A Retrospective Review of Bladder Cancer

at Charlotte Maxeke Johannesburg

Academic Hospital-University of The Witwatersrand - (2010–2020)

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University of Witwatersrand, Johannesburg, in fulfilment of the requirements for the

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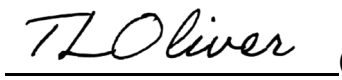
Declaration

I, Trenton Luke Oliver, declare that this research report is my work. It is being submitted for the degree of Master of Medicine in Radiation Oncology at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university.

This study has received ethical approval from the University of Witwatersrand. Human Research Ethics Committee (Medical) with clearance certificate number: M211024.


(Signature of candidate)

Signed at Johannesburg (University of Witwatersrand), South Africa, on the

7th day of August 2023

Dedication

This dissertation is dedicated to the following:

- ***God, Jeremiah 29:11*** *For I know the plans I have for you," declares the Lord, "plans to prosper you and not to harm you, plans to give you hope and the desires of your heart.*
- *My fantastic wife,* ***Avadhna Singh****, for her undying love and unwavering support.*
- *My wonderful son,* ***Ashton Oliver****, is the greatest joy in my life.*
- *My In-laws,* ***Eddy*** *and* ***Ragani Singh****, for your continuous support, prayers, and guidance.*
- *My uncle and mentor,* ***Dr Gregory Landers****, for being there every step of the way, instilling the value of knowledge and education.*
- *In loving memory of my late grandmother,* ***Ma Maggie,*** *who inspired me to walk this journey as she bravely faced Breast Cancer.*
- *In loving memory of my late father,* ***Bradley Oliver,*** *I will always continue to reach for the stars.*

Abstract

Introduction

Bladder cancer is among the most common urological cancers and the leading cause of cancer mortality worldwide. It is particularly prevalent in High-Income Counties (HICs), although its incidence is rising in Low-and-middle -income countries (LMICs). This review describes the profile, clinical presentation, and management of our institution's bladder cancer patients.

Method

A retrospective review of patients aged 18 years and above who were diagnosed with bladder cancer and managed at the Radiation Oncology department of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from January 2010 to December 2020. Data were collected on demographics, risk factors, clinic-pathological features, and specific therapies received by these patients. A comparison was made between patients presenting with squamous cell carcinoma and translational cell carcinoma of the bladder.

Results

Among 115 patients, the median age ± standard deviation was 60.7 ± 14.9, and 60.9% were males with a male-to-female ratio of 1.6:1. Few patients (4.4%) had a history of schistosomiasis, and 47.8% had a history of smoking. Tumour histology included transitional cell carcinoma (TCC) in 78 (67.8%), squamous cell carcinoma (SCC) in 31 (27.0%), and atypical tumour in 6 (5.2%). Most patients presented with Muscle-Invasive Bladder Cancer (MIBC) (61 (53.0%)) followed by Metastatic Urothelial Cancer (MUC) (n=52, 45.0%), while the remaining 2.0% (n=2) had Non-Muscle Invasive Bladder Cancer (NMIBC). More than half of the patients (59.1% n=68) had palliative treatment, 26 (22.6%) had radical treatment, and 21 (18.3%) patients did not receive radiotherapy. Patients who presented with TCC were more likely to be older (odd ratio (OR): 1.03, 95% Confidence Interval (CI): 1.01–1.06, p=0.029), male (OR: 2.60, 95% CI:1.10–6.04,

p=0.030), predominantly of the black population, but white patients are four times more likely to present with TCC than SCC (OR:4.22, 95% CI: 1.43–12.48, p=0.009).

Conclusion

The prevalence of TCC is still higher in our centre compared to SCC. Although the burden of bladder cancer is highest in HICs, with increasing exposure to risk factors, a shift is gradually experienced in LMICs.

Acknowledgements

I am expressing my sincere appreciation and gratitude to:

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Nomenclature and Abbreviations

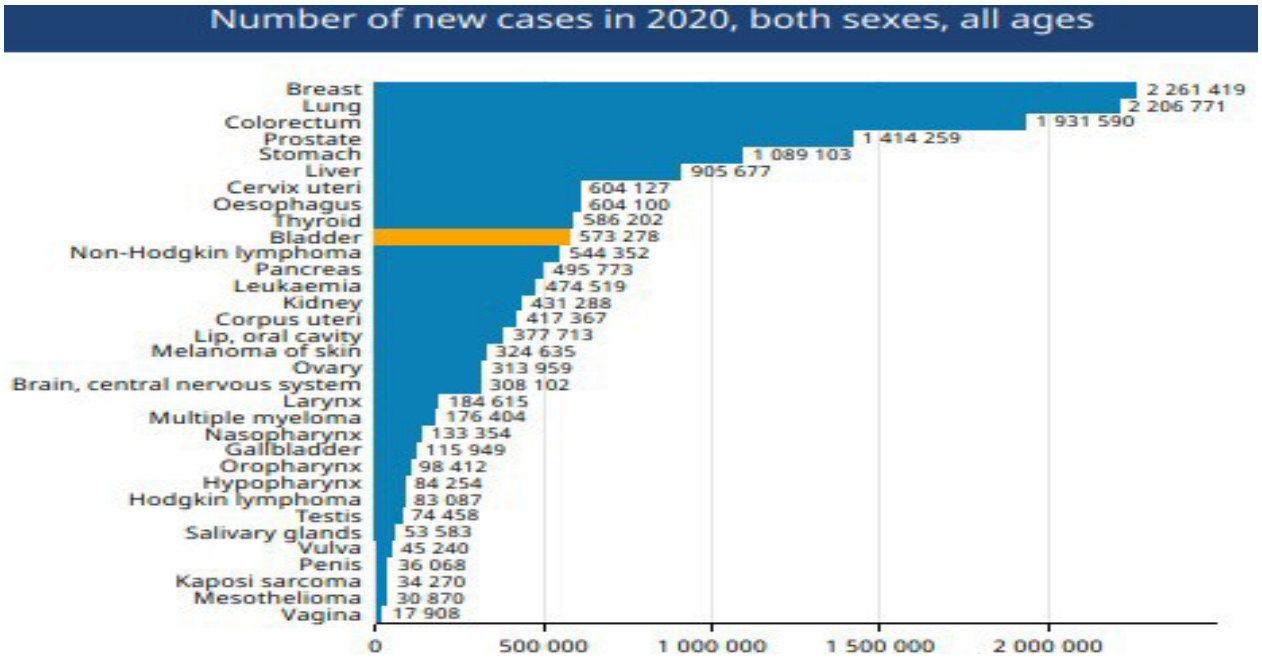
5-FU	5-Flurouracil
BCG	Bacillus of Calmette- Guerin
CCRT	Concurrent Chemoradiation
CMJAH	Charlotte Maxeke Johannesburg Academic Hospital
CIS	Carcinoma In Situ
ECOG	Eastern Cooperative Oncology Group
EBRT	External Beam Radiotherapy
G-CSF	Granulocyte Colony-Stimulating Factor
HICs	High-Income Countries
ICI	Immune Checkpoint Inhibitors
ILRC	Invasive Locoregional Control
LMICs	Low-and-Middle-Income Countries
LTFU	Lost to Follow-Up
LVSI	Lymph Vascular Space Infiltration
MIBC	Muscle-Invasive Bladder Cancer
MUC	Metastatic Urothelial Cancer
NCCN	National Comprehensive Cancer Network
NMIBC	Non-Muscle Invasive Bladder Cancer
RT	Radiation Therapy
SA	South Africa
SCC	Squamous Cell Carcinoma
SSA	Sub-Saharan Africa
TCC	Transitional Cell Carcinoma
TMT	Trimodal Therapy
TURBT	Transurethral Resection of the Bladder Tumour

CHAPTER ONE

1.0 INTRODUCTION

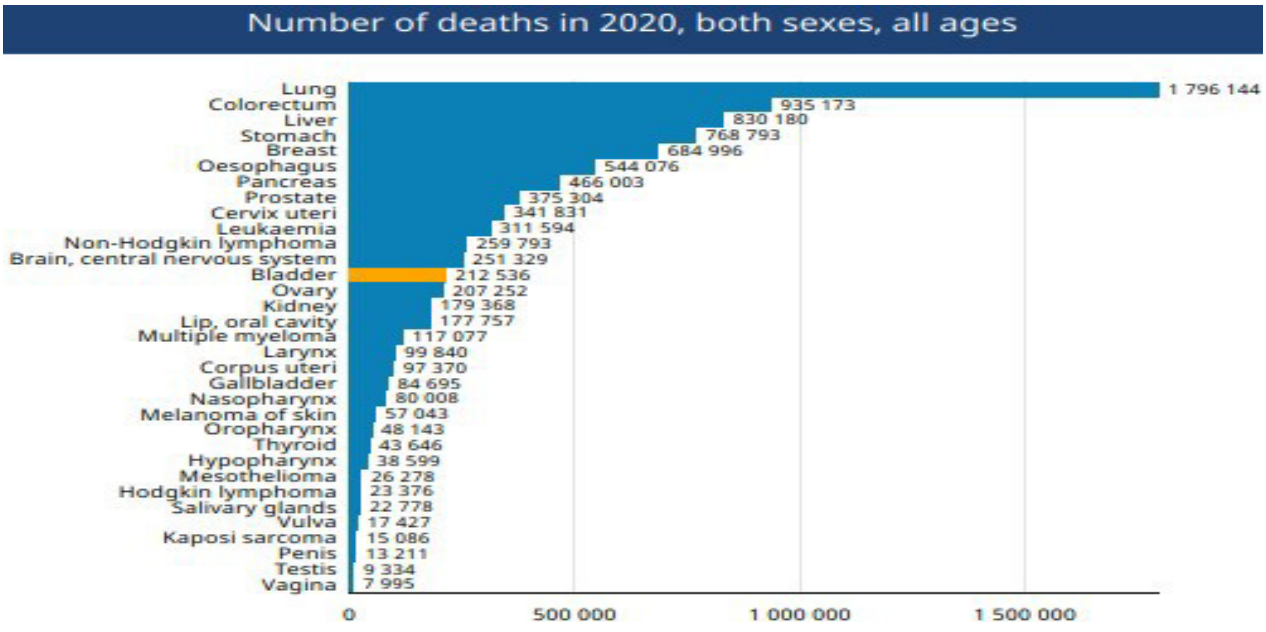
1.1 Background

Bladder cancer is one of the most-common urological cancers and is among the leading causes of cancer mortality worldwide [1]. It accounts for 3% of global cancer diagnoses and is particularly prevalent in the developed world [1]. It also remains a problem in the developing world, and its incidence is increasing [1]. According to the Global Cancer Statistics estimates, it is the tenth most common cancer worldwide (with an incidence of 573 278 new cases per year) and 13th in terms of mortality rate, with 212 536 deaths in 2020 [2]. The global statistics for bladder cancer in terms of incidence and mortality are shown in Figures 1.1 and 1.2, respectively. Globally, bladder cancer is estimated to be the 6th most diagnosed cancer in men, accounting for 4.4% of the total new cases. Bladder cancer is cancer in industrialised nations with an age-standardised incidence rate, which is three times greater in high-income countries (HICs) versus low-and-middle-income countries (LMICs) [3]. The highest incidence of bladder cancer in both sexes is found in Europe and North America, with 26.5% and 18.1%, respectively [2] and Figures 1.3 and 1.4. Europe's Cancer Burden statistics estimate bladder cancer to be the fifth most common cancer in both sexes and the third most common amongst men in Europe. The highest incidence rates in Europe are seen in Greece in Southern Europe, with 5645 cases diagnosed in 2020 [4]. The American Cancer Society estimated 64 280 new bladder cancer cases in men, ranking it the fourth most common cancer in western countries such as the United States in 2021 [5]. Despite the higher incidence of bladder cancer in HICs, mortality rates are more significant in LMICs [6].



Globocan World Health Organization. Global Bladder Cancer Statistics. Who [Internet]. 2020;1–2. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/30-Bladder-fact-sheet.pdf

Figure 1.1 Estimated bladder cancer incidence worldwide in 2020



Globocan World Health Organization. Global Bladder Cancer Statistics. Who [Internet]. 2020;1–2. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/30-Bladder-fact-sheet.pdf

Figure 1.2 Estimated bladder cancer mortality worldwide in 2020

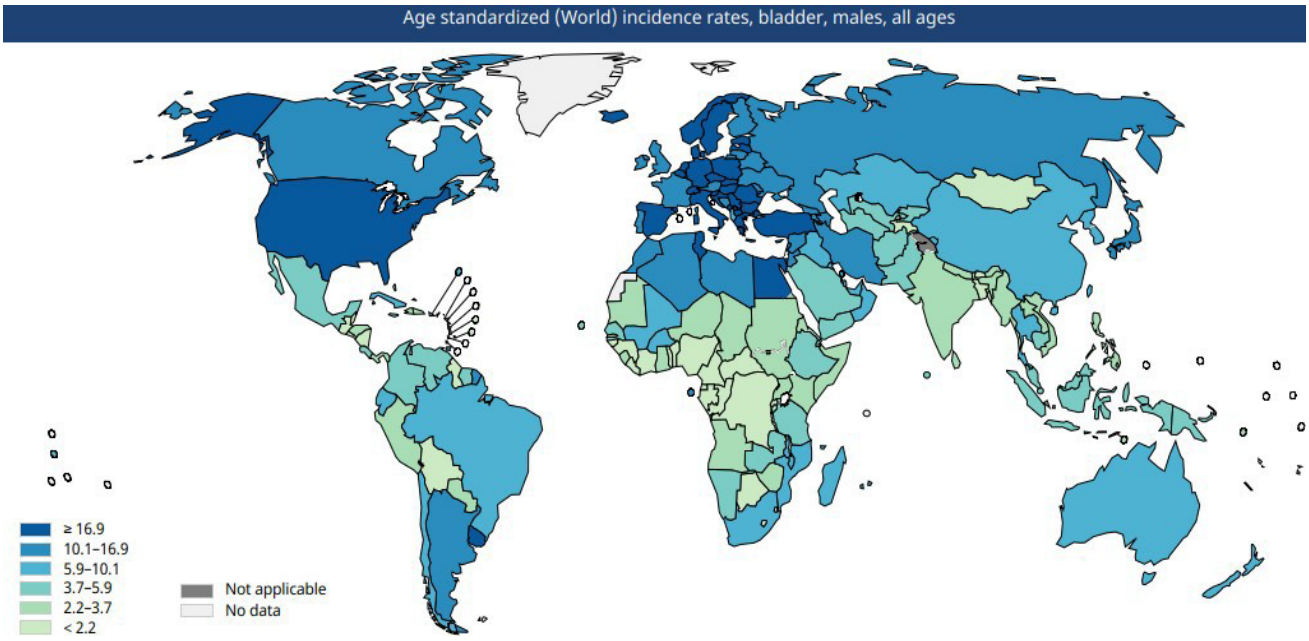


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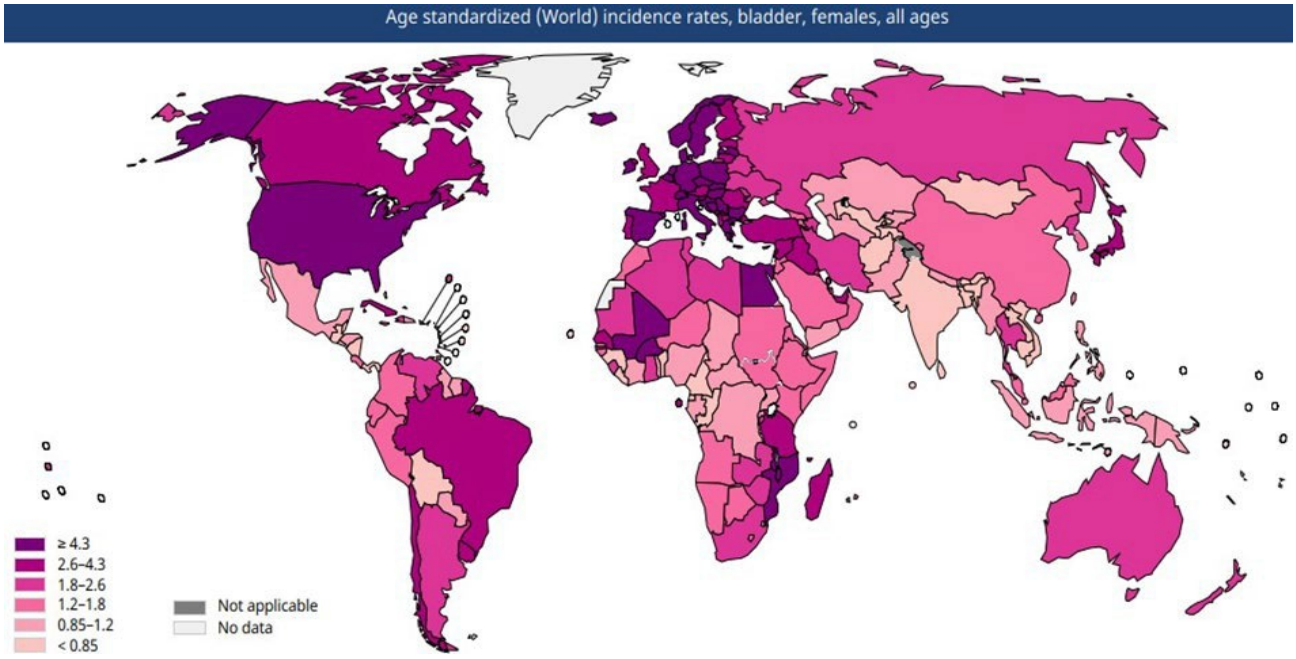
Figure 1.3 Global distribution of bladder cancer incidence rates in males (all ages)



Globocan World Health Organization. Global Bladder Cancer Statistics. Who [Internet]. 2020;1–2. Available from: https://gco.iarc.fr/today/data/factsheets/cancers/30-Bladder-fact-sheet.pdf

Figure 1.4 Global distribution of bladder cancer incidence rates in females (all ages)

Bladder cancer statistics for African countries on incidence, prevalence, and mortality are vastly underrated [7]. The incidence, mortality, and prevalence rates of bladder cancer in South Africa (SA) are shown in Figure 1.5. According to the GLOBOCAN 2020 estimates for SA, bladder cancer is recorded as the twelfth most common cancer representing 1.9% of all new cancer diagnoses and 1.4% of all cancer deaths [8], epidemiologically indicating that it is clinically and socially unresolved [9].

South Africa

Source: Globocan

Incidence, Mortality and Prevalence by cancer site

	New cases				Deaths				5-year prevalence (all ages)	
Cancer	Number	Rank	(%)	Cum.risk	Number	Rank	(%)	Cum.risk	Number	Prop. (per 100 000)
Breast	15 491	1	14.3	5.60	4 664	3	8.2	1.74	47 818	158.90
Prostate	13 152	2	12.2	7.87	3 896	4	6.9	2.27	39 863	136.44
Cervix uteri	10 702	3	9.9	3.58	5 870	2	10.3	2.10	26 486	88.01
Lung	8 950	4	8.3	2.21	7 730	1	13.6	1.94	9 709	16.37
Kaposi sarcoma	3 984	5	3.7	0.50	723	17	1.3	0.09	11 010	18.56
Colon	3 657	6	3.4	0.86	2 053	7	3.6	0.47	8 293	13.98
Non-Hodgkin lymphoma	3 500	7	3.2	0.58	1 797	9	3.2	0.32	9 630	16.24
Oesophagus	3 323	8	3.1	0.80	3 176	5	5.6	0.78	3 555	5.99
Rectum	3 232	9	3.0	0.72	1 545	10	2.7	0.34	7 934	13.38
Liver	2 435	10	2.3	0.52	2 285	6	4.0	0.50	2 805	4.73
Corpus uteri	2 225	11	2.1	1.02	612	20	1.1	0.26	6 768	22.49
Bladder	2 104	12	1.9	0.49	801	16	1.4	0.18	5 348	9.02
Pancreas	2 029	13	1.9	0.46	1 982	8	3.5	0.46	1 685	2.84
Lip, oral cavity	1 933	14	1.8	0.45	814	15	1.4	0.20	4 716	7.95
Leukaemia	1 922	15	1.8	0.35	1 458	12	2.6	0.27	5 036	8.49
Melanoma of skin	1 777	16	1.6	0.37	480	22	0.85	0.11	4 781	8.06
Stomach	1 744	17	1.6	0.39	1 484	11	2.6	0.33	2 348	3.96
Ovary	1 471	18	1.4	0.56	974	13	1.7	0.39	3 559	11.83
Kidney	1 333	19	1.2	0.28	622	19	1.1	0.14	3 601	6.07
Thyroid	1 305	20	1.2	0.24	146	28	0.26	0.04	4 023	6.78

GLOBOCAN TGCO. Population Fact Sheets - South Africa. 2020;491:1–2. Available from: https://gco.iarc.fr/

Figure 1.5 The incidence, mortality, and prevalence of Bladder Cancer in South Africa

1.2 Literature review

Bladder cancer is a multifactorial disease with vast patterns of behaviour, with predicting spectrums differing from rarely harmful in low-risk tumours to high mortality rates in high-risk disease. A significant factor contributing to the complexity of managing bladder cancer is the burden of variable presenting characteristics.

1.2.1 Prevalence of bladder cancer by age, gender, and race

The risk of developing cancer increases with age, which is also the case with bladder cancer. In a systematic review of risk factors for bladder cancer conducted by Cumberbatch et al., the risk of bladder cancer increases with age, with an increase in the age-specific curves steeply after the age of 50 years [10]. Several studies have been conducted previously on the prevalence of bladder cancer by race and gender [11]. A study using data obtained in the Global Burden of Disease study performed in 2017 found that the prevalence and mortality were three times higher in males than in females [12]. Bowa *et al.* conducted a study reviewing meta-analysis data of bladder cancer and the associated prevalence among the diverse racial groups within SA, with higher results of Squamous cell carcinoma (SCC) reported in African racial groups and as low as 6% and 2% prevalent in coloured and white patients compared with the prevalence of Transitional cell carcinoma (TCC) in these groups [13].

A study including 477 patients with bladder cancer at Groote Schuur Hospital, Cape Town, SA, found that among the ethnicity distributions, coloured males make up the majority, 54.8%, white patients accounting for 16%, blacks for 12.4%, and Indians 2.2% of the detected bladder cancer cases [14]. Gauteng is the smallest of SA's provinces. However, it is home to almost a quarter (24.1%) of the national population, and nearly half (44%) of Gauteng's population is within the Johannesburg Metropolitan Municipality [15,16]. According to the Johannesburg

Population Statistics (2021), the African racial group accounts for 76.4% of the total population of the Johannesburg Metropolitan Municipality [17]. Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), located in Parktown, drains Johannesburg and most of the Ekurhuleni and West Rand District Metropolitan Municipalities [18].

1.2.2 Risk Factors

Identifying exposed risk factors related to bladder cancer is associated with prognostic. A literature search shows variable-related risk factors and their clinical significance. A significant presenting factor that alters different presentations in bladder cancer is the identified histopathological subtypes [13]. TCC is most prevalent in developed countries due to higher exposure to carcinogenic chemicals, while in sub-Saharan Africa (SSA), populations are burdened with the SCC subtype [7].

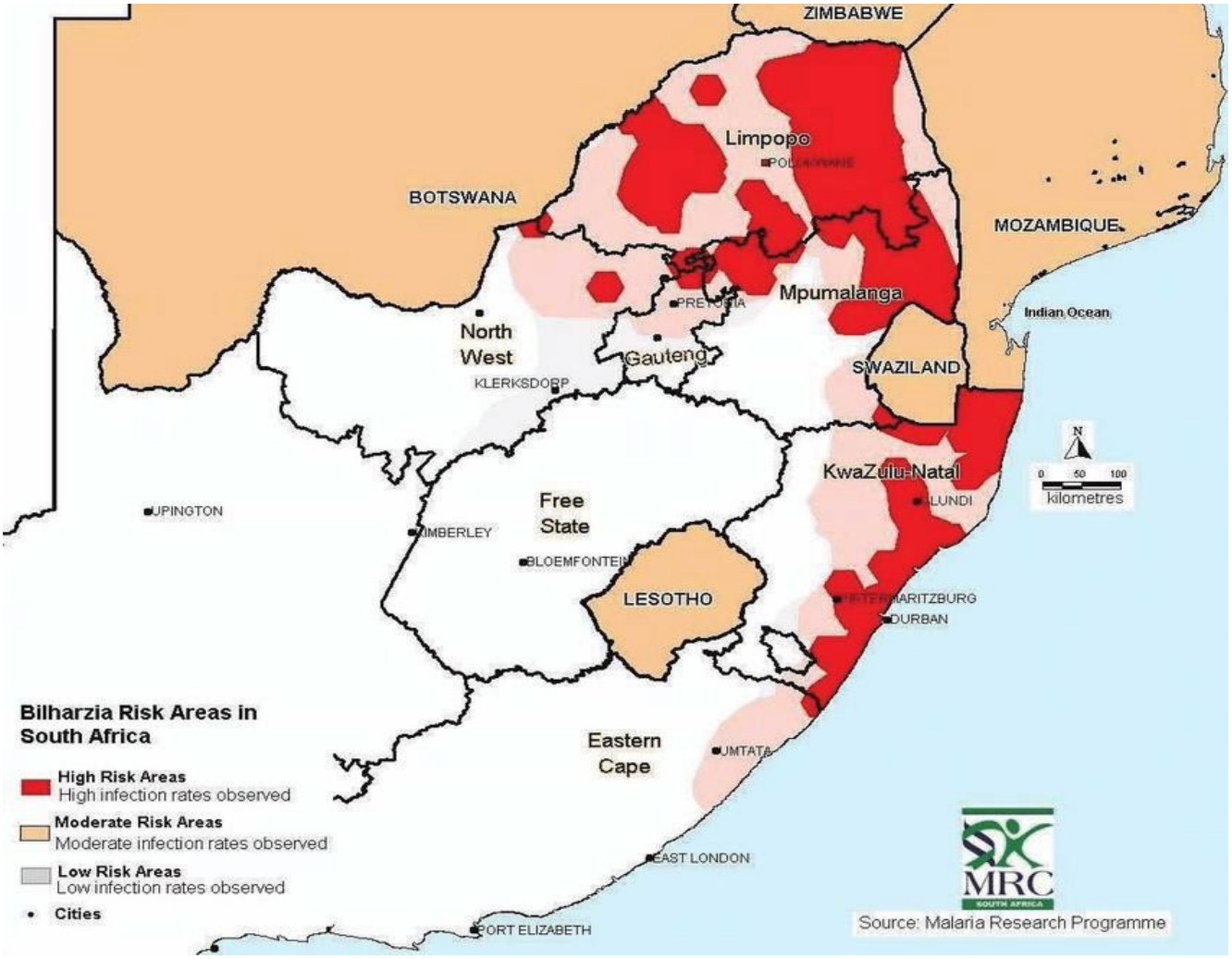
A) Smoking and Occupational risk

Cigarette smoking has a strong association with bladder cancer, and there is also an association with a higher mortality rate of bladder cancer with cigarette smoking.[19]. Following smoking, carcinogenic exposure to aromatic amines and polycyclic and chlorinated hydrocarbons from occupational sources is also considered an important risk factor for bladder cancer [11]. The associated increased risk is mainly the employed in industrial areas processing paint, textile dye, printing and rubber tire industries, metal, and petroleum [11].

B) Bilharzia

Schistosomiasis, a well-established tropical disease in Sub-Saharan Africa (SSA), is a known risk factor for bladder cancer [20]. In SA, areas with endemic schistosomiasis (bilharzia) caused by parasitic schistosomes (blood flukes) are provinces such as KwaZulu-Natal, Eastern Cape, Limpopo, Northwest, and Mpumalanga, hence the high incidence of SCC in these areas [21].

Many studies have looked at the association between urinary schistosomiasis and SCC of the bladder in SA. Still, few studies have focussed on tertiary hospitals in Gauteng in particular, despite the province being geographically near endemic areas for schistosomiasis. Cooper et al. conducted a study including 25 samples of bladder SCC associated with Schistosoma haematobium from patients aged 29–72 years in Gauteng. They found that schistosomiasis plays a significant role in the pathogenesis associated with the development of SCC of the bladder [22]. There is good evidence regarding the relationship between endemic areas of urinary schistosomiasis and the high incidence of Bladder cancer [7].



malaria resource programe - Search [Internet]. [cited 2023 Aug 1]. Available from: https://www.bing.com/search?q=malaria+resource+programe&qs=n&form=QBRE&sp=-1&lq=0&pq=malaria+resource+programe&sc=2-26&sk=&cvid=20C4468E1CF341F887C6FFE3F396DA17&ghsh=0&ghacc=0&ghpl=

Figure 1.6 Areas of South Africa endemic to urinary schistosomiasis

C) Therapy-related carcinogenesis

The cytotoxic alkylating agent cyclophosphamide, as conventional chemotherapy with urotoxic-mediated effects, has been widely used to treat many neoplastic diseases, particularly haematological disorders such as lymphomas, leukaemias, and multiple myeloma as well as indicated for treating various solid tumours such as breast, ovarian cancer, and sarcomas [11]. Traditionally, cyclophosphamide at high doses was initially used for Stem cell transplantation, but as an effective immunosuppressor, has also helped treat non-neoplastic diseases such as systemic lupus erythematous, severe rheumatoid arthritis, multiple sclerosis, wegener's granulomatosis, good pasture syndrome, and nephrotic syndrome minimal change disease [23]. Cyclophosphamide-induced urothelial cancer of the bladder is a well-known entity, and the risk grows with the duration and dosage of cyclophosphamide therapy. A study by Lois *et al. o*n patients with Non-Hodgkin's Lymphoma found a substantial 4.5-fold absolute risk of bladder cancer (95% confidence interval (CI) = 1.5–13.6) and a solid cumulative dose-dependent relationship following cyclophosphamide treatment [24].

Radiation Therapy (RT) is widely used for treating pelvic tumours and is well-established in the risk of radiation carcinogenesis [11]. Wei Chao *et al.* conducted a systematic review and meta-analysis using 19 studies' results showing an increased risk of secondary-induced bladder cancer following RT for primary pelvic tumours (Relative Risk (RR) 1.75, 95% CI: 1.50–2.05) [25]. John *et al.* conducted a case-control study of women who had previously been treated for ovarian cancer; 66 secondary bladder cancer tumours were identified and matched with 188 control women who had previously been treated for ovarian cancer. They found an increased risk of secondary-induced bladder malignancies, which was the most remarkable for patients who had both RT and chemotherapy with an

RR of 5.2, 95% CI: 1.6–16 and for those that had RT alone, RR of1.9; 95% CI: 0.77–4.9 compared with patients being treated with surgery alone [26]. Radiation-induced carcinogenic bladder malignancies have indistinguishable biological behaviour, which is predicted by no significant survival difference compared with bladder cancer with no risk factor for previous pelvic RT [27].

1.2.3 Clinical Presentation

The presenting clinical symptoms of bladder cancer vary depending on the stage at presentation, with 85% most commonly presenting with painless macroscopic haematuria and 25% with irritable bladder symptoms such as frequency, urgency, dysuria, and nocturia. Other symptoms, such as suprapubic pain, urinary or rectal obstructive symptoms, and signs of a clinical palpable hypogastric mass or an obstruction on the digital rectal examination, indicate locally advanced disease [8]. Systemic symptoms such as swelling of the legs, bone pain, constitutional weight loss, fatigue, and clinical signs of abdominal organomegaly and pulmonary manifestations are associated with metastasis and predict a poor prognosis in bladder cancer [28].

1.2.4 Imaging and staging

When there is a clinical suspicion of bladder cancer, the initial radiological investigation is an ultrasound of the urinary tract, which is cheap, quick, and non-invasive. Using ultrasound is advantageous as it may help assess for the presence of any bladder mass, or the size of a bladder tumour, distinguish solid from cyst-filled tumours, assess for the presence of hydronephrosis, and aid with guided biopsy. The disadvantage of ultrasound is that the image quality produced is operator-dependent and may miss a bladder tumour [29]. In addition to sonography, imaging of the urinary tract and renal pelvis with IV

pyelography is optional before excisional biopsy to exclude synchronous primaries [30]. Computerised Tomography (CT) urography, including the pelvis and abdomen, is the gold standard and imaging modality of choice; it has a high sensitivity of 85% and specificity of 92%, with superior image quality for assessing bladder wall thickness, extra vesicle extension, regional and non-regional lymph node metastasis [30]. Two significant limitations of CT urography used as imaging in suspected bladder cancer are 1) its inability to distinguish non-muscle versus muscle-invasive bladder cancer and 2) its contraindicated use of contrast in patients with poor renal function associated with advanced disease [29]. Magnetic Resonance Imaging (MRI) of the bladder is preferred for patients with poor renal function. It provides superior soft tissue image quality in staging primary tumour extent and invasion of adjacent organs [30]. ^{18}F-fluorodeoxyglucose (FDG) PET/CT may assist in superior evaluation of lymph node staging and helps detect distant metastasis [29].

The stage at diagnosis is the most critical factor for a patient's prognosis and is central to treatment decisions. The most recently published 2017 American Joint Committee on Cancer- tumour, nodes, metastasis (AJCC/TNM) staging, 8th edition for bladder cancer, is internationally used and is based on three key entities T, N, and M components. T, N, and M represent primary tumours, regional lymph nodes, and distant metastasis, respectively. The T category of bladder cancer is determined by the invasion of depth through the bladder wall and local extension into nearby tissues of the primary tumour. The N category is determined according to the number and location of cancer spread to lymph nodes near the bladder. The M category is based on the spread of cancer to distant sites or lymph nodes that are not near the bladder [31].

Recent advancements made in the characterisation, diagnosis, and reporting of bladder cancer staging have progressed from the historical grading classifications to the development of 3 well-known groups: Non-Muscle Invasive Bladder Cancer (NMIBC), Muscle-Invasive Bladder Cancer (MIBC), and Metastatic Urothelial Cancer (MUC) (29).NMIBC comprises about 75% of all newly diagnosed bladder cancer and includes non-invasive carcinoma confined to the bladder mucosa, with stage Ta being the papillary stage, Tis carcinoma in situ (CIS), and limited to invasive carcinoma involving the submucosa in stage T1 [30]. The remaining presenting as either MIBC or denovo mUC. MIBC involves a disease that invades the bladder muscle (stage T2), perivesical tissues (stage T3), adjacent organs, pelvic or abdominal wall (stage T4), and the regional lymph nodes near the bladder limited to the common iliac nodes. MUC involves distant metastasis, including the spread of cancer to nodes beyond the common iliac and other distant sites such as bone, lung, or liver [31].

NMIBC is rarely lethal, with a 5-year overall survival rate of approximately 90%, but a high rate of recurrence of about 60% when managed with surgical resection alone and a 15% rate of transformation to MIBC, hence the need to significantly improve risk stratification and for earlier definitive treatment for high-risk NMIBC. MIBC tends to have a worse prognosis with a 5-year survival rate of 45- 50% following RT or surgical treatment. MUC accounts for less than 10% at presentation, having an inferior prognosis with a 5-year relative survival rate of around 6% and a median survival of 12 to 18 months [32].

1.2.5 Treatment of Bladder cancer

(A) Non - muscle - invasive bladder cancer

The treatment strategy for NMIBC includes the transurethral resection of the bladder tumour (TURBT) followed by intravesical immunotherapy with the bacillus of Calmette-Guerin (BCG) or intravesical chemotherapy, depending on the grade of the bladder tumour and other prognostic risk factors for recurrence [33-34]. Both intravesical BCG and chemotherapy can be given, and the most used chemotherapy agents are mitomycin C and gemcitabine [35-36]. Unfortunately, despite proper intravesical instillation, up to 40% of patients present with local failure within two years, requiring radical cystectomy or bladder-preserving therapies [37]. Patients with unresponsive disease have a high risk of progression and metastasis, and radical cystectomy with pelvic lymph node dissection and urinary diversion is the gold standard treatment [38–40]. Bladder cancer surgery is associated with much morbidity and mortality and can negatively affect one's quality of life; as a result, many patients decline surgical intervention [103].

(B) Muscle-invasive bladder cancer

Evidence-supported guidelines recommend two broad categories of primary definitive treatment for MIBC: radical cystectomy and trimodal therapy (TMT) [35,41]. Radical cystectomy is an effective treatment option for MIBC [42, 43]. TMT, which involves maximal transurethral resection of the tumour followed by concurrent radiosensitising chemotherapy and radiotherapy, is a treatment option for those refusing or deemed not a candidate for cystectomy [44]. TMT remains the most-studied conservative bladder-sparing approach. TMT comprises maximal TURBT followed by ≥ 60-Gy RT with concurrent radiosensitising chemotherapy delivered in a split or continuous course [45]. The goal of TMT is to preserve the bladder and quality of life (QoL) without compromising oncological outcomes. The rationale behind combining TURB with RT is to

achieve maximal local control in the bladder and adjacent lymph nodes. Ploussard et al. showed that a standard radiation schedule includes external beam RT to the bladder and limited pelvic lymph nodes to an initial dose of 40 Gy [46]. A boost to the whole bladder to 54 Gy and a further tumour boost (which incorporates all TURBT and radiographic information) to 64–65 Gy is also recommended [41,47]. EBRT for MIBC can be given in a continuous or split-course regimen. The latter has the advantage that an early response assessment is carried out to allow immediate salvage cystectomy for tumours not responding to the radio (-chemo) therapy. Potential disadvantages are that early assessment leads to unnecessary salvage cystectomies, which would be avoided when a later assessment is carried out. In this setting, the overall treatment is prolonged, which can result in inferior locoregional control, as suggested by De Neve et al. and Maciejewski and Majewski [48,49].

The addition of concurrent systemic chemotherapy can improve locoregional control, in addition to addressing micrometastases [39,50]. Randomised clinical trials (RCT) have demonstrated improved outcomes; reduced rates of pelvic relapse, improved locoregional disease-free survival, bladder-cancer-specific survival, and a trend towards improved OS with chemoradiotherapy compared with RT alone [51,52]. Radiotherapy with concurrent cisplatin-based chemotherapy or 5-FU plus mitomycin C as a radiosensitiser is the most common and well-studied chemoradiation method used to treat MIBC [51,53- 57]. The following radiosensitising regimens are recommended: doublet 5-FU plus mitomycin C or single agent cisplatin is generally preferred. Cisplatin plus 5-FU, cisplatin plus paclitaxel, or low-dose gemcitabine may be considered as an alternative regimen [58, 59].

The radiotherapy dose-response effect has been suggested in several series [60,61].

Altered fractionation has been explored in bladder cancer with a decrease in overall treatment time (less than six weeks), which typically avoids clonogenic tumour repopulation, which accelerates after a lag period of about 5–6 weeks following the start of treatment [62]. Moderate hypofractionated accelerated radiotherapy has been assessed in five trimodal therapy trials (including one trial using non-chemotherapy-based radiosensitisers) [51,63-65]. Radiotherapy was delivered continuously over four weeks on the whole bladder to a total dose of 52.5–55.0 Gy. No direct comparison of hypofractionated versus conventional fractionated radiotherapy for trimodal therapy exists; however, an individual patient data meta-analysis of two-phase III randomised trials comparing the two most widely used timetables in the UK has been published [51,61]. The conventional 64 Gy in 32 fractions versus 55 Gy in 20 patients, among 782 patients, showed a similar toxicity profile, and the hypofractionated was non-inferior to the conventional timetable in terms of OS. The superiority of the hypofractionated timetable was demonstrated for invasive locoregional control (ILRC) for locally advanced MIBC. ILRC (adjusted HR 0.71 [95% CI 0.52- 0.96] [66].

(C) Metastatic urothelial carcinoma

Approximately 50% of patients with MIBC will relapse, local recurrences account for about 10%-30% of relapses, while distant metastases are more common. About 5% of the patients have metastatic disease at diagnosis [67]. Patients who present with disseminated metastatic disease are generally treated with systemic therapy [35]. Standard first-line treatment for fit patients with good renal function is cisplatin-based combination chemotherapy. The most used regimens are cisplatin-gemcitabine (having less toxicity) or dose-dense MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) with granulocyte colony-stimulating factor (G-CSF) demonstrating a median overall survival of 12–14 months [68-69]. Long-term survival with combination chemotherapy

alone has been reported only in good-risk patients, defined as those with good performance status, no visceral (i.e., liver, lung), or bone disease. [28]. Overall survival ranges between 9 and 15 months in patients with locally advanced or metastatic urothelial carcinoma treated with first-line platinum-based chemotherapy [70-72].

Recently, immune checkpoint inhibitors (ICI) targeting programmed death-1 or programmed death-ligand 1 (PD-1/PD-L1) have gained approval for use in patients with locally advanced or MUC, showing higher response rates and improved survival, with a more durable response than chemotherapy [73-76]. The current NCCN Guidelines recommend using anti-PD-1 therapy (pembrolizumab) as the preferred second-line option following platinum-based chemotherapy [35]. Anti-PD-L1 therapies' avelumab may be considered as an alternative regimen [74-76]. Treatment options have been limited for patients who are refractory to or ineligible for systemic therapy and have no access to ICIs. [35,77,78].

1.2.6 Role and clinical practice of radiation therapy in bladder cancer

Advanced age, stage at diagnosis, and multi-morbidity are known factors that impact the quality of life of patients with bladder cancer, which has been studied from the patient's perspective [33]. For example, despite having medically or surgically inoperable disease, patients with bladder cancer undergoing radiation treatment have reported favourable improvement after therapy [35]. Many radiation oncology centres have adopted protocols using shorter radiation schedules that can assist with pre-treatment delays or gaps in therapy as an option, such as hypofractionation for bladder cancer and still achieving adequate tumour control and acceptable toxicity [24]. For patients with locally advanced bladder cancer using a shorter treatment period of 20 days with a hypofractionated

timetable of 55 Gy is superior to conventional treatment in disease control and non-inferior with toxicities [66]. In addition to its use in a curative setting, radiotherapy can provide significant palliation in patients with metastasis or patients not candidates for definitive therapy. Prolonged haematuria is a frequent and debilitating complication in patients with bladder cancer, and the efficacy of palliative RT for haematuria has been reported in several retrospective studies [79-81]. Most timetables favour hypofractionation, and the most frequently used dose fractionation regimen was 30 Gy in 10 fractions, followed by 20 Gy in 5 fractions [79-81].

1.3 Study Objectives

This study aims to determine the profile, clinical presentations, and management of patients with bladder cancer at the Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) Department of Radiation Oncology from January 2010—December 2020.

1.3.1 Specific objectives

The specific objectives of this study are:

- To describe the socio-demographic characteristics of patients diagnosed with bladder cancer at the CMJAH Department of Radiation Oncology from January 2010 to December 2020.
- To describe the clinical presentation of patients diagnosed with bladder cancer at the CMJAH Department of Radiation Oncology from January 2010 to December 2020.
- To describe the treatment received by patients with bladder cancer at the CMJAH Department of Radiation Oncology from January 2010 to December 2020.

CHAPTER TWO

2.0 METHODOLOGY

2.1 Study design and setting

This is a retrospective analysis of patients diagnosed with bladder cancer utilising clinical data collected from the Radiation Oncology department at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from January 2010 to December 2020.

2.2 Study population and sample

The study population included all patients referred to the department of Radiation Oncology, urological cancer outpatient clinic between January 2010 and December 2020 following the diagnosis of bladder cancer.

2.2.1 Inclusion criteria

- All patients with histological diagnosis of bladder cancer were referred to the Radiation Oncology department between January 2010 and December 2020 for treatment.
- Patient age: 18 years and older with a registered assessment consultation case record

2.2.2 Exclusion criteria

- Patients without histopathological confirmation of bladder cancer
- Patients whose medical records were missing or not retrievable.

2.3 Data collection

A patient file review was conducted to complete an excel spreadsheet tool with the desired pre-specified variables on demographics, Identifiable risk factors, clinic-pathological features, and specific therapies received by the patients. Demographics included the patient's gender, age, and race: identifiable risk factors for bladder cancer such as smoking, schistosomiasis, family history of bladder cancer, a history of urolithiasis, previous pelvic radiotherapy, and previous chemotherapy.

Clinical characteristics, such as comorbidities and performance status, were captured. The patient's performance status at presentation also used the Eastern Cooperative Oncology Group (ECOG) scale. The scores were defined as follows: 0=asymptomatic, 1= restricted in physically strenuous activity, 2= unable to work but out of bed for more than 50% of waking hours, 3= limited self-care, confined to bed or chair more than 50% of waking hours, 4=no self-care, completely disabled, and totally confined to bed or chair.

Pathological characteristics include the histopathological variant of bladder tumour (transitional cell carcinoma, squamous cell carcinoma and others (atypical, mixed variant or adenocarcinoma), and pathological features in radical cystectomy tissues were captured. The stage or disease category (Non-muscle Invasive bladder cancer (NMIBC), Muscle-Invasive Bladder Cancer (MIBC), or Metastatic Urothelial Cancer (MUC). Therapy-related variables such as chemotherapy (Intravesical, neoadjuvant or adjuvant), surgery (transurethral resection of bladder tumour, radical cystectomy, or urinary diversion), and radiation therapy (radical or palliative) were noted. The radiation dose received/fractionation (conventional versus hypofractionation timetable) and concurrent chemotherapy with radiotherapy (chemoradiation). Furthermore, various indications for palliative radiotherapy, treatment outcome, and toxicities were recorded.

2.4 Data analysis

Data were entered into secure Microsoft Excel software. The data were analysed using Stata version 16. Descriptive statistics for continuous variables were analysed using mean and standard deviation (SD) after assessing for normality using the histogram plot with a super-imposed standard curved and the Shapiro Wilk test for normality. Box and whisker plots were used to describe the age distribution. Categorical variables were reported as frequencies and percentages. Results are presented in tables and charts (bar, column and pie charts). To examine associations with the histopathological variants, we used a bivariate logistic regression model reporting an odds ratio (OR) with a 95% confidence interval (CI). Variables for which Wald testing p-values were <0.5 were considered significant throughout.

2.5 Ethics

Permission to access patients' medical records was obtained from the Chief Executive Officer of CMJAH. (See appendix 2). Ethics approval was granted on 02/11/2021 and was given by the Human Research Ethics Committee (HREC) of the University of the Witwatersrand. The Ethics clearance certificate number for the study was M211024.

CHAPTER THREE

3.0 RESULTS

3.1 Socio-demographic characteristics of the patients

During the period under review (2010- 2020), 115 patients diagnosed with bladder cancer were referred to the Radiation–Oncology Department, CMJAH. Of these, 2010 had the highest number of bladder cancer presentations, with 19 (16.5%) patients, followed by 2015, 13 (11.3%) patients,12 (10.4%) patients in 2013, and 9 (7.8%) patients in 2020 [Figure 3.1].

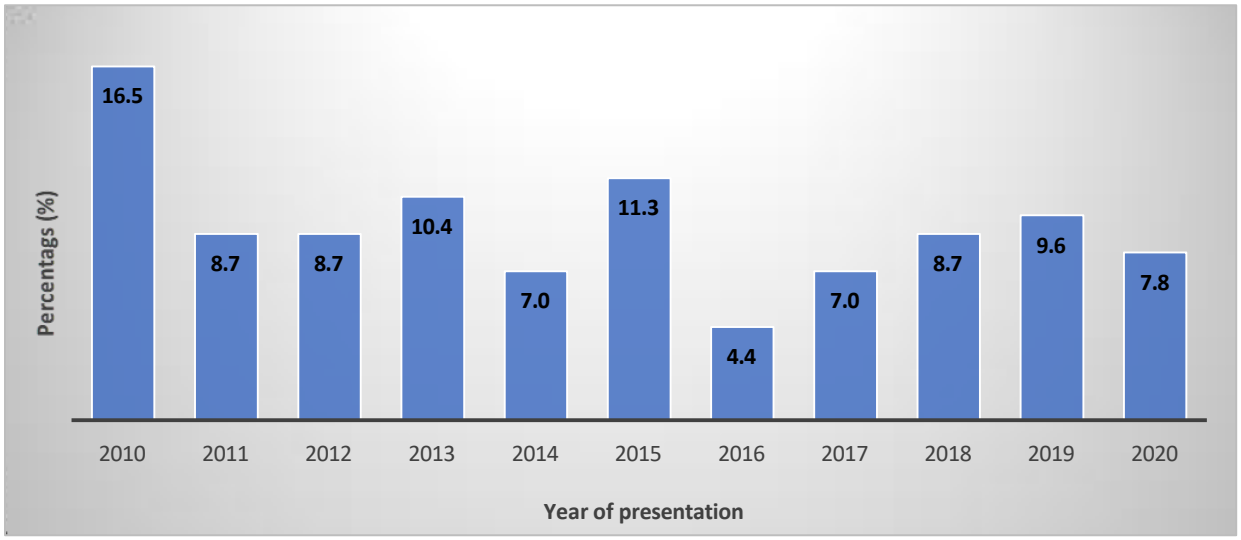


Figure 3.1 The year of presentation of patients diagnosed with bladder cancer at CMJAH from 2010–2020.

The mean ± SD age for the patients was 60.7 ± 14.9 years (Figure 3.2 and Table 3.1), and the age distribution is shown in Figure 3. 2.

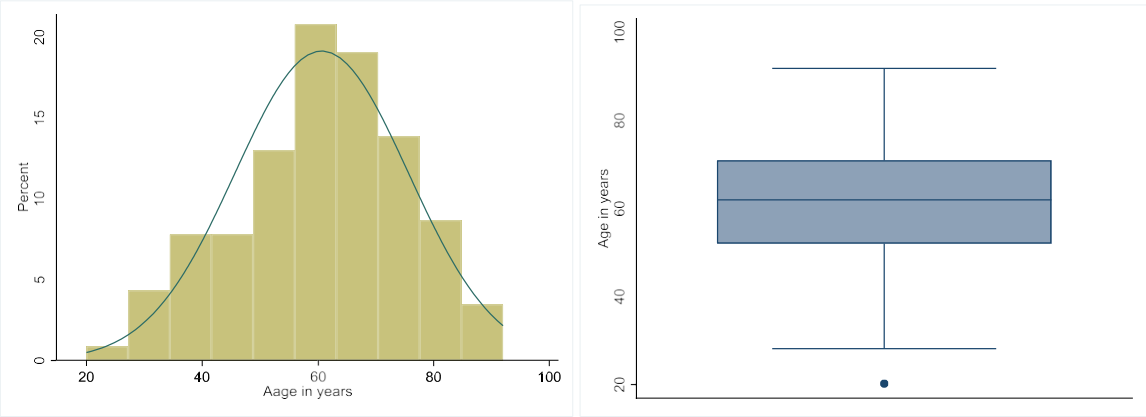


Figure 3.2 Age distribution for patients diagnosed with bladder cancer at CMJAH from 2010–2020.

The socio-demographic characteristics of these patients are summarised in Table 3.1. Most patients were male 70 (60.9%), with a male-to-female ratio of 1.6: 1. Most patients were also of black race 60 (52.2%), followed by white patients 36 (31.3%), 13 (11.3%) were coloured, and 6 (5.2%) were Asians. Less than 5% (n=5) of the patients had a history of schistosomiasis, 0.9% (n=1) had a history of urolithiasis, and 6.1% (n=7) had a family history of bladder cancer. Most patients presented with an ECOG of 2 (40.0%) and 1 (36.5%) (Table 3.1).

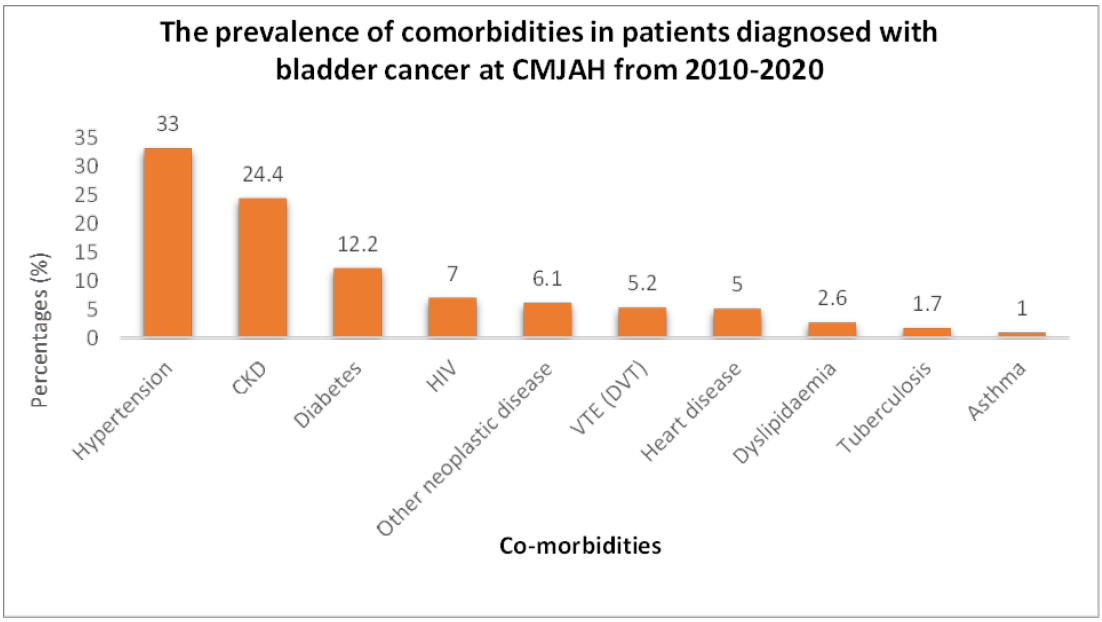
Table 3.1 The Socio-demographic characteristics of patients diagnosed with bladder cancer at CMJAH from 2010 - 2020.

Variables	**Categories**	**Frequencies N=115**	**Percentage (%)**
Age in years, mean ± SD		60.7 ± 14.9	
Gender	Male	70	60.9
	Female	45	39.1
Gender ratio	Male: Female	1.6: 1	-
Race	Black	60	52.2
	White	36	31.3
	Coloured	13	11.3
	Asian (Indian)	6	5.2
History of smoking	No	60	52.2
	Yes	55	47.8
History of schistosomiasis	No	110	95.7
	Yes	5	4.4
History of Urolithiasis	No	114	9.1
	Yes	1	0.9
Previous pelvic radiotherapy	No	113	98.3
	Yes	2	1.7
Previous chemotherapy	No	112	97.4
	Yes	3	2.6
Family history of bladder cancer	No	108	93.9
	Yes	7	6.1

*ECOG performance status	0	7	6.1
	1	42	36.5
	2	46	40.0
	3	18	15.7
	4	2	1.7

*ECOG (Eastern Cooperative Oncology Group)

The comorbidities the patients presented with are summarised in Figure 3.3. The common comorbidities were hypertension, which was reported in 33% (n=38) of the patients, chronic kidney disease (CKD) was reported in 24.4% (n=28), diabetes was reported in 12.2% (n=14) of the patients, and 7% (n=8) were HIV positive.

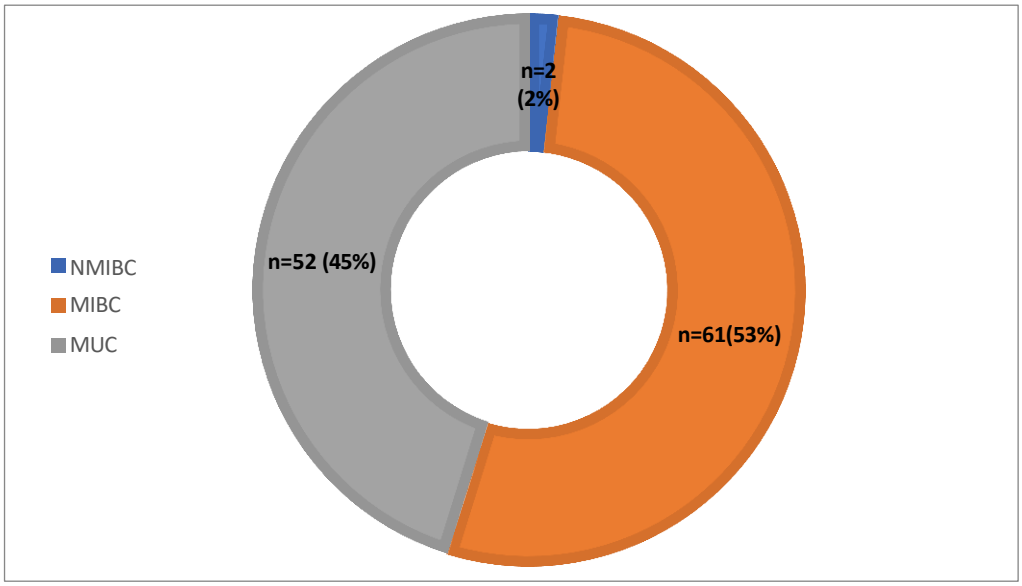


*CKD (chronic kidney disease), HIV (human immunodeficiency virus), VTE (Venous thromboembolism), DVT (deep vein thrombosis)

Figure 3.3 The prevalence of comorbidities in patients diagnosed with bladder cancer at CMJAH from 2010 – 2020.

3.2 Clinicopathologic features

About half of the patients (n=61, 53.0%) presented at the MIBC stage, followed by the MUC stage (n=52, 45.0%), while the remaining 2.0% (n=2) had an NMIBC stage (Figure 3.4).



** NMIBC (Non-Muscle Invasive Bladder Cancer), MIBC (Muscle-Invasive Bladder Cancer), MUC(Metastatic Urothelial Cancer)*

Figure 3.4 Disease stage at presentation of patients diagnosed with bladder cancer at CMJAH from 2010–2020.

Regarding the pathology of bladder cancer in the cohort, the majority (n=78, 67.8%) of the patients had TCC, while 27% (n=31) had SCC. Regarding tumour grade, most patients (80.8%) had grade 3 disease, while grades 1 and 2 accounted for 5.2% and 14% of the patients, respectively. Pathological analysis of the tumours also showed lymph vascular space invasion (LVSI) in 29.6% (n=34) (Table 3.2).

Table 3.2 Pathological features of bladder cancer diagnosed at CMJAH from 2010-2020.

Variables	Categories	Frequencies N=115	Percentages (%)
Histology	TCC	78	67.8
	SCC	31	27.0
	Atypical	6	5.2
Tumour grade	1	6	5.2
	2	16	14.0
	3	93	80.8
LVSI	No	81	70.4
	Yes	34	29.6

*TCC (Transitional cell carcinoma,) SCC (Squamous cell carcinoma), LVSI (Lymph vascular space infiltration)

*

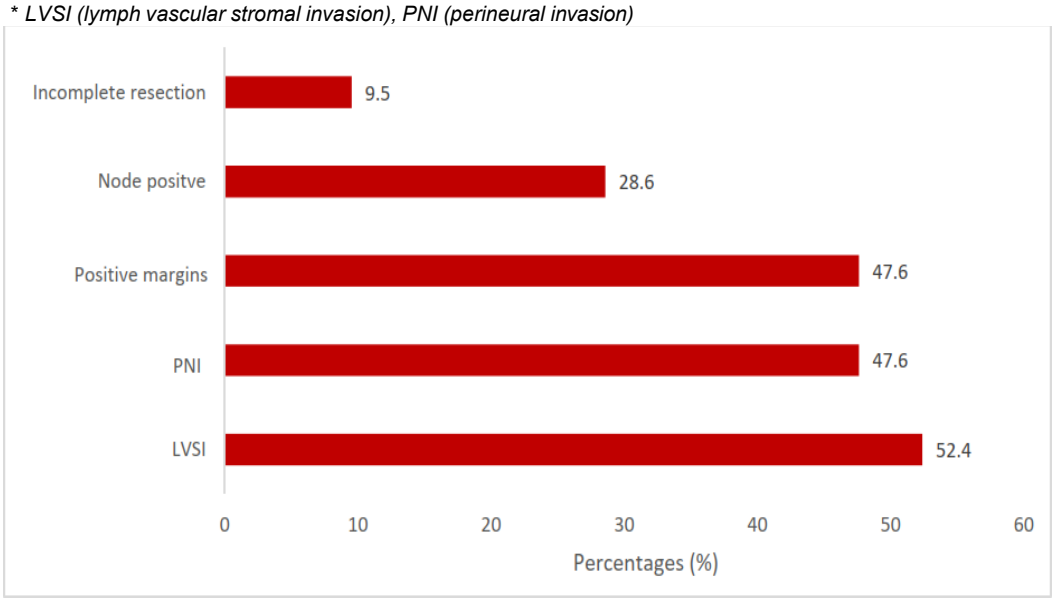


Figure 3.5 Pathological/post-op findings of radical cystectomy tissue following surgery in 21 patients who were diagnosed with bladder cancer at CMJAH from 2010-2020.

3.3 Treatment characteristics of bladder cancer patients

Bladder cancer-related therapies received by the patients are summarised in Table 3.3. There were 3.5% (n=4) of the patients who previously received intra-vesical chemotherapy and 5.2% (n=6) who previously received platinum-based neoadjuvant chemotherapy, mostly cisplatin and gemcitabine. There were 67% (n=77) and 18.3% (n=21) who had transurethral resection of bladder tumour (TURBT) and radical cystectomy, respectively. The post- cystectomy tissue examination outcomes are shown in Figure 3.5. The most common high- risk pathological feature was lymph vascular space infiltration (LVSI) reported in 52.4% (n=11/21) of the cohort of patients who had radical cystectomy. Positive margins (defined as a tumour on ink) and perineural invasion (PNI) were observed in 47.6% (n=10/21). In comparison, node-positive disease (defined as lymph nodes identified in the pelvic dissection) was reported in 28.6% (n=6/21) of the patients before being referred for adjuvant radiotherapy.

Table 3.3 Bladder cancer-related therapy at CMJAH from 2010–2020.

Group	Variables	Categories	Frequencies N=115	Percentages (%)
Previous chemotherapy	Intra-vesical	No	111	96.5
		Yes	4	3.5
	Neoadjuvant	No	109	94.8
		Yes	6	5.2
Previous surgery	TURBT	No	38	33
		Yes	77	67
	Cystectomy	No	94	81.7
		Yes	21	18.3
	Urinary diversion	No	69	60
		Yes	46	40
Previous bladder radiation therapy	CCRT	No	114	99
		Yes	1	1
Planned radiation treatment		Palliative	68	59.1
		Radical	26	22.6
		RT not received	21	18.3

**TURBT (Transurethral resection of bladder tumour), CCRT (Concurrent chemoradiotherapy), RT (Radiotherapy)*

Among the 115 patients that presented with bladder cancer, 81.7% (n=94) were planned for radiation therapy. More than half of the patients (59.1% n=68) were prescribed palliative treatment, 22.6% (n=26) were prescribed radical treatment and 18.3% (n=21) of the patients that presented to the department did not receive radiotherapy.

Palliative radiotherapy for various indications is shown in Table 3.4. The main indication for palliative radiotherapy in our study was “inoperable disease” (n=29/68 (42.7%)), followed by "bleeding from a tumour" (n=14/68 (20.6%)). One patient (1.5%) received palliative radiotherapy due to bulky and symptomatic lung metastasis.

Table 3.4 Indications for palliative radiotherapy in patients diagnosed with bladder cancer at CMJAH from 2010–2020.

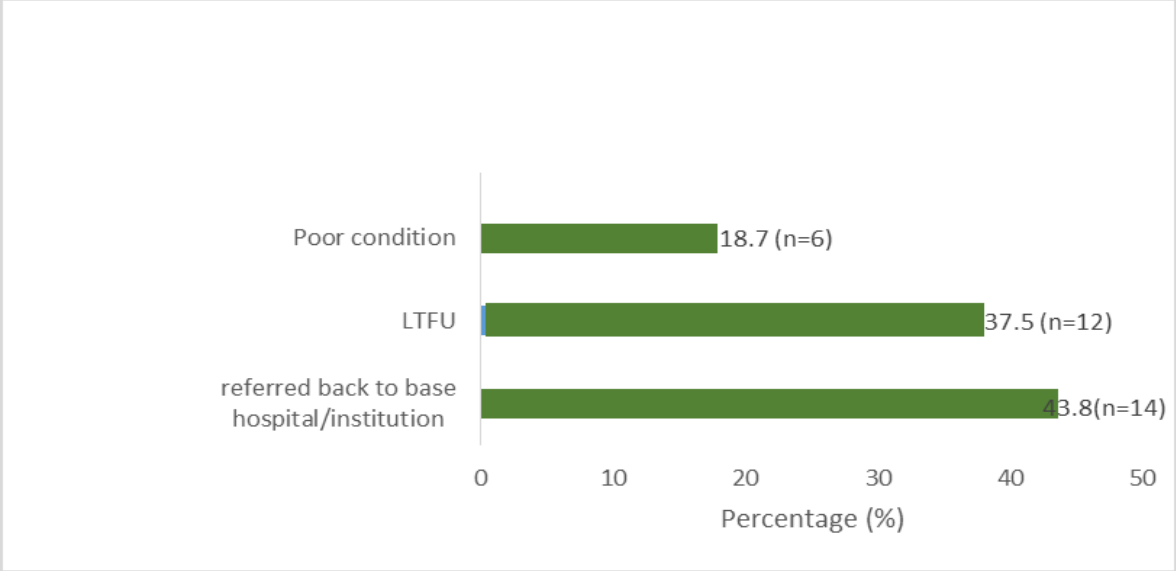
Group name	**Frequencies N=68**	**Percentages (%)**
Inoperable disease	29	42.7
Bleeding (Haematuria)	14	20.6
Intolerable pelvic pain	10	14.6
Spinal cord compression	6	8.8
Bone metastasis	5	7.4
Brain metastasis	3	4.4
Lung metastasis (bulky and symptomatic)	1	1.5

The dose fractionation and total dose of radiotherapy received by the patients are shown in Table 3.5. Amongst the 26 patients planned for radical treatment, 20 (21.3%) received a hypofractionated dose (40-55Gy), while 6 (6.4%) patients received a conventional dose. The total dose of radiotherapy administered for palliative intent was < 30 Gy. Two (2.1%) patients received concurrent cisplatin with radiation treatment.

Table 3.5 Details of radiation therapy/chemoradiation received by the patients diagnosed with bladder cancer at CMJAH from 2010–2020.

Group	**Variables**	**Categories**	**Frequencies n=94**	**Percentages (%)**
Fractionation (Dose)	• Palliative • Hypofractionation • Conventional	<30 Gy 40–55 Gy 60–66 Gy	68 20 6	72.3 21.3 6.4
Concurrent Chemotherapy	Cisplatin	Yes No	2 92	2.1 97.9
Completed treatment		Yes No	62 32	66.0 34.0

Among the 94 (81.7%) patients that were planned to receive radiotherapy, treatment was only completed by two-thirds (66%, n=62) of the patients, whereas the remaining 32 (34.0%) patients did not complete their treatment (Table 3.5). The reasons for not completing radiotherapy are shown in Figure 3.6. Among those who could not complete the planned course of radiotherapy, (43.8%, n=14/32) were referred to their base hospital for supportive care, 37.5% (n=12/32) were lost to follow-up (LTFU), and 18.7% (n=6/32) were in poor condition. Among the 68 patients that had palliative radiotherapy, 38.2% (n=26) and 23.6% (n=16) were referred for palliative care and chemotherapy, respectively 22 (32.4%) patients were lost to follow-up, 2 (2.9%) patients discontinued treatment, and two patients (2.9%) died. Similarly, 88.5% (n=23/26) were lost to follow-up among the cohort that had a radical dose of radiotherapy. In contrast, only 2 (7.7%) patients remained on follow-up surveillance post-treatment, whereas a patient (3.8%) was referred for palliative chemotherapy (Table 3.6)



** LFTU (Lost to follow-up)*

Figure 3.6: Reasons for non-completion of radiotherapy in patients diagnosed with bladder cancer at CMJAH from 2010–2020

Table 3.6 Planned radiation therapy and outcomes in patients diagnosed with bladder cancer at CMJAH from 2010–2020

Outcome categories				
	Palliative Treatment n=68 (59.1%)	**Radical treatment** n=26(22.6%)	**Radiotherapy not given** n=21(18.3%)	**Total** n=**115**(%)
Lost to follow-up	22(32.4)	23(88.5)	11(52.4)	56(48.7)
Referred for palliative care	26(38.2)	0	1(4.7)	27(23.5)
Referred for palliative chemotherapy	16(23.6)	1(3.8)	6(28.6)	23(20.0)
Referred for surgery	0	0	3(14.3)	3(2.7)
Discontinuation of treatment due to poor condition	2(2.9)	0	0	2(1.7)
Devised	2(2.9)	0	0	2(1.7)
Follow-up for surveillance	0	2 (7.7)	0	2(1.7)

While on treatment, some patients developed radiation-induced toxicities or adverse effects, as shown in Table 3.7. Less than one-third (n=26, 27.7%) of the patients reported fatigue, genitourinary, and gastrointestinal side effects experienced by 8.4% (n=8) and 25.6% (n=24), respectively. Some patients (n=20, 21.3%) also developed acute radiation-induced dermatitis, while 3.2% (n=3) developed leukopenia. Overall, nine (9.6%) patients did not complete treatment because of the adverse effects of radiotherapy, and subsequently, they were lost to follow-up. No mortality was reported while the patients were receiving radiation therapy.

Table 3.7 Radiation therapy adverse effects amongst patients diagnosed with bladder cancer at CMJAH from 2010–2020.

Group	Variables	Categories	Frequencies (n)	Percentage (%)
Adverse effects	Fatigue	Yes	26	27.7
	Haematological	leukopenia	3	3.2
	Genitourinary	G1-cystitis G2-cystitis G3-cystitis	2 5 1	2.1 5.3 1.1
	Gastrointestinal	G1 G2 G3	14 6 4	14.9 6.4 4.3
	Skin	G1 G2	8 12	8.5 12.8
Follow-up	Lost to follow up while on treatment	No Yes	85 9	90.4 9.6

** G1 (Grade 1), G2 (Grade 2), and G3 (Grade 3).*

Table 3.8 Association of gender and treatment received with the smoking status of patients presenting with bladder cancer at CMJAH from 2010–2020.

Variables	**Non-smoker**	**Smoker**	**P-value**
Gender, N=115 (%)			
Male	28 (46.7)	42 (76.4)	**0.001**
Female	32 (53.3)	13 (23.6)	
Treatment received, n=94 (%)			
Radical	11 (22.9)	10 (24.4)	0.870
Palliative	37 (77.1)	31 (75.6)	

Among patients with bladder cancer at this institution, compared with non-smokers, those that are smokers are significantly more likely to be males (76.4% vs 46.7%, p=0.001). No significant association exists between treatment received and smoking status (Table 3.8).

Table 3.9: Bivariate analysis of factors associated with TCC and SCC diagnosed subtypes.

Variable	**SCC**	**TCC**	**Bivariate analysis**	**P-value**
	N=31 (%)	**N=78 (%)**	**OR (95% CI)**	
Age in years, mean ± SD	55.0 ± 17.2	62.5 ± 13.8	1.03 (1.01–1.06)	**0.029**
Race				
African	24 (77.4)	33 (42.3)	1.00 (Reference)	
Coloured	2 (6.5)	10 (12.8)	3.64 (0.73–18.13)	0.115
Indian/Asian	0 (0.0)	6 (7.7)	Undefined	
White	5 (16.1)	29 (37.2)	4.22 (1.43–12.48)	**0.009**
Gender				
Female	17 (54.8)	25 (32.1)	1.00 (Reference)	**0.030**
Male	14 (45.2)	53 (67.9)	2.60 (1.10–6.04)	
Smoking status				
Non-smoker	17 (54.8)	39 (50.0)	1.00 (Reference)	
Smoker	14 (45.2)	39 (50.0)	1.20 (0.53–2.79)	0.649
The race for smokers				
African	9 (64.3)	10 (27.0)	1.00 (Reference)	
Coloured	2 14.3)	5 (13.5)	2.25 (0.35–14.61)	0.396
Indian/Asian	0 (0.0)	2 (5.4)	Undefined	
White	3 (21.4)	20 (54.1)	6.00 (1.32–27.19)	**0.022**
Stage				
1	17 (54.8)	41 (54.0)	1.00 (Reference)	
2	14 (45.2)	35 (46.0)	1.04 (0.45–2.39)	0.933

SD (Standard deviation), SCC (Squamous cell carcinoma), TCC (Transitional cell carcinoma), OR (Odds ratio), CI (Confidence interval)

We compared patients who presented with TCC (n=78) to those who presented with SCC (n=31). Patients who presented with TCC were more likely to be older (62.5 vs 55.0 years, p=0.029); for every one-year increase in age, the patients in this study were 3% more likely to present with TCC. Patients presenting with TCC are more likely to be white race (37.2% vs 16.1%) and male (67.9% vs 45.2%) than patients presenting with SCC (Table 3.9). White patients are four times more likely to present with TCC compared with black patients (OR:4.22, 95% CI: 1.43–12.48, p=0.009), and males are more than twice as likely as females to present with TCC (OR: 2.60, 95% CI:1.10–6.04, p=0.030). There was no significant association between smoking and TC; however, amongst smokers, white patients are six times more likely to present with TCC (OR: 6.00, 95% CI 1.32– 27.19, p=0.022) (Table 3.9).

CHAPTER FOUR

4.0 Discussion

This is a single-institution audit of patients with bladder cancer referred to the Radiation Oncology department at CMJAH for treatment. This local study is the first to consider an audit on patients diagnosed with bladder cancer in CMJAH. Our study showed that within 11 years, 115 patients presented with bladder cancer, and the highest number of patients were referred for treatment in 2010 (n=19, 16.5%).

In this study, the mean age was 60.7± 14.9 years; this agrees with the higher incidence of cancer occurring in older age groups and is like studies conducted in India and Iran, which found the mean ages to be 60.2 and 61.9 years, respectively [85,86]. More males (n=70 (60.9%)) presented with bladder cancer in our study, which supports a recent survey by Karimi A et al., indicating that the burden of bladder cancer is higher in males than in females [87]. The predominant histological subtype of bladder cancer in our study was TCC; however, the black population among our cohort still had the most significant proportion of SCC (24/31, 77.4%), which is consistent with the previous study from South Africa [13].

Smoking history is significant in almost half of the patients' cohort, which remains a strong risk factor for developing the TCC subtype of bladder cancer. In the bivariate analysis, white patients are four times more likely to present with TCC, which agrees with studies from HICs; this association is increased among smokers showing an effect modification of the association of white race with TCC in smokers. The most prevalent comorbidities among the patients' cohort are hypertension, chronic kidney disease, and diabetes mellitus.

Cigarette smokers have a higher incidence of bladder cancer [88,89]. The increased risk of bladder cancer seen in smokers from an aetiological perspective is complex. However, evidence from scientific studies has correlated several carcinogenic processes, mainly aromatic amines (2-naphthylamine, 4-aminobiphenyl and N-acetyltransferase-2 acetylators), resulting in many mutations [90]. In our study, 47.8%(55 of 115) of the patients were smokers. Studies have analysed p53 mutations in patients who smoke with bladder cancer, and of note, only an increase in quantity was seen; there was no difference in type, site, or histological variant, suggesting that smoking may directly increase the incidence related to mutations but not always necessarily the type, behaviour, or site in the carcinogenic process [91].

In our study in the bivariate analysis, comparing patients who presented with TCC to those who presented with SCC, those that were smokers trended towards more likely to present with TCC (50% vs 45,2%), but histologically overall no difference (statistically insignificant p=0.649), theoretically in keeping with the carcinogenic pattern variabilities. As mentioned, our study's predominant histological subtype of bladder cancer was TCC. In association with smoking, the relationship reflects the socio-demographic profile in keeping with westernised lifestyles in favour of TCC. Among patients with bladder cancer at this institution, smokers are significantly more likely to be male (76.4% vs 46.7%, p=0.001) and white. The white patients are four times more likely to present with TCC, which agrees with studies from HIC; this association is increased among smokers (OR: 6.00, 95% CI: 1.32–27.19, p=0.022) showing effect modification of the association of the white race with TCC in smokers.

Most of the patients presented at a late stage of the disease, the majority (n=61, 53.0%) presented at the MIBC stage, followed by the MUC stage (n=52, 45.0%), together comprising 98% of our patients, while only 2% at an early stage (NIMBC) hence a reflection of the palliative care treatment that most of the patients received. The treatment of late-stage bladder cancer is quite

challenging, especially in Africa, where resources are limited.

The ideal treatment approach in this study was not tailored towards standard guidelines. The treatment approach appears to have been performed on a case-by-case basis; primary tumour resection, in the form of TURBT, was offered to 67% (n=77) of the patients across the different stages of the disease. Adjuvant radiotherapy using a curative dose was offered to 22.6% (n=26) of the patients, post-TURBT or cystectomy. Only two patients received chemoradiation using platinum-based agents in the entire cohort. Chemoradiation is an essential component of curative intent tri-modality therapy for selected patients do not fit for cystectomy or refusing surgery [51]. Patients offered curative radiotherapy were in the MIBC category, except two that were in the NMIBC category, with a high risk for recurrence.

Pathological examination of all cystectomy tissues (21 patients) showed that the tumours, all MIBC categories, were characterised by two or more high-risk features of recurrence or metastasis. These features include incomplete tumour resection, positive surgical margins, positive pelvic lymph nodes, evidence of perineural invasion, and lymph vascular space invasion. Subsequently, adjuvant radiotherapy was offered post-cystectomy in these 21 patients.

More than half of the patients (n=68) received a palliative dose of radiotherapy, for specific clinical indications, even without any treatment for the primary tumour in the bladder, whereas others post TURBT or cystectomy. The most typical indications for palliative radiotherapy in our study were "inoperable disease" and 'bleeding" (gross haematuria). Several studies have shown the efficacy of radiotherapy in managing haematuria from advanced bladder cancer, a common presentation in patients with this clinical entity [79-81,92].

Overall, only two patients continued to follow-up post-treatment and were in the curative radiotherapy arm. A significant number (n=45, 47.9%) of patients did not continue to follow -up after the completion of radiotherapy, 22 of 68 patients in the palliative radiotherapy arm, and 23 of 26 patients in the curative radiotherapy arm. This loss of follow-up may be due to the systemic failures to ensure adequate post-treatment care and the presumed dismal clinical outcome that characterises bladder cancer patients with advanced disease at presentation, especially in a resource constraint setting. The stage at diagnosis is the single most important prognostic factor for invasive bladder cancer. At the same time, the histological grade is the most important prognostic factor for non-invasive bladder cancer, with patients with grade 3 cancer having poorer survival [85-87].

4.1 Study Limitations

Some limitations should be noted. The patients with bladder cancer seen at other departments at CMJAH, but not referred to the department of Radiation Oncology are not accounted for in the study and therefore we might have underestimated the prevalence of bladder cancer seen at CMJAH. This is a single-center study; therefore, the findings might not be generalisable. Our sample size was small compared to large studies from HICs. The data is retrospective, and there were missing data in the information collected. We did not have information on the date of death because the patients were not actively followed -up and could not comment on survival. Despite these, this is the first study on the epidemiology of bladder cancer in our centre and Gauteng province.

CHAPTER FIVE

5.0 CONCLUSION

The burden of bladder cancer is highest in HICs, but with increasing exposure to risk factors, a shift is gradually experienced in LMICs. Many of the risk factors can be controlled/prevented with reduced exposure to schistosomiasis, smoking cessation programmes, and exposure to occupational chemical exposures. Health awareness in our environment might help reduce the proportion of patients with advanced-stage disease. Improving the follow-up of patients with bladder cancer patients will improve the data available on bladder cancer and tailor treatment better in terms of disease outcome and treatment toxicities.

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7.0 APPENDIXES

APPENDIX 7.1 Ethics Clearance Certificate

IJNIVERSITYOI"TIII: WITWATERSRAND, JOHANNESRU RG

R14/49 Dr Trenton Luke Oliver

HUMAN RESEARCH ETHICS COMMITTEE (MEDICAL)

CLEARANCE CERTIFICATE NO. M211024

NAME: (Principal Investigator)	Dr Trenton Luke Oliver
DEPARTMENT:	School of Clinical Medicine Radiation Science Charlotte Maxeke Johannesburg Academic Hospital
PROJECT TITLE:	A Retrospective Review of Bladder Cancer at Charlotte Maxeke Johannesburg Academic Hospital-University of The Witwatersrand - (2010-2020)
DATE CONSIDERED:	29/10/2021
DECISION:	Approved unconditionally
CONDITIONS:	
SUPERVISOR:	Dr M. Hugo (Erasmus)
APPROVED BY:	Dr CB Penny, Chairperson, HREC (Medical)
DATE OF APPROVAL:	02/11/2021

This clearance certificate is valid for 5 years from date of approval. Extension may be applied for.

DECLARATION OF INVESTIGATORS

To be completed in duplicate and **ONE COPY** returned to the Research Office Secretary on the Third Floor, Faculty of Health Sciences, Phillip Tobias Building, 29 Princess of Wales Terrace, Parktown, 2193, University of the Witwatersrand. I/we fully understand the conditions under which I am/we are authorized to carry out the above-mentioned research and I/we undertake to ensure compliance with these conditions.Should any departure be contemplated, from the research protocol as approved, I/we undertake to resubmit the application to the Committee. I **agree to submit a yearly progress report**. The date for annual re-certification will be one year after the date of convened meeting where the study was initially reviewed. In this case, the study was initially reviewed in **October** and will therefore be due in the month of **October** each year. Unreported changes to the application may invalidate the clearance given by the HREC (Medical).

Principal Investigator Signature

02/11/2021
Date

PLEASE QUOTE THE PROTOCOL NUMBER IN ALL ENQUIRIES

APPENDIX 7.4 Turnitin Originality Report

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< 1% match (Porter, G.J.R.. "Patterns of metastatic breast carcinoma: influence of tumour histological grade", Clinical Radiology, 200412)
Porter, G.J.R.. "Patterns of metastatic breast carcinoma: influence of tumour histological grade", Clinical Radiology, 200412

A Retrospective Review of Bladder Cancer at Charlotte Maxeke Johannesburg Academic Hospital-University of The Witwatersrand - (2010–2020) Dr Trenton Oliver A Research Report Submitted to the Faculty of Health Sciences, University of Witwatersrand, Johannesburg, in fulfilment of the requirements for the Degree of Master of Medicine (M. Med) in the branch of Radiation Oncology Johannesburg 2023 i Declaration I, Trenton Luke Oliver, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in Radiation Oncology at the University of Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other university. This study has received ethical approval from the University of Witwatersrand. Human Research Ethics committee (Medical) with clearance certificate number: M211024. _____ (Signature of candidate) Signed at Johannesburg (University of Witwatersrand), South Africa, on the _____day of February 2023 ii Dedication This dissertation is dedicated to the following: ? God, Jeremiah 29:11 For I know the plans I have for you," declares the Lord, "plans to prosper you and not to harm you, plans to give you hope and the desires of your heart. ? My fantastic wife, Avadhna Singh, for her undying love and unwavering support. ? My wonderful son, Ashton Oliver, is the greatest joy in my life. ? My In-laws, Eddy and Ragani Singh, for your continuous support, prayers, and guidance. ? My uncle and mentor, Dr Gregory Landers, for being there every step of the way, instilling the value of knowledge and education. ? In loving memory of my late grandmother, Ma Maggie, who inspired me to walk this journey as she bravely faced Breast Cancer. ? In loving memory of my late father, Bradley Oliver, I will always continue to reach for the stars. iii Abstract Introduction Bladder cancer is among the most common urological cancers and the leading cause of cancer mortality worldwide. It is particularly prevalent in High-Income Counties (HICs), although its incidence is rising in Low-and-middle -income countries (LMICs). This review describes the profile, clinical presentation, and management of our institution's bladder cancer patients. Method A retrospective review of patients aged 18 years and above were diagnosed with bladder cancer and managed at the Radiation Oncology department of Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) from January 2010 to December 2020. Data were collected on demographics, risk factors, clinic-pathological features, and specific therapies received by these patients. A comparison was made between patients presenting with squamous cell carcinoma and translational cell carcinoma of the bladder. Results Among 115 patients, the median age ± standard deviation was 60.7 ± 14.9, and 60.9% were males with a male-to-female ratio of 1.6:1. Few

APPENDIX 7.5 Permission Approval from HOD

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
DEPARTMENT OF RADIATION ONCOLOGY

16 August 2021

To: Mrs. Gladys Bogoshi: CEO Charlotte Maxeke Johannesburg Academic Hospital
17 Jubilee Road
Parktown
Johannesburg
South Africa

Re: Approval of request to conduct research at Charlotte Maxeke Johannesburg Academic Hospital Department of Radiation Oncology

Dear Ms. Bogoshi

Dr Trenton Luke Oliver (Student number 2426410), a registrar in the Department of Radiation Oncology at Charlotte Maxeke Johannesburg Academic Hospital, intends to do a research project towards an MMed (RadOnc) degree at the University of the Witwatersrand. He would like to conduct his research in the Department of Radiation Oncology at Charlotte Maxeke Johannesburg Academic Hospital and will require access to patients' records.

The study is entitled "A Retrospective Review of Bladder Cancer at Charlotte Maxeke Johannesburg Academic Hospital-University of The Witwatersrand -(2010-2020)".

He requires access to our clinical files, record books and the data base. Clinical files will not be removed from the Department of Radiation Oncology. Patients' identities will be protected, and he will get ethical approval prior to starting the study.

I have approved for him to conduct the above-mentioned research in the department.

Best,

Dr Duvern Ramiah
Head of Department of Radiation Oncology and Head Division of Radiation Oncology
CMJAH and Wits University
DR@RONCOLOGY.COM
0114812144

APPENDIX 7.6 Permission Approval from CEO CMJAH

GAUTENG PROVINCE
HEALTH
REPUBLIC OF SOUTH AFRICA

CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL (CMJAH)
OFFICE OF THE SENIOR CLINICAL MANAGER

Enquiries: *Ms. TT Mahlangu*
Email: Thandi.Mahlangu4@gauteng.gov.za
Tel: *011 488 3365*
Ref: *1/7/2*
Date: 03 December 2021

GP_202110_014

Dear Dr Trenton Luke Oliver

RE: FINAL APPROVAL OF STUDY

TITLE: A RETROSPECTIVE REVIEW OF BLADDER CANCER AT CHARLOTTE MAXEKE JOHANNESBURG ACADEMIC HOSPITAL-UNIVERSITY OF THE WITWATERSRAND - (2010-2020)

Permission is granted for you to conduct the above-mentioned study as described in your request provided:

1. Charlotte Maxeke Johannesburg Academic Hospital will not in any way incur or inherit costs as a result of the said study.
2. Your study shall not disrupt services at the study sites.
3. Strict confidentiality shall always be observed.
4. Informed consent shall be solicited from patients participating in your study.

Please liaise with the HOD and Unit Manager or Sister in charge to agree on the dates and time that would suit all parties.

Kindly forward this office with the results of your study on completion of the research.

Supported/~~Not Supported~~

Dr J. Punwasi
Clinical Director

Approved/~~Not Approved~~

Ms. G Bogoshi
Chief Executive Officer: CMJAH

Title of Research Project

APPENDIX 7.7 NHRD Registration

A Retrospective Review of Bladder Cancer at Charlotte Maxeke Johannesburg Academic Hospital-University of The Witwatersrand - (2010-2020)

Status of Application

Pending (New Application)

Status of Project

On-Going

Research Staff assigned to Project/Proposal

Title	Name	Surname	Role	CV/Resume

Aim and Objectives

Study Objectives This study aims to determine the profile, clinical presentations, and management of patients with bladder cancer at the CMJAH Department of Radiation Oncology from 2010 to 2020 Specific objectives: 1. To describe the socio-demographic characteristics of patients diagnosed with bladder cancer at the CMJAH Department of Radiation Oncology from January 2010 to December 2020. 2. To describe the clinical presentation of patients diagnosed with bladder cancer at the CMJAH Department of Radiation Oncology from January 2010 to December 2020. 3. To describe the treatment received by patients with bladder cancer at the CMJAH Department of Radiation

Academic Study

Yes

Study Area(s)/Field(s)

Description

Study Design(s)

Description

Data Collection Method(s)

Method Category	Method Description
-	Medical Records Audit

Interview Request(s)

Position

Sample

Study design: Retrospective record review Study site: Department of Radiation Oncology urological cancer outpatient clinic. Inclusion Criteria: -Patients from the Department of Radiation Oncology urological cancer outpatient clinic diagnosed with bladder cancer during the period January 2010 to December 2020 -Age -18 years and older with a registered patient assessment consultation case record- -Both males and females will be enrolled -Patients from all South African race categories and other Sampling: Retrospective data to be abstracted from the CMJAH patient records for the radiation oncology during the period 1 January 2010 to 31 December 2020. All patients that

Data Analysis Tool(s)

Tool Description

Information / Data Request ?

No

Information / Data request details.

No Data Requested

Locations(s) where study will be conducted

Facility

Charlotte Maxeke Hospital

Anticipated Start Date

2021/11/01

Anticipated Completion Date

2022/04/30

Institution(s) which gave ethical approval

Institution
Wits - Human Research Ethics Committee(Medical), University of the Witwatersrand

Ethics Approval Number

"PENDING"-APPLICATION SUBMITTED, AND RECIEVED IN SEPTEMBER

Date of Ethical Approval

10/7/2021 12:00:00 AM

Date Ethical Approval Expires

10/14/2021 12:00:00 AM

If Clinical Trial, MCC Approved

No

National Clinical Trials Registry Number

No Clinical Trial

Funding source

Researcher

Budget (in ZAR)

0 - 1 000