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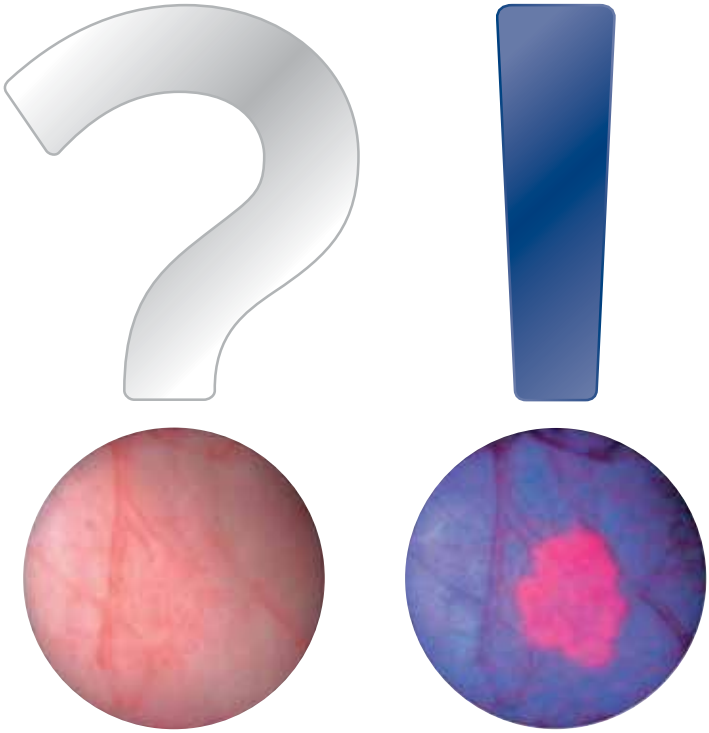

Blue Light Cystoscopy with CYSVIEW®

Cysview Indication

- Cysview is an optical imaging agent indicated for use in the cystoscopic detection of non-muscle invasive papillary cancer of the bladder among patients suspected or known to have lesion(s) on the basis of a prior cystoscopy
- Cysview is used with the KARL STORZ D-Light C Photodynamic Diagnosis (PDD) system to perform cystoscopy with the blue light setting (Mode 2) as an adjunct to the white light setting (Mode 1)

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Important risk & safety information

Cysview is not a replacement for random bladder biopsies or other procedures used in the detection of bladder cancer and is not for repetitive use.

Anaphylaxis reactions including anaphylactoid shock, hypersensitivity reactions, bladder pain, cystitis, and abnormal urinalysis have been reported after administration of Cysview. The most common adverse reactions seen in clinical trials were bladder spasm, dysuria, hematuria, and bladder pain.

Cysview should not be used in patients with porphyria, gross hematuria, or with known hypersensitivity to hexaminolevulinate, or in patients receiving intravesical chemotherapy or BCG treatment within 3 months of Cysview photodynamic blue-light cystoscopy. There are no known drug interactions with hexaminolevulinate; however, no specific drug interaction studies have been performed. Using Cysview, fluorescence of non-malignant areas may occur, and Cysview may fail to detect some malignant lesions.

Safety and effectiveness have not been established in pediatric patients. Cysview should only be used during pregnancy if the potential benefit justifies the potential risk to the fetus. It is not known whether hexaminolevulinate is excreted in human milk. Because many drugs are excreted in human milk, exercise caution when Cysview is administered to nursing mothers. No clinically important differences in safety or efficacy have been observed between older and younger patients.

Cysview is approved for use with the Karl Storz D-Light C Photodynamic Diagnostic (PDD) system. For system set up and general information for the safe use of the PDD system, please refer to the Karl Storz instruction manuals for each of the components

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Red, White and Blue Light Cystoscopy: New Technology Arms Patients and Physicians in the Fight Against Bladder Cancer

By Dr. TRACY DOWNS, MD FACS, Director of Bladder Cancer & Intravesical Therapy Programs, Associate Professor, University of Wisconsin School of Medicine

In an article entitled "A Few Good Men and Bladder Cancer" published on October 24, 2009 by Salem News, author Robert O'Dowd reports about the possible occupational exposure to toxic chemicals encounter by both men and women during their service to our country, as members of the United States Armed Forces.

Exposure to organic solvents like trichloroethylene (TCE) has been linked to various cancers, including bladder cancer and other diseases. Dr. Robert Schlesinger, a retired Army Colonel and urologist, commented "Organic compounds in general and benzene containing compounds specifically are recognized as carcinogenic for the lining of the entire urinary tract, kidneys, ureters and bladder. There is no dispute regarding this."

Bladder cancer is the fourth most common cancer and in the United States alone, it is estimated that 74,690 patients' were newly diagnosed with bladder cancer in 2013. The two most well established risk factors for bladder tumors are cigarette smoking and occupational exposure to carcinogens. Cigarette smoking is the most important risk factor, accounting for 50% of cases in men and 35% in women1. Most new bladder cancer cases, ≈ 50,000 patients (70%) are diagnosed early with disease limited to the shallow or superficial lining of the bladder also known as non-muscle invasive bladder cancer (NMIBC).

Although most patients are diagnosed at a relatively early stage, with NMIBC, the risk of dying from high-grade NMIBC remains significant. Bladder cancer prognosis is affected in part by the high risk of tumor recurrence, (61% in the first year and 78% within 5 years) depending on the grade upon initial diagnosis, after initial bladder tumor removal (resection). Additionally, the risk of their bladder cancer spreading into the deep layers of the bladder (muscle invasive bladder cancer) is estimated up to 17% at 1 year and up to 45% at 5-years. Regular cystoscopic follow up2, 3 and surveillance makes bladder cancer one of the most costly cancers to treat 4 with an estimated lifetime cost of ~$200,000 per patient 5. There is a high medical need to improve the detection as well as management of all bladder tumors.

Bloody urine or a detection of blood in a routine urinalysis leads a patient to undergo a complete and through cystoscopic bladder examination in the clinic before a bladder cancer diagnosis is made. The patient is then referred to undergo Trans Urethral Resection of the Bladder (TURBT). The current standard of care for early stage bladder cancer patients, involves White Light Cystoscopy (WLC), which allows the urologist to map the location and remove (resect) all visible lesions. While the classic bladder tumor has a very characteristic appearance (i.e. cauliflower shape), not all cancerous areas may be readily visible using white-light cystoscopy (WLC). Despite our best efforts, the full extent of an individual patient's tumor burden may be difficult to confirm on WLC alone as small "satellite" tumors or areas of carcinoma in situ (CIS) may be missed 6-14.

A new technique to improve the visualization of tumors, combining an intravesical agent with a specific blue light cystoscopic system was approved by the Food and Drug Administration (FDA) in 2010. Hexaminolevulinate HCL (HAL) is a photosensitizing agent and is available in the United States as Cysview (Photocure US, Princeton, NJ, USA). In Europe it has been available for several years under the brand name of Hexvix.

When Cysview is instilled into a patient's bladder (using a catheter), the medication becomes preferentially over- accumulated in cancerous cells compared to normal bladder cells. With the use of a blue light equipped cystoscope, the abnormal cancerous areas become fluorescent and glow, hence the term blue light cystoscopy with Cysview (BLCC). The technology allows physicians to more clearly detect and define tumor boundaries in the bladder during a cystoscopic biopsy or transurethral resection (removal) of bladder tumor(s).

Several clinical studies to date have demonstrated that Blue light cystoscopy with HAL (Cysview) can improve the detection of NMIBC beyond the current standard of care using white light cystoscopy (WLC). As a result, patients can benefit from a more complete tumor removal (resection) and more accurate initial staging resulting in more

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appropriate management decisions, resulting in reduced risk of tumor recurrence and prolonging the time to bladder cancer recurrence. Patients recommended to undergo blue light cystoscopy with Cysview include patients having transurethral resection for the first time as well as when they have recurrence of their bladder cancer.

Currently this technology is available at the time of outpatient bladder cancer surgeries (cystoscopic biopsy, transurethral resection of bladder tumors) and clinical research is being actively conducted towards making this valuable technology available at the time of an office based cystoscopy procedure.

Blue Light Cystoscopy with Cysview is the only innovation in over 25 years in the detection of bladder cancer tumors and is rapidly becoming a standard of care in most institutions. Given the current landscape of bladder cancer patients, this important innovation is a very helpful tool for all urologists to better detect bladder cancer tumors and offer better solutions for effective management of the disease for appropriate bladder cancer patients

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About Bladder Cancer

Bladder cancer is a disease in which malignant (cancer) cells form in the tissues of the bladder.

The bladder is a hollow organ in the lower part of the abdomen. It is shaped like a small balloon and has a muscular wall that allows it to get larger or smaller. The bladder stores urine until it is passed out of the body. Urine is the liquid waste that is made by the kidneys when they clean the blood. The urine passes from the two kidneys into the bladder through two tubes called ureters. When the bladder is emptied during urination, the urine goes from the bladder to the outside of the body through another tube called the urethra.

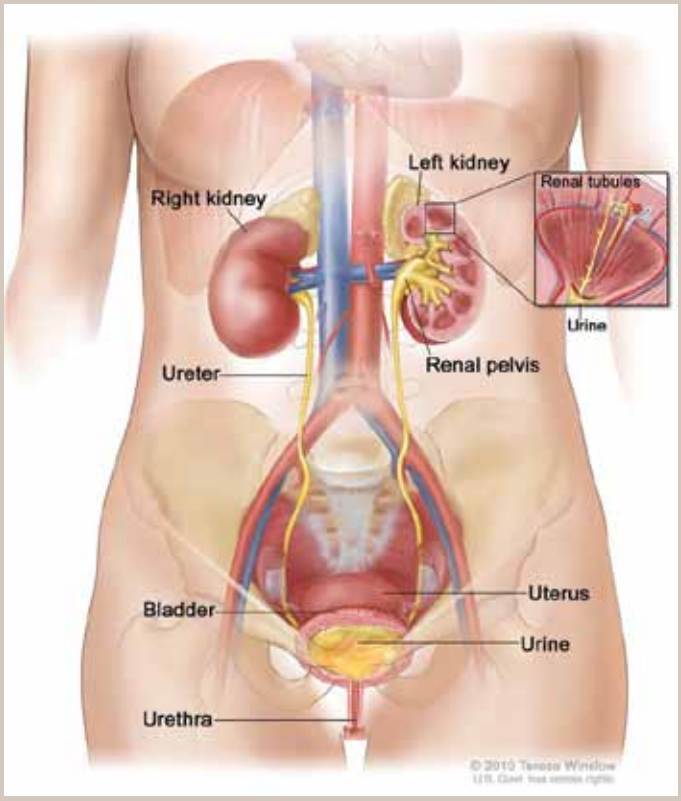
There are three types of bladder cancer that begin in cells in the lining of the bladder. These cancers are named for the type of cells that become malignant (cancerous):

- Transitional cell carcinoma: Cancer that begins in cells in the innermost tissue layer of the bladder. These cells are able to stretch when the bladder is full and shrink when it is emptied. Most bladder cancers begin in the transitional cells. Transitional cell carcinoma can be low-grade or high-grade:
  - Low-grade transitional cell carcinoma often recurs (comes back) after treatment, but rarely spreads into the muscle layer of the bladder or to other parts of the body.
  - High-grade transitional cell carcinoma often recurs (comes back) after treatment and often spreads into the muscle layer of the bladder, to other parts of the body, and to lymph nodes. Almost all deaths from bladder cancer are due to high-grade disease.
- Squamous cell carcinoma: Cancer that begins in squamous cells, which are thin, flat cells that may form in the bladder after long-term infection or irritation.
- Adenocarcinoma: Cancer that begins in glandular (secretory) cells that are found in the lining of the bladder. This is a very rare type of bladder cancer.

Cancer that is in the lining of the bladder is called superficial bladder cancer. Cancer that has spread through the lining of the bladder and invades the muscle wall of the bladder or has spread to nearby organs and lymph nodes is called invasive bladder cancer.

The following tests and procedures may be used to help detect (find) and diagnose bladder cancer.

- **Physical exam and history**: An exam of the body to check general signs of health, including checking for signs of disease, such as lumps or anything else that seems unusual.



A history of the patient's health habits and past illnesses and treatments will also be taken.

- **Internal exam**: An exam of the vagina and/or rectum. The doctor inserts gloved fingers into the vagina and/or rectum to feel for lumps.
- **Urinalysis**: A test to check the color of urine and its contents, such as sugar, protein, red blood cells, and white blood cells.
- **Urine cytology**: Examination of urine under a microscope to check for abnormal cells.
- **Cystoscopy**: A procedure to look inside the bladder and urethra to check for abnormal areas. A cystoscope is inserted through the urethra into the bladder. A cystoscope is a thin, tube-like instrument with a light and a lens for viewing. It may also have a tool to remove tissue samples, which are checked under a microscope for signs of cancer.

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