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Review

Image-Guided Transurethral Resection of Bladder Tumors – Current Practice and Future Outlooks

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Abstract. Transurethral resection of bladder tumor (TURBT) under white light cystoscopy (WLC) is the cornerstone for the diagnosis, removal and local staging of non-muscle invasive bladder cancer (NMIBC). Despite technological improvements over the decades, significant shortcomings remain with WLC for tumor detection, thereby impacting the surgical quality and contributing to tumor recurrence and progression. Enhanced cystoscopy modalities such as blue light cystoscopy (BLC) and narrow band imaging (NBI) aid resections by highlighting tumors that might be missed on WLC. Optical biopsy technologies such as confocal laser endomicroscopy (CLE) and optical coherence tomography (OCT) characterize tissue in real-time to ensure a more thorough resection. New resection techniques, particularly en bloc resection, are actively under investigation to improve the overall quality of resections and aid pathologic interpretation. Moreover, new image processing computer algorithms may improve perioperative planning and longitudinal follow-up. Clinical translation of molecular imaging agents is also on the horizon to improve optical diagnosis of bladder cancer. This review focuses on emerging technologies that can impact the quality of TURBT to improve the overall management of NMIBC.

Keywords: Urinary bladder neoplasms, hexaminolevulinic acid, cystoscopy, narrow band imaging, confocal microscopy, computer-assisted, optical coherence tomography, laser surgery, molecular imaging, antigens CD47

INTRODUCTION

Since the first description of endoscopic fulguration of papillary bladder tumors in 1910 [1], transurethral resection of bladder tumor (TURBT) under white light cystoscopy (WLC) has played the central role in bladder cancer diagnosis, removal, and local staging. The goal of TURBT is complete resection of all papillary tumors with concomitant biopsy of suspicious flat lesions. For non-muscle invasive bladder cancer (NMIBC), high quality TURBT is critical in reducing tumor recurrence and progression [2].

Advances in modern WLC and TURBT include fiber-optic illumination, high definition cameras, and bipolar resection [3]. Nevertheless, significant shortcomings remain including missed tumors, incomplete resection, difficult differentiation of carcinoma *in situ* (CIS) from inflammation, and understaging [4]. In patients undergoing second look TURBT, residual tumors are noted in up to 80% of the surgical specimens within 6 weeks of initial resection [5, 6]. Substantial understaging of high risk bladder cancer

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Case study

A 60 years old male with a significant history of smoking developed gross hematuria and underwent office cystoscopy as part of workup. A 3 cm papillary tumor was found on the right lateral wall and bladder wash cytology was suspicious. At a later date, monopolar TURBT under WLC was performed under spinal anesthesia and an additional patch of erythema along the posterior bladder was noted and biopsied. During the tumor resection, a significant obturator reflex was triggered and the procedure was terminated. Pathology revealed high grade T1 papillary urothelial carcinoma with muscle present. Biopsy of the erythematous area was inconclusive. Five weeks later, a second look TURBT was performed under general anesthesia. An additional 0.5 cm tumor was found in the right anterior bladder, along with erythematous patches in posterior bladder. The tumor was resected, the erythematous patches biopsied, and deeper resection of the prior resection bed performed. Pathology showed HG T1 cancer, negative resection bed biopsy, and CIS.

Potential benefits of advanced technologies

BLC, NBI or molecular imaging

- *Small papillary tumor found on second TURBT may have been present during the first procedure but not obvious under WLC alone*
- *Inconclusive erythematous patch may have been initially found to be CIS*

CLE

- *May provide adjunctive information on the erythematous lesion for targeting biopsy site with sufficient urothelium for pathological analysis.*

OCT

- *Provide real time assurance of adequate depth of resection*

Bipolar energy

- *May reduce the risk of obturator nerve reflex.*

3D reconstruction and digital bladder mapping

- *Improve perioperative planning and longitudinal follow-up*
- *3D images might indicate if tumor on the second TURBT was initially missed or a recurrence.*

is noted in about 50% of cases when comparing TURBT clinical staging with pathologic staging from cystectomy [7]. Indeed, second look TURBT is recommended for high risk NMIBC after suboptimal initial TURBT, as incomplete resection and understaging have potentially lethal consequences for these patients.

Significant advances in optical imaging technologies and resection techniques have been developed with the goal of assisting surgeons to better identify bladder lesions and improve the quality of TURBT. Enhanced cystoscopy technologies are supported by several prospective trials and meta-analysis [8–10] and included in European Association of Urology (EAU) and American Urology Association (AUA) guidelines for NMIBC [2, 11]. Emerging optical biopsy technologies hold the promise to significantly augment the precision of TURBT in regards to providing real time tissue characterization. New *en bloc* resection techniques preserve tumor architecture, facilitates better pathological assessment, and potentially offer improved safety profile [12].

The hypothetical case in Box 1 illustrates some of the well-known challenges associated with standard TURBT under WLC, including missed tumors, flat lesion characterization, resection margin assessment, complications of obturator reflex, and pathologic assessment. Here, we review emerging imaging and resection technologies that offer opportunities to significantly enhance TURBT and potentially improve bladder cancer management.

IMPROVING TUMOR DETECTION AND CHARACTERIZATION

Tumor persistence and early recurrence may be due to missed tumors, incomplete resection, reimplantation of tumor cells after resection, and *de novo* tumor formation [13]. CIS is particularly problematic given the challenges of distinguishing CIS from benign bladder lesions leading to a high risk of cancer recurrence and progression.

Blue light cystoscopy (BLC), also known as photodynamic diagnosis or fluorescence cystoscopy, is the most well validated form of enhanced cystoscopy to improve tumor detection [8]. BLC requires preoperative intravesical instillation of hexaminolevulinate (HAL), a photosensitizer that preferentially accumulates in neoplastic cells. Under blue light, red fluorescence is emitted by neoplastic cells (Fig. 1A). A meta-analysis of 2,949 patients revealed 92% sensitivity with BLC for tumor detection compared with 71% with WLC alone [14]. Another meta-analysis of 551 patients showed 87% detection rate for CIS with BLC combined with WLC, whereas WLC alone had 75% detection rate [15]. In addition, under BLC up to 20% more bladder tumors can be detected with a 39% increase in detection of CIS [16]. A prospective, randomized study found a delay in time to tumor recurrence after BLC-assisted TURBT (16.4 months) compared to WLC alone (9.4 months) [17], and meta-analysis with 634 patients noted a recurrence rate of 34.5% with BLC at 12 months and 45.4% without BLC [8].

Since HAL is not completely cancer-specific, false positive findings associated with BLC can occur [18], particularly in patients with inflammation, recent TURBT, or recent treatment with bacillus Calmette-Guerin (BCG) [19, 20]. The meta-analysis by Mowatt et al. showed that WLC has a higher specificity than BLC (72% vs 57%) [14]. There have been negative studies as well. BLC did not improve the detection rate for patients with known positive cytology in a prospective multicenter randomized trial [21] and other prospective randomized studies did not find improvement on disease recurrence rates with addition of BLC [14, 22, 23]. Weighing the benefit of improved sensitivity in detecting bladder cancer against the drawback of higher false-positive rate, a cost effectiveness study reported that the incorporation of BLC resulted in lower costs over 5 years compared to WLC alone ($25,921 vs $30,581, respectively) [24]. In an earlier study looking at BLC with 5-ALA instillation in 191 patients in Germany over 99 months, BLC resulted in €1597 lower cost compared to WLC [25]. A study in Sweden of 2032

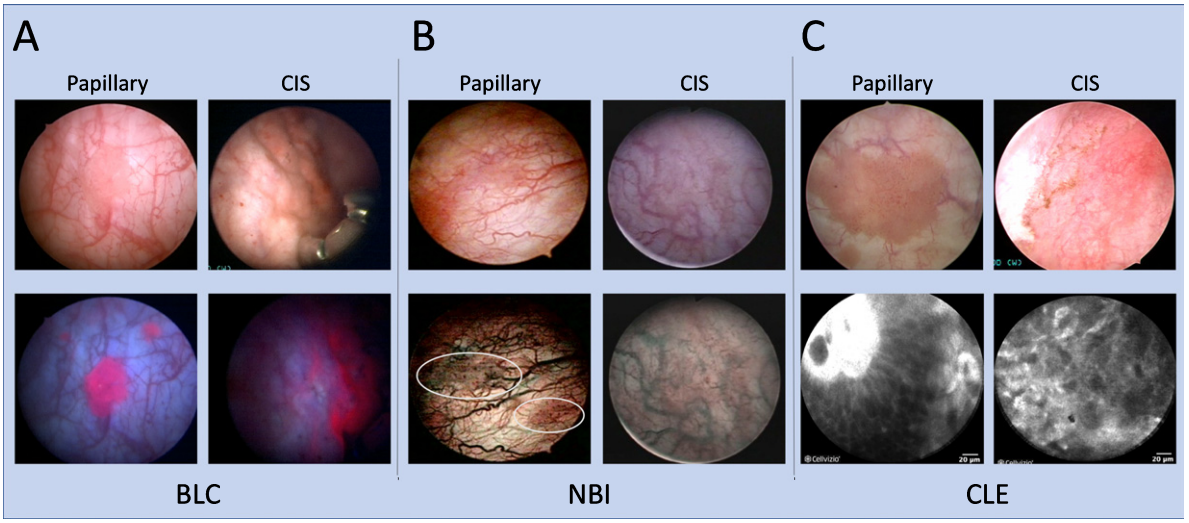

Fig. 1. Imaging modalities for improved bladder tumor detection. Papillary and CIS bladder lesions visualized with BLC, NBI, and CLE with corresponding white light images. (A) Positive, red fluorescence of small, satellite papillary tumors seen on BLC that may be missed on WLC. For CIS, red fluorescence also noted on BLC of what appears to be normal urothelium on WLC. (B) NBI improves visualization of aberrant tumor vasculature. Two papillary tumors are more easily visualized on NBI (encircled). For CIS detection, a patch of erythema is more pronounced under NBI compared to a relatively normal appearing urothelium on WLC. *CIS images for NBI obtained with permission from* [80]. (C) CLE of papillary tumors and CIS provide microscopic detail that can augment macroscopic imaging. A fibrovascular stalk may be visualized as noted in the top left of the papillary CLE example. CIS is notable for a disorganized architecture with pleomorphic cells and indistinct cellular borders.

newly diagnosed bladder cancer patients predicted a total saving of SEK1,321,716 with the use of BLC as an adjunct to WLC, with reduction of 23 cystectomies and 180 TURBTs [26]. While the number of studies calculating cost effectiveness is limited, current data indicates a potential for long term cost savings with the use of BLC.

Under narrow band imaging (NBI), white light is filtered into blue (415 nm) and green (540 nm) wavelengths that are preferentially absorbed by hemoglobin. NBI improves visualization of tumor-associated aberrant mucosal and submucosal vasculature, without the need for exogenous imaging agents (Fig. 1B). NBI has been shown to increase detection of both papillary and flat lesions compared to WLC (94.7% versus 79.2%, respectively) [27], and NBI-assisted TURBT decreased 1-year recurrence compared to standard WLC TURBT (32.9% versus 51.4%, respectively) [28]. A meta-analysis of 1557 patients from six studies found a decreased recurrence rate at 12 months with NBI-assisted TURBT compared to WLC (26% versus 38.6%, respectively) [29]. However, a multicenter randomized trial comparing NBI with standard WLC TURBT revealed no difference in recurrence rates at 1 year follow up (27.1% WLC, 25.4% NBI). It was notable, however, that there was a significant decrease in recurrence in low risk patients (27.3% WLC, 5.6% NBI) [30]. NBI has relatively high false positive rates ranging from 36% to 50% [29, 31, 32], likely related to the subjective nature of image interpretation.

Optical biopsy technologies, which provide high spatial resolution and sub-surface imaging, are complementary to wide field imaging modalities such as WLC, BLC, and NBI. In particular, confocal laser endomicroscopy (CLE) provides micron-scale, histology-like imaging. CLE is FDA approved for application within the urinary tract. For CLE in the bladder, intravesical or intravenous fluorescein is given as the contrast agent and for image acquisition, a fiber-optic probe based on a 488-nm laser is inserted via the working channel of standard cystoscopes and placed in direct contact of the tissue [33–35]. Video sequences (up to 12 hertz) display dynamic imaging of tissue micro-architecture, cellular morphology and vascular flow. Using CLE image criteria described for diagnosis and grading of bladder tumors [36], a study of inter-observer agreement revealed that the sensitivity for discerning cancerous lesions was 89% for urologists using WLC and CLE together [37]. As CIS is often difficult to differentiate from benign flat lesions under WLC, CLE provides microscopic details (Fig. 1C) to better characterize cellular features that may improve the yield of targeted biopsy. As CLE is probe-based with cross-platform compatibility, it may be combined with WLC and enhanced cystoscopy technologies (BLC and NBI).

High resolution cross-sectional imaging including CT and MRI, as the standard to evaluate the upper urinary tract, has been investigated in pre-TURBT settings for tumor characterization and staging. In a prospective study of 22 patients, Rosenkrantz et al. investigated the accuracy of MRI alone and 18F-FDG simultaneous PET/MRI using a diuresis protocol in bladder cancer patients [38]. PET/MRI increased bladder tumor detection from 77% to 86%, metastatic pelvic lymph nodes detection from 76% to 95% and non-nodal pelvic malignancy to 91% to 100% compared to MRI alone. Further investigation is needed with larger sample sizes to assess the possibility of applying this approach in initial bladder cancer evaluation.

IMPROVING BLADDER TUMOR RESECTION

In addition to better visualization and characterization of tumors and suspicious lesions, adjunctive imaging technologies enhance the technical implementation of TURBT and the completeness of resection. Incomplete resection contributes to understaging of disease that has been noted in up to 50% of patients correlating TURBT-based clinical staging to matched cystectomy specimen [7]. Factors contributing to incomplete TURBT also include decreased visibility due to bleeding and cautery artifacts, and inadequate visualization/differentiation of cancerous tissue at the resection margins.

A key strength of enhanced cystoscopy with BLC and NBI is that the surgeon can toggle back-and-forth between WLC and the enhanced imaging mode, thereby facilitating dynamic implementation during TURBT. This dynamic response allows for real-time assessment of the resection margin. Figure 2A and 2B show resection sites with residual disease identified by BLC and NBI, respectively. Residual tumor that is challenging to detect under WLC may appear to be well delineated compared to the surrounding benign mucosa under BLC as shown in Fig. 2A where the residual BLC enhanced areas correspond to low grade (Patient 1 and 2) and high grade papillary urothelial carcinoma (Patient 3). Future works are needed to

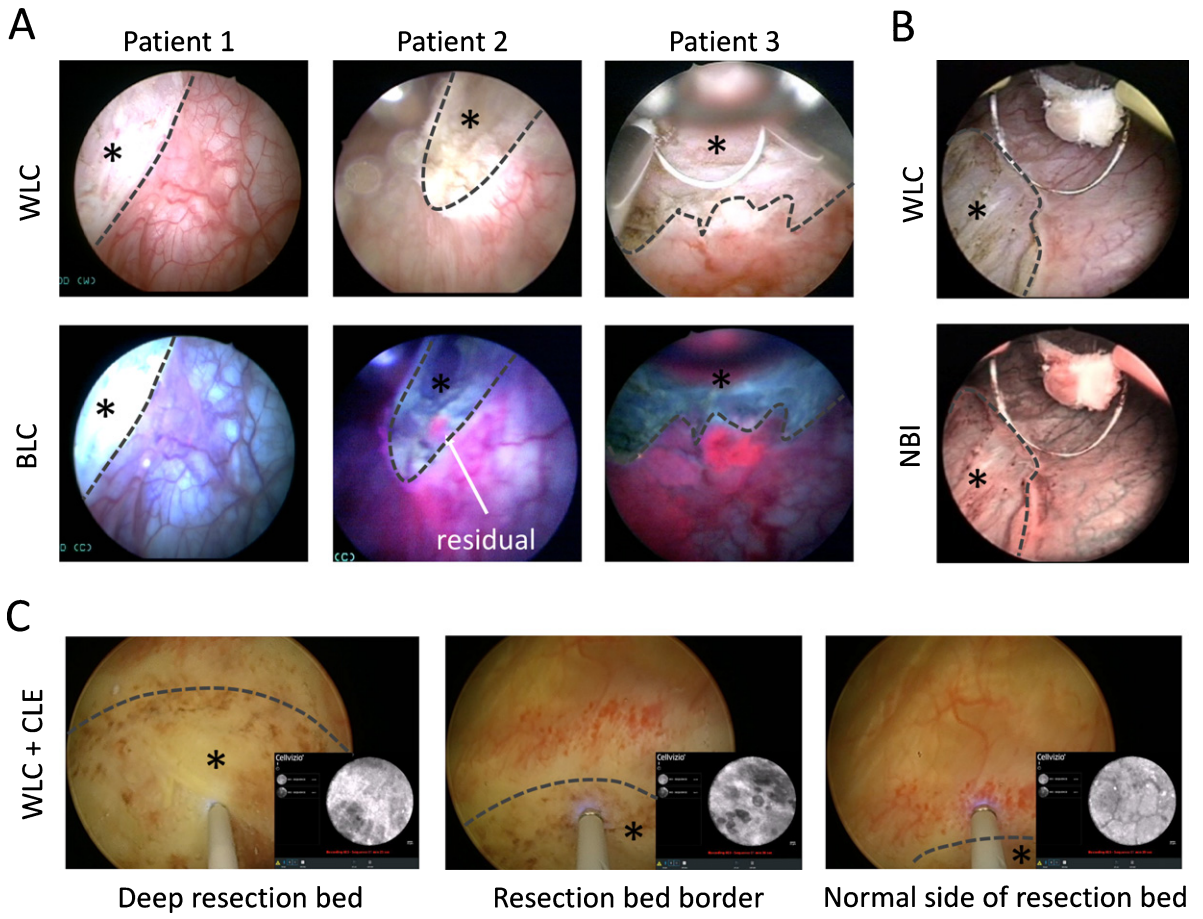

Fig. 2. Imaging of resection bed. (A) BLC can be used to detect residual tumor during TURBT as positive fluorescence is noted at the outside edges of the resection beds in these examples. There are residual tumors noted for patients 2 and 3 even within the resection bed on BLC that is not noted on WLC. (B) Residual tumor at the edge of the resection bed is noted on NBI. *NBI images obtained with permission from* [80]. (C) CLE can be used to interrogate the resection bed to determine adequate depth of resection. Features such as elastin strands, muscle fibers and perivesical fat can be visualized in the deep resection bed to verify adequate resection to the muscle layer in real time. All three WLC + CLE images with picture-in-picture are from the same resection bed. In the first image, elastin strands are noted on CLE in the deep resection bed. At the resection bed border, cautery artifact is noted with mostly absence of features seen in the muscle layer. On the normal side of the resection bed, CLE visualizes a capillary network typically seen in normal lamina propria. * – Indicates area within the resection bed. Dashed lines delineate the resection bed border.

determine objectively how enhanced imaging technologies can improve the dynamic aspects of TURBT.

Whereas enhanced cystoscopy technologies are useful to assess the edges of the resection bed, optical biopsy technologies may be utilized to investigate microscopic features of the resection bed, including muscularis propria and perivesical fat [33, 36, 39]. Figure 2C shows an example of using a 0.85 mm CLE imaging probe to interrogate the resection bed, border, and surrounding benign mucosa. Further studies are needed to prospectively determine the clinical utility of resection bed imaging and in combination with enhanced imaging technologies. Nevertheless, this strategy may provide additional confirmation regarding the depth of resection and residual disease at the time of TURBT.

OCT is another optical biopsy technology that provides mucosal and submucosal imaging in the Z-axis to a depth of 2 mm and spatial resolution of 10 μm, and does not require exogenous contrast agents [40]. A key strength of OCT is the depth of penetration, which enables the possibility of tumor staging. OCT is currently under clinical investigation, with results from several single center studies reported. A single center, retrospective analysis comparing staging by *in vivo* OCT with histopathology revealed 100% sensitivity and 90% specificity in detecting muscle invasive bladder tumors [41], and another single

center prospective study reported 100% sensitivity in detecting invasion of tumors beyond the lamina propria but only 65% overall specificity for bladder tumor detection [40]. Additional studies are needed to determine the suitability of OCT for resection bed imaging.

NEW RESECTION TECHNIQUES

Beyond innovations in imaging modalities, the quality of TURBTs can be improved with advancements in resection techniques. Bipolar, or plasmakinetic, TURBT has emerged in recent years as an alternative to standard monopolar TURBT. The main advantages of bipolar resection include the ability to use isotonic irrigation fluids to decrease the risk of TUR syndrome and potentially improved safety profile compared to monopolar energy [3]. Numerous studies that compared bipolar with monopolar TURBT have found decreased bladder injury associated with obturator nerve reflex [42–44] and improved detrusor sampling [45]. The advantages of bipolar resection may be limited to the safety of the surgical procedure and not clinical outcomes, as most studies find no significant effect of bipolar resection on recurrence rates [42, 46, 47].

Pathological interpretation of TURBT samples are known to be challenging, as resected tumor fragments are subjected to cautery damage, crush artifacts, tangential sections, and lack of spatial orientation caused by random embedding of bladder tissue [12]. *En bloc* resection improves pathological assessment by better preserving tumor architecture and orientation. *En bloc* resection can be performed using standard electrocautery, lasers, or water jet combined with monopolar energy [48]. Laser sources including holmium [49], thulium:YAG [50], and potassium-titanyl-phosphate (green light) [51] have been investigated.

In addition to better preservation of tissue orientation, laser-based *en bloc* resection may reduce surgical morbidity by decreasing bladder perforation through obturator nerve reflex, and post-operative bladder irritation [52]. Impact on cancer-specific outcomes are mixed, as no significant differences in recurrence using *en bloc* resection was noted in 3 prospective studies [53–55], but one small prospective study showed a significant decrease in recurrence (*en bloc* 28.6%, standard TURBT 62.5%) [56]. A multicenter study did not show differences in recurrence between laser (holmium and thulium) or electrical (monopolar and bipolar) sources [57]. The utility of *en bloc* resection is still under investigation with additional studies needed for validation of cancer-specific outcomes, and standardization of the technique will need to be addressed to facilitate comparison of the various approaches.

PERIOPERATIVE PLANNING AND LONGITUDINAL FOLLOW UP: 3D BLADDER RECONSTRUCTION

Improvements in perioperative care and long term follow up can positively impact bladder cancer management and patient outcomes. Currently, standard documentation of suspicious bladder lesions from cystoscopy, whether in the office or operating room settings, is based on a written description of lesion location, number, size, and morphology. To standardize documentation, the use of a bladder diagram has been advocated in urologic guidelines [2, 58]. Particularly in settings where multiple urologists (e.g. second opinion) are involved in treatment, improved documentation could facilitate communication and follow-up, pre-TURBT surgical planning, and longitudinal surveillance of suspected mucosal lesions. Modern WLC, particularly with the new generation of cameras and videoendoscopes, generates high definition (HD) videos and has enormous data potential. However, WLC is typically used only for real-time guidance and data are not routinely stored.

Recently, a computational method to reconstruct and visualize a 3D model of organs from standard cystoscopic HD videos that captures the shape and surface appearance of the organ has been developed [59]. The algorithm utilizes advanced computer vision techniques and standard cystoscopes for image acquisition (Fig. 3). In contrast to prior efforts [60–62], this algorithm does not require additional hardware. It uses *a priori* data to reconstruct the bladder surface, and presents a complete software-based pipeline to convert the cystoscopic images into a 3D textured model of the bladder. The image preprocessing technique utilizes a structure-from-motion algorithm and the robustness of the reconstruction was tested using tissue-mimicking bladder phantoms. Potential clinical utility was demonstrated using intraoperative cystoscopy videos. Successful reconstruction was achieved for 66.7% of the datasets whereas the definition of successful was that at least 25% of the camera poses could be computed.

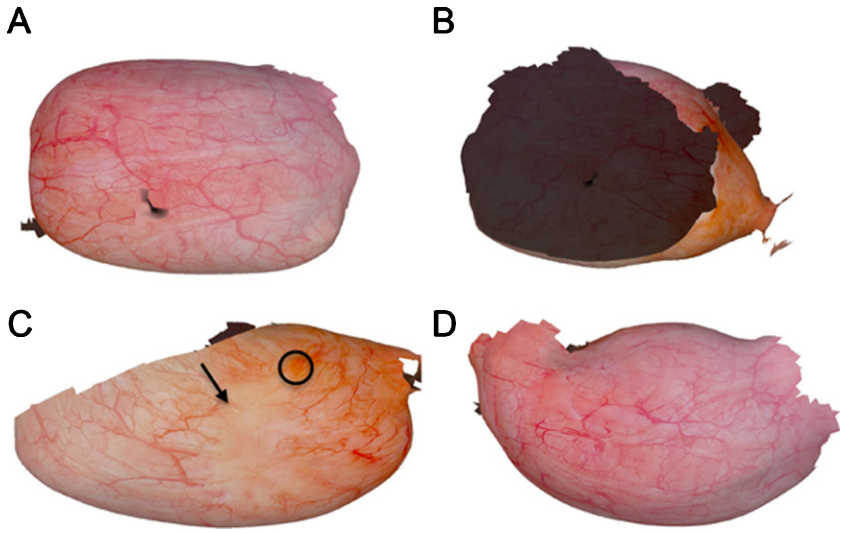

Fig. 3. Reconstruction from a clinical dataset of human bladder. Cystoscopy image reconstruction views from the (A) anterior, (B) posterior, (C) left lateral, and (D) right lateral walls. Black circle and arrow in (C) show regions of a papillary tumor and scarring, respectively. Regions that appear dark represent the interior of the bladder. From [59] with permission.

In a separate 2017 study, image processing and stitching software was used in 12 consecutive whole organ cystoscopies of patients undergoing TURBT to generate panoramic images of the bladders. The authors successfully created HD panoramic images (4096 × 2048 pixel) in 10 out of 12 cases. However, with this technique there was decreased resolution of the anterior bladder wall as well as low image quality in patients with severe gross hematuria, which interfered with collection of high quality images [63].

Potential applications of these promising 3D reconstruction algorithms include a platform for complete visual medical record of bladder lumen that may be utilized for preoperative surgical planning, cancer surveillance through longitudinal studies of mucosal changes, and trainee or patient education. However, these techniques are at early stage and need further clinical validation. A critical point to consider is that while these emerging technologies provide adjunctive information to standard WLC, timely access to office cystoscopy for hematuria work-up and standard TURBT needs to be prioritized, regardless of the availability of adjunctive imaging technologies [64, 65].

MOLECULAR IMAGE-GUIDED SURGERY – THE FUTURE?

Optical molecular imaging enables the visualization and characterization of biological processes at the molecular level [66, 67]. To improve the specificity of intraoperative cancer imaging, there is significant interest to develop targeted imaging agents based on fluorescent antibodies, peptides or small molecules. The urinary bladder is an ideal organ for molecular imaging as intravesical application of imaging and therapeutic agents are well established. Through the instillation of molecular imaging agents that bind to specific cancer targets, malignant tumors can be differentiated from benign lesions using endoscopic imaging modalities. The ideal imaging agents would be safe, stable, have appropriate pharmacokinetics, and sensitive and specific for cancer.

For imaging applications, surface antigens are easily accessible for binding to fluorescently labeled antibodies. Although epidermal growth factor (EGFR) and prostate stem cell antigen (PSCA) are potential targets due to contrasting expression patterns between malignant and benign urothelial carcinomas [68–72], they are not ubiquitously expressed on bladder tumors and thus lack the sensitivity needed as imaging targets. CD47, a cell surface protein that is a negative regulator of phagocytosis, is a promising imaging target [73, 74]. CD47 is expressed on the surface of more than 80% of bladder cancer cells but is not expressed on the luminal cells of normal urothelium [74, 75]. Successful *ex vivo* endoscopic imaging of bladder cancer using an anti-CD47 antibody has been reported [75]. Both CLE and BLC were used to detect an intravesically instilled fluorescently tagged antibody

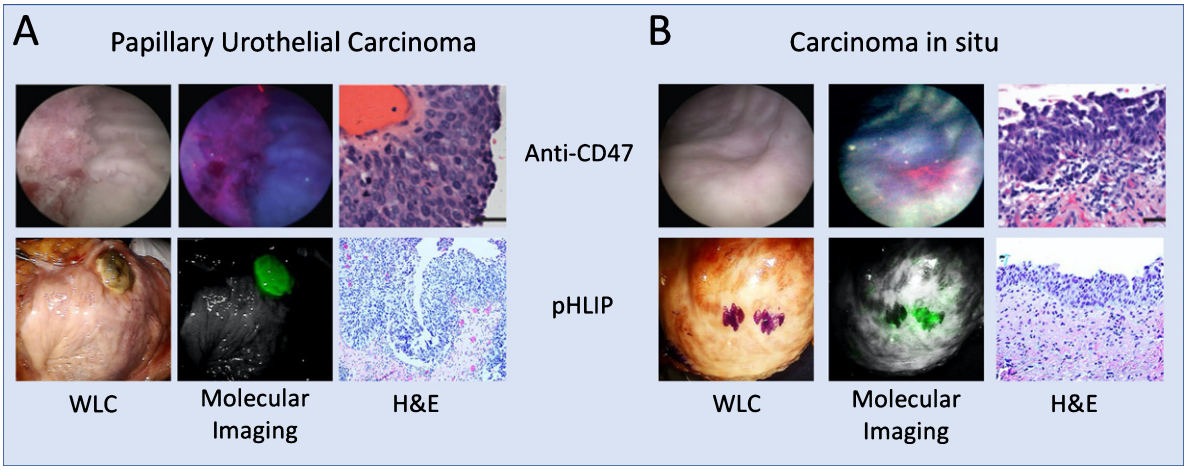

Fig. 4. Molecular imaging of human bladder tumors. *Ex vivo* molecular imaging of human bladder using anti-CD47-Qdot625 (Anti-CD47) imaged with BLC and indocyanine green with pH low insertion peptide (pHLIP) agent imaged with da Vinci Si NIRF imaging system. The respective imaging systems for the two molecular imaging strategies are capable of detecting both (A) papillary tumors and (B) CIS with high sensitivity and specificity. Anti-CD47 images from [75], reprinted with permission from AAAS. pHLIP images obtained from [79] with permission from PNAS.

against human CD47 in *ex vivo* human bladders. BLC imaging of the fluorescent anti-CD47 had 82.9% sensitivity and 90.5% specificity for bladder cancer (Fig. 4).

Small peptides such as pH low insertion peptides (pHLIPs) are a class of membrane-binding peptides that specifically target acidic cells by crossing through the cell membrane in low pH extracellular environments [76, 77]. Tumor cells typically have higher metabolic activity leading to the production of acidic environments [78] that could be targets for pHLIPs. A near infrared fluorescence (NIRF) imaging system was used to image indocyanine green (ICG) conjugated pHLIPs in an *ex vivo* study of radical cystectomy specimen from 22 patients (Fig. 4) [79]. Sensitivity was 97% and specificity was 100% in detecting bladder cancer. However, when necrotic and post-chemotherapy tissue were included, the false positive rate increased and the specificity dropped to 80%. The strategy of developing targeted, specific imaging agents is promising, and further studies are needed to assess *in vivo* performance and toxicity.

The molecular imaging approaches discussed (CD47 and pHLIPs) are in early stages of investigation, and *in vivo* human studies have not been established, pending development of clinical grade labeled antibodies and peptides for *in vivo* human appliactions. Further investigations are needed before potential application in the clinical setting. However, targeted molecular imaging is a promising avenue toward improved sensitivity and specificity for cancer detection.

CONCLUSION

The technologies highlighted in this review illustrate the range of technologies at various stages of development aimed at addressing the shortcomings of standard WLC based TURBT. BLC and NBI are recommended in current practice guidelines while molecular imaging of bladder cancer has only been demonstrated to date in *ex vivo* models. As the clinical impact and efficacy of these technologies are validated with further studies, we envision that the future TURBT will harness and combine the advantages of multiple adjunctive technologies to improve the overall quality of TURBT.

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