BLADDER TUMORS

When we discuss about bladder tumors we specifically think on urothelial cancer.

The same type of epithelium is lining bladder surface, ureters and collecting systems of kidneys and it is called urothelium. Former term was transitionall epithelium.

The vast majority of bladder tumors (98%) are of epithelial in origin: 92% of these are urothelial cell carcinoma, 7% are squamous cell carcinoma and 1-2% are adenocarcinoma.

Nonepithelial tumors such a sarcomas, pheocromocytomas, lymphomas and primary carcinoid are extremely rare.

Epidemiology

Bladder cancer is the second most common cancer of the genitourinary tract and 9th most common cancer worldwide. The age-standardized incidence is a 9.0 for men at 2,2 for women worldwide and 19 and 4 in EU respectatively.

Incidence rates vary across the world with the highest occurring in developed and industrialized countries (Southern and Eastern Europe, North America) and the lowest occurring in Asia and underdeveloped areas in Africa, suggesting a strong association between industrial and environmental toxins and urothelial cancer.

In North America and Europe 95-97% of cases of bladder cancers are urothelial carcinoma; in Africa 10-40% are squamous cell carcinomas because of the endemic infections with Schistosoma species.

The incidence and prevalence rates increase with age, peaking in the 8th decade of life.

Bladder cancer is very rare (less than 1%) in patients younger than 40 years. Addolescents and young adults tend to develope well- differentiated non-invasive tumors with exellent prognosis.

Probability for developing bladder cancer during life is 4% for men and 1.2% for women.

The male-female ratio is 3-4 : 1, presumably because of an increased prevalence of smoking and exposure to environmental toxins.

ETIOLOGY

Bladder cancer is caused by genetic abnormalities and external risk factors including carcinogen exposure, nutritional factors, infection, chemotherapy and radiation.

Genetic factors. Like in any other cancer, bladder cancer development is a consequence of a structural changes of two groups of genes that control cell division and apoptosis.

The first group are oncogenes that can be activated by the way of point mutation, translocation, amplification or by loosing regulatory sequencies thus leading to malignant transformation. The most common affected oncogenes are Ha-ras family of genes and c-erb B1 and c-erb B-2 located on the long (q) arm of chromosome 17.

The second group of genes are tumor supressor genes that can be inactivated thus leading to uncontrolled cell proliferation and loosing control over programmed cel death called apoptosis.

The most common affected are tumor supressor genes on short arm of 17^{th} gene (p 53), long arm of 13^{th} gene (retinoblastom gene) and short arm of 9^{th} gene (p 15 and p16 proteins).

External risk factors. In addition to the skin and lung the bladder is the main internal organ affected by exposure to external and occupational carcinogens. About 15-35% of bladder cancers in men and 1-6% in women are associated with industrial exposure of some type and primary culprits are the aromatic amines that bind to DNA.

Persons with occupational exposures to dyes, rubber, leather and leather products, paint and organic chemicals are at risk for bladder cancer developement.

Environmental carcinogens enter the body throgh skin or by the way of inhalation.They are metabolized and excreted in urine, but there is a long latency period of 10-20 years between the individual exposure and the formation of bladder cancer. Therefore it is difficult to estimate real impact of certain industrial toxin on bladder cancer developement.

Smoking. Tabacco is the main known cause for urothelial cancer formation, particularly cigarette smoking and accounts for 60% of all urothelial cancers in males and 30% in females.There is a two to six times greater chance of developing urothelial cancer with smoking ; the intensity and duration of smoking are linearly related to the increased risk. If a person smokes 1 to 9 cigarettes versus more than 21 cigarettes per day the relative risk for bladder caner is 1.5 versus 5.4 respectively.

The risk of secondhand smoke in bladder cancer formation is a low and not statistically different from that of nonsmokers. It is important to note that smoking cessation does make a difference in urothelial cancer formation, but it takes more than 15 years of smoking cessation to equal the risk for cancer formation with nonsmokers.

Nutritional factors. Most nutrients or other metabolites are excreted in the urine and have prolonged contact with the bladder urothelium; therefore nutrition plays a role in urothelial cancer formation.

In general, a Mediterranean diet leads to the lowest urothelial cancer risk, probably because of the increased ingestion of fruits and vegetables. Both fruits and vegetables - specifically citrus, apples,berries, tomatoes, carrots and cruciferous vegetables contain active compounds that are important in detoxification (polyphenols, antioxidants). Micronutrients associated with a preventive effect on urothelial cancer formation are mainly antioxidants including vitamins A,C and E, selenum and zinc.

Occurrence of urothelial cancer is moderately higher in coffee and tea drinkers, but this may be compounded by smoking or other dietary factors associated with people who drink coffee and tea.

In conclusion,even if not directly causative, there is a very clear association between a healthy diet and a decreased risk of urothelial cancer formation.

Fluid intake. Urogenesis theory prescribes that decreased fluid intake leads to less micturition and higher concentrations of potential carcinogens in the urine and thus an increased risk of bladder cancer.

Although it makes sense that increased fluid intake would decrease the concentration of potential carcinogens and thus decrease the risk of bladder cancer, the scientific data supporting this theory are inconclusive.

Artifitial sweeteners. In almost every textbook of urology artifitial sweeteners are mentioned as a possible risk factor for bladder cancer. So far epidemiological studies in humans have shown no evidence of an increased risk of bladder cancer in consumers of artifitial sweeteners.

In fact, some animal studies have shown that large doses of saccharine or cyclamates may influence the developement of bladder cancer. But these studies are controversal because very high doses of sacchrine and cyclamates were provided to the animals, doses that men would never consume. This is an example of unnecessary repetition of invaluable data.

Infection is clearly a contributor to the formation of squamous cell carcinoma in patients chronically infected with Schistosoma hematobium (Egypt, Middle East).

Chronic **bacterial** infections, stones and long term catheter use play a role in bladder cancer formation.

Chronic urinary tract infections are associated with bladder cancer with 14 to 16 relative risk of developing bladder cancer for any history of urinary tract infection versus none.

Radiation also can be causative factor in bladder cancer formation. Patients with prostate and cervical cancer who were treated with radiation therapy are at increased risk for bladder cancer developement.

Chemotherapy destroys malignant cells by causing significant DNA and cellular damage and also have profound effect on rapidly dividing urothelial cells.The only chemotherapeutic agent that has been proven to cause bladder cancer is cyclophosphamide.

Heredity also can be a contributing factor for bladder cancer formation. First degree relatives of patients with bladder cancer have a twofold increased risk of developing urothelial carcinoma themselves.

Pathology of urothelial cancers

Actual histological nomenclature was proposed by WHO in 2004. For didactic reasons it is presented here in somewhat simplified manner:

- Urothelial dysplasia
- Urothelial carcinoma in situ (CIS)
- Urothelial papilloma
- Papillary urothelial neoplasm of low malignant potential
- Low-grade papillary urotheliel carcinoma
- High- grade papillary urotheliel carcinoma

Staging of urothelial bladder carcinoma

Currently, the most common used staging system allows for a precise an simultaneous description of the primary tumor (T stage), the status of lymph nodes (N stage), and metastatic sites (M stage) is proposed by American Joint Committee on Cancer in 1997. It is important for students and practitioners to be familiar with tumor stage of bladder cancer.

Bladder wall is composed of 3 distinct histological layers:

- Epihetlial linning called urothelim
- Suburothelial loose connective tissue called lamina propria
- muscularis

According to the depth of bladder involvement bladder cancers can be devided in two main groups:

1. Non-muscle invasive tumors
   a) Ta - tumor confined to the urothelium……70%
   b) T1 - tumor invades lamina propria…… 20%
   c) CIS - carcinoma in situ…… 10%

2. Muscle-invasive tumors – tumor invades muscle layer of the bladder

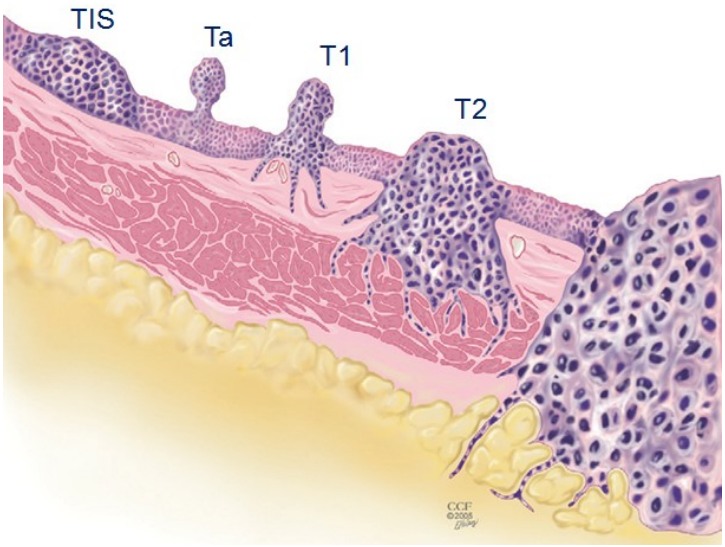


Figure1. Schematic diagram of T staging

It is of utmost importance to emphasize that non-muscle invasive tumors and muscle- invasive tumors are two very different groups of tumors concerning their malignant potential. Though they affect the same organ these are two distinct diseases with significantly different clinical course, prognosis and treatment.

At initial presentation 80% of bladder cancers are non-muscle invasive and 20% are muscle invasive. Among non-muscle invasive cancers special consideration deserves carcinoma in citu – CIS. It is intraepithelial lesion, always high-grade and is a precursor of muscle-invasive cancers.

Symptoms

Gross, painless hematuria is the primary symptom in 85% of patients with a newly diagnosed bladder tumors, and microscopic hematuria occurs in virtually all patients. Fifty percent of patients with gross hematuria will have a demonstrable cause, 20% will have urologic malignancy, and 12% will have a bladder cancer.

Gross hematuria is allways intermittent and intensity does not matter. The same importance have two or three drops of blood and massive bleeding.

All urologic textbooks insist on assessing the character of hematuria and to distinquish is it initial (urethra or prostate), terminal (prostate or bladder) or total (bladder , urethra, kidneys).

But when a patient pases bloody urine he (or she) is so excited and sometimes frightened and is not able to locate precisely which part of urinary stream is bloody. Physicians should not insist on character of gross, painless hematuria,the only question he should ask the patient is: is there visible blood in the urine, and the answer is yes or no.

Remember : Painless, gross hematuria means a tumor of urogenital tract unless proven otherwise.

Such a patient should be sent to urologist immediately for further evaluation !!

Even in nowadays episode of gross, painless hematuria is misinterpretated by physicians as a lower urinary tract infection and patient is treted with antibiotics, instead to be sent to the urologist.The consequences of such a praxis could be serious.

Vesical irritability is present in 25% of patients (urgency, frequency, nocturia, urgency incontinence) and in that case CIS must be considered.

Diagnosis of bladder cancer

Diagnosis of bladder cancer is simple, quick and accurate. A full evaluation of hematuria includes cystoscopy and upper urinary tract imaging, primarily CT urography.

Complementary diagnostic procedures are urine cytology and determination of urine markers for urothelial carcinoma.

Cystoscopy is a visual exploration of bladder cavity with rigid or flexible endoscope and is done as a outpatient procedure.Flexible cystoscopy is a new technique that is reliable as a rigid cystoscopy but is more comfortable for patients.

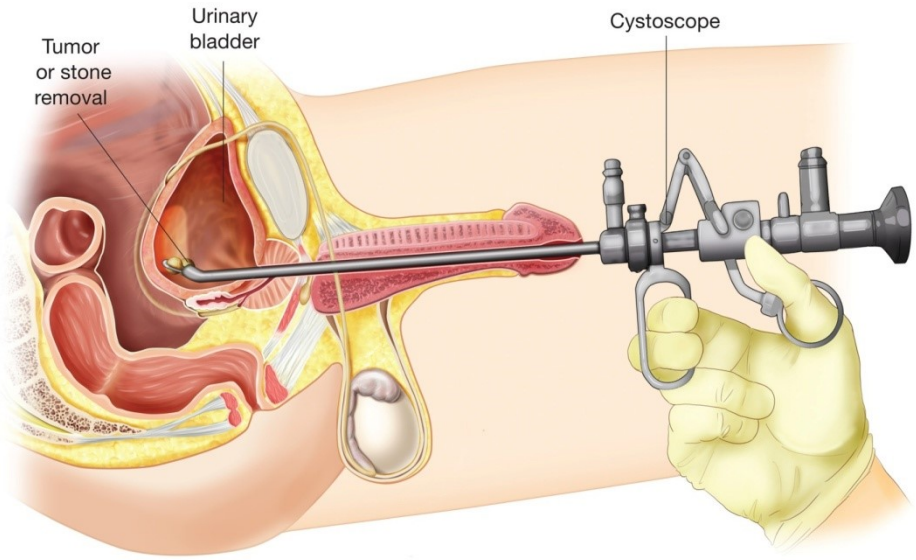
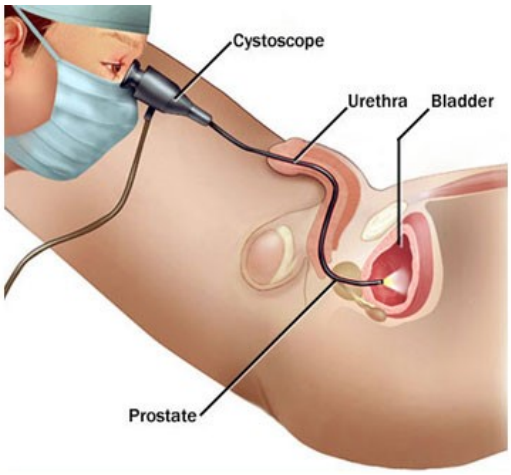


Figure 2. A rigid cystoscopy in male



Fgure 3. A flexible cystoscopy in male

White light cystoscpy is the gold standard in detecting bladder cancers.It has excelent sensitivity and specifity for papillary tunor, more than 90%. Though very objective and precise, difficulties exist in detecting CIS and small papillary lesions. In such a cases blue light cystoscopy is advisable. In that procedure intravesically applicated photoactive porphyrine dye emit flourescence under blue wavelight.

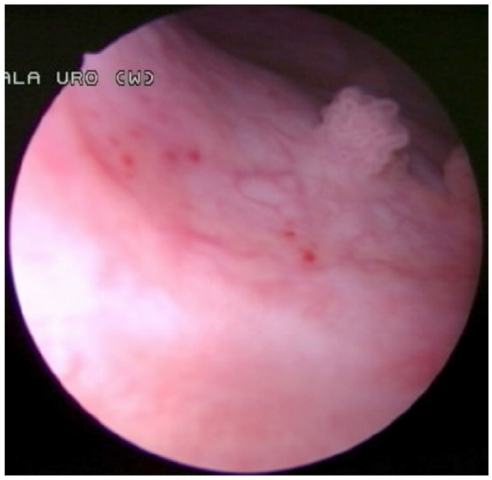


Figure 4. White light cystoscopy showing small papillary tumor

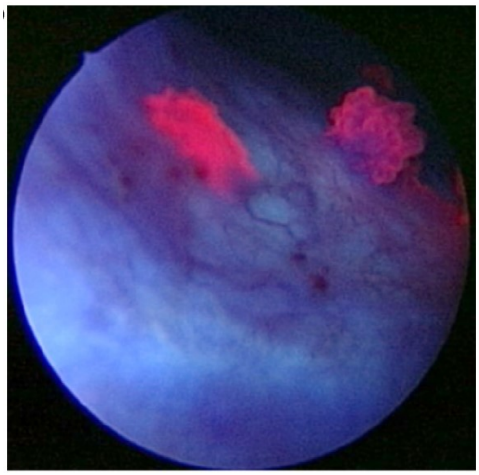


Figure 5. The same patient examined with blue light cystoscopy detecting area of carcinoma in situ

When performing cystoscopy urologist notes the number of tumors,their size, location and configuration. Papillary configuration indicates low malignant potential and probably non-muscle invasive tumor. Solid configuration suggests a tumor with high malignant potential and muscle invasive disease.

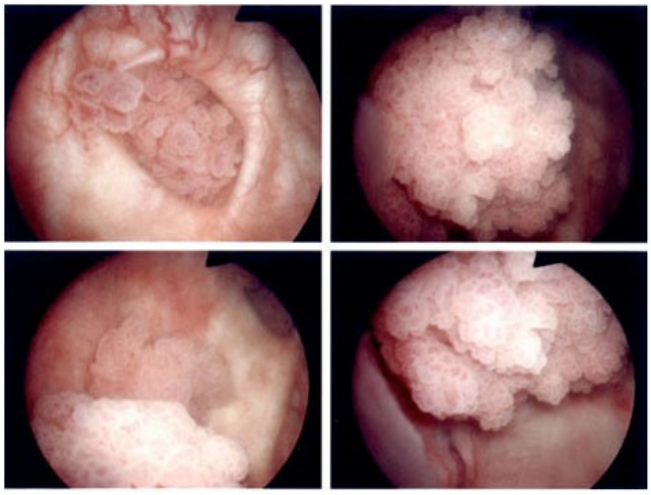


Figure 6. Cystoscsopic view of papillary tumors

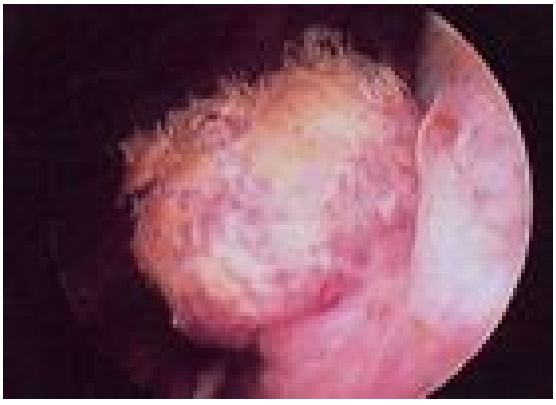


Figure 7. Cystoscopic view of solid tumor

Imaging

CT urogarphy is a diagnostic and staging methode of choice in dealing with bladder cancer. It gives an insight of collecting system morphology, status of renal parenchima and other intraabdominal organs.

Concomitant tumors of ureter and pelvis can be detected in 2-4% patients with bladder carcinoma.

Routinely performed ultra-sound of urinary tract can also detect bladder tumor in an asymptomatic patient.

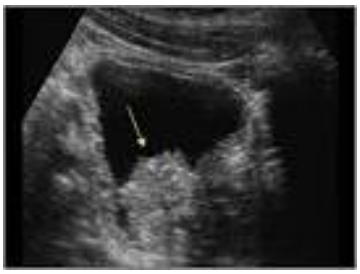


Figure 8. Bladder cancer detected by ultrasound

Urine citology is a test for detecting abnormal or malignant cells in urine sediment.Overall, the sensitivity and specifity for citology in detecting bladder cancer is 40% to 62% and 94% to 100% respectively.Positive urine citology is virtually diagnostic of a bladder tumor.

Because many physicians and patients consider cystoscopy too aggresive procedure a lot of work is done to develop less invasive test that would replace it. Such an effort is a determination of degradable products of malgnant cells in the urine. There are more than 20 tests for detecting biomarkers in urine (BTA stat, NMP 22, Immunocyt…). To date, none of these markers have a high enough sensitivity or specifity to replace office cystoscopy.

Treatment of non-muscle invasive bladder cancer

As mentioned before term non-muscle invasive tumors (formerly called superficial) encompasses tumors confined to mucosa (Ta), those that invade lamina propria (T1) and carcinoma in situ (CIS).

This is a very heterogeneous group of tumors with high tendency to recur and moderate tendency to progress. Recurrence means a new tumor occurrence at a different site on bladder mucosa after initial resection. Recurrence rate for non-muscle invasive tumors is 80-90% five years after initial resection. Early recurrence (within 3 months after initial resection) means inadequate initial resection and late recurrence represents the very character of the disease.

Progression of disease is a recurrence with muscle involvement and is most important event in the evolution of non-muscle invasive tumors.

Progression rate after 3 years following initial resection is 4% for solitary, low grade papillary tumors and 48% for high grade tumors that invade lamina propria (T1G3). The most important risk factor for progression is a grade of tumor

Recurrence and progression rates depend of tumor characteristic:

- grade
- stage
- size and number of tumors
- concomitant dysplasia and CIS
- configuration (papillary vs. solid)

The aim of treatment is to remove all visible lesions with transurethral resection and to prevent recurrence and progression. This goal is achieved by applying intravesically immunomodulators (BCG) and chemotherapeutic agents after resection.

Transurethral resection is initial treatment modality in dealing with bladder cancer and quality of its performance essentially determines outcome of treatment. Adequatelly performed transurethral resection will remove all visible lesions and provide specimens for pathologic examination. The specimen **must contain muscle**, without it adequate T staging is not possible.

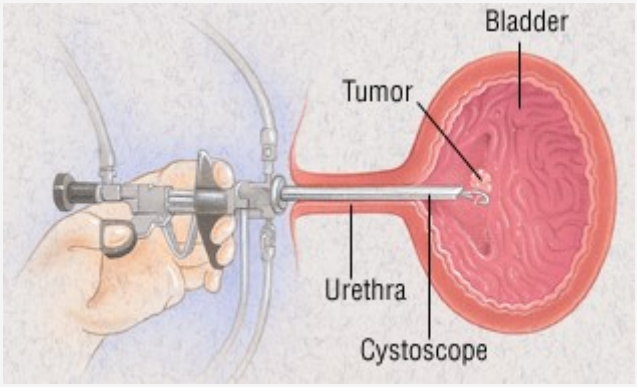


Figure 9. Transurethral resection of bladder tumor

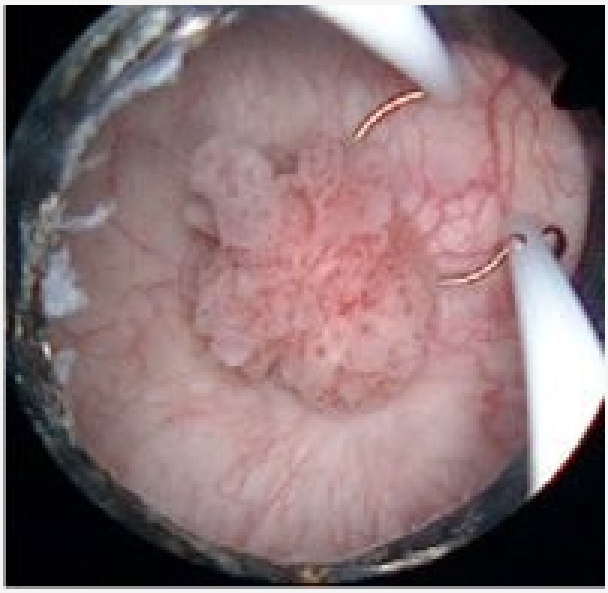


Figure 10. Cutting loop at the tip of resectoscope, 6 mm wide

There are three crucial questions in pathological report that must be answered in order to select the mode of treatment:

- histologic type of tumor …… urothelial mostly
- level of differentiation ……...grade of tumor
- invasion through the bladder wall…..stage of tumor

Additional resection (second look TUR) is indicated in all T1 tumors, large tumors and when there is no muscle in the specimen. This procedure is performed 2-6 weeks after initial resection.

Therapeutic approach depends on probability for recurrence and progression.

Patients with initially low-grade, small solitary tumors are at low risk of recurrence and progression and may be treated by transurethral resection alone followed by surveilance.

Patients with T1, high-grade, multiple, large, recurrent tumors or associated with CIS are at higher risk of recurrence and progression. They should be treated with intravesical chemotherapy or immunotherapy (BCG) after complete transurethral resection.

Intravesical chemotherapy. Chemotherapeutic agents can be istilled into the bladder directly via catheter, thereby avoiding the morbidity of systemic administration.

Intravesical chemotherapy may be delivered in 3 different fashions:

a) **Adjunctive –** a single postoperative instillation within 6 hours after resection. Intravesically applied chemotherapeutic agents act by destroying tumor cells that are floating in the irrigation fluid and by preventing their implantation on the bladder wall. It is belived that tumor cell implantation immediately after resection is responsable for many early recurrences
b) **Prophylactic –** after complete transurethral resection to prevent or delay recurrence and progression.Most agents are administered weekly for 6-8 weeks.
c) **Therapeutic-** after incomplete transurethral resection to cure residual disease. Tlhis mode of application is seldom or never used in hands of skilful endoscopic surgeon.

Most often applied agents are Mitomycin C, Thiotepa and Doxorubicin. The effect of intravesical chemotherapy is a moderate reduction of recurrence rate with no impact on the progression.

Intravesical immunotherapy. Baillus Calmette Guerin (BCG) is attenuated strain of Mycobacterium bovis developed as a vaccine for tuberculosis. BCG applied inravesically has a unique ability to provoke massive local humoral and cellular response. After BCG instillation high concentrations of cytokines can be detected in urine (interleukines, interferone-γ, tumor necrosis factor-α). Biopsies done after BCG instillation demonstrate infiltration of bladder wall with immunocompetent cells (NK cells, macrophage, dendritic cells, helper and suppressor lymphocyte).

Treatment begins in third or fourth week after tumor resection, the most common rcommended induction regimen is of 6 weekly instillations.

For high risk patients maintenance therapy is prefered with monthly instillations for one year or 3 weekly instillations every six months until 2 years after initial resection.

Meta-analyses have confirmed that BCG immunotherapy is superior to TUR of bladder tumor alone or TUR plus intravesical chemotherapy in preventing recurrence rate and what is more important BCG immunotherapy prevents or et least delays progression.

The effects of BCG immunotherapy are long lasting but are associated with more side effects compared to intravesical chemotherapy. More than 90% of patients have symptoms of cystitis: fever low grade, hematuria and bladder irritability – so called minor (or expected) side effects.

Major side-effects are encountered in 5% of patients (high fever, hepathitis, renal abscess,sepsis) and require therapy with triple antituberculotics; lethal outcome is possible.

Followup of patients with non-muscle invasive bladder cancer is life long and is based on cystoscopy and urine cytology. CT urography is done every 3-4 years. Cystoscopy is performed every 3 months during first year after resection, than every six months for one year and further annually life long.

Prognosis for patients with non-muscle invasive disease is excellent. Though it has an impact on quality of life the disease does not affect survival.

In case of disease progression prognosis in serious and corresponds with a survival rates of patients with muscle-invasive tumors (see later!)

Treatment of muscle – invasive bladder cancer

As pointed out earlier non-muscle invasive tumors and muscle-invasive tumors are two different diseases that affect the same organ with significantly different prognosis. Muscle-invasive tumors tend to spread locally and to metastase to distant organs and should be treated aggressively

Tha majority (80%) of patients with muscle invasive tumors present de novo with muscle invasive disease as its first manifestation.

The remaining 15-20% progress from non-muscle invasive cancers after transurethral resection and treatment with intravesical therapy.

Computed tomography (CT) is the diagnostic method of choice in staging of muscle-invasive tumors. It provides data about local extent of tumor and local spreading, gives an insight on status of regional lymph nodes and possible existence of visceral metastases.

Magnetic resonance also may be used in staging of bladder cancer with comparable specifity and sensitivity.

Nowadays multimodal therapy and multidisciplinary approach is an imperative in treatment of muscle-invasive bladder cancer. The urologist, medical oncologist and radiation oncologist play a central role in integrating the discipline of surgery, chemotherapy and radiation therapy in order to achieve the goal of long term cancer control.

Radical cystectomy is the standard treatment for localized muscle-invasive bladder cancer and for patients who are good surgical risk (concerning age and comorbidities) and willing to undergo surgery.

Partial cystectomy is also possible if tumor is smaller than 3 cm, located at the dome of bladder and away from ureteral orifices. Only 5% of patients with muscle-invasive bladder cancer fullfil criteria for this operation..

Figure 11. Small tumor at the dome of the bladder, suitable for partial cystectomy

Radical cystectomy provides excellent local control of the primary tumor and should include the bladder and surrounding perivesical soft tissue, prostate and seminal vesicles in men and the ovaries, uterus and anterior vagina in women.

Pelvic lymphadenectomy is an integral part of radical cystectomy and the status of regional lymph nodes is the most important prognostic factor. Patients with positive regional lymph nodes have significantly decreased recurrence free survival and overall survival compared with that for patients with negative regional lymph nodes.

After bladder removal some type of urinary diversion is performed. Different types of segments of the intestinal tract have been used to reconstruct the urinary tract, including the stomach, ileum, colon and appendix. The most common performed urinary diversion is ileal conduit ((uretero-ileo-cutaneostomia).

The conduit is constructed using an isolated segment of terminal ileum 20 cm long. Oral end of ileum is closed and ureters are implanted in end-to side fashion; aboral end is brought through abdominal wall and anchored to skin surface forming stoma over which urinary receptaculum is applied.

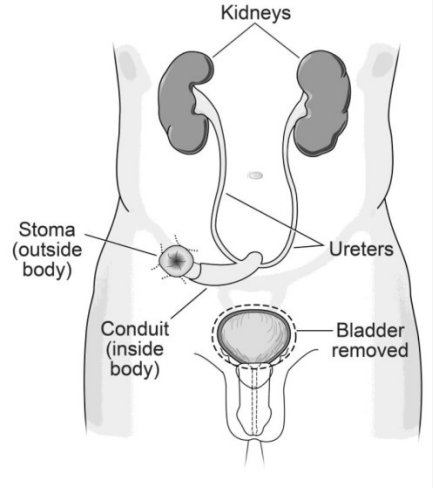


Figure 12. Uretero-ileo-cutaneo-stomia (Brickers procedure)

The other possibility to provide urinary diversion is forming an orthotoptic neobladder.

Orthotoptic neobladder is a urinary reservoir fashioned from a bowel segment that is in normal position of the bladder and attached directly to the urethra with discharge of urine through urethra.

The most common performed procedure for orthotoptic neobladder formation is by using isolated segment of terminal ileum 40-60 cm in length.

Isolated ileal segment is detubularized and folded to create spherical shape and low-pressure neobladder. Ureters are implanted at the dome of neobladder and the base of neobladder is sutured to the urethra so that patient can urinate through urethra

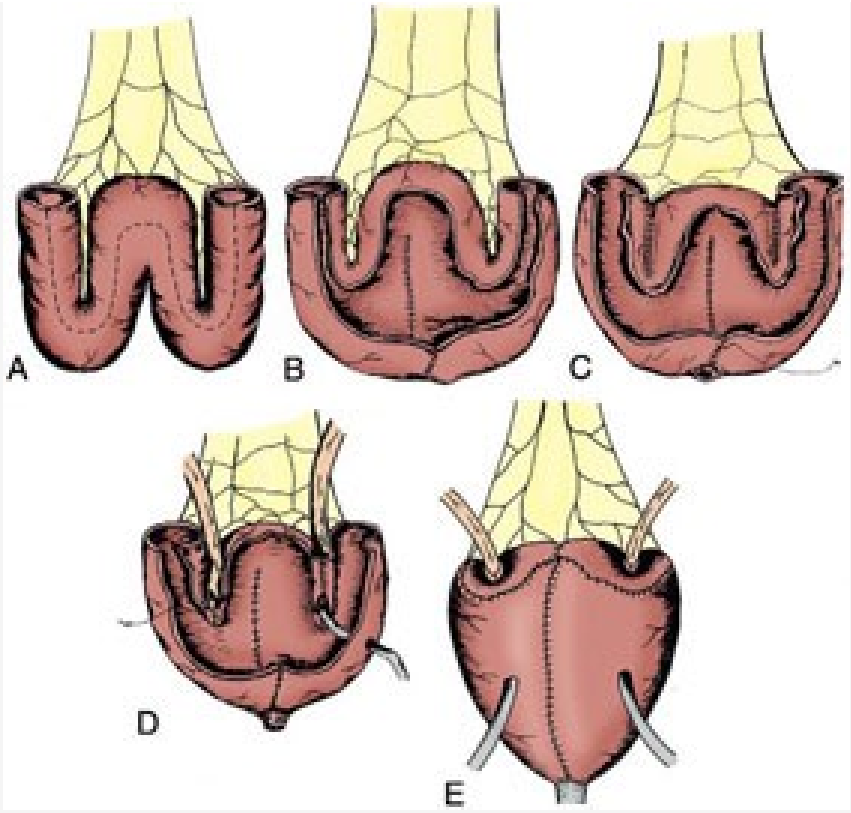


Figure 13. Schematic diagrams of an orthotoptic neobladder.A, Isolated segment of ileum. B and C, The ileal segment is detubularized and refashioned in a spherical shape. D, Ureters are implanted and intubated with endoprothesis. E, Neobladder created and sutured to the urethra

Uretero-cutaneostomia to the abdominal wall is the simplest form of supravesical urinary diversion. Technically,ureters are mobilized and brought through abdominal wall and directly sutured to the skin on both sides; urinary receptaculum is applied over ureteral stoma. It is a safe procedure and is performed in older, or otherwise compromised patients. Strictures at the site of uretero-cutaneous junction are common.

Results of radical surgery. Radical cystectomy is mutilating procedure that affects a lot the quality of life. Reporeted peri-operative mortality is about 3% and morbidity 50-60%.

Patients undergoing radical cystectomy for bladder cancer have a five-year recurrence-free survival 58% and cancer specific survival 66%.

Radiation therapy. External beam irradiation (5000-7000 cGy) delivered in a fractions over 5- to 8- week period is an alternative to radical cystectomy in well selected patients with localized and locally advanced muscle-invasive bladder cancer. As a monotherapy is offered only to those patients who are poor surgical risk candidates due to advanced age or significant comorbidity.

Chemotherapy

Approximately 15% of patients who present with bladder cancer are found to have regional or distant metastases; approximately 30-40% of patients with muscle-invasive disease develop distant metastases despite radical cystectomy or definitive radiotherapy. These patients with metastatic disease are candidates for treatment with chemotherapeutic agents.

The single most active agent is cisplatin which, used alone, produces responses in approximately 30% patients. Other effective agents include metotrexate, doxorubicin, vinblastine and 5-fluorouracil. Response rates improve when active agents are combined.

The regimen of metotrexate, vinblastine, doxorubicin (Adriamycin), and cisplatin (MVAC) has been most common used for patients with advanced bladder cancer.

Chemotherapy can be given in neodjuvant fashion before planned radical cystectomy in attempt to decrease recurrence rates, and in selected cases allow for bladder preservation. Neoadjuvant chemotherapy increases survival rates 5-7% (level of evidence 1a).

Level of evidence (LE) 1a : evidence obtained from meta-analyses of randomized trials.

Chemotherapy also can be given to patients initially treated with radical cystectomy (adjuvant) who are at increased risk of systemic relapse due to the presence of lymph node metastases or regionally advanced disease. Though seems reasonable to apply adjuvant chemotherapy results from 1a level of evidence are lacking. Chemotherapy can also be applied in combination with irradiation. Trials of single agent chemotherapy and irradiation have shown better local response rates then are found in historical trials of irradiation alone.

TUMORS OF URETER AND RENAL PELVIS

Carcinomas of the renal pelvis are rare accounting for only 4% of all urothelial cancers. The ratio of bladder-renal pelvic-ureteral carcinomas is 51:3:1.

The main age at diagnosis is 65 years, and the male-female ratio is 2-4:1.

Patients with a single upper – tract carcinoma are et risk of developing bladder carcinomas (30-50%) and contralateral upper tract carcinoma (2-4%). Conversely, patients with primary bladder cancer are at low risk (about 2-6 %) of developing upper urinary tract carcinoma.

Etiology

As with bladder carcinoma, smoking and exposure to certain industrial dyes or solvents are associated with an increased risk of upper urinary tract carcinoma. A long history of excessive analgesic intake (acetaminophen, aspirin, caffeine and phenacetin) and Balkan nephropathy are also established risk factors for upper urinary tract carcinoma.

Balkan nephropathy is an interstitial inflammatory disease of the kidneys that affects inhabitans of some Balkan countries (Romania,Bulgaria,Greek, Serbia); the exact mechanism of tumor induction is unknown.

The mucosal lining of the renal pelvis and ureter is similar to that of urinary bladder and is called urothelium. Thus, most pelvic and ureteral tumors (90% and 97% respectively) are urothelial cancers. Squamous cell carcinomas account approximately 10% of renal pelvic cancers and are rarely encountered in the ureter.

Grading system is similar to that for bladder carcinoma.

Symptoms

As in bladder cancer, gross hematuria is most prominent symptom and is noted in 70-90% patients.

Flank pain is present in 8 -50% of the patients and is the result of ureteral obstruction from blood clots or tumor fragments.

Constitutional symptoms of anorexia, weight loss and lethargy are uncommon and are usually associated with metastatic disease.

Diagnosis

CT urography is an imaging method of choice for upper tract cancer detecting.

The most common abnormalities identified include an intraluminal renal pelvis filling defect, nonvisualisation of collecting system and hydronephrosis.

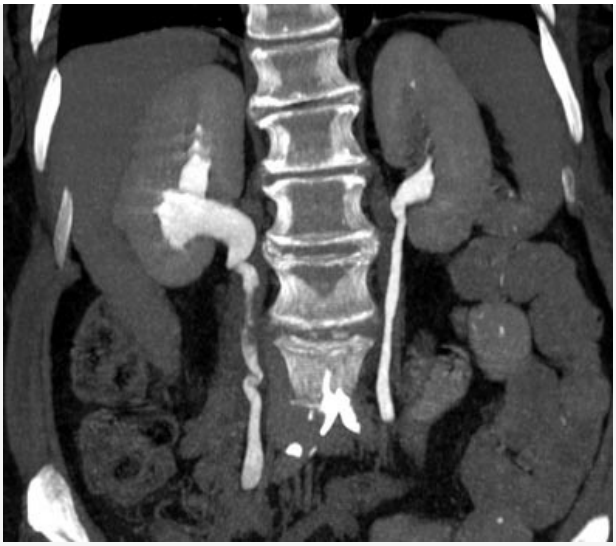


Figure 14. CT urograpy. Filling defect in proximal right ureter due to urothelial cancer

In a case that CT urography is not diagnostic, retrograde pyelography is performed. It allows more accurate visualization of collecting-system abnormalities and simultaneous collection of cytologic specimens.

Novel adjunctive diagnostic method is rigid and flexible uretero-pyeloscopy. Endoscopic instrument is passed transurethraly through ureteral orifice to explore ureter end collecting system of kidney.This procedure allows direct visualisation of tumor and taking biopsy specimens. On occasion complete tumor resection, fulguration or laser vaporization are possible ednoscopically.

Treatment

Standard therapy for upper urinary tract carcinoma is nephroureterectomy with excision of a bladder cuff. If intramural part of ureter is not excised recurrence rate is a high as 30% within this segment of ureter.

Indications for renal-sparing procedures include tumor in the collecting system of a solitary kidney, or in patients with bilateral upper urinary tract tumors.

Follow-up is lifelong and includes urine cytology, cystoscopy and CT-urography every 3-4 years depending of grade of tumor.

Cystoscopy is mandatory because of high probability of tumor recurrence within bladder urothelim – up to 30-50%.

BENIGN PROSTATIC HYPERPLASIA

The prostate gland is a male reproductive organ whose main function is to secrete prostate fluid, one of the components of semen.

Anatomically, it resides deep inside male pelvis, is a chesnut - shaped and normal prostate weigts about 20-30 g; with aging prostate size and volume is growing.

Two distinctive features of prostate anatomy must be emphasized.

First, posterior urethra passes through prostate, thus the size and configuration of prostate can influence on quality of urinary stream.

Second, prostate rests directly on rectal ampulla (separated by duplicature of Denonvilliers fascia) and is accessible for digital rectal examination.

The main purpose of prostate is to secrete slightly alkaline fluid which is rich in enzymes, sugars, proteins and minerals that protect and nurish sperm. Prostatic secretion represents about 30% of seminal fluid, the rest is screted by seminal vesicles. Sperms account only 1-2% of seminal fluid.

The alkaline chemicals in prostate secretion neutralize acid vaginal secretions and promote survival and motility of sperm.

The prostate is composed of both stromal and epithelial elements, and each, either alone or in combination can give rise to hyperplastic nodules and symptoms associated with benign prostatic hyperplasia (BPH). Each element may be targeted in medical management schemes.

Histopathologically, BPH is characterized by an increased number of epithelial and stromal cells in the periurethral area of the prostate. Therefore correct denomination is hyperplasia and not hypertrophy of the prostate, a term often found in older literature.

Historically, voiding symptoms have been related to obstruction of the bladder caused by enlarged prostate. This concept was sometimes misleading, thus resulting in inadequatetreatment.

Nowadays, it is well recognized that voiding symptoms can be influenced by various conditions, and can be related to bladder dysfunction (overactive or hypoactive), urethral stricture, neurologic diseases, urinary tract infections, urothelial malignancy.. etc.

The term lower urinary tract symptoms (LUTS) was introduced in the urological praxis and nomenclature in 1994. and adequately denotes variety of possible ethiological factors that can affect quality of voiding.

Voiding symptoms related to the prostate pathology are only a part of lower urinary tract symptoms; precise diagnosis is possible and thus targeting therapy to the ethiological factor.

For example, weak urinary stream can be consequence of bladder weakness, though prostate is normal sized and does not represent true anatomical subvesical obstruction.

BPH is the most common benign tumor in men, and its incidence is age related. The prevalence of histologic BPH in autopsy studies rises from approximately 20% in men aged 41-50, to 50% in men aged 51-60 and to > 90% in men older than 80 years.

Although clinical evidence of disease occurs less commonly, symptoms of prostatic obstruction are also age related. At age 55, approximately 25% of men report obstructive voiding symptoms. At age 75, 50% of men complain of a decrease in the force and caliber of their urinary stream.

Etiology

The etiology of BPH is not completely understood, but it seems to be multifactorial and endocrine controlled by androgens.

In a given organ the number of cells, and the volume of the organ is dependent on the equilibrium between cell proliferation and programmed cell death – apoptosis. An organ can enlarge not only by an increase in cell proliferation but also by a decrease in cell death.

Androgens not only are required for normal cell proliferation and differentiation in the prostate but also actively inhibit cell death.

Circulating testosterone diffuses into prostate epithelial and stromal cells and is converted by 5-α reductase enzyme to a dihydrotestosterone (DHT) which is a more potent androgen. DHT has a high affinity for binding to an androgen receptors in cytoplasm. DHT- receptor complex binds to a specific DNA binding sites in the nucleus, which results in increased transcription of androgen-dependent genes and ultimatively stimulation of protein synthesis.

Physicians and students should be familiar with androgen metabolism, because it can be affected at different levels in medical treatment of BPH and prostate cancer.

Estrogens may also play a role in BPH developement. Serum estrogens levels increase in men with age, absolutely or relative to testosterone levels. Intraprostatic levels of estrogens are also increased in men with BPH. Increasing intraprostatic levels of estrogens act by causing induction of the androgen receptor which thereby sensities the prostate to androgens. It is also well documented that patients with larger volumes of BPH tend to have higher levels of estradiol in the peripheral circulation.

Positive family history also represent risk factor for BPH developement because first degree male relatives from patients surgically treated for BPH have risk for developing BPH 4:1 versus controls.

Pathology

BPH develops in the transition zone of prostate gland and is hyperplastic process resulting from an increase in cell number. Microscopic evaluation reveals a nodular growth pattern that is composed of stroma and epithelium. Stroma is composed of varying amounts of collagen and smooth muscle. As BPH nodules in the transition zone enlarge, they compress the outer zones of the prostate, resulting in the formation of a so-called surgical capsule.

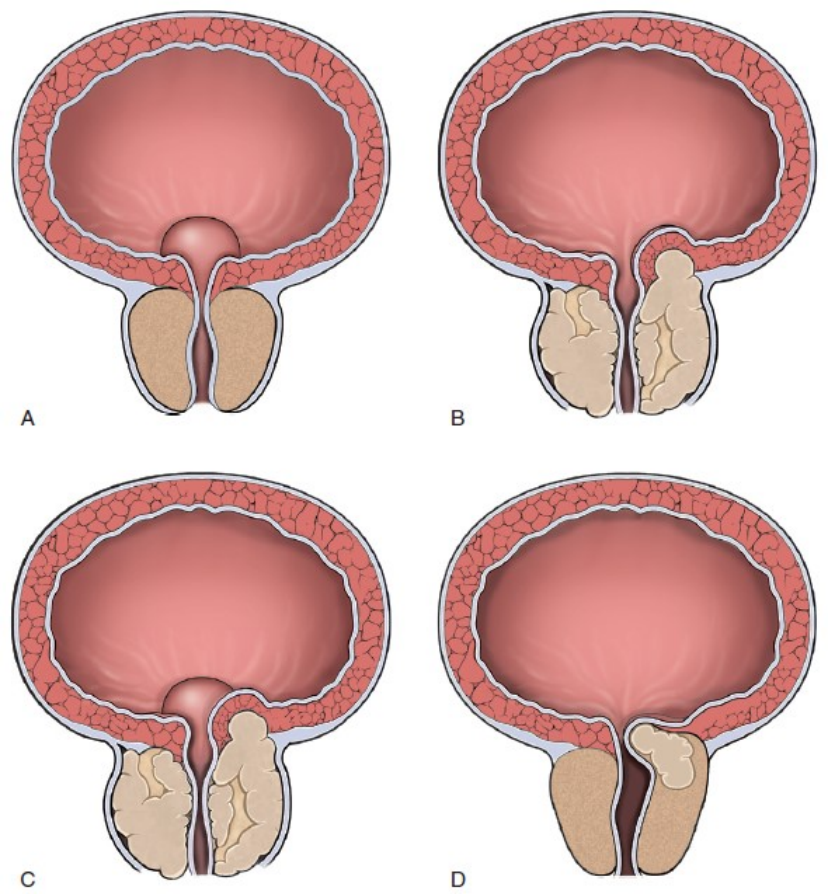


Figure 15. Diagrams of hyperplastic prostatic tissue obstructing the prostatic urethra forming "lobes." A, Isolated middle lobe enlargement. B, Isolated lateral lobe enlargement. C, Lateral and middle lobe enlargement. D, Posterior commissural hyperplasia (median bar)

Patophysiology

Prostatic hyperplasia increases urethral resistence, resulting in compensatory changes in bladder function. The elevated detrusor pressure required to maintain urinary flow in the presence of increased outflow resistence occurs at expense of normal bladder storage function.

Bladder outlet obstruction leads to detrusor muscle hypetrophy and collagen deposition resulting in detrusor instability. Among thickened detrusor muscle bundles mucosal herniations occur causing diverticula formation.

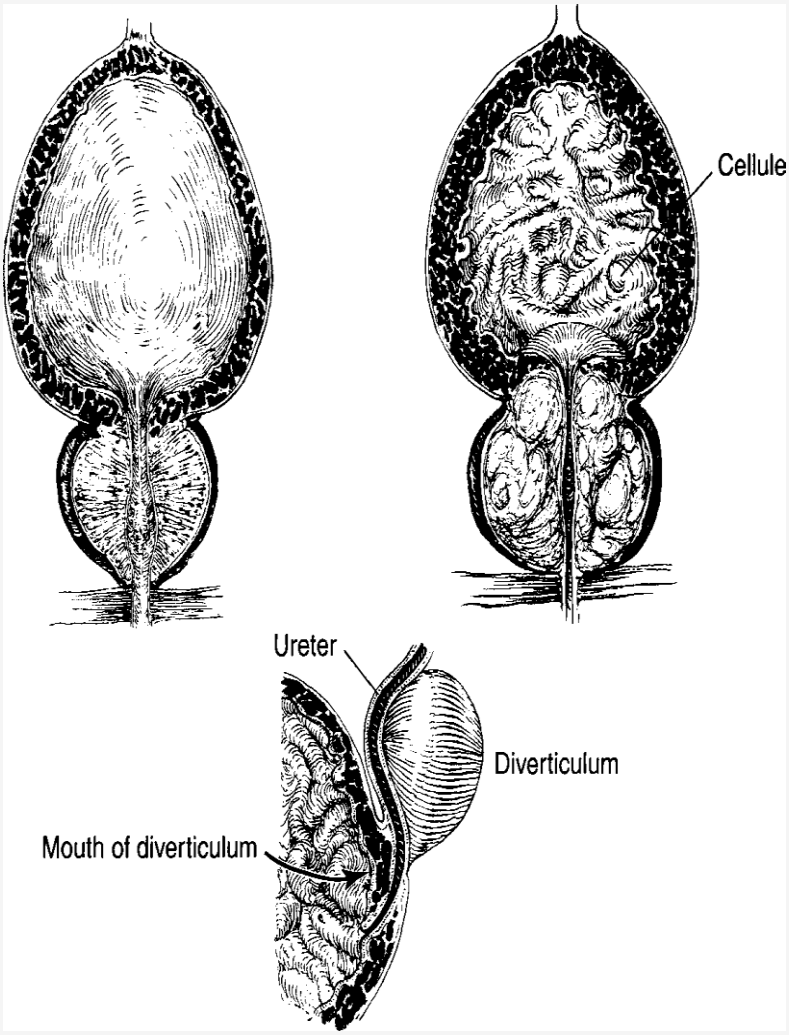


Figure 16. Changes in the bladder developing from obstruction. **Upper left:** Normal bladder and prostate. **Upper right:** Obstructing prostate causing trabeculation,cellule formation, and hypertrophy of the interureteric ridge. **Bottom:** Marked trabeculation (hyprtrophy) of the vesical musculature; diverticulum displacing left ureter.

Symptoms

The symptoms of BPH can be divided into obstructive and storage complaints. Obstructive symptoms include hesitancy, intermittency, straining to urinate, slow stream, terminal dribbling and are related to enlarged prostate.

Storage symptoms include altered bladder sensation, increased daytime frequency, nocturia, urgency and urgency incontinence.

Storage symptoms are related to bladder dysfunction and are far more bothersome for the patients than obstructive, specially in case of urgency incontinence.

Urgency is defined as a sudden compelling need to urinate that can not be suppressed or difficult to defere.

Storage symptoms overlap with clinical manifestation of overactive bladder (OAB), a condition that can exist in presence of normal sized prostate or is a part of symptoms related to BPH.

If BPH is left untreated detrusor muscle weakens and can not expeal the whole amount of urine from bladder. The some amount of urine rests in the bladder after micturition as a **residul urine.**

This amount of urine can affect the clinical course of BPH. Residual urine diminishes functional bladder capacity and is a risk factor for bladder stone formation and bacterial infection of lower urinary tract (epididymitis, prostatitis).

When bladder muscle loses all its strength urine can not be expelled from the bladder and acute urinary retention is a consequence. Patients with acute urinary retention experience severe pain in suprapubic area and distended bladder can be palpated as a "globus vesicalis".

In the end stage of untreated BPH urinary bladder is fully decompensated without its motoric and sensory function, so patients do not experience any pain though bladder is distended and full with urine. In such a cases bladder capacity may be abnormally large, reaching volume of 2-3 litres.

The urine secreted from kidneys is transported through ureters to the distended bladder and overflows through bladder neck and urethra. In this situation patients urinate very often, almost constantly and this condition is called **chronic urinary retention** with overflow incontinence as a clinical manifestation. If chronic urinary retention lasts long enough urine pressure is transmitted to upper urinary tract causing acute postrenal failure with high serum creatinine concentrations and hyperkaliemia.

Patients with BPH can develop gross hematuria and form clots. This is an urgent situation that needs urinary catheter insertion and lavage of urinary bladder. Sometimes hematuria is so massive that demands blood transfusion. Gross hematuria must be evaluated (cystoscopy, CT – urography) to exclude possible existence of urotract malignancy.

If no other cause of gross hematuria is not detected, and hematuria persists surgical treatment of BPH is indicated.

Another urgent situation is when urethral catheter , owing to urethral stricture, can not be inserted into bladder of patient with acute urinary retention or gross hematuria. In such a situations percutaneous cystostomy should be placed.

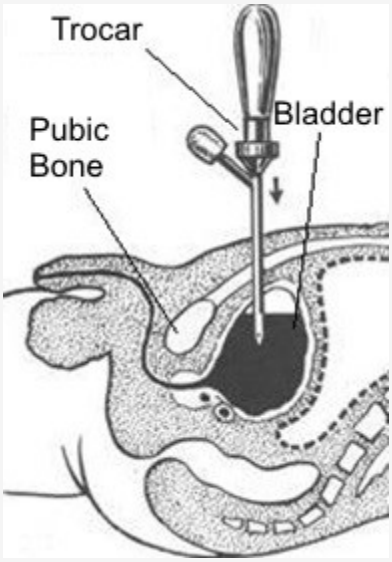


Figure 17. Perutaneous cystostomy

Diagnosis

Taking precise medical history is a first step in evaluation patients with BPH. The medical history aims to identify the potential causes and relevant comorbidities. Special attention should be payed on existence of diabetes mellitus, nervous system diseases (Parkinson disease or previous stroke), or prior surgery of lower urinary tract. In addition, current medications, lifestyle habits, emotional and psychological factors must be reviewed.

In evaluation of BPH patients, symptom score questionnaires are helpful tool in assassement the severity and frequency of obstructive and storage symptoms.

The **I**nterntional **P**rostate **S**ymptom **S**core (IPSS) is a recommended for the baseline assessement of symptoms in men presenting with LUTS. The IPSS is an 8-item questionnaire consisting of seven symptom questions and one for quality of life.Three of these questions are related to obstructive symptoms and four to storage symptoms. Patients score severity and frequency of symptoms in gradation from 1 to 5, maximum score is thus 35.

The IPSS score is categorized as "asymptomatic" (0 points), "mildly symptomatic" (1-7 points), "moderately symptomatic" (8-19 points) and "severely symptomatic (20-35 points).

Digital rectal examination (DRE) is the simplest way to assess prostate size, consistency and mobility or fixation. DRE establishes the approximate size of the prostate; it is important to remember that prostate size does not correlate precisely with symptom severity and treatment outcome. The presence of induration or nodule must alert the physician to the possibility of prostatic cancer and need for further evaluation (prostate biopsy). Performing DRE physician also estimates anal sphincter tone and possible neurologic problems that may cause the presenting symptoms.

Urine analysis should be done by using a dipstick test or microscopic examination of the spun sediment to rule out urinary tract infection (UTI), hematuria and diabetes mellitus, either of which strongly suggests a non-BPH pathologic process as a cause of symptoms. If a dipstisck approach is used, a test that includes leukocyte esterase and nitrite test for the detection of pyuria and bacteriuria should be used.

In men with severe irritable symptoms and dysuria, especially if they have a smoking history, urine cytology should be done for possible detection of carcinoma in situ of the bladder.

Carcinoma in situ of the bladder (CIS) is a diagnosis that may have serious consequences if overlooked.

Laboratory findings. Renal function is estimated by determinating serum creatinine concentration. About 11% of men with LUTS have a renal insufficiency, which is important risk factor if surgical treatment is considered. BPH patients with renal insufficiency have increased risk for postoperative complications and mortality increases up to sixfold.

PSA testing.

Prostate **S**pecific **A**ntigen (PSA) is an androgen-dependent serine protease enzyme produced exclusively both by prostate epithelial cells and prostate cancer cells, which means that this enzyme (not a tumor marker!) is organ specific but not cancer specific. Its physiological function is in the liquefaction of seminal fluid.

PSA levels are elevated in prostate cancer , and is an invaluable tool for early prostate cancer detection and also in monitoring patients treated for prostate cancer, either surgically or conservatively.

In benign prostate PSA level is a surrogate of its size (volumen) meaning that in larger prostates there are greater number of epithelial cells producing this enzyme, resulting in higher PSA concentration in serum.

Other benign conditions that can cause elevated levels of PSA are:

- Prostate inflammation

  Lower urinary tract infection

  Medical procedures such placement of urinary catheter, cystoscopy

  DRE

  Ejaculation, mild increase, returns to normal level in 2-3 days

Though there is a significant overlap between the serum PSA values of men with BPH and men with clinically localized prostate cancer, PSA testing should be performed in patients with BPH especially < 70 years and younger with positive familial history.

Atlhough routine imaging of upper urinary tract is not recommended in men with LUTS, it is wise to perform ultrasound (US) to all patients with BPH.

It is a lower cost, simple procedure that enables simultaneous evaluation of the bladder, prostate size and postvoidal residual urine. US allows for better characterisation of renal masses, the possibility of investing liver and retroperitoneum and detection of obstructive uropathy.

Prostate imaging can be performed by transabdominal US, transrectal ultrasound (TRUS), computed tomography (CT) and magnetic resonance imaging. However, in daily practice, prostate imaging is performed by transabdominal ultrasound or TRUS.

Though prostate size does not correlate with severity of voiding symptoms, it is important for selection of surgical treatment, i.e. open prostatectomy versus endoscopic techniques.

Urethrocystoscopy is indicated in BPH patients with a history of gross or microscopic hematuria, urethral stricture or bladder cancer. It also helps in making decision concerning surgical approach if surgery is indicated.

Treatment of BPH

Therapeutic approach is adjusted according to the severity of voiding symptoms and their impact on quality of life. Many men with BPH are not troubled enough by their symptoms to need medical treatment or surgical intervention.

Watchful waiting is a viable option for many men with non-bothersome BPH/LUTS as few will progress to acute urinary retention and complications such a renal insufficiency or bladder stone formation. Many patients can remain stable for years and should be managed with behavioural and dietary modifacations. It is customary for this type of management to include the following components:

- Education about patients condition
- Assurance that cancer is not a cause of the urinary symptoms
- Life style advice:
    a) Reduction of fluid intake of specific times aimed to reduce urinary frequency (et evening for example)
    b) Avoidance or moderation of intake of caffeine and alcohol which may have diuretic effect
- Treatment of constipation
- Avoiding unnecessary sitting position

- Periodic monitoring

There now exist evidence (LE:1b) that self-management as a part of watchful waiting reduces both symptoms and progression

Level of evidence 1b represents data obtained from et least one randomized trial.

Medical therapy.

The role of this therapeutic approach is to mitigate voiding symptoms and to prevent or delay occurrence of complications that need surgical treatment.

Medical therapies widely used today for treatment of BPH are targeted to diminis bladder outlet obstruction by reducing prostate volume and relaxing prostate smooth muscle tension.[7] Clinical data demonstrate that androgen suppression and α-blockade relieve and increase urinary flow rates in men with BPH; these data have been used to support the hypothesis that the pathophysiology of "prostatism" is due to bladder outlet obstruction.

Among medical agents most common used for BPH treatment are α – adrenergic blockers, 5-alpha reductase inhibitors (5 ARI) , 5 - phosphodiesterase inhibitors, antimuscarinics and plant extracts.

Alpha-adrenergic blockers achieve their effect by blocking α-adrenergic receptors in smooth muscle in prostate stroma, thus increasing quality of voiding and alleviating symptoms.

Among several agents availably tamsulosin is most common prescribed. Effects take a few weeks to develop fully, but significant efficacy over placebo can occur within hours to days.

Appliance of α- blockers do not adversely affect libido, have a small beneficial effect on erectile function, but sometimes cause abnormal ejaculatin.

Therapy with α- blockers is longlasting and is considered the first line drug treatment of male LUTS because of their rapid onset of action, good efficacy, and low rate and severity of adverse events.

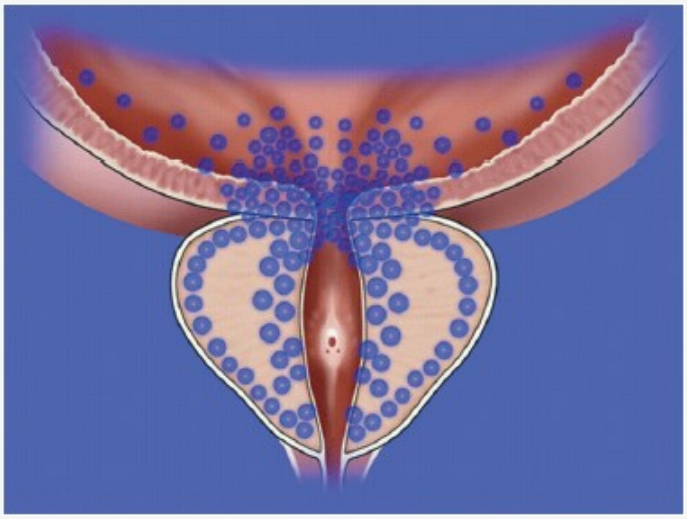


Figure 18. Distribution of α-adrenergic receptors in the lower urinary tract

5-alpha reductase inhibitors (5 ARI). As mentioned earlier, prostate is an androgen dependent organ with DHT being most potent and main androgen. 5- ARI act by blocking the conversion of testosterone to DHT, which is mediated by enzyme 5-alpha reductase.

Two isoforms of this enzyme exist, type1 and type 2, the last with predominant expression and activity in prostate. Two 5-ARI are available for clinical use: finasteride (Proscar) and dutasteride (Avodart). Finasteride inhibits only 5-α reductase type 2, whereas dutasteride inhibits5-α reductase types 1 and 2 with similar potency.

5-ARI act by inducing apoptosis of prostate epithelial cells leading to prostate size reduction of about 18-28% and decrease in circulating PSA levels of about 50% after six to twelve months of treatment. Mean prostate volume reduction and PSA decrease may be even more pronounced after long –term treatment.

After two to four years of treatment 5-ARI improve IPSS approximately 15-30%, decrease prostate volume by 18-28% and improve quality of life. This therapeutic approach can prevent disease progression and decrease the occurrence of acute urinary retention by 57% and need for surgery by 34%. This therapy should be considered in men with moderate-to-severe symptoms and an enlarged prostate (more than 40 ml); both finasteride and dutasteride are equally effective in accomplishing therapeutic goal.

The most relevant adverse effects of 5-ARI are related to sexual function, including reduced libido and erectile dysfunction.

Combination therapy with α-blockers and 5 ARI. The rationale for this therapeutic approach is the fact that prostate is composed of stromal and epithelial elements. Stromal elements are targeted by α-blockers and epithelial by 5-ARI.The mode of action of both medications is in concordance because of slow onset of action of 5-ARI which is covered with relatively rapid onset of efficacy of α-blockers.

Compared with α-blocker or 5-ARI monotherapy, combination therapy results in greater improvement in LUTS and is superior in prevention of disease progression. Combination therapy is also associated with higher rate of adverse events, and should therefore be prescribed primarily in men who have moderate-to-severe LUTS and are at risk of disease progression.

Antimuscarinic therapy. The aim of antimuscarinic therapy is to improve quality of voiding by decreasing severity and frequency of storage symptoms which are manifestation of bladder dysfunction. Antimuscarinic agents act by blocking M-cholinoreceptors on the smooth muscle cells of detrusor thus reducing activity of main neurotransmitter acetylcholine. Among new generation of muscarinic receptor antagonists most common prescribed are solifenacin, darifenacin, oxybutynin, trospim chloride …etc.

Controlled randomized trials have shown that antimuscarinics significantly improve quality of voiding by decreasing severity and frequency of storage symptoms compared with placebo.

Antimuscarinic drugs show good safety profile. Most common drug-related adverse events include dry mouth (up to 16%), constipation (up to 4%), and micturition difficulties (up to 2%).

Phosphodiesterase 5 inhibitors were the first drugs with scientifically proven efficacy in treatment of erectile dysfunction in men. In a smaller doses they can improve quality of voiding by decreasing severity of storage symptoms. Several randomized controlled trials have demonstrated that phosphodiesterase 5 inhibitors reduce IPSS, storage and voiding LUTS and improve quality of life. Nowadays, only tadalafil (5 mg once daily) is licensed for the treatment of male LUTS.

Phytotherapy refers to the use of plants or plant extracts for medical purposes. Posssible relevant compounds include phytosterols, β-sitosterol, fatty acids and lecitine.

In vitro, plant extracts can have anti-inflammatory, anti-androgenic and oestrogenic effects, but these effects have not been confirmed in vivo.

The use of phytotherapy in BPH is popular in Europe as a result of patient-driven enthusiasm.

The extracts of the same plant produced by different companies differ in concentrations of active ingredients, and do not necessarily have the same biological and clinical effects; therefore the effects of one brend can not be extrapolated to others. In fact, batches from the same producer may contain different concentrations of active ingredients.

In conclusion, the mechanism of action of phytotherapeutic agents is unknown and the efficacy and safety of these agents have not been well tested in randomized, double-blind, placebo-controlled studies.

Surgical treatment of BPH

Indication for surgical treatment of BPH include:

- Urinary retention
- Recurrent urinary tract infections
- Frequent episodes of gross hematuria
- Postrenal insufficiency caused by enlarged prostate
- Associated conditions sucha a bladder stones or bladder diverticula
- Severe vodinig symtoms with IPSS score 20-35, refractory to medical treatment

Obstructing prostatic tissue can be removed by open surgery or by transurethral approach.

Transurethral approach includes transurethral resection of prostate (TURP) and severel relatively new techniques known as “minimally invasive endoscopic procedures”

Open prostatectomy is the oldest surgical treatment for moderate-to-severe LUTS secondary to bladder prostatic obstruction (BPO). Obstructive adenomas are enucleated using the index finger approaching from within bladder (Freyer procedure) or through anterior prostatic capsule (Millin procedure). It is used for substantially enlarged glands > 100 ml.

Nowadays open prostatectomy is rarely performed because of advance in transurethral techiques end need for less traumatic-invasive treatment.

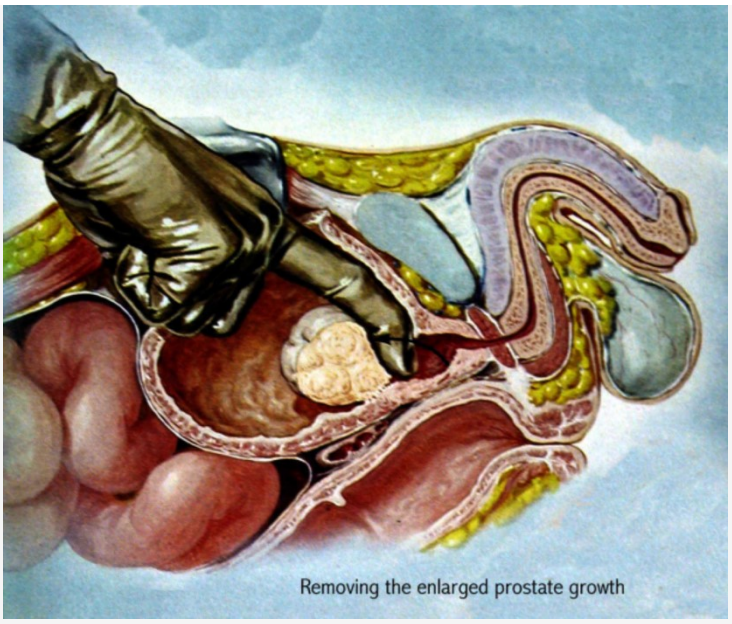


Figure 19. Open prostatectomy

Endoscopic procedures. Transurethral resection of prostate (TURP) in now gold standard for the surgical management of BPH. More than 90% of prostatectomies can be done endoscopically.

Endoscopic instrument (resectoscope) is inserted in bladder through urethra; at the tip of the instrument is cutting loop 6 mm wade. Prostatic tissue is removed in many peaces by cutting loop using high-frequency electrical current. Depending on surgeons skill prostate up to 100 g can be removed. Symptom score and flow rate improvement with TURP is superior to that of any minimally invasive procedures.

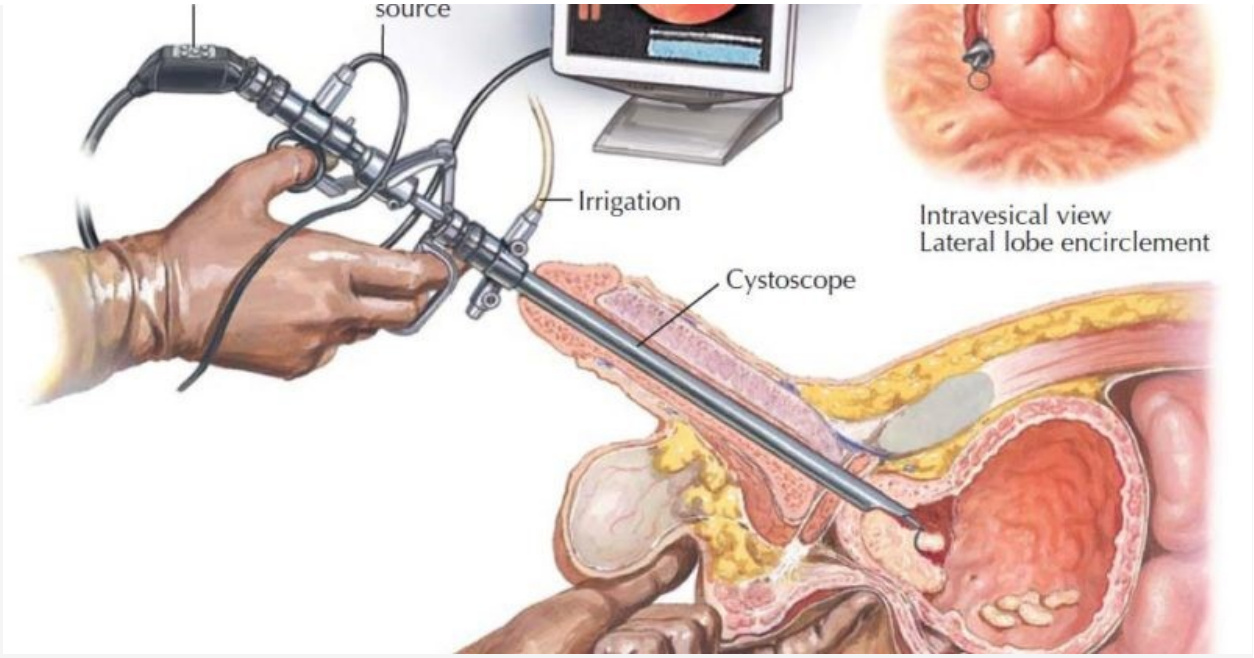


Figure 20. Transurethral resection of prostate

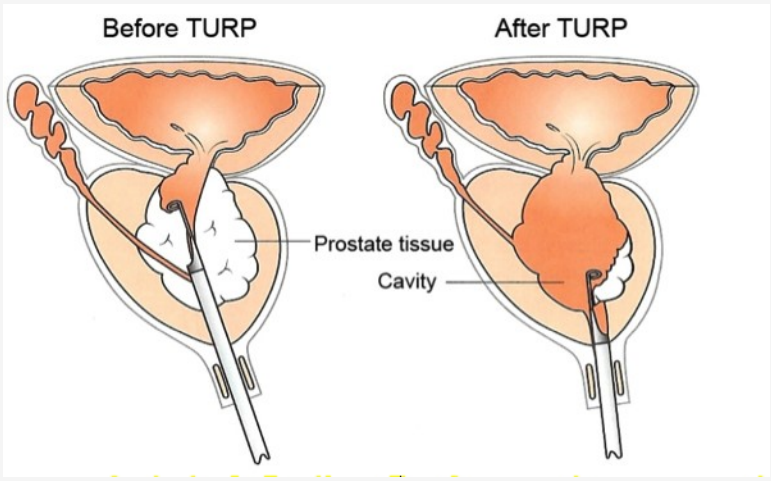


Figure 21. Schematic view of TURP

Minimally invasive endoscopic procedures.

Transurethral incision of the prostate (**TUIP**) involves incising the bladder outlet without tissue removal; it is suitable for small prostate, sizes < 30 ml.

Transurethral microwave therapy (**TUMT**) works by emitting microwave radiation through an intraurethral antenna that delivers heat into into the prostate.Tissue is destroyed (coagulation necrosis) by being heated at temperature above cytotoxic thresholds (> 45). The heat may also cause apoptosis and denrvation of α-receptors, thereby decreasing the smooth muscle tone to the prostatic urethra.

Transurethral needle ablation of the prostate (TUNA).

In this procedure transurethral needle ablation device delivers low-level radiofrequency energy to the prostate vie needles inserted transurethrally into the prostatic parenchyma under direct vision using an attachment to the standard cystoscope.

The energy induces coagulation necrosis in the transition zone resulting in reduction of prostate volume and BPO.

Laser treatments of prostate

Lasers use concentrated light to generate precise and intense heat to the prostatic tissue leading to tissue coagulation necrosis or vaporization.

The efficacy of laser treatment is comparable to that after TURP in decreasing LUTS. Compared with TURP laser tehrapy has shorter catheterisation time and hospital stay, reduced blood loss but a longer operation time.