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Review – Bladder cancer

Beyond the photodynamic diagnosis: Searching for excellence in the diagnosis of non-muscle-invasive bladder cancer

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A B S T R A C T

Cystoscopy is the gold-standard method in non-muscule-invasive bladder cancer diagnosis. In the cystoscopic exploration 30% of tumors could be overlooked: it is due to flat forms, small tumors or difficult visualization. Photodynamic diagnosis reduces overlooked tumor rates, and has improved diagnosis on flat forms, with the consequence of increasing relapse time to recurrence and decreasing the number of iterative cystoscopies; nevertheless the false positive rate is high. In recent years new optical devices have been developed which seek to improve diagnostic sensitivity in cystoscopy –alone or associated– without diminishing specificity. Among new devices we must emphasize some like Narrow Band Imaging, Optical Coherence Tomography and Laser Confocal Endomicroscopy.

Más allá del diagnóstico fotodinámico: buscando la excelencia en el diagnóstico del cáncer vesical no músculo-invasivo

Palabras clave:
Cáncer de vejiga
Narrow band imaging
Tomografía de coherencia óptica
Endomicroscopía láser confocal

R E S U M E N

La cistoscopia es el método de elección en el diagnóstico positivo del cáncer vesical no músculo-invasivo. La tasa de tumores que pasan inadvertidos durante la cistoscopia puede llegar al 30%; esto es debido a factores como la existencia de formas tumorales planas, de pequeño tamaño o de difícil visualización. El diagnóstico fotodinámico ha conseguido disminuir la tasa de tumores que pasan inadvertidos, y ha conseguido mejorar el diagnóstico de lesiones planas, con el consiguiente aumento del tiempo libre de recidiva y disminuyendo el número de actuaciones endoscópicas iterativas, pero a costa de una tasa de falsos positivos elevada. En los últimos años se han desarrollado una serie de sistemas ópticos que pretenden, solos o asociados mejorar la sensibilidad diagnóstica de la cistoscopia sin menoscabo de su especificidad. Entre estos sistemas debemos destacar algunos como Narrow Band Imaging, la Tomografía de Coherencia Óptica y la Endomicroscopía Láser Confocal.

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Introduction

Non-muscle-invasive bladder cancer (NMIBC) is the second most common urologic cancer, and one of the most prevalent in the Western world.[1] Its natural history, characterized by a chronic course with a series of surgical events, challenges urologists to face relapse early and to act before progression ensues.

In the daily practice of urology, we know that the resection of NMIBC must always be as complete as possible. The quality of the resection determines the short- and medium-term rate of relapse and the rate of progression, with a resulting decrease in the number of resections per patient and a reduction of expenditure per patient. Brausi's classic study[2] showed a great variability in recurrence depending on the center and the surgeon; for single tumors, recurrence occurs at a rate of 3.4% to 20.6% per year, and for multifocal tumors, the rate is 7.4% to 45.6% per year. This fact cannot be explained by a variability in the tumor's biological behavior.

Thus, urologists have attempted excellence in the identification and subsequent resection of NMIBC; the main objective is to locate flat lesions and to find as many neoplastic and preneoplastic lesions as possible, which are potential relapses and constitute the embryo of the future early relapse. To achieve this objective, urologists have developed a number of techniques to show the presence of bladder cancer, including photodynamic diagnosis (PDD) with 5-amino levulinic acid (5-ALA) or with hexaminolevulinate (HAL). PDD has been shown to be superior to conventional white light cystoscopic diagnosis (WL), but has the limitation of an increased cost in the medium and short terms. The aim of this article is to analyze new imaging techniques that together with, or apart from, PDD, improve urologists' ability to diagnose NMIBC.

Photodynamic diagnosis

Photodynamic diagnosis is a cystoscopic diagnostic technique that enhances the visualization of bladder neoplastic lesions. It is based on the fluorescence emitted by neoplastic tissues subjected to a light of a certain wavelength; an intravesical substance -5-ALA or HAL- is administered beforehand, and is avidly uptaken by the neoplastic tissue. The tissues soaked in this photosensitizing substance emit a typical red fluorescence when they are illuminated by a light beam of a certain wavelength.

Clinical trials with PDD using HAL (553 patients) have shown that PDD surpassed the detection by WL by 29%. If we break down the rate of detection per type of lesion, compared to WL, PDD diagnoses 89% more dysplasias, 59% more CIS, 17% more tumors in stage Ta, and 12% more tumors in stage T1; the rate of false positives is 30%.[3-8]

Photodynamic diagnosis is excellent to detect carcinoma in situ (CIS); in the series studied by Hungerhuber,[9] the sensitivity of detection of CIS reached 92% with 5-ALA. This author reported an incidence of 17% of CIS in his series of tumors (the usual incidence is 3% of NMIBC). More recently, other authors reported detection rates of 97%.[6] This fact renders PDD a key tool for the diagnosis of CIS. The European Association of Urology Clinical Guidelines indicate the use of PDD with a grade of recommendation B and a level of evidence Ilb.[10,11] On the other hand, the clinical guidelines of the Austrian Association of Urology recommend using PDD in cases with positive cytology but no cystoscopic findings, and to follow-up high-risk tumors.[10,11] For further information about the indications of photodynamic diagnosis, readers are directed to an article recently published by our team in which we advocate for and justify the universal use of this technique (tables 1 and 2).[12]

While there are no long-term studies on HAL PDD, there are medium- and long-term studies with 5-ALA. Denzinguer[13,14] reports on the follow-up of a group undergoing NMIBC resection with PDD (5-ALA) vs. a group undergoing conventional WL resection; after 8 years, the relapse-free survival was 71% with PDD and 45% with WL. This difference between the two arms is because PDD allows for a better resection, which reduces the number of overlooked tumors that are grounds for relapse in the medium- and short-terms. These facts are supported by other series, including Filbeck's,[15,16] who reported a 59% decrease in the rate of recurrence, and Daniltchenko's,[17] who reported an increased disease-free survival of 67% (table 3) (fig. 1).

Current limitations of photodynamic diagnosis

There are currently two limitations of photodynamic diagnosis: a high rate of false positives, and the high cost of the photosensitizing agent, which increases short-term healthcare expenses but becomes cost-effective in the medium and long terms.

Table 1 – Diagnostic capability of PDD vs WL for CIS[3,5,6]

	n	CIS-PDD (HAL)	CIS-WL
Jocham 2005[3]	62	59 (95%)	42 (68%)
Loidl 2005[5]	51	47 (92.2%)	34 (66.6%)
Schmidbauer 2004[6]	177	172 (97%)	103 (58%)

Table 2 – Sensitivity, specificity, and negative and positive predictive values of PDD vs. WL for NMIBC[7]

	NMIBC-PDD (HAL)	NMIBC-WL
Sensitivity	76% (108/143)	46% (65/140)
Specificity	79% (221/278)	93% (255/274)
Positive predictive value	65% (108/165)	77% (65/84)
Negative predictive value	86% (221/256)	77% (255/330)

Table 3 – Medium- and long-term recurrence-free survival[13]

Relapse-free survival	PDD (5-ALA) (%)	WL (%)
2 years	88	73
4 years	84	64
6 years	79	54
8 years	71	45

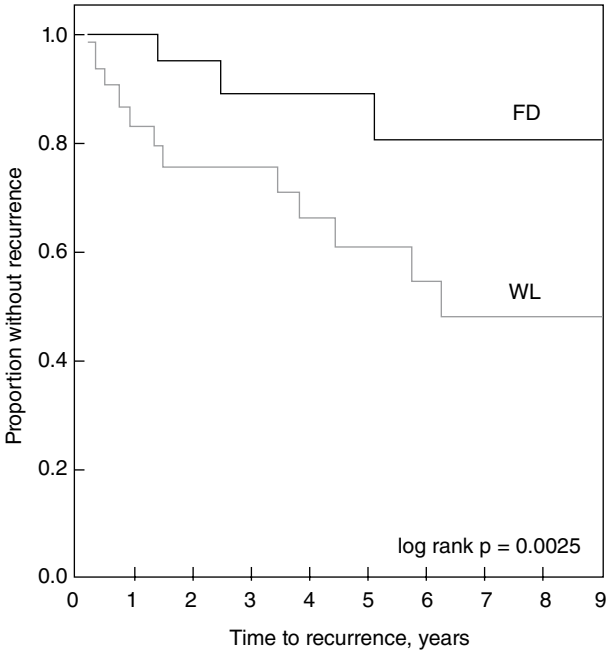

Figure 1 – From[13]. Y axis: Proportion without recurrence; X axis: Time to recurrence. (WL) Conventional cystoscopy. (FD) Photodynamic diagnosis.

The rate of false positives with PDD ranges between 30 and 40%, while with WL it is 21-31%,[8] when the rate of false positives is analyzed in the context of prior BCG instillation, it rises to 47%; considering that most patients undergoing PDD are on treatment with BCG, the high rate of false positives will be a constant.[18]

A rigorous statistical analysis was recently conducted to identify the prognostic factors of PDD false positives. With 306 patients undergoing PDD (5-ALA) cystoscopy for 1874 biopsies in 552 endoscopic procedures, the conclusion was that there is a higher rate of false positives in women, in patients who have recently undergone resections, and in those with previous BCG instillations; the former two variables are independent predictors of false positives. The authors recommend using PDD between 9 and 12 weeks after the latest resection of BCG instillation.[19]

The photosensitizing agent costs approximately €420. This means that using PDD elevates the cost of treating patients with NMIBC, but cost-benefit studies conducted so far show a reduction in healthcare resource expenditures because the time to relapse and progression is prolonged and because the rate of residual tumors is lower, so there are fewer cystoscopies and fewer repeat resections; this more than compensates for the cost of the photosensitizing agent.[17] At the same time, in patients at high risk of progression, the rate of progression declines, but the number of cystoscopies increases, for cystectomies are delayed or avoided in many patients, and early diagnosis increases in patients with flat, high grade lesions (CIS); these patients remain in the group of high-risk NMIBC and require more frequent cystoscopic controls. Readers are directed to a PDD cost-benefit analysis published by our team.[12]

Thus, we can identify the weak points of PDD: Firstly, the moderate or high rate of false positives or its slightly low specificity; and secondly, the price of the sensitizing agent that increases the short-term costs but decreases them in the medium- and long-terms. These two factors have led us to review new NMIBC diagnostic techniques that might complement photodynamic diagnosis.

Narrow band imaging

Narrow band imaging (NBI) is an image-enhancement optical system. It is based on the use of two short wavelength light beams of 415 and 540 nm. The light from these beams penetrates the superficial tissues and is avidly absorbed by hemoglobin. The longer the wavelength, the stronger the penetration capacity; thus, the bladder's vascular network appears dark and contrasts with the light color and semi-transparence of the bladder epithelium. The vascular structure underlying the transitional epithelium can be observed; it displays a characteristic pattern which changes around neoplasms in the overlying urothelium[20-22] (figs. 2 and 3).

Subjectively, NBI provides a clear view of the superficial capillaries, which have a bluish hue that becomes greenish as they go deeper. The underlying vasculature of tumor lesions are dark green to almost black; papillae display a dark brown spotting that corresponds to the cross-sectional view of their vascular axes (figs.4-6).

Some authors have already reported on the diagnostic capabilities of NBI; four studies have been published. In the first, by Bryan,[23] 29 patients with a history of NMIBC stage pTa G1,G2 underwent conventional white light cystoscopy (WL) followed by an NBI cystoscopy. WL identified 64 neoplastic lesions with a mean 2.21 lesions per patient (0-6), while NBI identified 79 lesions with a mean 2.72 lesions per patient (1-7). The 15 additional lesions observed with NBI were detected in 12 of the 29 patients: one additional lesion was found in ten patients, and two and three additional lesions in two other patients, respectively.

One of the largest series is that of Herr;[24] a total of 427 patients with a history of NMIBC underwent WL and NBI

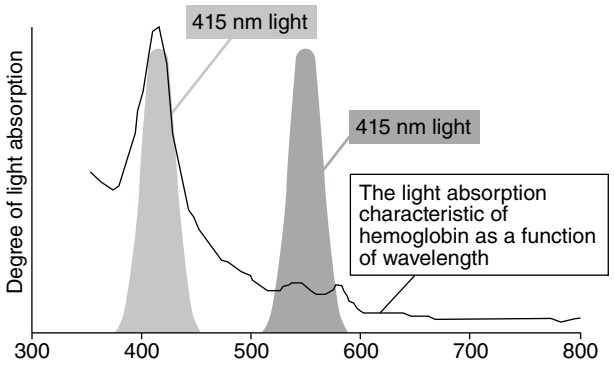

Figure 2 – Physical characteristics of the NBI double beam. Y axis: Light absorption by hemoglobin; X axis: wavelength in nm. From[23].

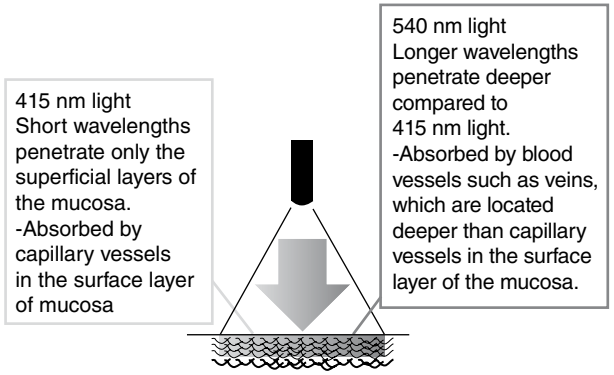

Figure 3 – Behavior of the various wavelengths that constitute the NBI beam. Shorter wavelengths penetrate only the superficial layers of the bladder wall, and longer wavelengths penetrate deeper. Both are avidly absorbed by the hemoglobin circulating in the capillaries. From[23].

Figure 4 – Penetration capability according to the wavelength of the incident light. From[23].

cystoscopy; recurrence was found in 103 of the 427 patients; 79% had multiple recurrences, and 67% had CIS. WL identified the relapse in 87%, and NBI in 100% of cases; this means that in 13% of cases the diagnosis of recurrence was exclusively attributable to NBI. All the lesions found with WL were visible with NBI. WL identified 231 lesions with a mean 2.3 lesions per patient (0-11), while NBI identified 334 lesions with a

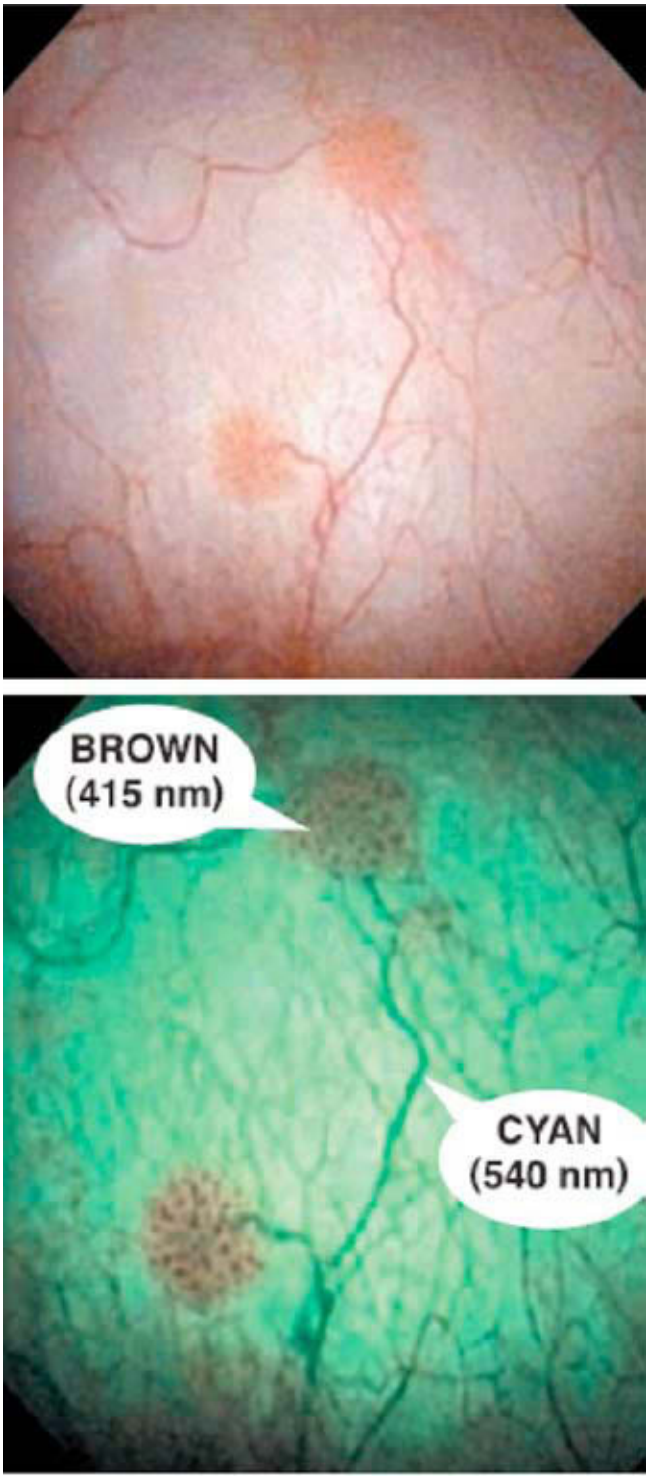

Figure 5 – Images of NMIBC with WL and with NBI. From[23].

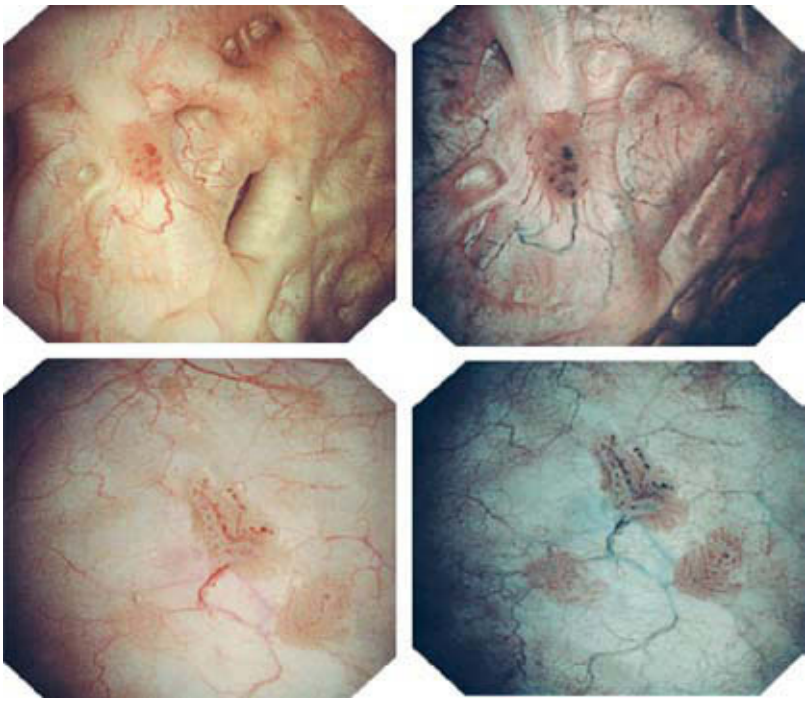

Figure 6 – Images of several NMIBC with WL and with NBI. From[23].

mean 3.4 lesions per patient (1-15). NBI identified pre-cancer lesions in 58 cases, which represents 56% of all cases; they consisted of 33 CIS, 25 pTa, and three pT1. NBI detected one or more cancer lesion in 28% of patients, two or more in 22%, three or more in 6%, and for or more in 3% of patients. All this mandates paying the price in the form of false positives, which amounts to 36% for a total of 162 biopsies, a rate not very different from that of WL, which was 33% for a total of 136 biopsies (tables 4 and 5).

Other centers report similar results. A Japanese team reported the outcomes of 147 biopsies in 82 patients, where 71% of lesions were visible with WL and NBI. Cancer was diagnosed in 58 patients, of whom 83% had lesions detected only by NBI, and 34% had lesions detected only by NBI. The authors report a sensitivity of 94% and a specificity of 60.2%.[25]

Other authors reported their experiences with NBI for restaging high-grade bladder tumor after primary resection. Two hundred thirty-five biopsies with WL and 54 with NBI were taken from 35 patients. WL detected cancer in six patients and NBI in 13 patients; the former identified high-grade neoplasm in five cases and NBI did so in 13 cases.[26]

Table 4 – Sensitivity, specificity, and negative and positive predictive values of NBI vs. WL for NMIBC[24]

	NMIBC-WL (%)	NMIBC-NBI (%)
Sensitivity	87	100
Specificity	85	82
Positive predictive value.	66	63
Negative predictive value	96	100

Table 5 – Sensitivity, specificity, and negative and positive predictive values of NBI vs. WL for CIS[24]

	CIS-WL (%)	CIS-NBI (%)
Sensitivity	83	100
Specificity	76	72
Positive predictive value.	36	36
Negative predictive value	97	100

Optical coherence tomography

Optical coherence tomography (OCT) is a new cystoscopy system that allows real-time visualization of the microarchitecture of the bladder wall by providing cross-sectional images. It is intended as a complement to conventional cystoscopy.

The physical principle of this technique is similar to that of B-mode ultrasound, but a near-infrared wavelength is employed instead of sound. The image obtained derives

from the difference between the wavelengths of the incident light and its scattering in the tissue. The wavelength of the light reflected depends on the depth and condition of the tissue.

The various tissue patterns are translated into a grayscale, providing a histopathological-like image; the lateral resolution is 10 µm, the axial resolution is 3 µm, and the depth reached is 1-2 mm.[20-22]

OCT image patterns were obtained from early studies with surgical pieces, which were subsequently correlated with histopathological sections and a microscopic examination of the tissue; thus, OCT patterns were associated with healthy tissue and cancer tissue.[27]

OCT was applied to 142 histopathological pieces obtained from bladder resections, prostatectomies, and cystectomies, of which 105 were healthy, 35 had carcinoma, and two had CIS. The OCT image was correlated to the histopathological findings bearing in mind that the fixation, dehydration, freezing, and staining of the sample can affect the OCT[27] (fig. 7).

aI-aII: HEALTHY WALL: The urothelium appears as a thin structure with little scattering, somewhat darker than the subepithelial tissue. The basal membrane appears as a thin layer with minimal signal intensity and slight scattering. Most of the dispersion in the image is in the lamina propria.

bI-bII: CIS: The basal membrane looks intact, with a normal appearance; the urothelium does not look homogenous, and there is major alteration of the subepithelial tissue compared to healthy tissue.

cI-cII: MUSCLE-INVASIVE CANCER: There is no differentiation between the strata, the basal membrane disappears, there is a continuum between the urothelium lamina propria and the muscle layer. The pattern is one of thick granularity.

Of the 105 healthy samples, 82 were identified correctly (specificity 78%, false positives 5.7%); six healthy samples were interpreted as neoplastic, none was considered CIS, and 16.2% of cases were unclassifiable. Of the 35 cases with cancer, 29 were correctly staged (82.9%), and none was labeled non-neoplastic. Overall sensitivity for bladder tumor was 83%.[27]

The most representative *in vivo* series in humans so far was reported by Goh et al.[28] They used 10-20-µm resolution OCT with a 2 mm penetration and a scanning time of 1.5

Table 7 – Diagnostic capability of WL, PDD, and PDD combined with OCT[29]

	WL	PDD	PDD+OCT
Sensitivity	69.3%	97.5%	97.5%
Specificity	83.7%	78.6%	97.9%
Positive predictive value	77.9%	79.1%	96.4%
Negative predictive value	76.7%	97.5%	97.9%
LR+	4	5	46
LR–	0.367	0.032	0.026

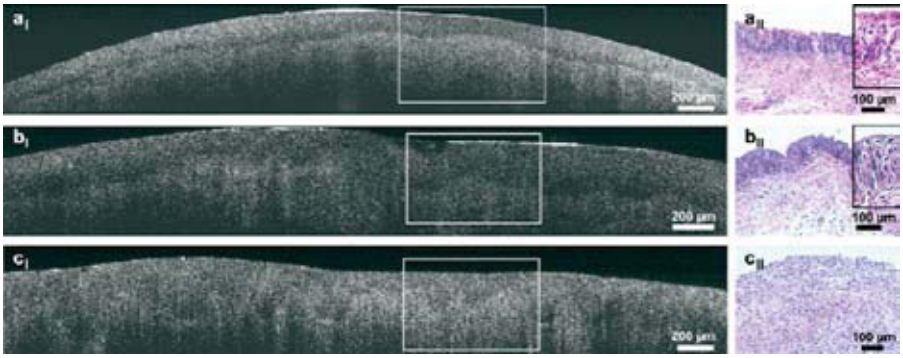

Figure 7 – From[27].

Table 6 – Diagnostic capability of OCT for various levels of bladder wall invasion[28]

	Sensitivity	Specificity	Positive predictive value (%)	Negative predictive value (%)
No invasion of the lamina propria	90% (18/20)	89% (16/18)	90	89
Invasion of the lamina propria	75% (3/4)	97% (33/34)	75	97
Invasion of the muscular layer	100% (7/7)	90% (28/31)	70	100
Any kind of invasion	100% (11/11)	89% (24/27)	79	100

seconds. The researchers performed OCT on 32 patients: 24 with a history of superficial bladder cancer, six with an initial cystoscopic diagnosis of bladder cancer, one with prostate cancer, and one with hematuria with no cystoscopic or sonographic findings. Ninety-four images from suspicious areas were obtained, and 38 of the 94 lesions were biopsied. The diagnostic capability of OCT was established for detecting tumors with no involvement of the lamina propria, with involvement of the lamina propria, and with invasion of the muscle; the various imaging patterns found were also described (table 6).

Regarding the problem of the relatively low specificity of PDD, we cite one study that combines the application of hexaminolevulinate PDD and OCT. Once the usefulness of photodynamic diagnosis for the detection of flat lesions is demonstrated, the next task is to reduce the rate of false positives by using PDD and OCT. In this study, 66 patients with a diagnosis or a suspicion of NMIBC underwent white light cystoscopy (WL), hexaminolevulinate cystoscopy (PDD) and, finally, OCT. Two hundred and thirty-two suspicious lesions were biopsied (118 papillary and 114 flat lesions); 132 normal-appearing areas were also biopsied, for a total of 364 samples.[29]

PDD diagnosed 12 additional papillary lesions that were not visible with WL (13.2%) and 19 additional CIS not visible with WL (48.7%). PDD detected a tumor in six patients with negative WL cystoscopy. Ninety-six papillary lesions were diagnosed, of which 79 (86.8%) were diagnosed with WL, and all but one with PDD. The rate of false positives with WL was 11%, and with PDD it was 36.8% (42 samples).

OCT identified as non-neoplastic 36 of the 42 false positives identified with PDD (85.7%). Of the 132 biopsies of normal tissue according to the three techniques, histology demonstrated three CIS and one papillary urothelial neoplasm of low malignant potential (PUNLMP).

In terms of rate of detection per patient, WL detected a tumor in 52 patients, which represents a detection of 89.7%, while PDD and PDD+OCT diagnosed 100%. PDD specificity was 62.5%; when PDD was combined with OCT the specificity rose to 87.5%; this confirms our hypothesis that OCT may be a useful tool to reduce the false positives of PDD (table 7) (figs. 8-12).

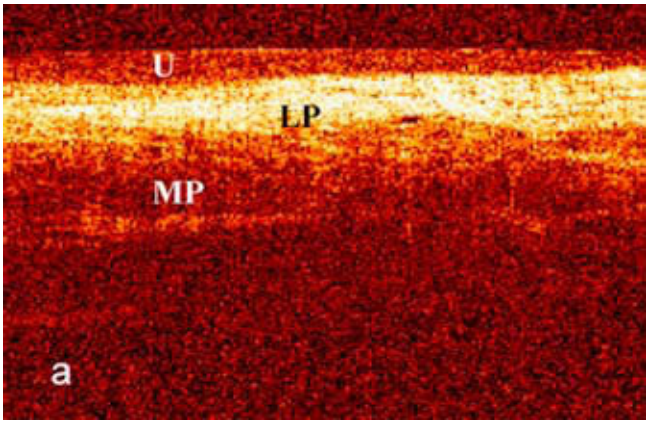

Figure 8 – a) Healthy wall: Clear urothelial layer. The stratified structure is preserved. Clear, bright lamina propria followed by muscularis propria, followed by muscle stratum. (U) Urothelium. (LP) Lamina propria. (MP) Muscularis propria. From[29].

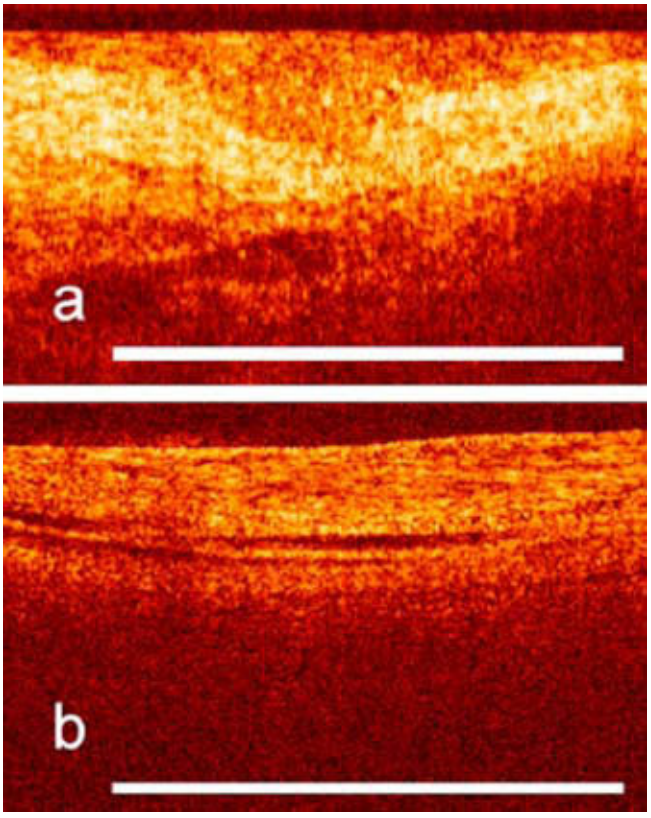

Figure 9 – a) Dysplasia: High contrast between strata. Pronounced border between the urothelium and the lamina propria. The urothelium remains uniform. From[29]. b) CIS: No clear separation between the urothelium and the lamina propria. Image appears as a single, brighter stratum. The muscularis propria looks independent. From[29].

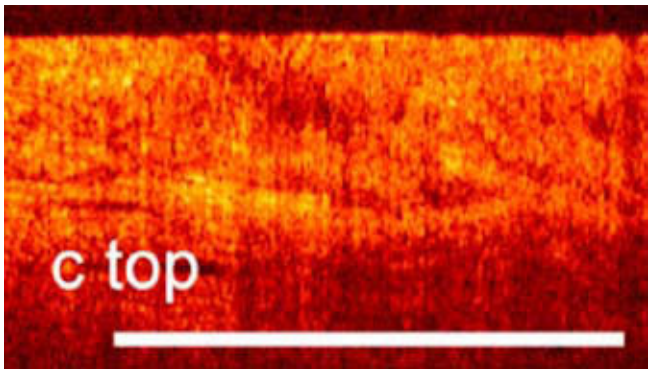

Figure 10 – Ta: Top pattern: Low contrast with no stratification. The lamina propria is intact. From[29].

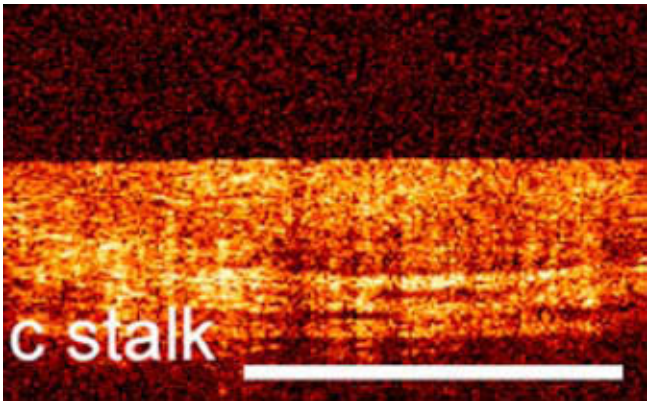

Figure 11 – Ta: Stalk pattern: High contrast with stratification. The lamina propria is intact. From[29].

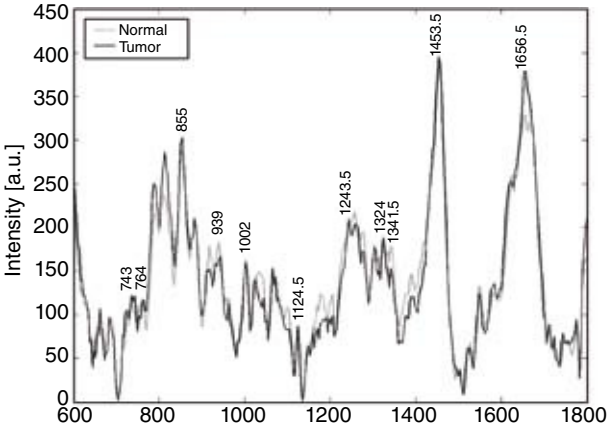

Figure 13 – Comparison of Raman spectra of normal tissue and cancer tissue. From[20].

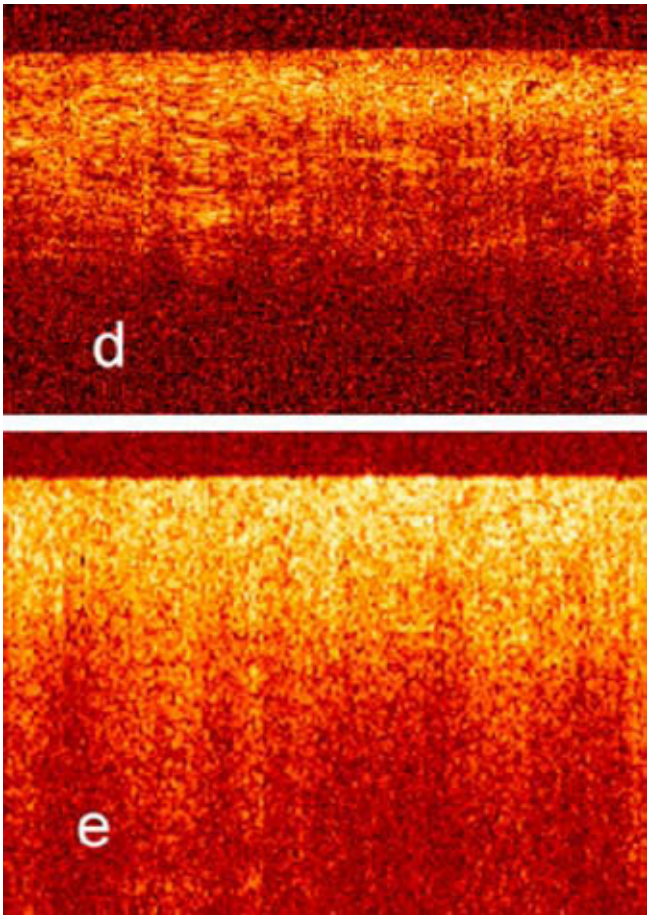

Figure 12 – d) pT1: Strata can be guessed, the urothelium is not distinguishable, and the lamina propria is not defined. From[29]. e) pT2: Stratification is completely absent. From[29].

Raman spectroscopy

Raman Spectroscopy (RS) is a system that can measure tissue components quantitatively and qualitatively. It is based on an optical effect described in 1928 by Sir C.V. Raman-the Raman effect or inelastic scattering. This phenomenon occurs when the photons of a beam interact with the molecules of the tissue causing a change in the vibrational status of the tissue molecules and thus the release of a photon of a certain wavelength as a result of the scattering of the light beam in the tissue. Each molecule has a specific vibrational level with its corresponding wavelength. The spectrum resulting from the energetic release caused by the action of a beam on each molecule of the tissue is the Raman spectrum. This spectrum of the bladder wall changes with neoplastic or inflammatory alterations, which permits the determination of whether or not there is inflammatory or neoplastic tissue[20,21] (fig. 13).

Early studies were conducted *ex vivo* and report a sensitivity of 92% and a specificity of 94% for the discrimination between healthy and neoplastic tissue in 15 samples.[30]

A larger series with 75 tissue samples discriminated between neoplastic, benign, and inflammatory tissues with a 90-95% sensitivity and a 95-98% specificity. For the discrimination between pT1-2 and pT3, sensitivity and specificity exceed 93%.[31]

Confocal laser endomicroscopy

Confocal laser endomicroscopy (CLE) is an optical system for real-time visualization of the bladder wall. In the past few years, the miniaturization of confocal laser endomicroscopy has permitted its application in gastroenterology, and the technique has been used *ex vivo*. CLE provides information about the microarchitecture of healthy and neoplastic urothelial tissues; intravenous infusion or intravesical instillation of fluorescein are administered beforehand.[32]

Only one *in vivo* study has been reported to date.[33] In this study, a 2.6-mm fiber through which a bundle of 30,000 laser fibers are passed that are connected to a 480 nm laser source, was used. This allows for a 60-µm penetration into the bladder wall, a 1-µm lateral resolution, and a field amplitude of 240 µm in diameter. The incidence of laser light

on the fluorescein-impregnated tissue causes the emission of fluorescence retrieved by the same fibers that emit the laser light at a rate of 8-12 frames per second. Five minutes prior to the examination, 300-500 cc of a 0.1% fluorescein solution is instilled, and/or 5 mL of 10% fluorescein are administered intravenously.

The procedure was performed on 27 patients suspected of, or diagnosed with, NMIBC. First, the pattern of the healthy urothelial tissue was described; as the laser fiber is pressed on the bladder wall, a deeper stratum can be observed. The most superficial is the large-cell stratum; here, urothelium cells are evident because of the distribution of fluorescein in the cellular interstice; as we go deeper, the cells become smaller in the deeper portions of the urothelium; in a third stratum, the vascular plane originated by the fluorescence in the vascular bed is observed; occasionally, red blood cells can be seen circulating through the capillaries. The vascular stratum is less obvious when fluorescein is administered intravesically only.

The authors report that nine of the 27 patients did not evidence cancer, nine had a low-grade tumor, and 9 had a high-grade neoplasm, including carcinoma in situ. In patients in whom a tumor was found histopathologically, CLE evidenced structural differences between healthy tissue and low- and high-grade tumors; in low-grade tumors there is a higher cell density but no loss of tissue structure, and cells are distributed uniformly. High-grade tumors display a clear alteration of the structure, and great variability of cellular size. Information about the aspect of the nuclei cannot be obtained because fluorescein does not penetrate inside the cells. Involvement of the muscle layer cannot be determined with penetration depths of 60 µm (figs. 14 and 15).

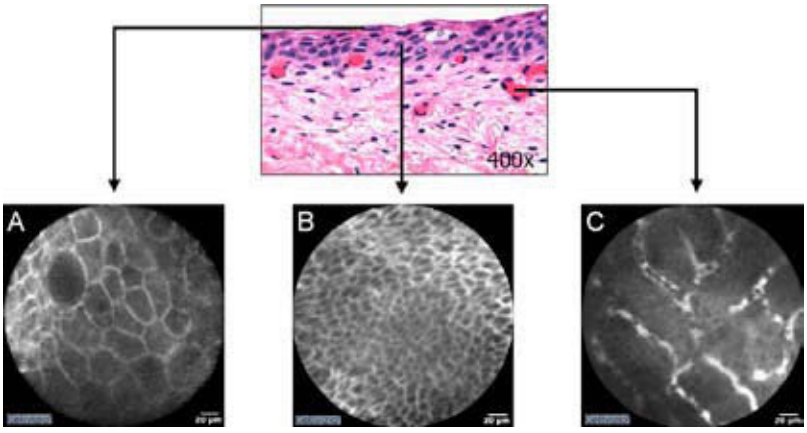

Figure 14 – Comparison between a healthy urothelium section stained with hematoxylin-eosin and the various strata visible with CLE. (A) Large umbrella cells in the superficial stratum. (B) Deeper stratum, narrow portion of umbrella cells in the transitional epithelium. (C) Vascular stratum with red blood cells circulating in the capillaries. From[33].

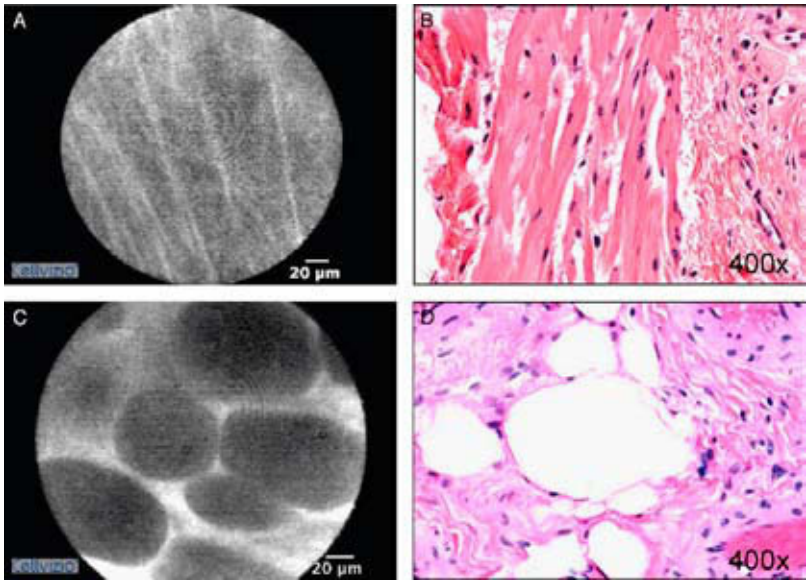

Figure 15 – (A), (B) Endomicroscopic image of the resection bed of NMIBC and view of the histological section stained with hematoxylin-eosin, showing muscle stratum cells. (C), (D) Endomicroscopic image of the resection bed. From[33].

Endocystoscopy

This system developed by Olympus Medical Systems is not widely used; it consists of the cystoscopic application of a 3.5-mm diameter rod in intimate contact with the bladder wall; the bladder is previously bathed in a methylene blue solution; the system magnifies the contact area up to 450-fold, which provides images comparable to microscopy visualization.[34]

Intravesical capsule

Capsules carrying a microcamera that transmit images is a technique that has been widely employed in gastroenterology for ten years. The technique is currently being reproduced in urology. Experimental use in pig models has been reported. The capsule transmits 4 frames per second; the camera is passively moved by the animal's movements, and actively from outside by magnetic plates. The entire bladder mucosa has been visualized with this technique[35] (fig. 17).

Conclusions

With the exception of PDD, all the techniques described here require further research in order to demonstrate their true clinical utility and to assess their systematization. Moreover, the universally accepted indication of PDD is unquestionable for the detection of CIS in cases of positive cytology in the absence of cystoscopic findings. There is no question that PDD offers a more complete resection with a lower rate of residual tumor and recurrence. Additionally, it is accepted that its use implies a considerable increase in costs, which is reduced in the medium- and long-terms due to savings in cystoscopies and repeat resections. Finally, the high rate of false positives with PDD, between 30 and 40%, must be accepted.

NBI is applicable at any time in any patient, and requires no prior instillation of a substance; it has no systemic contraindications, and it implies only a slight increase in costs; it can be used either alone or together with PDD to reduce the rate of false positives. The medium- and long-term prognostic implications of this technique is yet to be assessed (table 8).

OCT and RS provide real-time information about the extent and the histopathological characteristics of the tumor.

Figure 17 – Wireless Capsule Endoscope (WCE). On the right hand side, the optical system, and on the left the magnetic guidance system. From[35].

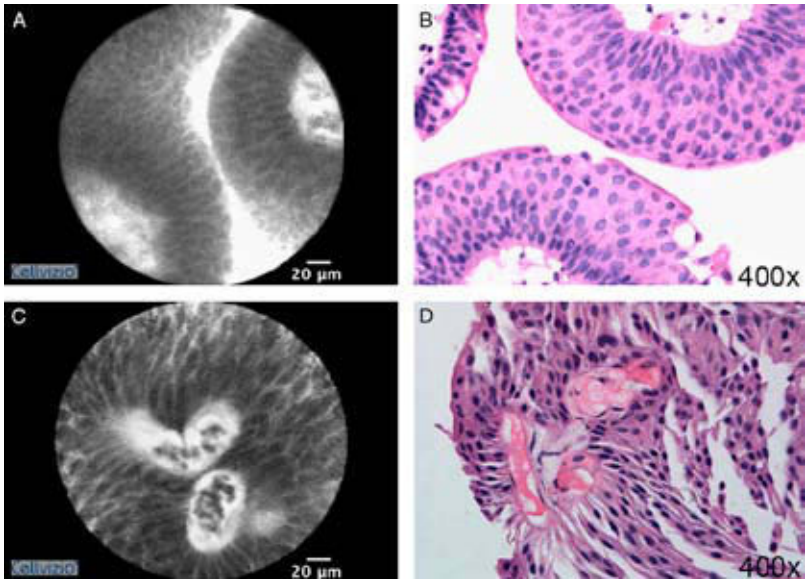

Figure 16 – (A), (B) Endomicroscopic image of the resection bed of a low-grade papillary NMIBC and view of the histological section stained with hematoxylin-eosin. (C), (D) Endomicroscopic image of the resection bed of a high-grade papillary NMIBC and view of the histological section stained with hematoxylin-eosin. From[33].

Table 8 – Comparison of diagnostic systems for NMIBC

	Objective	Physical principle	Stage of development	Sensitivity (%)	Specificity
PDD[12]	Optimization of visualization of cancer	Fluorescence	Human *in vivo*	82-97	41.4-91.5
NBI[23,24]	Optimization of visualization of cancer	Adsorption	Human *in vivo*	100	82%
OCT[28,29]	Prediction of histopathological diagnosis	Scattering	Human *in vivo*	83.8-100	78.1-89%
RS[30,31]	Prediction of histopathological diagnosis	Scattering	Human *ex vivo*	90-95	94-98%
WL[12]	–	–	–	62-84	43-98%

They may aid PDD by also reducing the rate of false positives. A complete screening of the bladder is not possible with OCT and RS, nor has their ability to result in more complete resections been assessed; the potential presence of artifacts in the edges of the resection would limit the use of OCT. OCT and RS could be used to identify flat neoplastic lesions in the upper urinary tract. The remaining techniques such as CLE, endocystoscopy, and intravesical capsules are still in very early stages of development.

Conflict of interest

The authors state that they have no conflicts of interest.

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