# Introduction

Bladder cancer is recognized as one of the most prevalent malignancies worldwide, with approximately 20% of those diagnosed ultimately succumbing to the disease (**Warrick, Joshua I., et al. 2024**).

Bladder cancer exhibits the highest incidence in Europe, followed by the United States and Egypt **(Babjuk, Marko, et al. 2022).**

Bladder cancer is 3 to 4 times more common in men than women. It's incidence increase in the sixth decade of life **(Aveta, Achille, et al. 2022).**

It is the 2nd common site of cancer in men as it represent 12.7% **(Ibrahim, Nurul Khalida, et al. 2022).**

Transitional cell carcinoma (TCC) is the most common type of bladder tumor, presenting as a superficial disease at the time of initial diagnosis in approximately 75% of cases **(Gravas, Stavros, et al. 2023).**

Transurethral resection of bladder tumor(s) (TURBT), is considered the treatment of choice **(Mohanty, Sambit K., et al. 2023).**

Despite achieving visually complete resection, bladder cancer is associated with a high recurrence rate, potentially due to tumor cell implantation following transurethral resection of bladder tumor (TURBT) or the presence of residual microscopic disease. **(Zhang, Yongzhen, et al., 2018).**

The high rates of recurrence and stage progression present a significant clinical challenge. Intravesical instillation of chemotherapeutic or immunotherapeutic agents following transurethral resection of bladder tumor (TURBT) plays a crucial role in reducing the risk of recurrence and disease progression. Immunotherapeutic agents, such as Bacillus Calmette-Guérin (BCG), may enhance the body's immune response, exerting a direct effect on tumor cells **(Bazargan, Sarah, et al. 2023).**

Local side effects are observed in approximately 90% of patients receiving Bacillus Calmette-Guérin (BCG) therapy. More serious systemic complications may occur, including hemodynamic instability, persistent high-grade fever, allergic reactions such as arthralgia and rash, or involvement of solid organs (e.g., epididymitis, liver, lung, kidney, osteomyelitis, and prostate). These complications can necessitate discontinuation of treatment and, in some cases, have resulted in fatal outcomes **(Babjuk, Marko, et al. 2022).**

Despite the significant morbidity associated with BCG therapy, an improvement in overall survival has not been demonstrated, with only approximately two-thirds of patients showing a response to the treatment **(Claps, Francesco, et al. 2023).**

Research has thus focused on developing new drugs or novel drug combinations for intravesical instillation. Gemcitabine (GEM) has demonstrated efficacy with minimal bladder irritation and is generally characterized by rapidly self-resolving side effects **(Tomko, Andrea M. et al. 2022).**

Gemcitabine is an active systemic chemotherapeutic agent in the management of advanced bladder cancer and it has also been evaluated in the management of superficial disease **(Bazargan, Sarah, et al. 2023).**

Gemcitabine has a molecular weight of 299 Da, which is lower than that of most commonly used intravesical chemotherapeutic agents. This molecular size facilitates its penetration into the bladder mucosa, enhancing its therapeutic efficacy, while remaining sufficiently large to prevent significant systemic absorption. Additionally, its favorable pharmacokinetic profile makes gemcitabine an optimal candidate for regional therapy **(Li, Changjiu, et al. 2024).**

Intravesical gemcitabine is a promising drug that may be an option in treating patients with non muscle invasive bladder cancer **(Chen, Wujun, et al. 2022).**

Comparative trials of intravesical gemcitabine and Bacillus Calmette-Guérin (BCG) have yielded comparable outcomes regarding recurrence rates and disease progression, with the gemcitabine group experiencing fewer side effects **(Bazargan, Sarah, et al. 2023).**

# Aim of The Work

The aim of this work is to evaluate the efficacy and

safety of Gemcetabine as a local intravesical adjuvant

treatment of non muscle invasive TCC in reducing the risk

of recurrence and progression after TURBT in comparison

to BCG.

# Chapter (1) Non Muscle Invasive Bladder Cancer

**Introduction and incidence**

Bladder tumor is the 9th most commonly diagnosed tumor in the world and the 2nd most common malignancy of the urogenital tract **(Chen, Ji-Qing, et al. 2022).** It's causing more than 130,000 deaths annually **(ŞEN, Selda, et al. 2021).**

Bladder cancer is more prevalent in developed countries and demonstrates a pronounced gender disparity, with an incidence ratio of approximately 4:1 favoring males over females **(Ferlay, Jacques, et al. 2020).**

The incidence and prevalence of bladder tumors increase in the sixth decade of life, reaching a peak in the seventh and eighth decades, which predominantly characterizes the disease as one affecting the elderly **(Aveta, Achille, et al. 2022).**

The highest incidence of bladder cancer has been observed in Europe, the United States, and Egypt, whereas the lowest incidence rates are reported in Sub-Saharan Africa, Asia, and South America **(Babjuk, Marko, et al. 2022).**

About 75% of bladder tumors are non-muscle invasive at initial diagnosis **(Tran, Linda, et al. 2021).** Sixty percent of these patients experience recurrence and ten percent experience progression in 5 years **(Ferro, Matteo, et al. 2022).**

**Risk Factors of Bladder Cancer**

* **Smoking :**

Cigarette smoking is the most significant risk factor for bladder cancer, although its association is not as strong as that observed with respiratory tract cancers. Tobacco smoke is estimated to be responsible for approximately 50% of bladder cancer cases, contributing substantially to the disease burden. Carcinogenic urinary compounds derived from cigarette smoking include aromatic amines, inorganic substances such as arsenic, polyaromatic hydrocarbons, and aldehydes. Moreover, electronic cigarette use may not be risk-free, as the complex composition of e-cigarette liquids can contain or generate, through vaporization, known bladder carcinogens, including aromatic amines, aldehydes, and polyaromatic hydrocarbons **(Jubber, Ibrahim, et al. 2023).**

* **Occupation :**

Occupational exposure is recognized as the second most significant risk factor for bladder cancer, with estimates suggesting that such exposures may account for up to 20% of all cases. Agents such as naphthylamine, 4-aminobiphenyl (ABP), and benzidine—primarily encountered among workers in the textile dye and rubber tyre industries—have been associated with bladder cancer. Due to stringent regulations, these chemicals are now banned from the workplace and contribute minimally to the current incidence of bladder cancer in Western countries. Nonetheless, several other potential carcinogens persist, such as orthotoluidine, which is currently used in the manufacture of dyes, rubber chemicals, pharmaceuticals, and pesticides. Recent studies have further revealed that cumulative occupational exposure to aromatic acids is linked to an elevated risk of bladder cancer **(Zhao, Xiaohu, et al. 2022).**

* **Bacterial Infections :**

Several investigators have proposed that chronic bacterial infections may contribute to the development of bladder cancer. Clinically, conditions such as prolonged catheter use, urolithiasis, and persistent infections have been associated with bladder carcinoma, although the precise mechanisms underlying neoplastic transformation remain poorly understood. It is hypothesized that factors such as immunological dysregulation, chronic chemical and mechanical irritation, and the production of carcinogens like nitrosamines may play a role in this process. Notably, chronic urinary tract infections have been linked to bladder cancer, with individuals exhibiting a relative risk of 1.4 to 1.6 for developing the disease following any history of such infections **(Huan, Jianya, et al. 2022).**

* **Radiation and Chemotherapy :**

Second malignant neoplasms represent late complications following exposure to genotoxic therapies, including radiotherapy and certain chemotherapeutic agents. Notably, the development of urothelial cancer after radiation exposure is not age-dependent, typically emerging after a latency period of 15 to 30 years. Furthermore, the increased risk of urothelial cancer in patients with prostate or cervical cancer treated with radiation therapy further substantiates the carcinogenic potential of radiation in the bladder **(Goswami, Ritabrita, et al. 2024).**

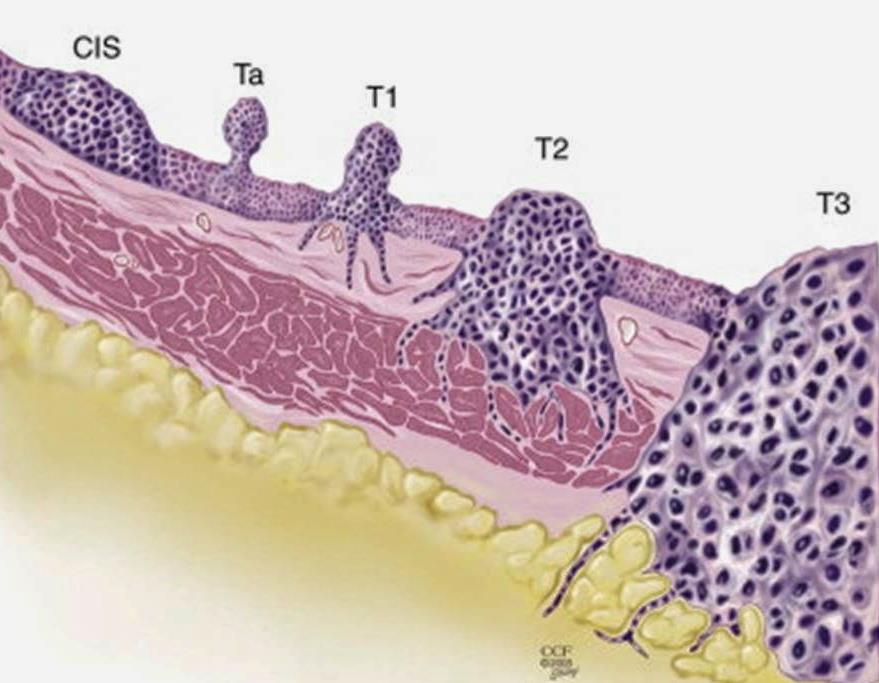
Chemotherapy exerts its cytotoxic effects on malignant cells by inducing significant DNA and cellular damage; however, it may also adversely affect rapidly dividing normal epithelia, such as those found in the bladder. Notably, cyclophosphamide is the only chemotherapeutic agent that has been conclusively linked to the development of bladder cancer **(Zuo, Mingshun, et al. 2023).**

* **Genetic Factor :**

Genetic predisposition influences the incidence of bladder cancer by modulating an individual's susceptibility to other risk factors. Exposure to arsenic in drinking water has been shown to elevate the risk of bladder cancer, while the chlorination process, which increases trihalomethane levels in water, may also contribute to carcinogenic risk **(Babjuk, Marko, et al. 2022).**

A link between dietary habits and BC risk has been suggested **(Jubber, Ibrahim, et al. 2023).** While family history seems to have little impact **(Adrien, Oriane, et al. 2023).**

**Staging and Classification Systems**

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**Figure (1):** Histopathological classification of bladder cancer

***(Babjuk et al., 2021).***

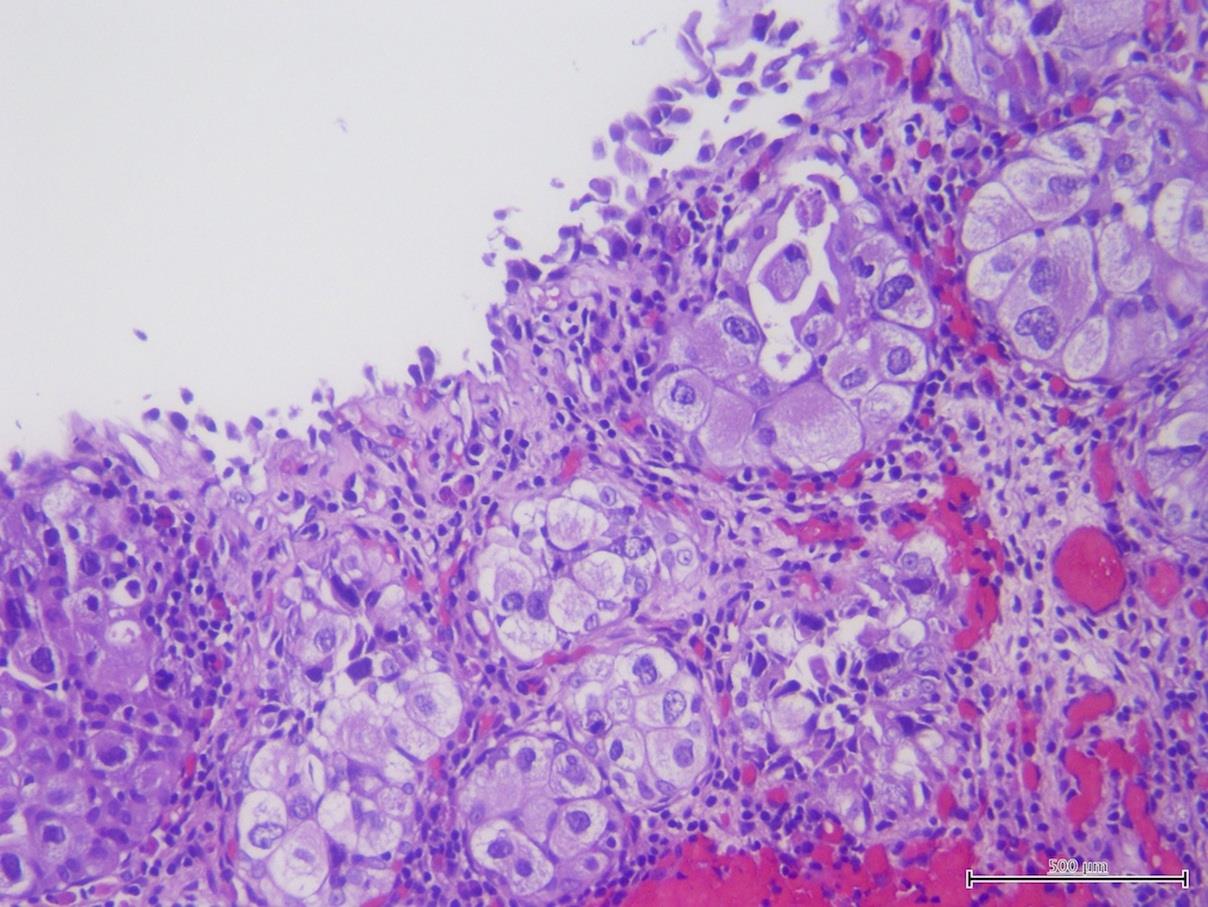
**Table (1):** 2017 TNM classification of urinary bladder

cancer ***(Babjuk et al., 2021)***

|  |  |
| --- | --- |
| **T: Primary tumor** | |
| **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 muscle |
| **T2a** | Tumor invades superficial muscle (inner half) |
| **T2b** | Tumor invades deep muscle (outer half) |
| **T3** | Tumor invades perivesical tissue |
| **T3a** | Microscopic invasion |
| **T3b** | Macroscopic invasion (extravesical mass) |
| **T4** | Tumor invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall |
| **T4a** | Tumor invades prostate stroma, seminal vesicles, uterus or vagina |
| **T4b** | Tumor invades pelvic wall or abdominal wall |
| **N: Regional lymph nodes** | |
| **N** | Regional lymph nodes cannot be assessed |
| **N0** | No regional lymph node metastasis |
| **N1** | Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral) |
| **N2** | Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral |
| **N3** | Metastasis in common iliac lymph node(s) |
| **M: Distant metastasis** | |
| **M0** | No distant metastasis |
| **M1a** | nonregional lymph nodes |
| **M1b** | Other distant metastases |

Papillary tumors confined to the mucosa and invading the lamina propria are classified as stage Ta and T1, respectively (fig.1), according to the TNM classification system **(Brierley et al., 2017).**

Flat, high- grade tumors confined to the mucosa are classified as CIS (carcinoma in situ) (Tis) (fig. 2). All of these tumors are grouped under the heading of NMIBC (non-muscle invasive bladder cancer).



**Figure (2):** Carcinoma in situ ***(Magers et al., 2019).***

**CIS and its classification :**

CIS is a flat, high-grade, noninvasive urothelial carcinoma. It can be missed or misinterpreted as an inflammatory lesion during cystoscopy if not biopsied. CIS is often multifocal and can occur in the bladder, as well as the upper urinary tract (UUT), prostatic ducts, and prostatic

urethra **(Babjuk et al., 2021).**

**CIS can be classified as follows :**

*  Primary: isolated CIS with no previous or concurrent

papillary tumors and no previous CIS.

*  Secondary: CIS detected during follow-up of patients

with a previous tumor that was not CIS.

*  Concurrent: CIS in the presence of any other urothelial

tumor in the bladder.

**Histological grading of non–muscle-invasive bladder urothelial carcinomas**

WHO and the International Society of Urological Pathology (ISUP) in 2016 updated a histological classification of urothelial carcinomas that provides a different patient stratification between individual categories compared to the older 1973 WHO classification **(Moch et al., 2016)** (Tables 2 and 3). In 2016, an update of the 2004 WHO grading classification without major changes **(Moch et al., 2016).**

**Table (2):** WHO grading in 1973 and in 2004/2016 ***(Moch et al., 2016).***

|  |
| --- |
| **1973 WHO grading** |
| Grade 1: well differentiated  Grade 2: moderately differentiated  Grade 3: poorly differentiated |
| **2004/2016 WHO grading system (papillary lesions)** |
| Papillary urothelial neoplasm of low malignant potential (PUNLMP)  Low-grade (LG) papillary urothelial carcinoma  High-grade (HG) papillary urothelial carcinoma |

**Table (3):** WHO 2004 histological classification for flat lesions ***(Babjuk et al., 2020).***

|  |
| --- |
| **Non-malignant lesions** |
| * Urothelial proliferation of uncertain malignant potential (flat   lesion without atypia or papillary aspects   * Reactive atypia (flat lesion with atypia) * Atypia of unknown significance * Urothelial dysplasia |
| **Malignant lesion** |
| * Urothelial CIS is always high grade |

**Diagnosis of Cancer Bladder**

* ***Signs and Symptoms***

1. Gross painless hematuria is the most common finding in NMIBC. Visible hematuria was found to be associated with higher-stage disease compared to nonvisible (microscopic) hematuria **(Ramirez et al., 2016)**. CIS might be suspected in patients with lower urinary tract symptoms, especially irritative voiding.
2. Voiding symptoms although most people with bladder cancer do not have symptoms, some have voiding symptoms, such frequency or urgency during the day or night and/or urge-incontence **(Rais-Bahrami and Pietryga, 2016).**

* ***Imaging***

**Ultrasonography (U/S)** facilitates the characterization of renal masses, detection of hydronephrosis, and visualization of intraluminal bladder masses. While U/S can differentiate between fluid-filled cysts and solid tumors (Fig 3), it cannot ascertain the malignancy of a tumor **(Messina, Emanuele, et al. 2023).** Moreover, U/S is unable to exclude all potential causes of hematuria, does not reliably rule out the presence of upper tract urothelial carcinoma (UTUC), and therefore cannot substitute for CT urography.



**Figure (3):** Urinary bladder mass in U/S ***(Salmanoglu et al., 2018).***

**Computed tomography** (CT) (of the abdomen and pelvis) urography is used to detect papillary tumors in the urinary tract as mass lesion enhanced with cotrast, as showen in (fig. 4) and/or hydronephrosis. The CT scan can show the extent of a cancer, and determine if the cancer has

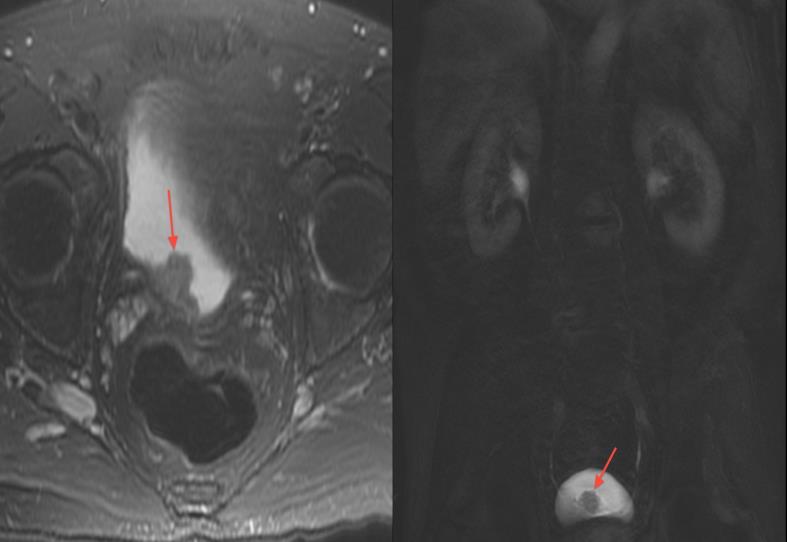
spread outside the bladder **(Trinh et al., 2018).** The incidence of simultaneous upper tract urothelial carcinoma (UTUC) is low (1.8%), but increases to 7.5% for tumors located in the trigone **(Lee & Chang, 2018).**



**Figure (4):** CT scan shows tumor as intraluminal enhancing mass

(arrows) ***(Vikram et al., 2009)***

**Magnetic resonance imaging (MRI)** of the kidney, ureters, and bladder (fig.5) may provide additional information in staging bladder cancer and can be used in people with allergies to contrast dye **(Rais-Bahrami and Pietryga 2016).**



**Figure (5):** Bladder mass in MRI ***(Verma et al., 2012)***

* ***Urine Cytology***

Examination of voided urine or bladder-washing specimens for exfoliated cancer cells has high sensitivity in high-grade tumors (84%), but low sensitivity in low grade tumors (16%). The sensitivity for CIS detection is 28-100% **(Liem et al., 2018).**

Cytological interpretation is user-dependent. Evaluation can be hampered by low cellular yield, urinary tract infections, stones, or intravesical instillations; however, in- experienced hands the specificity exceeds 90% **(Goutas et al., 2021).**

* ***Urinary Molecular Marker Tests***

Numerous urinary tests have been developed as NMP22, Lewis X, FISH, CYFRA 21.1. None of these markers can replace cystoscopy in routine practice, but the knowledge of positive test results can improve the quality of follow-up cystoscopy **(Hu, Xinzi, et al., 2022).**

* ***Endoscopic Evaluation***

**White light cystoscopy (WLC)**

WLC is an endoscopic technique to visualize the urethra, bladder, and ureteric orifices. It is the gold standard for the examination and diagnosis of cancer of the lower urinary tract, using either flexible or rigid cystoscopy **(Babjuk et al., 2017).**

WLC has a sensitivity of 85–90% for detecting papillary tumors and lower sensitivity (up to 67%) to detect CIS **(Daneshmand et al., 2018).**

* *Advantages of semi-rigid WLC:-*

WLC has the advantage of being widely available and has lower cost than all the newer endoscopic techniques.

* *Disadvantages of semi-rigid WLC:-*

WLC has lower sensitivity to detect flat and CIS lesions, has limited ability to differentiate benign from malignant lesions, and is operator dependent **(Tschirdewahn et al., 2020).**

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**Figure (6):** Instruments of semi-rigid cystoscopy ***(Ku, 2019).***

**Flexible Cystoscopy**

Flexible cystoscopy is often performed for initial diagnosis and surveillance.

* *Disadvantages of Flexible Cystoscopy:-*

It can miss up to 10% of papillary tumors when compared to rigid cystoscopy **(Daneshmand et al., 2018).** The diagnostic yield of endoscopic removal of the tumor using flexible cystoscopy is limited, which can potentially compromise grading and staging of the tumor **(Bourlotos, Georgia, et al., 2024).**

* *Advantages of Flexible Cystoscopy:-*

While flexible cystoscopy is more comfortable and convenient for the patient, and has higher cost than semirigid cystoscopy.

Flexible cystoscopy thus can be used in the primary evaluation or surveillance of BC patients, and (Transurethral resection of bladder tumor) (TURBT) can be then conducted using rigid cystoscopy when needed **(Tschirdewahn et al., 2020).**

**Fluorescent Cystoscopy (FC)**

FC, also known (photodynamic diagnosis) PDD, is a modification of WLC where an intravesical agent is instilled, and blue light (375-440 nm) is used for visualization. The instilled agents are photoactive porphyrin analogs, such as a 5-aminolevulinic acid (5-ALA) and hexaminolevulinate, which are taken up by epithelial cells and used in the formation of intermediate photoactive porphyrins. Intermediate porphyrins accumulate preferentially in neoplastic cells because of the accelerated enzymatic activity, and after excitation with blue light will return to lower energy levels and fluoresce. Tumor tissues will thus appear as well demarcated bright red lesions against a dark blue background (Fig. 7) **(Soubra & Risk, 2015).**