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New Optical Imaging Technologies for Bladder Cancer: Considerations and Perspectives

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Abstract

Purpose—Bladder cancer presents as a spectrum of different diatheses. Accurate assessment for individualized treatment depends on initial diagnostic accuracy. Detection relies on white light cystoscopy accuracy and comprehensiveness. Aside from invasiveness and potential risks, white light cystoscopy shortcomings include difficult flat lesion detection, precise tumor delineation to enable complete resection, inflammation and malignancy differentiation, and grade and stage determination. Each shortcoming depends on surgeon ability and experience with the technology available for visualization and resection. Fluorescence cystoscopy/photodynamic diagnosis, narrow band imaging, confocal laser endomicroscopy and optical coherence tomography address the limitations and have in vivo feasibility. They detect suspicious lesions (photodynamic diagnosis and narrow band imaging) and further characterize lesions (optical coherence tomography and confocal laser endomicroscopy). We analyzed the added value of each technology beyond white light cystoscopy and evaluated their maturity to alter the cancer course.

Materials and Methods—Detailed PubMed® searches were done using the terms “fluorescence cystoscopy,” “photodynamic diagnosis,” “narrow band imaging,” “optical coherence tomography” and “confocal laser endomicroscopy” with “optical imaging,” “bladder cancer” and “urothelial carcinoma.” Diagnostic accuracy reports and all prospective studies were selected for analysis. We explored technological principles, preclinical and clinical evidence supporting nonmuscle invasive bladder cancer detection and characterization, and whether improved sensitivity vs specificity translates into improved correlation of diagnostic accuracy with recurrence and progression. Emerging preclinical technologies with potential application were reviewed.

Results—Photodynamic diagnosis and narrow band imaging improve nonmuscle invasive bladder cancer detection, including carcinoma in situ. Photodynamic diagnosis identifies more papillary lesions than white light cystoscopy, enabling more complete resection and fewer residual tumors. Despite improved treatment current data on photodynamic diagnosis do not support improved high risk diathetic detection and characterization or correlation with disease progression. Prospective recurrence data are lacking on narrow band imaging. Confocal laser endomicroscopy

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and optical coherence tomography potentially grade and stage lesions but data are lacking on diagnostic accuracy. Several emerging preclinical technologies may enhance the diagnostic capability of endoscopic imaging.

Conclusions—New optical imaging technologies may improve bladder cancer detection and characterization, and transurethral resection quality. While data on photodynamic diagnosis are strongest, the clinical effectiveness of these technologies is not proven. Prospective studies are needed, particularly of narrow band imaging, confocal laser endomicroscopy and optical coherence tomography. As each technology matures and new ones emerge, cost-effectiveness analysis must be addressed in the context of the various bladder cancer types.

Keywords

urinary bladder neoplasms; fluorescence; cystoscopy; lasers; tomography; optical coherence

Bladder cancer is the fifth most common cancer in the United States[1] and the sixth in the developed world.[2] Most patients present with nonmuscle invasive bladder cancer and are at risk for recurrence. A significant proportion is also at risk for progression.[3] The consequent need for continued surveillance and repeat treatment makes bladder cancer one of the most expensive cancers to manage.[4] As a critical component of bladder cancer evaluation, the quality of endoscopy and tumor resection may directly influence the cancer outcome.

The ideal endoscopic imaging modality is highly sensitive for cancer detection, distinguish between benign and malignant lesions, and characterize grade and stage. Such endoscopic and ultimately histopatho-logical information could permit urologists to stratify the patient risk of disease recurrence and/or progression, and potentially individualize and optimize treatment.

WLC, the traditional standard for initial bladder cancer diagnosis, has several shortcomings. Flat malignant lesions (CIS) are difficult to visualize and distinguish from benign inflammatory lesions. Missed tumors may be high grade or unexpectedly invasive.[5] Imprecise localization and demarcation can also impede complete resection/cauterization. WLC guided TUR of nonmuscle invasive bladder cancer underscores the shortcomings of WLC to diagnose papillary lesions in that inadequate visualization of all tumors that may be present or of diffuse tumor borders may result in missed or incompletely resected lesions. In this regard many patients with Ta tumors may be at increased risk for recurrence. Moreover, up to half of high grade Ta or T1 cases may be under staged at TUR,[6] leading to second look TUR to reassess resected areas as well as attempts to completely resect all lesions to allow more accurate staging and treatment selection, and avoid progression.

Thus, the motivation for new imaging technologies has focused on enhanced visualization of bladder tumors to improve diagnostic accuracy and re-section thoroughness. We reviewed 4 new optical imaging technologies that have been applied clinically, including fluorescence cystoscopy/PDD, NBI, CLE and OCT. While all 4 technologies have been applied in vivo, clinical evidence of maturity varies from feasibility studies for CLE and OCT to clinical efficacy for PDD and NBI.

To expand beyond recent reviews[7–10] we evaluated the current maturity of each technology in the context of its ability to identify and distinguish different tumor diatheses, and the potential for recurrence and progression. We also assessed any potential or validated added value to the current diagnostic standard. Several emerging preclinical technologies were also examined since they may potentially enhance future diagnostic capability.

MATERIALS AND METHODS

We searched the English language literature for original and review articles in PubMed® using the terms “fluores-cent cystoscopy,” “photodynamic diagnosis,” “narrow band imaging,” “optical coherence tomography” and “confocal laser endomicroscopy.” All articles on in vivo or ex vivo use of these technologies in the urinary tract were identified for analysis. Similar searches were performed for “optical diagnostics,” “single-fiber endoscopy,” “Raman spectroscopy,” “two-photon microscopy” and “endocytoscopy” coupled with “bladder cancer” or “urothelial carcinoma” to assess the status of emerging technologies for bladder cancer diagnosis and assessment. Articles were published from 1995 to 2011, including approximately 70% in the last 5 years.

RESULTS AND DISCUSSION

Technical Considerations

The primary goal of optical imaging technology is to better identify and characterize bladder lesions beyond what is possible with standard WLC. The technology is intended to augment rather than replace WLC. Table 1 lists the technical specifications of the 4 modalities, including the image acquisition method, need for exogenous contrast agents and image resolution. PDD and NBI require specialized cystoscopes and/or cameras while CLE and OCT are based on fiberoptic probes used with standard cystoscopes. PDD and CLE require a priori instillation of exogenous fluorescent contrast medium. While such exogenous contrast agents are essential for diagnostic capability, they contribute to technical complexity and cost.

Imaging technologies are classified based on macroscopic or microscopic field of view (fig. 1). PDD and NBI, the macroscopic modalities, survey a large area of bladder mucosa in a manner similar to WLC and provide additional contrast enhancement to highlight suspicious lesions and distinguish them from surrounding, presumably noncancerous mucosa. CLE and OCT, the microscopic modalities, enable high resolution subsurface characterization of suspected lesions, providing information on tissue microarchitecture and cellular morphology that is not possible with macroscopic imaging technology. No modality is truly cancer specific, given the overlapping morphological characteristics between benign lesions and cancer, and the lack of molecular specificity in image acquisition.

Macroscopic Imaging

PDD—This modality uses photosensitive protoporphyrin analogues as intravesical contrast agents combined with a blue light source (375 to 440 nm) to stimulate fluorescence. Selective accumulation of the photosensitizers 5-ALA or HAL by cancer cells causes tissue to appear red when visualized under blue light (fig. 2, *A*). While most PDD studies are based

on 5-ALA, HAL is more potent and the one approved for clinical use as Hexvix® in Europe and Cysview® in the United States. HAL is instilled intravesically via straight catheterization 1 to 2 hours before PDD.[11]

An attractive aspect of PDD is the relative ease of interpreting images based on visualizing red fluorescent areas under blue light, although false fluorescence can result if the light source is applied tangential to the lesion.[12,13] Up to a 30% false-positive rate was reported, particularly with prior BCG treatment and during the PDD learning curve.[14] PDD is approved for single administration since data are lacking on potential drug hypersensitivity with repeat exposure. Other technical limitations include preoperative catheterization and decreased visualization with inadequate hemostasis.

NBI—This technique enhances tissue contrast between bladder cancer and normal urothelium but does not require exogenous contrast agents (fig. 2, *B*). NBI is based on a light source that filters white light into 2 wavelengths (415 and 540 nm) that are strongly absorbed by hemoglobin, enhancing the contrast between capillaries and mucosa. Enhanced contrast helps differentiate the more vascularized malignant areas from normal and benign urothelium. Interpreting NBI images is inherently subjective since it relies on surgeon ability to detect visual change in the vasculature around and in suspicious areas. The false-positive rate of NBI of up to 36% is similar to that of PDD and BCG may affect diagnostic accuracy.[15,16] Bleeding during TUR also decreases overall bladder illumination and hampers accurate, enhanced visualization.

Microscopic Imaging

CLE—This modality combines the principles of confocal microscopy with those of fiberoptics. CLE is currently approved for clinical use in the gastrointestinal and respiratory tracts, where standard white light endoscopy faces diagnostic challenges parallel to those in the urinary tract.[17–19] Of the 4 technologies CLE has the highest resolution (2 to 5 μm) and can provide optical biopsy by revealing the microarchitecture and cellular morphology of suspected lesions in vivo.[20,21] Confocal images reminiscent of histology are acquired as video sequences, providing the possibility for real-time differentiation of bladder cancer grade (fig. 2, *C*). Fluorescein, which is Food and Drug Administration approved for ophthalmic applications and has a well established safety profile, is introduced intravesically or intravenously just before imaging.[17,20]

The 2.6 mm diameter imaging probe is inserted through the working channel of a standard cysto-scope or resectoscope. Direct en face contact of the imaging probe with tissue is required, which makes acquiring images of some areas, such as the dome and bladder neck, potentially difficult through a rigid cystoscope. This may be overcome by a smaller 1.4 mm imaging probe that fits in a flexible cysto-scope.[22] CLE relies on WLC to first identify lesions of interest for characterization since it is not practical to use CLE to survey the entire bladder, given its narrow field of view.

OCT—This method uniquely offers the potential of real-time bladder cancer staging by cross-sectional imaging below the mucosal surface (fig. 2, *D*).[23,24] OCT is based on elastic light scattering and analogous to ultrasound but for OCT light is emitted instead of sound.

Depth is determined by the amplitude of scattered light, which varies according to bladder tissue layer. When bladder cancer invades beyond the lamina propria, demarcation of these 3 layers is disrupted and can be visualized. For image acquisition OCT is similar to CLE in that it is probe based and depends on WLC to identify areas of interest for further characterization.

More Significant Tumors Detected?

The objectives of macroscopic and microscopic imaging are to improve bladder tumor detection and characterization, respectively. Detecting additional tumors is particularly relevant to eradicate all existing lesions, such that tumor persistence does not cause rapid recurrence. This can potentially prolong recurrence-free survival through more complete re-section of all visible lesions.

Given the differences in the biological potential for low grade Ta with high grade T1 and CIS tumors,[25] macroscopic imaging should ideally detect more tumors as well as tumors with the highest risk of recurrence and progression. Several prospective studies suggest that PDD detects more papillary lesions and CIS on initial cystoscopy.[26–29] Overall detection sensitivity is 87% to 97% and specificity is 43% to 76%. In several single center studies patient stratification by diathesis revealed 93% to 98% sensitivity for CIS compared to 50% to 70% for WLC alone with 30% to 50% of CIS lesions visualized only by PDD. The detection rate for Ta lesions also appears to be better for PDD, that is 94% to 97% vs 83% to 88% for WLC alone.[27,28] For T1 disease 2 groups reported improved detection with PDD, that is about 10% greater than for WLC. Others noted similar detection rates.[27–29] Few groups have described the detection of invasive disease but Schmid-bauer et al suggested that the detection rate is similar.[28]

For NBI between 93% and 100% detection sensitivity was reported in retrospective studies, mostly in patients with nonmuscle invasive disease.[16,30,31] Also, 90% sensitivity for detecting CIS was reported, significantly better than the 50% for WLC alone.[16] For Ta disease NBI found 16% of lesions not identified by WLC alone and 26% of T1 lesions thought to be negative by WLC alone.[30] Overall NBI specificity is 65% to 82% for all disease stages and 75% for CIS.[16,30,31]

There are several inherent limitations to these technologies in regard to cancer detection. Outstanding questions remain to be addressed that are not strictly cancer specific. The potential costs of additional biopsies due to false-positive findings have not been well studied. Regardless of technology, imaging in the post-BCG setting is challenging. PDD and NBI have shown a high false-positive rate in the post-BCG setting that did not improve on WLC results.[14–16] Some studies excluded or had few patients treated with BCG, which then had a false-positive rate comparable to that of WLC.[11,29,32] PDD is currently not recommended within 3 months after BCG treatment. Lastly, it is unclear whether these technologies simply provide an added effect, such that second look WLC alone would also improve tumor detection.[33]

Tumor Histology and Stage Predicted?

As microscopic imaging, CLE and OCT have the potential to characterize bladder lesions in ways that are not possible with macroscopic imaging, namely determining tumor grade and stage. Promising published reports are largely of a clinical feasibility nature and lack the sample size needed to draw definitive conclusions.

CLE for bladder cancer was applied in more than 70 patients at a single center under an investigational protocol.[20–22] Recently an imaging atlas was published that details the in vivo microscopic features of benign and inflammatory lesions, and low and high grade bladder cancer.[21] A prospective diagnostic accuracy study of CLE, including bladder cancer grading, is currently under way. The diagnostic sensitivity of OCT for bladder cancer is between 75% and 100%. In some studies 100% sensitivity for detecting muscle invasiveness was reported[23,24] as well as 90% and 75% for Ta and T1 lesions, respectively.[34] Specificity is between 65% and 90% for overall cancer detection.[23,24]

CIS detection poses special challenges for each microscopic technology. 1) Each is limited by reli ance on WLC to identify suspicious lesions. Combining macroscopic with microscopic technologies (multimodal imaging) may potentially overcome this limitation.[35] 2) Since CIS may be less adherent and often presents with bladder urothelium denudation, precise pathological correlations with in vivo imaging (co-registration) may be challenging.

For microscopic imaging technology real-time image interpretation may be challenging in that the urologist must intraoperatively play the role of a pathologist with CLE or a radiologist with OCT. The learning curve and interobserver variance associated with image interpretation are currently unknown. CLE and OCT false-positive can occur from inflammatory states, eg after BCG, and scarring, similar to PDD.[23]

Better TUR Promoted?

Improved optical imaging could ideally promote better TUR, resulting in decreased tumor persistence, recurrence and progression. In a randomized single center study the residual tumor rate at second look TUR was significantly decreased when initial TUR was done with PDD than with WLC alone for different stages, including CIS (4% vs 28%), high grade pT1 (15% vs 35%) and any high grade, nonmuscle invasive disease (17% vs 37%).[26] Subgroup analysis of patients with a solitary papillary tumor less than 3 cm vs those with multiple tumors or tumors greater than 3 cm revealed a decreased residual disease rate at second look TUR in each group with initial PDD guided TUR but the difference was only significant for those who presented with multiple or large tumors.[27] All study patients received mitomycin postoperatively, potentially qualifying the beneficial effects of PDD alone for decreasing the recurrence rate.

Groups have suggested that improved CIS detection using PDD decreases tumor persistence. This remains controversial since CIS is considered a field effect disease and is treated with intravesical therapy. To our knowledge whether PDD adds value in the setting of positive cytology and random biopsies has not been explored.

Eradicating persistent Ta disease is likely to decrease the recurrence rate and patient morbidity. However, for low grade lesions this may not change the disease course or its fundamental significance. This diathesis is generally acknowledged to be low risk and recurrence is considered mainly a nuisance issue. On the other hand, improved TUR for T1 disease factors into bladder preservation due to its potential for progression if not completely excised. Thus, it could promote bladder preservation.

In a prospective, single center study of second look TUR with NBI after initial WLC only TUR identified persistent or missed disease in a third of patients.[36] To our knowledge no randomized studies have assessed cancer persistence when initial resection was done with NBI. A multicenter, randomized trial is currently under way that may clarify this question.[37]

Disease Recurrence and Progression Affected?

The long-term goal of detecting more tumors and promoting better TUR is to improve overall RFS and PFS for patients with bladder cancer. Of the 4 technologies data are available only for PDD and NBI to possibly address these outcome measures in a value added manner.

Table 2 lists the 4 randomized, multicenter PDD trials. In the 2 European studies by Schumacher[29] and Stenzl[32] et al, respectively, RFS and PFS did not improve. They used the older photosensitizer 5-ALA. Despite this caveat data on 5-ALA and HAL are included in the discussion since they are considered equivalent for cancer detection.[38] In each seriesWLC was the surveillance method.

According to the 2 HAL studies RFS measured by surveillance WLC at 9 and 12 months improved in the PDD group.[11,39] However, PFS, which was described as disease progression within 12 months, was only measured by Stenzl et al.[32] From a value added perspective it was not significantly improved. Subgroup analysis in the study by Stenzl et al revealed decreased recurrence only for low grade Ta tumors. However, few patients were in the other groups. In contrast to other series, PDD significantly decreased recurrence in patients with recurrent disease as well as in those with newly diagnosed disease.[11] These findings served as the basis for Food and Drug Administration approval of PDD in the United States.

None of the 3 studies of PFS showed improvement with PDD. However, followup may have been too brief for full assessment. In a smaller randomized study with 7-year long-term followup Denzinger et al studied RFS and PFS in 46 patients with high grade T1 disease with PDD using 5-ALA.[40] RFS was significantly improved in the PDD group but no significant difference in PFS was observed.

These studies have several limitations. 1) Intravesical chemotherapy, eg mitomycin, was not controlled postoperatively, which might complicate the interpretation of recurrence data. Determining whether patients were truly disease free may be also be challenging in those with CIS, for which followup is done with WLC. All subgroup analysis involved few patients, highlighting the need for larger studies with adequate followup to truly determine whether PDD can improve PFS. Furthermore, since these trials were multicenter, experience

with PDD may have varied. Two of the 3 randomized trials showed a similar rate of largely minor adverse events in the PDD and placebo arms.[11,32] The trial by Schumacher et al showed a higher rate of adverse events in the PDD arm.[29]

When exploring NBI Herr and Donat assessed RFS in patients using a within patient, case control design and found significantly improved RFS in those treated with NBI assisted TUR (13 vs 29 months).[15] However, prospective studies are lacking to support a decreased recurrence rate for NBI while to our knowledge PFS data are not available. Currently a multicenter, randomized trial of NBI vs WLC is ongoing with surveillance at 3 and 12 months.[37]

Cost Considerations

The costs of optical imaging technologies include instrumentation, contrast agents as needed and additional operative time. The recently approved Karl Storz® PDD system in the United States costs approximately $40,000, which includes specialized cystoscopes, light source and light cables. Each HAL dose costs approximately $600. In contrast, NBI is marketed by Olympus® as a standard functionality of the current generation of endoscopic tower at approximately $33,000, including the light source and video processor. Integrated videoscopes with NBI capability are also available for flexible cystos-copy and ureteroscopy. Given that exogenous contrast agents are not needed, NBI may offer the potential advantage that a lower threshold is needed for clinically adopting this technology, including the outpatient clinic setting.

Limited data on the cost-effectiveness of PDD using 5-ALA are only available from Europe. In these studies investigators found modest savings of $230 to $500 per year based on decreased disease recurrence. To our knowledge the costs of the additional operative time, pathological analysis and added patient morbidity in the context of different health care systems remain to be addressed.

Emerging Applications and Technologies

Multimodal imaging.—Given the unique capabilities of the different imaging technologies, some could be combined to maximize the potential benefit. Multi-modal imaging is commonly done for gastrointestinal endoscopy. Combining technologies that better identify suspicious lesions, eg PDD and NBI, with those that enable more detailed characterization, eg OCT and CLE, may prove useful. For example, in a single center study in which OCT was used in conjunction with PDD the combination decreased the false-positive rate to 2% by enabling better lesion characterization.[35] Similarly CLE may be combined with PDD or NBI.

Computer-assisted image interpretation.—This technique could improve the efficiency of and add objectivity to the subjectivity associated with image interpretation. The mosaic technique used in CLE enables adjacent images to be fused together, creating a wider field of view.[21] A content based video retrieval method was reported that uses a video mosaic method of geometric and spatial relationships to retrieve images with patterns associated with malignancy for CLE in the gastrointestinal tract.[41]

Preclinical emerging imaging modalities.—Scanning fiber endoscopy uses 1 fiber and a rotating motor to enable 360-degree surveillance of spherical structures and a mosaic method to create a panoramic image that can be analyzed offline.[42] Two photon microscopy, which has currently only been used ex vivo, detects molecular autofluorescence in the ultraviolet range. Characteristic fluorescent ratios of molecules, eg the nicotinamide adenine dinucleotide-to-hydrogen flavin adenine dinucleotide ratio, can be used to discriminate benign from malignant tissue.[43] Endocytoscopy uses a 450× magnifying lens to microscopically characterize the cellular morphology of tissue stained with methylene blue, which is clinically feasible in vivo.[44] High frequency endoluminal ultrasound achieves high resolution at a greater penetration depth that enables even large tumors to be accurately staged. The clinical feasibility of endoluminal ultrasound was reported with 88% overall staging accuracy.[45] Macroscopic technologies for whole bladder surveillance also include Raman spectroscopy, which uses molecule specific photon scattering to analyze target molecular composition. Normal and cancerous tissues can be differentiated by their unique spectra. This technique was applied in vitro for bladder cancer with 85% sensitivity and 79% specificity.[46]

Molecular imaging—Cancer specific contrast agents conjugated to fluorophores could improve specificity, as demonstrated in the gastrointestinal tract to improve the diagnosis of colonic dysplasia in conjunction with CLE.[47] These molecular contrast agents could be antibodies or peptides known to have molecular specificity for high grade bladder cancer, allowing for tumor specific visualization and decreasing the false-positive caused by inflammatory lesions. In the future the ability to perform targeted imaging may facilitate the development of targeted therapy for bladder cancer.

CONCLUSIONS

Several new optical imaging technologies have emerged for endoscopic management of bladder cancer that may offer the urologist an improved vantage to detect and characterize bladder lesions. Each new imaging technology is at a different point in its progress toward implementation as a validated instrument that adds value to the current standard of care (fig. 3). While new imaging modalities currently do not replace histopathological analysis after resection, they hold great potential for more accurate localization and characterization of bladder lesions, which may enable more accurate biopsy and resection. These technologies come with increased financial and patient costs. To assess their value critical evaluation is needed of the impact of new technology on cancer detection and characterization, and correlations of recurrence and progression outcomes with each placed in the context of a cost-benefit evaluation.

Adequately powered studies stratified by cancer risk are needed to determine the patients who will benefit most from PDD and whether PDD can prevent disease progression in those at high risk. NBI requires prospective, randomized studies to better understand its potential role in bladder cancer diagnosis. While they are clinically feasible and provocative, OCT and CLE require multicenter studies to determine accuracy and their optimal role as adjuncts to macroscopic imaging for cancer detection.

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Abbreviations and Acronyms

5-ALA	5-aminolevulinic acid
BCG	bacillus Calmette-Guérin
CIS	carcinoma in situ
CLE	confocal laser endomicroscopy
HAL	hexaminolevulinate
NBI	narrow band imaging
OCT	optical coherence tomography
PDD	photodynamic diagnosis
PFS	progression-free survival
RFS	recurrence-free survival
TUR	transurethral resection
WLC	white light cystoscopy

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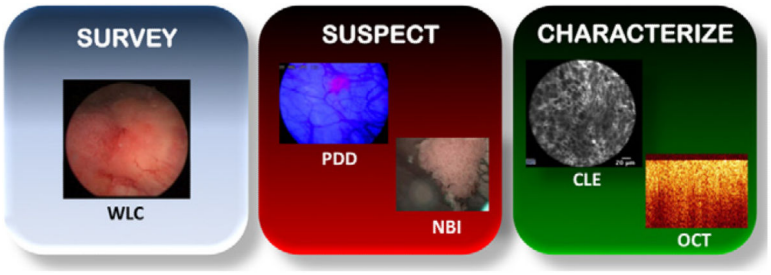

Figure 1.

Optical imaging for bladder cancer diagnosis. WLC is standard approach for general bladder survey. Macroscopic fluorescence cystoscopy/PDD and NBI improve bladder tumor detection through contrast enhancement of suspected lesions from surrounding benign mucosa. Microscopic CLE and OCT improve suspected tumor characterization through high resolution subsurface imaging.

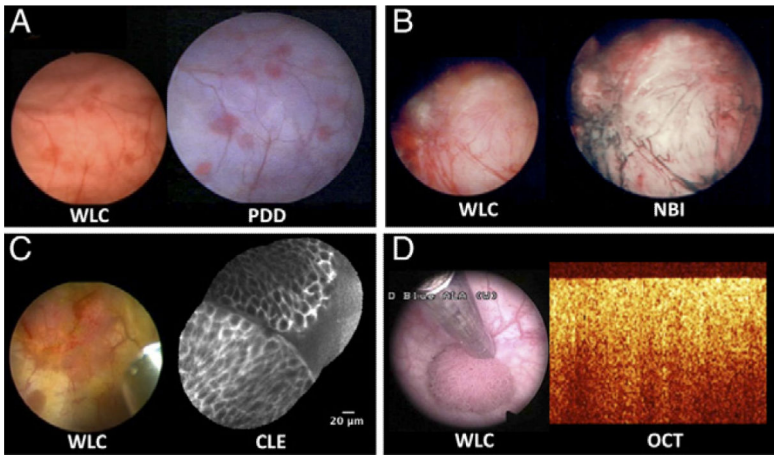

Figure 2.

Representative in vivo images acquired by new optical imaging technologies with corresponding WLC images. PDD and NBI require specialized camera filter. CLE and OCT are based on imaging probes inserted through standard cysto-scopes and resectoscopes. OCT image reproduced with permission from Elsevier.[35]

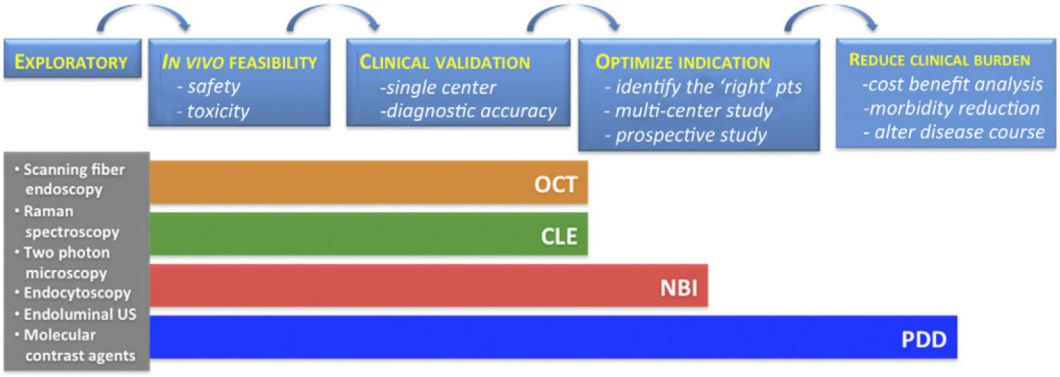

Figure 3.

Phases of technology development and validation for current and emerging optical imaging technologies for bladder cancer. *US*, ultrasound.

Table 1

New imaging technology specifications and technical considerations

	PDD	NBI	CLE	OCT
Field of view	Macroscopic	Macroscopic	Microscopic	Microscopic
Contrast medium	HAL	No	Fluorescein	No
Scope/probe size (mm)	5–7	5–7	1–2.8	2.7
Depth	Surface	Surface	120 μm	1–3 mm
Resolution	mm-cm	mm-cm	2–5 μm	10–20 μm
Vendor	GE™ Healthcare/Karl Storz	Olympus	Mauna Kea Technologies	Imalux®

Table 2

Double-blind, placebo controlled PDD trials

	Stenzl et al[32]	Schumacher et al[29]	Stenzl et al[11]	Hermann et al[39]
Study site	Europe	Europe	Europe + United States	Europe
No. PDD pts	370	141	365	115
Excluded:	5-ALA	5-ALA	HAL	HAL
Recent BCG	No	No	Yes	No
Inexperience	No	No	No	Not reported
Followup (mos)	12	12	9	12
% False-pos vs WLC	12 vs 16	11 vs 12	12 vs 11	25 vs 16
Improved:				
RFS	No	No	Yes	Yes
PFS	No	No	No	Not measured
Post-TUR mitomycin	No	Yes	No	No