Bladder Cancer - Risks and Treatment Issues

S Vasudevan

Department of Urology, Medical College, Trivandrum*

Published on 30th December 2013

Bladder cancer is a common cause for painless hematuria with clot passage in any age especially past the third decade. Histologically 90% of bladder cancers are of urothelial origin. 5% are squamous cell carcinoma and less than 2% are adenocarcinomas or other variants.[1] Urothelial carcinoma is the most common malignancy of the urinary tract and is the second most cause of death among genitourinary tumours.

The presence of bladder cancer is usually suspected by hematuria. Painless gross hematuria occurs in 85% of patients with bladder cancer and requires a complete evaluation that includes Cystoscopy, urine cytology, CT scan, and a PSA blood test. High risk individuals are those with a smoking history and should be evaluated every six months. Low risk patients do not need repeat evaluation. Patients with gross hematuria have reported rates of bladder cancer 13-34.5%[2] while microscopic hematuria is associated with 0.5-10.5% bladder cancer.[3] Several risk factors are described for bladder cancer,[4] some of which are commonly seen in the present day industrialisation scenario.

General

1. ***Gender:*** Men are at a higher risk than women of getting bladder cancer. According to the American Cancer Society, men have an approximately 1 in 26 chance of developing bladder cancer in their lifetime. For women, this chance is about 1 in 86.
2. ***Age:*** Most people who get bladder cancer are older in age. The average age at diagnosis is 73, and 90 percent of patients are over age 55.
3. ***Race:*** Bladder cancer is twice as common among Caucasians as African Americans. This disease is less common among Hispanics, Asians and Native Americans.

Genetics

1. ***Family history:*** Individuals with a family member who has or has had bladder cancer are at an increased risk for developing this malignancy. Sometimes, family members with bladder cancer have all been exposed to the same carcinogen. Other times, they may all have certain genetic abnormalities associated with bladder cancer. Specifically, mutations in genes known as GNT and NAT may trigger changes in the body's breakdown of some toxins, which can in turn lead to malignancies in the bladder wall.
2. Other inherited genetic syndromes are also considered bladder cancer risk factors, such as:
    1. ***Rb1:*** An altered form of Rb1, retinoblastoma gene, is associated with cancer of the eye in infants, and may increase your bladder cancer risks.
    2. ***Cowden disease:*** This syndrome, linked to an abnormal form of the gene PTEN, can trigger cancers of the breast and thyroid, and increases the risk of bladder cancer.
    3. ***Lynch syndrome:*** This genetic condition, also known as hereditary non-polyposis colorectal cancer, is usually tied to colon and endometrial cancer. However, this syndrome can also increase the risk of bladder cancer and cancer of the ureter.

Lifestyle

Smoking: Cigarette smoking is the single greatest risk factor for bladder cancer. Smokers are more than twice as likely to get bladder cancer compared to non-smokers. Inhalation during cigarette smoking brings some of the cancer-causing chemicals in cigarettes out of the lungs and into the blood. These carcinogens are then filtered by the kidneys and deposited into urine. As urine is held in the bladder, the carcinogens present in the fluid can damage the cells on the bladder wall, increasing the risk of cancer developing.

Workplace exposure: Some chemicals used in the dye

Corresponding Author:
Dr S Vasudevan, Additional Professor Urology, Medical College, Trivandrum.
Phone: 9447124246. E-mail: periamana@gmail.com

industry, such as benzidine and beta-naphthyl amine, have been associated with bladder cancer. Other industries where chemicals are used that may cause bladder cancer include rubber, leather, textiles, paint manufacturing and printing. Jobs that may raise the risk of bladder cancer include painters, machinists, printers, hairdressers (due to hair dye exposure) and truck drivers (due to diesel fume exposure).

Arsenic: Drinking water that contains arsenic has been linked to bladder cancer. Exposure depends on where a person lives and the water source. In the United States, there are safety measures in place that limit the level of arsenic in public drinking water.

Low fluid consumption: Drinking plenty of fluids daily can diminish your bladder cancer risks. Likewise, not drinking enough may increase this risk because chemicals are left in the bladder longer.

Other Conditions

1. ***Chronic bladder infections and irritation:*** Problems associated with increased bladder cancer risks include urinary infections, kidney and bladder stones, and other causes of bladder irritation. Schistosomiasis, a parasitic infection, can reach the bladder and is associated with an increased risk of squamous cell bladder cancer. In the United States, Schistosomiasis is very rare. In Africa and the Middle East, where this parasite is more common, squamous cell bladder cancer is more common.
2. ***Personal history of bladder cancer:*** Cancer can occur in other regions of the urothelium, such as in the lining of the kidneys, ureter and urethra. Cancer in any of these areas can increase the risk of another tumor in this layer of cells. People who have bladder cancer need to be closely monitored following treatment because additional tumors in the urothelium are so common.
3. ***Bladder defects from birth:*** Normally, there is a connection between the belly button and the bladder before we are born that disappears before birth. Sometimes, part of this connection remains after birth, and can become cancerous. In another birth defect, the bladder and abdominal wall become fused together, leaving the inner lining of the bladder exposed to other areas of the body. Even following corrective surgery, people who have or had this problem are at a higher risk for bladder cancer.

Previous Treatments

- ***Chemotherapy and radiation therapy:*** Long-term use of the chemotherapy drug cyclophosphamide is associated with a heightened risk of bladder cancer. Drinking extra fluids while taking this drug can help lower this risk. Radiation aimed at the pelvis is also considered a risk factor for bladder cancer.

Management Issues

The management of bladder cancer is stage dependent. Accurate staging is done after a contrast enhanced CT scan is performed. The management of non-muscle invasive (NMIBC) and muscle invasive TCC (MIBC) differs in several aspects. Superficial TCC Bladder is treated primarily by transurethral resection (TURBT) and followup. One third of the cases with Superficial TCC Bladder later develop muscle invasion and hence need change in the approach towards treatment. Superficial TCC with the following criteria – size of growth more than 2 cm, multi-focal, non-papillary morphology, recurrence within one year, migration to higher grade on recurrence all are indications for instillation of intra-vesical BCG to enhance the immune status of the patient helping reduce further recurrence and prevent development of muscle invasion. Intravesical instillation of mitomycin C and 5 Fluro-Uracil is practiced with fewer efficacies compared to BCG to prevent recurrence. Laser coagulation allows minimally invasive ablation of tumours upto 2.5 cms in size. Repeat TURBT is usually appropriate in the evaluation of T1 tumours because repeat TUR can demonstrate worse findings in upto 25% patients. Many patients with small (0.5 cms) low grade recurrences can be managed safely in the office setting using diathermy of laser ablation under intravesical local anaesthetia.[5]

The management of MIBC is more varied and subject to patient preferences. The gold standard of treatment for MIBC with no extra-vesical involvement is radical cysto-prostatectomy with bilateral pelvic and iliac lymphadenectomy and appropriate urinary diversion. Adoption of minimally invasive techniques like Laparoscopy and robotics has been reported from many centres with excellent results. The other options include radical radiation as bladder preservation protocol and a combination of radiation and chemotherapy preceding radical cystectomy with a view to downstage the tumour pre-operatively. Chemotherapy alone is ineffective in producing tumour clearance.

Recent Bladder preservation protocols involve radiation with machines having organ conforming 3D protocols and intensity modulated radio-therapy fields (IMRT) to reduce adjacent organ damage common in earlier protocols. Non-responders will need radical cystectomy. Post-radiation surgery involves more technical difficulty and morbidity.

Urinary diversions have evolved over years from ureterosigmoidostomy, ileal conduits, and self catheterising Indiana pouches to orthotopic pouches.[6] These have resulted in reduced morbidity, mortality and better quality of life.

There are three types of urinary diversion:

Ileal conduit: A piece of the small intestine is used to create a "pipe" that connects the ureters to the surface of the skin in the navel. Urine is continuously drained into an uro-stomy bag worn on the outside of the body. It is a simple and efficient procedure, but some patients may have issues with wearing an external bag.

Ileal neo-bladder: Part of the ileum (small intestine) is used to make a new bladder, allowing for "normal" urination. This procedure is more successful for men. It provides good day-time urinary control, with about a 20% chance of night-time incontinence. Some women may have trouble completely emptying the neo-bladder and may sometimes need to use a catheter.

Continent reservoir: Intestinal tissue is used to create an internal pouch that is connected to the navel. The patient uses a catheter to drain the pouch every three to four hours. This procedure is done less frequently.

Advanced surgical and reconstructive procedures

- Laparoscopic robotic surgery
- Conformal 3D and IMRT radiotherapy
- Immunotherapy, including Bacillus Calmette-Guérin (BCG)
- Latest chemotherapy options

Our skilled surgeons, who utilize the latest bladder cancer and reconstruction techniques, are among the most experienced in the nation. This can make an essential difference in the success of your treatment and recovery.

Surgery

Surgery is part of almost every bladder cancer patient's treatment. Other types of treatment often are given before or after surgery.

Transurethral resection (TUR) may be used for early-stage or superficial bladder cancer. A resectoscope, which is a thin tool with a wire loop on the end, is threaded through the urethra to the bladder, and then the tumor is scraped from the bladder wall. Fluorescence cystoscopy, a special way of looking at the bladder wall, may be used to enhance bladder cancer detection.

Cystectomy, which is removal of the bladder, is often used in more advanced bladder cancer. Usually the entire bladder is removed, but partial cystectomies may be appropriate for a small number of patients. Lymph nodes near the bladder also will be removed. The prostate is removed in men, and in women the uterus, ovaries, fallopian tubes and often a small part of the vagina are removed.

Minimally invasive surgery techniques such as laparoscopy and robotic procedures are available at MD Anderson for some bladder cancer patients.

Bladder Reconstruction Surgery

When the bladder is removed to treat bladder cancer, surgical procedures known as urinary diversions are performed to give your body a way to store and remove urine. Urinary diversions are done at the same time as a cystectomy.

There are three types of urinary diversion:

Ileal neobladder: Part of the ileum (small intestine) is used to make a new bladder, allowing for "normal" urination. This procedure is more successful for men. It provides good daytime urinary control, with about a 20% chance of nighttime incontinence. Some women may have trouble completely emptying the neobladder and may sometimes need to use a catheter.

Ileal conduit: A piece of the small intestine is used to create a "pipe" that connects the ureters to the surface of the skin in the navel. Urine is continuously drained into a urostomy bag worn on the outside of the body. It is a simple and efficient procedure, but some patients may have issues with wearing an external bag.

Continent reservoir: Intestinal tissue is used to create an internal pouch that is connected to the navel. The patient uses a catheter to drain the pouch every three to four hours. This procedure is done less frequently.

Chemotherapy

Chemotherapy plays a major role in the treatment of bladder cancer that has spread (metastasized) to the

lymph nodes, lungs, liver and other parts of the body. In these patients, chemotherapy is the frontline treatment.

The main chemotherapy for metastatic bladder cancer is a combination of four drugs known as MVAC: methotrexate, vinblastine, adriamycin and cisplatin. MVAC has provided good response rates since the 1980s. In recent years, the MVAC treatment regimen has been decreased from four weeks to two weeks, with less impact on the body and an improved response rate of 50% and higher.

Another chemotherapy regimen for bladder cancer is a combination of gemcitabine and cisplatinum. It has less impact on the body than MVAC, with similar response rates. Both chemotherapies have an average survival rate of 14 months.

A number of new chemotherapy treatments are being studied in clinical trials for their effectiveness for advanced bladder cancer, including two developed at MD Anderson:

- A three-week regimen of ifosphamide, adriamycin and gemcitabine
- A two-week regimen of cisplatinum, gemcitabine and ifosphamide

Chemotherapy also is used with surgery when bladder cancer has a high risk of metastasis. Bladder tumors that have invaded the muscle wall and have the potential to spread can benefit from chemotherapy before surgery (neoadjuvant therapy).

MD Anderson researchers are continuing to study chemotherapy combinations and dosages to improve response rates, slow tumor regrowth and decrease side effects for bladder cancer patients.

Radiation Therapy

Although surgery is the frontline treatment for bladder cancer, radiation treatment has a role in certain patients. Simultaneous radiation and chemotherapy with cisplatin may be used instead of surgery in an effort to save the bladder. However, only about 40% of patients who have this treatment will be able to keep their bladders and not have the cancer come back.

The best candidates for radiation therapy:

- Have tumors that are localized in the bladder and have not spread
- Have only one tumor site
- Can tolerate chemotherapy and 35 radiation treatments
- Are willing to undergo rigorous follow-up after treatment

New radiation therapy techniques and remarkable skill allow MD Anderson doctors to target bladder cancer tumors more precisely, delivering the maximum amount of radiation with the least damage to healthy cells.

MD Anderson provides the most advanced radiation treatments for bladder cancer, including:

- 3D-conformal radiation therapy: Several radiation beams are given in the exact shape of the tumor
- Intensity-modulated radiotherapy (IMRT): Treatment is tailored to the specific shape of the tumor

Immunotherapy

Bacillus Calmette-Guérin (BCG), a bacterial organism used to treat tuberculosis, is the standardimmunotherapy for superficial bladder cancer. First, the bladder wall is scraped to remove superficial tumor cells. Then, the bladder is filled with a solution containing BCG. The BCG, delivered through a catheter, stimulates an immune response within the bladder to destroy any remaining cancer cells. BCG is the most effective agent for keeping the bladder cancer from spreading or coming back, and the success rate is 70% to 80%.

Gene Therapy

We have the expertise to examine each bladder cancer tumor carefully to determine gene-expression profiles. Ongoing research will help us determine the most effective and least invasive treatment targeted to specific cancers. This personalized medicine approach sets us above and beyond most cancer centers and allows us to attack the specific causes of each cancer for the best outcomes.

END NOTE

Author Information

Dr S Vasudevan, Additional Professor Urology, Medical College, Trivandrum.Phone: 9447124246.
E-mail: periamana@gmail.com

Conflict of Interest: None declared

Cite this article as: S Vasudevan. Bladder cancer risks and treatment issues. Kerala Medical Journal. 2013 Dec 30;6(4):79-83

REFERENCES

1. Lopez-Beltran A. Bladder cancer: clinical and pathological profile. Scand J Urol Nephrol Suppl. 2008 Sep;(218):95–109.
2. Varkarakis MJ, Gaeta J, Moore RH, Murphy GP. Superficial bladder tumor. Aspects of clinical progression. Urology. 1974 Oct;4(4):414–20.
3. Khadra MH, Pickard RS, Charlton M, Powell PH, Neal DE. A prospective analysis of 1,930 patients with hematuria to evaluate current diagnostic practice. J Urol. 2000 Feb;163(2):524–7.
4. Bladder cancer Risk Factors: Gender, Genetics, others CTCA.
5. The management of Non-Muscle-Invasive Bladder Cancer – American Urological Association
6. Types of urinary diversion: Indiana Pouch & More : Cleveland Clinic