

## Lecture- 3

### Objectives:

1. To know the common benign bladder tumors.
2. To know the epidemiology and types of malignant tumors.
3. To know the etiology, presentations, pathology, diagnosis and treatment of malignant tumors.
4. To know the types and management of bladder injuries.

## Bladder tumours

### Benign tumour of the bladder

There are numerous benign tumors of the bladder, but the more common ones include papilloma, epithelial metaplasia, leukoplakia, inverted papilloma, nephrogenic adenoma, leiomyoma, cystitis cystica, and cystitis glandularis

### Malignant bladder tumour

#### Epidemiology

- It is the second most common urological cancer in USA and 1<sup>st</sup> in Iraq. It is the 4<sup>th</sup> common cancer after bronchogenic, prostatic and colonic cancer in men and 8<sup>th</sup> common cancer in women
- Because urothelial cancer is a cancer of the environment and age, the incidence and prevalence rates increase with age, peaking in the 8th decade of life, and there is a strong association between environmental toxins and urothelial cancer formation. Bladder cancer is 3 times more common in men than in women.
- At the time of diagnosis 85% are localized to the bladder and 15 % are spread to the regional lymph node or distant areas.

#### Types:

**I- Primary tumour:** 98% are epithelial and 2% are nonepithelial.

#### A. Epithelial tumour:

**1. Transitional cell carcinoma:** (90%) it is either

- **Papillary (Cauliflower):** exophytic, not sessile tumour, grow into the lumen of bladder, single or multiple not invasive, mostly at trigone and lateral wall, have narrow stalk.
- **Invasive type:** it is solid disc shape (bun) large irregular sessile with broad base (sometime ulcerate), it is invasive with high incidence of metastasis.
- **Carcinoma insitu (cis):** 5%, it is flat nonpapillary anaplasia, it is considered an early invasive tumour, because it progress very quickly, the tumour is with in the mucosa, flat, velvet.

**2. Squamous cell carcinoma:** (5-10%), it is solid nodular, invasive at diagnosis, it is due to

- Chronic infection ( Bilharziasis)
- Stone
- Chronic catheterization
- Foreign body .....etc.

**3. Adenocarcinoma:** < 2% of all bladder tumour. It is localized at the time of diagnosis but muscular invasion may be seen.

It is either

- Acquired: lie at the base of bladder
- Congenital: arises at the fundus near the site of urachus.

It is preceded by cystitis glandularis or metaplasia.

**4. Undifferentiated carcinoma:** < 2%

**5. Mixed carcinoma:** 4-6%

## Lecture- 3

### 6. Other rare epithelial tumour:

- Villous adenoma - Carcinoid tumour - Carcinosarcoma
- Melanoma

### B. Non-epithelial tumours:

- Pheochromocytoma
- Choriocarcinoma
- Lymphoma
- Hemangioma
- Lymphoma
- Mesenchymal tumours:
  - Osteogenic sarcoma
  - Myosarcoma

### II- Secondary tumours:

- **Direct invasion** from the prostate, cervix and rectum
- **Hematogenous metastasis** from malignant melanoma, lymphoma, stomach, lung, kidney and breast.

### Etiology and risk factors:

1. **Cigarette smoking:** is the cause in 50% of men and 31% of women , the causative agents are thought to be due to alpha and beta-naphthylamine which are secreted in the urine of smokers.
2. **Occupational exposure to carcinogens,** in particular aromatic hydrocarbons like aniline. Occupations associated with transitional cell carcinoma: Rubber manufacture, dye manufacture, fine chemical manufacture, painters, plumbers, leather worker, hair dressers .....etc.  
A latent period of 25-45 years exists between exposure and carcinogenesis.
3. **Chronic inflammation of bladder mucosa:** stone, long-term catheters and schistosomiasis are implicated in the development of squamous cell carcinoma.
4. **Drugs:** Cyclophosphamide, phenacetin, saccharine and caffeine.
5. **Pelvic radiotherapy.**
6. **Environmental carcinogens**
7. **Age increases the risk.**
8. **Race:** black people have lower incidence than white people, but they appear to carry a poorer prognosis.
9. **Genetic factors:** Loss or inactivation of tumour suppressor genes, these genes regulate cell proliferation and prevent tumour formation. If these genes are lost or deleted, the tumour will develop.
  - a. Loss of genetic material on long arm of chromosome 9 found in all tumour grade.
  - b. Deletion of genetic material on short arm of chromosome 11& 17 is more common in high grade tumours
  - c. Increase expression of c-Ha-ras oncogen P2, noted in high grade tumour.
  - d. Mutation of P53; commonly occurs in colon and bladder cancers.

### Pathology:

**Tumour grading:** WHO-ISUP system of grading:

- 1- PUNLMP: papillary urothelial neoplasm of low malignant potential= Grade I
- 2- Low grade= Grade II
- 3- High grade= Grade III.

### Tumour spread:

- 1- **Direct invasion** to involve the detrusor, ureteric orifices, prostate, urethra, uterus, vagina, perivesical fat, bowel, or pelvic sidewall.

## Lecture- 3

- 2- **Implantation** into wound or percutaneous catheter tracts.
- 3- **Lymphatic infiltration** of the iliac and paraaortic nodes.
- 4- **Hematogenous**, most commonly to the liver(38%), lung(36%), adrenal gland (21%) and bone (27%), any other organ may be involved.

### Staging

- 1- **Marschall modified the Jewett and strong**(1946) staging system.
- 2- **The union international centre le cancer(UICC)** recommended a TNM staging system.

**Clinical stage:** based on physical examination and imaging.

**Pathological stage:** based on removal of the bladder and regional lymph nodes.

### Primary Tumor (T)

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

### Regional Lymph Nodes (N)

Regional lymph nodes include both primary and secondary drainage regions. All other nodes above the aortic bifurcation are considered distant lymph nodes.

<b>NX</b>	Lymph nodes cannot be assessed
<b>N0</b>	No lymph node metastasis
<b>N1</b>	Single regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node)
<b>N2</b>	Multiple regional lymph node metastasis in the true pelvis (hypogastric, obturator, external iliac, or presacral lymph node metastasis)
<b>N3</b>	Lymph node metastasis to the common iliac lymph nodes

### Distant Metastasis (M)

<b>M0</b>	No distant metastasis
<b>M1</b>	Distant metastasis

## Diagnosis

### Clinical features:

#### A. Symptoms:

- **Hematuria:** is the most common presentation ~ 90% which is painless, intermittent, frank and total.
- **Irritative symptoms:** Frequency, urgency, dysuria, mostly occur with carcinoma insitu.
- **Symptoms of metastasis:** bone pain, flank pain due to retroperitoneal metastasis or ureteric obstruction.
- **Anemia.**

## Lecture- 3

- Retention due to bladder outlet obstruction.

**B. Signs:** Hepatomegally, supraclavicular lymph nodes, lymphedema due to obstruction to the pelvic lymph nodes.

**Bimanual examination or examination under anesthesia(EUA).**

**T<sub>1</sub>:** not palpable.

**T<sub>2</sub>:** Palpable as thickening of bladder wall.

**T<sub>3</sub>:** Palpable mobile mass

**T<sub>4</sub>:** Palpable fixed mass.

### Investigations:

The most common laboratory abnormality is hematuria.

**1. Urinalysis:** hematuria, pyuria( due to concomitant UTI)

**2. CBP:** Anemia due to chronic blood loss or replacement of bone marrow with metastatic disease.

**3. Urine cytology:** it is identification of exfoliated cell from both normal and neoplastic urothelium from voided urine, also can be achieved by irrigation of the bladder with isotonic saline solution through catheter or cystoscopy.

**The importance of cytology examination:**

- **Detection of** cancer in symptomatic patients
- **Assessing** response to treatment.
- **Follow up**
- **Screen high risk population**

Detection rates are high for tumors of high grade and stage as well as CIS but not as impressive for low grade superficial tumors.

**4. Renal function test:** Azotemia may be noted in patients with ureteral occlusion owing to the primary bladder tumor or lymphadenopathy.

**5. Tumour markers:** Several new tests have been developed in order to overcome the shortcomings of urinary cytology such as the low sensitivity for low-grade superficial tumors and inter-observer variability. Commercially available tests include,

- the BTA test
- the BTA stat test
- the BTA TRAK assay
- determination of urinary nuclear matrix protein (NMP22)
- Immunocyt
- Telomerase
- Lewis x-Ag
- **Flow Cytometry:** measures the DNA content of cells whose nuclei have been stained with a DNA-binding fluorescent dye. Therefore, it can quantitate the aneuploid cell populations and the proliferative activity (percentage of S phase cells) in a tumor. It can detect 80% of bladder cancer.
- Hyaluronic acid.
- Hyaluronidase
- BICA-4
- Cytokeratin 20

These tests can detect cancer specific proteins in urine (BTA/NMP22) or augment cytology by identifying cell surface or cytogenetic markers in the nucleus.

**6. IMAGING:** used to:

- evaluate the upper urinary tract and, when infiltrating bladder tumors are detected,
- assess the depth of muscle wall infiltration and
- detect the presence of regional or distant metastases.

**a. Intravenous urography(IVU) (excretory urography):** Bladder tumors may be recognized as pedunculated, radiolucent filling defects projecting into the lumen nonpapillary, infiltrating tumors

## Lecture- 3

may result in fixation or flattening of the bladder wall. Hydronephrosis from ureteral obstruction is usually associated with deeply infiltrating lesions and poor outcome after treatment

**b. Ultrasonography (abdominal & endovesical):** recognize echogenic foci projecting into the lumen, detect bladder tumour and upper tract abnormalities.

**c. Both CT and magnetic resonance imaging (MRI)** have been used to characterize the extent of bladder wall invasion and detect enlarged pelvic lymph nodes, with overall staging accuracy ranging from 40% to 85% for CT and from 50% to 90% for MRI.

**d. Chest x-ray:** to detect metastasis to the lung.

**e. Radionuclide bone scan:** Bone scans can be avoided if the serum alkaline phosphatase is normal.

### 7. **CYSTOURETHROSCOPY & transurethral resection (TURBT):** Used for

- The diagnosis
- initial staging of bladder cancer
- Complete excision of low grade tumour.

**Fluorescence Cystoscopy:** Photoactive porphyrins accumulate preferentially in neoplastic tissue. Under blue light they emit red fluorescence, which can help in the diagnosis of indiscernible malignant lesions. Intravesical application of 5-aminolevulinic acid (5-ALA), a precursor of photoactive porphyrin, or more lipophilic ester, hexaminolevulinate (HAL), are used.

## **Treatment: Should be tailored to the stage of tumour**

**A. Intravesical Chemotherapy and Immunotherapy:** instilled into the bladder directly via catheter, thereby avoiding the morbidity of systemic administration in most cases. Intravesical therapy can have a prophylactic or therapeutic effect.

It may be delivered in 3 different fashions

**Adjunctive :** At TUR to prevent implantation

**Prophylactic:** After complete TUR to prevent or delay recurrence or progression

**Therapeutic:** After incomplete TUR to cure residual disease

**1. Mitomycin C**—Mitomycin C is an antitumor, antibiotic, alkylating agent that inhibits DNA synthesis. With a molecular weight of 329, systemic absorption is minimal. Side effects are noted in 10–43% and consist of irritative voiding symptoms including urinary frequency, urgency, and dysuria. Unique to this drug is rash on the palms and genitalia in approximately 6% of patients, but this effect can be alleviated by washing the hands and genitalia at the time of voiding after intravesical administration.

**2. Thiotepa**—Thiotepa is an alkylating agent with a molecular weight of 189.

Cystitis is not uncommon after instillation but is usually mild and selflimited.

Myelosuppression manifested as leukopenia and thrombocytopenia occurs in up to 9% of patients owing to systemic absorption.

**3. Doxorubicin:** is a 580-kD anthracycline antibiotic . Side effects: cystitis & myelosuppression.

**4. BCG (Bacillus Calmette-Guérin)** —BCG is an attenuated strain of *Mycobacterium bovis*. Many different strains of BCG exist. The exact mechanism by which BCG exerts its antitumor effect is unknown, but it seems to be immunologically mediated. It appears to be the most efficacious intravesical agent for the management of CIS. BCG has been shown to be superior to intravesical

## Lecture- 3

chemotherapy in preventing recurrence in patients with high-risk superficial bladder cancer. Side effects:

- urinary frequency and urgency.
- Hemorrhagic cystitis occurs in approximately 7% of patients
- evidence of distant infection is found in <2%.
- BCG sepsis (eg, high fever, chills, confusion, hypotension, respiratory failure, jaundice) should be treated with isoniazid, rifampin, and ethambutol. The addition of cycloserine or prednisolone (40 mg daily) increases survival rates.

**Note :** Intravesical chemotherapy decrease recurrence of tumour while immunotherapy decrease both recurrence and progression.

### 5. $\alpha$ interferon.

### 6. Intravesical gemcitabine

### 7. Keyhole-limpet hemocyanin (KLH)

8. Bropiramine is an oral arylpyridinone that is excreted in urine.

## B. Surgery

1. **TUR:** TUR is the initial form of treatment for all bladder cancers.

- It allows a reasonably accurate estimate of tumor stage and grade.
- Used for patients with single, low-grade, non-muscle-invasive tumors.

**Follow up:** Careful follow-up of patients with non-muscle-invasive bladder cancers is mandatory because disease will recur in 30–80% of patients, depending on cancer grade, tumor stage, and number of tumors. Repeat cystoscopy and urine cytology testing are recommended for surveillance

### 2. Laser Therapy

- Laser coagulation allows minimally invasive ablation of tumors up to 2.5 cm in size.
- The neodymium : yttrium-aluminum-garnet (Nd : YAG) laser has the best properties for use in bladder cancer.

3. **Partial cystectomy**— For

- patients with solitary, infiltrating tumors (T1–T3) localized along the posterior lateral wall or dome of the bladder
- patients with cancers in a diverticulum.

**To minimize tumor implantation** resulting from contamination of the wound with cancer cells at the time of surgery,

- short-course, limited- dose (1000–1600 cGy) irradiation can be used, and
- an intravesical chemotherapeutic agent can be instilled preoperatively

4. **Radical cystectomy**— This remains the “**gold standard**” of treatment for patients with muscle-invasive bladder cancer.

Radical cystectomy implies removal of the anterior pelvic organs:

in men, the bladder with its surrounding fat and peritoneal attachments, the prostate, and the seminal vesicles;

in women, the bladder and surrounding fat and peritoneal attachments, cervix, uterus, anterior vaginal vault, urethra, and ovaries.

A bilateral pelvic lymph node dissection and urinary diversion are usually performed simultaneously with radical cystectomy. Lymph node metastases are identified in approximately 20–35% of patients

### 5. Radiotherapy:

External beam irradiation (5000–7000 cGy), delivered in fractions over a 5- to 8-week period, is an alternative to radical cystectomy in well-selected patients with deeply infiltrating bladder cancers. radiation as monotherapy is usually offered only to those patients who are poor surgical candidates due to advanced age or significant comorbid medical problems.

### 6. Systemic Chemotherapy: for metastatic disease.

Approximately 15% of patients who present with bladder cancer are found to have regional or distant metastases; approximately 30–40% of patients with invasive disease develop distant metastases despite radical cystectomy or definitive radiotherapy.

**Lecture- 3**

The regimen of methotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (MVAC) has been the most commonly used for patients with advanced bladder cancer

Other newer agents demonstrating activity in this disease include ifosfamide, gemcitabine, paclitaxel, and gallium nitrate

**7. COMBINATION THERAPY**

Chemotherapy and radical cystectomy.

Chemotherapy and radiotherapy.

**8. Radical TUR alone** may be a viable option in select patients with T2 disease particularly if no tumor is found on repeat resection since 10-year survival rates as high as 83% can be achieved

**Initial Treatment Options for Bladder Cancers.**

Cancer Stage	Initial Treatment Options
Tis	Complete TUR followed by intravesical BCG
Ta (single, low-to-moderate grade, not recurrent)	Complete TUR
Ta (large, multiple, highgrade, or recurrent)	Complete TUR followed by intravesical chemo- or immunotherapy
T1	Complete TUR followed by intravesical chemo- or immunotherapy
T2–T4	Radical cystectomy Neoadjuvant chemotherapy followed by radical cystectomy Radical cystectomy followed by adjuvant chemotherapy Neoadjuvant chemotherapy followed by concomitant chemotherapy and irradiation
Any T, N+, M+	Systemic chemotherapy followed by selective surgery or irradiation

**Prognosis:**

15% of bladder cancer have regional or distant metastasis at the time of diagnosis, 30-40% of invasive tumour develop distant metastasis despite radical cystectomy or definitive therapy.

**INJURIES TO THE BLADDER**

**Causes:**

- External force (blunt trauma):** are often associated with pelvic fractures. (5% to 10% all pelvic fractures are associated with concomitant bladder) **The most common associated injury is pelvic fracture, which is associated with 83% to 95% of bladder injuries**
- Penetrating trauma,**
- Iatrogenic surgical complications**
- Spontaneous rupture** in patients with a history of neuropathic disease, pre-existing bladder disease, or prior urologic surgery.

**Types:**

- Extraperitoneal bladder injury:** is usually associated with pelvic fracture.
- Intraperitoneal injuries:** can be associated with pelvic fracture but are more commonly due to penetrating injuries or burst injuries at the dome by direct blow to a full bladder.

## Lecture- 3

### Clinical Findings

Pelvic fracture accompanies bladder rupture in 90% of cases. The diagnosis of pelvic fracture can be made initially in the emergency room by lateral compression on the bony pelvis, since the fracture site will show crepitus and be painful to the touch.

#### A. SYMPTOMS

There is usually a history of lower abdominal trauma. Blunt injury is the usual cause. Patients ordinarily are unable to urinate, but when spontaneous voiding occurs, gross hematuria is usually present. Most patients complain of pelvic or lower abdominal pain.

#### B. SIGNS

Heavy bleeding associated with pelvic fracture may result in hemorrhagic shock, usually from venous disruption of pelvic vessels. Evidence of external injury from a gunshot or stab wound in the lower abdomen should make one suspect bladder injury, manifested by marked tenderness of the suprapubic area and lower abdomen. An acute abdomen may occur with intraperitoneal bladder rupture. On rectal examination, landmarks may be indistinct because of a large pelvic hematoma

### Investigation

#### 1- Laboratory Finding

Catheterization usually is required in patients with pelvic trauma but not if bloody urethral discharge is noted. Bloody urethral discharge indicates urethral injury, and a urethrogram is necessary before catheterization. When catheterization is done, gross or, less commonly, microscopic hematuria is usually present. Urine taken from the bladder at the initial catheterization should be cultured to determine whether infection is present.

2- **A plain abdominal film** generally demonstrates pelvic fractures. There may be haziness over the lower abdomen from blood and urine extravasation.

3- **IVU or A CT scan** should be obtained to establish whether kidney and ureteral injuries are present.

4- **Cystography:** Bladder disruption is shown. The bladder should be filled with 300 mL of contrast material and a plain film of the lower abdomen obtained. Contrast medium should be allowed to drain out completely, and a second film of the abdomen should be obtained. The drainage film is extremely important, because it demonstrates areas of extraperitoneal extravasation of blood.

- **A dense, flame-shaped collection of contrast material in the pelvis is characteristic of extraperitoneal extravasation.**
- **Intraperitoneal extravasation is identified when contrast material outlines loops of bowel and/or the lower lateral portion of the peritoneal cavity.**

5- **CT-cystography** is an excellent method for detecting bladder rupture.

6- **Urethrogram:** if there is blood at the urethral meatus (suspected urethral injury).

### Complications

- 1- A pelvic abscess may develop from extraperitoneal bladder Rupture
- 2- delayed peritonitis.
- 3- Partial incontinence may result from bladder injury when the laceration extends into the bladder neck.
- 4- Nephrogenic adenoma
- 5- Vesicovaginal fistula.

### Treatment

#### A. EMERGENCY MEASURES

Shock and hemorrhage should be treated.

#### B. SURGICAL MEASURES



## Lecture- 3

### Indications for Immediate Repair of Bladder Injury

1. Intraperitoneal injury from external trauma
2. Penetrating or iatrogenic nonurologic injury
3. Inadequate bladder drainage or clots in urine
4. Bladder neck injury
5. Rectal or vaginal injury
6. Open pelvic fracture
7. Pelvic fracture requiring open reduction and internal fixation
8. Selected stable patients undergoing laparotomy for other reasons
9. Bone fragments projecting into bladder

**1. Extraperitoneal bladder rupture**—Extraperitoneal bladder rupture can be successfully managed with urethral catheter drainage only. (Typically 10 days will provide adequate healing time.)

**2. Intraperitoneal rupture**—Intraperitoneal bladder ruptures should be repaired via a transperitoneal approach after careful transvesical inspection and closure of any other perforations.

**3. Pelvic fracture**—Stable fracture of the pubic rami –the patient is ambulatory within 4–5 days without damage or difficulty.

Unstable pelvic fractures ---- external fixation

**4. Pelvic hematoma**—

packing the pelvis often controls the problem.

Embolization of pelvic vessels with Gelfoam or skeletal muscle under angiographic control is useful in controlling persistent pelvic bleeding.

### Prognosis

With appropriate treatment, the prognosis is excellent.