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Diagnosis and Therapy Using Light (Fluorescence) for Bladder Cancer

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Abstract: Bladder cancer, also known as urological cancer, is the 10th most common cancer in the world. The incidence of this cancer is steadily increasing, especially in well-developed countries. The frequent occurrence of the disease and its susceptibility to recurrence and progression despite treatment significantly burdens healthcare systems. A more modern advancement of the gold standard in diagnostics is fluorescence cystoscopy and imaging using a narrow light beam. White light cystoscopy requires the use of a photosensitizer, allowing for more precise visualization of changes within the mucous membrane. An alternative method is narrow-band imaging, which relies on limiting the spectrum of light illuminating the tissue, enabling the use of differences in light absorption by hemoglobin. Two wavelengths are used for this purpose: 415 nm and 540 nm. Diagnostics using photodynamics is considered the most precise method for imaging cancerous tissues. However, despite diagnostic techniques' high effectiveness and widespread availability, their use is limited because only selected tissues and organs are suitable for imaging with diagnostic light. Experience gained over many years of using fluorescence-based methods would allow for the detection of bladder cancer in its early stages, which are often overlooked even by modern tests.

Keywords: bladder cancer; fluorescence cystoscopy; photodynamics.

1. Introduction

Bladder cancer, also known as urological cancer, is the 10th most common cancer in the world [1,2]. In 2012, this cancer ranked 9th [3]. The incidence of this cancer is steadily increasing, especially in well-developed countries such as the United States, where it is the 6th most common cancer [1,4]. The frequent occurrence of the disease and its susceptibility to recurrence and progression despite treatment significantly burden healthcare systems [3]. According to the latest GLOBACAN data, bladder cancer accounts for 3% of all diagnosed cancers worldwide [4]. Statistics indicate that bladder cancer is typically diagnosed in people over 55 years of age, with men being four times more likely to be affected than women [4]. As many as 4 out of 10 cases are detected early (Table 1), significantly improving survival and

allowing resections [4]. It has been proven that genetics plays a role in only 7% of cancer cases, with the majority of cases being caused by lifestyle factors, particularly environmental and occupational exposure [5].

Table 1. Shows new cases and deaths from bladder cancer in 2018 [2].

Cancer Type	Number of New Cases (% of all cancers)	Number of Deaths (% of all cancers)
Bladder Cancer	219,420 (1.2%)	165,087 (1.7%)

The 5-year survival rate for bladder cancer in the USA is 77.1%, reflecting the success of early diagnosis but also the poor prognosis for metastatic bladder cancer. The 5-year survival rate in the USA has increased over the past 4 decades from 71.9% for diagnoses in 1975 to 79.3% for diagnoses in 2011. In the USA, the 10-year survival rate is 70%, and the 15-year survival rate is 65% [4].

2. Materials and Methods

2.1. Anatomy.

The urinary bladder is located in the lower abdomen. It is a hollow organ whose main function is to store urine filtered by the kidneys [1]. The interior of the bladder and the urinary tract are lined with urothelial cells. These cells are most vulnerable to environmental factors, as they are filtered into urine by the kidneys [1]. Urothelial tumors are characterized by multifocality, and the current carcinogenesis model suggests that malignant tumors represent a clonal expansion of one or several cancerous stem cells, which proliferate through asymmetric differentiation and may differentiate into heterogeneous lines of cancer cells [6]. When cell division occurs, one cell is capable of further division, while the progeny cell is genetically plastic [6]. According to the 2023 guidelines from the National Comprehensive Cancer Network (NCCN) for bladder cancer, there are three clinical categories based on differences in prognosis, treatment, and therapeutic goals: non-muscle-invasive bladder cancer (NMIBC), muscle-invasive bladder cancer (MIBC), and metastatic disease [7]. The urinary bladder is an organ into which light can be introduced, and the entire epithelial layer can be exposed to radiation. It is within this layer that neoplastic and precancerous changes occur [8].

2.2. Bladder cancer.

Transitional cell carcinoma (TCC) of the bladder accounts for 95% of all bladder cancers. Disease recurrences and progressions are frequent. During routine diagnostics, bladder cancer can easily be missed using white-light cystoscopy, ultrasound, and urography. The cells comprising the tumor are flat and indistinct. Using photodynamic diagnostic methods, urologists can detect bladder cancer at an earlier stage with greater effectiveness [9-17]. The economic aspect is also critical, as due to the large patient population, constant monitoring of disease progression is necessary, which significantly burdens the healthcare system [18-20]. Screening for bladder cancer is not recommended [21-22].

2.3. Symptoms.

The detection of bladder cancer begins with the observation of initial symptoms. Hematuria is the primary symptom, followed by confirmation through cystoscopy, telescopic endoscopy of the bladder, abdominal ultrasound, or computed tomography (CT) urography [4].

Hematuria often occurs in the advanced stages of the disease. In the early stages, irritative symptoms from the lower urinary tract, such as frequent urination, pain during urination, and a feeling of urgency, can be observed [9]. Bladder cancer is also studied for genetic susceptibility and interactions between genes and the environment. It has been shown that genotypes of the NAT2 slow acetylator and GSTM1 null genotypes are prone to bladder cancer. Furthermore, these genotypes interact with each other. Additional genes are currently being studied that are likely genetically predisposed to bladder cancer [8]. Symptoms reported by patients may also occur in many other conditions [23].

2.4. Diagnostics.

The first and most fundamental action by a doctor when suspecting bladder cancer based on symptoms is a patient interview. In cases of non-invasive forms of bladder cancer, physical examination is not helpful, and the mobility of the organ can only be assessed. Therefore, imaging tests play the most important role in diagnosing bladder cancer. Cytological examination of urinary sediment is commonly performed for diagnostic purposes and is highly specific, although its sensitivity depends on the clinical stage and malignancy of the tumor [24-26]. Cytology is highly sensitive for high-grade tumors but much less so for low-grade tumors [27]. Interpretation difficulties arise when the sediment is poor or when infection is present [28]. Molecular markers are increasingly being considered in diagnostics. Numerous studies are regularly conducted to evaluate the properties of chemical compounds that could serve as bladder cancer markers (Figure 1). The goal is to accelerate diagnosis and treatment verification [27]. However, it has been unanimously agreed that no single marker can replace more accurate cystoscopy [29]. The gold standard for diagnosing bladder cancer remains cystoscopy, although it is an invasive test. It provides information about the tumor's location, size, and appearance of changes [27]. A more advanced form of cystoscopy is fluorescent cystoscopy and narrow-band imaging. White-light cystoscopy is performed using a photosensitizer that is introduced into the bladder two hours before the procedure. These include 5-aminolevulinic acid (5-ALA) or hexylaminolevulinate (HAL). They bind to the urothelial cell membrane. The photosensitizer is excreted from the cells over time, depending on whether it has bound to a healthy or cancerous cell. This process takes around 90 minutes for healthy cells, while for cancer cells, it takes several hours [27]. Narrow-band imaging involves limiting the spectrum of light illuminating the mucous membrane, thus utilizing the difference in absorption of wavelengths by hemoglobin. Two bands are typically used—415 and 540 nm [27-29].

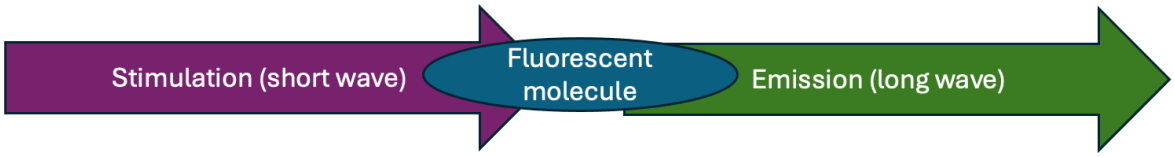

Figure 1. The fluorescence process. Figure done by coauthor Sara Bień.

2.5. Imaging methods.

2.5.1. Ultrasound.

The primary imaging method used in the diagnostic evaluation of the urinary system is ultrasound. It is a cheap, non-invasive, and radiation-free method for detecting bladder cancer. However, the role of ultrasound is currently quite limited, and it is used alongside the patient's

history or histopathological examination to help differentiate between diseases [7]. Intra-bladder ultrasound allows for a detailed evaluation of the bladder walls, but it is less frequently performed due to limited accessibility. Transrectal ultrasound in men can assess both the prostate and seminal vesicles [27]. In bladder cancer patients, the occurrence of urothelial cancer in the upper urinary tract is 1.8%, but if tumors are located in the bladder triangle, the risk increases to 7.5% [30].

2.5.2. MRI.

MRI is increasingly used in the imaging of bladder cancer due to its high tissue contrast and spatial resolution. However, it is the most expensive method and is essential for evaluating the depth of bladder wall invasion and assessing the extent of involvement of neighboring anatomical structures [7].

2.5.3. CT scan.

CT in bladder cancer evaluates the degree of tumor advancement. Compared to traditional ultrasound, it is a more sensitive method not only for analyzing the bladder itself but also for detecting enlarged lymph nodes in the pelvis [31]. This method does not provide information about the bladder's layers, so it is not indispensable for differentiating early-stage disease [32].

2.5.4. Urography with cystography.

Urography with cystography is a method that allows assessment of the urinary tract and bladder shape (figure 2). It is useful for the primary diagnosis of bladder cancer. It reduces unwanted symptoms patients experience following standard diagnostic tests [33-36]. Photodynamic diagnostics offer the most precise method for imaging cancerous tissues [37]. Despite its widespread use, this diagnostic test is not often applied because only certain tissues and organs are accessible to diagnostic light [38].

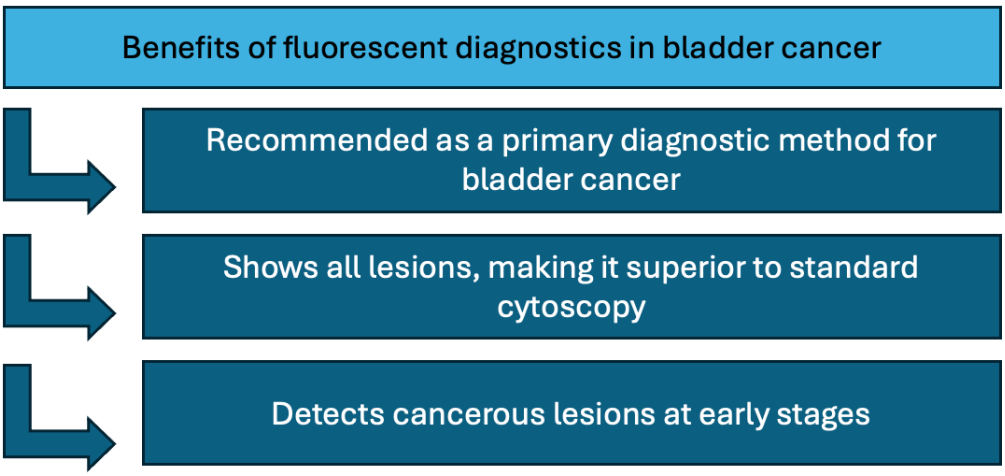

Figure 2. Benefits of fluorescence diagnostics in bladder cancer. Figure done by coauthor Sara Bień.

2.6. Diagnostics and treatment elements.

A procedure used not only for diagnostics but also for treating bladder cancer is transurethral resection of the bladder tumor (TURBT). If the tumor is small (less than 1 cm), it is removed, along with a fragment of the muscle layer. Larger tumors are removed in fragments

[39]. After the tissue is collected and sent for further diagnostics, the histological result will provide information not only about the malignancy of the tumor but also about the depth of invasion. These data are crucial for predicting recurrence and progression [40].

2.7. Adjuvant treatment.

Adjuvant treatment should be considered in every case depending on the likelihood of recurrence and progression. If recurrence and progression are deemed low, one intravesical chemotherapy installation should be given within 24 hours of TURBT [27,41]. In cases with medium or high recurrence and progression risk, chemotherapy instillations should be given cyclically every 6-12 months, or a 12-month regimen with BCG vaccine instillations should be used [42]. Unfortunately, in severe cases where treatment is ineffective, bladder removal may be necessary, but each case should be considered individually [27].

2.8. History.

The first reports of tissue fluorescence came from the works of Raab and von Tappeiner in 1900 [43]. Through the fluorescent activity of porphyrins, the accumulation of photosensitizers in tumors, and the accumulation of hematoporphyrin derivatives in cancerous tissues, a groundbreaking study in urology in 1976 demonstrated the use of fluorescence diagnostics for transitional cell carcinomas of the bladder [43,44]. In the following years, numerous studies, including laboratory observations of photo optics, were conducted [43,45]. Initially, spectrofluorimeters with fiber optics were used for measurements, and later modifications led to the development of devices for photodynamic therapy (PDT) [43].

2.9. FISH Method in Bladder Cancer Diagnostics.

Absorbance and emission spectra of radiation with specific energy can be associated with chemical compounds, which can also emit light. This allows for the observation of light emission under a microscope. In fluorescence microscopy, visible light is turned off, and the sample is illuminated only with UV light [46]. There is a method that uses fluorescence microscopy and the nucleic acid hybridization technique called Fluorescent In Situ Hybridization (FISH). This method is applied to DNA diagnostics using peripheral blood lymphocytes and urine cells [47,48]. The FISH method is used to diagnose bladder cancer. Transitional cell carcinoma (TCC) is primarily characterized by additional chromosomes 3, 7, 17, and a deletion of the 9p21 region. As the cells for analysis are obtained from urine sediment, there is a rapid test for detecting genomic changes [48-55].

3. Conclusions

Bladder cancer is the 10th most common and 13th most fatal cancer worldwide. Although women are diagnosed much less frequently than men, increasing trends in bladder cancer incidence are still observed. Bladder cancer can be categorized into groups of varying malignancy. The most common symptom reported by patients is painless hematuria, which affects 85% of those with the disease. Management of bladder cancer depends on its stage and malignancy. Bladder cancer diagnostics using light, as opposed to conventional cystoscopy, reveal all cancer foci, even in the early stages. Therefore, it should be used as the first and primary method in diagnostics. The experience gained over the years through the use of fluorescence-based methods should lead to improving this diagnostic technique in future years.

Author Contributions

Conceptualization, S.B.; D.L.; D.B.-A.; and D.A.; methodology, S.B.; D.L.; D.B.-A.; and D.A.; software, S.B.; D.L.; D.B.-A.; and D.A.; validation, S.B.; D.L.; D.B.-A.; and D.A.; formal analysis, S.B.; D.L.; D.B.-A.; and D.A.; investigation, S.B.; D.L.; D.B.-A.; and D.A.; resources, S.B.; D.L.; D.B.-A.; and D.A.; data curation, S.B.; D.L.; D.B.-A.; and D.A.; writing—original draft preparation, S.B.; D.L.; D.B.-A.; and D.A.; writing—review and editing, S.B.; D.L.; D.B.-A.; and D.A.; supervision D.A.; project administration, S.B.; D.L.; D.B.-A.; and D.A.; All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

Declared none.

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