# BLUE LIGHT CYSTOSCOPY IN MANAGEMENT OF NON-MUSCLE INVASIVE BLADDER CANCER

ESSAY

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BY

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# ABBREVIATIONS

| | | | |
|---|---|---|---|
| **ALA** | Aminolevulinic acid | **NDA** | New drug Application |
| **A-NVH** | Asymptomatic NVH | **NHS** | National Health Service |
| **BC** | Bladder Cancer | **NICE** | UK National Institute of health and Care Excellence |
| **BCG** | Bacillus-calmette gurin | **NMIBC** | Non-Muscle Invasive BC |
| **BLC** | Blue Light Cystoscopy | **NMP22** | Nuclear Matrix Protein 22 |
| **CCU** | Camera Control Unit | **NVH** | Non-Visible Hematuria |
| **C-HT** | Chemohyperthermia | **OCT** | Optical Coherent Tomography |
| **CIS** | Carinoma In Citu | **PDD** | Photo Dynamic Diagnosis |
| **CT** | Computed Tomography | **PpIX** | Protoprphyrine IX |
| **DFS** | Disease Free Survival | **PFS** | Progression Free Survival |
| **EAU** | European Association Of Urology | QALY | Quality Adjusted Life Years |
| **EMDA** | Elective Motive Drug Administration | **RFS** | Recurrence Free Survival |
| **FC** | Fluorscene Cystoscopy | **SCC** | Squamous Cell Carcinoma |
| **FDA** | Food & Drug Administration | **S-NVH** | Symptomatic-NVH |
| **H.M. CYSTOSCOPY** | High Magnification C. | **TAC** | Technology Adoption Center |
| **HLA** | Hexaminolevulinic acid | **TCC** | Transitional Cell Carcinoms |
| **ICER** | Incremental Cost Effectiveness Ratio | **TURBT** | Trans-Urethral Resection Of Bladder Tumor |
| **LUT** | Lower Urinary Tract | **UUT** | Upper Urinary Tract |
| **MIBC** | Muscle Invasive BC | **VH** | Visible Hematuria |
| **MMC** | Mitomycine C | **WHO** | World Health Organization |
| **NBI** | Narrow Band Imaging | **WLC** | Wight Light Cystoscopy |

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# INTRODUCTION

Bladder cancer the ninth most common cancer, it is up to three times more common in men than women. It is also one of the commonest 5 malignancies in males & one of the commonest 10 malignancies in females [Burger *et al*. 2013].

The cardinal symptom of urothelial bladder cancer (UBC) is painless visible haematuria , occurring in more than 80 percent of patients at presentation, and requiring prompt investigation. A small but significant proportion of patients present with irritative urinary tract infection (UTI)-like symptoms in the absence of visible haematuria, and this is often associated with a delay in the diagnosis of UBC [Wallace *et al*. 2002].

Further investigation of patients suspected of having UBC requires multiple diagnostic procedures, including imaging of the upper urinary tract, urine cytology and cystoscopy, and in most cases the diagnosis is subsequently confirmed following transurethral resection of a bladder tumour(TURBT) [Kufman *et al*. 2009].

At presentation, 75–80 percent of patients will be diagnosed wi non-muscle-invasive tumours (NMIBC: stages Ta, T1 and Tcis),with the remainder diagnosed with muscle-invasive bladder cancer (MIBC,stages T2–4) [Bryan *et al*. 2013].

Transurethral resection (TUR) with cystoscopy is the current main treatment for non-muscle-invasive bladder cancer (NMIBC), but residual tumour was found in 30%–44% patients after treatment. This rate could exceed 70% for high grade tumours such as carcinoma in situ (CIS) [Jamal *et al*. 2011]. Furthermore, the probability for recurrence of NMIBC at 1 and 5 years had been reported as 15%-61% and 31%–78%, respectively, whereas the rate for progression at 1 and 5 years had been reported as <1%–17% and <1%-45%, respectively [Sylveste *et al*. 2006].

Residual tumours that were undetected or overlooked during initial TUR may contribute to recurrence. White light cystoscopy (WLC) was considered the current standard method for detecting tumours during TUR, however, its sensitivity and specificity was not entirely satisfactory. Small papillary bladder tumours and CIS were very difficult to detect using WLC; therefore, this method was associated with a potential risk of recurrence [Madeb *et al*. 2007].

An important factor that influences the outcome of TURBT is the visibility of tumors, especially of flat lesions, CIS and low-grade tumors. The visibility is thought to be optimized by using an installation of a photosensitizing drug in that its metabolites accumulate in cells of abnormal growth allowing them to emit red color under blue light this procedure is called Blue Light Cystoscopy (BLC). [Schmidbauer *et al*. 2004]

Blue light cystoscopy (BLC) is a new diagnostic procedure utilizing photoactive porphyrins to enhance the detection of bladder cancer. BLC is accomplished by administration of 5-aminolevulenic acid (5-ALA) or hexaminolevulinate (HAL). [Schmidbauer *et al*. 2004]

The metabolism of ALA is the first step in the biochemical pathway resulting in heme synthesis. ALA is not a photosensitizer, but rather a metabolic precursor of protoporphrin IX (PpIX), which is a photosensitizer. PpIX selectively accumulates in rapidly proliferating cells and are detected at light wavelength of 360-450 to distinguis between cancerous and normal tissue. [Schmidbauer *et al*. 2004]

Over the last decade improvements such as intravesical rather than systemic administration, use of newer photoactive porphyrins, shorter installation time, better contrast and less photobleeching have made this technique significantly better at detecting bladder cancer and much more practical . HAL is the photoactive porphyrin that has shown to be most effective and is the primarily one in use today. HAL lipophilic nature has made this technique practical by shortening the infusion time. [Schmidbauer *et al*. 2004]

Blue light cystoscopy (BLC) had been introduced for NMIBC diagnosis and treatment. Using this method, photoactive porphyrins such as 5-ALA or HAL were used to instill into the bladder and areas of abnormal cellular growth show emitted red fluorescence under blue light. This method, also known as photodynamic diagnosis (PDD) or Flourescene cystoscopy (FC) & had been studied extensively in recent years. [Blaise. 2010]

Several studies had demonstrated that BLC was more sensitive than WLC in detecting small papillary bladder tumours and CIS, thus improving tumour detection rates and decreasing residual tumour rates. [Groin *et al*. 2011]

Furthermore, no significant adverse effects related to the use of this method had reported till date. BLC had received approval for use in the detection of bladder cancer in several countries [Schmidbauer *et al*. 2004].

BLC (Blue Light Cystoscopy),also known as PDD (PhotoDynamic Diagnosis), or FC (Flourescene Cystoscopy) is a new technology so there is lack of knowledge about it and its benefits. Here we will give sufficient recent information about all aspects of BLC including its development, application, outcome of its use in NMIBC management, major disadvantage & new measures to avoid it. All this data is based on the recent papers, studies & articles deals with BLC over the last years.

CHAPTER 1

# BLADDER CANCER & NON-MUSCLE INVASIVE BLADDER CANCER (NMIBC)

Bladder cancer the **ninth** most common cancer over the world, it is up to three times **more common in men** than women, but women tend to present with more advanced disease and have worse outcomes. Around eight in 10 cases are diagnosed in individuals over the age of 65, and Caucasians generally have a higher risk of bladder cancer than people of other ethnicities. [Griffiths. 2012]

**Transitional cell carcinoma** (TCC; also known as urothelial cancer) represents over 90% of bladder cancers. Less common types include squamous cell carcinoma, adenocarcinoma and small cell carcinoma. Around 70–85% of TCCs are superficial [stages Ta, T1, carcinoma in situ (CIS)] at presentation and are now commonly termed non-muscle invasive bladder cancer (NMIBC), and the rest is diagnosed as muscle invasive TCC (T2–T4) (MIBC) which has less favorable outcomes. [Griffiths. 2012]

In the Middle East and Africa, squamous cell carcinoma was typically more common than in the developed world, largely caused by Schistosoma haematobium infection. However, improved knowledge of schistosomiasis over the last three decades has led to a reduction in squamous cell carcinoma such that TCC is now also the predominant type of bladder cancer in these countries. [Griffiths. 2012]

## Risk factors for bladder cancer

Numerous risk factors for bladder cancer have been identified. **Smoking** is implicated in approximately two-thirds of bladder cancers in men and up to one-third in women. There is a fourfold increased incidence in current smokers relative to never-smokers, and bladder cancer risk is correlated with the number of cigarettes smoked, duration of smoking and age at smoking initiation. Those who stop smoking reduce their bladder cancer risk by 10–40% within 4 years, although former smokers retain a twofold higher incidence than never-smokers. [Griffiths. 2012]

Data from Western Europe suggest that around 4–7% of bladder cancers in men are attributable to a known **occupational carcinogen**; the latent period between exposure and the development of cancer is about 20 years. Exposure to aniline dyes, aromatic amines (used in the manufacture of textiles, paints, plastics and rubber industries) and polycyclic aromatic amines are the primary toxins. Continuous arsenic exposure and ingestion has been reported to increase the risk of bladder cancer by as much as one thousand times. [Griffiths. 2012]

Carcinogen-metabolising enzymes are in part controlled by **genetic** polymorphism. Approximately 20% of Europeans affected by bladder cancer are homozygous for a non-coding single nucleotide polymorphism (8q24.21) located close to the c-Myconcogene. [Griffiths. 2012]

Older studies have shown that pelvic **radiotherapy** for was associated with increased risk of secondary bladder cancer. However, with contemporary radiotherapy, this risk has been reduced to a minimal level. [Griffiths. 2012]

It has been reported that treatment with **cyclophosphamide** for primary malignancies and autoimmune disease increases the risk of bladder cancer, and is higher with greater cumulative doses and longer duration of exposure. [Fairchild *et al*. 1979]. Mesna (2-mercaptoethanesulfonic acid) is commonly co-administered with cyclophosphamide to decrease the development of cyclophosphamide induced bladder cancer. As it counteracts the toxic effects of acrolein, an inactive metabolite of cyclophosphamide. [Links *et al*. 1999]

The oral antidiabetic drug **pioglitazone** show a small excess of bladder cancer cases was shown in two studies evaluating its role in the management of diabetes more than 2 years. [Dormandy *et al*. 2005].

There are also reported associations between increased risk of urothelial cancers and **Aristolochia fangchi** (a Chinese herb found in some over-thecounterdiet pills). [Nortier *et al*. 2000]

# Pathology

## Histopathology

Histologically, the predominant type of urinary bladder cancer is **transitional cell carcinoma**, which constitutes 96% of all the ca
Other types include squamous cell carcinoma (induced primarily by chronic infection with *S.haematobium*) and urachal adenocarcinoma, and occasionally small cell carcinoma, melanoma, and lymphoma of the urinary bladder. [Moyer. 2011]

## TNM classification

The (TNM) classification of malignant tumours is widely used to describe the extent of cancer spread. **[Table 1]**

(T) represent tumor itself and according to it UBC is classified to NMIBC & MIBC. (N) represent the lymphnode. Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes. (M) for metastasis. [Sobin *et al*. 2009]

## Primary Tumor (T)

| | |
|---|---|
| TX | Primary tumor cannot be assessed |
| T0 | No evidence of primary tumor |
| Ta | Noninvasive papillary carcinoma |
| Tis | Carcinoma in situ: “flat tumor” |
| T1 | Tumor invades subepithelial connective tissue |
| T2 | Tumor invades muscularis propria |
| pT2a | Tumor invades superficial muscularis propria (inner half) |
| pT2b | Tumor invades deep muscularis propria (outer half) |
| T3 | Tumor invades perivesical tissue |
| pT3a | Microscopically |
| pT3b | Macroscopically (extravesical mass) |
| T4 | Tumor invades any of the following: prostatic stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall |
| T4a | Tumor invades prostatic stroma, uterus, vagina |
| T4b | Tumor invades pelvic wall, abdominal wall |

## Regional Lymph Nodes (N)

| | |
|---|---|
| NX | Lymphnode cannot be assessed |
| N0 | lymphnode metastasis |
| N1 | Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node) |
| N2 | Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis) |
| N3 | Lymphnode metastasis to the common iliac lymph nodes |

## Distant Metastasis (M)

| | |
|---|---|
| M0 | No distant metastasis |
| M1 | Distant metastasis |

**[Table 1]**

BC TNM classification [Sobin *et al*. 2009]

## Characteristics of Grade

1973 WHO Classificatio

Grade 1: well differentiated tumo

Grade 2: moderately differentiated tumc

Grade 3: poorly differentiated tumc

2004 WHO Classificatio

- Urothelial papilloma
- Papillary urothelial neoplasm of low malignant potential (PUNLMP)
- Low-grade papillary urothelial carcinoma
- High-grade papillary urothelial carcinoma

The 1973 WHO system classifies tumours according to three grades of increasingly aggressive behavior, grades 1, 2 and 3, whereas the 2004 system classifies tumours as papillary urothelial neoplasm of low malignant potential, low-grade urothelial carcinoma and high-grade urothelial carcinoma. Controversy exists as to the more accurate system for prognostication so that specialist uro-oncology histopathologists use both systems for UBC reporting. [Chen *et al*. 2012]