From candlelight to digital imaging cystoscopy: A comprehensive review of bladder’s endoscopy evolution

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Abstract
The birth of modern cystoscopy begun two centuries ago after the initial invention of Bozinni’s prototype urethroscope that used candlelight. Since then cystoscopy has been submitted to several improvements ranging from practical instrumentation modifications to advanced light source systems and enhanced image quality. Visualization melioration of the bladder used technological innovations, such as fiber-optics, and led to flexible endoscopes with digital imaging. The last two decades, systems with image enhancement capabilities have emerged in an effort to improve endoscopic vision and detection of bladder pathological lesions. The present review includes the main hallmarks of the historic evolution of today’s cystoscopes, the current endoscopic systems and the future trends in bladder’s visualization.

Introduction
Cystoscopy is a compound word that originates from the Ancient Greek language. Etymologically, is formed by the noun cyst- ‘κύστις’, the Greek word for the bladder and scopy- ‘σκόπηση’, a suffix of the verb ‘σκοπέω’, which means to observe, to examine, to investigate. Similarly, the term endoscopy originates from the suffix endo- ‘ἐνδο’, which means internal/inside. Practitioners had realized the benefit of minimally invasive surgery and the necessity to explore into natural orifices since the Hippocrates ages (circa 400 BC) who was one of the first to describe an endoscopic approach of rectum diagnosis of hemorrhoids with a “speculum”. 1500 years later, Abu-al-Qasim, a Spanish Surgeon described several instruments that referred to endoscopic illumination¹. Nevertheless, the true story of cystoscopy begins in the early 19th century after the development of the first lightreflecting urethrocystoscope and continues up to nowadays with flexible digital scopes and numerous image enhancement systems that use fancy technological advancements.
The beginning of cystoscopy

The beginning of modern cystoscopy rightfully belongs to Phillip Bozzini, a young physician from Frankfurt who developed an instrument that could reflect the light from a candle through a metallic lumen in order to aspect natural cavities under direct vision. His invention called “Lichtleiter” or “Light Conductor” was presented in 1805 (Figure 1) and was demonstrated in nasal cavity and pharynx. There is some evidence that the Lichtleiter was tested in cadaveric urethral samples but is rather unlikely that ever applied on real patients for urological reasons. The first real uretrocystope was developed by a French famous Urologist, Pierre Salomon Segalas, who improved Bozzini’s invention in 1826 using a double candle-light source instrument with improved lens viewing named “spéculum uréthro-cystique”. Later, in 1853, Antoine Jean Desormeaux from Paris further improved endoscopic vision using a cystoscope that reflected convergent light of a gasogene mix lamp and succeeded the first endoscopic procedure, utilizing the era of operative endoscopy. The light source was submitted to further changes using a Petroleum-camphor mix (Cruise, 1965) and magnesium light (Stein, 1967). Stein, in addition, established for the first time the beginning of scientific endoscopy, photography in 1874. The idea of direct illumination cavities belongs to a Polish dentist named Julius Bruck, who developed an instrument in 1867 with an incandescent platinum wire, as a light source, introduced into his “stomatoscope”. A water bath was necessary to cool down the filament. Due to the size of his instrument, he proposed the illumination of the bladder in a diaphanoscopic way using the rectum or the vagina. Gustave Trouvé, a French inventor, designed a miniaturized instrument called “polyscope” following Bruck’s philosophy in 1973, yet, the first working platinum wire cystoscope was finally developed by Maxmilian Nitze from Berlin and Joseh Leiter, using a complex cooling system in 1879. In the meantime, Dierdich Rutenbrg from Vienna introduces the basic principles of air cystoscopy in 1876, a technique that was abandoned by the mid 20th century. After the hallmark invention of the electric bulb by Thomas Edison in 1879 that changed the world, David Newman first adapted a miniature bulb at the distal tip of a cystoscope in 1883, but it was again Nitze who presented his second-generation operating cystoscope with an Edison lamp attached, in 1886.

In the early 20th century, Reinhold Wappner, an American Engineer and founder of the American Cystoscope Makers Inc. (ACMI), worked with William K. Otis on Nitze’s cystoscope and improved its vision using a wide-angle lens system. Three years later, in 1908, Ringleb managed to solve the so-called “Nitze’s error”, the inverted image, with an upgraded stereoscopic cystoscope. At the same period, Hans Goldschmidt introduced irrigation urethroscopy using both air and water in the urethra. Later, in 1918, Georges Luys from Paris, published his work presenting a new type of operating cystoscope with electocoagulation and aspirating tube. During the following decades, significant advancement was made in the field of Laparoscopy (Kelling, Jacobeus) and the resectoscope development (Stern, McCathy).  

The flexible story

Several scientists were experimenting since the late 19th century on light transmission systems. In 1930, Heinrich Lamm showed that a bundle of glass fibers could be bent without distorting the transmitted image, but it was not until 1954 that Harold Hopkins, an English physics professor, and Narinder Kapany initiated in London the fiberscope and introduced the term “fiber-optics”. Simultaneously, Van Heel published his innovation of cladding fiber-optic system. A few years later, in 1959, Hopkins patented the glass rod-lens system which had better light transmission than the traditional lenses. The basic principle of the Hopkins rod-lens system is that the scope tube consists of glass within thin lenses of air (in contrast to the traditional system), resulting in an increase of total light transmission up to 80 times, and better brightness and contrast images. Due to Hopkins’ lack of financial support, a South African gastroenterologist named Basil Hirschowitz, further developed Hopkins fiberscope and introduced the first flexible gastroscope in 1957. In 1960, Karl Storz came up with the idea of using an external light source to transmit light through the same
flexible glass fibres of the fibroscope resulting in the development of extracorporeal cold light. Five years later, Hopkins and Storz combined their innovations creating the modern flexible cystoscope. The main hallmarks of bladder endoscopy history are summarized in Table 1.

**Image enhancement Systems**

**Photodynamic diagnosis (PDD)**

The first significant attempt to enhance the standard white light (WL) vision for better bladder visualization was fluorescence cystoscopy. According to its principal, PDD is based on the phenomenon of different emission of fluorescence molecules between normal and abnormal tissue when they are examined under a specific wavelength light (blue light). Thus, PDD requires the instillation of a fluorescence substance that is absorbed into the urothelial cells by hemoglobin and accumulates in abnormal-cancer cells. As a result, abnormal lesions re-emit red fluorescence but normal tissues don’t, when the bladder wall is illuminated by blue light (380-450nm). The first clinical study using haematoporphyrin derivative (HpD) was conducted by Kelly in 1975, for patients with bladder cancer. Nowadays, the two main photosensitizing agents are 5-aminolevulinic acid (5-ALA) and hexylester hexaminolevulinate (Hexvix). Even though papillary lesions can be effectively identified using standard cystoscopy, flat lesions, such as carcinoma in situ (CIS), may be missed.

A recent large systematic review on CIS resulted in 91–97% detection rate for PDD compared to 23-68% for WL. Accordingly, overall recurrence rates are significantly lower when the resection is performed with PDD assistance than WL alone (34.5% vs. 45.4% (p=0.006)), as well as in all subgroups. Initial high costs can be counterbalanced with the long-term benefit from reduced recurrence rate. A relative drawback is that PDD cystoscopy has lower specificity compared to WL (63% vs. 81%, respectively) and when considering patients under BCG therapy for nonmuscle-invasive bladder cancer (NMIBC) can render false positive results (OR: 1.49, p=0.001) up to 3 mo after the instillation. Finally, PDD is recommended in patients with negative WL cystoscopy and positive urinary cytology or history of high-grade tumor.

**Virtual cystoscopy**

In 1996 two investigators independently published the first reports on virtual cystoscopy using high-resolution Computed Tomography. The first used the early contrast medium enhanced phase, and the second helical CT in a CO2 distended bladder achieving 3D rendering of bladder cavity and identifying all tumors. Virtual cystoscopy has demonstrated excellent results in small non-randomized studies equal to cystoscopy, but these data have low evidence. Magnetic Resonance Imaging is an alternative option for virtual cystoscopy. Virtual cystoscopy has the advantage of a non-invasive technique. Still, the major demerit is the inability to detect flat lesions or CIS.

**Digital cystoscopes**

45 years after the first flexible fiber-optic cystoscope, ACMI (ACMI, Southborough, MA, USA) sponsored the first digital cystoscope in 2005. This cystoscope had a distal digital sensor at its tip which derived from the digital camera chips of the late 1960’s, charge-coupled device (CCD) and complementary metal oxide semiconductor (CMOS), that were used to store and
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<tr>
<th>Year</th>
<th>Name</th>
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<tr>
<td>1805</td>
<td>Phillip Bozzini</td>
<td>The Lichtleiter - first potential urethroscope</td>
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<td>1826</td>
<td>Pierre Segalas</td>
<td>Improved candle-light urothrocystoscope</td>
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<td>Antoine Desormeaux</td>
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<td>1867</td>
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<td>Maximilian Nitze</td>
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<td>1959</td>
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<td>1960</td>
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<td>1960</td>
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<td>2005</td>
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<td>2005</td>
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<td>2013</td>
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<td>2014</td>
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PDD = Photodynamic diagnosis, NBI = Narrow-bang imaging, SPIES = Storz professional image enhancement system, HD = High definition, ACMII = American cystoscopemakers Inc.

Transfer pictures by electrical signals recorded as pixels. These photosensitive chips are able to produce better enhanced images, with high spatial resolution and eliminate the pixeled vision of formed conventional scopes. Digital cystoscopes have less weight than fiber-optic scopes and are thinner. CMOS sensors are still expensive and very sensitive. To compare optic, performance and durability of digital and fiber-optic cystoscopies Okhunov et al. conducted a prospective trial of subjective scoring favoring digital cystoscopies (8.6 vs. 7.9, respectively ($p=0.0001$)). An objective trial demonstrated in vitro superiority of digital scopes by the means of resolution, contrast, and color discrimination.

**Narrow-banding Imaging (NBI)**

NBI was initially launched by Olympus in 2005. NBI technology is based on the fact that when the broad-
band visible light (400-700 nm) is narrowed to 415 and 540 nm, which are the two peak absorption points for hemoglobin, using optical filters, the image of vascularized lesions is enhanced. With this technique, the mucosal microvessels appear darker than the rest of bladder surface that scatters the light. The first NBI cystoscope used a CCD sensor which was able to interchange the light spectrum with no need of a fluorescence medium. NBI superiority of detecting bladder cancer over conventional WL cystoscopy has recently demonstrated by a meta-analysis that showed an additional 25% of tumors detected in an additional 17% of patients. Regarding bladder CIS, NBI was by 28% more accurate than WL.

Storz Image Enhancement System (SPIES)

Storz Co launched in 2013 a novel system for endoscopy, the SPIES. SPIES uses a digital enhancement image platform with four different modalities (CLARA, CHROMA, SPECTRA A and SPECTRA B) to shift the spectrum of colors in the standard WL image, in order to create high-contrast images and increased sharpness. SPIES is also provided with a Full High Definition monitor (1920x1080 pixels) with LED light source that had originally initiated by the same company in 2007. The system is currently under evaluation. Only preliminary results of a small randomized trial are published showing a superiority of SPIES cystoscopy vs. WL cystoscopy during follow-up of patients with NMIBC (61.5% vs. 47%, respectively) and a positive correlation with positive urinary cytology. The latest innovation of SPIES system launched in 2014 combining this technology with 3D-FHD visualization that is currently being used for Laparoscopic Surgery. Figure 2 illustrates the current main 3 image enhancement systems.

The future directions

Capsule cystoscopy

The idea of capsule cystoscopy derives from wireless capsule endoscopy (WCE) of the gastrointestinal tract. In the field of Urology, it has only been tested experimentally in a pig model with promising results. More recently, an anti-biofilm capsule was tested for its long-term efficacy in a lab animal model, successfully.

Raman Spectroscopy (RS)

RS is based on the Raman's effect, initially discovered in 1928, which implies to the phenomenon of light scattering of different molecule bonds after their exposure in monochromatic (785–845 nm) laser light. The result is a “molecular fingerprint” of the examined area. RS has been tested in an in vivo study using a specialized probe into the cystoscope resulting in 85% sensitivity and 79% specificity for bladder cancer detection.

Microscopic imaging

Confocal Laser Endomicroscopy (CLE) is a microscopic technique that is applicable in the field of gastroenterology and respiratory system for 15 years. CLE uses laser fibers with high resolution (1-5 μm) that can visualize in real-time the microarchitecture of urinary mucosa by magnifying the image. The system (Mauna Kea Technologies, Paris, France) provides this technology with a small probe through the standard cystoscope that emits light from a 488-nm laser fiber and processes the image from scattered light from the tissues. To achieve this image, a previous installation of fluorescein, a contrast medium, must be applied. CLE can give information about tumor grade which is particularly useful in the upper urinary tract. Recently, diagnostic criteria for urinary tumors were standardized.

Optical Coherence Tomography (OCT) is an alternative system for real-time in vivo microscopic evaluation of bladder’s epithelium. OCT uses a technology, like ultrasound, that can render highresolution imag-
The γέννηση της σύγχρονης κυστεοσκόπηση άρχισε πριν από δύο αιώνες μετά την αρχική εφεύρεση του πρωτοτύπου ουρηθροσκόπιου από τον Bozzini που χρησιμοποιούσε το φως των κεριών. Από τότε η κυστεοσκόπηση έχει υποβληθεί σε αρκετές βελτιώσεις που κυμαίνονται από πρακτικές τροποποιήσεις των οργάνων μέχρι σε εξέλιξη συστημάτων φωτισμού και βελτίωση της ποιότητας της εικόνας. Η βελτίωση της ενδοσκόπησης της ουροδόχου κύστης ακολούθησε τεχνολογικές καινοτομίες, όπως τις οπτικές ίνες, και οδήγησε σε δημιουργία εύκαμπτων ενδοσκοπίων με ψηφιακή απεικόνιση. Στις τελευταίες δύο δεκαετίες, τα συστήματα με δυνατότητες βελτίωσης της εικόνας έχουν εμφανιστεί σε μια προσπάθεια να βελτιωθεί η ενδοσκοπική όραση και η ανίχνευση παθολογικών αλλοιώσεων της ουροδόχου κύστης. Η παρούσα ανασκόπηση περιλαμβάνει τους βασικούς ιστορικούς σταθμούς στην ιστορική εξέλιξη της σημερινών κυστεοσκοπίων, τα σημερινά ενδοσκοπικά συστήματα και τις μελλοντικές τάσεις στην απεικόνιση της ουροδόχου κύστης.

**Ultraviolet (UV) cystoscopy**
The idea of using UV light inside the bladder started in 1965 but was abandoned due to disappointing results. UV cystoscopy is based on the principle that endogenous molecules, such as NAD, emit autofluorescence after exposure to UV laser light (360 and 450 nm excitation wavelengths). The concept is that using UV light, normal mucosa and abnormal tissue discrimination is feasible. Recently, in a pilot *in vitro* study the correlation between UV finding and the actual histological tumor was 100%, promising effectiveness of this technique in a real-time endoscopic setting.

**Conclusion**
Approximately 200 years of endoscopic evolution have led to significant technological advancements on bladder’s illumination. The initial curiosity of former practitioners to inspect the bladder through a lumen under the light of the candles has now been replaced by various modern and complicated instruments that facilitate our endoscopic view for the benefit of the patients. Future directions aim to combine endoscopic high-quality vision with several scientific innovations to that perspective.

**Conflicts of interest**
The author declared no conflict of interest.
References


