



Review

Artificial Intelligence in Bladder Cancer Diagnosis: Current Applications and Future Perspectives

Giulio Rossin ¹, Federico Zorzi ¹, Luca Ongaro ¹ , Andrea Piasentin ¹ , Francesca Vedovo ¹, Giovanni Liguori ¹, Alessandro Zucchi ² , Alchiede Simonato ³ , Riccardo Bartoletti ², Carlo Trombetta ¹ , Nicola Pavan ³ and Francesco Claps ^{1,*}

¹ Urology Clinic, Department of Medical, Surgical and Health Sciences, University of Trieste, Cattinara Hospital, Strada di Fiume, 447, 34149 Trieste, Italy

² Department of Translational Research and New Technologies, University of Pisa, 56126 Pisa, Italy

³ Urology Clinic, Department of Surgical, Oncological and Stomatological Sciences, University of Palermo, 90127 Palermo, Italy

* Correspondence: claps.francesco@gmail.com

Abstract: Bladder cancer (BCa) is one of the most diagnosed urological malignancies. A timely and accurate diagnosis is crucial at the first assessment as well as at the follow up after curative treatments. Moreover, in the era of precision medicine, proper molecular characterization and pathological evaluation are key drivers of a patient-tailored management. However, currently available diagnostic tools still suffer from significant operator-dependent variability. To fill this gap, physicians have shown a constantly increasing interest towards new resources able to enhance diagnostic performances. In this regard, several reports have highlighted how artificial intelligence (AI) can produce promising results in the BCa field. In this narrative review, we aimed to analyze the most recent literature exploring current experiences and future perspectives on the role of AI in the BCa scenario. We summarized the most recently investigated applications of AI in BCa management, focusing on how this technology could impact physicians' accuracy in three widespread diagnostic areas: cystoscopy, clinical tumor (cT) staging, and pathological diagnosis. Our results showed the wide potential of AI in BCa, although larger prospective and well-designed trials are pending to draw definitive conclusions allowing AI to be routinely applied to everyday clinical practice.

Keywords: bladder urothelial carcinoma; artificial intelligence; diagnosis; biomarker; machine learning; deep learning



Citation: Rossin, G.; Zorzi, F.; Ongaro, L.; Piasentin, A.; Vedovo, F.; Liguori, G.; Zucchi, A.; Simonato, A.; Bartoletti, R.; Trombetta, C.; et al. Artificial Intelligence in Bladder Cancer Diagnosis: Current Applications and Future Perspectives. *Biomedinformatics* **2023**, *3*, 104–114. <https://doi.org/10.3390/biomedinformatics3010008>

Academic Editors: Shuncong Wang and Peihua Zhao

Received: 6 January 2023

Revised: 20 January 2023

Accepted: 22 January 2023

Published: 1 February 2023



Copyright: © 2023 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Urothelial carcinoma (UC), which encompasses bladder cancer (BCa) and upper tract urothelial carcinoma (UTUC), represents the sixth most diagnosed cancer in Western countries [1,2]. Focusing on BCa as the most common, it can present as a very heterogeneous disease comprising both non-muscle-invasive (NMIBC) and muscle-invasive (MIBC) with different oncological outcomes. Although several clinical and pathological tools have demonstrated acceptable reliability both in terms of diagnostic and prognostic settings, there are currently no molecular biomarkers used in the clinical daily practice [3–10]. Nowadays, medical decisions should be tailored to the individual patient based on diagnostic risk-based pathways [11] and the predicted response to local treatment and systemic agents, including conventional chemotherapy and novel immune checkpoint inhibitors (ICIs), or targeted agents in both neoadjuvant or adjuvant settings [12].

Pathological and molecular diagnosis upon transurethral resection of bladder tumor (TURBt) and radical cystectomy (RC) specimens are critical in providing prognostic information and driving subsequent management [8,13,14]. Despite their importance, all of the aforementioned diagnostic methods are strongly operator-dependent and biased by interobserver variability, entailing the risk of misdiagnosis [15,16].

In the era of precision medicine, the support of technological innovation tries to address these gaps to enhance the diagnostic performance in these “grey areas”. The exponential development of bioinformatics is an innovative and promising tool [17]. Artificial intelligence (AI) is one of the most innovative tools; however, it remains less explored than applications of bioinformatics in medical practice. AI refers to a computational technology that imitates human skills, such as learning and problem-solving [18]. Machine learning (ML) is a sub-field of AI that harnesses dynamic algorithms to resolve complex tasks through a data-driven training pathway [19]. Deep learning (DL) represents another subtype of AI based on a ML technique called artificial neural networks (ANN), which is able to extract patterns and produce predictions from large datasets [20].

Exploratory studies have evaluated the potential applications of AI and ML in different fields of urology, mainly in the diagnostic and prognostic assessment of genitourinary cancers; experiences in other urological areas, such as urolithiasis, kidney transplantation, urinary infections and functional urology, have also been reported [21].

Nevertheless, it should be noted that AI medical applications go far beyond the urological field. Since John McCarthy’s first definition of artificial intelligence in 1956 [22], medical applications of this computational technology have been adapted to numerous different areas and subjects. In recent decades, AI medical applications have been commonly divided in “virtual” and “physical” branches [23]. The virtual branch refers to all the medical applications aiming to provide an AI enhanced decision-making, for example interpretations of radiological images, such as X-ray mammography (computer-assisted diagnosis, CAD) or endoscopic gastroenterological images. On the other hand, the physical branch refers to the development of high precision medical instruments through AI implementation, such as surgical devices including the DaVinci Xi Surgical Robot provided by Intuitive Surgical or innovative rehabilitation instruments such as active articular prosthesis [23]. AI technologies are also widely applied in molecular and pharmacological fields. New innovative drugs tailored on specific genomic mutations have been developed from a big data analysis carried out through ML [24].

In this narrative review, we aim to summarize the most recent applications of AI in BCa management, focusing on how this emerging platform of interest could impact physicians’ accuracy in three widespread diagnostic areas: cystoscopy, clinical tumor staging (cT), and pathological diagnosis.

2. Materials and Methods

A bibliographic search for relevant publications using Medline and EMBASE was performed in November 2022. We chose the following keywords: “Machine”, “Deep Learning”, “Bladder cancer”, and “Artificial Intelligence”. Only original articles published in the English language were considered. Suitable publications were reviewed to determine whether they were eligible for inclusion (Figure 1). Case reports, reviews, and editorial comments were excluded.

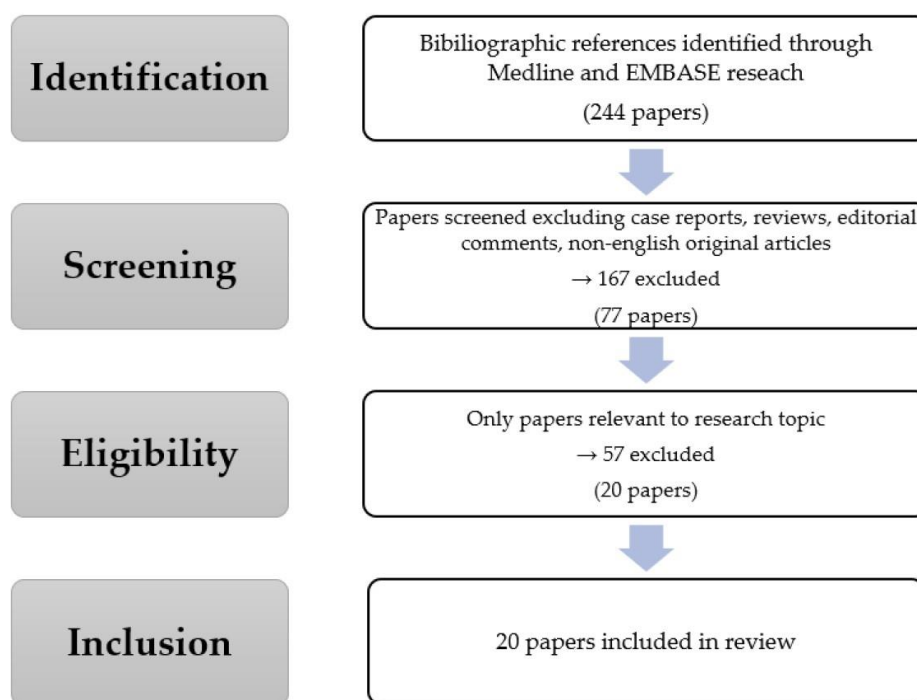


Figure 1. Flow diagram of the literature review for artificial intelligence bladder cancer studies.

3. AI-Enhanced BCa Diagnostical Pathway

3.1. AI-Enhanced Cystoscopy

White-light cystoscopy (WLC) is commonly used for BCa detection and follow-up after initial treatment of NMIBC. Despite its availability, WLC is affected by low sensitivity, mainly due to its operator-dependent nature. One of the most difficult challenges is to distinguish flat lesions from misleading mucosal non-specific reactivity [25]. Shkolyar et al. proposed an image analysis platform based on convolutional neural networks (CystoNet); they showed a per-frame sensitivity and specificity of 90.9% and 98.6%, respectively, in 54 prospective cases, resulting in three on three correct diagnoses of flat tumors on the final pathology report [26]. Wu et al. described a cystoscopy artificial intelligence diagnostic system (CAIDS) as being quicker and more accurate than expert urologists in the diagnostic assessment. With a latency diagnostic time of 12 s and a high accuracy evaluated as an area under the curve (AUC) of 0.94, the authors claimed to improve the detection of commonly misdiagnosed cases such as flat carcinoma in situ (cis) [27]. Recently, Yoo et al. presented an AI-enhanced platform able to predict BCa grading based on tumor color with the red/green/blue (RGB) method; the performance was $\geq 98\%$ for the diagnosis of benign vs. low- and high-grade tumors and $>90\%$ for the diagnosis of chronic non-specific inflammation vs. cis compared to conventional WLC [28]. Mutaguchi et al. aimed to reduce the risk of early recurrence due to overlooking of tumors during endoscopic resections by proposing a diagnostic system (Dilated U-net) trained on 1790 cystoscopy images categorized by the pathological T score from 120 patients who underwent TURBt [29].

In the context of imaging-enhanced visualization, blue light (BL) photodynamic diagnosis (PDD) provides better diagnostic accuracy and more complete tumor resection at the time of TURBt, potentially reducing BCa recurrence [30]. However, controversy exists about its impact, which was recently highlighted by Heer et al. within an open label randomized clinical trial including 538 NMIBC patients [31]. Thus, novel emerging AI-based algorithms have been advocated to refine such a diagnostic pathway. Ali et al. proposed an AI platform able to predict malignancy, invasiveness, and grading from BL cystoscopy images. The results showed a sensitivity and specificity of 95.77% and 87.84%, respectively, for BCa diagnosis, while the mean sensitivity and mean specificity for tumor invasiveness were 88% and 96.56%, respectively [32].

Notably, AI technology displays interesting potential as a learning tool, which may improve urologists' performance and cystoscopy skills depending on their experience level [33]. Ikeda et al. concluded that physicians' diagnostic accuracy can be objectively evaluated using their GoogLeNet platform since its detection accuracy was comparable to the one of an expert urologist [34]. The most relevant limitation of AI-enhanced cystoscopy imaging is the limited availability of the ML platforms. To address this issue, Du et al. presented the EasyDL platform designed as an application for mobile phones. This system showed an accuracy rate of 96.9% in BCa detection, which encompasses, at the same time, significantly more manageable possibilities of utilization as the software provides an output based on cystoscopy images uploaded through common smartphones [35]. Table 1 shows the most recent studies focusing on AI applied to cystoscopic diagnosis.

Table 1. Deep Learning approach applied to cystoscopy diagnosis.

Author	Year	Patients/Images	AI Technology	Outcomes
Shkolyar et al. [26]	2019	95 patients/2752 frames (internal)	CystoNet	Prospective validation in an additional cohort of 54 patients. Per-frame sensitivity and specificity: 90.9% (95% CI, 90.3–91.6%) and 98.6% (95% CI, 98.5–98.8%), respectively. Per-tumor sensitivity: 90.9% (95% CI, 90.3–91.6%). CystoNet detected 39 of 41 papillary and 3 of 3 flat BCas.
Du et al. [35]	2020	175 patients/1736 frames	Caffe deep learning framework and EasyDL platform	Accuracy rate in BCa detection: 82.9% based on Caffe framework, 96.9% on the EasyDL platform.
Ali et al. [32]	2021	216 blue-light frames (multicentric, from 4 urological departments)	InceptionV3 network, MobileNetV2 network, ResNet50 network, VGG16 network	Classification of malignant lesions sensitivity/specificity: 95.77% and 87.84% respectively; tumor invasiveness mean sensitivity/specificity: 88% and 96.56%, respectively.
Ikeda et al. [34]	2021	2104 frames (external—ImageNet data set)	GoogLeNet	95.4% sensitivity and 97.6% specificity (superior diagnostic accuracy when tumors occupied >10% of the image)
S. Wu et al. [27]	2021	10,729 patients/69,204 frames	Cystoscopy Artificial Intelligence Diagnostic System (CAIDS)	CIADS diagnostic accuracies: 0.977 (95% CI 1/4 0.974 to 0.979) in the internal validation set and 0.990 (95% CI 1/4 0.979 to 0.996), 0.982 (95% CI 1/4 0.974 to 0.988), 0.978 (95% CI 1/4 0.959 to 0.989), and 0.991 (95% CI 1/4 0.987 to 0.994) in different external validation sets. CAIDS vs. urologist comparisons: high accuracy and sensitivity (accuracy 1/4 0.939, 95% CI 1/4 0.902 to 0.964; sensitivity 1/4 0.954, 95% CI 1/4 0.902 to 0.983) with a short latency of 12 s, which was more accurate and quicker than the expert urologists.
Yoo et al. [28]	2022	1310 patients/10,991 frames	Mask RCNN with a ResNeXt-101-32 × 8d-FPN backbone	Sensitivity, specificity, diagnostic accuracy, and DSC of AI: 95.0%, 93.7%, 94.1%, and 74.7%, respectively. AI-diagnostic performance in WLI: ≥98% benign vs. low-and high-grade tumors, >90% non-specific inflammation vs. carcinoma in situ.
Mutaguchi et al. [29]	2022	120 patients/1790 frames	Dilated U-Net	Overlooking bladder tumors risk reduction: PWSe, PWSp, PWPPV, and DSC of the dilated U-Net were 84.9%, 88.5%, 86.7%, and 83.0%, respectively.

Abbreviations are as follows: CI: confidence intervals; PWSe: pixel-wise sensitivity; PWSp: pixel-wise specificity; PWPPV: pixel-wise positive predictive value; DSC: dice similarity coefficient, BCa: bladder cancer; BL: blue light.

In summary, AI applied to cystoscopy assessment attempts to fill the gap due to interobserver variability and to reduce the risk of misdiagnosis, especially when non-univocal findings are detected during routine cystoscopy. Data from the recently reported studies showed promising results in terms of accuracy; however, the use of AI is still

limited by the low availability of AI platforms, which does not allow the application of these systems in current clinical daily practice.

3.2. AI-Enhanced Radiological Imaging

Current International guidelines highlight the role of computed tomography (CT)-urography scanning and multi-parametric magnetic resonance imaging (MRI) in BCa cT staging [36]. AI and DL platforms are well applied to radiological images re-laboration tasks, ensuring enhanced accuracy in radiological diagnosis across different settings and clinical scenarios [37]. In a retrospective study on 441 BCa patients, Zhang et al. aimed to validate a DL model able to preoperatively predict BCa invasiveness status by analyzing CT images. The authors divided the study population into development, internal validation, and external validation cohorts. The performance of the model was compared to the individual subjective assessment of two different radiologists. The model showed a relatively good performance in all cohorts and outperformed the two radiologists regarding the accuracy, reaching a sensitivity of 0.733 and a specificity of 0.810 in the internal validation cohort and a sensitivity of 0.710 with a specificity of 0.773 in the external validation cohort. Of note, the model demonstrated a lower sensitivity compared to the radiologists. As a limitation, the authors noticed that the DL model considered tumor size above 4 cm as the key feature to detect muscular invasion, potentially leading to misdiagnosis in some cases [38]. Similarly, Yang et al. developed a DL convolutional neural network with the aim to distinguish MIBC and NMIBC on CT scan frames. In this study, eight algorithms were tested and exhibited an AUC ranging between 0.762 and 0.997 [39]. Liu et al. elaborated a DL model intended for the prediction of BCa stage before surgery; according to the authors, the sensitivity rate of DL diagnosis was 94.74% notwithstanding CT detection drawbacks such as poor spatial resolution; therefore, there was a need to combine more frames to obtain an adequate positioning [40]. Taguchi et al. prospectively applied DL technology to improve the T2-weighted MRI frame output of new generation 3T MRI. Denoising DL-mediated processing of raw MRI images has been proven to enhance the accuracy of the VI-RADS score calculation for BCa detrusor invasion [41]. Yu et al. have recently proposed their Cascade Path Augmentation Unet (CPA-Unet) based on T2-weighted MRI frames, which could elaborate proper segmentation of bladder wall layers, identifying the depth of local tumor infiltration [42]. An interesting application of ML applied to CT scans was described by Cha et al. [43]; they proposed a CT-based computerized decision-support system for MIBC patients undergoing neoadjuvant chemotherapy (NAC). The ML-platform showed enhanced performance in identifying patients who would have achieved a complete response to NAC by analyzing post-therapy CT scans. Table 2 presents the main findings of the studies focusing on AI applied to the radiological assessment of BCa.

To summarize, AI, particularly DL, could play an interesting role in enhancing the radiological diagnosis of BCa. However, DL models still suffer from a lack of satisfactory sensitivity as well as from some intrinsic limitations of the systems, as such, the identification of the radiological features necessary to produce a correct diagnosis. Moreover, many studies are affected by the limited number of patients enrolled. In light of the above, despite several encouraging results, further studies are pending in order to produce more robust evidence allowing the stable introduction of these DL systems.

Table 2. Deep learning approach applied to diagnostic imaging.

Author	Year	Imaging	Patients/Frames	AI Technology	Outcomes
Cha et al. [43]	2018	CT	123 patients/157 ROI (MIBC foci)	CDSS-T	Mean AUCs for the assessment of pathologic T0 disease after NAC in MIBC: 0.80 for CDSS-T alone, 0.74 for physicians not using CDSS-T, and 0.77 for physicians using CDSS-T. The increase in the physicians' performance was statistically significant ($p < 0.05$).
Zhang et al. [38]	2021	CT	441 patients	Filter-guided Pyramid Network (FGP-Net)	Prediction ability of muscle-invasive status: sensitivity: 0.733, specificity: 0.810 (internal validation cohort); sensitivity 0.710, specificity 0.773 (external validation cohort).
Taguchi et al. [41]	2021	T2W MRI	98 patients	"Next-generation" 3T-MRI with dDLR	The optimal cut-off value of the VI-RADS score was determined to be 4, and the accuracy of diagnosing MIBC by VI-RADS 4 was 94% (AUC 0.92). The AUC for assessment of final VI-RADS score was significantly improved from 0.84 with T2WI alone to 0.88 with T2WI + dDLR ($p < 0.01$).
Yang et al. [39]	2021	CT	369 patients/1200 cross-sectional CT frames	VGG16, VGG19, Xception, InceptionV3, InceptionResNetV2, Dense-Net121, DenseNet169, DenseNet201	Ability to classify MIBC vs. NMICB: the AUC of the validation and testing datasets for the small DL-CNN was 0.946 and 0.998, respectively. The AUROCs of eight deep learning algorithms with pretrained bases ranged from 0.762 to 0.997 in the testing dataset. The VGG16 model had the largest AUROC of 0.997 among the eight algorithms with a sensitivity and specificity of 0.889 and 0.989, respectively.
Liu et al. [40]	2022	CT	76 patients	ResNet18 network	To predict BCa staging through DL enhanced high-resolution CT scans: 52 cases were diagnosed <T1 stage, 16 cases belonged to T2 stage, 2 cases T3 stage, and 2 cases T4 stage. The sensitivity rate of experimental diagnosis was 94.74%, which was not significantly different from the sensitivity rate of preoperative pathological diagnosis.
Yu et al. [42]	2022	T2W MRI	1545 T2-weighted MRI scans	CPA-Unet network	Segmentation accuracy of IW, OW, and BCa through MRI scans: CPA-Unet achieves superior segmentation results in terms of DSC and HD (IW:DSC = 98.19%, HD = 2.07 mm; OW:DSC = 82.24%, HD = 2.62 mm; BCa:DSC = 87.40%, HD = 0.76 mm).

Abbreviations are as follows: CT: computer tomography; AUC: area under the curve; MRI: magnetic resonance imaging; CDSS-T: computerized decision-support system for muscle-invasive bladder cancer treatment response assessment; dDLR: denoising deep-learning reconstruction, CPA-Unet: cascade path augmentation unet, IW: inner bladder walls; OW: outer bladder walls, DSC: dice similarity coefficient; HD = Hausdorff distance.

3.3. AI-Enhanced Histopathology Diagnosis and Molecular Subtyping Analysis

Due to its prognostic importance, pathological evaluation of histological samples plays a key role in BCa management. Of note, interobserver variability may lead to incorrect pathological interpretation [16]. AI technologies may provide an integrative tool in this scenario, aiming to enhance interpretation reproducibility through a semi or fully automated slides reading procedure. Jansen et al. [44] proposed an automated detection and grading network for NMIBC based on DL technology. The authors showed a correct grading of 76% low-grade and 71% of high-grade BCa, according to the consensus reading. Chen et al. proposed a ML-model able to develop automatic diagnostic and clinical prognostic models based on histological samples, displaying high accuracy rates. Despite these promising results, the authors acknowledged limitations of the retrospective design and the lower accuracy of ML diagnosis compared to traditional diagnosis performed by an experienced uro-pathologist [45]. Yin et al. developed a model able to distinguish between Ta or T1 features on sample images using six supervised learning methods (91–96%

accuracy) [46]. AI-enhanced histological evaluation could play a role also in MIBC setting. Harmon et al., in a study including 307 patients, proposed an AI-enhanced model based on features of hematoxylin and eosin-stained RC specimens slides, which was not able to predict the risk of lymph node metastases [47]. Table 3 shows the main findings of recent studies regarding AI applied to histopathological assessment

Table 3. Artificial intelligence technologies applied to diagnosis and molecular subtyping analysis.

Author	Year	H&E Stains	Specimen	AI Technology	Outcomes
Jansen et al. [44]	2020	328	TURBt	U-Net based segmentation network—deep learning	Automated classification correctly graded 76% low-grade cancers and 71% high-grade cancers
Chen et al. [45]	2021	643	Radical/partial cystectomy	Machine learning algorithm	Cross-verified automatic diagnosis accuracy: AUC of 96.3%, 89.2%, and 94.1% (for three testing cohorts), prognosis accuracy: AUC values of 77.7%, 83.8%, and 81.3% (for 1-, 3-, and 5-y overall survival prediction of patients with BCa)
Yin et al. [46]	2020	1177	Surgical excision	Imaging processing software: ImageJ and CellProfiler—Machine learning	Distinguish between Ta or T1 images with six supervised learning methods (91–96% accuracy) vs. CNN (84% accuracy)
Harmon et al. [47]	2020	307	Radical cystectomy	DL (ResNet-101)	Comparison on likelihood of positive lymph nodes between clinicopathologic model vs. AI score respectively (AUC of 0.755, 95% CI 0.680 to 0.831 vs. AUC of 0.866, 95% CI 0.812 to 0.920; $p = 0.021$)

Abbreviations are as follow: AUC: area under the receiving operator characteristic curve; BCa: bladder cancer; CNN: convolutional neural network; CI: confidence interval; DL: deep learning; TURBt: trans urethral resection of bladder tumor.

Substantial work by multiple groups has defined key molecular subtypes of UC characterized by distinct gene signatures, varying expression of potential drug targets, and differing therapy sensitivity [48–50]. In this context, AI-enhanced molecular analysis is another innovative frontier in detecting mutations in key molecular pathways potentially providing tailored management in BCa systemic therapies, including conventional chemotherapy and novel targeted therapies. For instance, the literature has produced robust evidence on the role of fibroblastic growth factors receptor (FGF-R) pathways in BCa tumorigenesis and progression [8,13,51]. Nevertheless, mutational status detection still demands genetic sequencing techniques. Loeffler et al. and Velmahos et al. described an ML algorithm able to identify FGFR2/3 mutational status based on AI-assisted analysis of diagnostic hematoxylin and eosin-stained BCa slides, which might improve the suitability of FGFR inhibitor administration [52,53]. In addition, Xu et al. developed a model able to identify a specific AI-derived gene signature (AIGS) for predicting the therapeutic response or providing prognostic information for individualized follow-up. However, some limitations have been acknowledged such as the retrospective design [54]. Data from recent studies regarding AI application in molecular analysis are presented in Table 4.

Considering these findings, AI also displays interesting perspectives in pathological and molecular evaluation. A recent review on this topic has been published by Wessels et al. [55]; the authors included 16 studies regarding AI-enhanced hematoxylin and eosin-stained slide analysis, focusing not only on BCa, but also on upper-tract urothelial carcinoma, prostate cancer, and renal cell carcinoma. One interesting perspective described by Wessels et al. is the potential ability of AI-trained models to detect new and still unknown histological patterns with prognostic significance. This new scenario can potentially lead to

an improvement in risk stratification and oncological outcomes; however, the prognostic significance of these patterns is yet to be established.

Table 4. Artificial intelligence technologies applied to molecular analysis.

Author	Year	Pathway/Genes	AI Technology	Outcomes
Loeffler et al. [52]	2021	FGFR3/327	DL network	The accuracy in detecting FGFR3 mutations in the three cohorts were 0.701 ($p < 0.0001$), 0.725 ($p < 0.0001$), and 0.625 ($p = 0.0112$)
Xu et al. [54]	2022	1218	ML AIGS (artificial intelligence-derived gene signature)	AIGS demonstrated superior performance among 76 model types: higher risk of mortality, recurrence, and disease progression. AIGS demonstrated superior performance on clinical traits and molecular features
Velmahos et al. [53]	2021	FGFR/418	Convolutional neural network (CNN) identified tumor-infiltrating lymphocytes (TIL)—DL	Predictive model identifies patients with FGFR gene aberrations with a sensitivity of 0.89, specificity of 0.42, and AUROC = 0.76. A similar model predicting FGFR2/FGFR3 mutation was also highly sensitive and specific (sensitivity = 0.82, specificity = 0.85, AUROC = 0.86)

Abbreviation are as follows: DL: deep learning; ML: machine learning; AIGS: artificial intelligence-derived gene signature; CNN: convolutional neural network; TIL: identified tumor-infiltrating lymphocytes.

On the other hand, larger datasets are required to train DL models to enable them to produce a satisfactory performance; this could turn into a thorny issue when considering rare diseases such as variant histology BCa [46,56]. Many of the previous DL models were set up using only specimens from the primary tumor, while including samples from metastatic sites as well could eventually enhance the accuracy of DL-assisted diagnosis [53]. Moreover, many studies still suffer from a retrospective design and a limited cohort. Thus, AI needs further validation in the field of histological and molecular pathology before entering into routine clinical practice.

4. Conclusions and Future Perspectives

We aimed to highlight the potential role of AI in supporting physician diagnostic performance in BCa assessment. A strength of our work is that we followed a standardized diagnostic pathway from clinical diagnosis to pathological examination to provide the reader with a more comprehensive view about how AI could be applied to conventional urological practice. Moreover, bioinformatic AI technologies may also lead to new applications in BCa diagnosis or follow-up handling. In this context, Sokolov et al. described an innovative approach in diagnostic imaging based on nanoscale-resolution scanning of surfaces of cells collected from urine samples using atomic force microscopy (AFM), subresonance tapping, and ML analysis. This new approach led to a 94% detection rate for BCa [57]. In summary, with regards to BCa, there is a growing interest in AI applications in urological practice even though its current routine use is still limited. Notably, a recent paper published by Joshi et al. proposed accurate research about all AI and ML FDA-approved medical devices—including those in the urological field—to emphasize how the transition to new AI-supported decision-making medicine is not only possible, but already underway [58]. However, it is necessary to point out some limitations of AI in diagnostic applications, such as the lack of availability of large datasets of images, heterogeneity of the clinical data, and lack of short-mid-long term oncological outcomes in patients diagnosed through computational technologies and enhanced instruments; therefore, it becomes hard to perform any cost-benefit analysis and encourage health-care systems to adopt AI enhanced software. Further prospective trials are required to confirm these preliminary findings and to provide a comprehensive reliability of the role of AI in the BCa scenario.

Author Contributions: Project administration: F.C. and N.P.; Formal analysis: F.Z., G.R., L.O. and A.P.; Investigation: G.R., F.Z., F.V. and A.Z.; Methodology: F.C., N.P. and C.T.; Supervision: N.P., F.C., A.S., C.T., G.L., A.Z. and R.B.; Visualization: A.P., G.R. and F.Z.; Writing original draft: G.R., F.Z., A.P., L.O. and F.C. Writing review and editing: F.C., N.P., C.T., G.L., A.S., A.Z. and R.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was designed according to national regulations and the principles of the Declaration of Helsinki in accordance with Good Clinical Practice guidelines.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Siegel, R.L.; Miller, K.D.; Fuchs, H.E.; Jemal, A. Cancer Statistics, 2021. *CA A Cancer J. Clin.* **2021**, *71*, 7–33. [[CrossRef](#)] [[PubMed](#)]
2. Khadhour, S.; Gallagher, K.M.; MacKenzie, K.R.; Shah, T.T.; Gao, C.; Moore, S.; Zimmermann, E.F.; Edison, E.; Jefferies, M.; Nambiar, A.; et al. The IDENTIFY Study: The Investigation and Detection of Urological Neoplasia in Patients Referred with Suspected Urinary Tract Cancer—A Multicentre Observational Study. *BJU Int.* **2021**, *128*, 440–450. [[CrossRef](#)]
3. Laukhtina, E.; Pradere, B.; Lemberger, U.; Karakiewicz, P.I.; Fajkovic, H.; Shariat, S.F. Molecular Biomarkers to Help Select Neoadjuvant Systemic Therapy for Urothelial Carcinoma of the Bladder. *Curr. Opin. Urol.* **2022**, *32*, 561–566. [[CrossRef](#)] [[PubMed](#)]
4. Laukhtina, E.; Boehm, A.; Peyronnet, B.; Bravi, C.A.; Batista Da Costa, J.; Soria, F.; D’Andrea, D.; Rajwa, P.; Quhal, F.; Yanagisawa, T.; et al. Urethrectomy at the Time of Radical Cystectomy for Non-Metastatic Urothelial Carcinoma of the Bladder: A Collaborative Multicenter Study. *World J. Urol.* **2022**, *40*, 1689–1696. [[CrossRef](#)] [[PubMed](#)]
5. Claps, F.; van de Kamp, M.W.; Mayr, R.; Bostrom, P.J.; Boormans, J.L.; Eckstein, M.; Mertens, L.S.; Boevé, E.R.; Neuzillet, Y.; Burger, M.; et al. Risk Factors Associated with Positive Surgical Margins’ Location at Radical Cystectomy and Their Impact on Bladder Cancer Survival. *World J. Urol.* **2021**, *39*, 4363–4371. [[CrossRef](#)]
6. Claps, F.; Rai, S.; Mir, M.C.; van Rhijn, B.W.G.; Mazzon, G.; Davis, L.E.; Valadon, C.L.; Silvestri, T.; Rizzo, M.; Ankem, M.; et al. Prognostic Value of Preoperative Albumin-to-Fibrinogen Ratio (AFR) in Patients with Bladder Cancer Treated with Radical Cystectomy. *Urol. Oncol.* **2021**, *39*, 835.e9–835.e17. [[CrossRef](#)]
7. Laukhtina, E.; Pradere, B.; Mori, K.; Schuettfort, V.M.; Quhal, F.; Mostafaei, H.; Sari Motlagh, R.; Aydh, A.; Moschini, M.; Enikeev, D.; et al. Prognostic Blood-Based Biomarkers in Patients Treated with Neoadjuvant Chemotherapy for Urothelial Carcinoma of the Bladder: A Systematic Review. *Urol. Oncol.* **2021**, *39*, 471–479. [[CrossRef](#)]
8. Mertens, L.S.; Claps, F.; Mayr, R.; Bostrom, P.J.; Shariat, S.F.; Zwarthoff, E.C.; Boormans, J.L.; Abas, C.; van Leenders, G.J.L.H.; Götz, S.; et al. Prognostic Markers in Invasive Bladder Cancer: FGFR3 Mutation Status versus P53 and KI-67 Expression: A Multi-Center, Multi-Laboratory Analysis in 1058 Radical Cystectomy Patients. *Urol. Oncol.* **2022**, *40*, 110.e1–110.e9. [[CrossRef](#)]
9. Mori, K.; Abufaraj, M.; Mostafaei, H.; Quhal, F.; Karakiewicz, P.I.; Briganti, A.; Kimura, S.; Egawa, S.; Shariat, S.F. A Systematic Review and Meta-Analysis of Variant Histology in Urothelial Carcinoma of the Bladder Treated with Radical Cystectomy. *J. Urol.* **2020**, *204*, 1129–1140. [[CrossRef](#)]
10. Claps, F.; Mir, M.C.; van Rhijn, B.W.G.; Mazzon, G.; Soria, F.; D’Andrea, D.; Marra, G.; Boltri, M.; Traunero, F.; Massanova, M.; et al. Impact of the Controlling Nutritional Status (CONUT) Score on Perioperative Morbidity and Oncological Outcomes in Patients with Bladder Cancer Treated with Radical Cystectomy. *Urol. Oncol.* **2023**, *41*, 49.e13–49.e22. [[CrossRef](#)]
11. de Kruijff, I.E.; Beije, N.; Martens, J.W.M.; de Wit, R.; Boormans, J.L.; Sleijfer, S. Liquid Biopsies to Select Patients for Perioperative Chemotherapy in Muscle-Invasive Bladder Cancer: A Systematic Review. *Eur. Urol. Oncol.* **2021**, *4*, 204–214. [[CrossRef](#)] [[PubMed](#)]
12. Claps, F.; Mir, M.C.; Zargar, H. Molecular Markers of Systemic Therapy Response in Urothelial Carcinoma. *Asian J. Urol.* **2021**, *8*, 376–390. [[CrossRef](#)] [[PubMed](#)]
13. Mertens, L.S.; Claps, F.; Mayr, R.; Hodgson, A.; Shariat, S.F.; Hippe, K.; Neuzillet, Y.; Sanders, J.; Burger, M.; Pouessel, D.; et al. The Search for the Optimal Cut-off Value of P53-Immunohistochemistry to Predict Prognosis of Invasive Bladder Cancer: A Multi-Center, Multi-Laboratory Analysis. *Int. J. Surg. Pathol.* **2022**, *24*, 10668969221095172. [[CrossRef](#)]
14. Claps, F.; Pavan, N.; Umari, P.; Rizzo, M.; Barbone, F.; Giangreco, M.; Liguori, G.; Mir, C.M.; Bussani, R.; Trombetta, C. Incidence, Predictive Factors and Survival Outcomes of Incidental Prostate Cancer in Patients Who Underwent Radical Cystectomy for Bladder Cancer. *Minerva Urol. Nephrol.* **2021**, *73*, 349–356. [[CrossRef](#)] [[PubMed](#)]
15. Li, H.; Liu, L.; Ding, L.; Zhang, Z.; Zhang, M. Quantitative Assessment of Bladder Cancer Reflects Grade and Recurrence: Comparing of Three Methods of Positioning Region of Interest for ADC Measurements at Diffusion-Weighted MR Imaging. *Acad. Radiol.* **2019**, *26*, 1148–1153. [[CrossRef](#)]
16. Cimadamore, A.; Lonati, C.; Di Trapani, E.; De Cobelli, O.; Rink, M.; Zamboni, S.; Simeone, C.; Soria, F.; Briganti, A.; Montorsi, F.; et al. Variant Histologies in Bladder Cancer: Does the Centre Have an Impact in Detection Accuracy? *Urol. Oncol.* **2022**, *40*, 273.e11–273.e20. [[CrossRef](#)]

17. Azad, R.K.; Shulaev, V. Metabolomics Technology and Bioinformatics for Precision Medicine. *Brief. Bioinform.* **2019**, *20*, 1957–1971. [[CrossRef](#)]
18. Gupta, R.; Srivastava, D.; Sahu, M.; Tiwari, S.; Ambasta, R.K.; Kumar, P. Artificial Intelligence to Deep Learning: Machine Intelligence Approach for Drug Discovery. *Mol. Divers.* **2021**, *25*, 1315–1360. [[CrossRef](#)]
19. Choi, R.Y.; Coyner, A.S.; Kalpathy-Cramer, J.; Chiang, M.F.; Campbell, J.P. Introduction to Machine Learning, Neural Networks, and Deep Learning. *Transl. Vis. Sci. Technol.* **2020**, *9*, 14. [[CrossRef](#)]
20. Tran, K.A.; Kondrashova, O.; Bradley, A.; Williams, E.D.; Pearson, J.V.; Waddell, N. Deep Learning in Cancer Diagnosis, Prognosis and Treatment Selection. *Genome Med.* **2021**, *13*, 152. [[CrossRef](#)]
21. Checcucci, E.; Autorino, R.; Cacciamani, G.E.; Amparore, D.; De Cillis, S.; Piana, A.; Piazzolla, P.; Vezzetti, E.; Fiori, C.; Veneziano, D.; et al. Artificial Intelligence and Neural Networks in Urology: Current Clinical Applications. *Minerva Urol. E Nefrol. Ital. J. Urol. Nephrol.* **2020**, *72*, 49–57. [[CrossRef](#)] [[PubMed](#)]
22. McCarthy, J.; Minsky, M.L.; Rochester, N.; Corporation, I.B.M.; Shannon, C.E. A proposal for the dartmouth summer research project on artificial intelligence. *AI Mag.* **1955**, *27*, 12.
23. Hamet, P.; Tremblay, J. Artificial Intelligence in Medicine. *Metabolism* **2017**, *69*, S36–S40. [[CrossRef](#)] [[PubMed](#)]
24. Zhong, F.; Xing, J.; Li, X.; Liu, X.; Fu, Z.; Xiong, Z.; Lu, D.; Wu, X.; Zhao, J.; Tan, X.; et al. Artificial Intelligence in Drug Design. *Sci. China Life Sci.* **2018**, *61*, 1191–1204. [[CrossRef](#)]
25. Isfoss, B.L. The Sensitivity of Fluorescent-Light Cystoscopy for the Detection of Carcinoma in Situ (CIS) of the Bladder: A Meta-Analysis with Comments on Gold Standard. *BJU Int.* **2011**, *108*, 1703–1707. [[CrossRef](#)]
26. Shkolyar, E.; Jia, X.; Chang, T.C.; Trivedi, D.; Mach, K.E.; Meng, M.Q.-H.; Xing, L.; Liao, J.C. Augmented Bladder Tumor Detection Using Deep Learning. *Eur. Urol.* **2019**, *76*, 714–718. [[CrossRef](#)]
27. Wu, S.; Chen, X.; Pan, J.; Dong, W.; Diao, X.; Zhang, R.; Zhang, Y.; Zhang, Y.; Qian, G.; Chen, H.; et al. An Artificial Intelligence System for the Detection of Bladder Cancer via Cystoscopy: A Multicenter Diagnostic Study. *J. Natl. Cancer Inst.* **2022**, *114*, 220–227. [[CrossRef](#)]
28. Yoo, J.W.; Koo, K.C.; Chung, B.H.; Baek, S.Y.; Lee, S.J.; Park, K.H.; Lee, K.S. Deep Learning Diagnostics for Bladder Tumor Identification and Grade Prediction Using RGB Method. *Sci. Rep.* **2022**, *12*, 17699. [[CrossRef](#)] [[PubMed](#)]
29. Mutaguchi, J.; Morooka, K.; Kobayashi, S.; Umehara, A.; Miyauchi, S.; Kinoshita, F.; Inokuchi, J.; Oda, Y.; Kurazume, R.; Eto, M. Artificial Intelligence for Segmentation of Bladder Tumor Cystoscopic Images Performed by U-Net with Dilated Convolution. *J. Endourol.* **2022**, *36*, 827–834. [[CrossRef](#)]
30. Burger, M.; Grossman, H.B.; Droller, M.; Schmidbauer, J.; Hermann, G.; Drăgoescu, O.; Ray, E.; Fradet, Y.; Karl, A.; Burgués, J.P.; et al. Photodynamic Diagnosis of Non-Muscle-Invasive Bladder Cancer with Hexaminolevulinic Acid Cystoscopy: A Meta-Analysis of Detection and Recurrence Based on Raw Data. *Eur. Urol.* **2013**, *64*, 846–854. [[CrossRef](#)]
31. Heer, R.; Lewis, R.; Vadiveloo, T.; Yu, G.; Mariappan, P.; Cresswell, J.; McGrath, J.; Nabi, G.; Mostafid, H.; Lazarowicz, H.; et al. A Randomized Trial of PHOTodynamic Surgery in Non-Muscle-Invasive Bladder Cancer. *NEJM Evidence* **2022**, *1*, EVIDoA2200092. [[CrossRef](#)]
32. Ali, N.; Bolenz, C.; Todenhöfer, T.; Stenzel, A.; Deetmar, P.; Kriegmair, M.; Knoll, T.; Porubsky, S.; Hartmann, A.; Popp, J.; et al. Deep Learning-Based Classification of Blue Light Cystoscopy Imaging during Transurethral Resection of Bladder Tumors. *Sci. Rep.* **2021**, *11*, 11629. [[CrossRef](#)] [[PubMed](#)]
33. Claps, F.; Amparore, D.; Esperto, F.; Cacciamani, G.; Fiori, C.; Minervini, A.; Liguori, G.; Trombetta, C.; Porpiglia, F.; Serni, S.; et al. Smart Learning for Urology Residents during the COVID-19 Pandemic and beyond: Insights from a Nationwide Survey in Italy. *Minerva Urol. Nefrol. Ital. J. Urol. Nephrol.* **2020**, *72*, 647–649. [[CrossRef](#)] [[PubMed](#)]
34. Ikeda, A.; Nosato, H.; Kochi, Y.; Negoro, H.; Kojima, T.; Sakanashi, H.; Murakawa, M.; Nishiyama, H. Cystoscopic Imaging for Bladder Cancer Detection Based on Stepwise Organic Transfer Learning with a Pretrained Convolutional Neural Network. *J. Endourol.* **2021**, *35*, 1030–1035. [[CrossRef](#)] [[PubMed](#)]
35. Du, Y.; Yang, R.; Chen, Z.; Wang, L.; Weng, X.; Liu, X. A Deep Learning Network-Assisted Bladder Tumour Recognition under Cystoscopy Based on Caffe Deep Learning Framework and EasyDL Platform. *Int. J. Med. Robot. Comput. Assist. Surg. MRCAS* **2021**, *17*, 1–8. [[CrossRef](#)]
36. Babjuk, M.; Burger, M.; Capoun, O.; Cohen, D.; Compérat, E.M.; Dominguez Escrig, J.L.; Gontero, P.; Liedberg, F.; Masson-Lecomte, A.; Mostafid, A.H.; et al. European Association of Urology Guidelines on Non-Muscle-Invasive Bladder Cancer (Ta, T1, and Carcinoma in Situ). *Eur. Urol.* **2022**, *81*, 75–94. [[CrossRef](#)]
37. Loehfelm, T.W. Artificial Intelligence for Quality Improvement in Radiology. *Radiol. Clin.* **2021**, *59*, 1053–1062. [[CrossRef](#)]
38. Zhang, G.; Wu, Z.; Xu, L.; Zhang, X.; Zhang, D.; Mao, L.; Li, X.; Xiao, Y.; Guo, J.; Ji, Z.; et al. Deep Learning on Enhanced CT Images Can Predict the Muscular Invasiveness of Bladder Cancer. *Front. Oncol.* **2021**, *11*, 654685. [[CrossRef](#)]
39. Yang, Y.; Zou, X.; Wang, Y.; Ma, X. Application of Deep Learning as a Noninvasive Tool to Differentiate Muscle-Invasive Bladder Cancer and Non-Muscle-Invasive Bladder Cancer with CT. *Eur. J. Radiol.* **2021**, *139*, 109666. [[CrossRef](#)]
40. Liu, D.; Wang, S.; Wang, J. The Effect of CT High-Resolution Imaging Diagnosis Based on Deep Residual Network on the Pathology of Bladder Cancer Classification and Staging. *Comput. Methods Programs Biomed.* **2022**, *215*, 106635. [[CrossRef](#)]
41. Taguchi, S.; Tambo, M.; Watanabe, M.; Machida, H.; Kariyasu, T.; Fukushima, K.; Shimizu, Y.; Okegawa, T.; Yokoyama, K.; Fukuhara, H. Prospective Validation of Vesical Imaging-Reporting and Data System Using a Next-Generation Magnetic Resonance Imaging Scanner-Is Denoising Deep Learning Reconstruction Useful? *J. Urol.* **2021**, *205*, 686–692. [[CrossRef](#)] [[PubMed](#)]

42. Yu, J.; Cai, L.; Chen, C.; Fu, X.; Wang, L.; Yuan, B.; Yang, X.; Lu, Q. Cascade Path Augmentation Unet for Bladder Cancer Segmentation in MRI. *Med. Phys.* **2022**, *49*, 4622–4631. [[CrossRef](#)] [[PubMed](#)]
43. Cha, K.H.; Hadjiiski, L.M.; Cohan, R.H.; Chan, H.-P.; Caoili, E.M.; Davenport, M.S.; Samala, R.K.; Weizer, A.Z.; Alva, A.; Kirova-Nedyalkova, G.; et al. Diagnostic Accuracy of CT for Prediction of Bladder Cancer Treatment Response with and without Computerized Decision Support. *Acad. Radiol.* **2019**, *26*, 1137–1145. [[CrossRef](#)] [[PubMed](#)]
44. Jansen, I.; Lucas, M.; Bosschieter, J.; de Boer, O.J.; Meijer, S.L.; van Leeuwen, T.G.; Marquering, H.A.; Nieuwenhuijzen, J.A.; de Bruin, D.M.; Savci-Heijink, C.D. Automated Detection and Grading of Non-Muscle-Invasive Urothelial Cell Carcinoma of the Bladder. *Am. J. Pathol.* **2020**, *190*, 1483–1490. [[CrossRef](#)] [[PubMed](#)]
45. Chen, S.; Jiang, L.; Zheng, X.; Shao, J.; Wang, T.; Zhang, E.; Gao, F.; Wang, X.; Zheng, J. Clinical Use of Machine Learning-Based Pathomics Signature for Diagnosis and Survival Prediction of Bladder Cancer. *Cancer Sci.* **2021**, *112*, 2905–2914. [[CrossRef](#)]
46. Yin, P.-N.; Kc, K.; Wei, S.; Yu, Q.; Li, R.; Haake, A.R.; Miyamoto, H.; Cui, F. Histopathological Distinction of Non-Invasive and Invasive Bladder Cancers Using Machine Learning Approaches. *BMC Med. Inform. Decis. Mak.* **2020**, *20*, 162. [[CrossRef](#)] [[PubMed](#)]
47. Harmon, S.A.; Sanford, T.H.; Brown, G.T.; Yang, C.; Mehravivand, S.; Jacob, J.M.; Valera, V.A.; Shih, J.H.; Agarwal, P.K.; Choyke, P.L.; et al. Multiresolution Application of Artificial Intelligence in Digital Pathology for Prediction of Positive Lymph Nodes From Primary Tumors in Bladder Cancer. *JCO Clin. Cancer Inform.* **2020**, *4*, 367–382. [[CrossRef](#)]
48. Article, O. Comprehensive Molecular Characterization of Papillary Renal-Cell Carcinoma. *N. Engl. J. Med.* **2016**, *374*, 135–145. [[CrossRef](#)]
49. Choi, W.; Porten, S.; Kim, S.; Willis, D.; Plimack, E.R.; Hoffman-Censits, J.; Roth, B.; Cheng, T.; Tran, M.; Lee, I.-L.; et al. Identification of Distinct Basal and Luminal Subtypes of Muscle-Invasive Bladder Cancer with Different Sensitivities to Frontline Chemotherapy. *Cancer Cell* **2014**, *25*, 152–165. [[CrossRef](#)]
50. Sjödal, G.; Eriksson, P.; Liedberg, F.; Höglund, M. Molecular Classification of Urothelial Carcinoma: Global mRNA Classification versus Tumour-Cell Phenotype Classification. *J. Pathol.* **2017**, *242*, 113–125. [[CrossRef](#)]
51. Kardoust Parizi, M.; Margulis, V.; Lotan, Y.; Mori, K.; Shariat, S.F. Fibroblast Growth Factor Receptor: A Systematic Review and Meta-Analysis of Prognostic Value and Therapeutic Options in Patients with Urothelial Bladder Carcinoma. *Urol. Oncol.* **2021**, *39*, 409–421. [[CrossRef](#)] [[PubMed](#)]
52. Loeffler, C.M.L.; Ortiz Bruechle, N.; Jung, M.; Seillier, L.; Rose, M.; Laleh, N.G.; Knuechel, R.; Brinker, T.J.; Trautwein, C.; Gaisa, N.T.; et al. Artificial Intelligence-Based Detection of FGFR3 Mutational Status Directly from Routine Histology in Bladder Cancer: A Possible Preselection for Molecular Testing? *Eur. Urol. Focus* **2022**, *8*, 472–479. [[CrossRef](#)] [[PubMed](#)]
53. Velmahos, C.S.; Badgeley, M.; Lo, Y.-C. Using Deep Learning to Identify Bladder Cancers with FGFR-Activating Mutations from Histology Images. *Cancer Med.* **2021**, *10*, 4805–4813. [[CrossRef](#)]
54. Xu, H.; Liu, Z.; Weng, S.; Dang, Q.; Ge, X.; Zhang, Y.; Ren, Y.; Xing, Z.; Chen, S.; Zhou, Y.; et al. Artificial Intelligence-Driven Consensus Gene Signatures for Improving Bladder Cancer Clinical Outcomes Identified by Multi-Center Integration Analysis. *Mol. Oncol.* **2022**, *16*, 4023–4042. [[CrossRef](#)]
55. Wessels, F.; Kuntz, S.; Kriehoff-Henning, E.; Schmitt, M.; Braun, V.; Worst, T.S.; Neuberger, M.; Steeg, M.; Gaiser, T.; Fröhling, S.; et al. Artificial Intelligence to Predict Oncological Outcome Directly from Hematoxylin and Eosin-Stained Slides in Urology. *Minerva Urol. Nephrol.* **2022**, *74*, 538–550. [[CrossRef](#)]
56. Hughes, C.; Iqbal-Wahid, J.; Brown, M.; Shanks, J.H.; Eustace, A.; Denley, H.; Hoskin, P.J.; West, C.; Clarke, N.W.; Gardner, P. FTIR Microspectroscopy of Selected Rare Diverse Sub-Variants of Carcinoma of the Urinary Bladder. *J. Biophotonics* **2013**, *6*, 73–87. [[CrossRef](#)]
57. Sokolov, I.; Dokukin, M.E.; Kalaparthy, V.; Miljkovic, M.; Wang, A.; Seigne, J.D.; Grivas, P.; Demidenko, E. Noninvasive Diagnostic Imaging Using Machine-Learning Analysis of Nanoresolution Images of Cell Surfaces: Detection of Bladder Cancer. *Proc. Natl. Acad. Sci. USA* **2018**, *115*, 12920–12925. [[CrossRef](#)]
58. Joshi, G.; Jain, A.; Adhikari, S.; Garg, H.; Bhandari, M. *FDA Approved Artificial Intelligence and Machine Learning (AI/ML)-Enabled Medical Devices: An Updated 2022 Landscape*; Health Informatics: Glenn Dale, MD, USA, 2022. [[CrossRef](#)]

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.