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REVIEW ON URINARY BLADDER CARCINOMA

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ABSTRACT

The main aim of this review to know the symptoms, causes, treatment & overall information of urinary bladder cancer. Bladder cancer occurs when cells in the bladder start to grow out of control. Almost all bladder cancers develop in the transitional cells of the inner layer of the bladder which is in contact with urine. Some can grow into the deeper bladder layers. The main test for diagnosing bladder canceris a cystoscopy. The urologist looks inside your bladder by inserting a small camera through the urethra (the tube that carries your wee out of the body) into the bladder. A Radical Cystectomy or RC is a surgery to remove your bladder as a treatment for invasive bladder cancer. BCG is used to treat higher risk non-invasive bladder cancers. BCG treatment has the widest range of experiences from "not a problem at all" through to "that was hellon earth".

KEYWORDS: Cystoscopy, BCG (Bacillus Calmette-Guérin**)**, Radical Cystectomy.

INTRODUCTION

Bladder cancer occurs when cells in the bladder start to grow out of control. Almost all bladder cancers develop in the transitional cells of the inner layer of the bladder which is in contact with urine. Some can grow into the deeper bladder layers. As cancer grows through these layers into the wall of the bladder, it becomes harder to treat. The transitional cells lining the bladder are also found in the inner layers of the renal pelvis, ureters and urethra. Similar cancers can occur in these areas, though much less frequently. Carcinoma of the bladder is the seventh most common cancer worldwide. It comprises 3.2% of all cancers, with an estimated 260000 new cases each year in men and 76000 in women. The highest incidence rates in males and females occur in Western Europe, North America and Australia. The UK annual incidence is over 10000 new cases, with a male: female ratio of 5:2.

Urothelial carcinoma is the most common type of bladder cancer. However, there is significant geographic variation, and in certain regions of the world, such as Egypt and parts of Africa, squamous cell carcinoma (SCC) of the bladder predominates. Urothelial carcinomas of the renal pelvis, ureter and urethra are less common, accounting for approximately 10% of all urinary tract neoplasms. It should be noted that the formerly used term ‘‘transitional cell carcinoma (TCC)’’ is now largely replaced by ‘‘urothelial carcinoma,’’ although you will still hear urologists and pathologists use both interchangeably.

HISTOPATHOLOGY

The histopathology lesions observed in the urinary bladder epithelium of rats treated with BBN have been classified into four types: simple hyperplasia, papillary or nodular hyperplasia, papilloma and carcinoma simple hyperplasia consists of diffuse or focal thickening of the epithelium with four to eight layers of transitional epithelial cells. In papillary or nodular hyperplasia, the epithelium is six to eight cells thick, and in most cases the changes are strictly localized. Cellular atypia and mitotic figures are only rarely observed in areas of hyperplasia. Areas of hyperplasia demonstrate either exophytic growth, with a delicate fibro vascular core and protrusion into the lumen of the urinary bladder, or entophytic growth. Papillomasare defined as benign epithelial tumors in which the transitional epithelium cells are arranged in branched finger-like processes surrounding a delicate fibro vascular core. They are generally exophytic but may show an entophytic growth pattern. Cellular irregularity is slight and few mitotic figures are present. Carcinomas have morphologic characteristics of atypia, invade the muscular is and demonstrate a high degree of mitotic activity.

Classification of Urinary Bladder Cancer Promoters

1. Sodium or potassium salts

- Sodium saccharin
- Sodium L-ascorbate
- Sodium o-phenylphenate
- Sodium bicarbonate
- Sodium citrate
- Sodium phenobarbital
- Potassium carbonate with or without ascorbic acid

2. Urolithiasis-inducing chemicals

- Uracil
- Diphenyl

3. Antioxidants

- Butylatedhydroxyanisole
- Butylatedhydroxytoluene
- Ethoxyquin
- t-Butylhydroxyquinone
- 2-t-Butyl-4-methylphenol

4. Anticancer agents

- Adriamycin
- Mitomycin C

5. Amino acids

- DL-Tryptophan
- L-Leucine
- L-Isoleucine

6. Others

- Urinary components (fractions I and II)
- Allopurinol

SIGNS AND SYMPTOMS

- Blood in the urine
- Painful urination
- Urgent need to urinate
- Feeling the need (but not being able) to pass urine
- Abdominal pain
- Fatigue
- Lower back pain
- Appetite or weight loss

1. Blood in the urine (haematuria)

This is the most common symptom of bladder cancer. It can happen suddenly and may come and go. Your urine may look pink, red or sometimes brown. Or you may see streaks or clots of blood in it. If you see blood in your urine, it is important to get it checked by your GP straight away. Sometimes blood in the urine can't be seen and is found during a urine test. This is called non-visible or microscopic haematuria. If you have urinary symptoms (see below), your doctor will ask you to provide a sample of urine. They test this for non-visible blood.

2. Pain in the lower part of the tummy or back

This is less common, but it may happen in some people. There are different causes for these symptoms, such as an infection, kidney stones or bladder stones. But if you have any of these symptoms, it's important to get them checked by your GP. The earlier bladder cancer is diagnosed, the more likely it is to be cured. Some people have a burning feeling when they pass urine. Or, they feel the need to pass urine more often or urgently. These symptoms are usually caused by infection rather than cancer. Some people may need more tests to find out the cause of their urinary symptoms.

Risk factors and causes of bladder cancer

- Smoking
- Age
- Gender
- Exposure to chemicals at work
- Infection
- Previous treatment for cancer
- Family history

1. Smoking

Smoking is the biggest risk factor for bladder cancer. About 1 in 3 cases of bladder cancer may be caused by it. The longer person smokes and the more cigarettes they smoke, the greater the risk. Chemicals that can cause cancer are present in cigarette smoke. When smokers inhale, some of these chemicals get into the blood and end up in the urine after being filtered bythe kidneys. The chemicals can damage the cells that line the bladder and, over many years, this may cause cancer. Smoking also irritates the bladder, so stopping will help reduce some treatment side effects, as well as having other benefits to your health.

2. Age

Bladder cancer is more common in older people. It's rare for anyone under 40 to develop it.

3. Gender

Bladder cancer is more common in men than in women. Exposure to chemicals at work. These include chemicals previously used in dye factories, rubber, leather, textiles, printing, gasworks, plastics, paints and in other chemical industries. Many of these chemicals are now banned, but it can take up to 25 years after exposure for bladder cancers to develop. The Department of Workand Pensions (dwp.gov.uk) has information about the chemicals involved and claiming for Industrial Injuries Disablement Benefit.

4. Infection

Repeated urinary infections and untreated bladder stones have been linked with a less common type of bladder cancer called squamous cell cancer. People who are paralyzed have more bladder infections and a higher risk of getting bladder cancer.

5. Family history

The risk of developing bladder cancer is slightly increased if you have a close relative who has had bladder cancer. Sarcomatoid Carcinoma in the human.

DIAGNOSIS

Diagnosis is done by different methods:

1. MRI

This test uses magnetism to build up a detailed picture of areas of your body. The MRI is a powerful magnet so you may be asked to complete and sign a checklist to make sure it's safe for you. The checklist asks about any metal implants you may have, such as a pacemaker, surgical clips or bone pins, etc. You should also tell your doctor if you've ever worked with metal or in the metal industry as very tiny fragments of metal can sometimes lodge in the body. If you do have any in your body, it's likely that you won't be able to have an MRI scan. In this situation, another type of scan can be used. Before the scan, you'll be asked to remove any metal belongings including jewellery. Some people are given an injection of dye into a vein in the arm, which doesn't usually cause discomfort. This is called a contrast medium and can help the images from the scan to show up more clearly. During the test, you'll lie very still on a couch inside a long cylinder (tube) for about 30 minutes. It's painless but can be slightly uncomfortable, and some people feel a bit claustrophobic. It's also noisy,

but you'll be given earplugs or headphones. You can hear, and speak to the person operating the scanner.

2. PET and PET/CT PET-CT scan:

This is a combination of a CT scan, which takes a series of x-rays to build up a three dimensional picture, and a positron emission tomography (PET) scan. A PET scan uses low-dose radiation to measure the activity of cells in different parts of the body. PET-CT scans give more detailed information about the part of the body being scanned. You may have to travel to a specialist centre to have one. You can't eat for six hours before the scan, although you may be able to drink. A mildly radioactive substance is injected into a vein, usually in your arm. The radiation dose used is very small. The scan is done after at least an hour's wait. It usually takes 30–90 minutes.

3. Bone scan

A bone scan can show any abnormal areas of bone. It may be done to find out if the cancer has spread to the bones. A small amount of a mildly radioactive liquid is injected into a vein, usually in your arm. The level of radioactivity used doesn't cause any harm. Abnormal bone absorbs more of the radioactive substance than normal bone. These areas show up as highlighted on the scan. They are known as hot spots. After having the injection, you will have to wait for up to three hours before you have a scan of your whole body. This gives time for the bone to absorb the radioactive substance. You may want to read a book or magazine to help pass the time. A bone scan can show conditions other than cancer, such as arthritis. In this case, you may need to have further tests, such as an x-ray of the abnormal area. Diagnosing invasive and advanced bladder cancer Positron emission tomography (PET) represents a biological rather than exact anatomical imaging modality, which is nowadays commonly combined with diagnostic CT. Depending on the tracer used for PET imaging metabolism or expression of certain antigens can be visualized and attributed to exact anatomical structures or organs especially when fused to corresponding CT images. For BCa most studied tracers represent 18F-FDG, 11C-choline (or 18F-choline) and 11C-acetate.

- **18F-FDG**

Until now primarily 18F-fluorodeoxyglucose (18F-FDG; half-life 109 min) has been used as tracer in staging of BCa patients. 18F-FDG is taken up into metabolic active cells through glucose transporters, where it is phosphorylated by hexokinase and trapped intracellularly as

no further metabolization takes place. However, apart from previous transurethral resections and postoperative reactive changes, especially renal excretion of 18F-FDG and subsequent accumulation of the tracer in urine and in the bladder render detection and assessment of local bladder tumors difficult. Some modifications have been introduced in order to bypass these problems, such as flushing the bladder[20,21], application of diuretics or early scanning 2–4 min after tracer injection. Unfortunately, still false-positive findings can be observed furthermore, in the subpopulation with metastatic disease, PET/CT could visualize bone metastases confirmed by conventional bone scan.

- **11C-Choline**

11C-Choline is another alternative tracer that exhibits a much shorter half-life of 20 min. After cellular uptake, it is integrated into the cell membrane of metabolic active cells. The tracer undergoes predominantly hepatic instead of renal excretion, thus facilitating the evaluation of the bladder and pelvic region The results from 11C-Choline-PET/CT or diagnostic conventional CT alone (each reviewed by two independent radiologists or nuclear medicine physicians/radiologists) were compared to histopathological findings on a patient level as well as field-based. No significant differences between 11C-Choline-PET/CT and diagnostic CT alone regarding local tumor staging, patient-, and field-based analysis were observed.

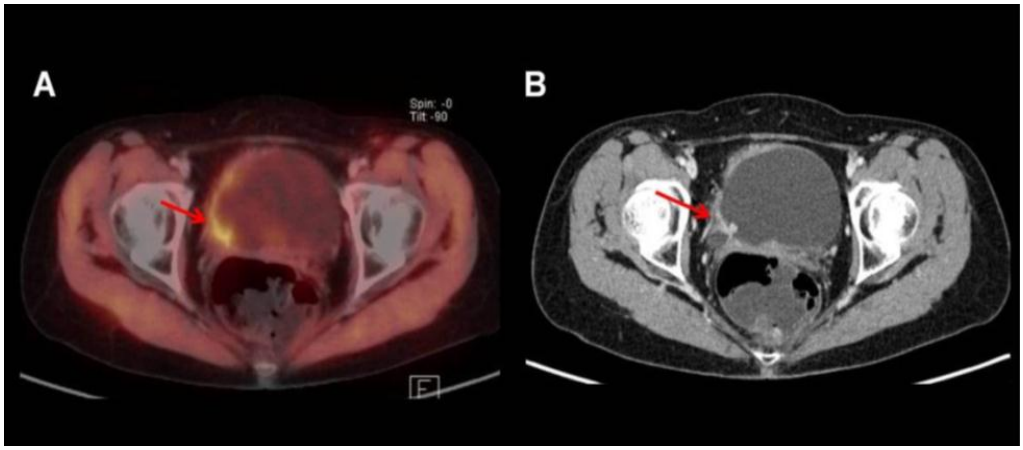

Figure: Bladder tumor with tracer uptake in the right posterior-lateral bladder wall as visualized by 11Choline-PET/CT. Note that there is excellent delineation of tumor and bladder lumen due to the fact that 11C-Choline is usually not excreted by the urine (A: fused dataset). However, anatomical detail is superior in the contrast enhanced CT part of the PET/CT (B).

Detection of malignant lesions of the urinary bladder using urine cytology and correlating with the histopathology

Bladder cancer is the fourth most common cancer in men (6%) and the tenth most common cancer in women (2%), accounting in men for 3% of cancer deaths in 2004 in United States. The carcinoma of the bladder is more common in men than in women, in the industrialized countries than in developing countries, and in urban than in rural dwellers. There are approximately 50,000 new cases and 10,000 deaths from urothelial carcinoma in each year in United States. The male to female ratio for transitional cell tumour is approximately 5: 1. About 80% of patients are usually between the ages of 50 and 80 years. A number of factors (multi-factorial) have been implicated in the causation of transitional cell carcinoma. The ideal diagnostic test should be rapid, inexpensive and non-invasive with high sensitivity and specificity. Urinary Cytology is an accepted procedure for screening and follow-up of patients with bladder tumors.

Types of Tests Used to Diagnose Bladder Cancer

1. Radiological Tests

One of two radiological tests is prescribed by the urologist to explore possible reasons for the patient's hematuria or irritative symptoms. Historically, the IVP or intravenous pylegram, using dye, or contrast, with conventional x-ray technology to evaluate the urinary tract system has been the principal test prescribed. Before the IVP, a complete medical history is taken to determine if there are any medical conditions (such as allergy to contrast material or "dye," asthma, or kidney disease) which might alter the way the procedure is performed. However, in many hospitals, the CT urogram, a CT scan using contrast to examine the kidneys, ureters and bladder is the recommended procedure. Because the CT urogram provides a three dimensional view of the kidneys and urinary system, the urologist is able to use this to also rule out any kidney tumors. In addition, other organs in the abdomen, such as the liver or lymph nodes, can be viewed to ensure that a tumor from the bladder has not spread to those areas. Similar to the IVP, a complete medical history must be performed prior to the procedure

2. The Gold Standard although the radiological tests

Provide important information about the kidneys and the ureters, cystoscopy is still the best method of evaluating the bladder and the urethra. The cystoscope, a long thin tube, is inserted through the urethra. Today, with the widespread use of the flexible cystoscope most of these

diagnostic procedures are done in the outpatient setting with little or no discomfort. As the urologist looks through the cystoscope, the locations where the reappears to be abnormal features are noted and recorded. During the cystoscopy, the urologist may choose to take a small piece of what appears to be abnormal tissue (biopsy) and send it to the pathologist to read and analyze. In addition, a sample of the urine from the bladder is frequently sent for analysis (cytology) to determine if there are any cancer cells. The biopsy specimen as well as the urine sample will help the urologist make recommendations about your future care. Patients will go home after the cystoscopy if it is done in the doctor's office. Patients should expect that there may be some bleeding and possible irritative bladder symptoms following the cystoscopy for a day or two. Although seeing blood in the urine may be very troubling for the patient, **t**he urologist, understanding that even small amounts of blood can affect the color of the urine dramatically, may not be concerned.

3. Staging and Grading of Bladder Cancer

Ninety-five percent of bladder tumors arise from the bladder lining surface (epithelium). Those that arise from that surface are either papillary (tumors that grow out from the surface) or sessile tumors (which are low and flat). While occasionally a benign tumor can arise in the bladder, the overwhelming majority of bladder tumors are malignant, or cancers. A biopsy can distinguish the benign from the malignant cancers. Grade and Stage describe the bladder tumor, helping to provide guidance for the urologist in choosing the best treatment option(s). Staging is a careful attempt to find out the extent of the cancer. Staging will define whether the cancer has invaded into or through the bladder wall, whether the disease has spread, and if so, to what parts of the body. The higher the stage the further the cancer has grown away from its original site on the surface of the bladder. Grade refers to what the cancer cells look like, and how many cells are multiplying. The higher the grade, the more uneven the cells are and the more the cells are multiplying.

TREATMENT

Bladder cancer can be a rollercoaster of tests and treatments with side effects that can range from "not a problem at all" to "the worst ever". At Fight Bladder Cancer, we know that passing on the best tips and advice from other patients and carers can really help if you've just been diagnosed, or if you're having a difficult time with a particular treatment. You can get really good advice – at anytime – on our Confidential Forum, where there are thousands of other patients and carers who are happy to help. It provides information, tips and advice

from people who understand what you are going through. We have organized this advice according to the different tests and treatments,

1. Cystoscopy
2. TURBT (trans urethral resection of a bladder tumour)
3. Chemotherapy
4. BCG treatment
5. Radiotherapy
6. Radical cystectomy

1. CYSTOSCOPY

The main test for diagnosing bladder canceris a cystoscopy. The urologist looks inside your bladder by inserting a small camera through the urethra (the tube that carries your wee out of the body) into the bladder. The procedure is carried out using acystoscope, which is a thin fiber-optic tube with a light and camera at one end. Although the thought of this might be embarrassing, it is quite a simple procedure. Most cystoscopies are done as outpatient procedures, so you'll be able to go home on the same day.

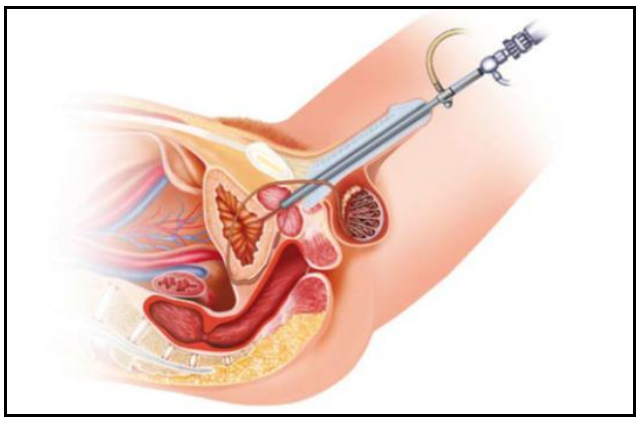

Fig: Cystoscopy.

Is a Cystoscopy painful?

A flexible cystoscopy is usually carried out using a local anesthetic or spray to numb the urethra. This will reduce any discomfort when the cystoscope is inserted into the urethra. A rigid cystoscopy is usually carried out under general anesthetic (when you're asleep), or after having an epidural that numbs everything below your waist. However, the procedure may feel uncomfortable for some people and can lead to mild side effects afterwards, such as muscle pain and nausea. For a few days after the procedure, you may feel a burning sensation when you wee and you may pass blood in your urine. This is normal and isn't something to

worry about, unless it's severe and lasts longer. Before your cystoscopy appointment you'll be sent information on which type of cystoscopy you will be having and instructions you should follow. If you're having a local anesthetic you can eat and drink normally on the day of the appointment. With a spinal epidural or general anesthetic, you won't be able to eat or drink for several hours before. If you have a local anesthetic you'll be able to go home shortly afterwards. It usually takes a few hours to recover from the effects of an epidural or general anesthetic so you'll need to arrange for someone to take you home. You should rest for 24 hours and avoid driving, operating complex or heavy machinery, and drinking alcohol for 48 hours. Most prescription medication can be taken as usual on the day of your appointment. However, you may not be able to take aspirin, warfarin or ibuprofen, because they could cause excessive bleeding during the procedure.

Recovering from a cystoscopy

The type of anesthetic used will affect how long it takes to recover from a cystoscopy. It'snormal to have some side effects for a few days afterwards. Most people experience burning pain when passing urine for the first few days after a cystoscopy. This is normal, and it should stop within a few days. Having blood in your urine or bleeding from your urethra (the tube that carries urine out of the body) is also common in the first few days after a cystoscopy, particularly when a biopsy was also carried out. Drinking plenty of water can ease both of these symptoms. Very occasionally, you might be unlucky and have some other side effects, but you should contact the hospital if:

- your urine becomes so bloody that you can't see through it
- you notice clots or tissue in your urine
- you experience severe pain while urinating
- the pain and bleeding last more than a few days
- you're unable to pass urine more than eight hours after the procedure
- you develop a high temperature (fever)of 38°C (100.4°F) or above
- your urine smells unpleasant
- you have nausea or vomiting
- You have pain in your lower back or side Before being discharged, you'll be given a contact telephone number for the hospital.

Risks of a cystoscopy

A cystoscopy is usually a very safe procedure, and serious complications are rare. Occasionally, patients may have problems passing urine or an infection may develop.

URINARY TRACT INFECTIONS

- Urinary tract infections (UTIs) are infections of the urethra, bladder or kidneys. Symptoms of a UTI can include:
- a burning sensation when urinating that lasts longer than two days
- a high temperature (fever) of 38°C(100.4°F) or above
- unpleasant smelling urine
- nausea and vomiting
- pain in your lower back or side Contact your GP or hospital staff as soon as Possible if you have any of these symptoms.
- Antibiotics can be used to successfully treat most UTIs.

PROBLEMS PASSING URINE

Some people find it difficult to pass urine after a cystoscopy. This is known as urinary retention. Urinary retention after a cystoscopy is uncommon in women, but men with preexisting problems are at a higher risk. There are a number of different treatments for non-invasive bladder cancer. The type you may need depends on the particular type of bladder cancer and how aggressive it is (the grade).The following list is not exhaustive, but it explains most of the treatments available for this form of cancer. If you're having a different treatment, do make sure that your medical team to explain the reason for the treatment, any possible side effects and all the risks.

TURBT (Trans Urethral Resection of a Bladder Tumour)

Generally, after the diagnosis of a bladder tumour, the urologist will suggest that the patient have an outpatient procedure in the hospital to examine the bladder more completely under anaesthesia (general or spinal) and to remove the tumour if possible. The TURBT is "incision-less" surgery usually performed as an outpatient procedure under general anesthetic. Like the cystoscope, the resectoscope (the instrument used to remove the tumour in the TURBT) is introduced through the urethra into the bladder. Attached to this scope is a small, electrified loop of wire which is moved back and forth through the tumour to cut and remove the tissue. Electricity is also used to seal off any bleeding vessels. This is sometimes

called electro cauterization or fulguration. The advantages of this procedure are that it can be performed repeatedly at minimal risk to the patient and with excellent results. There is a less than 10%risk of infection or injury to the bladder and both are easily correctable. After surgery, you should be given a single dose of chemotherapy directly into your bladder, using a catheter. The solution is kept in your bladder for around an hour before being drained away. Before the operation you will be asked to put on a gown and some tight-fitting antithrombusstockings. These help to prevent blood clots from forming in your legs. You will then be taken to theatre by a member of the ward staff.

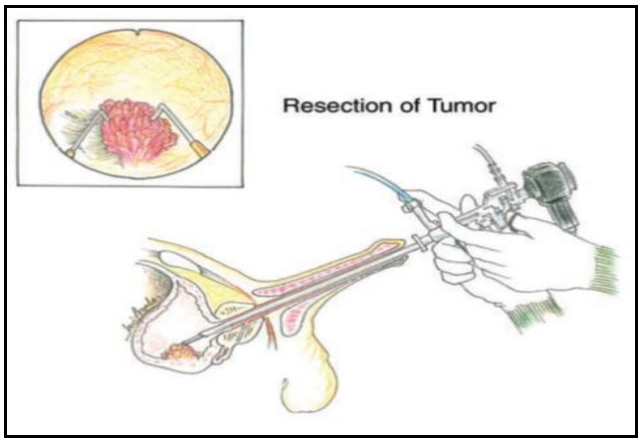

Fig: Resection of a Bladder Tumour.

CHEMOTHERAPY TREATMENT

For some forms of non-invasive bladder cancer you will be offered a course of at least six doses of intravesical chemotherapy, where the liquid is placed directly into your bladder, using a catheter, and kept there for around an hour before being drained away. You should be offered follow-up appointment sat 3 months, 9 months and 18 months, and then once every year. At these appointments, your bladder will be checked using acystoscopy. If your cancer returns within five years, you'll be referred back to a specialist urology team. Some residue of the chemotherapy medication may be left in your wee after treatment, which could severely irritate your skin. For men, it helps if you wee while sitting If you're worried about anything, just ask.Treatmentsfightbladdercancer.co.uk de effects & how to cope down, and be careful not to splash yourself for the toilet seat. After weeing, wash the skin around your genitals with soap and water. If you're sexually active, it's important to use a barrier method of contraception such as a condom. This is because the medication maybe present in your semen or vaginal fluids, which can cause irritation. You also shouldn't try to get pregnant or father a child while having chemotherapy for bladder cancer, as the medication can increase

the risk of having a child with birth defects. Although no agent has been shown to be superior to BCG in head to head studies, single-dose intravesical chemotherapy, given in the immediate post-operative period for low-risk papillary disease, does have a clear role. A meta-analysis of seven randomized trials that included 1476 patients found a statistically significant decrease in the risk of recurrence (48 versus 37 percent, odds ratio 0.61). Agents that have been evaluated in the trials included in the meta-analysis were mitomycin, epirubicin, thiotepa and pirarubicin. An even greater absolute reduction (about 17 percent) was observed for patients with multifocal tumors, but this was felt to be insufficient therapy, since 65 percent of patients still recurred. For patients with low-grade disease that has previously recurred or is multifocal, six weekly courses of intravesical chemotherapy is considered a reasonable alternative to BCG for initial management. Failure on such a regimen does not appear to adversely affect subsequent response to BCG.

Mitomycin

Intravesical mitomycin has been used with multiple schedules, including single dose, multiple weekly administrations, or with a maintenance regimen. Mitomycin is the most commonly used intravesical chemotherapeutic agent, although the optimal schedule is not known and it has not been approved by the Food and Drug Administration for Intravesical use. In a meta-analysis that was included in the American Urological Association guidelines, a single dose post-operative instillation of mitomycin provided an average absolute benefit of a 17 percent reduction in early tumor recurrence. The activity of mitomyc in with extended maintenance therapy was illustrated in a multicenter trial in which 495 patients were randomly assigned to intravesical therapy with BCG (weekly for six doses), mitomycin (20 mg weekly for six weeks), or mitomycin (20 mg weekly for six weeks, then monthly forthree years).[104] The three-year recurrence-free rates with six-week courses of either BCG or mitomycin were inferior to that achieved with maintenance mitomycin (66 and 69 percent versus 86percent). Other randomized trials have suggested improved results with a variety of approaches to enhance the efficacy of mitomycin. These approaches have included an "optimized" regimen using a longer dwell time, increasing the intravesical drug concentration by decreasing the volume in which the drug is instilled (40 mg in 20 cc), decreasing urine volume by dehydration and complete emptying and by alkalinizing the urine to stabilize the drug, electromotive instillation to accelerate drug delivery into and across biologic membranes, and microwave hyperthermia. The optimized regimen was proven superior to standard administration of 20 mg diluted in 20 cc volume in a randomized clinical trial and

many have adopted this as the standard of care. Although the other variations have shown benefits compared to standard Intravesical mitomycin or BCG, confirmatory trials are required before they can be adopted as standard therapy.

Toxicity

Mitomycin is an alkylating agent that is minimally absorbed from the bladder into the systemic circulation. Chemical cystitis contraction of bladder. Rash hypersensitivity reaction. Nausea, Vomiting

Anthracyclines

Epirubicin, doxorubicin, and valrubicin are anthracyclines with limited systemic absorption following intravesical instillation. Studies have demonstrated activity for these agents but the role of anthracyclines remains limited. Although epirubicin is more active than either placebo or interferon (IFN) alfa, it was less active than BCG in a trial of 957 patients with intermediate and high-risk Ta and T1 papillary bladder cancer. Patients were randomly assigned to Intravesical epirubicin or BCG. Both groups then received maintenance treatment with three weekly intravesical doses of either agent every three months for 36 months. Treatment with BCG resulted in a significantly longer time to first recurrence compared to epirubicin and a higher three-year recurrence-free survival (65 versus 49 percent). Furthermore, at a median follow-up of 9.2 years, risks of first recurrence and distant metastases were significantly lower with BCG compared to epirubicin death from all causes and death from bladder cancer were significantly reduced with BCG compared with epirubicin. The anthracycline valrubicin is approved by the United States Food and Drug Administration (FDA) forintravesical use in patients with T is lesions who have failed intravesical BCG, and in whom immediate cystectomy is either refused or contraindicated. The efficacy of valrubicin in this setting was supportedby a series of 90 patients with recurrent Tis after multiple prior courses of intravesical therapy, including BCG. Each patient received six weekly instillations (800 mg) and was evaluated atthree-month intervals following treatment. Complete remission was noted in 19 patients (21 percent). Median time to failure or last follow-up for complete responders was more than 18 months. The main side effects are reversible local bladder symptoms. Gemcitabine — Based upon results from small, nonrandomized studies, Intravesical gemcitabine has been proposed as an alternative to BCG or for patients who have progressed on BCG. As an example, the activity of intravesical gemcitabine was illustrated by a series of 30 patients who were refractory or

intolerant to intravesical BCG and who refused cystectomy. Patients were treated with a dose of 2000 mg twice weekly for three weeks.

BCG TREATMENT(Bacillus Calmette-Guérin)

BCG is used to treat higher risk non-invasive bladder cancers. BCG treatment has the widest range of experiences from "not a problem at all" through to "that was hellon earth". BCG is a live vaccine used to vaccinate against TB (tuberculosis), but it is also used to treat bladder cancer. It is put into the bladder through a catheter to stop or slow down the re-growth of bladder cancer. When it is put into your bladder it triggers an immune response that causes inflammatory changes in the bladder. BCG treatment is normally given once a week for 6 weeks and continues with a maintenance regime for 3 years. BCG a live attenuated form of Mycobacterium bovis is the most commonly used agent for Intravesical therapy. A number of other Intravesical agents have been compared to BCG, but none has proved consistently superior.

Mechanism of action

Although the exact mechanism of its antitumor action is unknown, intravesical instillation of BCG triggers a variety of local immune responses which appear to correlate with antitumor activity. These include: Intravesical BCG causes a mononuclear cell infiltrate that consists predominantly of CD4 T cells and macrophages. BCG treatment is associated with the presence of interferon-gamma (IFNg) in the bladder. IFNginduces bladder cancer cell expression of class II MHC molecules, such as HLA-DR and intercellular adhesion molecule (ICAM)-1, which are absent prior to treatment. IFN-gamma also can cause bladder tumor cells to become sensitive targets for lymphokine-activated killer (LAK)cells and antigen-presenting cells for BCG. Cytokine levels, such as interleukin (IL)-1, IL-2, IL-6, IL-8, IL-12, IFNg, tumor n **Dose and schedule** BCG is typically instilled into the bladder weekly for six weeks. Each dose consists of a vial of reconstituted Theracys (81 mg) or one 2 mL ampule of TICE® BCG (50 mg), plus 50 mL of sterile saline injected into the bladder through a catheter and retained for two hours. Ecrosis fact or Complications — In a Cochrane database review of six randomized trials involving 585 eligible patients, toxicities associated with Intravesical BCG included frequency (71 percent), cystitis (67percent), fever (25 percent), and hematuria (23 percent).[79] There were no reported BCG-associated deaths. In addition to acute toxicities, both localized and systemic infectious complications can occur after Intravesical administration of BCG.

RADIOTHERAPY

Radiotherapy is used in muscle-invasive bladder cancer. Radiotherapy involves using carefully measured doses of radiation treatment to target the cancer. These abnormal cancer cells are more sensitive to radiotherapy than normal cells and will be destroyed. Normal cells can be damaged along with the cancer cells, which are why there are potential side effects, as with any treatment. In general the side effects are linked to the areas of normal healthy tissue that are close to the bladder such as the small bowel, the rectum(lower part of the bowel), the bladder itself and the skin in the area that is treated. Radiotherapy for bladder cancer is given from outside of the body (external beam radiotherapy). The number and frequency of radiotherapy sessions will depend on the extent, size and type of the tumour. Radiotherapy treatment is painless, and will not make you radioactive! It is very important that female patients tell their oncologist immediately if they suspect they may be pregnant.

The role of radiotherapy in urinary bladder cancer

The role of radiotherapy (RT) in the treatment of urinary bladder cancer has undergone several modifications along the last decades. In the beginning, definitive RT was used as treatment in an attempt to preserve the urinary bladder; however, the results were poor compared to those of radical surgery. Recently, many protocols have been developed supporting the use of multi-modality therapy, and the concept of organ preservation began to be reconsidered. Although phase III randomized clinical studies comparing radical cystectomy with bladder preservation therapies do not exist, the conservative treatment may present low toxicity and high indexes of complete response for selected patients. The aim of this study was to review the literature on the subject in order to situate RT in the current treatment of urinary bladder cancer.

Radiotherapy for superficial cancer

Information on the use of RT in the treatment of superficial urinary bladder cancer dates from before the success obtained with endoscopic treatments. Nowadays, there is no support in the literature that justifies its routine use in this group of patients. In most reports, RT is used in patients with progressive disease or in recurrences, after many transurethral resections of bladder tumors (TURB) combined or not with intravesical therapy. Despite of the relatively high rate of complete responses in stages T is and Ta, it is known that approximately 50% of the patients will present recurrence in the first year after RT; in five years, this rate will be 90%. There is no evidence that RT offers higher probability of urinary bladder preservation

than other treatments (TURB and Intravesical therapy). However, Weiss et al. suggested that TURB followed by radio chemotherapy could be an alternative treatment for high-risk tumors (T1, G3). In view of the satisfactory results obtained with TURB and BCG, the use of RT in this context is rarely justified and therefore, should be considered only in an individual basis. Radiotherapy for Invasive Cancer.

Preoperative Radiotherapy

Preoperative RT emerged in an attempt to minimize the possible dissemination of the disease during surgery, as well as to eradicate microscopic tumor focuses that might had been situated beyond the resection margins. At the beginning, many retrospective studies confirmed a real benefit in the use of preoperative RT compared to cystectomy alone. Conflicting results were found in studies that compared preoperative RT followed by immediate radical surgery versus radical treatment with RT and salvage surgery at recurrence. It is important to note that the RT scheme used was different in each of these studies. And, most of the times, a small number of patients were included which limited the statistical power of these analyses. Except for the MD Anderson experience (Miller) that showed statistically significant benefit favoring bimodal therapy, the other studies did not find any difference in terms of patient's survival in the evaluated groups. However, the study of Miller also must be interpreted with caution considering the small number of patients analyzed and the fact that only patients with largeT3 tumors were considered. Moreover, a meta-analysis involving five randomized studies concluded that the available data from those clinical studies do not support the routine use of preoperative RT. Therefore, although it has been considered an option in the past, preoperative RT is not recommended in the treatment of invasive urinary bladder cancer. After radical cystectomy, RT is rarely administered in the postoperative setting of patients with urinary bladder cancer. This is mainly due to the presence of high rates of side effects related to irradiation in the postsurgical period, after the abdominal manipulation and consequent fixation of both large and small bowel to the pelvis, as the neo-bladder itself. Complication rates vary around 20%. Nevertheless, the pelvic control of the diseases in general satisfactory with surgery only, Positive margins or lymph node involvements are adverse risk factors for recurrence and patient survival. Postoperative RT should be considered only in individualized situations such as recurrences of pelvic disease. Definitive Radiotherapy Until the development of modern surgical techniques for the performance of cystectomy, RT was widely used as a radical and exclusive treatment modality. Nowadays, RT alone should be used only in patients who present a high risk of

complications during surgery or with advanced disease. RT effectiveness in the treatment of urinary bladder cancer was repeatedly demonstrated in retrospective studies in Europe and Canada. However, these studies, most of the time, demonstrated lower local control and shorter patient survival when compared to cystectomy.

SIDE EFFECTS OF RADIOTHERAPY

EARLY REACTIONS

1. Fatigue

As radiotherapy can damage normal tissues close to or in the treated area, your body will use a great deal of energy to repair these damaged cells. This means that tiredness is a very common side effect of radiotherapy. If you feel fit enough, gentle exercise can help. Do not force yourself to do things you do not have the energy to do. Sore, red skin (erythema) Radiotherapy can make the skin in the treated area itchy, red, and sore. You can minimize this side effect by following the advice of the radiographers.

2. Bladder symptoms

You may experience changes in the flow of your wee, a need to wee more often, a need to wee urgently, a burning sensation when you wee and/or a small amount of blood in your wee. Your consultant may be able to prescribe you something to help with these symptoms. Drink plenty of water-based fluids such as cordial. Tea and coffee can make the symptoms worse. Some people find cranberry juice helpful. Tell the radiographers about any of these symptoms so they can ensure you do not have an infection. Always report any difficulty in weeing to your medical team.

3. Bowel symptoms

Treatment may irritate your bowel and make you need to go to the toilet more often. Medication such as Fybogel may be prescribed for you. You may developtenesmus, which is an urge to open your bowels without passing anything. This can feel like constipation. You may also notice an increase in the amount of wind you pass. If opening your bowels becomes painful or you notice some spotting of blood, let your medical team know. These side effects are not uncommon so do not be alarmed. Please do not modify your diet or take any medication for your bowels without discussing it with radiographer or consultant.

SIDE EFFECTS OF RADIOTHERAPY

LATE REACTIONS

Radiotherapy to the lower abdomen in women is likely to induce the menopause. A reaction called vaginal stenosis may occur as a result of scar tissue forming after radiotherapy. Vaginal dilators can be given to those having their pelvis treated to try to prevent this from happening. For men, radiotherapy can result in a lack of semen or a reduced sperm count, which may result in infertility. Radiotherapy may lead to more urgent and frequent bowel opening and weeing. Bleeding from the back passage may occur which can require medication or surgery. Always make sure you let the radiographers know exactly how you feel and whether you experience any side effects. There are a number of dietary tips that can help during radiotherapy. It is important to eat well and maintain your weight whilst undergoing radiotherapy.

General tips/advice

- Try to eat small frequent meals and snacks.
- Maintain a good fluid intake. It may be helpful to limit hot drinks and include more cold drinks, but avoid alcohol.
- Choose foods which you enjoy and find easy to swallow.
- Don’t worry too much about having foods that are low in fat and sugar for the time being (unless you have another medical condition).
- Some people find that including live yoghurt in their diet can help with diarrhoea.
- Check with a dietician or chemotherapy nurse if you are also having chemotherapy.

1. Sickness

Try to eat small amounts, little and often. Some people find that food and drink containing ginger helps with nausea.

2. Bladder symptoms

You may experience changes in the flow of your wee, a need to wee more often, a need to wee urgently, a burning sensation when you wee and/or a small amount of blood in your wee. Your consultant may be able to prescribe you something to help with these symptoms. Drink plenty of water-based fluids such as cordial, at least four pints or eight mugs a day. Tea and coffee can make the symptoms worse. Some people find cranberry juice helpful. Some patients will have specific advice regarding how much fluid they drink before their radiotherapy treatment. It is important to follow this advice.

3. Fatigue

As radiotherapy can damage normal tissues close to or in the treated area, your body will use a great deal of energy to repair these damaged cells. This means that tiredness is a very common side effect of radiotherapy. If you feel fit enough, gentle exercise can help. Do not force yourself to do things you do not have the energy to do. Sore mouth / difficulty swallowing avoid smoking which can prevent your body from repairing itself. Avoid drinking alcohol, especially spirits, which can irritate your mouth and make it sore. Avoid food that is very hot, spicy, acidic, hard or crunchy. It may be necessary to move to a softer, more liquid diet in some cases.4.Bowel symptoms. Please do not modify your diet or take any medication for your bowels without discussing it with a radiographer or consultant.

4. Dietary fiber

There are 2 types of dietary fiber, and each works in a different way.

- **Soluble fiber**

Foods containing soluble fiber soften the stools and absorb water as they move through the body. Examples are fruits, vegetables, pulses and oats, which you should include in your diet.

- **Insoluble fiber**

Foods containing insoluble fiber increase the speed at which food moves through the body. Examples are wholegrain cereals and whole meal bread. Avoid these foods whilst you are experiencing diarrhoea. If you are having problems with excessive wind and bloating, you might find it helpful to cut down on peas, beans, lentils, cabbage and fizzy drinks. Always make sure you let the radiographers know if you experience any side effects. They need you to tell them about your general well being.

RADICAL CYSTECTOMY (RC)

A Radical Cystectomy or RC is a surgery to remove your bladder as a treatment for invasive bladder cancer. It also involves removing the nearby lymph nodes, part of the urethra, the prostate (inmen) and the cervix and womb (in women). It is a major operation, lasting at least 6 hours. Recently, some RCs have been carried out using robotic surgery, but currently there is limited evidence about whether this is better than the traditional surgeon’s method as far as long term prognosis is concerned. However, we do know that this surgery is very important for some patients for whom traditional surgery would be dangerous due to other health issues as it is better for blood loss and generally you will have a quicker recovery.

Multimodal therapy

The rational of a multidisciplinary approach of invasive bladder cancer is based on the promising results of combined therapeutic modalities when compared to radical surgery. TURB is used to reduce the tumor volume to be irradiated. Moreover, it is known that transitional cell carcinoma of the bladder is highly chemoresponsible. Chemotherapy attempts to eradicate local and systemic disease and to increase RTeffect on loco regional control. INTRAVESICAL THERAPY — Intravesical therapy permits high local concentrations of a therapeutic agent within the bladder, potentially destroying viable tumor cells that remain following TURBT and preventing tumor implantation. The decision to proceed with intravesical therapy depends upon various risk factors and the likelihood of whether or not the patient will have a recurrence. Intravesical therapy is generally used in the adjuvant setting, to prevent further recurrence. Less commonly, intravesical therapy may be given for residual disease that remains in the bladder following TURBT. This situation is relatively infrequent, except in cases with diffuse CIS. Indeed, BCGis considered the treatment of choice for patients with CIS. In a meta-analysis of 700 patients with CIS, 68 percent achieved a complete response with BCG versus 51 percent with chemotherapy. Furthermore the long-term 3.6-year durability of response to BCG was significantly better than with mitomycin (47 versus 26 percent). All Intravesical therapies can cause symptoms of bladder irritation (dysuria and frequency). In addition, systemic effects may occur if the agent is absorbed through the mucosa. The latter phenomenon depends partly upon the size of the molecule and the pH in the bladder at the time of instillation. The presence of mucosal damage at the time of instillation can permit systemic absorption of the agent. Deferring intravesical therapy for two to three weeks following TURBT allows healing and reduces the likelihood of severe local or systemic toxicities. The most commonly used agent for intravesical therapy is Bacillus Calmette-Guerin (BCG). A number of other agents also have activity, including mitomycin, the anthracyclines, thiotepa, gemcitabine, interferon and docetaxel.

Gemcitabine

Based upon results from small, nonrandomized studies, Intravesical gemcitabine has been proposed as an alternative to BCG or for patients who have progressed on BCG. As an example, the activity of Intravesical gemcitabine was illustrated by a series of 30 patients who were refractory or intolerant to Intravesical BCG and who refused cystectomy. Patients were treated with a dose of 2000 mg twice weekly for three weeks Thiotepa — **Thiotepa.**

Thiotepa was the first intravesical agent to be used for non-muscle invasive bladdercancer. A randomized trial conducted by the National Bladder Cancer Collaborative Group showed thatintravesicalthiotepa (30 or 60 mg) was associated with a significant reduction in recurrence rate. However, it can cause irritative voiding symptoms in up to 69 percent of patients. Because of its relatively small molecular weight (186 daltons), thiotepa is absorbed systemically, and the incidence of myelosuppression may be as high as 54 percent. Furthermore, thiotepa is a potent carcinogen and has been linked to the development of secondary leukemia in patients treated for non-muscle invasive bladder cancer. Because of these acute side effects and late complications, intravesical thiotepa is seldom used. **Docetaxel** Intravesical docetaxel may have activity in patients with no muscle invasive urothelial bladder cancer that is refractory to BCG. In a phase I study of 18 patients, four (22 percent) remained disease-free at a median follow-up of 48 months following one course of six weekly intravesical. Photodynamic therapy — In addition to its use in the initial management of patients with non-muscle invasive bladder cancer, photodynamic therapy using the photosensitizing agents5-aminolevulinic acid (ALA) or porfimer (Photofrin) may have a role in patients with refractory on-muscle invasive disease. Results from the two largest series are summarized: In a report of 31 patients with recurrent disease who were followed for 24 months after intravesical application of ALA and transurethral light exposure, 16 were free of tumor recurrence, including four of ten patients with prior BCG treatment. Treatment was well tolerated. Long-term benefit was suggested in a series of 34 patients with refractory Tis (n = 29) or multiple small papillary Ta or T1 lesions (n = 5) who underwent therapy with porfimer followed by transurethral light exposure.

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