STANDARD TREATMENT GUIDELINES
UROLOGY

Ministry of Health & Family Welfare
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Contents

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HAEMATURIA

Introduction:-

Hematuria is the presence of red-blood cells (RBC) in urine.

- It may be categorized as gross (visible to naked eye) or microscopic (detected in urine microscopy). The recommended definition of microscopic hematuria is three or more red blood cells per high-power field on microscopic evaluation of urinary sediment from two of three properly collected urinalysis specimens.
- It may arise from any part of the urinary tract, from glomerulus to meatal tip and may be characterized as initial, terminal or total, which points to the approximate site of origin (distal to external sphincter, proximal urethra-bladder neck, and bladder and upper tracts, respectively).
- Severity of hematuria bears no relation with the etiology, therefore, its presence must be considered serious unless proven otherwise.

Prevalence:-

The prevalence of asymptomatic microscopic hematuria varies from 0.19 percent to as high as 21 percent any varies widely with different age groups.

Differential diagnosis

Hematuria is a manifestation of a myriad of varied clinical diagnoses ranging from exercise-induced to cancer-related. The differential diagnosis can be classified on the basis of site of origin as shown below:

Origin	Etiologies
Glomerular	Acute glomerulonephritis, lupus nephritis, benign familial hematuria, Bergerôs disease, Goodpastureôs disease, exercise hematuria.
Renal	Polycystic kidney disease, Medullary sponge kidney, papillary necrosis, renal infarct, lymphoma, multiple myeloma, amyloidosis, inflammation and infections, vascular malformation
Urologic	Neoplasia, calculi, benign Prostatic hyperplasia, urethral stricture, endometriosis, diverticulitis, infection, foreign body, GUTB
Adjacent organ	Abdominal aortic aneurysm, appendicitis, infiltrating malignancy
Hematologic	Congenital and acquired coagulopathy, therapeutic anticoagulation, sickle-cell disease and trait, sickle-cell thalassaemia, sickle-cell Hemoglobin-C disease
Fictitious	Vaginal bleed
False hematuria	Food pigments, drug metabolites, malingering

Diagnosis and evaluation:
Once a patient presents with history of hematuria, first step is detailed history and clinical examination.

1. History should include nature of hematuria whether intermittent / continuous, total / initial / terminal, or episodic.

2. Associated symptoms

3. passage of stones, tissues, clots; shape of clots (tubular, small).

4. Lower urinary tract symptoms (poor stream, frequency, urgency, nocturia, incontinence, dysuria, etc.

5. Pain, location (flank, groin, suprapubic, other), nature and other characteristics.

6. History of fever, facial puffiness, pedal edema.

7. Medications (e.g. oral contraceptives, analgesics, anticoagulants, others)

8. Co-morbidity like tuberculosis, diabetes mellitus, hypertension,

9. Coagulation disorders and family history of renal disease.

10. General physical examination and a focused examination pertaining to genitourinary system.

Next step is to perform a urine microscopy to confirm presence of RBCs and to rule out other causes of red brown colour in urine;
Dipstick tests commonly available will be positive in presence of RBCs, hemoglobin or myoglobin, therefore not specific for hematuria. Therefore, a positive dipstick must be followed by a microscopy.

Urine analysis:

- Ideally the sample is collected in the lab. rather than brought from home (a urine sample not freshly voided or collected from drainage bag is unreliable for analysis).

- For male and female adults, clean catch mid-stream urine sample should be evaluated. In female the technique is similar but requires more attention as chances of contamination are much higher.

- In children the method is similar for those who can be made to follow the instructions. Otherwise, after cleansing, a sterile plastic bag is placed over penis / vulva. In case the specimen is not satisfactory, suprapubic aspiration may be done (easy in small children because intra-abdominal location of bladder).

One aliquot of the sample is subjected to routine examination (color, transparency, specific gravity, chemical analysis for pH, protein, etc.).
Ten milliliters of the second aliquot of urine is centrifuged at 2000rpm for 5min, and supernatant is discarded.
The sediment is re-suspended, a drop of which is examined under microscope for cells, crystals and casts.
RBCs are easily visible in X400 power. Microhematuria is diagnosed in presence of more than 3 RBCs per high power field in adults and 5 or more in children and in trauma cases. The morphology of RBC as well as presence of RBC clumps and casts should be seen. Phase contrast microscopy is the best way to detect dysmorphic RBCs. Dysmorphic RBCs are suggestive of a renal or glomerular source of hematuria.
Hematuria must be interpreted as part of complete urine analysis, as presence of other anomalies e.g. proteins, casts, crystals and pus cells, etc. may suggest towards diagnosis.
After confirmation of erythrocytouria, the next logical step is to differentiate between:

- Glomerular hematuria (presence of dysmorphic RBC, and RBC casts and clumps and usually associated with proteinuria).

- Nonglomerular hematuria - an ultrasonography of abdomen is the next step to detect any anatomical abnormality in the urinary tract (e.g. stones, renal cysts, renal mass, bladder tumor, prostatomegaly, hydronephrosis, etc.).

- For those with history suggestive of infection and associated pyuria, a urine culture and sensitivity should be done to rule out infection,

- Complete blood count, renal functions, blood sugar and coagulogram (if appropriate), must be done to rule out other causes and as a part of workup for surgery if an abnormality is detected on ultrasonography.

In absence of features of glomerular hematuria, urinary tract infection and USG evidence of renal mass, most patients would require cystourethroscopy. Certain investigations are suggested, before proceeding for the same-

1. Urine cytology for malignancy
2. Urine for AFB
3. Intravenous urography / CT urography.

Management:

After complete evaluation approximately overall, 1/3rd will have origin in kidney and the rest in middle and lower urinary tract.

a. Further management needed in,
   b. 25% with urinary tract infection
   c. 20% will be diagnosed as malignancy (bladder cancer, kidney cancer),
   d. 20% with urinary stone disease.
   e. Rest 15% other causes

f. 20% are diagnosed as benign essential hematuria (of obscure origin) and these require careful follow up.

Treatment is guided by the underlying cause of hematuria.

As general practitioners are the frequently the first contact clinicians, they should perform the initial workup (urine analysis, urine culture, ultrasonography) and based on the presentation and these investigation. Uncomplicated UTIs may be managed at the community level. Others should be referred to appropriate specialist (nephrologists, urologist).

Those with glomerular cause of hematuria (fever , facial puffiness, pedal edema, hypertension and presence of dysmorphic RBCs on microscopy) require a nephrology referral for further diagnosis and management.

Those patients diagnosed with a malignancy/renal stone as the cause, need appropriate urology referral to a higher center for further evaluation and management.

Resources required

1. Facility for routine and microscopy of the urine.
2. Ultrasonography.
3. Microbiological services.
4. Radiological services (preferably with facility of computed tomography).

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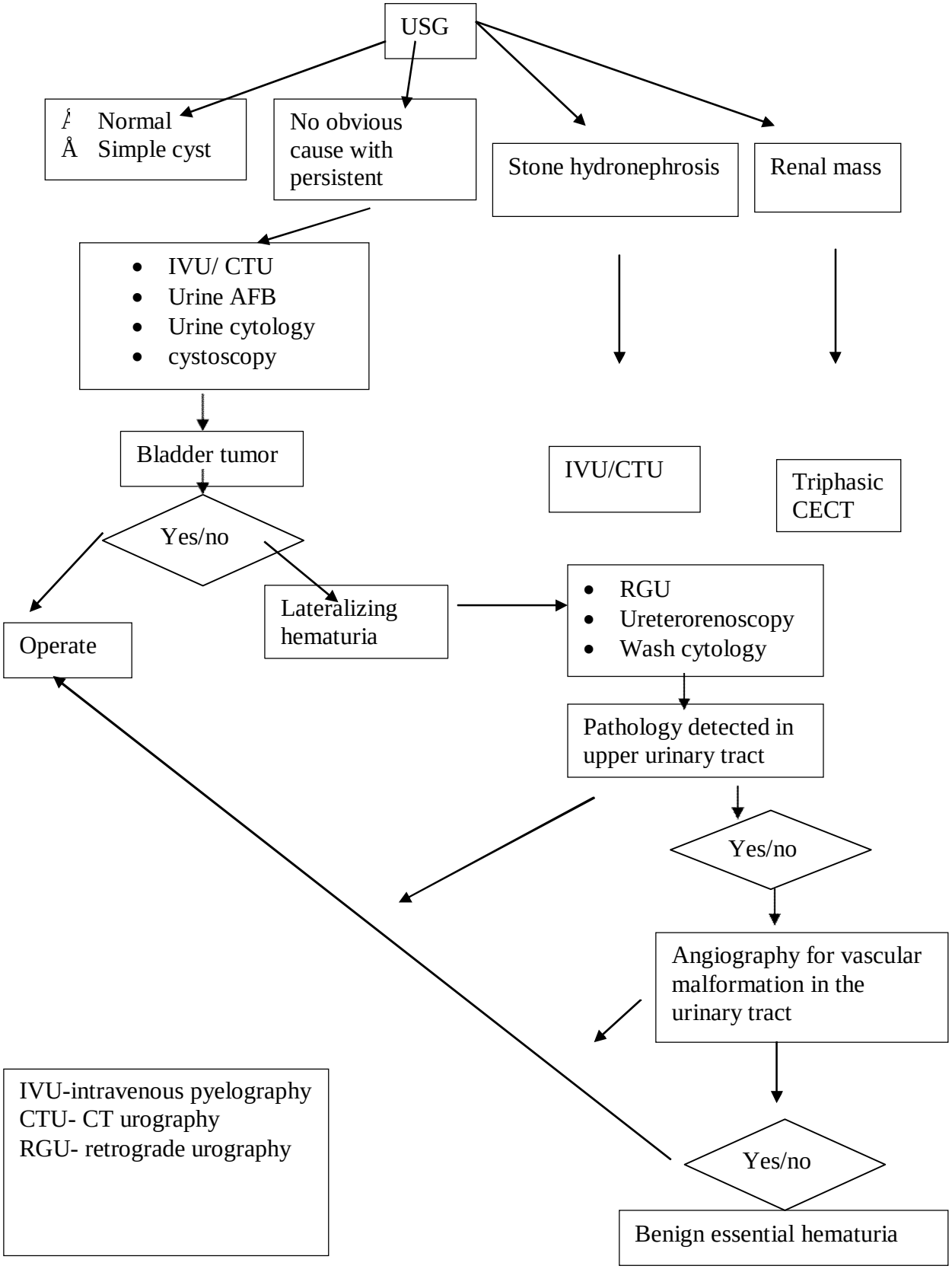
Suggested algorithm of evaluation of surgical hematuria:



URINARY AND MALE GENITAL TRACT INFECTIONS

Introduction

Infections of the urinary tract pose a serious health problem, also because of their frequent occurrence.
Clinical and experimental evidence support that the ascent of micro-organisms within the urethra is the most commom pathway leading to urinary tract infections, especially for organisms of enteric origin (I.e Escherichia coli and other Enterobacteriaeae). This is a logical explanation for the greater frequency of UTIs in women than in men and the increased risk of infection following bladder catherisation or instrumentation.

Classification of Urinary and Male Genital Tract Infections

For practical clinical reasons, urinary tract infections (UTIs) and male genital tract infections are classified according to entities with predominating clinical symptoms: (I) uncomplicated lower UTI (cystitis); (2) uncomplicated pyelonephritis; (3) complicated UTI with or without pyelonephritis; (4) Urosepsis; (5) urethritis; and (6) prostatitis, epididymitis, orchitis.

Definitions

the definitions of bacteriuria and pyuria are as follows:
Significant bacteriuria in adults:

- $\geq 10^3$ uropathogens/ml of midstream urine in acute uncomplicated cysitis in female;
- $> 10^4$ uropathogens/ml of midstream urine in acute uncomplicated pyelonephritis in female;
- $> 10^4$ uropathogens/ml of midstream urine of women or 10^4 uropathogens/ml of midstream urine in men (or in catheter, urine specimen in women) with complicated UTI.

  In a suprapubic bladder puncture specimen any count of bacteria is relevant.

Asymptomatic bacteriuria (ABU)
ABU is defined as two positive urine cultures taken more that 24h apart with 10^5 uropathogens/ml of the same bacterial strain.

Pyuria

The requirement for pyuria is 10 white blood cells per high power field in the resuspended sediment of a centrifuged aliquot of urine or per mm^3 in unspun urine. For the routine, a dipstick method can also be used, including leukocyte esterase test, or nitrite reaction.

Table 1. Classification of prostatitis according to NIDDK/NIH

I	**Acute bacterial prostatitis (ABP)**
II	**Chronic bacterial prostatitis (CBP)**
III	**Chronic pelvic pain syndrome (CPPS)**
	A Inflammatory CPPS: WBC in EPS/voided bladder urine-3 (VB^3) or semen
	B Noninflammatory CPPS: no WBC/EPS/VB3/semen
IV	**Asymptomatic inflammatory prostatitis**

Diagnosis

Disease history, physical examination and urine analysis by dipstick including white and red blood cells as well as nitrate reaction is recommended for routine diagnosis.

In case of suspicion of pyelonephritis, evaluation of the upper urinary tract may be necessary to rule out upper urinary tract obstruction or stone disease.

Table 2. Recommendations for antimicrabial therapy in urology

Diagnosis	**Most Frequent pathogens**	**Initial, empiric antimicrobial therapy**	**Therapy duration**
Cystitis, acute, Uncomplicated	E.coli Klebsiella Proteus Staphylococcus	Trimethoprim/ sulfamethoxazole	3 days
		Fluroquinolone[a]	3 days
		Alternatives:	
		Fosfomycin	1 day
		Nitrofurantoin	7 days
Pyelonephritis, acute, uncomplicated	E.coli	Fluroquinolone	7-10 days
	Proteus	Cephalosporin Gr. 2b/3a	
	Klebsiella	Alternatives	
	Other Enterobacteria	Aminopenicillin / BLI	
	Staphylococcus	Aminoglycoside	
UTI with complicating	E.coli	Fluoroquinolone	3-5 days after defervescence or control/ examination of complicating factor

Factors	Enterococcus	Aminopenicillin / BLI	
Nosocomial UTI	Staphylococcus	Celphalosporin Gr. 2	
Pyelonephritis, acute,	Klebsiella	Celphosporin Gr. 3 a	
Complicated	Proteus	Aminoglycosides	
	Enterobacter	In case of failure of initial therapy within 1-3 days or in clinically severe cases:	
	Other Enterobacteria	Anti-Pseudomonas active:	
	Pseudomonas	Fluroquinolone, if not used initially Acylaminopenicillin/BLI	
	(Candida)	Cephalosporin Gr. 3B	
		Carbapenem	
		+ Aminoglycoside	
		In case of Candida	
		Fluconazole	
		Amphotericin B	
Prostatitis, acute, chronic	E.coli	Fluroquinolone[a]	Acute : 2 weeks
Epididymitis,acute	Other Enterobacteria	Alternative in acute bacterial prostatitis	
	Pseudomonas	Cephalosporin Gr. 2	Chronic : 4-6 weeks or longer
	Enterococcus	Cephalosporin Gr. 3a/b	
	Staphylococcus	In case of Chlamydia or Ureaplasma:	
	Chlamydia	Doxycyline	
	Ureaplasma	Macrolide	
Urosepsis	E.coli	Cephalosporin Gr. 3a/b	3-5 days after defervescence or control/ elimination of complicating factor
	Other Enterobacteria	Fluorquinolone[a]	
	After urological interventions -	Anti-Pseudomonas active	
	Multiresistant	Acylaminopenicillin/BLI	

	pathogens:		
	Proteus	Carbapenem	
	Serratia	Aminoglycosides	
	Enterobacter		
	Pseudomonas		

a Fluroquinolone with mainly renal excretion; BLI= B- lactamase inhibitor.
B 1st,2nd and 3rd generation respectively (3*a* - without; 3*b* - with anti-Pseudomonas activity)

Treatment

Treatment of UTI is dependent on a variety of factors. An overview of most frequent pathogens, antimicrobial agents and duration of treatment in various conditions is given in table 2. Patients with recurrent UTI may be recommended prophylactic treatment. The following regimens have a documented effect in preventing recurrent UTI in women (table 3).

Table 3. Antimicrobial regimens for prevention of acute uncomplicated urinary infection in women

Agent	**Dose**
Standard regimens (taken at bedtime)	
Trimethoprim / sulfamethoxazole	40/200mg/day or
	3 times weekly
Trimethoprim	100mg/days
Nitrofurantoin	50mg/day
Others	
Cephalexin	125 or 250 mg/day
Norfloxacin	200 mg/day
Ciprofloxacin	125 mg/day

Special situations:

- UTI in pregnancy. Asymptomatic bacteriuria is treated with a 7 day course based on sensitivity testing. For recurrent symptomatic infections, either cephalexin 125-250 mg/day or nitrofurantoin 50 mg/day may be used.

- UTI in postmenopausal women. In women with recurrent infection intravaginal estriol is recommended. If this does not work, in addition antibiotic prophylaxis is indicated.

- UTI in children. Treatment perioud should be extended to 7-10 days. Tetracyclines and fluroquinolones should not be used due to effects on teeth and cartilage.

- Acute uncomplicated UTI in young men. The treatment should last at least 7 days.

- UTI in diabetes mellitus and renal insufficiency. After treatment, a prophylactic regimen may be recommended afterwards.

- Complicated UTI due to urological disorders. The underlying disorded must be managed if permanent cure is to be expected. In order to avoid inducing resistant strains, treatment should be guided by urine culture whenever possible.

- Sepsis syndrome in Urology (urosepsis).

Patient with UTI may develop sepsis. Early signs of systemic inflammatory response (fever or hypothermia, tachycardia, tachypnea, hypotension,oliguria, leukopenia) should be recognized as the first signs of possible multiorgan failure. In conjunction with appropriate antibiotic therapy, life supporting therapy in collaboration with an intensive care specialist may be necessary. Any obstruction in the urinary tract needs to be drained.

Follow-up of patients with UTI

for follow-up after uncomplicated UTI and pyelonephritis in women, a urinanalysis by dipstick is enough for routine use.

In women who will have recurrence within 2 weeks, repeated urinary culture with antimicrobial testing and evaluation of the urinary tract is recommended.

In the elderly, newly developed recurrent UTI may warrant a full evaluation of the urinary tract.

In men with UTI, a urologic evaluation should be done when the patient is in adolescence, in cases with recurrent infection and in all causes with pyelonephritis. Also patients with prostatitis, epididymitis and orchitis should follow these recommendations.

In children, investigations are indicated after two episodes of UTI in girls and one episode in boys. Recommended investigations are ultrasonography of the urinary tract supplemented by voiding cystourethrography.

Urethritis

Symptomatic urethritis is characterized by dysuria and purulent discharge

Diagnosis

The Gram stain of secretion or urethral smear showing more than 5 leukocytes per high power field (HPF) (1,000) and eventually gonococci located intracellularly as Gram-negative diplococci indicate a pyogenic urethritis. A positive leukocyte

esterase test or more than 10 leukocytes per high-power field (400) in the first voiding urine specimen are diagnostic.
Therapy

The following guidelines for therapy comply with the recommendations of the Centre for Disease Control and Prevention (1998).

For the treatment of gonorrhea the following antimicrobials can be recommended:

Cefixime 400 mg orally As a single dose	Ciprofloxacin 500 mg orally as a single dose
Cefriaxone 250 mg i.m. As a single dose (i.m. with local anaesthetic)	Ofloxacin 400 mg orally as single dose

As gonorrhea is frequently accompanied by chalamydial infection, an antichlamydial active therapy should be added. The following treatment has been successfully applied in C. trachomatis infections :

First choice	**Second choice**
Azithromycin 1 g (=4 caps.@250 mg) orally as single dose	Erythromycin 500 mg orally 4 times daily for 7 days
Doxycycline 10 mg 2 times daily orally for 7 days	Ofloxacin 200 mg orally for 7 days

if therapy fails, one should consider infections by T. vaginalis and / or Mycoplasma, which can be treated with a combination of metronidazole (2 g orally as single dose) and erythromycin (4 times daily 500 orally for 7 days).

Prostatitis, Epididymitis and Orchitis

Prostatitis

Treatment

g. Acute bacterial prostatitis can be a serious infection and parenteral administration of high doses of bactericidal antibiotic such as aminoglycosides and a penicillin derivative or a 3rd generation cephalosporin are required until defervescence and normalization of infection parameters. In less severe cases a fluoroquinolone may be given orally for at least 10 days.
h. In chronic bacterial prostatitis and chronic inflammatory pelvic pain syndrome, a fluoroquinolone or trimethorpim should be given orally for 2 weeks after the initial

diagnosis. Then the patient should be reassessed and antibiotics only continued if pretreatment cultures were positive or if the patient reports positive effect of the treatment. A total treatment period of 4-6 weeks is recommended.

Epididymitis, Orchitis

The majority of cases of epididymitis are due to common urinary pathogens. Bladder outlet obstruction and urogenital malformations are risk factors for this type of infection.

Treatment

Prior to antimicrobial therapy a urethral swab and midstream urine should be obtained for microbiological investigation. Fluoroquinolones, preferably those which react well against C. trachomatis (**e.g**. ofloxacin, levofloxacin) should be first choice drugs because of their broad antibacterial spectra and their

Table 4. Recommendations for perioperative antibacterial prophylaxis in urology

Procedure	**Most common pathogens (s)**	**Antibiotic(s) of choice**	**Alternative antibiotic(s)**	**Remarks**
Open operations urinary tract including bowel segments	Enterobacteria Enterococci Anaerobes Wound infection: Staphylococci	Aminopenicillin + BLI Cephalosporin 2^0+ Metronidazole	In high-risk patients: Cephalosporin3 Acylaminopenicillin + BLI	In all patients
Urinary tract without bowel segments	Enterbacteria Enterococci Wound infection: staphylococci	Fluoroquinolone Cephalosporin 2^0 Aminopenicilin +BLI	in high-risk patients: Cephalosporin3 Acylaminopenicillin + BLI	in patients with increased risk of infection
Implant / prosthesis: penis, sphincter Reconstructive genital operation	Staphylococci Staphylococci	Cephalosporin $1^0/2^0$ Cephalosporin $1^0/2^0$		in all patients in secondary operations & in patients with increased risk of infection
Other interventions outside of the	Staphylococci	Cephalosporin $1^0/2^0$		in patients with increased risk of infection

urinary tract				
Endoscopic – instrumental operations Urethra, prostate, bladder, ureter, kidney, incl. percutaneous litholapaxy and ESWL	Enterobacteria Staphylococci Enterococci	Fluoroquinolone Aminopenicillin + BLI Cephalosporin 2^0 Fosfomycin Trometamol	Cotrimozazole Aminoglycoside	In patients with increased risk of infection
Diagnostic intervention Transrectal biopsy of the prostate (with thick needle)	Enterobacteria Enterococci Anaerobes Streptococci	Fluoroquinolonea Aminopenicllin + BLI Cephalosorin 2^0+ Metronidazole	Aminoglycoside Cotrimozazole	In all patients
Perineal biopsy of the prostate, urethrocystoscopy, ureterorenoscopy, percutaneous pyeloscopy, laparoscopic procedures	Enterobacteria Enterococci Staphylococci	Fluoroquinolonea Aminopenicillin + BLI Cephalosporin 2^0	Cotrimoxazole	In patients with increased risk of infection

BLI = B- Lactamase inhibitor, *ESWL*- extracorporeal shock-wave lithotripsy. 1^0,2^0,3^0 = 1^{st}, 2^{nd}, 3^{rd} generation respectively.

11. Fluroquinolone with sufficient renal excretion

Favorable penetration into the tissues of the urogenital tract. In case C. trachomatis has been detected as etiologic agent, treatment could also be continued with doxycycline 200 mg/day for a total treatment period of at least 2 weeks. Macrolides may be alternative agents. In case of C .trachomatis infection, the sexual partner should be treated as well.

Antibiotics and α Blockers in combination

Urodynamic studies have shown increase urethral closing pressure in patients with chronic prostatitis. A combination treatment of α blockers and antibiotics is reported to have a higher cure rate than antibiotics alone in inflammatory CPPS. This is a treatment option favored by many urologists.

In general, surgery should be avoided in the treatment of prostatitis patients except for drainage of prostatic abscesses.

Perioperative Antibacterial Prophylaxis in Urological Surgery

The main aim of antimicrobial prophylaxis in urology is to prevent symptomatic / febrile genitourinary infections, such as acute pyelonephritis, prostatitis, edpididymitis and urosepsis as well as serious wound infections.

Antibiotic prophylaxis is recommended only for a maximum of 24 hours after surgery in most situations. More rampant use leads to antibiotic resistance and places an additional economic burden. Prophylaxis does not substitute for poor surgical asepsis.

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STANDARD TREATEMTN GUIDELINES

UROLITHIASIS AND URETERIC COLIC

When to suspect /recognize

Introduction:-

American urological association (AUA) has been the frontrunner in formulating guidelines for Urolithiasis since 1991. Since then, editions of guidelines have been published with the 2005 guidelines on staghorn calculus being the latest [(1)] The European association of urology(EAU) has published similar guidelines since 2000. The latest updates have been published in 2010[(2).]

The significant differences in the socioeconomic and disease pattern (mode of presentation, stone bulk, health care delivery facilities) for urolithiasis in India make it imperative to formulate our own guidelines.

We have reviewed the literature for drafting the guidelines. The recommendations drawn are largely based on the AUA/EAU guidelines with modifications recommended where appropriate. Indian references have been cited, particularly so, if they are prospective randomized studies and/or metanalysis. Recommendations have been given when adequate literature support is available. The referral criteria are noted when appropriate.

Case definition

The index patients are defined as follows:-

Ureteral stones

A non pregnant adult patient with unilateral ureteral calculi (no renal stones) and normal functioning contralateral kidney, the body habitus, anatomy and medical condition should not preclude the application of any of the available treatment options [2]

Staghorn calculi

A staghorn calculi is defined as a stone with central body and at least one calyceal branch. A partial staghorn calculus fills part of the collecting system. A complete staghorn fills all the calyces and the renal pelvis.

***Index patient (staghorn calculi)*:-**

Adult with a staghorn stone (non Cystine, non uric acid) who has two functioning kidneys (functioning both kidneys) or a solitary kidney with normal function. The patients overall medical condition, body habitus and anatomy should permit any of the available intervention [1].

Non staghorn calculi

Any pelvic and /or calyceal calculi which do not fit in the definition of staghorn calculi [2].

Incidence in our country

Although a few studies have been reported for a small group of subjects in screening camps. The true incidence of urolithiasis in India is still not known. It is commonly seen in western states, hypothetically, attributable to high salinity of water .The presentation of a patient with urolithiasis differs in India. Large stone bulk on presentation is commonly seen in India.

What should be the optimal?

Renal stones

Investigations:-

Imaging is absolutely imperative if, the patient has a solitary kidney or a history of fever. If the diagnosis of stone is in doubt then imaging is mandatory.[2] **Execratory urography has been the gold standard in the work up for urolithiasis.** Non contrast computerized tomography(NCCT) scan is quick and safe, contrast free alternative to excretory urography. Randomized studies have shown that non contrast helical CT has similar or superior results to excretory urography in acute flank pain[3] **Contrast media should not be given or should be avoided when there is a elevated creatinine level, pregnancy or lactation**[4][5] Additional information can be gained by contrast enhanced CT scan(CTU), however at the moment **there is no level 1 evidence to suggest that CTU is superior to IVU** in the work up of urolithisis.[6]. X-ray KUB and ultrasound is used by few clinicians as a measure of preoperative investigations, however this cannot be considered as a standard. These investigations help to plan access and predict the possible success rates.

Recommendation:-Excretory urography is the gold standard in work up for urolithiasis and is mandatory in solitary kidney, history of fever and when the diagnosis is in doubt.

NCCT is the investigation of choice in acute flank pain due to stone.

Analysis of stone composition

Stone analysis is desirable in recurrent stone formers. The preferred analytical procedures are:-[2]

1) X ray crystallography.

2) Infrared spectroscopy.

The other methods of stone analysis are:-

1) Radiographic characteristics of the stone.

2) Microscopic examination of the urinary sediments to detect crystals.

3) Urine Ph (alkaline in infection stones and acidic in uric acid stones.

4) Urine culture.

Special investigations which are ordered on case to case merit are renal scintigraphy, antegrade, retrograde contrast study.

Indications for intervention

The indication for stone removal depends on the size, site and shape of the calculus. The likelihood of spontaneous passage, presence of obstruction should be assessed.

The indications for intervention are:-

1) When the stone diameter is more than 7 mm (because of low rate of spontaneous passage).

2) When adequate pain relief is not achieved.

3) When there is stone obstruction associated with infection.

4) Pyonephrosis.

5) Obstruction in single kidney.

6) Bilateral obstruction.

Recommendation:-For1, 2 stone removal with or without prior decompression(depending on the clinical situation) is recommended ,in situation ,3,4,5,6 emergency deobstruction of the collecting system is recommended.

The choice of decompression can be with ureteric stents, percutaneous nephrostomy depending on surgeon preference, expertise and the level of obstruction [7] [8] [9] [10]

Treatment (including standard operating procedure)

I) Extracorporeal shock wave lithotripsy(ESWL)

The success of lithotripsy depends on the body habitus, location of the stone, efficacy of the lithotripter, stone bulk. **The contraindications for ESWL for renal stones include pregnancy, bleeding disorders, uncontrolled urinary tract infections, morbid obesity, aortic aneurysms close to F1**[(2)]

i) Role of stents

Routine use of stents is not recommended for ESWL for renal stones. [(11)]

ii) Location of stones

The stone clearance is lower for stones in the lower calyx as compared to anywhere else in the kidney. Various studies have attempted to show the correlation of geometry of the lower calyx to predict the clearance of stone in this location. However the calyceal stone burden is the most important factor in predicting the clearance.

Although there is no critical size, 20 mm should be considered the upper limit for stones in the lower calyx to be recommended for ESWL. The EAU guidelines recommend ESWL as the treatment of choice for renal stones less than $20mm^2$($300mm^2$) [(2).] A multicentre trial has compared ESWL and Flexible ureteroscopy for lower calyceal stones. It failed to show any difference in the clearance rates [(12)]

iii) Total stone burden

It is recommended that stones smaller than $20mm^2$ to be treated with ESWL , while for larger stones more than $20mm^2$($300mm^2$), PCNL should be considered the treatment of choice.[(2)]

iv) Composition and hardness of stone

The **composition of the stone is an important factor for predicting the success rates** of renal calculi. Specific stone compositions have different clearance rates because of the varying

fragility of stones. Cystine stones are harder to fragment, hence cystine stones larger than 15mm should not be treated with ESWL.PCNL would be a good option in these patients[2]

The **measurement of stone density with NCCT** helps in predicting success rates of ESWL. **Stones with greater than 1000 Hounsfield units (HU) show poor results with ESWL**.[13][14]

v) **ESWL-procedural standard operating protocol**

Simultaneous fluoroscopy and ultrasound monitoring is desirable.[2] The acoustic coupling between shock head and the skin should be optimal. Ultrasound gel is the best available gel. The ultrasound gel should be applied straight from the container rather than by hand.[15][16]. Level 4 evidence is available to suggest that proper analgesia results in limited movement and respiratory excursions. **Better fragmentation can be achieved with starting the fragmentation at lower energy setting and then ramping up the power**[17] . the manufacturers recommendation regarding the number of shocks and frequency should be followed.The optimal shock wave frequency is 1.0 Hz[18] It is **important to limit the number of shocks and the power,** due to concerns regarding damage to the kidney.

In case of infected stones, **antibiotics should be given according to urine culture sensitivity**, the same should be continued after surgery for 4 days [2] Clinical experience suggests that stones in the ureter rather than the kidney should be treated with shorter intervals between sessions.

vi) **Complications**

The complications which are likely to be encountered and which should be counseled to the patient prior to surgery are:-

5. Pain
6. Hydronephrosis
7. Fever
8. Urosepsis

Recommendations:-

It is recommended that stones smaller than 20mm^2 to be treated with ESWL. Routine use of stents is not recommended for ESWL for renal stones.The contraindications for ESWL for renal stones include pregnancy, bleeding disorders, uncontrolled urinary tract infections, morbid obesity, aortic aneurysms close to F1. Antibiotics should be given according to urine culture sensitivity, the same should be continued after surgery for 4 days. The physicians should refer to the manufacturer recommendation regarding the decision of number, frequency and power of shocks.

II)Percutaneous Nephrolithotomy

Technically most of the renal stones can be managed with a percutaneous nephrolithotomy. However the **usual indications for PCNL are larger than 20mm^2, staghorn, partial staghorn calculi and stones in patients with chronic kidney disease.**

Standard operating protocol

General anaesthesia is preferable, although studies have demonstrated the utility of regional anaesthesia [19] PCNL has been **performed traditionally in a prone position** however it can technically also be performed in supine position, the advantage of this (supine position) approach is that the retrograde access is easier in supine position, anesthetist has a better control over the airway and simultaneous ureteric and renal stones can be managed without changing the position.[20][21] The access to the collecting system can be gained either **ultrasound guided or fluoroscopy guided depending on the availability of instruments and expertise**. The advantage of ultrasound guided access is the potential to avoid major visceral injuries.[22] The access site should be the posterior calyx. The **tract should be the shortest possible tract from**

the skin to the desired calyx traversing the papilla. Depending on the stone configuration a calyx should be selected (Supracostal, infracostal or subcostal) so that maximum stone bulk can be cleared minimum number of tracts. [23] Renal tract dilatation either balloon, amplatz or metallic dilators are a matter of surgeon preference and availability [2]. In lower polar stones ESWL, PCNL and flexible ureterorenoscopy are competing procedures with different success rates and complications [12][24].**In complicated cases or when secondary intervention is required a nephrostomy tube which serves the dual purpose of tamponade and a conduit for second look is placed.**

In uncomplicated cases, tubeless percutaneous nephrolithotomy with or without application of tissue sealants is a safe alternative [25] [26]

i) <u>Complications</u>

The patients should be **counseled regarding the complications** which are likely to be encountered such as life threatening bleeding with a possible need for angioembolisation or even nephrectomy. It may be associated with infective complications leading to urosepsis. The **patients should be counseled regarding the possibility of residual calculi and the consequences thereof.** The procedure becomes challenging in complex stones, although the complications are not specific to them. Such cases should be **identified and managed by experienced surgeons.**

<u>Recommendations</u>

Technically, most of the renal stones can be managed with a percutaneous nephrolithotomy. However the **uasual indications for PCNL are larger than 20mm^2, staghorn, partial staghorn calculi and stones in patients with chronic kidney disease.** The access to the collecting system

can be gained either **ultrasound guided or fluoroscopy guided depending on the availability of instruments and expertise**. Renal tract dilatation either balloon, amplatz or metallic dilators are a matter of surgeon preference and availability. **In complicated cases or when secondary intervention is required a nephrostomy tube which serves the dual purpose of tamponade and a conduit for second look is placed.** In uncomplicated cases, tubeless percutaneous nephrolithotomy with or without application of tissue sealants is a safe alternative.

III) Flexible ureterorenoscopy

Flexible ureteroscopy offers a good treatment option for calculi less than 20mm in size. Due to improved technology and development in accessories and optics the role of flexible ureteroscopy is likely to be expanded in the future. The procedure wherein flexible ureteroscopy is used in the kidney is called as retrograde intrarenal surgery (RIRS**). Flexible URS is not recommended as a first line of treatment for renal calculi. It has been demonstrated as a effective way of treating stones which are refractory to ESWL.** It has also been seen useful when simultaneously used with PCNL, in this way it reduces the number of tracts during the procedure

It is **recommended that sterile urine should be documented** prior to intervention. [27][28]

Standard technique for flexible ureteroscopy

- Fluoroscopy equipment is advisable in all cases
- Preoperative imaging helps to determine the size and location of the stone.
- The use of safety wire is recommended (0.035 floppy tip) .
- The ureteroscope can be introduced over a guide wire (back loaded) or they may be advanced through a ureteral access sheath.
- Stone extraction blindly without endoscopic vision should not be done

- Small stones can be extracted with baskets of forceps.
- Intracorporeal lithotripsy can be performed with holmium laser. The other alternatives are ballistic, ultrasonic or electrohydraulic lithotripsy. [2]. The holmium Yag laser is the preferred modality for flexible ureteroscopy [29]

- The stenting after an uncomplicated flexible ureteroscopy is optional. The indications for stenting after completion of URS are ureteral stricture, ureteral injury, solitary kidney, renal insufficiency, large stone burden residual stones.

Accessories and instrumentation

A 365 micron laser fiber is suited for ureteral stones. The 200 micron fiber preserves tip deflection. Holmium laser is the preferred energy source for flexible ureteroscopy. **Nitinol baskets preserve tip deflection**, in addition the tipless design reduces the mucosal injury, hence they are more suited for flexible ureteroscopy.[30]

Access sheaths have been used by various workers. The size of the available access sheaths ranges from 9-16Fr, they have a hydrophilic coating. Generally they are introduced over a wire. The advantages of access sheath are reducing the operating time particularly in large stone burden. Another theoretical advantage is, it helps in maintaining a low pressure in the pelvicalyceal system.[31]

Recommendations:-

Flexible ureteroscopy offers a good treatment option for calculi less than 20mm in size. Flexible URS is not recommended as a first line of treatment for renal calculi. It has been demonstrated as a effective way of treating stones which are refractory to ESWL. Stenting after a uncomplicated ureteroscopy is optional.It is **mandatory that sterile urine should be documented prior to intervention.**

Staghorn calculi:-

A retrospective study with 200 patients has shown that renal deterioration occurs in 28% of patients with staghorn calculi treated conservatively. This emphasizes the fact that **staghorn stones should be aggressively managed surgically**[32] **PCNL should be the recommended modality as clearance rates are greater than 3 times that of ESWL**.[33]

The following are the treatment options in staghorn calculi:-

1) **Percutaneous nephrolithotomy** should be the **first treatment** utilized for most patients. (level2)

2) ESWL should not be used as the preferred treatment modality for staghorn stones.

3) Open surgery should be recommended only if the stones are not expected to be removed in a reasonable number of stages.

4) **Nephrectomy should be considered in non functioning kidneys**. [1]

Recommendations:-

PCNL is the first choice for staghorn calculi. Open surgery is desirable in the situation when expertise is not available wherein the stone can be cleared in reasonable number of stages and tracts. Nephrectomy should be considered for non functioning kidneys.

Management of ureteric calculi and ureteric colic

The most common cause for ureteric colic is ureteric calculus. The priority in these patients should be relief of pain. The subsequent management of patients with ureteric colic would be determined by the level of obstruction and the stone size.

i) Agents recommended for relieving pain

It is recommended that pain should be relieved with diclofenac whenever possible. A alternative drug might be used if pain persists. Further more it has been shown that the resistive index significantly reduces if diclofenac is administered.. **Level 4 evidence suggests that hydromorphine might be helpful, however there is a significant risk of vomiting** [34] [35] [36] **Diclofenac can affect renal function in patients with already reduced function.** There is however no effect if the kidneys are functioning normally. [37]

ii) Agents for preventing episodes of renal colic

Diclofenac sodium is recommended for the purpose. Studies indicate that the incidence of recurrent renal colic decreases with administration of diclofenac sodium. [38] When the pain is unremitting the treating urologist should think of alternative measures such as drainage by stenting or percutaneous nephrostomy or even removal of the stone.

iii) Medical expulsive therapy (MET)

The beneficial effect of these drugs is attributed to ureteral smooth muscle relaxation mediated through inhibition of calcium channel pumps or alpha receptor blockade. The prerequisite for this approach is that the patient should be comfortable this approach. And there should not be any immediate indication for stone removal.. **Studies indicate that alpha blockers facilitate ureteral passage ,while nifedipine provides marginal benefit. Alpha blockers are recommended for MET[2]**

Ureteric calculi

Guidelines for Index patients

- Patients with bacteriuria should be treated with appropriate antibiotics
- Blind basketing without visualization endoscopically should not be performed.

- Patients with newly diagnosed stones less than 6 mm and well controlled symptoms, should be advised MET
- Patients who opt for Medical expulsion therapy should have well controlled pain, no evidence of sepsis, and adequate functional reserve, such patients should be periodically observed for stone position and assessment of hydronephrosis.
- Stone removal is recommended in persistent obstruction, failure of stone progression. or increasing or unremitting colic.
- Patient should be informed about the available treatment options.
- Both ESWL/ flexible URS are the preferred treatment options for upper ureteric calculi less than 1cm in size. For larger stones Antegrade ESWL/PCNL/laproscopic removal are recommended depending on expertise and instruments available
- URS is the preferred modality for distal and midureteric calculus.

Recommendations:-

Alpha blockers are recommended for MET. It is recommended that pain should be relieved with diclofenac whenever possible. Patients with newly diagnosed stones less than 6 mm and well controlled symptoms, should be advised MET .Patients who opt for Medical expulsion therapy should have well controlled pain, no evidence of sepsis, and adequate functional reserve, such patients should be periodically observed for stone position and assessment of hydronephrosis. Both ESWL/ flexible URS are the preferred treatment options for upper ureteric calculi less than 1cm in size. For larger stones antegrade ESWL/PCNL/laproscopic removal are recommended depending on clinical situation expertise and instruments available. URS is the preferred modality for distal and midureteric calculus

Treatment of calculi in special situations

Calyceal diverticular stones

Once symptomatic all these stones require treatment. **ESWL, PCNL, laparoscopy and observation remain the treatment options which can be offered to the patient**. As the drainage of the calyx in concern is at times questionable ESWL has rather poor results. Sometimes the combination this treatment modality is recommended [(39)].

Anomalous kidneys

These group of patients include those patients with stones in ectopic, horseshoe or kidneys with fusion anomalies. The approach to managing these stones should be individualized. The factors to be taken into consideration are the stone bulk, the location of the stone, the vascular and the anatomy of the pelvicalyceal system. Ultrasound helps in gaining access in ectopic kidney apart from being a diagnostic tool. **CT is pivotal in deciding the management and choosing the method of treatment in anomalous kidney**..

CT will also give the attenuation values and be a deciding factor in deciding ESWL or flexible ureteroscopy. Flexible ureteroscopy will be useful tool in stones small burden stones in size with the availability of smaller flexible ureteroscopes, and access sheaths. However the surgeon should consider complete “on table” clearance in these patients as the drainage is likely to be impaired. USG guided approach for ectopic kidneys should be done by surgeons well versed with it. Laparoscopic assisted PCNL has shown good clearance rates with minimal morbidity and less likely hood of ancillary procedures. Although adequate fragmentation can be achieved with ESWL, the drainage of fragments might be impaired due to the anatomical abnormalities. The choice of ESWL as a treatment option should be done prudently.[(40)]

Pediatric urolithisis

Although the treatment modalities used are same in children as in adults. Specific points should be noted in children. **The indications for ESWL are similar to those in adults. Stones in Children with a diameter of less than 20mm are ideal cases. The success rates decreases as stone burden increases. Larger stones should be treated with PCNL** [(2).]

They are as follows:-

1) Children have a tendency to pass larger fragments.

2) Ultrasound should be the modality for localization of stone when ESWL is the modality chosen.

3) Smaller instruments should be used for endourologic manipulations[(2)]

Role of open surgery in the current era

In a developing country such as India, the cost factor plays a major role, which is mostly borne by the patient or a health care delivery mechanism, A study from India by Sinha et al , which although is a retrospective data and has a small sample size suggests that PCNL is less costly and as effective as open surgery. However randomized level 1 evidence by Al Kohlany et al comparing open surgery with PCNL suggests that PCNL offers equivalent clearance as open pyelolithotomy, with less morbidity, short hospital stay.and less renal damage. **The trade off in a Indian clinical scenario will be to offer the best cost effective alternative available**.[(41)(42)(43)]

Nephrolithiassis –metabolic work up

See recommendation in section on- Nephrolithiassis –metabolic work up .

Who does what/ and timeline

Doctor

The treating doctor ideally should be an Urologist or a surgeon trained in Urology. He is responsible for the initial workup of the patient and subsequent management of the patient. He is responsible for counseling the patient regarding the success rates, complications and possible outcome of any given procedure. All possible treatment options in a given clinical situation should be discussed with the patient. The patient on discharge should be given instructions for follow up and measures (dietary and pharmacologic) to prevent stone recurrence.

Nursing and technical staff:-The nursing staff should be trained in the aspect of maintenance and use of endourologic equipment, considering the fragility and cost of these equipments. The responsibility of sterilization of these equipment lies with these personnel .The technical/nursing staff prepares the trolley and assists the surgeon during the procedure.

Referral criteria:-

The criterion for referral remains, lack of appropriate infrastructure and expertise at primary level.

The indications for referral to tertiary care centre in managing stones disease are:-

!)Complex calculi (multiple stones , staghorn calculi, stones with CKD, stones with obstructive uropathy) where in the opinion of the treating physician , the patient needs nephrolurological care and advanced surgical and medical care from a infrastructure standpoint

2) Special situations such as pediatric urolithiasis, stones in ectopic kidney.

Annexure 1

Indications and selection of modality for treating calculi in a index patient

It depends on the stone size location, stone composition and BMI of the patient

The following are the guidelines to be followed

1) Stone less than 1cm in the kidney -ESWL

2) Stone more than 1cm and less than 2cm in the kidney , -Flexi URS/ESWL/PCNL

3) Any stone more than 2cm in the kidney-PCNL

4) All staghorn and partial staghorn-PCNL

5Non progressive more than 6mm stone in the mid and lower ureter-semirigid URS.

6) Stones less than 1cm in upper ureter-ESWL

7) stones larger than 1cm in upper ureter-PCNL/ESWL/Flexi URS

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Annexure 1

Resources required for one patient/procedure (units)

Human resources

ESWL

i. Urologist-1

j. Technician-1

k. Anesthetist-1

PCNL

12. Urologist-1
13. Surgical assistant-1
14. Technician/Nurse-2
15. Anesthetist-1

Flexible ureteroscopy

1) Urologist-1

a) Surgical assistant-1

3) Technician/Nurse-2

4) Anesthetist-1

Investigations:- As detailed in previous section

Drugs and consumables

List of consumables for PCNL

Normal saline 1000ml-(n=4)

5% Dextrose 1000ml-(n=2)

Normal saline -3000ml-(n=3)

Iv set – (n=1)

Injection Fortwin – (n=1)

Injection Metoclopromide-(n=4)

Injection Tramadol 50 mg –(n=4)

Injection ranitidine-50 mg-(n=4)

Foley catheter 16 fr-(n=1)

Urobag-(n=2)

Irrigation set-(n=1)

Phosphate enema-(n=1)

Injection glycopylorrate-(n=1)

Antibiotic according to clinical situation

List of consumables for ureteroscopy

Normal saline 1000ml-(n=4)

5% Dextrose 1000ml-(n=4)

Normal saline -3000ml-(n=3)

Iv set – (n=1)

Injection Fortwin – (n=1)

Injection Metoclopromide-(n=4)

Injection Tramadol 50 mg –(n=4)

Injection ranitidine-50 mg-(n=4)

Foley cathter 16 fr-(n=1)

Urobag-(n=1)

Irrigation set-(n=1)

Phosphate enema-(n=1)

Injection glycopylorrate-(n=1)

Antibiotic according to clinical situation

Equipment

Trolley preparation for PCNL

Tray with cover-2

Legging-2

Towel clips-5

Towel -2

Surgeon gown -3

Gloves -3

Hole towel-2

Artery forcep-2

Needle holder-1

Number 11 knife-1

Sponge holder -1

Scissor-1

Knife holder-1

Thread-1

20cc syringe-2

10 cc synringe-1

Bowl-1

Xylocaine jelly-2

Cystoscope sheath (19 Fr/20 Fr)

Telecope-30 degree

Light cable with cord 1 in number

Open end ureteric cathter-1 in number

Nephroscope -24-26 Fr (depending on availability)

Suction pipe-1

Stone holding forcep-1

Spanner -1

Ultrasound probe (optional)

Puncture needle-1

Metal rod/Telescopic metal dilators (till 24 Fr)-1

J tip guide wire/ glidewire-1

Teflon dilator with Upto 14 Fr-1

Ampatz dilator set-1

Amplatz sheath (size depends on surgeon preference)

Nephrostomy catheter (Nelaton preferable)

Trolley preparation for URS

Trolley with cover-1

Legging-2

Hole towel-1

Gown with napkin-1

Gloves-3

Towel clip-2

Sponge holder-1

Bowl-1

Scissors-1

Ureteric cathter-1

Ureteric dilator set-1

Irrigation tube-1

Cystoscope sheath with bridge-1

Telescope-30 degree-1

Guide wire 0.035/glide wire-1 each

Ureteroscope (depends on surgeon preference)-1

Benign Hyperplasia Of Prostate (BPH)

Prof. Nitin S. Kekre, Professor and Head
Dr. Arabind Panda, Associate Professor
Department of Urology
CMC Medical College, Vellore

General comments:
Clinical guideline are supposed to be reflections of the best currently available evidence. They have 2 parts ï

a. A systematic review of the best available evidence and the strength of that evidence.
    I. The methodology of systematic review is important. This should be clearly stated. All relevant studies should be studied. If Indian studies are available, then they should be included. The evidence should then be ranked using a standard system e.g. levels of evidence - Oxford Centre for Evidence-based Medicine [1]. If necessary relevant focused questions can be framed in order to exactly define the purview of the exercise.
b. Recommendations for practice based on that evidence. These should be graded according to the level of available evidence.

This standard treatment guideline on BPH does not state the methodology used to arrive at the recommendations. The levels of evidence are not mentioned. There is no grading of the recommendations. The document is without any references to back up the claims.
The authors should be clearly mentioned in the published version (we understand this is not desirable in a document for peer review). A conflict of interest declarations should be included in the final document.
Use of the term benign hyperplasia of the prostate (BPH) ï BPH is a histological diagnosis. It symptoms come under the umbrella of lower urinary tract symptoms. While BPH occurs in the vast majority of elderly men, it can be difficult or impossible to directly attribute the symptoms of the patient to BPH.

Introduction
Line 17 ï 20 : òHowever, a significant proportion, particularly in rural areas tend to disregard symptoms till complications develop and this segment requires a more proactive and individualized approach.” – There is no evidence that the rural population disregard symptoms more than the urban people. The lack of access to effective health care in rural areas will make a proactive and individualized approach difficult. It is important for guidelines to be applicable to the entire populations of the country.

Evaluation of BPH

1. Symptom assessment – Need to state the complete term International Prostatic Symptom Score before using the abbreviation IPSS.

Mandatory diagnostic tests

2. PSA measurement – Need to state the complete term. There is no evidence that prostate specific antigen measurement has any role in the routine management

of BPH. The role of PSA screening for prostate cancer is controversial. Metaanalysis of the recent evidence showed screening to have no significant impact on either overall mortality or death from prostate cancer with significant overdiagnosis and overtreatment and is unlikely to save lives. It cannot be recommended in India. A patient anxious about prostate cancer should be explained about the benefits and risks of PSA screening and about the available evidence. He should be then in a position to make an informed choice.

3. Abdominal ultrasound evaluation –Upper tract imaging is not required for routine evaluation of BPH. The estimation of prostate size by abdominal ultrasound is also unreliable. Ultrasound evaluation should be restricted to the bladder and post void residual urine as an optional test.
4. Uroflowmetry – This is not mandatory even in developed countries. The equipment is specialized, expensive (Indian makes cost Rs. 50000/- approx., foreign equipment – 1.5 – 2.5 lacs/ - approx.) and require regular maintenance and calibration. It cannot be mandatory and should be an optional test.

Optional diagnostic tests

2. Blood urea – Blood urea estimation is superfluous when creatinine is being measured. It is not as accurate indicator of renal function as creatinine. Unnecessary.

3. Urine Cytology – Urinary cytology is a specialized test with low sensitivity. In absence of microscopic haematuria, it is unlikely to be useful.

6. Urethrography – An uroflowmerty is a non invasive test which can indicate a possible urethral stricture. An urethrography is invasive and will require prior urine culture sensitivity before its performance.

Uroflowmetry and ultrasound abdomen can be added as optional tests.

Treatment options

2. a. “Dose titration is not essential for Alfuzosin and Tamsulosin ” should read - Dose titration is not required for extended release Alfuzosin and Tamsulosin.

“Hypotensive episodes are least seen with use of Alfuzosin” – The vasodilatory effects of Alfuzosina nd Tamsulosin are similar. There are no statistical differences between the two in this regard [4].

b. 5 Alpha reductase inhibitors: “Reduction of blood loss during TURP is evident only after long term use of 5 ARI’s.” - The evidence is very weak and not enough for a recommendation[5,6,7,8].

c. Combination therapy: “Concominant use of Alpha adrenergic blockers and 5Alpha reductase inhibitors is appropriate therapy for patients with LUTS due to BPH, particularly if response has been insufficient with either drug.” - Combination

therapy is necessary in those who are at risk of progression (moderate to severe LUTS, enlarged prostates, and reduced Qmax) . Response is not a criterion for combination therapy [9].

3. **Indications for surgery**

   "Patients presenting with chronic low pressure require catheterization and urodynamic evaluation" – Catheterization is not required unless the patient has acute on chronic retention, overflow incontinence or obstructive uropathy with raised creatinine.

4. Minimally invasive procedures
   TUNA and intraprostatic stents – Cannot be recommended based on current evidence.

5. **Surgical (endoscopic and open) procedures**
   - "Open prostatectomy is still an acceptable procedure for glands exceeding 100 gms in wt." – Any gland over 60 gms can be managed with open prostatectomy if TURP is not available.

   f) "Follow-up with IPSS, DRE & PSA recommended every 3 to 6 months initially and annually thereafter." – Three monthly follow up is not required after surgery. PSA is certainly not needed.

Conclusions: Very poorly written clinical practice guideline. It is unfit for use in its present form. Needs extensive revision.

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RENAL CELL CARCINOMA (RCC)

Renal cell carcinoma (RCC), which accounts for 2% to 3% of all adult malignant neoplasms, is the most lethal of the urologic cancers. The mortality rate of RCC is as much as twice that of bladder cancer[1,2]. There is no epidemiological data available from Indian subcontinent. However, the disease is fairly prevalent in our country.

In 2010, an estimated 58,240 Americans were diagnosed with renal malignancies and 13,040 deaths were estimated[3]. In 2008, there were an estimated 88,400 new cases and 39,300 kidney cancer–related deaths from RCC in Europe[4].

Surgical excision remains the only curative treatment as this tumor is remarkably resistant to radiotherapy and chemotherapy.

Presentation –

- **Incidental:** detected on imaging (CT / ultrasound) performed for other indication
- **Symptomatic:** local / metastatic / paraneoplastic
    - Flank pain, hematuria, mass
    - Weight loss, fever, night sweats, recent onset hypertension, anemia / polycythemia
    - Cervical lymphadenopathy / non-reducing varicocoele / pathological fracture
    - others

Workup –

Any mass lesion detected on ultrasound needs further imaging.

b) **CT / MRI abdomen & pelvis/ MR Urography –** both without and with contrast (if renal functions permissible). MRI specifically indicated if disease is infiltrating adjacent organs or IVC thrombus (triphasic multiplanar CT or high resolution color Doppler ultrasound optional for the latter).

c) **Blood investigations –** Hemogram, kidney functions, alkaline phosphatase (ALP), calcium, albumin, lactate dehydrogenase (LDH)

d) **Chest X-ray –** in all cases. Further imaging (CT scan) required only if clinically indicated or primary tumor locally advanced or lymph-nodes enlarged

e) **Bone scan –** only if clinically indicated (bone pain, raised ALP) or primary tumor locally advanced or lymph-nodes enlarged.

f) **PET CT –** not routinely recommended in the workup for RCC. Has good specificity but low sensitivity in the evaluation of metastatic disease. Currently, it may be considered in case of equivocal findings on conventional imaging, where detection of metastatic disease will influence management decision.

g) **Biopsy / FNAC –** not required in most cases. Acceptable in the following indications:

    h) Considering inflammatory mass / lymphoma / metastasis, vague Radiology, multiple masses, associated significant lymphadenopathy

    i) Considering non-surgical therapy (e.g. cryotherapy, systemic therapy in case of metastatic disease) / active surveillance (small renal masses) / watchful waiting

Staging (American Joint Committee on Cancer, TNM staging system for renal cancer, 7th ed, 2010) –

Primary tumor	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1a	Tumor dia ≤ 4 cm confined to kidney
T1b	Tumor dia > 4-7cm confined to kidney
T2a	Tumor dia > 7-≤10cm confined to kidney
T2b	Tumor dia > 10cm confined to kidney

T3a	Tumor grossly extends into renal vein or its muscle-containing branches; tumor invading perirenal or sinus fat
T3b	Tumor grossly extends into vena cava below diaphragm
T3c	Tumor grossly extends into vena cava above diaphragm or invades its wall
T4	Tumor invades beyond Gerota's fascia (including contiguous spread into ipsilateral adrenal)
Regional lymph nodes	
Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in single regional lymph node (s)
Distant metastasis	
M0	No distant metastasis
M1	Distant metastasis

Stage Grouping			
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T1-2	N1	M0
	T3	N0-1	M0
Stage IV	T4	Any N	M0
	Any T	Any N	M1

Stage wise treatment –

In addition to clinical stage, patient's performance status (ECOG[5]) should be taken into consideration before deciding the treatment options.

Stage I

Preferred – nephron-sparing surgery if technically feasible

Optional – radical nephrectomy*

Others

9. Active surveillance

10. Ablative therapies (cryotherapy, radiofrequency ablation, microwave thermotherapy, high frequency focussed ultrasound, etc.)

Adrenalectomy / lymphadenectomy: not indicated, unless grossly involved intraoperatively (staging changed)

** In patients with early stage RCC radical nephrectomy is justified when NSS is technically not feasible / the patient understands the other option (NSS) and opts for RN.*

Stage II

Preferred – radical nephrectomy

Optional (imperative setting**) – nephron-sparing surgery

Adrenalectomy / lymphadenectomy: not indicated

*** Imperative indications of NSS: solitary kidney, compromised function or reserve of contralateral kidney (chronic renal insufficiency, severe diabetes mellitus, severe hypertension), bilateral synchronous tumors, familial RCC*

Stage III

Preferred – radical nephrectomy, with tumor thrombectomy (if present)

Lymphadenectomy – may be performed for better staging. LND in patients with high-risk disease improves stage assessment and may prolong survival[6,7]. A mere sampling of the renal hilar lymph nodes is insufficient for pathologic staging. For right sided tumor, paracaval and interaortocaval lymph nodes and for left sided tumor para-aortic and interaortocaval lymph nodes should be removed from the crus of the diaphragm to the common iliac artery. If disease is confirmed within the interaortocaval nodes, a complete retroperitoneal LND is recommended to define the full extent of metastatic lymph node involvement[8].

Adrenalectomy: not required unless direct invasion or tumor nodule (stage changed)

Stage IV

16. Nephrectomy with adjacent organ excision

17. Metastasectomy (if solitary metastasis)

18. Adrenalectomy

19. Cyto-reductive nephrectomy

Patients of stage IV disease are candidates for adjuvant systemic therapy (*vide infra*).

Socio-economic and facility issues –

Advanced –

- staging tools
- surgical facility
- follow up facility
- socio-economic support

may not be available everywhere.

Centers which intend to treat RCC must be equipped with facility for histopathology / CECT / Blood transfusion.

If above facilities not available / locally advanced disease / patient wants NSS → ref. to higher center.

Follow up protocol after definitive local treatment –

Risk grouping (UCLA integrated staging system)[9]:

T stage	1				2	3				4
Furhman grade	1-2		3-4		1-4	1		2-4		1-4
ECOG PS	0	≥ 1	Any	≥ 1	Any	0	≥ 1	0	≥ 1	Any
Risk group	Low	Intermediate							high	

Follow up protocol based on the above risk grouping[10] –

		6m	12m	18m	24m	30m	36m	42m	48m	54m	60m	6y	7y	8y	9y	10y
Hx/Ex/labs	L	-	√	-	√	-	√	-	√	-	√	-	-	-	-	-
	I	√	√	√	√	√	√	-	√	-	√	√	√	√	√	√
	H	√	√	√	√	√	√	-	√	-	√	√	√	√	√	√

CT chest*	L	-	√	-	√	-	√	-	√	-	√	-	-	-	-	-
	I	√	√	√	√	√	√	-	√	-	√	√	√	√	√	√
	H	√	√	√	√	√	√	-	√	-	√	√	√	√	√	√
CT abdomen	L	-	-	-	√	-	-	-	√	-	-	-	-	-	-	-
	I	-	√	-	√	-	-	-	√	-	-	√		√		√
	H	√	√	√	√	-	√	-	√	-	√	√		√		√

*** CT chest can be replaced with CxR after initial 3 years.**

L – low risk; I – intermediate risk; H – high risk group.

Systemic therapy –

Indications:

l. Metastatic RCC with resectable disease (cytoreductive nephrectomy and metastatectomy should be done whenever feasible)

m. Non-resectable Locally advanced / metastatic RCC

Agents–

	Name
Å	Sunitinib
Å	Sorafenib
Å	Pazopanib
Å	Bevacizumab + IFN-α
Å	Tamsirolimus
Å	Everolimus
Å	IFN-α
Å	High dose IL-2

Targeted therapy in the form of tyrosine kinase inhibitors (1-4) and m-TOR inhibitors (5-6) have become first line systemic treatment for management of metastatic RCC. A substantial improvement in progression-free survival and overall survival has been

achieved in large randomized controlled trials, when compared to Interferon-α. These agents have also been found to be effective in non-clear cell RCC, which are typically resistant to cytokines and interferons. Sarcomatoid variant is associated with poor prognosis, and a modest response with doxorubicin & gemcitabine is observed.

Limitations –

- high cost and limited availability
- significant side-effects
- efficacy

Note : Targetted therapy for metastatic RCC/ locally advanced RCC should be decided by Urologist and given in supervision of a Urologist.

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BLADDER CANCER

I. WHEN TO SUSPECT / RECOGNIZE?

a) Introduction / b) Case definition: Bladder carcinoma is the most common malignancy of the urinary tract and is the 9th most common cancer diagnosis worldwide. At the initial diagnosis of bladder cancer, 70% of cases are diagnosed as non-muscle-invasive bladder cancer (NMIBC) and approximately 30% as muscle-invasive disease. [1, 2]

Non-muscle-invasive bladder cancer: Bladder cancer that does not involve the muscularis propria.

Invasive bladder cancer: Bladder cancer that histologically invades the muscularis propria.

- Risk factors [3,4,5,6]
  - ï Tobacco consumption
  - ï Occupational exposure to chemicals
  - ï Radiation therapy
  - ï Chronic urinary tract infection
  - ï Bladder schistosomiasis
  - ï Chemotherapy – Cyclophosphamide
- Å Active and passive tobacco smoking continues to be the main risk factor, while exposure-related incidence is decreasing.

II. INCIDENCE OF THE CONDITION IN OUR COUNTRY: Exact incidence is unknown. The recent trends indicate increasing incidence of bladder cancer. This may be partially attributed due to better detection and improved health care. Expected to be of same incidence as the western world.

III DIFFERENTIAL DIAGNOSIS:

20. Chronic cystitis
21. Tuberculous cystitis
22. Bladder calculi
23. Interstitial cystitis
24. Radiation cystitis
25. Eosinophilic cystitis

IV. PREVENTION AND COUNSELING:

11. Mass education about bladder cancer and its relationship with tobacco use
12. Anti-tobacco campaign
13. Careful history about smoking, occupational exposure to risk factors and storage LUTS
14. Detailed evaluation of all patients with gross hematuria and elderly patients (>40 years) with microscopic hematuria and associated risk factors like smoking
15. **All patients with hematuria should undergo full urological evaluation**

16. Prompt referral of men with advanced bladder cancer to higher centers for further evaluation

V. OPTIMAL DIAGNOSTIC CRITERIA, INVESTIGATIONS, TREATMENT & REFERRAL CRITERIA

Diagnostic criteria:

1. History of gross painless hematuria
2. History of severe storage LUTS – may be due to CIS
3. Recurrent cystitis in elderly
4. Positive cytology
5. Cystoscopic examination and imaging studies showing tumour(s) in the bladder.

Diagnosis –The diagnosis mainly depends on the cystoscopic examination of the bladder, biopsy, and urine cytology. The initial therapy for bladder tumours is complete macroscopic transurethral resection of bladder tumours (TURBT) including a part of underlying muscle [7]. Cold cup biopsies should be discouraged.

A second TURBT should be considered [8]:

1. If there is suspicion that the initial resection was incomplete
2. When multiple or large tumours are present
3. When pathologist reported no muscle in the specimen
4. When a high grade tumour (pT1G3) was detected.

The management algorithm is based on the diagnosis of invasion of muscularis propria or not.

Routine bladder mapping biopsies are not indicated except in

1. Patients with positive urine cytology with normal looking mucosa in cystoscopy
2. Biopsy of the apical prostatic urethra when there is a bladder neck tumour or when abnormalities of prostatic urethra are visible.

Carcinoma in situ (CIS) is diagnosed based on the histology of bladder mucosal biopsies. Fluorescent cystoscopy is recommended in these cases [9].

Investigations:

4. Urine cytology: Cytology is useful when a high-grade malignancy or CIS is present. It is used to predict high grade tumour before TUR. However, urinary cytology often is negative in the presence of low-grade cancer.
5. Ultrasonography (USG): Transabdominal USG permits characterization of renal masses, detection of hydronephrosis and visualization of intraluminal masses in the bladder. It can be as accurate as IVU for diagnosis of upper urinary tract obstruction [10]. The USG is thus a useful tool for investigation in patients with haematuria to detect obstruction; it cannot however exclude the presence of upper tract tumours.

6. Pelvic examination (Bimanual examination) under anaesthesia: Helpful in assessment of local staging in muscle invasive bladder cancer and advanced cases. Not of much value in superficial bladder cancers. Should be done along with TURBT.[11]
7. Cystoscopy & TURBT: Cystoscopy should describe all macroscopic features of the tumour (site, size, number and appearance) and mucosal abnormalities. A bladder diagram is recommended. The gold standard in establishing the diagnosis of bladder tumour is TURBT.
8. Intravenous Urography (IVU): Intravenous urography (IVU) is used to detect filling defects in the calyces, renal pelvis and ureters, and hydronephrosis. Acceptable for staging of muscle invasive bladder cancer when CT Urography is not readily available [12].
9. CT Urography (CTU): CTU is mainly recommended for histologically proven muscle invasive bladder cancers for staging. It is not useful for making a diagnosis of muscle invasive bladder cancer. Pre TURBT CTU is indicated in select group of patients in whom it would significantly alter the management. Especially in muscle invasive tumours of the bladder and in upper tract tumours, CT urography gives more information than IVU does (including status of lymph nodes and neighbouring organs) [12].
10. MRI – abdomen and pelvis/ MR Urography: Optimal investigation for staging in muscle invasive bladder cancer Recommended only when there is definite contraindication for CT urography or IVU like contrast allergy and renal failure.
11. Serum alkaline phosphatase – if elevated indicates metastatic bone disease.
12. Bone scan –Indicated in patients with raised alkaline phosphatase and with bone pain.
13. CT scan of chest is recommended for optimal staging in muscle invasive bladder cancer; if not available chest X-ray is acceptable.

Staging of bladder cancer:

Based on Tumour Node Metastasis (TNM) classification of carcinoma bladder (2010) [13].

- **T - primary tumour**
- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour
- Ta Non-invasive papillary carcinoma
- Tis Carcinoma in situ. 'flat tumour'
- T1 Tumour invades subepithelial connective tissue
- T2 Tumour invades muscle
    - T2a Tumour invades superficial muscle (inner half)
    - T2b Tumour invades deep muscle (outer half)
- T3 Tumour invades perivesical tissue
    - T3a Macroscopically
    - T3b Microscopically (extravesical mass)

- T4 Tumour invades any of the following: Prostate, uterus, vagina, pelvic wall, abdominal wall
    - T4a Tumour invades prostate, uterus or vagina
    - T4b Tumour invades pelvic wall or abdominal wall
- **N - regional lymph nodes**
- NX 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 a multiple lymph nodes in the true pelvis (hypogastric, obturator, external iliac or presacral)
- N3 Metastasis in a common iliac lymph node(s)
- **M - distant metastasis**
- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis

Characteristics of Stages Ta, T1, and Tis

Stage Ta tumours are confined to the urothelium, have a papillary configuration of their exophytic part, and do not penetrate from the urothelium into the lamina propria or detrusor muscle.

Stage T1 tumours originate from the urothelium but penetrate the basement membrane which separates the urothelium from the deeper layers. T1 tumours invade into the lamina propria, but are not so deep that they reach the detrusor muscle.

Carcinoma in situ (Tis) is a high-grade (anaplastic) carcinoma confined to the urothelium, but with a flat non-papillary configuration. Unlike a papillary tumour, Tis appears as reddened and velvety mucosa and is slightly elevated but sometimes not visible. Tis can be local or diffuse.

Three types of Tis are distinguishable;

- Primary Tis (no previous or concurrent papillary tumours);
- Secondary Tis (with a history of papillary tumours);
- Concurrent Tis (in the presence of papillary tumours).

Characteristics of grade [14]:

1973 WHO Classification

Apart from their architecture, the individual cells show different degrees of anaplasia:

Grade 1: well differentiated tumour

Grade 2: moderately differentiated tumour

Grade 3: poorly differentiated tumour

2004 WHO Classification

A new classification system was initially proposed by the WHO/ISUP in 1998 and updated by the WHO in 2004. For non-invasive urothelial neoplasias, the categories are:

- **Flat lesions**
- Hyperplasia (flat lesion without atypia or papillary)

- Reactive atypia (flat lesion with atypia)
- Atypia of unknown significance
- Urothelial dysplasia
- Urothelial carcinoma *in situ* (CIS*)*
- **Papillary lesions**
- Urothelial papilloma (a completely benign lesion)
- Papillary urothelial neoplasm of low malignant potential
- (PUNLMP)
- Low-grade papillary urothelial carcinoma
- High-grade papillary urothelial carcinoma

The 2004 WHO grading system defines Tis as a non-papillary, i.e. a flat, lesion in which the surface epithelium contains cells that are cytologically malignant. Papillary tumours are classified as either papillary urothelial neoplasms of low malignant potential (PUNLMP) or as urothelial carcinomas, with the latter being subdivided into two grades: low grade and high grade. The intermediate group (G2) has been eliminated; this group was the subject of controversy in the 1973 WHO classification. Use of the 2004 WHO classification is advocated, as this should result in less diagnostic variability among pathologists.

Predicting recurrence and progression of tumours [15,16]:

TaT1 tumours

The pattern of recurrence and progression depends on the following clinical and pathological factors:

1. Number of tumours
2. Tumour size
3. Prior recurrence rate
4. T-category
5. Pesence of concurrent CIS
6. Tumour grade.

CIS

No prognostic factors are well established. Retrospective studies suggest the following:

1. Concurrent CIS with T1 tumours have worser prognosis than primary CIS and secondary CIS [17, 18]
2. Responders to BCG have better prognosis than those non-responders. [19]

Treatment: Treatment strategy varies according to the stage and grade of bladder cancer.

Non-muscle invasive bladder cancer (superficial bladder cancer) NMIBC:

The standard initial therapy for Ta and T1 papillary bladder tumours is complete TURBT. Tumours less than 1cm in size can be resected enbloc. Larger tumours should be resected in fractions, which include the exophytic part, the underlying bladder wall and the edges of resection area. Complete and correct TUR is essential to achieve a good prognosis [20].

Prognostic Factors and Adjuvant Treatment

TaT1 papillary tumours

Recommendations for Low Risk Tumours

Patients with a single, small, low grade Ta tumour without CIS, who are at low risk for both recurrence and progression, should receive:

1. A complete TUR.
2. An immediate single post-operative instillation with a chemotherapeutic agent (drug optional – Mitomycin C preferred). [21]
3. No further treatment is recommended prior to recurrence.

Recommendations for High Risk Tumours

Patients with TaT1 high grade tumours with or without CIS and those with CIS alone are at high risk of progression. Treatment should consist of:

1. Complete TUR of papillary tumours followed by an immediate post-operative instillation with a chemotherapeutic agent (drug optional – Mitomycin C preferred).[21]
2. A second TUR after 4–6 weeks.[9]
3. Adjuvant intravesical immunotherapy with BCG (full dose or reduced dose in case of side effects). Maintenance therapy for at least 1 year (monthly once) is necessary [22,23] although the optimal maintenance scheme has not yet been determined.
4. Immediate cystectomy may be offered to patients at highest risk of tumour of progression (Patients with multiple tumours, large tumours (> 3 cm), and highly recurrent tumours (> 1 recurrence/year), stage T1 tumours with high grade tumours, and CIS).
5. In patients with BCG failure, cystectomy is recommended. [24]

Recommendations for Intermediate Risk Tumours

In the remaining intermediate risk patients, adjuvant intravesical therapy is necessary but no consensus exists regarding the optimal drug and the most appropriate scheme. BCG is more effective than chemotherapy in both reducing recurrence and progression. The major issue in the management of intermediate risk tumours is to prevent recurrence and progression, of which recurrence is clinically the most frequent. Treatment should include:

1. Complete TUR followed by an immediate postoperative instillation with a chemotherapeutic agent (drug optional).
2. A second TUR after 4–6 weeks when the initial resection was incomplete.

3i. Adjuvant intravesical chemotherapy (drug optional), schedule: optional although the duration of treatment should not exceed 1 year. **(Or)**

3ii. Adjuvant intravesical immunotherapy with BCG (full dose or reduced dose in case of side effects). Maintenance therapy for at least 1 year (monthly once) is necessary although the optimal maintenance schedule has not yet been determined.

Carcinoma *in situ*

CIS have a high risk of progression to muscle invasive disease which exceeds 50% in some studies. BCG intravesical immunotherapy (induction and maintenance) is superior to intravesical chemotherapy in increasing the complete response rate and the overall percent of patients remaining tumour free. Moreover, BCG reduces the risk of

progression as compared to either intravesical chemotherapy or a different immunotherapy [25]. Early radical cystectomy at the time of diagnosis provides excellent disease-free survival, but over-treatment occurs in up to 50% of patients.

Recommendations for the treatment of CIS

1. In concurrent CIS, the initial strategy (TUR, early intravesical instillation, a second TUR) is based on the features of the papillary tumour.
2. Intravesical BCG immunotherapy including at least 1 year maintenance.
3. After the 6 week induction course, a second course of 6 weekly BCG instillations or maintenance cycles consisting of 3 weekly instillations may be considered in non-responders since about 40-60% of these patients will respond to additional treatment with BCG. [23]
4. In BCG non-responders at 6 months, radical cystectomy is recommended. [26].

Muscle invasive bladder cancer:

Neo-adjuvant chemotherapy:

Neo-adjuvant cisplatin-containing combination chemotherapy improves overall survival by 5-7% at 5 years [27]. It should be considered irrespective of the type of definitive treatment. Neo-adjuvant chemotherapy is not recommended in patients with performance status (PS) > 2 and impaired renal function [28].

Radical Surgery and Urinary Diversion

Cystectomy is the preferred curative treatment for localized muscle invasive bladder cancer [29].

Radical cystectomy includes removal of regional lymph nodes, the extent of which has not been sufficiently defined [30]. A delay in cystectomy increases the risk of progression and cancer-specific death [31]. No pre-operative radiotherapy should be administered. Radical cystectomy in both sexes must not include the removal of the entire urethra in all cases, which may then serve as outlet for an orthotopic bladder substitution. If no bladder substitution is attached, the urethra must be checked regularly. Terminal ileum and colon are the intestinal segments of choice for urinary diversion. The type of urinary diversion does not affect oncological outcome.

Contraindications for orthotopic bladder substitution [32]:

1. Positive margins at the level of urethral dissection
2. Positive margins anywhere on the bladder specimen (in both sexes), if the primary tumour is located at the bladder neck or in the urethra (in women), or if tumour extensively infiltrates the prostate.

Pre-operative bowel preparation is not mandatory.

Before cystectomy, the patient should be counselled adequately regarding all possible alternatives, and the final decision should be based on a consensus between patient and surgeon.

For patients with inoperable locally advanced tumours (T4b), primary radical cystectomy is a palliative option and not recommended as a curative treatment.

Neoadjuvant Radiotherapy in Muscle-Invasive Bladder Cancer [33]
Pre-operative radiotherapy does not increase the survival for operable muscle invasive bladder cancer.

Bladder-Sparing Treatments
Radical TURBT
Radical TURBT is not recommended except in a rare situation when patient not willing for open surgery or unfit for radical cystectomy [34].
External beam radiotherapy [35, 36]
External beam radiotherapy alone should only be considered as a therapeutic option when the patient is unfit for cystectomy or a multimodality bladder-preserving approach Radiotherapy can also be used to stop bleeding from the tumour when local control cannot be achieved by transurethral manipulation because of extensive local tumour growth.
Chemotherapy [37,38]
*Although ci*splatin-based chemotherapy, as primary therapy for locally advanced tumours in highly selected patients, has led to complete and partial local responses, the long-term success rate is low.

Multimodality treatment [39,40]
There are comparable long-term survival rates in cases of multimodality treatment success. Delay in surgical therapy can compromise survival rates.

Adjuvant Chemotherapy [41]
Adjuvant chemotherapy is advised within clinical trials, but not for routine use.

Metastatic Disease [42 -47]
Urothelial carcinoma is a chemosensitive tumour. Performance status (PS) and the presence or absence of visceral metastases are independent prognostic factors for survival.
These factors are at least as important as the type of chemotherapy administered.
Cisplatin-containing combination chemotherapy is able to achieve a median survival of up to 14 months, with long-term disease-free survival reported in about 15% of patients with nodal disease and good PS. Single-agent chemotherapy provides low response rates of usually short duration. Post-chemotherapy surgery after a partial or complete response may contribute to long-term disease-free survival. Prognostic factors should guide the treatment selection.
NOTE : All chemotherapeutic drugs/ targeted therapy should be decided and administered in consultation with a Urologist.
First-line treatment for "fit" patients:
Use cisplatin-containing combination chemotherapy with GC, MVAC, preferably with GCSF, or HD-MVAC with GCSF.
Carboplatin and non-platinum combination chemotherapy is not recommended.

First-line treatment in patients ineligible ('unfit") for cisplatin:
Use carboplatin combination chemotherapy or single agents.
For cisplatin-ineligible patients ('unfit') with either PS 2 or impaired renal function, or with poor prognostic factors, first-line treatment is carboplatin-containing combination chemotherapy, preferably with gemcitabine/carboplatin.

Second-line treatment:
In patients progressing after platinum-based combination chemotherapy for metastatic disease vinflunine should be offered, which has the highest level of evidence to date, or clinical trials of other treatments.

Follow-up for non-muscle invasive bladder tumours [48, 49]
Patients with non-muscle invasive bladder tumours need to be regularly followed up because of the risk of recurrence and progression; however, the frequency and duration of cystoscopies should reflect the individual patient's degree of risk.
The result of the first cystoscopy after TUR at 3 months is a very important prognostic factor for recurrence and for progression. The first cystoscopy should thus always be performed at 3 months after TUR in all patients with non-muscle invasive bladder tumour.
Recommendations for follow-up cystoscopy
Patients with tumours at low risk of recurrence and progression should have a cystoscopy at 3 months. *If negative, the following cystoscopy is advised at 9 months and consequently yearly for 5 years.*

Patients with tumours at high risk of progression should have a cystoscopy and urinary cytology at 3 months. If negative, the following cystoscopies and cytologies should be repeated every 3 months for a period of 2 years, every 4 months in the third year, every 6 months thereafter until 5 years, and yearly thereafter. A yearly evaluation of the upper tract by IVU or retrograde pyelogram is recommended.

Patients with intermediate-risk of progression (about one-third of all patients) should have an in-between follow-up scheme using cystoscopy and cytology, adapted according to personal and subjective factors.

Patients with Tis should be followed up for life due to the high risk of recurrence and progression, both within the bladder and extravesically. Urine cytology together with cystoscopy (and bladder biopsies in cytology positive cases) is essential for monitoring of treatment efficacy. The follow-up schedule is the same as for patients with high-risk tumours.

Follow up for muscle invasive bladder cancer [50]
Follow-up is based on the stage of initial tumour after cystectomy. At every visit, the following should be performed:

History, Physical examination, Serum chemistries and chest radiograph annually for pT1 disease; semiannual evaluation for patients with pT2 disease; and quarterly evaluation for patients with pT3 disease. For the last group, semiannual CT scan is recommended.
Bone scan only when indicated or symptomatic. IVU can be done for upper tract surveillance when CT scan is not readily available.
After 5 years of follow-up, stop oncological surveillance and continue with functional surveillance.

Referral criteria:

- Patients with gross painless hematuria with association with high risk factors
- Patients with severe storage LUTS with or without palpable pelvic mass suggestive of bladder cancer
- Those with advanced bladder cancer and metastases

*Situation 1: At Secondary Hospital / Non-Metro Situation: Optimal Standards Of Treatment In Situations Where Technology And Resources Are Limited.

a) **Clinical diagnosis:** Careful evaluation of patients with gross painless hematuria, Pelvic examination for bladder masses, not useful in non-muscle invasive bladder cancers.
b) **Investigations:** Urine microscopy for hematuria, urine cytology for malignant urothelial cells. Ultrasound of abdomen and pelvis - to localize the cause of hematuria like renal and bladder tumours. Cystoscopy in all cases of gross hematuria and those with bothersome severe storage LUTS and positive microscopic hematuria.
c) **Treatment:** According to the stage of the disease.

Standard operating procedure:

j) Inpatient:
k) Outpatient:
l) Daycare:

Referral criteria:
Patients with gross painless hematuria known to have bladder tumour
Positive urine dipstick or microscopic hematuria
Positive urine cytology

*Situation 2: At super specialty facility in metro location where higher end technology is available.

a) Clinical diagnosis: Evaluation of gross hematuria, positive microscopic hematuria and positive urine cytology. Pelvic examination – to look for bladder masses.

b) Investigations: All the possible investigations mentioned.

c) Treatment: According to the stage of the disease and the treatment options selected by the patient after counseling.

Standard operating procedure

a) Inpatient
b) Outpatient
c) Daycare

Referral Criteria:
For diagnosis and staging – CT Urography, molecular urinary markers.
Evaluation of metastatic disease – bone scan if required.

VI. WHO DOES WHAT? AND TIMELINES

n. Doctor – clinical diagnosis, treatment, follow-up
o. Nurse – counseling, preoperative preparation, essential post-operative care, stoma care and follow-up
p. Technician – Investigations and preoperative preparation.

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RESOURCES REQUIRED FOR ONE PATIENT /PROCEDURE (PATIENT WEIGHT 60 KGS)
(Units to be specified for human resources, investigations, drugs and consumables and equipment. Quantity to also be specified)

Situation	HUMAN RESOURCES	INVESTIGATIONS	DRUGS & CONSUMABLES	EQUIPMENT
1				
2				

PROSTATE CANCER

I. WHEN TO SUSPECT / RECOGNIZE?

- Introduction and Case definition: Cancer of the prostate (PCa) is now recognized as one of the most important medical problems facing the male population.[1]Prostate cancer is the 2nd most common cause of cancer death in men. Affects 4% of men in undeveloped countries & 15% of men in developed countries [2]
- Risk factors
    - Increasing age
    - Ethnical origin
    - Heredity
- Risk is doubled when one first line relative has prostate cancer. Risk is 5 – 11 fold when two or more first line relatives has PCa[3]

II. INCIDENCE OF THE CONDITION IN OUR COUNTRY: Exact incidence is unknown. Expected to be of same incidence as the western world.

III DIFFERENTIAL DIAGNOSIS:

m) Benign prostatic hyperplasia
n) Granulomatous Prostatitis
o) Transitional cell carcinoma of prostate
p) Chronic prostatitis
q) Prostatic calculi

IV. PREVENTION AND COUNSELING:

d) Mass education about prostate cancer
e) Opportunistic screening for prostate cancer with serum PSA
f) Counseling about serum PSA and its implications
g) Chemoprevention of prostate cancer
h) Recognizing bladder outflow obstruction and other complications in men due to prostate cancer
i) Thorough examination in elderly men who are at risk
j) Prompt referral of men with suspicion of prostate cancer to higher centres for further evaluation

V. OPTIMAL DIAGNOSTIC CRITERIA, INVESTIGATIONS, TREATMENT & REFERRAL CRITERIA

Diagnostic criteria: Screening & Early detection of prostate cancer

Population or mass screening is defined as the examination of asymptomatic men (at risk). It usually takes place as part of a trial or study and is initiated by the screener. In contrast, early detection or opportunistic screening comprises individual case findings, which are initiated by the person being screened (patient) and/or his physician. The primary endpoint of both types of screening has two aspects:

1. Reduction in mortality from PCa.
2. Quality-of-life adjusted gain in life years (QUALYs).

Screening for prostate cancer has conflicting results.

Based on the results of two large, randomised trials [4,5], it is accepted that at present widespread mass screening for PCa is not appropriate. Rather, early detection (opportunistic screening) should be offered to the well-informed man. Hence

- Å Early PSA testing should be a shared decision between patient and physician
- Å PSA testing & DRE – offered to men >40 years of age & expected life expectancy of atleast 10 years

Diagnosis –The main diagnostic tools to obtain evidence of PCa include digitial rectal examination (DRE), serum concentration of PSA and transrectal ultrasonography (TRUS).

Investigations:

1. DRE: Most prostate cancers are located in the peripheral zone of the prostate and may be detected by DRE when the volume is about 0.2 mL or larger. A suspect DRE is an absolute indication for prostate biopsy. In about 18% of all patients, PCa is detected by a suspect DRE alone, irrespective of the PSA level [6]
2. Serum PSA(Prostate-specific antigen) is organ-specific but not cancer-specific. Thus, serum levels may be elevated in the presence of benign prostatic hypertrophy (BPH), prostatitis and other non-malignant conditions. The level of PSA as an independent variable is a better predictor of cancer than suspicious findings on DRE or TRUS [7]. The level of PSA is a continuous parameter: the higher the value, the more likely is the existence of PCa. This means there is no universally accepted cut-off or upper limit.[8] As yet, there is no long-term data to help determine the optimal PSA threshold value for detecting non-palpable, but clinically significant, PCa. Modifications to improve the specificity of PSA in early detection of Ca.P
    a. PSA density
    b. PSA density of transition zone
    c. Age specific PSA
    d. PSA molecular forms – PCA3
    e. Free / Total PSA ratio (at PSA 4-10ng/ml) <0.10 – 56% biopsy positive
    f. PSA doubling time (PSADT)
    g. PSA velocity
    h. When in doubt, repeat PSA under standardised conditions
3. Transrectal ultrasound of prostate (TRUS) guided biopsy of prostate. Gray-scale TRUS does not detect areas of PCa with adequate reliability. It is therefore not useful to replace systematic biopsies with targeted biopsies of suspect areas.

However, additional biopsies of suspect areas may be useful. Transrectal ultrasonography (TRUS) guided biopsy under antibiotic cover with periprostatic nerve block– minimum 10 core laterally and posteriorly directed biopsy is recommended (>12 not significantly more conclusive). [9]The indications for a repeat biopsy (including TZ biopsy) [10] are:

a. Rising and/or persistent PSA, suspicious DRE;
b. Atypical small acinar proliferation (ASAP).
c. Extensive High-grade prostatic intraepithelial neoplasia (PIN)

Complications of biopsy – infection, sepsis < 1%, clot retention, acute urinary retention, bleeding from rectum, hematuria, hemospermia (the last 3 are mostly self limiting).

d. Pathology of prostate cancer:
    i. The Gleason score is the sum of the most dominant and second most dominant (in terms of volume) Gleason grade.
    ii. A diagnosis of Gleason score 4 or lower should not be given on prostate biopsies
    iii. Gleason score system is the single strongest prognostic factor for clinical behaviour and treatment response.

4. TRUS is also useful for staging of prostate cancer, however remains inadequate. [11]
5. MRI – abdomen and pelvis/ MR Urography [12] (risk stratification)
    a. Local staging (T-staging)
    b. MRI demonstrates higher accuracy for the assessment of uni- or bilobar disease (T2), Extracapsular extension (ECE) and Seminal vesicle invasion (SVI) (T3), as well as the invasion of adjacent structures (T4).
    c. Lymph node status (N-staging) is only important when potentially curative treatment is planned.
6. Pelvic lymph node dissection remains the only reliable staging method in clinically localized PCa. [13]
7. Bone scan - Skeletal metastasis (M-staging) is best assessed by bone scan. This may not be indicated in asymptomatic patients if the serum PSA level is less than 20 ng/mL (risk stratification) in the presence of well or moderately differentiated tumours.[14]
8. Serum alkaline phosphatase – if elevated, indicates metastatic bone disease.
9. Transurethral resection of prostate- In those men who come with bladder outflow obstruction in an unsuspected fashion and biopsy report may reveal carcinoma of prostate.

Staging of prostate cancer: Based on Tumour Node Metastasis (TNM) classification of carcinoma prostate [15].

- **T - primary tumour**
- TX Primary tumour cannot be assessed
- T0 No evidence of primary tumour

- T1 Clinically inapparenttumour not palpable or visible by imaging
  - T1a Tumour incidental histological finding in 5% or less of tissue resected
  - T1b Tumour incidental histological finding in more than 5% of tissue resected
  - T1c Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen [PSA] level)
- T2 Tumour confined within the prostate1
  - T2a Tumour involves one half of one lobe or less
  - T2b Tumour involves more than half of one lobe, but not both lobes
  - T2c Tumour involves both lobes
  - T3 Tumour extends through the prostatic capsule
    - T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement.
    - T3b Tumour invades seminal vesicle(s)
  - T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall
- **N - regional lymph nodes**
- NX Regional lymph nodes cannot be assessed
- N0 No regional lymph node metastasis
- N1 Regional lymph node metastasis
- **M - distant metastasis**
- MX Distant metastasis cannot be assessed
- M0 No distant metastasis
- M1 Distant metastasis
- M1a Non-regional lymph node(s)
- M1b Bone(s)
- M1c Other site(s)

- Group I T1a-c N0 M0 PSA < 10 Gleason < 6
  - T2a N0 M0 PSA < 10 Gleason < 6
- Group IIA T1a-c N0 M0 PSA < 20 Gleason 7
  - T1a-c N0 M0 PSA > 10 < 20 Gleason < 6
  - T2a, b N0 M0 PSA < 20 Gleason < 7
- Group IIb T2c N0 M0 Any PSA Any Gleason
  - T1-2 N0 M0 PSA > 20 Any Gleason
  - T1-2 N0 M0 Any PSA Gleason > 8
- Group III T3a, b N0 M0 Any PSA Any Gleason
- Group IV T4 N0 M0 Any PSA Any Gleason
  - Any T N1 M0 Any PSA Any Gleason
  - Any T Any N M0 Any PSA Any Gleason

ï (Note: When either PSA or Gleason is not available, grouping should be determined by cT category and whichever of either PSA of Gleason is available. When neither is available prognostic grouping is not possible, use stage grouping)

Treatment: Treatment of prostate cancer depends on the stage of the disease and prognostic information available.

- **Deferred treatment (Watchful waiting & Active surveillance) [16- 20]**

Make difference between active survillience and watchful waiting

Indications:

- **In presumed localisedPCa (Nx-N0, M0):**
  - **Stage T1a:** well and moderately differentiated tumours. In younger patients with a life expectancy of > 10 years, re-evaluation with PSA, TRUS and biopsies of the prostatic remnant is recommended
  - **Stage T1b-T2b:** well & moderately differentiated tumours. In asymptomatic patients with a life expectancy of < 10 years
  - **Inclusion criteria for active surveillance** with the lowest risk of cancer progression are:
    - PSA < 10 ng/ml, biopsy Gleason score < 6, < 2 positive biopsies, < 50% cancer per biopsy, cT1c-2a
- **In presumed localisedPCa (Nx-N0, M0):**
  - Stage T1b-T2b patients who are well informed and have well-differentiated (or Gleason 2-4) PCa and a life expectancy of 10-15 years.
  - All patients not willing to accept side-effects of active treatment.
  - Well-informed, asymptomatic patients with high PSA levels for whom cure is unlikely.
- **In locally advanced disease (stage T3-T4):**
  - Asymptomatic patients with well- or moderately differentiated cancer, PCa and a short life expectancy
  - PSA < 50 ng/mL and PSA doubling time > 12 months
- **In metastatic disease (M1):**
  - A very rare patient without any symptoms and the possibility of close follow-up

The criteria for active surveillance have not reached a consensus stage yet. Every institution has different parameters and that should be mentioned. Active surveillance is not the same as watchful waiting.

2. Radical Prostatectomy [21,22]period between biopsy and surgery

- **Indications**
  - In patients with low and intermediate risk localisedPCa (cT1a-T2b and Gleason score 2-7 and PSA < 20) and a life expectancy > 10 years
- **Optional**
  - Selected patients with low-volume high-risk localisedPCa (cT3a or Gleason score 8-10 or PSA >20)
  - Highly selected patients with very high-risk localisedPCa (cT3b-T4 N0 or any T N1) in the context of multimodality treatment

- **Recommendations**
  - Short-term (3 months) neoadjuvant therapy with gonadotrophin releasing-hormone analogues is not recommended in the treatment of stage T1-T2 disease
  - Nerve-sparing surgery may be attempted(offered) in pre-operatively potent patients with low risk for extracapsular disease (T1c, Gleason score < 7 and PSA < 10 ng/mL or see Partin tables / nomograms)
  - Unilateral nerve-sparing procedures are an option in stage T2a disease
  - Recommendation for Lymphadenectomy
  - Extended PLND is recommended for all patients who have a greater than 2% chance of having lymph node disease. (NCCN guidelines)

3. Definitive radiation therapy [23-28]

- **In localised prostate cancer T1c-T2c N0 M0**, 3D-CRT with or without IMRT is recommended even for young patients who refuse surgical intervention. There is fairly strong evidence that low-, intermediate- and high-risk patients benefit from dose escalation
- **For patients in the high-risk group,** short-term ADT prior to and during radiotherapy results in increased overall survival, but three years of adjuvant ADT are better according to the results of EORTC 22961
- Transperineal interstitial brachytherapy with permanent implants is an option for
  - Patients with cT1-T2a, Gleason score < 7 (or 3 + 4), PSA < 10 ng/mL, prostate volume < 50 mL, without a previous TURP and with a good IPSS
- Immediate post-operative external irradiation after RP for
  - Patients with pathological tumour stage T3 N0 M0 improves overall survival, biochemical and clinical disease-free survival with the highest impact in cases of positive margins (R1)
- An alternative option is to give radiation at the time of biochemical failure, but before PSA rises above 0.5 ng/mL
- In locally advanced prostate cancer T3-4 N0 M0, overall survival is improved by concomitant and adjuvant hormonal therapy for a total duration of 3 years, with external beam irradiation for patients with a WHO 0-2 performance status.
- For a subset of patients with T2c-T3 N0-x and a Gleason score of 2-6, short-term ADT before and during radiotherapy may favourably influence overall survival
- In very high-risk prostate cancer, c-pN1 M0 with no severe co-morbidity, pelvic external irradiation and immediate long-term adjuvant hormonal treatment improve overall survival, disease-specific failure, metastatic failure and biochemical control

4. Experimental local treatment of prostate cancer[29-32]under invstigations

- **Cyrosurgery:**

- ï Patients with low-risk PCa (PSA < 10 ng/mL, < T2a, Gleason score < 6) or intermediate-risk PCa (PSA > 10 ng/mL, or Gleason score > 7, or stage > 2b) represent potential candidates for CSAP.
- ï Prostate size should be < 40 mL at the time of therapy.
- ï Long-term results are lacking, while 5-year biochemical progression free rates are inferior to those achieved by RP in low risk patients. Patients must be informed accordingly.

Å Cryosurgery - a possible alternative treatment for PCa in patients who are unfit for surgery or with a life expectancy < 10 years.

Å All other minimally invasive treatment options – such as HIFU microwave and electrosurgery – are still experimental or investigational.

Å Focal therapy of PCa is still in its infancy and cannot be recommended as a therapeutic alternative outside clinical trials

r) Hormonal therapy[33-4]

Bone densitometry and bisphosphonates

17. In advanced PCa, androgen deprivation therapy (ADT)
    18. delays progression,
    19. prevents potentially catastrophic complications, and
    20. palliates symptoms effectively, but does not prolong survival.
21. In advanced PCa, all forms of castration used as monotherapy (e.g. orchiectomy, LHRH and DES) have equivalent efficacy.
22. Non-steroidal anti-androgen monotherapy (e.g. bicalutamide) is an alternative to castration in patients with locally advanced disease.
23. In metastatic PCa, the addition of a non-steroidal anti-androgen to castration (CAB) results in a small advantage in OS over castration alone, but is associated with increased adverse events, reduced QoL, and high costs.
24. Intermittent ADT should no longer be regarded as experimental, even though long-term data from prospective clinical trials are still awaited. 'Minimal' ADT should, however, continue to be seen as experimental.
25. In advanced PCa, immediate ADT (given at diagnosis) significantly reduces disease progression, as well as the complication rate due to progression itself, compared with deferred ADT (delivered at symptomatic progression). However, the survival benefit is at best marginal and not related to cancer-specific survival.
26. Bilateral orchiectomy might be the most cost-effective form of ADT, especially if initiated after the occurrence of symptoms from metastatic disease.

Follow-up [47-50]

After treatment with curative intent

14. In asymptomatic patients, a disease-specific history & a serum PSA measurement supplemented by DRE - recommended tests for routine follow-up. These should be performed at 3, 6 & 12 months after treatment, then every 6 months until 3 years, and then annually.
15. After radical prostatectomy, a serum PSA level of more than 0.2 ng/mL can be associated with residual or recurrent disease.

16. After radiation therapy, a rising PSA level over 2 ng/mL above the nadir PSA, rather than a specific threshold value, is the most reliable sign of persistent or recurrent disease.
17. Both a palpable nodule and a rising serum PSA level can be signs of local disease recurrence
18. Detection of local recurrence by TRUS and biopsy is only recommended if it will affect the treatment plan.
19. In most cases TRUS and biopsy are not necessary before second-line therapy.
20. Metastasis may be detected by pelvic CT/MRI or bone scan. In asymptomatic patients, these examinations may be omitted if the serum PSA level < 120 ng/mL.
21. Routine bone scans & other imaging studies are not recommended in asymptomatic patients. If a patient has bone pain, a bone scan should be considered irrespective of the serum PSA level.

After hormonal therapy [51-53]

- Patients should first be evaluated at three & six months after the initiation of treatment. (one month and 3 months after initiating treatment)
- As a minimum,
  - serum PSA measurement
  - digital rectal examination (DRE),
  - serum testosterone and careful evaluation of symptoms in order to assess the treatment response and the side-effects of the treatments given.
- Follow-up should be tailored for the individual patient, according to symptoms, prognostic factors and the treatment given.
- In patients with stage M0 disease with a good treatment response, follow-up is scheduled every six months, and should include as a minimum a disease-specific history, DRE and serum PSA determination
- In patients with stage M1 disease with a good treatment response, follow-up is scheduled for every three to six months.
- As a minimum, this should include a disease-specific history, DRE and serum PSA determination, and is frequently supplemented with haemoglobin, serum creatinine and alkaline phosphatase measurements.
- Patients (especially if M1b status) should be advised on the clinical signs that could suggest spinal cord compression
- When disease progression occurs, or if the patient does not respond to the treatment given, the follow-up needs to be individualised
- Routine imaging of stable patients is not recommended

Treatment of biochemical failure after treatment with curative intent [54- 61]

Presumed local failure after radical prostatectomy

- Patients with presumed local failure only may be candidates for salvage radiotherapy. At least 64 Gy given and preferably before PSA has risen above 0.5 ng/mL.
- Other patients are best offered a period of watchful waiting (active monitoring), with possible hormonal therapy later on

- Presumed local failure after radiotherapy
  - Selected patients may be candidates for salvage radical prostatectomy and patients should be informed about the higher risk of complications, such as incontinence and erectile dysfunction.
  - Salvage prostatectomy should only be performed in experienced centres. Other patients are best offered a period of watchful waiting (active monitoring), with possible hormonal therapy later on
- Presumed distant failure
  - There is some evidence that early hormonal therapy may be of benefit in +/- local failure, delaying progression, and possibly achieving a survival benefit in comparison with delayed therapy.
  - Local therapy is not recommended except for palliative reasons

Castration refractory prostate cancer (CRPC or HRPC)-

- **Definition:**
  - Serum castration levels of testosterone (testosterone < 50 ng/dL or < 1.7 nmol/L)
  - Three consecutive rises of PSA, 1 week apart, resulting in two 50% increases over the nadir, with a PSA > 2 ng/mL
  - Anti-androgen withdrawal for at least 4 weeks*
  - PSA progression, despite consecutive hormonal manipula□ons†
    - * Either anti-androgen withdrawal or one secondary hormonal manipulation should have been done in order to fulfil the criteria for CRPC.
    - † Progression of osseous lesions: progression or appearance of two or more lesions on bone scan or soft tissue lesions using RECIST (Response Evaluation Criteria in Solid Tumours) and with nodes > 2 cm in diameter.

CRPC-

Recommendation of treatment after hormonal treatment

- It is recommended to stop anti-androgen therapy once PSA progression is documented
- Four to six weeks after discontinuation of flutamide or bicalutamide, an eventual anti-androgen withdrawal effect is apparent
- No clear-cut recommendation can be made for the most effective drug for secondary hormonal manipulations. Secondary hormonal manipulations possibilities
- Abiraterone and Cabazitaxel have shown to prolong survival in CRPC after docetaxel chemotherapy. Sipuleucel T is prostate vaccine which is used and has been approved in the west for CRPC which is minimally symptomatic or asymptomatic. Not yet available in India.

Recommendation of cytotoxic therapy

26. Ideally, patients with CRPC should be counselled, managed and treated in a multidisciplinary team

27. In non-metastatic CRPC, cytotoxic therapy should only be considered in clinical trials
28. In patients with a PSA rise only, two consecutive increases of PSA serum levels above a previous reference level should be documented
29. Prior to treatment, PSA serum levels should be > 2 ng/mL to assure correct interpretation of therapeutic efficacy
30. Potential benefits of cytotoxic therapy and expected side-effects should be discussed with each individual patient
31. In patients with metastatic CRPC, and who are candidates for cytotoxic therapy, docetaxel at 75 mg/m2 every 3 weeks has shown a significant survival benefit
32. In patients with symptomatic osseous metastases due to CRPC, either docetaxel or mitoxantrone with prednisone or hydrocortisone are viable therapeutic options
33. Second-line docetaxel should be considered in previously responding patients to docetaxel.
34. Otherwise, treatment is tailored to the individual patient
35. Cabazitaxel should be considered as effective second-line treatment following docetaxel
36. Chemotherapeutic drugs/ targeted therapy for cancer prostate patients should be decided and administered under supervision of a Urologist.

Recommendation of palliative management

- Patients with symptomatic and extensive osseous metastases cannot benefit from medical treatment with regard to prolongation of life
- Management of these patients has to be directed at improvement of QoL and mainly pain reduction
- Effective medical management with the highest efficacy and a low frequency of side-effects is the major goal of therapy
- Bisphosphonates may be offered to patients with skeletal masses (mainly zoledronic acid has been studied) to prevent osseous complications. However, the benefits must be balanced against the toxicity of these agents, in particular jaw necrosis must be avoided
- Palliative treatments such as radionuclides, external beam radiotherapy, adequate use of analgesics should be considered early in the management of painful osseous metastases
- Spinal surgery or decompressive radiotherapy are emergency surgeries which have to be considered in patients with neurological symptoms might be an emergency

Denosumab is more efficacious in preventing skeletal related events than Zoledronic acid with no need to adjust dose for mild to moderate renal dysfunction

Referral criteria for Urologist :

- Men who come with LUTS with DRE showing hard nodular prostate
- Localized prostate cancer
- Men with advanced prostate cancer / metastases

***Situation 1: At Secondary Hospital / Non-Metro Situation: Optimal Standards Of Treatment In Situations Where Technology And Resources Are Limited.**

a) Clinical diagnosis:Hard, nodular, asymmetric prostatic enlargement in digital rectal examination.

b) Investigations: Ultrasound of abdomen and pelvis (preferably by trans rectal ultrasound) – to assess the size and echotexture of prostate and to assess the tumour factors.
c) Treatment:According to the stageof the disease.

Standard operating procedure:

Inpatient:
Outpatient
Daycare:

Referral criteria:

Men who come with LUTS with DRE showing hard nodular prostate
Localized prostate cancer
Men with advanced prostate cancer / metastases

*Situation 2: At super speciality facitlity in metro location where higher end technology is available.

a) Clinical diagnosis; DRE and look for metastatic lesions.

b) Investigations: All the possible investigations mentioned.

c) Treatment:According to the stage of the disease and the treatment options selected by the patient after counseling.

Standard operating procedure

a) Inpatient
b) Outpatient
c) Daycare

Referral Criteria:
For diagnosis and staging – TRUS guided biopsy of prostate (depending on centers of excellence)
Evaluation of metastatic disease – bone scan
Extensive metastatic disease requiring advanced speciality care like radiopharmaceuticals, spine decompression surgery and neurosurgery.

VI. WHO DOES WHAT? AND TIMELINES

q. Doctor – clinical diagnosis, treatment
r. Nurse – counseling, Preoperative preparation, essential post-operative care.
s. Technician – Investigations like serum PSA, bone scan and for administering treatment like radiopahramaceuticals.

VII. FURTHER READING / REFERENCES.

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RESOURCES REQUIRED FOR ONE PATIENT /PROCEDURE (PATIENT WEIGHT 60 KGS)
(Units to be specified for human resources, investigations, drugs and consumables and equipment. Quantity to also be specified)

Situation	HUMAN RESOURCES	INVESTIGATIONS	DRUGS & CONSUMABLES	EQUIPMENT
1				
2				

Testicular Swelling – Testicular Torsion

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General comments:

Clinical guideline are supposed to be reflections of the best currently available evidence. They have 2 parts ï

c. A systematic review of the best available evidence and the strength of that evidence.
    I. The methodology of systematic review is important. This should be clearly stated. All relevant studies should be studied. If Indian studies are available, then they should be included. The evidence should then be ranked using a standard system e.g. levels of evidence - Oxford Centre for Evidence-based Medicine [1]. If necessary relevant focused questions can be framed in order to exactly define the purview of the exercise.
d. Recommendations for practice based on that evidence. These should be graded according to the level of available evidence.

The standard treatment guidelines for testicular torsion fail to mention if it is based on based on current literature following a systematic review. If the literature on testicular torsion lacks well designed studies that are amenable to a structured analysis, this should be mentioned. The evidence for the statements made here should be mentioned. There is no grading of the recommendations. If due to lack of sufficient high quality evidence this document will largely be a consensus document, this should be mentioned.

Review

V. **OPTIMAL DIAGNOSTIC CRITERIA, INVESTIGATIONS, TREATMENT & REFERRAL CRITERIA**

Diagnostic criteria:

7. Blue dot sign – testicular appendix torsion – Unlikely to be seen in dark skin. This should be mentioned.

Investigation

The diagnosis of testicular torsion is mainly clinical as mentioned. In case of a strong suspicion of torsion testes, waiting for a USG (with or without Doppler) can result in significant delay and loss of viability.

If at all a USG is to be included in the guideline, it should be accompanied by a rider that - in case of a strong suspicion of torsion testes the USG cannot be performed within 30 minutes, scrotal exploration is recommended. It should be emphasized that by no means should be time between presentation to the surgeon and exploration in strongly suspected cases exceed 1 hour.

Treatment

It is not necessary to lay down the steps of surgery. Guidelines are not cookbooks. It is enough to recommend scrotal exploration and fixation of the contralateral testes. While fixation of the testes with in a subdartos pouch is a good technique, it is by no means the only technique.

Concluding remarks

With the above alterations, it will be suitable for publication.

References:

- Center for evidence based medicine, Oxford, UK http://www.cebm.net/index.aspx?o=1025. Accessed on 1st April, 2012.