NARRATIVE REVIEW

Blue light cystoscopy- as an improvised diagnostic modality for bladder tumours

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Abstract

Bladder cancer remains a significant global health concern, being the 10th most common malignancy worldwide and the 6th most common neoplasia in males, with alarming annual incidence and mortality rates. The current narrative review was planned to delve into the multifaceted landscape of bladder cancer, exploring its epidemiology, risk factors and diagnostic modalities. While white light cystoscopy has long been considered the gold standard for bladder cancer diagnosis and surveillance, the emergence of blue light cystoscopy has ushered in a new era of early detection. Numerous studies have demonstrated BLC's superiority in reducing the risk of progression and recurrence of this lethal cancer. However, the widespread adoption of this technology remains elusive. Recent advancements in diagnostic procedures have revolutionised imaging modalities, with blue light cystoscopy and narrow-band imaging emerging as promising replacements for white light cystoscopy. Clinical trials have underscored the superior performance of blue light cystoscopy over white light cystoscopy, with reduced recurrence and progression rates. For non-muscle invasive bladder cancer, Bacillus Calmette-Guérin immunotherapy remains the gold standard adjuvant therapy, while cystectomy is considered for cases resistant to Bacillus Calmette-Guérin or with a high risk of progression. Transurethral resection of bladder tumour followed by intravesical chemotherapy is a key intervention for early-stage bladder cancer. Blue light cystoscopy is poised to overcome the limitations of white light cystoscopy by providing comprehensive visualisation of neoplastic boundaries, particularly benefiting late-detected squamous-type non-muscle invasive urothelial carcinomas associated with lower survival rates. The current findings highlighted the transformative potential of blue light cystoscopy and other emerging diagnostic techniques, offering a ray of hope in the battle against bladder cancer, while emphasising the need for wider adoption and integration into clinical practice.

Keywords: Bladder carcinoma, Blue light cystoscopy, White light cystoscopy, Urothelial carcinoma, Non-muscle invasive carcinoma, Narrow-band imaging..

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Introduction

Bladder carcinoma (BCA), like any other solid tumour in the human body, arises as a result of uncontrolled division of the cells lining the lumen of the urinary bladder. According to the Global Cancer Observatory (GLOBOCAN) 2020 distribution, BCA is the 10th most common malignancy globally and the 6th most common neoplasia in males, with an estimated annual incidence and mortality of 573,000 and 213,000, respectively.[1] Region-wise, Southern and Western Europe along with North America are reported to have the highest incidence of BCA in the world.[1] Bladder cancer can be further subdivided into muscle-invasive, non-muscle-invasive, and metastatic cancer, with a 5-year survival rate of 5% in patients diagnosed with advanced cancer.[2] Statistics show that men are 4 times more likely to develop bladder cancer than women during their lifetime.[1] Apart from gender, other risk factors for the disease include advanced age with an average age of 65 years at the time of diagnosis, occupational exposure to certain chemicals, like arsenic and dyes containing benzene, schistosomiasis (a chronic parasitic infection), and cigarette smoking, which is the most important known risk factor for BCA.[2,3] Despite the increasing number of new cases, the world has witnessed a significant decline in the death rate from BCA.[4] The recent advances in the early detection and treatment of cancer over the past few years have, indeed, played a central role in the overall improvement in mortality rates.[4] Although white light cystoscopy (WLC) is regarded as the gold standard diagnostic and surveillance technique, blue light cystoscopy (BLC) in combination with WLC has made a breakthrough in the early BCA diagnosis. Several studies have revealed that out of all the emerging diagnostic tools, BLC is most effective in lowering the risk of progression and relapses of this deadly cancer.[5] Despite the effectiveness and the proven mortality benefits of BLC, this unique technology is still not being widely used in most parts of the world. In Pakistan, despite the establishment of multiple urology

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institutes, the use of BLC has not been initiated yet.

The current narrative review was planned to delve into the multifaceted landscape of BCA, exploring its epidemiology, risk factors and diagnostic modalities.

Risk factors of BCA

The occurrence of BCA depends on multiple factors which are divided into lifestyle, occupation, infections, iatrogenic causes, and race and gender. Amongst these, lifestyle risk factors, which include tobacco smoking, impose the highest risk of BCA. Various studies proved that smoking alone increases the risk of BCA by 50%. This is because carcinogens present in tobacco smoke, like aromatic amines and N-nitroso compounds, cause destruction of deoxyribonucleic acid (DNA), leading to cancer. Data extracted from a meta-analysis revealed an improved BCA death rate in ex-smokers (1.44) compared to current smokers (1.53) which indicates that abandoning smoking might help in lowering the risk of acquiring BCA.[6] Recent clinical trials conducted on e-cigarette users demonstrated BCA-related carcinogens in the urine of the participants. However, further studies are needed to prove the association of e-cigarettes with BCA. Additionally, a diet high in processed food, red meat, vitamin B1, high fat and sugar is linked to an increased risk.[7]

Certain occupations, like textile workers, engineering workers and hairdressers, are prone to developing BCA which is ascribable to certain chemicals utilised in these lines of work, such as aniline dyes, aromatic amines and polycyclic aromatic hydrocarbons, which contribute to the disease.[8] BCA is more prevalent in men compared to women. This disparity of BCA incidence observed in men and women could be due to certain liver enzymes responding differently to the exposed carcinogens, and thereby exposing urothelium to different levels of carcinogens. It is hypothesised that sex hormones could also provoke BCA development.[9] Compared to black individuals, white people and Asians are more likely to acquire BCA.

When considering the infectious causes, Schistosomiasis haematobium (SH), a liver fluke, is a known prime cause of BCA, especially in areas such as the Middle East and Africa. Recurrent irritation of the bladder mucosa due to SH eggs induces a severe inflammatory response, allowing reactive oxide species (ROS) formation, and thereby predisposing bladder mucosa to genetic mutations and newly formed carcinogens. The chronicity of this infection contributes significantly to the eventual development of BCA in most cases.

Iatrogenic causes include chemotherapy, radiation therapy, and the use of pioglitazone. BCA occurs more frequently in people who get pelvic radiation therapy for urogenital and gynaecologic malignant growths. Patients who receive cyclophosphamide treatment for autoimmune disorders or cancer are 4-9 times more likely to develop BCA. As the course of treatment and total doses lengthen, the risk increases.[6]

Types of BCA

BCA is categorised based on clinical disease states, which include non-muscle invasive, muscle-invasive and metastatic. Another classification focusses on the histological variants of BCA and is broadly categorised into urothelial and non-urothelial BCA. The most commonly occurring type of BCA based on histology is urothelial carcinoma (UC), which arises from the transitional cell epithelium that lines the bladder wall. It can further be subdivided, according to morphologic variants, that include nested, microcystic, micropapillary, lymphoepithelioma-like, plasmacytoid, sarcomatoid, giant cell, undifferentiated, clear cell, and lipoid. Non-urothelial cancer only makes up about 5% of all BCA. The variants of non-urothelial include squamous cell carcinoma (SCC), adenocarcinoma (AC) and small cell carcinoma (SC).[10]

Urothelial carcinoma (UC)

The specific type of UC is determined through a combination of tests, which include imaging, biopsies and pathological analysis. The squamous type of UC can be distinguished by the presence of keratin inclusions and/or intercellular bodies as histological hallmarks of this variant, whereas the glandular type comprising 10% of UCs demonstrates gland formation on histology.[10] Both of these are seen to have a worse prognosis than conventional UC without squamous or glandular features.[11] BLC is known to enhance the identification of UC lesions, specifically flat neoplastic growths, carcinoma in situ (CIS), and papillary tumours, that are often missed by WLC.[12] The non-muscle invasive lesions of squamous type of UC are mostly diagnosed at a high grade and high stage, and are considerably less responsive to intravesical chemotherapy or Bacillus Calmette-Guérin (BCG) instillations..[10]

Pure squamous cell carcinoma (SCC)

SCC of the bladder arises from squamous cells and is often associated with chronic irritation or infection in the bladder, smoking, urinary tract infections (UTIs), and schistosomiasis. Histological markers for SCC include keratinising squamous metaplasia, squamous CIS, and verrucous squamous hyperplasia. Most SCCs present with advanced, muscle-invasive disease.[11]

Primary adenocarcinoma (AC)

Primary AC, which has a prevalence of 0.5-2%, is an incredibly uncommon BCA, which usually presents at an advanced stage, like a muscle-invasive or metastatic disease. This variant is commonly observed in females with bladder exstrophy and intestinal metaplasia as the probable risk factors, while Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (PIK3CA) and Kirsten rat sarcoma virus (KRAS) are the frequently mutated genes.[11]

Small cell carcinoma (SC)

SC of the bladder is extremely rare, accounting for <1% of all bladder tumours, but it is a very aggressive malignancy characterised by small rounded cells with scanty cytoplasm and hyperchromatic nuclei. It is associated with genetic alterations, including tumour protein p53 (TP53) mutations and retinoblastoma protein (RB1) loss.[11] The genetic changes in SC are similar to those found in small-cell lung cancer, which suggests a common molecular pathogenesis between the two.[13] SC is generally believed to have a high metastatic potential. It is more common in older adults, and has a higher incidence in males (male-to-female ratio 5:1).[10]

There is still uncertainty regarding the prognosis and treatment of different UC histological variants, while proper identification and reporting of the variants can enable tailoring the treatment protocol effectively.

Grading and staging

Grading and staging of tumour allow modification of treatment and management strategies, and for urothelial bladder tumours, the grading criteria derived from the World Health Organisation (WHO) are widely followed. Cytoskeletal structure and nuclear changes are used to grade the tumours. Lack of noticeable change in nuclear size, little loss of nuclear polarity, and slight variation in nuclear size are characteristics of low-grade cancers. High-grade tumours, on the other hand, are distinguished with pronounced cytological and nuclear changes, such as loss of polarity, presence of pleomorphic nuclei, and abundance of mitotic figures.[14] The WHO criterion was first devised in 1973 (Table 1), and was then modified in 2004 (Table 2).[15] Subsequently, European Association of Urology (EAU) guidelines for muscle-invasive and metastatic BCA also came into play.[16] The tumour staging is done as per the TNM classification rule. (Table 3)

Table-1: WHO 1973 urothelial cancer grading criteria

Grades	Histological view
1	Well-differentiated
2	Moderately differentiated
3	Poorly differentiated

WHO: World Health organisation.

Table-2: WHO 2004 urothelial cancer grading criteria

1.	Papillary urothelial neoplasm of low malignant potential
2.	Low grade papillary urothelial carcinoma
3.	High grade papillary urothelial carcinoma

WHO: World Health organisation.

Table-3: TNM Classification of urinary bladder cancer

T - Primary Tumour		
1.	Tx	Primary tumour cannot be assessed
2.	T0	No evidence of primary tumour
3.	Ta	Non-invasive papillary carcinoma
4.	Tis	Carcinoma in situ: "flat tumour"
5.	T1	Tumour invades subepithelial connective tissue
6.	T2	Tumour invades muscle
	T2a	Tumour invades superficial muscle (inner half)
	T2b	Tumour invades deep muscle (outer half)
7.	T3	Tumour invades perivesical tissue:
	T3a	Microscopically
	T3b	macroscopically (extravesical mass)
8.	T4	Tumour invades any of the following: prostate stroma, seminal vesicles, uterus, vagina, pelvic wall, abdominal wall
	T4a	Tumour invades prostate stroma, seminal vesicles, uterus, or vagina
	T4b	Tumour invades pelvic wall or abdominal wall
N - Regional Lymph Nodes		
1)	Nx	Regional lymph nodes cannot be assessed
2)	N0	No regional lymph node metastasis
3)	N1	Metastasis in a single lymph node in the true pelvis (hypogastric, obturator, external iliac, or presacral)
4)	N2	Metastasis in multiple regional lymph nodes in the true pelvis (hypogastric, obturator, external iliac, or presacral)
5)	N3	Metastasis in a common iliac lymph node(s)
M - Distant Metastasis		
M0		No distant metastasis
	M1a	Non-regional lymph nodes
	M1b	Other distant metastasis

TNM: Tumour-Nodes-Metastasis.

Presentation

The presentation of bladder cancer varies from clearly visible to considerably inconspicuous symptoms. Common presenting complaints include gross haematuria, voiding difficulties, painful and frequent micturition, weight-loss and generalised weakness. According to the recent guidelines, microscopic haematuria (>3 red blood cells [RBCs] on high-power field [HPF]) in the absence of symptoms or any non-malignant cause should be considered for further evaluation to rule out BCA.[3]

Diagnosis

The diagnosis of BCA begins with classifying the presenting complaints and associated risk factors into low, moderate or high-risk categories. For macroscopic or visible

haematuria, cystoscopy is the prime investigation, but in the case of asymptomatic microscopic haematuria, age, gender or other associated risk factors are considered, and the diagnostic protocol is decided according to the risk classification.[3] According to American Urologic Association (AUA) guidelines, patients at low risk should meet all of the following clauses; women <50yrs; men <40yrs, no smoking history or smoker with <10 packs per year, and 3-10 RBCs in one urinalysis test. For low-risk individuals, a repeat urinalysis in 6 months is the preferred route. If a repeat test supports the initial test, the person is then categorised under the intermediate risk category. In case of intermediate risk, cystoscopy and renal ultrasound are the prime investigations. For high-risk individuals, cystoscopy along with axial upper tract imaging is the main investigation, with axial upper tract imaging including computed tomography (CT) urogram and magnetic resonance imaging (MRI) urogram, and, in case of contraindications to the two investigation modalities, renal ultrasound and retrograde pyelogram are preferred.[3] WLC is a widely used technique for the initial evaluation of BCA, but the sensitivity of WLC for small papillary bladder tumour or CIS is considerably less. Recently, due to advancements in diagnostic procedures, the imaging modalities have been significantly modified with BLC and narrow-band imaging (NBI) to replace the WLC practice. Other modalities include optical coherence tomography, confocal laser endomicroscopy, and molecular imaging techniques.[17]

Blue Light Cystoscopy (BLC)

Out of the proposed procedures, BLC proves to be the most effective approach, allowing increased sensitivity to high-grade lesions and reducing the chances of missing detection of bladder tumour compared to WLC. BLC utilises the precursor molecule of heme, hexaminolevulinate, which enters the heme biosynthesis process in the urothelial system. The tumorous cells then accumulate protoporphyrin IX (PPIX) in their mitochondria, and these cells then reflect bright red rays when illuminated with blue light.[17] Various clinical trials demonstrate the supremacy of BLC over WLC in the visualisation of low-grade tumour and CIS. A study proposed that 30-44% of cases that underwent WLC and transurethral resection of bladder tumour (TURBT) revealed tumour remnants attributable to incomplete resection of tumour margins due to reduced capacity of tumour visualisation by WLC.[18] Hence, improved demarcation of tumour margins, as observed in BLC, would permit complete resection of the neoplastic growth along with implementation of efficiently devised treatment plans, thereby ameliorating the survival outcomes as well. A trial reported a significantly reduced recurrence rate associated with BLC (47%) compared to WLC (56%). Another trial on disease progression (extension of neoplastic growth into deeper tissues, such as muscles) demonstrated BLC to have a lower progression rate of 6.8% compared to WLC's 10.7% after a follow-up period of 28 months.[19] These results could be due to the provision of the appropriate treatment plan concerning adequate estimation of tumour margins. Considering the side effect profile, the results of a meta-analysis showed no significant difference between BLC and WLC.[20] Despite the approval of BLC by the Food and Drug Administration (FDA) in 2010, it is only incorporated in the management plan of BCA in the United States and Europe.[21] Even though the initial investment in BLC might be higher than WLC, the collective cost of BCA management is significantly less with BLC.[5] Therefore, BLC could be included in the diagnostic as well as the management protocol of BCA as it might play a significant part in lowering the mortality rate of BCA.

Narrow-Band Imaging (NBI) and SPIES

According to 2022 EAU guidelines, NBI and Storz Professional Image Enhancement System (SPIES) have also been approved as an effective diagnostic approach for bladder tumours. NBI relies on contrast enhancement in vascular tumours, allowing efficient detection of tumours, thereby diminishing chances of recurrences. SPIES, now known as IMAGE1 S, utilises automated processing of certain light filters to improve image visualisation and has also proven to be superior to WLC.[22] However, further research is needed to validate the efficacy of this modality.

Urinary Biomarkers

The incorporation of urinary biomarkers in the guidelines issued by EAU and the National Comprehensive Cancer Network (NCCN) as a tool for the initial assessment of bladder tumour and for monitoring high-risk tumour allows a cheaper, non-invasive method for BCA evaluation. The FDA-approved urinary biomarkers include nuclear matrix protein (NMP22) and UroVysion. However, a study reported significantly decreased sensitivity associated with this technique in picking BCAs.[23] Further clinical trials are needed to generate reliable results, and to devise BCA diagnostic protocol accordingly.

A firm diagnosis relies on the combination of cytology, cystoscopy and TURBT, especially in the case of low-grade tumours.[24]

Treatment

Treatment for non-infiltrating tumours often consists of TURBT plus intravesically administered therapies, such as BCG or chemotherapy, and infiltrating tumours are typically treated more aggressively.[25] The gold standard adjuvant

therapy for non-muscle invasive bladder cancer (NMIBC) with an intermediate or high risk of advancement is BCG immunotherapy. Cystectomy is considered in cases of tumours that are resistant to BCG, or in NMIBCs with a high risk of progression.[25]

Surveillance Cystoscopy

In older individuals, conservative management that includes active surveillance and fulguration is preferred.[26] Active surveillance involves rigorous follow-up with cystoscopy and cytology to detect recurrence at an early stage, and thereby avoid surgery. Due to the high rate of recurrence, patients with NMIBC often need monitoring office-based cystoscopies every 3-6 months. The introduction of BLC has led to better surveillance and prediction of the recurrence of bladder tumour.[27] A recent retrospective assessment, which included recurrence monitoring of patients who had received BCG therapy, proved BLC's superiority over WLC, as WLC surveillance had missed 13% of high-grade recurrences of which 88% were CIS.[28]

Chemotherapy

Chemotherapy involves giving drugs to stop or limit the growth of cancer cells. Most cases of low- to medium-risk, NMIBC are treated with intravesical chemotherapy, which employs the use of a catheter to administer drugs directly into the bladder via the urethra.[29] BCG activates the immune system in the bladder, which subsequently fights the neoplastic cells.[29]

For high-risk, invasive cancers, mostly systemic therapies are used, which commonly include doxorubicin, mitomycin C, epirubicin, thiotepa, gemcitabine and doxorubicin in NMIBC.[30] The first-line therapy for metastatic disease includes combinations of cisplatin, such as gemcitabine-cisplatin (GC) or methotrexate-vinblastine-doxorubicin-cisplatin (M-VAC), both of which have comparable efficacies.[31] Role of M-VAC as a second-line agent was significant in patients whose disease had advanced, following GC failure as they responded well to the M-VAC regimen.[31]

Monoclonal antibodies which have FDA approval for the treatment of BCA, target either nivolumab-pembrolizumab (PD1), or atezolizumab-durvalumab-avelumab (PDL1).[32]

Up to 20% of individuals with advanced urothelial carcinoma have fibroblast growth factor receptor (FGFR) mutations, and, therefore, erdafitinib, a potent tyrosine kinase inhibitor of FGFR, can be an effective therapy for advanced UCs with a response rate of 49%.[33]

An appealing strategy to enhance therapeutic impact is to combine intravesical chemotherapy with in-situ immunotherapy, which allows direct action on the neoplastic cells.

Surgical Approach

TURBT is a procedure done under general anaesthesia, which involves the insertion of a cystoscope into the urethra to view the bladder, and then using a surgical loop to resect the tumour. This is followed by intravesical chemotherapy using the cystoscope.[34]

BLC has evolved as a supplementary technique to WLC that may enhance the detection of missing lesions, with the possibility of a more thorough resection.[35]

Stenzyl et al. reported that after a 9-month follow-up, disease recurrence occurred in 47% of patients treated with BLC versus 56% of patients treated with WLC.[36] When using BLC, recurrence rates at 12 months and 24 months were lower compared to WLC in a 2021 meta-analysis of 12 randomised controlled trials (RCTs).[37]

Despite being a common procedure, TURBT has its shortcomings which include increased recurrences due to dispersion of tumour cells following resection, obscure resection margins, and reduced capability to certify detrusor muscle incorporation in the final histopathology sample.[38] However, en-bloc transurethral resection of bladder tumour (ETURBT) enables overcoming these limitations by using a blade or energy device to make a circumferential cut around the tumour and removing the underlying detrusor muscle thereby providing a reasonable alternative to TURBT for NMIBC.[38] ETURBT allows for more precise staging by conserving the three-dimensional (3D) structure of the tumour, and reduces tumour spillage by avoiding tumour fragmentation, unlike conventional TURBT.[38]

Most urologists agree that radical cystectomy is the gold standard procedure for treating muscle-invasive transitional-cell BCA. This procedure includes a cystectomy, which is frequently followed by a prostatectomy (in some individuals, a prostate-sparing approach is available), an anexohysterectomy, a lymphadenectomy, and a urinary diversion.[39] Ileal conduit, continent cutaneous reservoir, and orthotopic neobladder are the available choices for urine diversion. In an orthotopic neobladder, the ureters are joined to an intestine segment that is attached to the urethra. With this treatment, the ileal conduit and the continent cutaneous reservoir are not necessary, which prevents the need for an abdominal wall stoma.[39] For radical cystectomy, the robotic technique has demonstrated its viability and safety in comparison to the open approach.

Trimodality treatment (TURBT + radiation therapy + chemotherapy) has gained popularity in recent years. This is a bladder-preserving therapy for muscle-invasive bladder cancer (MIBC) in which after TURBT, the bladder, distal ureter and proximal urethra (including the prostate) are targeted with a dose of 55-64Gy provided for 4-6 weeks (2-2.75Gy/day), along with concomitant administration of 5-fluorouracil + mitomycin, gemcitabine, or cisplatin.[41]

Limitations

The current narrative review has limitations as it mostly included the latest articles favouring the use of BLC, which may have added to the bias. Since any particular medical subject heading (MeSh) terminology was not created to run the search, therefore some studies with relevant and valuable data from the meta-analyses might have been missed. Some other diagnostic modalities may also have similar outcomes as BLC, but due to scarcity of research work done on them, the current review mainly focussed on BLC only.

Conclusion

In the light of the literature, BLC and NBI can be viewed as advanced diagnostic modalities for non-invasive bladder tumour, considerably improving both diagnosis and treatment. BLC is anticipated to circumvent the obstacles observed in WLC by offering comprehensive visualisation of neoplastic demarcations because squamous type non-muscle invasive UCs are more frequently detected late, and are, therefore, linked with worse survival chances. However, despite the established mortality and survival benefits of BLC, it is practised only in a few regions. Revising BCA management guidelines globally according to the recent interventions, with the inclusion of new diagnostic tools, will allow urologists to revamp their cystoscopy setups. The provision of government funds and awareness amongst the urological institutes regarding BLC and NBI is likely to aid in early detection and prompt initiation of the treatment. Taking into consideration the rising trend observed by bladder tumours and the success rate of BLC in achieving early diagnosis as well as enabling better treatment outcomes, other countries, such as Pakistan, with well-developed urology institutes should consider implementing the use of this new modality in their practice. The increasing patient flow in Pakistan also calls for introducing better diagnostic modalities to efficiently deal with the rising cases. Many urology institutes in Pakistan are well developed, and, hence, capable of welcoming new techniques.

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