Cancer Association of South Africa (CANSA)

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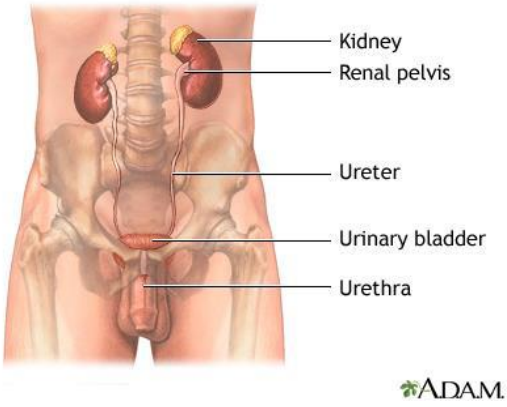
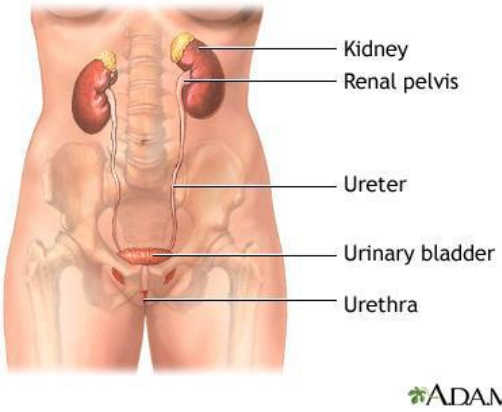
Fact Sheet on Bladder Cancer

Introduction

The urinary bladder is the organ that collects urine excreted by the kidneys before disposal by means of urination. It is a hollow muscular, and distensible (elastic) organ. The bladder is situated on the pelvic floor. Urine enters the bladder via the ureters and exits via the urethra.



[Picture Credit: Male Urinary Tract]



[Picture Credit: Female Urinary Tract]

Bladder Cancer

Bladder cancer is cancer that forms in tissues of the bladder. Most bladder cancers are transitional cell carcinomas (cancer that begins in cells that normally make up the inner lining of the bladder). Other types include squamous cell carcinoma (cancer that begins in thin, flat cells) and adenocarcinoma (cancer that begins in cells that make and release mucus and other fluids).

Researched and Authored by Prof Michael C Herbst
[D Litt et Phil (Health Studies); D N Ed; M Art et Scien; B A Cur; Dip Occupational Health; Dip Genetic Counselling; Dip Audiometry and Noise Measurement; Diagnostic Radiographer; Medical Ethicist]
Approved by Ms Elize Joubert, Chief Executive Officer [BA Social Work (cum laude); MA Social Work]

Esperto, F., Pang, K.H., Albisinni, S., Papalia, R. & Scarpa, R.M. 2020.
"The COVID-19 outbreak has led to the deferral of a great number of surgeries in an attempt to reduce transmission of infection, free up hospital beds, intensive care and anaesthetists, and limit aerosol-generating procedures. Guidelines and suggestions have been provided to categorize Urological diseases into risk groups and recommendations are available on procedures that can be or cannot be deferred. We aim to summarise updates on diagnosis, treatment and follow up of bladder cancer during the COVID-19 outbreaks."

Incidence of Bladder Cancer in South Africa

According to the outdated National Cancer Registry (2017), known for under reporting, the following number of bladder cancer cases was histologically diagnosed in South Africa during 2017:

Group - Males 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All males	1 058	1:143	2,65%
Asian males	63	1:90	6,49%
Black males	171	1:581	1,30%
Coloured males	170	1:93	3,58%
White males	654	1:57	3,10%

Group - Females 2017	Actual No of Cases	Estimated Lifetime Risk	Percentage of All Cancers
All females	344	1:677	0,83%
Asian females	19	1:451	1,48%
Black females	127	1:1 329	0,66%
Coloured females	48	1:548	1,06%
White females	150	1:270	0,88%

The frequency of histologically diagnosed cases of bladder cancer in South Africa for 2017 was as follows (National Cancer Registry, 2017):

Group - Males 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All males	3	2	9	60	172	310	353	149
Asian males	0	0	0	0	11	30	17	5
Black males	0	1	5	27	38	48	36	15
Coloured males	0	0	1	11	44	49	52	13
White males	2	1	3	22	79	183	248	116

Group - Females 2017	0 – 19 Years	20 – 29 Years	30 – 39 Years	40 – 49 Years	50 – 59 Years	60 – 69 Years	70 – 79 Years	80+ Years
All females	1	10	20	35	51	105	80	42
Asian females	0	0	2	0	4	4	5	4
Black females	0	7	15	25	22	32	17	9
Coloured females	0	0	2	2	9	14	16	5
White females	1	3	1	8	16	55	42	24

N.B. In the event that the totals in any of the above tables do not tally, this may be the result of uncertainties as to the age, race or sex of the individual. The totals for 'all males' and 'all females', however, always reflect the correct totals.

According to **Bruni, *et al*.,** (2019), the burden of Bladder Cancer for South Africa for 2018 was estimated as (based on Globocan estimates):

- Annual number of Bladder cancer cases 1 701
- Annual number of Bladder cancer deaths 848

Risk Factors for Bladder Cancer

The following are risk factors for bladder cancer:

- Use of tobacco products
- Obesity
- Increasing age
- Being white
- Being a male
- Exposure to certain chemicals
- Previous cancer treatment
- Chronic bladder inflammation
- Schistosomiasis (Bilharzia)
- Personal or family history of cancer
- Bladder birth defects
- Inherited gene mutations
- Low fluid consumption

Xu, Y., Wu, G., Li, J., Ruan, N., Ma, L., Han, X., Wei, Y., Li, L., Zhang, H., Chen, Y. & Xia, W. 2020.

"Bladder cancer (BLCA) is a common malignant cancer, and it is the most common genitourinary cancer in the world. The recurrence rate is the highest of all cancers, and the treatment of BLCA has only slightly improved over the past 30 years. Genetic and environmental factors play an important role in the development and progression of BLCA. However, the mechanism of cancer development remains to be proven. Therefore, the identification of potential oncogenes is urgent for developing new therapeutic directions and designing novel biomarkers for the diagnosis and prognosis of BLCA. Based on this need, we screened overlapping differentially expressed genes (DEG) from the GSE7476, GSE13507, and TCGA BLCA datasets. To identify the central genes from these DEGs, we performed a protein-protein interaction network analysis. To investigate the role of DEGs and the underlying mechanisms in BLCA, we performed Gene Ontology (GO) and Kyoto Gene and Genomic Encyclopedia (KEGG) analysis; we identified the hub genes via different evaluation methods in cytoHubba and then selected the target genes by performing survival analysis. Finally, the relationship between these target genes and tumour immunity was analysed to explore the roles of these genes. In summary, our current studies indicate that both cell division cycle 20 (CDC20) and abnormal spindle microtubule assembly (ASPM) genes are potential prognostic biomarkers for BLCA. It may also be a potential immunotherapeutic target with future clinical significance."

Signs and Symptoms of Bladder Cancer

People with bladder cancer may experience the following symptoms or signs:

- blood in urine (haematuria) — urine may appear dark yellow, bright red or cola coloured.
- frequent urination
- urgent need to urinate
- bladder spasm
- painful urination (dysuria)
- inability to urinate
- reduced bladder capacity
- back pain
- pelvic pain

Symptoms of advanced bladder cancer may include:

- pain
- unexplained appetite loss
- weight loss

Diagnosis of Bladder Cancer

Bladder cancers are usually found when a person goes to the doctor because of signs or symptoms they are having. If bladder cancer is suspected, tests will be needed to confirm the diagnosis.

- blood in the urine
- changes in bladder habits or irritating symptoms such as:
    - having to urinate more often than usual
    - feeling pain or burning during urination
    - feeling as if one needs to go right away, even when the bladder is not full
- medical history and physical exam
- urine culture
- urine tumour marker test
- biopsy
- intravenous pyelogram
- retrograde
- computed tomography (CT) scan
- magnetic resonance imaging (MRI) scan - Like CT scans but MRI scans use radio waves and strong magnets instead of x-rays
- ultrasound - uses sound waves to create pictures of internal organs

Bodgi, L., Bahmad, H.F., Arail, T., Al Chobog, J., Bou-Gharios, J., Cheaito, K., Zeidan, Y.H., Eid, T., Geara, F. & Abou-Kheir, W. 2019.

Background: Bladder cancer is the fourth most commonly diagnosed cancer among males worldwide. Current treatment strategies established for bladder cancer mainly consist of cystectomy yet advances in radiation therapy have pointed to the value of organ-preserving strategies in preserving patients' quality of life.

Aim: To study and compare the radiosensitivity in two-dimension (2D) and physiologically-relevant three-dimension (3D) *in vitro* culture of three human bladder cancer cell lines, RT4, T24, and UM-UC-3.

Materials and Methods: Clonogenic assay was performed to assess cells' radiosensitivity in 2D. Employing the 3D Matrigel™-based cultures to enrich for cancerstem cells (CSCs) allowed us to

assess the survival of this subpopulation of cells via evaluating the number, i.e., sphere forming unit (SFU), and the sizes of cultured spheres, formed from cells exposed to different radiation doses compared to non-irradiated cells.
Results: Irradiating cells with increasing radiation doses revealed highest survival rates with RT4 cells in 2D, followed by T24 and UM-UC-3. In 3D, however, UM-UC-3 cells were shown to be the most radio-resistant as evidenced by the number of spheres formed, yet they displayed the least efficient volume reduction/regression (VR), whilst the volume decreased significantly for both RT4 and T24 cells. Sphere VR and sphere ratio (SR) values were then plotted against each other demonstrating a linear correlation between volume and number with RT4 and UM-UC-3 cell lines, but not T24. Lastly, multiple regression model was employed to evaluate the possibility of obtaining a function combining both 3D parameters, SR and VR, with the surviving fraction (SF) in 2D, and showed a linear regression for T24 cells only, with a correlation coefficient of 0.97 for the combined parameters.
Conclusion: We were able to radiobiologically characterize 3 human bladder cancer cell lines showing differential effects of radiation between 2D and 3D culture systems, paving the way for achieving better assessment of radiosensitivity of bladder cancer *in vitro*.

Kim, H.S., Kwak, C., Kim, H.H. & Ku, J.H. 2019.
OBJECTIVES: To validate the Cancer of the Bladder Risk Assessment (COBRA) score for predicting cancer-specific survival (CSS) in comparison with the American Joint Committee on Cancer (AJCC) staging system using an external cohort of urothelial carcinoma of the bladder (UCB) from South Korea.
MATERIALS AND METHODS: The final validation cohort consisted of 855 patients who underwent radical cystectomy (RC) for UCB in a single institution. The impact of the COBRA score on CSS was estimated using Cox proportional hazard models. Discrimination accuracy was quantified with concordance index. Calibration plots were used to determine the relationship between model-predicted CSS and actual CSS at 2years and 5years after RC. Clinical usefulness of the COBRA score was assessed using decision curve analyses.
RESULTS: One-point increase in the COBRA score (range, 0-6) was closely related to a 1.50-fold increase (95% confidence interval [CI]: 1.39-1.62) in the risk of death from UCB. Discrimination accuracies of the COBRA score and AJCC staging system for CSS at 5years were 70.6% (95% CI: 67.2-74.0) and 68.3% (95% CI: 65.0-71.6), respectively. Compared to the AJCC staging system, the COBRA score was generally well-calibrated for predicting CSS at 2 and 5years after RC. On decision curve analyses, the use of the COBRA score showed more clinical net benefits across a wide range of threshold probabilities than the AJCC staging system.
CONCLUSIONS: Our external validation results suggest that although the COBRA score is not perfectly accurate, it shows a reasonable level of discriminative ability, adequate calibration, and meaningful net benefit gain for predicting CSS after RC in a Korean UCB cohort.

Types of Bladder Cancer
Types of bladder cancer include:
Transitional cell bladder cancer

- Non muscle invasive (superficial) bladder cancer
- Invasive bladder
- Squamous cell bladder cancer
- Adenocarcinoma of the bladder
- Small cell cancer of the bladder - it is very rare

Jalanko, T., de Jong, J.J., Gibb, E.A., Seiler, R. & Black, P.C. 2020.
Purpose of review: Molecular characterization of cancer allows us to understand oncogenesis and clinical prognosis as well as facilitates development of biomarkers and treatment. Our aim was to review the current literature on genomic characterization of bladder cancer, and how far we are in implementing genomics into clinical practice.
Recent findings: Bladder cancers are molecularly diverse tumors with a high mutational rate. On molecular level, bladder cancer can be categorized into at least six subtypes called luminal-papillary, luminal-unstable, luminal non-specified, basal-squamous, neuroendocrine-like, and stroma-rich. These subtypes have characteristic genomic and transcriptomic profiles and appear to have different prognoses. Several molecular subtypes have been identified in bladder cancer. Prospective trials are underway to validate the applicability of genomic subtypes for clinical decision making. Further integrative analyses of genomic alterations, gene expression, epigenetics, and proteomics need to be performed before genomic subtyping can be attained in clinical practice.

Reducing the Risk for Bladder Cancer
Bladder cancer cannot be prevented altogether, but one can reduce the risk for getting it:

- Do not smoke
- avoid exposure to industrial chemicals
- drink water throughout the day
- limit the intake of smoked or cured meats
- limit the intake of other processed foods

Staging of Bladder Cancer
The TNM staging system is used.
TNM is an abbreviation for tumour (**T**), node (**N**), and metastasis (**M**). Doctors look at these three factors to determine the stage of cancer:

- How large is the primary tumour and how deeply has it invaded the tissue? **(Tumour, T)**
- Has the tumour spread to the lymph nodes? **(Node, N)**
- Has the cancer spread (metastasised) to other parts of the body? **(Metastasis, M)**

Juri, H., Narumi, Y., Panebianco, V. & Osuga, K. 2020.
"The distinction of non-muscle-invasive bladder cancer and muscle-invasive bladder cancer is important for the selection of the optimal treatment. Multiparametric MRI (mp-MRI) has been an useful modality for the T staging of bladder cancer, and a systematic evaluation of mp-MRI is needed. The Vesical Imaging Reporting and Data System was designed to standardize the scanning and reporting criteria based on mp-MRI for clinical and research applications. This review briefly describes the method, interpretation, and timing of mp-MRI examinations in the clinical settings. Validation studies of Vesical Imaging Reporting and Data System and future perspectives are also considered."

Where Bladder Cancer Spreads to

Should bladder cancer spread to other parts of the body, it would most probably spread as indicated below:

Cancer Type:	Main Sites of Metastasis (Spread)
Bladder	Bone, liver, lung
Breast	Bone, brain, liver, lung
Colon	Liver, lung
Colorectal	Liver, lung, peritoneum (lining of abdomen)
Kidney	Adrenal gland, bone, brain, liver, lung
Lung	Adrenal gland, bone, brain, liver, other lung
Melanoma	Bone, brain, liver, lung, skin, muscle
Ovary	Liver, lung, peritoneum (lining of abdomen)
Pancreas	Liver lung, peritoneum (lining of abdomen)
Prostate	Adrenal gland, bone, liver, lung
Stomach	Liver, lung, peritoneum (lining of abdomen), ovaries
Thyroid	Bone, liver, lung
Uterus	Bone, liver, lung, peritoneum (lining of abdomen), vagina
Non-melanoma skin cancer	Very rare: lymph nodes, lung, bone (if in head/neck region)

Treatment of Bladder Cancer

The following comprises standard treatment for bladder cancer:

- Surgery - one of the following types of surgery may be done:
  - Transurethral resection (TUR) with fulguration
  - Radical cystectomy (surgical removal of the bladder)
  - Segmental cystectomy (surgical removal of part of the bladder
  - Urinary diversion - surgery to make a new way for the body to store and pass urine
- Radiation therapy
- Chemotherapy
- Biologic therapy
- Photodynamic therapy
- Immunotherapy

Larsen, E.S., Joensen, U.N., Poulsen, A.M., Goletti, D., Johansen, I.S. 2020.

"Bacillus Calmette-Guérin (BCG) immunotherapy for bladder cancer has been used since 1976 when the first evidence of its ability to lower recurrence and progression rates was published. Today, BCG immunotherapy is the choice of care for high-grade non-muscle invasive bladder cancer (NMIBC) after transurethral resection. This article presents indications and procedure of BCG instillations, and outlines the effects on recurrence and progression of NMIBC. The BCG-induced immunity in NMIBC is not yet fully understood. Animal studies point towards BCG inducing specific tumour immunity. We describe the current knowledge of how this immunity is induced, from internalization of BCG bacilli in urothelial cells, to cytokine- and chemokine-mediated recruitment of neutrophils, monocytes, macrophages, T cells, B cells and natural killer cells. In addition, we describe the process of trained immunity, the non-specific protective effects of BCG. Recent studies also indicate that dysbiosis of the urinary microbiome may cause lower urinary tract dysfunction. Side effects of BCG bladder instillations range from common, mild and transient symptoms, such as dysuria and flu-like symptoms, to more severe and rarely occurring life-threatening complications. We review the

literature and give an overview of reported incidences and management of BCG infections after intravesical instillation."

Lenis, A.T., Lec, P.M., Chamie, K. & Mshs, M.D. 2020.
Importance: Bladder cancer is a common malignancy in women and is the fourth most common malignancy in men. Bladder cancer ranges from unaggressive and usually noninvasive tumors that recur and commit patients to long-term invasive surveillance, to aggressive and invasive tumors with high disease-specific mortality.
Observations: Advanced age, male sex, and cigarette smoking contribute to the development of bladder cancer. Bladder tumors can present with gross or microscopic hematuria, which is evaluated with cystoscopy and upper tract imaging depending on the degree of hematuria and risk of malignancy. Non-muscle-invasive tumors are treated with endoscopic resection and adjuvant intravesical therapy, depending on the risk classification. Enhanced cystoscopy includes technology used to improve the detection of tumors and can reduce the risk of recurrence. Patients with high-risk non-muscle invasive tumors that do not respond to adjuvant therapy with the standard-of-care immunotherapy, bacille Calmette-Guérin (BCG), constitute a challenging patient population to manage and many alternative therapies are being studied. For patients with muscle-invasive disease, more aggressive therapy with radical cystectomy and urinary diversion or trimodal therapy with maximal endoscopic resection, radiosensitizing chemotherapy, and radiation is warranted to curb the risk of metastasis and disease-specific mortality. Treatment of patients with advanced disease is undergoing rapid changes as immunotherapy with checkpoint inhibitors, targeted therapies, and antibody-drug conjugates have become options for certain patients with various stages of disease.
Conclusions and relevance: Improved understanding of the molecular biology and genetics of bladder cancer has evolved the way localized and advanced disease is diagnosed and treated. While intravesical BCG has remained the mainstay of therapy for intermediate and high-risk non-muscle-invasive bladder cancer, the therapeutic options for muscle-invasive and advanced disease has expanded to include immunotherapy with checkpoint inhibition, targeted therapies, and antibody-drug conjugates.

Mottet, N., Ribal, M.J., Boyle, H., De Santis, M., Caillet, P., Choudhury, A., Garg, T., Nielsen, M., Wüthrich, P., Gust, K.M., Shariat, S.F. & Gakis, G. 2020.
"Median age at bladder cancer (BC) diagnosis is older than for other major tumours. Age should not determine treatment, and patients should be fully involved in decisions. Patients should be screened with Mini-Cog™ for cognitive impairment and the G8 to ascertain need for comprehensive geriatric assessment. In non-muscle invasive disease, older adult patients should have standard therapy. Age does not contraindicate intravesical therapy. Independent of age and fitness, patients with muscle-invasive BC should have at least cross-sectional imaging. Data suggest extensive undertreatment in older adult patients, leading to poor outcomes. Standard treatment for a fit patient differs between countries. Radical cystectomy and trimodality therapy are first-line options. Radical cystectomy patients should be referred to an experienced centre and prehabilitation is mandatory. Older adult patients should be considered for neoadjuvant and adjuvant therapy, according to guidelines. In urinary diversion, avoiding bowel surgery for reconstruction of the lower urinary tract significantly reduces complications. If a patient is unfit for or refuses standard treatment, RT alone, or TURBT in selected cases should be considered. In metastatic BC, older adult patients should receive standard systemic therapy, depending on fitness for cisplatin and prognosis. Efficacy and tolerability of immunotherapy (IO) appears similar to younger patients. Second line IO is standard in platinum pre-treated patients, with benefit and tolerability in the older adult similar to younger patients. The toxicity profile seems to favour IO in the older adult but more data are needed. Patients progressing

on IO may respond to further systemic treatment. In metastatic disease, palliative care should begin early."

About Clinical Trials

Clinical trials are research studies that involve people. They are conducted under controlled conditions. Only about 10% of all drugs started in human clinical trials become an approved drug.

Clinical trials include:

- Trials to test effectiveness of new treatments
- Trials to test new ways of using current treatments
- Tests new interventions that may lower the risk of developing certain types of cancers
- Tests to find new ways of screening for cancer

The **South African National Clinical Trials Register** provides the public with updated information on clinical trials on human participants being conducted in South Africa. The Register provides information on the purpose of the clinical trial; who can participate, where the trial is located, and contact details.

For additional information, please visit: www.sanctr.gov.za/

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