adoption. One review of AI in MIBC found that no study reported cost-effective analyses of their models, an essential part of AI adoption into clinical practice, especially since the initial investment of AI algorithms is high^[16,53]. Additionally, incorporation of automatic tumor region annotation may help to reduce time required for manual annotation and assist with implementation into large healthcare systems^[62].

Finally, interpretation of the majority of a patient's sample, rather than a glimpse of a specific tumor region, is needed to understand and characterize the variations and heterogeneity which may exist within a tumor. This indicates the need for AI algorithms to be able to analyze more than just a small subset of a WSI to truly represent tumor characteristics^[37]. The ability to analyze a sufficient portion of a WSI must therefore be accounted for when integrating AI into clinical settings to provide comprehensive reports^[19].

Conclusions and Future Directions

As integrated diagnostics and computational pathology continues to evolve, AI has potential to revolutionize the diagnostic man-

agement of bladder cancer by improving accuracy, precision and productivity. Proper integration of AI algorithms may assist in leading the future of personalized medicine in the diagnosis and treatment of bladder cancer. While AI can enhance diagnostic precision and efficiency, it is essential to understand that implementation of these AI programs requires strict collaboration with pathologist expertise to ensure accurate results and integration of complex clinical information prior to incorporation into the final diagnostic report, which must still be finalized by a pathologist. Thus, AI will serve as a tool to assist and aid clinical decision making, without replacement of pathologists.

Even while we await models with increased interpretability and larger, more representative data sets, applications of AI in bladder cancer diagnostics continue to evolve and computer-assisted diagnostics will be able to improve future efficiency and quality. Models which incorporate pathological features in addition to multi-modal data, such as clinical, radiological, and genomic markers, will be the most useful to generate enhanced comprehensive risk prediction for patients. Finally, AI may also bridge global healthcare gaps through promotion of better access to high-quality bladder cancer diagnostics in developing regions.

Abbreviations

ABC, AI for Bladder Cancer; AI, artificial intelligence; AUC, area under the curve; AUCS, atypical urothelial cells; AUROC, Area Under the Receiver Operating Characteristic Curves; BCG, Bacillus Calmette-Guerin; CHAI, computational histology AI; CNN, convolutional neural network; CPATH, computational pathology; FAIR, Findable, Accessible, Interoperable, and Reusable; FGFR3, fibroblast growth factor receptor 3; H&E, hematoxylin & eosin; HGUC, high-grade urothelial carcinoma; LNMDM, lymph node metastases diagnostic model; LVI, lymphovascular invasion; MIBC, muscle-invasive bladder cancer; NAS, neural architecture search; NMIBC, non-muscle-invasive bladder cancer; PAIDM, pathological AI diagnostic model; PD-1, programmed cell death protein-1; PD-L1, programmed cell death ligand-1; PUCAS-M, precision urine cytology AI solution for muscle invasion; SAI, selected area interpretation; TIL, tumor-infiltrating lymphocytes; TPS, The Paris System; TURBT, transurethral resection of bladder tumor; UTUC, upper tract urothelial carcinoma; VGG, visual geometry group; WSI, whole slide image.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Authors' contributions

RR: Completed literature review, wrote the manuscript, and prepared tables. AM: Created Figures 1 and 2, assisted with manuscript revision and additional writing of the manuscript. AVP: Also assisted with manuscript revision and additional writing of the manuscript.

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