A Review on: Treatment, Diagnosis And Method of Detection For Bladder Cancer

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Abstract- *T Bladder Carcinoma (BC) is the most common neoplasm of the Urinary System. Bladder cancer is the fourth most commonly diagnosed malignancy in men and the eighthmost common in women. It represents a spectrum of disease, ranging from superficial, well differentiated disease, which does not significantly impact survival, to highly malignant tumoursfor which long term survival may be dismal. Transitional-cell carcinoma, which constitutes thevast majority of bladder cancers in the United States, may develop as carcinoma in situ or asinvasive carcinoma. Bladder cancer is a highly prevalent disease and is associated with substantial morbidity, mortality and cost. Environmental or occupational exposures to carcinogens, especially tobacco, are the main risk factors for bladder cancer. Most bladder cancers are diagnosed after patients present with macroscopic haematuria, and cases are confirmed after transurethral resection of bladder tumour (TURBT), which also serves as the first stage of treatment. Bladder cancer develops via two distinct pathways, giving rise to non-muscle-invasive papillary tumours and non-papillary (solid) muscle-invasive tumours. In metastatic disease, advances in our genetic understanding of bladder cancer and in immunotherapy are being translated into new therapies. This article focuses onthe majoraspects of the disease, including the epidemiology, diagnosis and staging, and management(including organ preservation). Therapeutic options are explored, including surgery, radiotherapy, chemotherapy, and combined modality therapy.*

Keywords- Bladder Cancer,Urothelial Carinoma, Transitional –Cell Carcinoma, TURBT.

I. INTRODUCTION

Bladder carcinoma (BC) is the most common neoplasm of the urinary system. Urothelial carcinoma (UC) is the most common histologic type of BC (approximately 90%). The definition of UC is the invasion of the basement membrane or lamina propria or deeper by neoplastic cells of urothelial origin. The WHO has replaced the old term transitional cell carcinoma with urothelial carcinoma. Invasion is referred to as 'micro invasion' when the depth of invasion is 2 mm or less. The World Health Organization (2016) classifies bladder cancers based on differentiation as low grade (grade 1 and 2) or high grade (grade 3). The distinction between low-grade and high-grade urothelial disease has implications related to risk stratification and management of patient. [1]

Etiology:

There are multiple known risk factors for BC. Important risk factors include smoking, schistosomiasis infection, and occupational exposure to certain chemicals.[2][3][4] Smoking is the most important risk factor for BC. The risk of BC in smokers is 2 to 6 fold that of non-smokers; the risk depends on smoking duration and intensity. In developing countries, schistosomiasis infection is an important cause of BC. Schistosoma haematobium ova embed in the bladder wall leading to irritation, chronic inflammation, squamous metaplasia, and dysplasia, with further progression leading to squamous cell carcinoma of the urinary bladder. Occupational exposure to paint, rubber, petroleum products, and dyes correlate to BC. Chemicals associated with BC include arylamine dye, aniline dye, phenacetin (an analgesic), cyclophosphamide (a cytostatic drug), and arsenic.[5][6][7][8]

Pathophysiology:

UC develops via two distinct pathways, the first relates to papillary lesions, and the second relates to flat lesions. Copy number alterations and genetic instability correlate with tumour progression and poorer prognosis. Low-grade papillary tumours usually arise from simple hyperplasia and/or minimal dysplasia and are characterized by loss of heterozygosity (LOH) of chromosome 9 and activating mutations of fibroblast growth factor receptor 3 (FGFR3), telomerase reverse transcriptase (TERT), phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform (PIK3CA) and inactivating mutations of STAG2. Low-grade papillary non-muscle-invasive BC can progress to muscle-invasive BC as a result of gaining CDKN2A loss. Muscle-invasive BC arises from flat dysplasia or carcinoma in situ (CIS); the lesions show TP53 mutations and LOH of chromosome 9. The invasive carcinoma can then further gain RB1 and PTEN loss along with other alterations acquiring metastatic potential. Overall, non-muscle-invasive BC usually

show diploid or near-diploid karyotypes and fewer copy number alterations compared to muscle-invasive BC. Muscle-invasive BC is usually aneuploid, with numerous chromosomal alterations.[2][9]

Symptoms: BC is a tumour of old adults (> 60 years):

- Microscopic hematuria
- Gross hematuria
- Infection or obstruction.
- Painful micturition
- Fatigue ,Weight loss and Pelvic mass

II. EVALUATION

Diagnostic modalities used in diagnosing BC include Imaging (ultrasound, intravenous urography (IVU), computed tomography (CT), and magnetic resonance imaging (MRI)), cystoscopy, and biopsy. Cystoscopy is considered the gold standard for the initial management of BC. All abnormal lesions, such as flat reddish lesions, papillary lesions, or solid lesions, requires biopsy and histological evaluation. The ideal urinary bladder biopsy should include muscularis propria to assess for invasion (T1: subepithelial connective tissue invasion; T2: muscularis propria invasion). Fortunately, most patients present with non-muscularis propria invasion, which shows a better prognosis than muscularis propria invasion. With rare exceptions, muscle-invasive (T2) urothelial cancer is high grade. Renal and bladder ultrasound may be useful during the initial workup of some suspected bladder cancer cases. Some cases will benefit from CT urography (or IVU). Cytology remains an important diagnostic tool and should be performed on fresh urine. Cytology is also valuable in the follow-up of patients.[10][11][12]

III. DIAGNOSIS

- The majority of bladder cancer cases are diagnosed when patients are discovered to have blood in their urine.
- Cystoscopy, a procedure in which a small camera is inserted into the bladder, is used to diagnose bladder cancer through visual inspection.

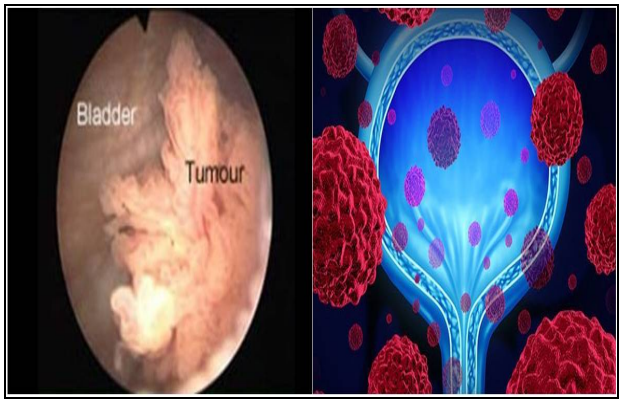

Figure 1. Bladder Cancer

- Biopsy of bladder cancer is performed as an outpatient procedure (in which the patient goes home the same day). The tumor can have many different appearances but often will appear as a lump of tissue that extends out from the interior bladder wall (as shown).
- The urologist removes the tumor from the bladder by scraping it out, with the intention of removing the entire tumor at one time. This tumor is sent to a pathologist who can determine the specific type of bladder cancer which then helps determine further treatment.
- CT scan (and in some cases MRI) are commonly used to evaluate whether bladder cancer has spread. This shows great detail of the kidneys as well as lymph nodes, lung, liver, and bones (organs in which bladder cancer may spread).
- A chest x-ray can show the spread of bladder cancer to the lungs and is often used for initial diagnosis and for follow-up appointments.
- Intravenous pyelograms, CT urograms, or retrograde pyelograms are procedures that are performed to determine whether cancer is present in the kidneys or kidney tubes (ureters).
- Bone scans and PET scans are x-rays that are only used in very specific situations.[13]

IV. TREATMENT

- Bladder cancer treatment is determined by how far the tumour extends into the bladder wall and the tumour type
- Bladder cancer is divided into superficial and invasive disease
- Treatment is determined based on whether the tumour is superficial or invasive, and whether it is low grade or high grade

- Below is a picture of how we determine the depth of tumour invasion into the bladder
    - Ta: Tumour only is within the superficial lining of the bladder wall
    - T1: Tumour is into the connective tissue layer (between the superficial lining and the muscle)
    - T2: Tumour extends into the muscle layer of the bladder
    - T3: Tumour extends into the fat layer of the bladder (beyond the muscle)
    - T4: Tumour extends into organs near the bladder (such as the prostate, vagina, or seminal vesicles)

Superficial Disease (Ta, T1):

- The majority of patients with superficial tumours (Stage Ta or T1) can be effectively treated with transurethral resection alone, especially those with Ta, low-grade tumours.
- Once treatment is complete, cystoscopies must be performed at varying intervals in the ensuing years since bladder cancer has a high rate of recurrence
- Further treatment is determined based on whether the tumour is considered low grade or high grade
    - Low-grade tumours may recur but are unlikely to spread
    - High-grade tumours may also recur, but also may spread
    - High-grade Ta or T1 tumours are likely to progress to "muscle invasive" (T2) disease and must be followed more closely than low-grade tumours
    - Additional therapies may include medication placed into the bladder
    - These medications include BCG, Mitomycin C, or Thiotepa, and are given to help prevent recurrences
    - BCG (Bacille Calmette-Guerin) is the most effective and commonly used form of intravesical therapy:
        - A standard course of BCG consists of 6 weekly installations.
        - Some patients will receive BCG for maintenance over the next 3 years
        - Because bladder cancers do have a high rate of recurrences, frequent surveillance cystoscopies in the ensuing months and years are required

Invasive Disease (T2, T3, T4):

- Invasive disease means that the bladder cancer has spread to the bladder muscle wall
- Treatment typically requires chemotherapy followed by surgery that removes the entire bladder (a radical cystectomy).
- A radical cystectomy should be considered a major surgery.
    - In males, the surgery involves removal of the bladder and typically the prostate as well.
    - In females, the surgery consists of removal of the bladder and often removal of the uterus, ovaries, fallopian tubes, and typically a portion of the vagina as well.
    - All patients must undergo a "urinary diversion" in which urine is diverted to a reservoir that is created from a piece of bowel.
- Urinary diversions include:

1. Urostomy or ideal conduit (external collecting bag in which urine freely flows into a bag without need for a catheter to drain it)
2. Catheterizable pouch (internal pouch made of intestines in which the patient uses a catheter to drain the reservoir)
3. Neobladder ("orthotopic diversion") (an internal pouch that is connected to the urethra in which patients can urinate, to offer more "normal" urinary function)

Image of transurethral resection of bladder cancer transurethral resection of the bladder cancer (TURBT) is performed as follows: after lumbar spine anaesthesia or general anaesthesia, a resection cystoscope is inserted through the urethra into the bladder without abdominal incision and non-muscle-invasive bladder cancer (cancer that has not invaded the muscle layer) is removed. The cancer is removed using a loop-shaped electric scalpel built into the cystoscope. Operation time is generally about one to two hours.

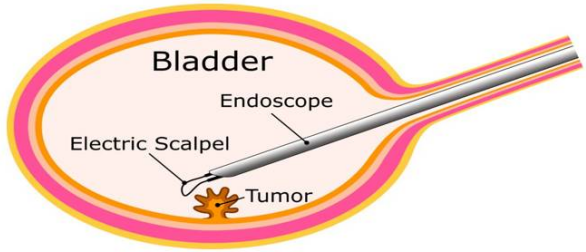

Figure 2. Treatment of Bladder Cancer

Endoscopic resection of bladder cancer, or TURBT, is a procedure whereby an endoscope is inserted through the urethra and the cancer is removed using a loop-shaped electric scalpel while observing the inside of the bladder (Fig. 2). Non-muscle-invasive bladder cancers frequently occur at multiple sites in the bladder. Small lesions spread around the papillary

carcinoma and the superficial flat cancers look normal and are hard to detect. The bladder can be preserved by TURBT, but some non-muscle-invasive bladder cancers are highly malignant, have a high rate of recurrence, and advance to more serious stages. The main cause of recurrence is considered to be the fact that small or flat cancers might not be detected by ordinary endoscopy and are easily overlooked. In order to reduce the risk of recurrence, it is important to improve the quality of TURBT so that cancers that are difficult to observe by appearance can be reliably detected, and residual cancer reduced (edited by the Japanese Urological Society Bladder Cancer Clinical Practice Guidelines 2019). After resection of the bladder cancer, a pathological diagnosis is performed to determine the degree of malignancy and the depth of the cancer lesion. When the pathological diagnosis indicates a high risk of recurrence, chemotherapeutic agents or attenuated Mycobacterium tuberculosis (BCG) may be injected into the bladder. BCG is a vaccine against tuberculosis and is considered to boost the immune response and act on cancer cells. Also, in consideration of the risk of recurrence, a cystoscopy must be performed regularly after surgery (three months after initial treatment, followed by at intervals according to the risk). If cancer returns, additional TURBT will be performed, and the cancer may progress gradually over the course of recurrence. After recurrence, if the cancer reaches its worst stage, the bladder may have to be removed.[14]

Detection of Bladder Cancer:

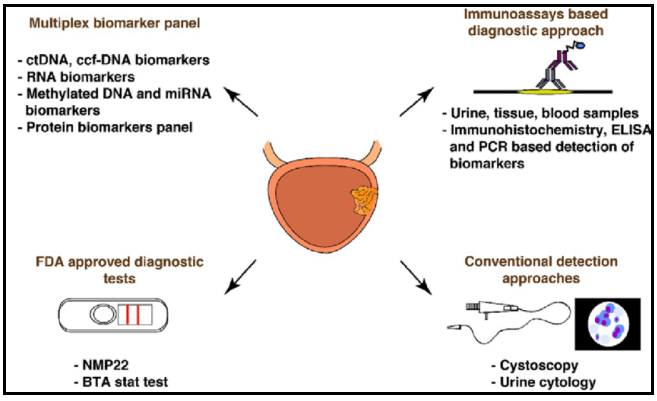

Figure 3: Current Approach for Early Detection of Bladder Cancer

Urinary Biomarker Panels for Bladder Carcinoma:

A widespread approach based on multiplex biomarker panel offers accurate and sensitive detection and diagnosis of bladder cancer patients. In a study by Kumar et al., a robust set of urine biomarkers for bladder cancer detection was identified. The study employed mass spectrometry-based quantitative proteomics approach to identify a panel of potential biomarkers: Coronin-1A, Apolipoprotein A4, Semenogelin-2, Gamma synuclein and DJ-1/PARK7. A multi-analyte assay was established for both non-muscle invasive (Ta/T1) and muscle invasive (T2/T3) bladder cancer detection in urine using MS-based stable isotope labelling approach for the biomarkers discovery. These biomarkers panels were validated in a large cohort of urine samples from 66 healthy subjects, 110 NMIBC (Ta/T1) patients and 63 MIBC (T2/T3) patients using RT-PCR, western blot and ELISA. In the western blot based validation, all the bladder carcinoma patients displayed elevated expression of at least three out of the five biomarkers. This panel achieved an AUC 0.92 and 0.98 respectively using ELISA and western blot data (79.2% and 93.9% sensitivity; 100% and 96.7% specificity). This panel also involves the potential for follow-up of patients and screening asymptomatic subject at high-risk of developing bladder carcinoma. Moreover, these five biomarkers are also able to differentiate between bladder carcinoma patients and patients with different benign conditions such as; inflammation of the bladder, benign prostrate hyperplasia or nephrolithiasis perhaps associated with haematuria [15].

V. CONCLUSION

Bladder cancer includes a broad spectrum of diseases. The majority of cases are superficial diseases that may have little impact on patient survival.Management of these tumors consists of endoscopic resection and continued surveillance to ensure that progression does not occur, or is detected early if itdoes occur. Escalating the understanding of the proteomic landscape of bladder carcinoma anticipates the discoveries of new proteomic biomarkers for bladder cancer detection and surveillance. Additionally, it has improved the usefulness and accuracy of diagnostic and prognostic significance in the prediction of cancer progression. Radical cystectomy remains the "gold standard" for those with muscle invasive disease. However, select patients may benefit from therapy designed for bladder preservation. This involves the use of aggressive TURBT combined with other treatment modalities, including radiation therapy and chemotherapy. Patients must be carefully selected and managed with input from a radiation oncologist, a medical oncologist, and a urologic oncologist. Metastatic bladder cancer is a highly lethal disease with limited two-year survival.Most therapy for this patient population should be managed with a palliative goal. All patients with good performance status should be considered for clinical trial participation.

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