TRANSITIONAL CELL CARCINOMA OF THE URINARY BLADDER

TITLE

TRANSITIONAL CELL CARCINOMA OF THE URINARY BLADDER AS SEEN AT KENYATTA NATIONAL HOSPITAL

A TEN YEAR RETROSPECTIVE STUDY ON CLINICOEPIDEMIOLOGICAL PATTERNS AND MANAGEMENT OF TRANSITIONAL CELL CARCINOMA OF THE URINARY BLADDER SEEN AT KENYATTA NATIONAL HOSPITAL OVER THE PERIOD, JANUARY, 1990 TO DECEMBER, 1999.

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DECLARATION

CANDIDATE

This thesis is my original work and has not been presented to any other university

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DEDICATION

This work is dedicated to my beloved wife, Judy Waihenya, my two sons, Peter Ndung'u and Delvin Kinyua and all those who were always a source of inspiration during the trying period of my postgraduate course. Their patience and understanding will always be dearly appreciated.

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ABBREVIATIONS

TURBT - Transurethral resection of bladder tumour

TUR - Trans urethral resection

KNH - Kenyatta National Hospital

TCC - Transitional cell carcinoma

KUB - Kidney, Ureter, Bladder

IVU - Intravenous Urography

CT - Computerised Tomography Scan

MRI - Magnetic Resonance Imaging

MVAC - Methotrexate, Vincristine, Andriamycin, Cyclophosphamide

INF α-2b- Interferon alpha 2b

SUMMARY

This is a retrospective descriptive study of transitional cell carcinoma of the urinary bladder. This study presents a ten year retrospective review of the clinico – epidemiological patterns and management of this disease at Kenyatta National Hospital for the year January 1990- December 1999.

Over this period 99,028 patients were admitted to all surgical wards in the hospital. Of these 224 patients were clinically diagnosed to have bladder cancer, of whom records were obtained for 127 patients. Of the later 52 patients fulfilled the study inclusion criteria and therefore were entered.

An average of 5.2 patients per year were seen. The male to female ratio was 3.7:1. The mean age was 57.19 years with a range of 57years (27 years to 84 years). The incidence increased with age with the majority of the patients being found in the age group 60-69 years with 30.8% of patients. The least affected age group was 20-29 years with 3.8% of patients.

The regional distribution (provincial) was; Central 46.2%, Eastern 30.8%, Nyanza 9.6%, Rift valley 5.8%, while Nairobi, North Eastern, Western and Coast provinces had 1.9% each.
In ethnic distribution, the Kikuyu tribe represented 51.9%, Kamba 17.3%, Meru 7.7%, and other tribes 17.3%.

The prevalence of risk factors include: Alcohol in 28.8%, cigarette smoking in 25%. There was no positive family history.

The types of occupations included; farming 65.4%, self employment 13.5%, salaried employment 9.6%. All of them were in the low income groups.

The commonest sign and symptoms were haematuria 98.1%, lower abdominal pains 71.1%, dysuria 32.7% and pelvic mass in 36.5%. They occurred in multiple combinations.

The main investigative procedures done in these patients included cystoscopy in 71.2%, ultrasound 46.2%, IVU 32.7% among others.

Histologically, transitional cell carcinoma accounted for 67% of all the urinary bladder tumours. In this group, various stages were, muscle invasive stage 42.3%, superficial 38.5%, metastatic 17.3% Ca in situ 1.9%. Majority of the patients 60% had advanced disease.

The treatment modalities were based on the stage of the disease and included surgery 48.1%, combination therapy in 23.1%, chemotherapy in 5.8% and radiotherapy in 3.8%.

Surgery was the mainstay of treatment, cystectomy was done in 26.9%, cystostomy and resection of tumour 26.9%. Other surgical methods carried out were transurethral resection (TUR), cystectomy and bladder substitution, channel transurethral resection, cystectomy and ileoconduit. Nine (9) patients (17.3%) were not given any treatment because either the disease was too advanced and died before any treatment was instituted or were lost to follow up.

Mortality and outcome of the disease was difficult to assess due to poor follow up, however 67.4 % of the patients were lost to follow-up, 25 % were alive two years after diagnosis and 7.6 % died within one year after of diagnosis.

The TCC in this study patterned late advanced disease. It is suggested that early diagnosis, early surgery and combination of other treatment modalities should improve the outcome. This can only be possible with further training of health personnel, the education of the public and availability of improved diagnostic as well as treatment facilities especially cystoscopes.

INTRODUCTION AND LITERATURE REVIEW

Urinary bladder cancer represents a significant proportion of urologist's caseload because of its ubiquity and, in the superficial disease long natural history. It is more common in men than women (2-3: 1). In men it is the fourth most common cancer after prostate, lung and colorectal tumours.[1]

Carcinoma arising from the bladder may be of three cell types; transitional, squamous, and adenocarcinoma. Bladder cancer is the most common cancer of the urinary tract and TCC accounts for more than 90% of bladder tumours in western countries.[2] In areas where Schistosoma haematobium is endemic the proportions are different. In a study by Ndaguatha P. L. W in KNH, 1990 in a review of urinary bladder cancers 53.3% were transitional cell, 17.3% were anaplastic, and 13.3% were squamous cell carcinomas and others were 16.1%.[3]

Although this tumour features the entire range of aggressiveness from benign papilloma to anaplastic carcinoma it tends to present as two distinguished entities: low-grade superficial and high-grade invasive cancers.

EPIDEMIOLOGY

Incidence rates

Bladder cancer is 2.7 times more common among men than women. The incidences are higher in whites than blacks, ratio 2:1,[4,5] however the increased risk in whites appears to be limited to patients with non-invasive tumours[6] The observation suggests that some superficial tumours in blacks may go undetected.

Age

Can occur at any age even in children but it is generally a disease of the elderly with the median age of diagnosis being approximately 67-70 years old.

AETIOLOGY

The aetiology of urinary bladder cancer remains unknown, but there are several predisposing factors, and increasing understanding of the genetics of the bladder cancer has provided insights into the basis of the clinical behaviour of the tumours.[5]

a) Chemicals

The first suspicion of a chemical cause of bladder tumours was raised by Rehn in 1894 when he recorded a series of tumours in workers in aniline dye factories.[7] Aniline dyes were introduced in the mid-1800s to colour fabrics. Other such chemicals (e.g. 1-naphthylamine, xenylanine, and benzidine) have since been identified.[8]

b) Cigarette smoking

There is a strong correlation between incidence of bladder cancer and cigarette smoking, with a four fold higher incidence of the disease in smokers.[9, 10, 11] The risk correlates with the number of cigarettes smoked, the duration of smoking, and the degree of inhalation of the smoke. This risk has been observed in both sexes. Ex-cigarette smokers have a reduced incidence of bladder cancer compared with smokers.[12] Other forms of tobacco are associated with only a slight higher risk for bladder cancer.[9, 13] An estimated one third of bladder cancer patients may be related to cigarette smoking.[14]

The specific chemical carcinogen has not been identified but nitrosamines as well as 2-naphthylamine are known to be present. Increased urinary tryptophan metabolites also have been demonstrated in cigarette smokers.[15]

c) Radiotherapy and chemotherapy

A significantly higher incidence of bladder cancer has been seen in-patients previously treated with pelvic irradiation or the chemotherapeutic drug cyclophosphamide.[5]

Chronic Cystitis / schistosomiasis

Chronic cystitis due to infections and bladder calculi have be associated with increased incidence of urinary bladder cancer.

In African patients schistosomiasis appears to be related to a high incidence of not only squamous cell carcinoma but also other histological types. In a recent study by Groeneveld et al, schistosomiasis of the bladder was found in 85% of patients with squamous cell carcinomas, 50% of those with undifferentiated tumours and adenocarcinoma, in 17% of those with mixed tumours or sarcomas and in 10% of the patients with transitional cell carcinoma.[16]

d) Bowel interposition.

The resurgence in the use of bowel in bladder augumentation, and orthotopic replacement of the bladder has led to an increase of reports of patients with bladder cancer arising in the interposed bowel. All patients with interposed bowel in the urogenital system need life long follow-up because of the potentially greater risk of neoplasia caused by increased formation of nitrites and nitroso compounds in the bladder hence the need for regular check cystoscopies.

CARCINOGENS USUALLY ASSOCIATED WITH TRANSITIONAL CELL CARCINOMA OF THE BLADDER.

- 4 amino biphenyl
- Benzidine
- Coal tar pitches
- Auramine
- Magenta
- O-toluidine, O-dionisidine.
- Some mineral oils
- *B*-naphthylamine
- *a*-naphthylamine (?only if associated with B-naphthylamine)

OCCUPATION IN WHICH EXPOSURE TO CARCINOGENS HAS BEEN REPORTED

- Manufacture, handling and maintenance of machinery used with the carcinogens.
- Coal gas manufacture (particularly in retort shop).
- Rubber manufacture and destruction.
- Cable manufacture.
- Manufacture of dyes.
- Manufacture of organic chemicals.
- Rodent extermination.
- Sewage work.
- Manufacture of fire fighters.
- Laboratory work.

OCCUPATIONS WITH POSSIBLE INCREASED INCIDENCE BUT IN WHICH NO CAUSAL RELATIONSHIP ESTABLISHED

- Leather work
- Security printing
- Hair dressing
- Medicine and nursing
- Textile printing and dyeing
- Aluminium production
- Drivers and transport workers.

MOLECULAR GENETICS

It is thought that tumour development and progression is driven by accumulation of multiple genetic alteration by the normal cell. Many phenotypic changes in tumour cell events that are secondary to primary genetic alterations and some of these may have been caused by changes in the environment.

The genetics of the bladder carcinogenesis is thought to be multifactorial, involving the activation of proto-oncogenes through mutation of gene amplification. Several proto-oncogenes are over-expressed in bladder cancer, these include, HRAS (ERBBI), EGFR (ERBB2), MYC and SRC.Their precise role is yet to be defined.

Several tumour suppressor genes e.g. (PTP53, RBI, DCC, DCKN2) have also been described, but the best studied is p53. The p53 is the proposed suppressor gene on chromosome 17p and has prevalence in patients with carcinoma *in situ* or invasive bladder cancer. Losses of heterozygosity have been identified in chromosome 9 in 57% of patients with bladder cancer, on chromosome 17p in 32%, on chromosome 8p in 23%, and on chromosome 13q in 15%. It is still unclear, however, how these alterations and deletions may be integrated in the development of bladder cancer.[17]

PATHOLOGY

Transitional cell carcinoma differ from normal urothelium by having an increased number of epithelial cell layers with papillary folding of the mucosa, loss of cell polarity, abnormal cell maturation from the basal to superficial layers, giant cells, nuclear crowding, increased nuclear–cytoplasmic ratio, prominent nucleoli clumping of chromatin and increased number of mitoses.[18] The most important criteria are prominent nucleoli, clumping of chromatin, increased cell layers, and loss of cell polarity.[19] Some of these same changes can occur in inflammatory, reactive or regenerative conditions.[20]

Transitional cell carcinoma manifest a variety of patterns of tumour growth including papillary, sessile, infiltrating, nodular, mixed, and flat intraepithelial growth. Because the bladder does not have a distinct basement membrane, it is difficult to demonstrate invasion of the lamina propria. Furthermore invagination of the normal urothelium into the submucosa as occurs with Von Brunn's nests sometimes is difficult to distinguish from cancer invasion.[20] Moreover cancer invasion into the smooth muscle cells of the tunica

muscularis mucosa sometimes can be mistaken for invasion into the bladder dextrusor muscle.[21]

Transitional cell epithelium has a great metaplastic potential; therefore, transitional cell carcinoma may contain spindle cells,[21] Squamous cells, or adenocarcinomatous elements. These elements are present in about one third of bladder cancers and some tumours may exhibit several different elements. Transitional carcinomas arise most commonly in the trigone/bladder base area and on the lateral bladder walls, however, they may arise anywhere within the bladder. About 70% of bladder tumours are papillary, 10% nodular, and 20% are mixed. Other bladder tumours comprise squamous cell carcinoma, adnocarcinoma and undifferentiated carcinomas.

Pathologically, bladder cancer appears to progress from carcinoma *in situ* to a fixed mass (T4b) with a worsening of prognosis in successive stage of the disease. Clinically, however, it is helpful to assess other factors (e .g number and size of the initial tumours and their biological activity after initial therapy) when considering prognosis and treatment, rather than relying on grade and stage alone. Further more carcinoma *in situ* may represent a parallel rather than a continuous form of the disease.

Of patients presenting with a solitary small (2cm diameter) tumour of low grade and stage, and who have no recurrence at the first check cystoscopy (usually at 3 months) only 25% will have a recurrence in the first 12 months, and only an additional 15% in the second year.[1]

Patients with adverse factors (e.g. multiple tumours at presentation, recurrence at first cytoscopy) have upto 80% chance of recurrence in the first 12months.
Patients presenting with apparently superficial tumours but of poor stage and grade (pTIG3) may comprise a significant at–risk group.

SCREENING

Ideally, screening for cancer should be undertaken in patients;

- Who have a high risk of developing the disease.
- In whom the disease can be reliably detected early.
- In whom early intervention will alter the predicted course of the disease, effecting a 'cure'.

Long-term screening for bladder cancer in individuals known to be at risk occupationally (e.g. those exposed to aniline dyes in rubber industry) has been under-taken by means of urine cytology for over 40 years but without substantial benefits. Recently studies in the U.K and U.S.A using urinary dip-stick testing for haematuria have demonstrated a 5% detection rate for bladder tumours in men over 50 years of age. These were single institution studies, but the detection rate is similar in other haematuria clinics and appears to be consistently about 5% in male of this age group.[22, 23]

These results should be considered against a background of up to 20% of males with positive dipstick haematuria 95% of who do not have bladder cancer. This seems to be vindication for a randomized prospective study of screening that would be sufficiently large to determine whether it is a justifiable expenditure of resources.[24] In U.K, however, overall death rate from bladder cancer is less than 1% and economic and social considerations must be added to the medical considerations.

Similar studies in women have not been undertaken, microscopic haematuria is reported to occur up to 30% of all women, and the yield of tumours, as incidences studies show, would be significantly lower than in men. Neither the sensitivity nor specificity would therefore seem to justify screening studies in women.

HISTOLOGICAL GRADING

'G0': Papilloma i.e. no evidence of anaplasia.

G1: High degree of differentiation.

G2: Medium degree of differentiation.

G3: Low degree of differentiation or undifferentiated.

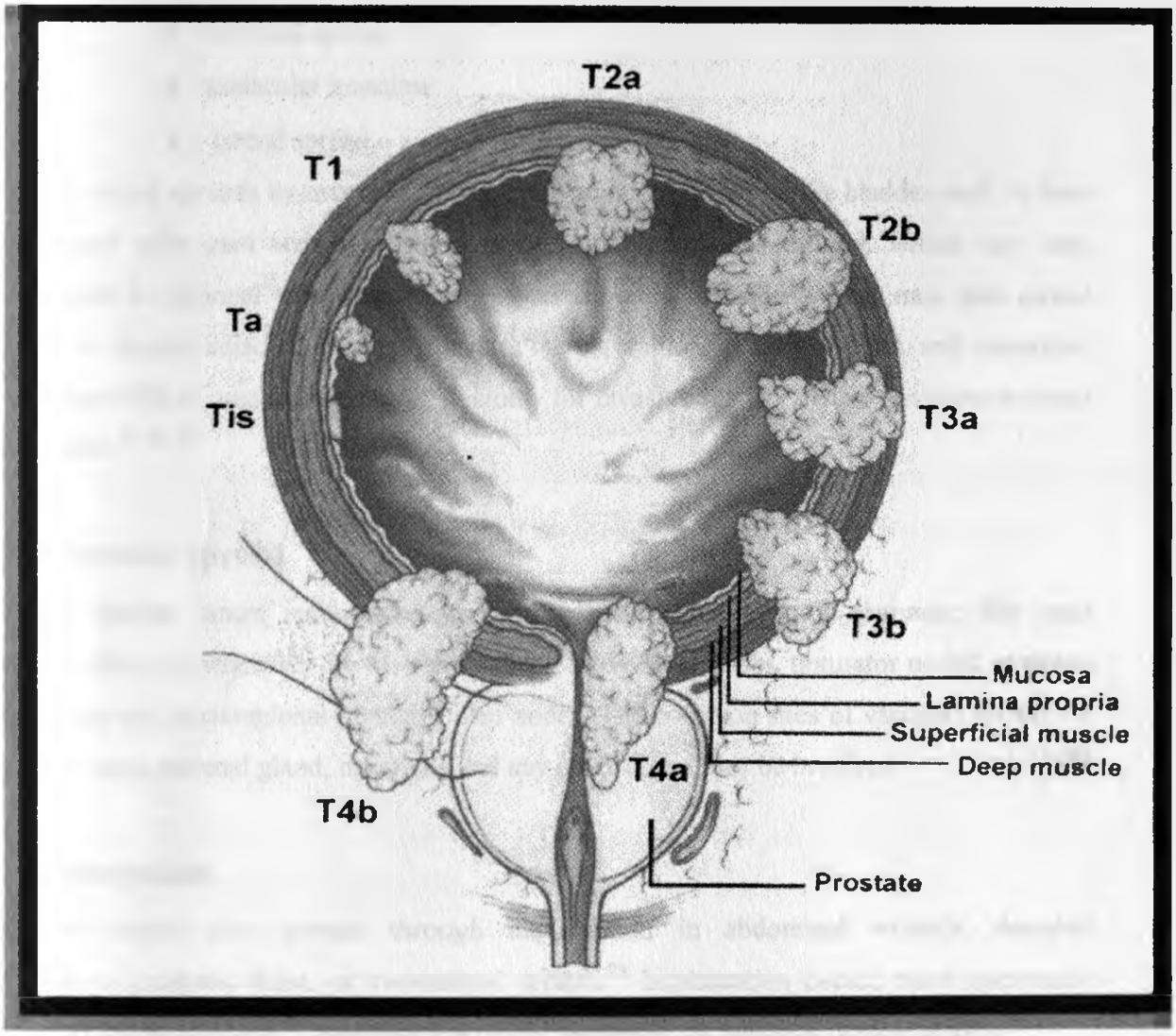
GX: Grade cannot be assessed.

STAGING

Formulated jointly by the International Union Against Cancer (UICC) and the American Joint Committee on cancer staging (AJC) (Hermareck and Sobin)

Findings	UICC stage
No tumour in the specimen	To
Carcinoma *in situ*	T is
Noninvasive papillary tumour	Ta
Submucosal invasion	T1
Superficial muscle invasion	T2
Deep muscle invasion	T3A
Invasion of perivesical fat	T3B
Invasion of contiguous organs	T4
Regional lymph node metastases	(N 1 –3)
Distance metastases	M 1

Clinical staging of TCC



PATTERN OF SPREAD

a) Direct Extension

Three mechanisms;

- en block spread.
- tentacular invasion.
- lateral spread.

Bladder cancer spreads by invading through the lamina propria into the bladder wall. In here the tumour cells gain access to blood vessels and lymphatics through which they may metastasize to regional lymph nodes and/or distant sites. Bladder cancer may also spread locally to invade adjacent organs, prostate, uterus, vagina, ureters, rectum and intestines. More than 40% of men undergoing cystectomy for invasive bladder cancer have involvement of prostate.[25, 26, 27]

b) Metastatic spread

Urinary bladder cancer metastasizes through vascular and lymphatic channels. The most common sites of metastases are the pelvic nodes, perivesical nodes, obturator nodes, common iliac nodes and juxtaregional common iliac nodes. The common sites of vascular spread are the liver, lung, adrenal gland, intestines and any other organ may be involved.

c) Implantation

Bladder cancer also spreads through implantation in abdominal wounds, denuded urothelium, prostatic fossa, or traumatised urethra.[28] Implantation occurs more commonly with high grade tumours.[29] Implantation can be prevented by radiation preoperatively.[30]

NATURAL HISTORY OF THE DISEASE

Approximately 70% of bladder cancers are low grade, superficial tumours. The majority of patients develop tumour recurrences following endoscopic resection.[31, 32, 33] Usually, tumours that are well differentiated and superficial at the time of initial diagnosis remain so throughout the life of the patient. Of these about 25% recur with high grade tumours.[34] Most recurrences are probably new

tumuors arising from other areas of dysplastic urothelium, but a significant proportion may be true recurrences resulting from inadequate treatment from tumour cell implantation.[35]

About 10-15% of patients with superficial tumours subsequently develop invasive or metastatic cancer.[31, 36]

Most patients (80-90%) with invasive bladder cancer already have invasive disease at the time of diagnosis.[37] About 50% of muscle invasive bladder cancer already have occult distant metastases. This limits the efficiency of local or regional forms of therapy. Most of the patients develop overt clinical evidence of distant metastases within one year.[38]

Nearly all patients with metastatic bladder cancer succumb within 2 years,[38] however about 5% of patients with established metastatic disease have "freak" cancers that run a more indolent clinical cause, lasting 5 years or more.[39]

Between 10 and 35% of patients with limited regional lymph node metastases survive 5 years or more without evidence of metastases following radical cystectomy and pelvic lymphadenectomy.[40] Many patients with incurable bladder cancer either may *not* develop severe local symptoms from the primary tumour or may have these symptoms controlled with conservative measures, such as transurethral resection or radiation therapy. It is conceivable that many such patients could retain the bladders even though they may ultimately die from metastatic bladder cancer.

MANAGEMENT

DIAGNOSIS

Signs and symptoms

The most common presenting symptom of bladder cancer is painless haematuria, which occurs in about 85% of patients.[41] The symptom complex of bladder irritability with urinary frequency, urgency, and dysuria is the second most common form of presentation and usually is associated with diffuse carcinoma *in situ* or invasive bladder cancer.

Other signs and symptoms include flank pain from ureteral obstruction, lower extremity oedema, and a pelvic mass. Occasionally, patients present with symptoms of advanced disease such as weight loss and abdominal or bone pain.

INVESTIGATIONS

URINARY CYTOLOGY

The normal bladder epithelial turnover (cells lost and replaced) under normal physiological conditions is low, but under abnormal states, e.g. infection or malignant transformation, detachment and desquamation occur more readily.[42] Malignant processes may reduce the ability of the cell to adhere to the extracellular matrix and to adjacent cell.[43] Investigators have shown that decreased cell adhesion result in increased sloughing of cell into the bladder lumen. Ultrastructural examination of the bladder TCC cells revealed a reduction in the number of desmosomes and ultrastructural defects in the adherent region malignant cell that may explain increased shedding.[44]

Currently, urine cytology remains the standard non-invasive in vitro test to detect primary and recurrent bladder cancer. The specimen can be obtained from a freshly voided urine sample or by a bladder wash with physiological solution. The analysis is most successful when the sample is immediately transported to the cytology laboratory for preparation. Improper handling of the freshly collected specimen, e.g. any delay in transfer for examination, may result in destruction or degradation of the cells. Similar alteration occur when the urine voided by the patient is not fresh, or

in the presence of infection. Urine cytology is based on the evaluation of morphological variables of the exfoliated cells. Therefore, it is most successful in diagnosing high grade bladder tumour and carcinoma in situ (CIS), as these lesions have a greater tendency to exfoliate, increasing the amount of cytological materials examined, and have more overt cancer- associated structural changes. Cytology is least successful in diagnosing low grade well differentiated tumours, as the cell in those lesions resemble normal urothelial cells. The diagnostic accuracy of urine cytology may vary among medical centres, but in the hands of professional cytologists the reported detected rate is 50-90%, depending mainly on histological grade, tumour stage and the presence of CIS.[45, 46, 47, 48] Urine cytology is simple, convenient and inexpensive; it remains the gold standard noninvasive *in vitro* method for detecting bladder cancer in voided urine.

BLOOD GROUP ANTIGENS: ABO AND LEWIS X

These antigens are found on the surface of normal cells: their presence represents normal differentiation and their absence is related to abnormal differentiation and malignant transformation. Using ABO immunostaining and determination of the DNA content, Orihula *et al.*[49] were able to predict the recurrence and progression of TCC after intravesical BCG instillation. Patients with type O blood commonly have high-grade cancer and are at higher risk of developing invasive disease.[50] This result on the efficacy of this marker were not duplicated by large scale studies, and thus this method should not be used routinely to monitor patients with TCC.[51]

Lewis related antigens are composed of four subclasses of molecules, but only Lewis X has shown an association with bladder cancer. This antigen is normally absent in adult urothelial cells, but this is expressed in >90% of TCC regardless of the tumour grade and stage, or the secretor status of the individual. Analysis of urine samples[52] has shown the advantage of Lewis X immunostaining over conventional cytology (with a sensitivity of 80% versus 61% respectively). Combining cytology with Lewis X immunostaining increased the sensitivity to 93%.

As false-positive results occurred in well-differentiated tumours further studies are needed to determine the ability of this marker to serve as a routine diagnostic method of TCC.

BLADDER TUMOUR ANTIGEN

The bladder tumour antigen (BTA) test (Bard Urological Covington, USA) is the first method to allow the physician to make a bed side analysis of voided urine : 3-5 drops of freshly voided urine are added to a special test – tube (like a pregnancy –test kit) and within 3 minutes a positive test appears as a colour change in the designated window of the tube. This test is based on the detection of basement membrane associated molecules, putatively released into the urine during malignant development and implantation. By mixing a urine sample containing these molecules with latex particles coated with human IgG, targeted against the BTA, an agglutination reaction occur that can be visualised by colorimetric changes within minutes. Recent studies report 96% specificity but low sensitivity (40-65%) for the BTA test.[53, 54] The test is relatively simple, inexpensive, rapid and easy to perform, and was recently approved by the USA Food and Drug Administration (FDA) for clinical use as an adjunct to cystoscopy. The result obtained immediately before cystoscopy inform the physician about the potential presence of tumour. The major limitations of the BTA test are false-positive results (4-34%) from other conditions, e.g. urinary stone disease, indwelling catheter and chronic irritation [53,55] and unpublished data). Quantitative assays with better sensitivity are currently under clinical evaluation, i.e. the BTA stat and the BTA trak tests. Both should be superior to BTA.[56]

NUCLEAR MATRIX PROTEIN 22 (NMP22)

This is a 'mail away' assay where the voided urine is sent to a central laboratory capable of performing the test, as the technology needed for the test is still too complex for a clinic setting. Nuclear proteins are special polypeptides that enter the cell nucleus after their synthesis in the cytoplasm. Nuclear Matrix Protein 22 is a protein that participates in the organisation of the DNA molecule, its organisation is of structural and functional importance. The DNA configuration determines the ability of some loci (genes) to participate in replication and transcription. Thus nuclear proteins are part of the regulatory mechanism in the cell cycle. Soloway et al.[57] studied the level of urinary NMP22 in 90 patients 5 days after tumuor removal and during follow-up cystoscopies 3 and 6 months later. The level of this marker was significantly higher in patients with tumour recurrence and in those who develop invasive disease; 86% of the patients who had an NMP22 level of <10 U/ml were

disease-free at the follow-up cystoscopies. A similar trial conducted by Carpinto et al. has shown a sensitivity of 70% and a specificity of 86%.[58] The NMP22 test is a quantitative assay and like PSA in prostate cancer, a critical threshold value for the diagnosis of malignancy has yet to be established. The major advantage of this marker is its better performance, with fewer false-positive results in patients with benign urological conditions. The main disadvantages of the NMP22 test are the need for a point-of-service laboratory and the high cost. The test has been approved by the FDA only for use in patients with bladder cancer as an additional measure to cystoscopy.

Other tumour markers include AN42 and BB639, Epithelial membrane antigen, 486P3/12 antigen, M344 and A211 antigens, Tissue polypeptide antigen (TPA), Cadherin E a glycoprotein, Psoriasin a calcium binding protein, integrins. Growth factors include transforming growth factor ß1 (TGF ß1), fibrin degradation products (FDP), microsatellite and toleromase.

FLOW CYTOMETRY.

Flow cytometry measures the DNA content of cells, therefore, it can quantitate the aneuploid cell population and proliferative activity in a tumour. Bladder washout activities are required for diagnostic purposes.

QUANTITATIVE FLOURESCENT IMAGE ANALYSIS

Is a cytologic technique that analyses smears on a microscopic slide to quantitatively measure DNA content in the cell.[59] It combines quantitative biochemical analysis and a more subjective visual evaluation of individual cell.

ULTRASONOGRAPHY AND INTRAVENOUS UROGRAPHY

There is controversy about whether ultrasonography of the urogenital tract or IVU should be used in the further investigation of patients presenting with haematuria. Ultrasonography is simpler and safer to use as a first line imaging modality. In expert hands, it can detect surprisingly small lesions of the bladder, however, ureteric tumours that are not causing

obstruction will not be detected. Upper tract renal pelvic lesions may also missed. IVU is useful in patients in whom a cause for haematuria has not been found, and reduces exposure to x-rays in this patient population.

CYSTOSCOPY AND BIOPSY

All patients require a cystoscopy, and the pathologist must confirm the diagnosis, not by urological opinion. Whether biopsy distant from an established bladder lesion that appears normal is beneficial or not is controversial and overall yield appear to be small. All abnormal areas of bladder mucosa should be biopsied. The findings of carcinoma *in situ* or even severe dysplasia may adversely affect the prognosis. Tumours are resected primarily to establish pathological type, grade and stage.

CT AND MRI

The presence of muscle invasion in a biopsy specimen means that other imaging modalities will be required usually CT of the pelvis and abdomen. MRI is also used, but there had been no study of the relative benefit of CT and MRI, and the type of imaging employed is usually dictated by access to scanners. CT scanning provides information about pelvic and para-aortic lymphadenopathy and adrenal metastases.[60]

TREATMENT

Patients presenting with favourable prognostic factors (solitary well differentiated, early stage small tumours) are often treated adequately by transurethral resection (TUR) alone. The addition of one dose of an intravesical chemotherapeutic agent has been shown to reduce the recurrence rate, but only further long term follow-up will demonstrate conclusively whether the progression rate in these patients (which may be less than 2 %) has also been reduced.[61] Patients presenting with multiple tumours, or who have recurrence at first cystoscopy, have a significantly higher rate of subsequent recurrence, and therefore a potential for progression. There is a controversy about the type of intravesical agent that should be used .In recent studies, all agents tested appear to reduce the recurrence rate, it remains to be determined in

suitably size multicentric studies whether reductions in recurrence rate are associated with reductions in progression rate. Some studies appear to show a definite benefit of BCG immunotherapy over intravesical chemotherapy with adriamycin,[62] however, studies from Europe show no difference between BCG and mitomycin C in the reduction of recurrence rate.[63]

Intravesical instillation of INFα-2b has also been used in reducing recurrence rate in superficial transitional cell carcinoma.

Carcinoma in situ

Upto 50% of patients with carcinoma *in situ* may progress rapidly to invasive disease. Both aggressive intravesical treatment and early definitive therapy with cystectomy without initial intravesical chemotherapy have been advocated.[25] BCG is effective initially in control of carcinoma *in situ*, but it is important that the long term durability of the response is appreciated. In one study of patients who received only one course of BCG, only 28% remained tumuor free for upto 6 years; the addition of a further six week course of BCG, increased this tumour free group to 41%. In both groups 20% had recurrences 2-5 years after initial therapy, and a further 20 % had recurrences after more than five years.[64]

Clinically the difficulty is whether failure to respond to one course of intravesical BCG should lead to early definitive cystectomy, or whether it is worthy trying at least two courses. It should be remembered that this might allow the cancer several months to progress to invasive and even metastatic disease. Progression despite use of two BCG courses has been reported in phase II studies, but definitive therapy is by no means curative. The relative risks must be discussed carefully with the patient.

The role of newer intravesical therapy e.g. (megadose vitamins, α - interferon) are still undergoing demonstration in randomised prospective studies. Giannakopoulos et al 1998 showed in study a significant advantage for adjuvant intravesical interferon alpha 2b (INFα-2b) treatment over TUR alone for 36 months of follow up. They followed 89 patients with primary or recurrent TCC stage Ta / T1 grade II.[65]

T1G3 Lesions

The T1G3 pathological type of lesion is relatively common in large randomised studies of superficial bladder cancer (14%). These tumours tend to undergo early invasion, and it has been proposed that the diagnosis, once established, should lead to early definitive therapy with cystectomy or radiotherapy. It has also been suggested, however, that early aggressive intravesical chemotherapy with an aggressive transurethral resection (TUR), possibly assisted by a course of systemic chemotherapy may achieve disease ablation with preservation of the bladder.[61] No adequate randomised prospective studies are available to compare these approaches, though single centre studies have shown benefits for intravesical chemotherapy, definitive local radiotherapy and early cystectomy.

Invasive bladder cancer

Prognosis of patients presenting with muscle invasive tumours is 50% survival at 2 years and 30% at 3 years. Survival declines gradually thereafter, though late recurrences are well recognized.

Surgery

Word wide, most patients presenting with muscle invasive bladder cancer are treated by radical cystectomy with formation of a conduit drainage system or orthotopic bladder substitution. Surgeons should offer bladder substitution (involving formation of a new bladder from detubularized small or large bowel) to patients with a favourable tumour grade, small tumour size, tumours located distant from the trigone and base of the bladder, and negative lymph nodes. These are the same patients whom the radiation oncologist would expect to respond to radiotherapy, with an excellent chance of tumour cure and preservation of a functioning bladder.

The role of partial cystectomy with neo-adjuvant or adjuvant chemotherapy is being considered in patients who wound also be suitable for bladder substitution or definitive radiotherapy.

Radiotherapy

Done in patients unfit for surgery or unwilling to accept consequences of surgery. These patients tend to be older and more frail, and possibly have a more advanced disease than a comparable cystectomy group.

Chemotherapy

Transitional cell carcinoma is sensitive to cisplatin. The use of chemotherapy, as either neo-adjuvant or adjuvant treatment along–side definitive therapy, has often resulted in 5-year survival rates of 60-70 % in small series. Neoadjuvant chemotherapy has shown no definitive improvement in survival compared with modern series of cystectomy alone and a low rate (20 %) of disease free bladder preservation.[66, 67]

Chemotherapy combination using M-VAC (methotrexate, vinblastine, adriamycin and cisplatin) and CMV (cisplatin, methotrexate, and vinblastine) appear to show extremely good response rates that are durable and accompanied by disease free interval.

FOLLOW-UP CYSTOSCOPY AND UROGRAPHY

The traditional follow-up program recommended for patients with superficial bladder cancer includes serial cystoscopies every 3 months for 2 years, then every 6 months for 2 years and then yearly. Either annual or biennial excretory urograms have been recommended. Other investigators believe that patients should be followed with cytology examination and cystoscopy less frequently.[68]

Approximately 2-5% of patients with bladder cancer subsequently develop upper urinary tract tumours.[69] Not all these tumours produce haematuria or positive cytological findings.[70] The mean interval to development of upper urinary tract tumours is 70 months.[71] Follow-up cystoscopy can be readily performed as an office procedure by use of flexible or rigid cystoscopies.[72]

RATIONALE

Transitional cell carcinoma of the urinary bladder consists the vast majority of all malignancies of this organ. It is an important cause of morbidity and mortality. Previous local studies have been done on carcinoma of the bladder in general and are old. No study has looked into transitional cell carcinoma and its various aspects. This study reviews this condition as seen and managed in Kenyatta National Hospital. It also recommends ways and means of standardization of the management protocol of this condition.

STUDY OBJECTIVES

BROAD OBJECTIVE.

To evaluate the epidemiology, presentation, management, and outcome of *Transitional Cell Carcinoma* of the urinary bladder as seen in Kenyatta National Hospital over a five year period (1990-1990).

SPECIFIC OBJECTIVES

1. To highlight the epidemiological pattern of presentation of patients with *transitional cell carcinoma* of the urinary bladder with regards to age, sex, ethnic origin and histopathological classification.

2. To identify the magnitude of *transitional cell carcinoma* of the urinary bladder over the study period.

3. To identify common presenting clinical features, investigations and management carried out and to recommend future approaches in dealing with *transitional cell carcinoma* of the urinary bladder.

MATERIALS AND METHODS

The study was carried out at Kenyatta National Hospital. This was a retrospective study covering a period of ten (10) years from January 1990 to December 1999.

Only those patients with histologically confirmed diagnosis of transitional cell carcinoma of the urinary bladder treated at KNH during the study period were included. The sample size was determined by the study period.

The relevant records of the patients with TCC were reviewed after approval of the study proposal by the KNH Research Committee.

The records scrutinized included in-patients files from the central medical records, data from cancer registry, histopathology and radiotherapy departments.

Information was obtained regarding age, sex, residence, occupation, relevant past medical history, clinical features, investigations and treatment modalities.

Data was collected using tally sheets and analysed using statistical computer programme SPSS.

RESULTS

During the period of 1990-1999, 92,028 patients were admitted to all surgical units of Kenyatta National Hospital. Of these 224 patients were clinically diagnosed to have urinary bladder cancer. Of these 127 (57%) files were traceable from which 79 had histologically proven bladder cancer. Fifty-two (52) patients of these were transitional cell carcinoma and were enrolled into the study.

The patients were from all parts of the country some seen primarily, others as referrals from Provincial, District and Mission Hospitals. The number of patients recorded from 1990 to 1999 varied from one (1) to ten (10) each year with an average of 5 patients per anum.

Table 1

The Yearly Distribution of Transitional Cell Carcinoma patients.

Year	No. of patients	Percentage
1990	3	5.8
1991	2	3.8
1992	4	7.7
1993	1	1.9
1994	1	1.9
1995	7	13.5
1996	10	19.2
1997	9	17.3
1998	10	19.2
1999	5	9.6
Total	52	100.0

Mean : 5.2 patients Range: 1-10 patients

The highest number of patients were seen and recorded in the period 1996-1998 constituting 69.2% of all the patients. The 1990-1994 figures were low and accounted for 21.1 %.

Figure 1

Yearly distribution of transitional cell carcinoma

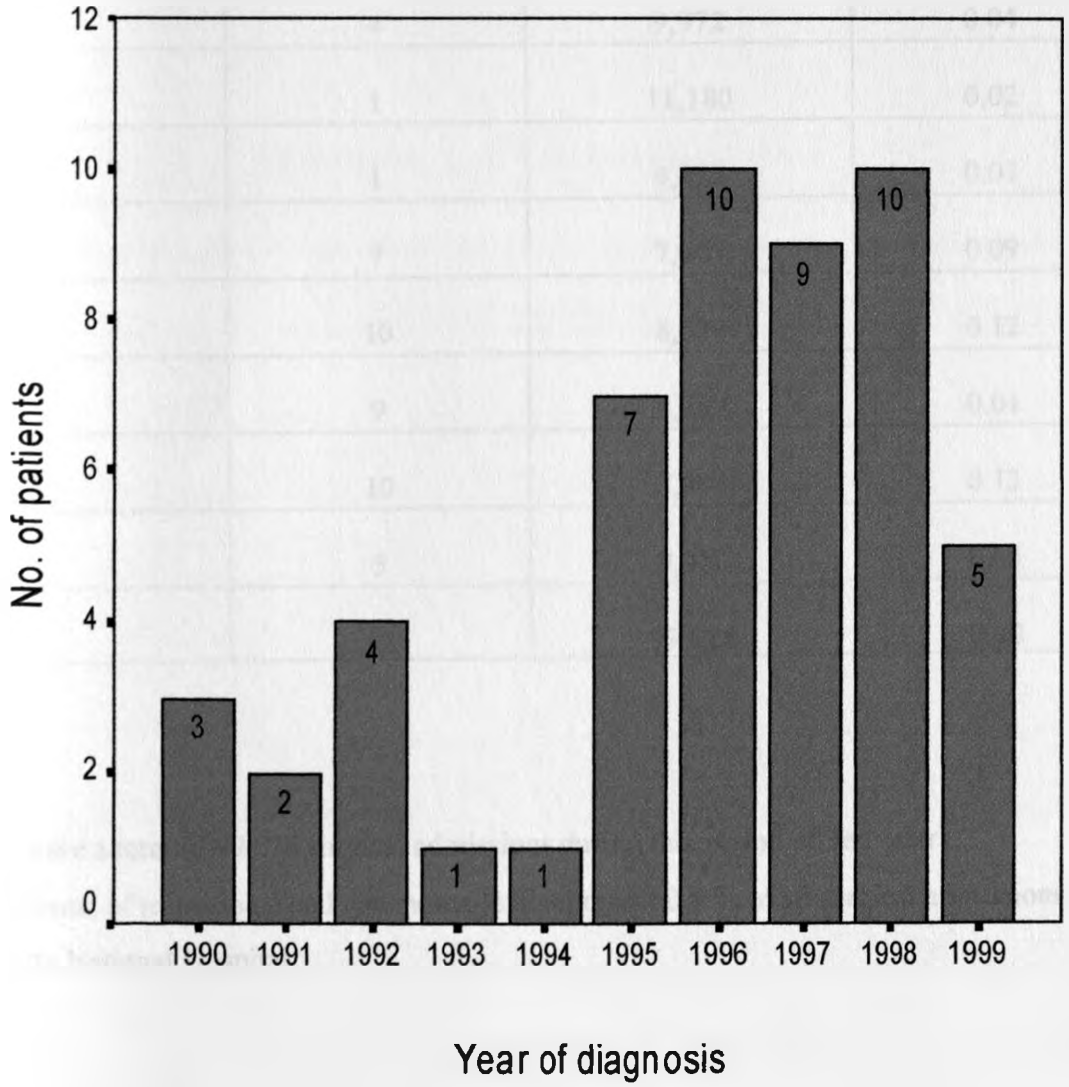


Table 2

Admissions of Transitional Cell Carcinoma patients compared to all Surgical admissions

Year	Number of TCC Patients	Number of surgical admissions	TCC as a percentage of Total
1990	3	12,022	0.03
1991	2	10,764	0.02
1992	4	9,972	0.04
1993	1	11,180	0.02
1994	1	9,222	0.01
1995	7	7,667	0.09
1996	10	8,621	0.12
1997	9	8,787	0.01
1998	10	7,801	0.13
1999	5	9,360	0.05
Total	52	99,028	0.60

There were a total of 99,028 surgical admissions during this period of ten years.

The patients of transitional cell carcinoma only represent 0.6 % of all surgical admissions in Kenyatta National Hospital.

AGE DISTRIBUTION

The 52 patients of transitional cell carcinomas were analysed according to the age at presentation. Incidence increased with age. The youngest recorded age was 27 years and the oldest was 84 years. The mean age at presentation was 57.19 years and the median age was 60 years. The range was 57 years.

The peak age group was 60-69 years accounting for 16 (30.8%) of the recorded patients. The other age groups had the following distribution, 20-29 years 2 patients (3.8%), 30-39 years 4 patients (7.7%), 40-49 years 11 patients (21.2%), 50-59 years 8 patients (15.4%), 70-79 years 7 patients (13.5 %), 80 years and above had 4 patients(7.7%)-(table3 and figure2).

Table 3

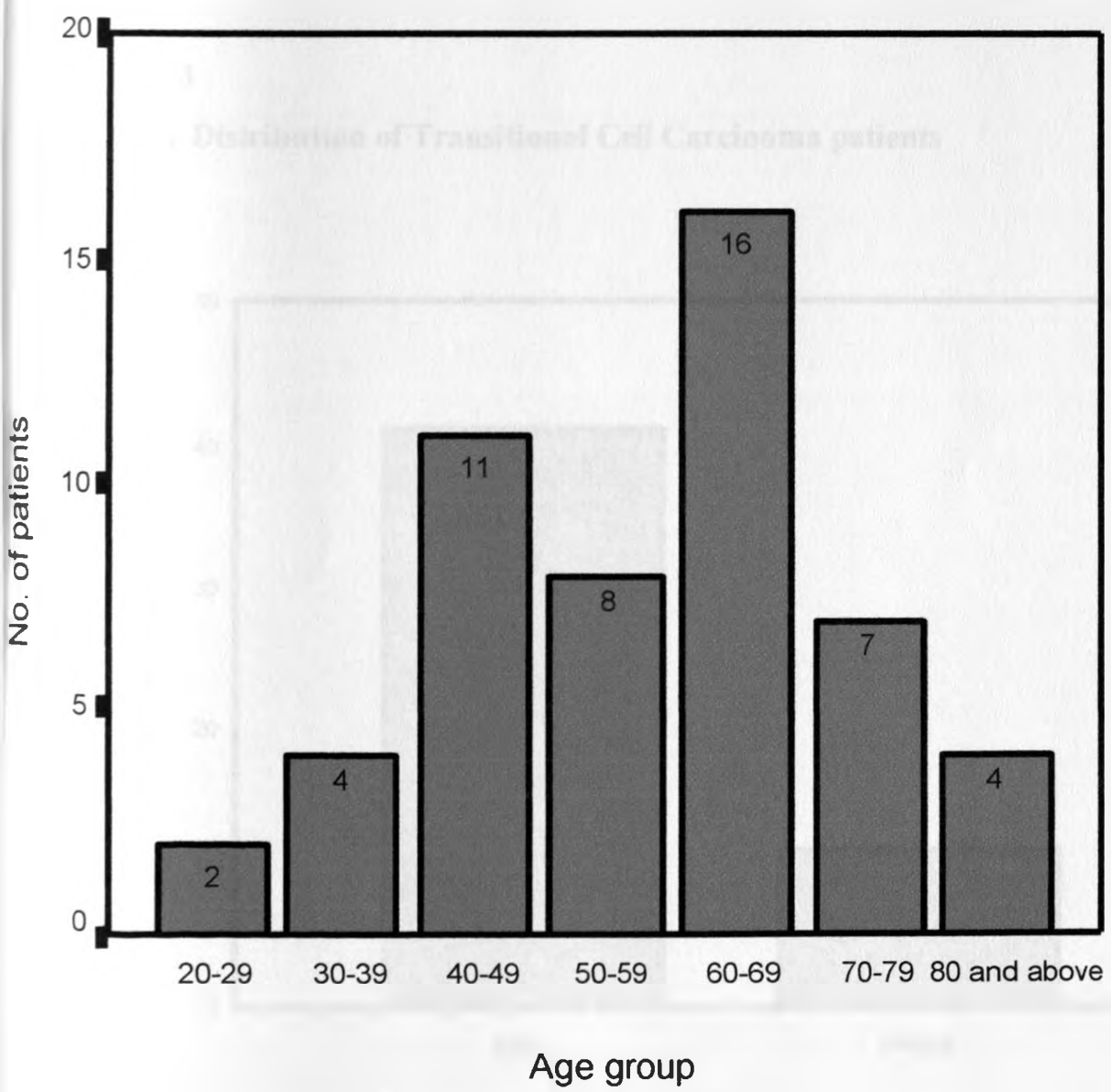
Age distribution of Transitional Cell Carcinoma patients

Age group	Number of patients	Percentage
20-29	2	3.8
30-39	4	7.7
40-49	11	21.2
50-59	8	15.4
60-69	16	30.8
70-79	7	13.5
80 and Above	4	7.7
Total	52	100.0

Mean age: 57.19 years. Median age : 60 years Range : 27 - 84 years.

Figure 2

Distribution of Transitional Cell Carcinoma patients by age



SEX DISTRIBUTION OF TRANSITIONAL CELL CARCINOMA

The 52 patients were analysed according to gender presentation, 78.8%were males and 21.2% were females. The Male : Female ratio was 3.7:1. There were 3.7 times the number of males compared to females with the disease.

Figure 3

Gender Distribution of Transitional Cell Carcinoma patients

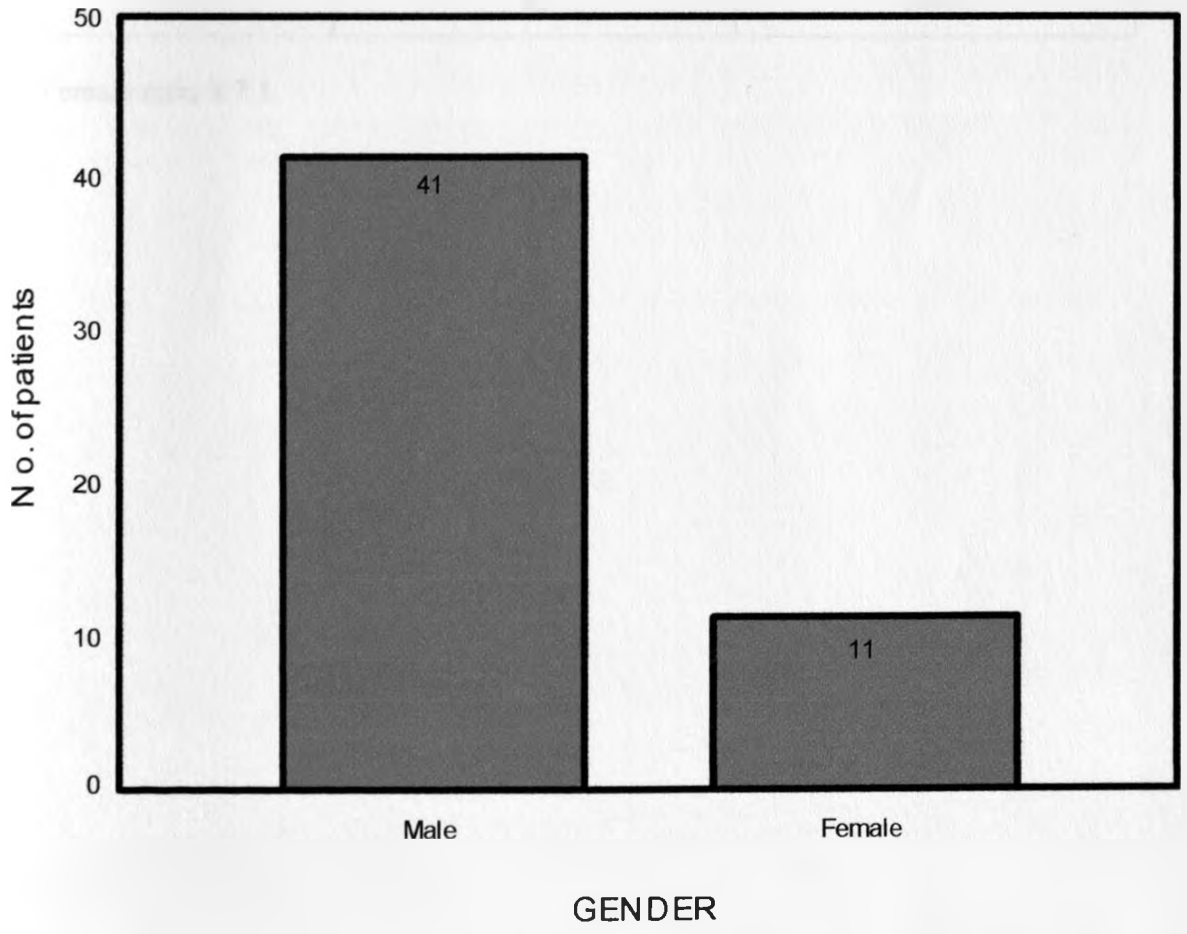


Table 4
Distribution of Transitional cell carcinoma patients by sex

Sex	No. of patients	Percent
Male	41	78.8
Female	11	21.2
Total	52	100.0

Male: Female ratio 3.7:1

REGIONAL AND ETHNIC DISTRIBUTION

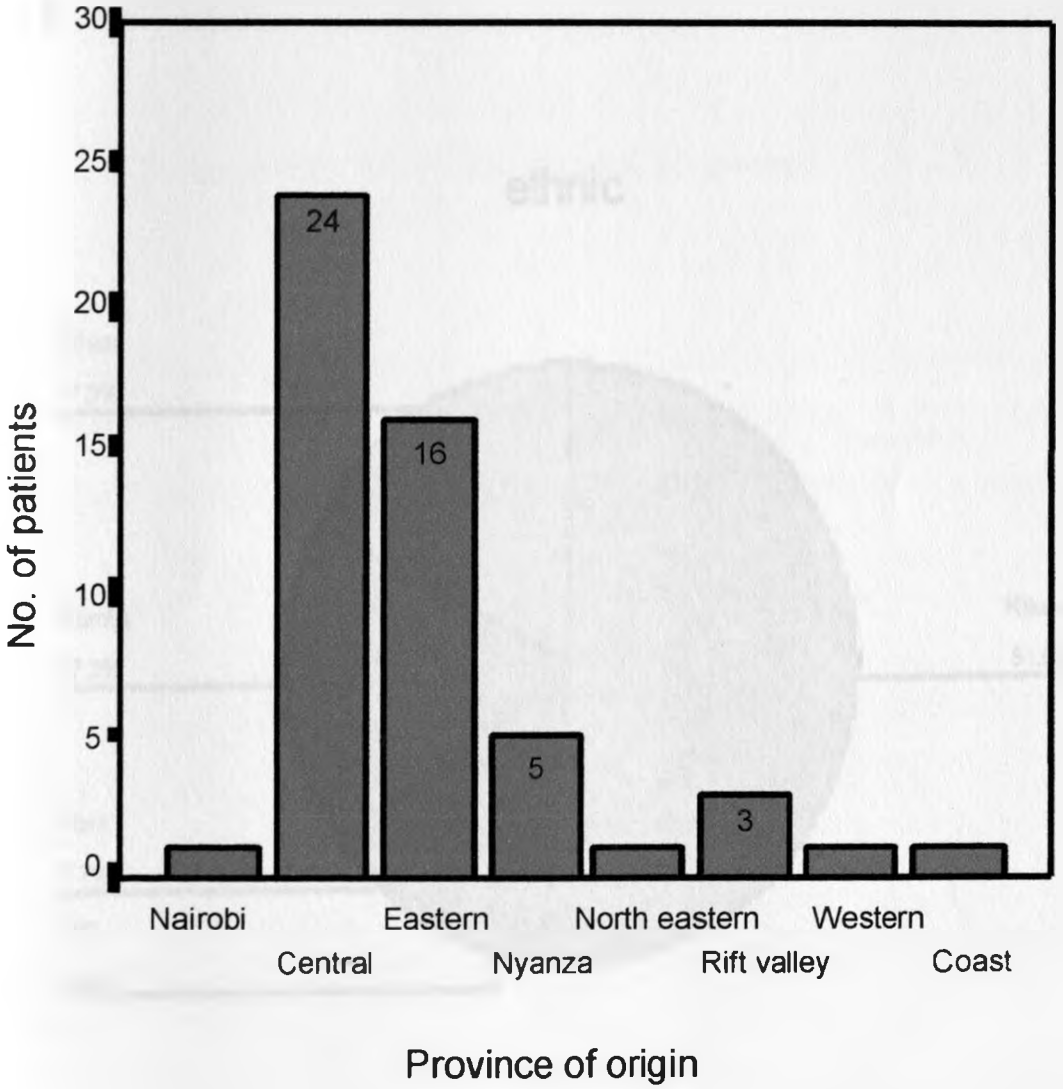
The provincial distribution was central province 24 patients (46.2%), Eastern province 16 patients (30.8%), Nyanza 5 patients (9.6%), Rift Valley 3 patients (5.8%), Nairobi, North Eastern, Western and Coast had 1 patient each (1.9%).

Table 5
Regional (Provincial) patterns

Province	No. of patients	Percent
Nairobi	1	1.9
Central	24	46.2
Eastern	16	30.8
Nyanza	5	9.6
North Eastern	1	1.9
Rift Valley	3	5.8
Western	1	1.9
Coast	1	1.9
Total	**52**	**100.0**

Figure 4

Regional (Provincial) patterns of patients

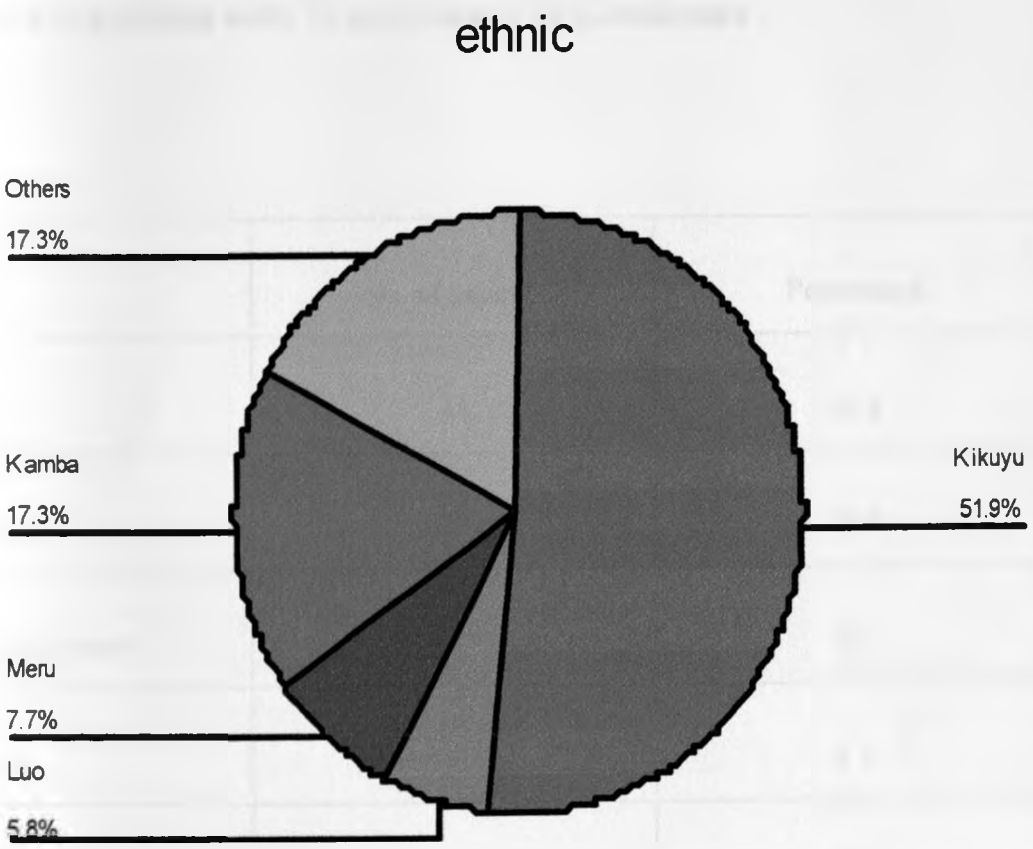


The ethnic distribution was as follows:

Kikuyu: 27 (51.9%), Kamba 9 (17.3%), Meru 4 (7.7%),

Luo 3(5.8%) and other tribes 9 (17.3%) (See fig.5)

Figure 5



OCCUPATION

Most of the patients were farmers constituting of 34 patients (65.4%). No information in most of the files what kind of farming they were engaged in. Others were as follows; self employed 7 patients (13.5%), salaried employment 5 patients (9.6%), unemployed 1 patient (1.9%). Information about 5 patients (9.6%) was missing from the files.

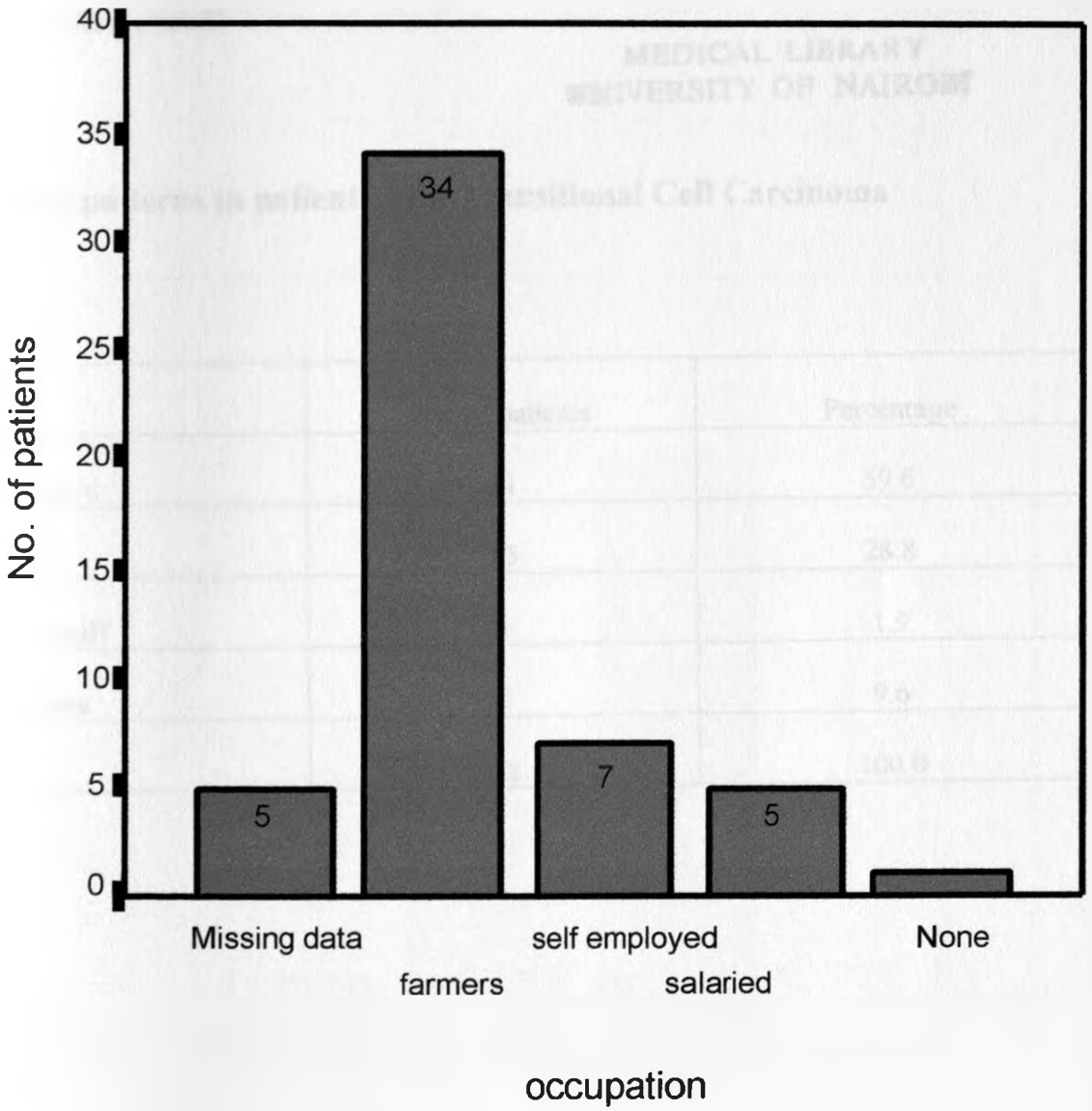
Table 6

Occupation of patients with Transitional Cell Carcinoma

Occupation	No. of patients	Percentage
Farmers	34	65.4
Self employed	7	13.5
Salaried employment	5	9.6
Unemployed	1	1.9
Missing data	5	9.6
Total	52	100.0

Figure 6

Distribution of Transitional Cell Carcinoma patients by occupation



RELEVANT FAMILY SOCIAL HISTORY

Smoking and alcohol consumption are known risk factors of TCC and were analysed in the 52 patients.

It was found that majority of the patients did not smoke (59.6%), smokers were 28.8%. One patient was using tobacco snuff.

Table 7

Smoking patterns in patients with Transitional Cell Carcinoma

	No. of patients	Percentage
Non-smokers	31	59.6
Smokers	15	28.8
Tobacco snuff	1	1.9
Missing data	5	9.6
Total	52	100.0

Figure 7

Distribution of smoking among Transitional Cell Carcinoma patients

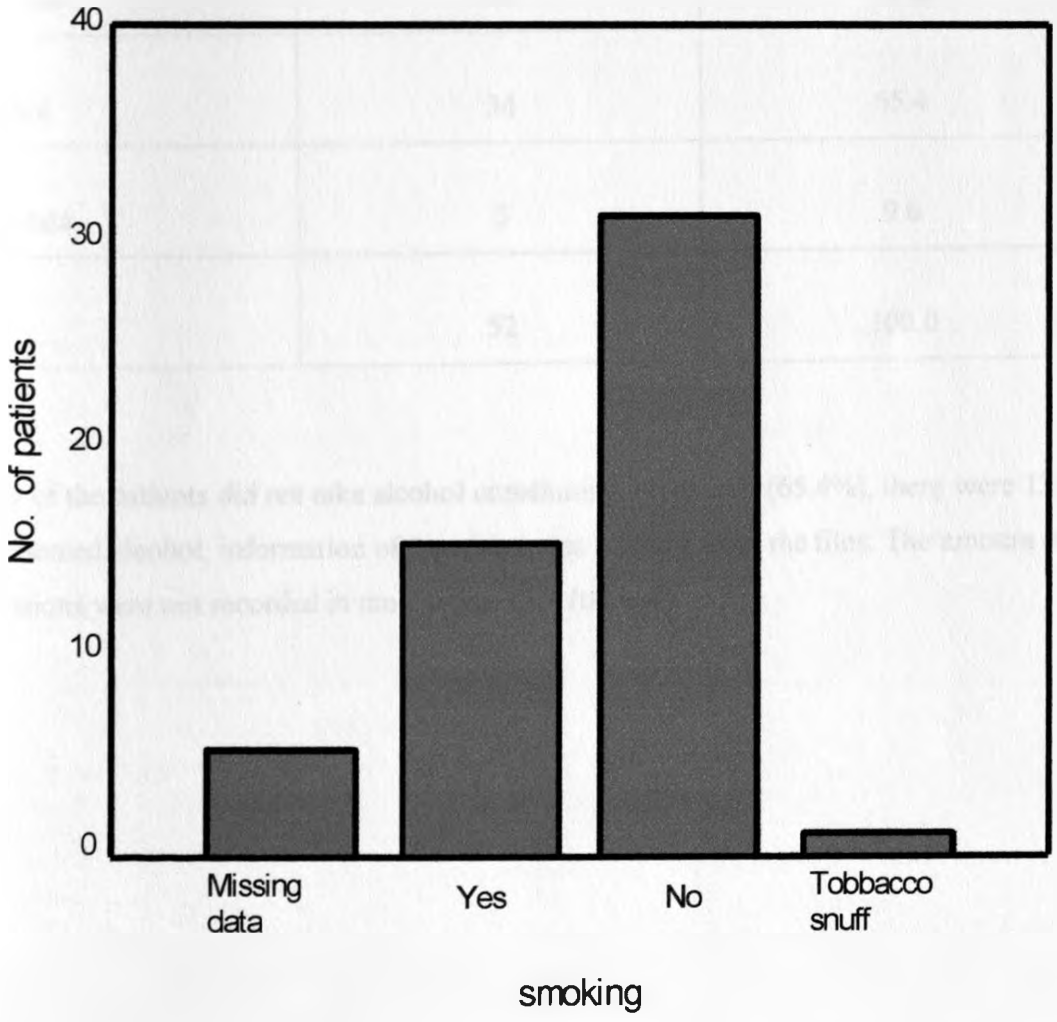


Table 8

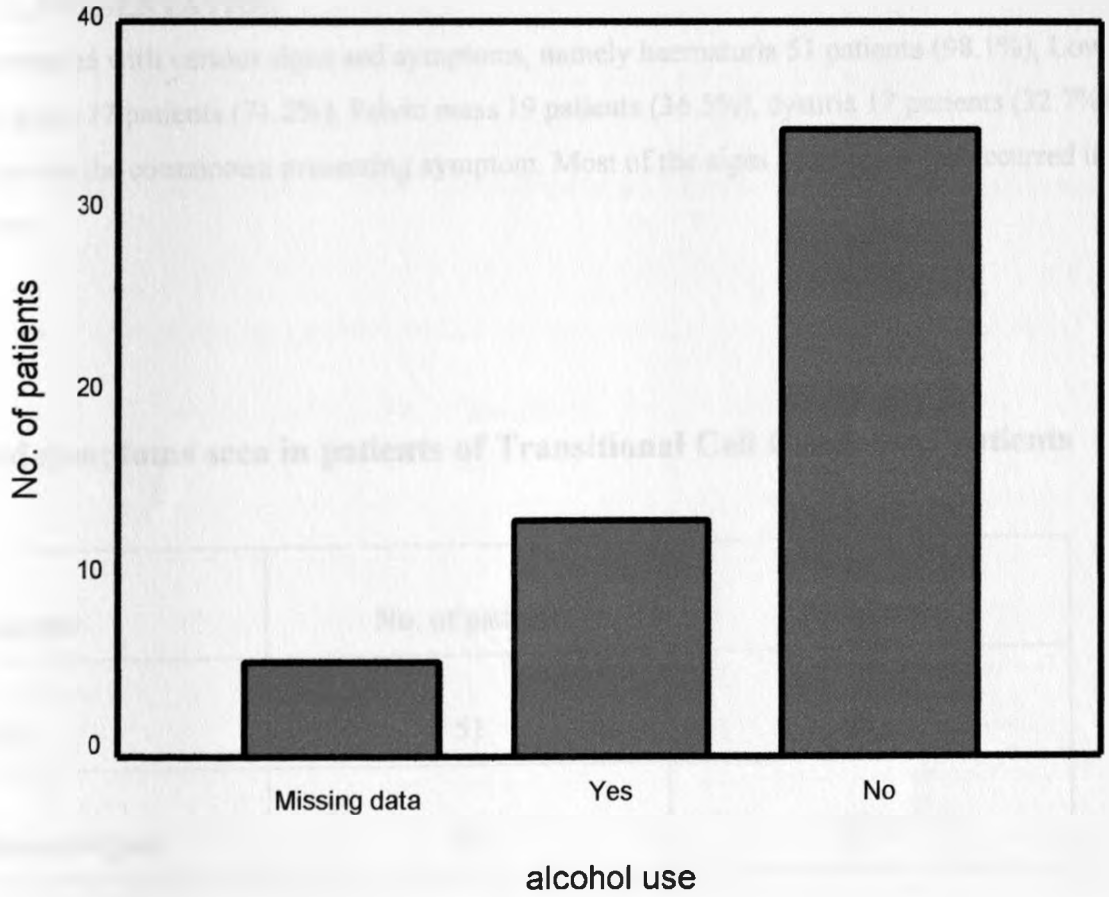
Alcohol consumption among patients with Transitional Cell Carcinoma

	No. of patients	Percentage
Alcohol use	13	25.0
No alcohol	34	65.4
Missing data	5	9.6
Total	52	100.0

Majority of the patients did not take alcohol constituting 34patients (65.4%), there were 13 patients who consumed alcohol, information of 5 patients was missing from the files. The amount consumed and durations were not recorded in most of the files (table 8).

Figure 8

Alcohol use in patients with transitional cell carcinoma of the urinary bladder



RELEVANT PAST MEDICAL AND SURGICAL HISTORY

Relevant past medical and surgical history is used in this context to mean any condition that could have caused or related to the presence of Transitional Cell of the urinary bladder in the patients. These conditions were cystitis, surgery (bladder augmentation), chemotherapy, lower abdominal and irradiation. In this study none of the patients had any such history.

CLINICAL PRESENTATION

Patients presented with various signs and symptoms, namely haematuria 51 patients (98.1%), Low abdominal pains 37 patients (71.2%), Pelvic mass 19 patients (36.5%), dysuria 17 patients (32.7%). Haematuria was the commonest presenting symptom. Most of the signs and symptoms occurred in combination.

Table 9

Signs and symptoms seen in patients of Transitional Cell Carcinoma patients

Sign/Symptoms	No. of patients	Percentage
Haematuria	51	98.1
Lower abdominal pain	37	71.2
Pelvic mass	19	36.5
Dysuria	17	32.7

INVESTIGATIVE PROCEDURES

Various investigations were carried out on the patients. Most of them, 37 (71.2%) had cystoscopy and biopsy done. Others were urine cytology 7 patients (13.5%), open cystostomy and biopsy done in other centers before patients were referred to Kenyatta National Hospital.

Radiological investigation included Ultrasonography in 24 patients (46.2%), CT scan in 3 patients(5.8%), IVU in 17 patients (32.7%), plain abdominal X-ray in 1 patient (1.9%). None of the patient had MRI as an investigative procedure.

Table 10

Breakdown of investigations done for patients of Transitional Cell Carcinoma

Investigation	No. of patients	Percentage
Cystoscopy	37	71.2
Ultrasonography	24	46.2
IVU	17	32.7
Urine cytology	7	13.5
Open cystostomy	5	9.6
CT-Scan	3	5.8
KUB	1	1.9
MRI	0	0

HISTOLOGICAL DIAGNOSIS

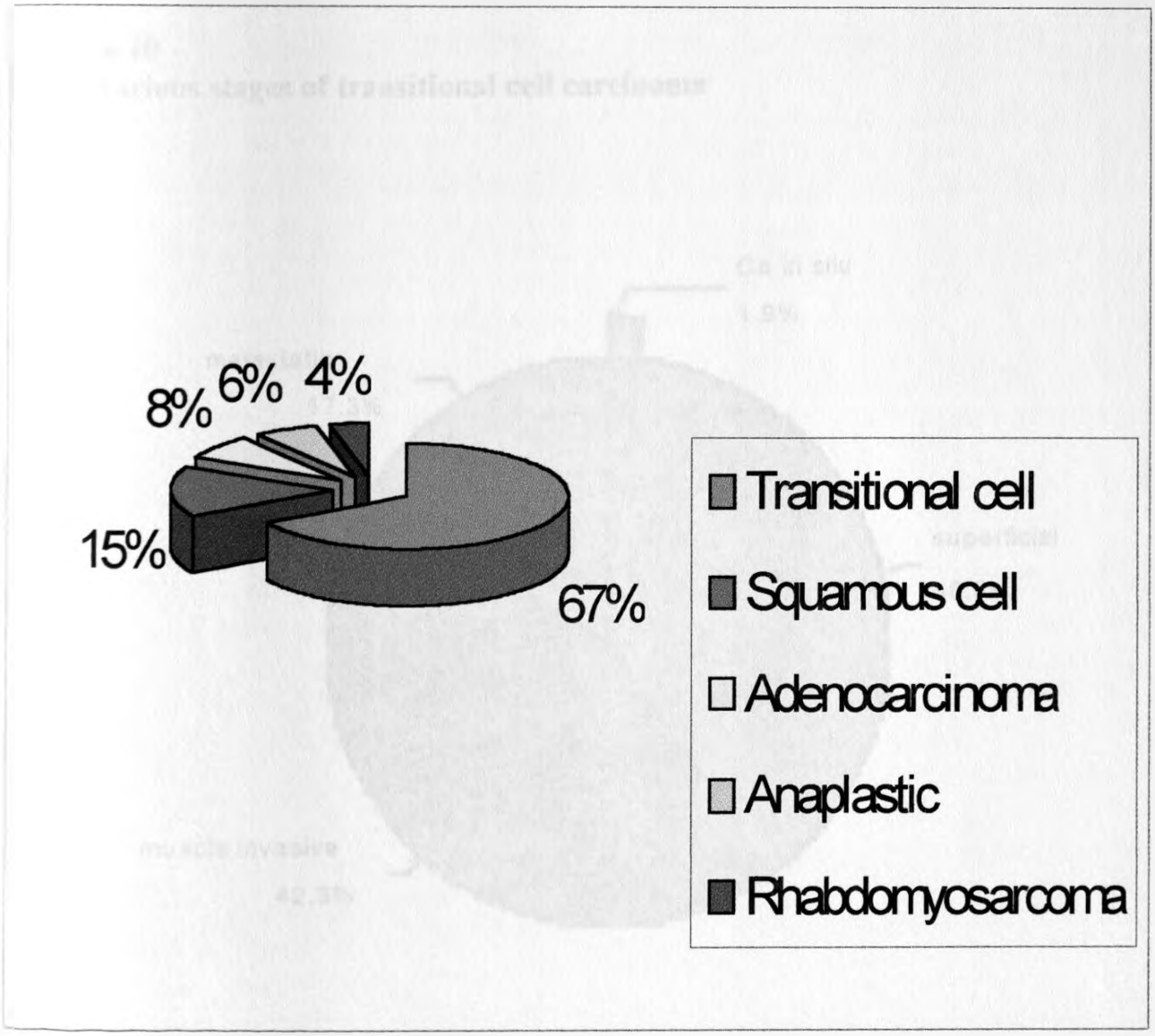
There were a total of 78 patients seen in the hospital with all urinary bladder cancers for the 10 year period. Fifty-two (52) (67%) of the patients were Transitional Cell Carcinomas, 12 (15%) of the patients were squamous cell carcinomas, 6 (8%) of the patients were adenocarcinomas, 5 (6%) were anaplastic and 3 (4%) were rhabdomyosarcomas. These figures show that TCC is the commonest histological type of all urinary bladder cancer followed by squamous cell, adenocarcinoma, anaplastic, rhabdomyosarcoma in that order of occurence

Table 11
Histological types of all urinary bladder cancers

Histology	Number of patients	Percentage
Transitional cell	52	67
Squamous cell	12	15
Adenocarcinoma	6	8
Anaplastic	5	6
Rhabdomyosarcoma	3	4
Total	78	100

Figure 9

Histological types of all urinary bladder cancers.



The commonest stage of TCC was muscle invasive 22patients (42.3%), superficial 20 patients (38.5%), metastatic 9patients (17.3%) and carcinoma in situ 1 patient (1.9%) (figure 10, table12). Overall majority of the patients had invasive disease 59.6% as compared to superficial 40.4%

Figure 10
The various stages of transitional cell carcinoma

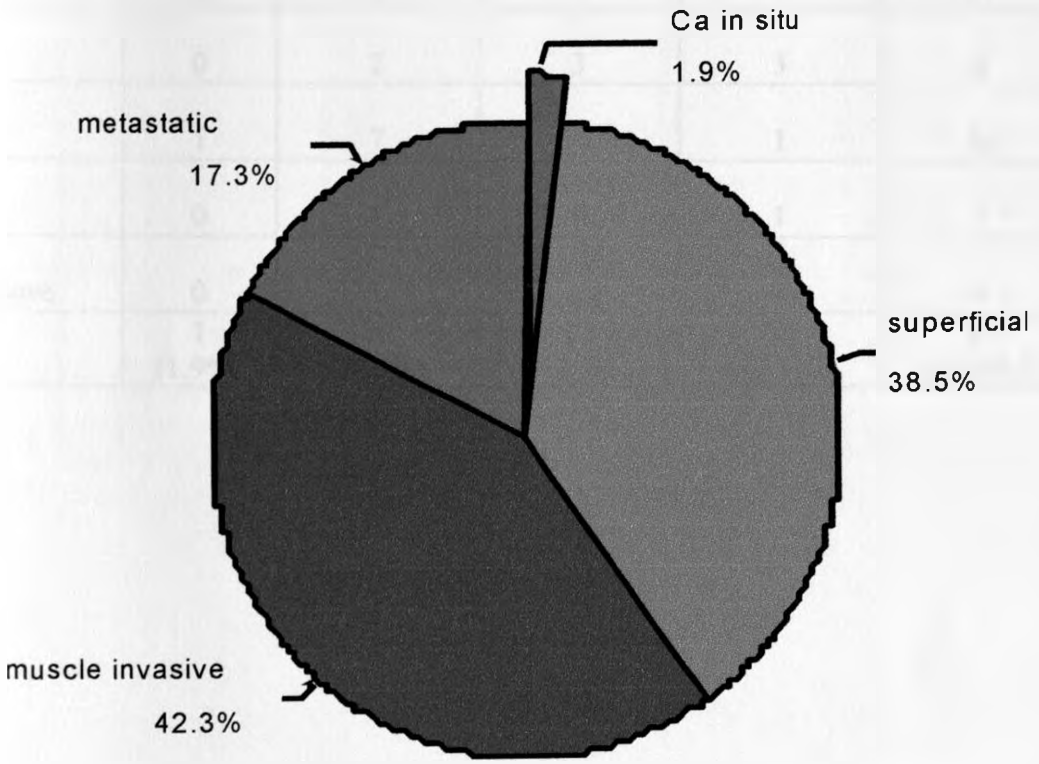
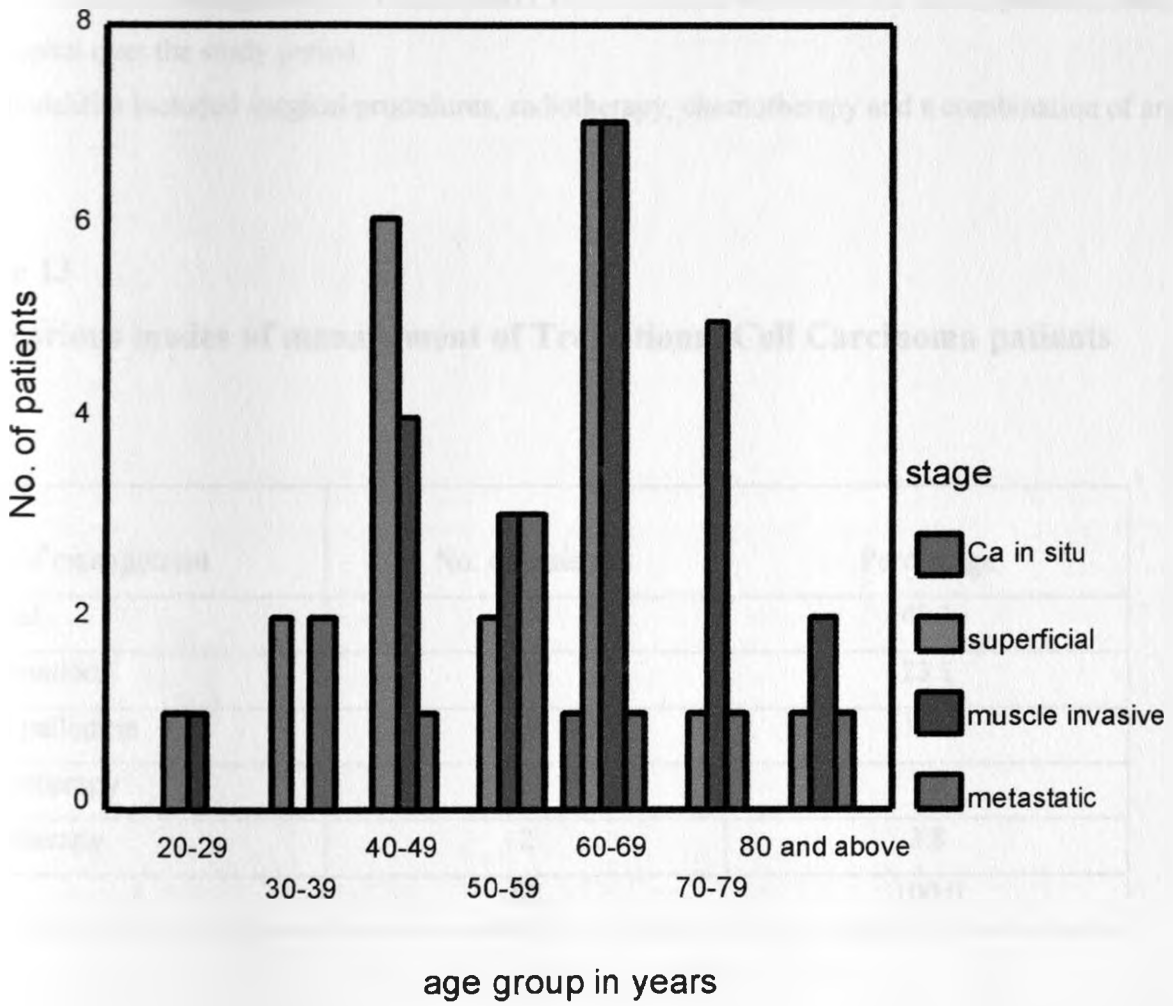


Table 12

Distribution of Histological stages of Transitional Cell Carcinoma by age

Age group	Cis	Superficial	Muscle invasive	Metastatic	Total
20-29	0	1	1	0	2
30-39	0	2	0	2	4
40-49	0	6	4	1	11
50-59	0	2	3	3	8
60-69	1	7	7	1	16
70-79	0	1	5	1	7
80 and above	0	1	2	1	4
Total	1 (1.9%)	20 (38.5%)	22 (42.3%)	9 (17.3%)	52 (100%)

Figure 11
Distribution of Histological stages of Transitional Cell Carcinoma by age



Carcinoma in situ was only recorded in the peak age 60-69 years. Metastatic disease was more common in the age 30-59 years than in older patients.

MANAGEMENT OF THE PATIENTS WITH TRANSITIONAL CELL CARCINOMA SEEN IN KENYATTA NATIONAL HOSPITAL

Various modes of management of Transitional Cell Carcinoma were used for the 52 patients seen in the hospital over the study period.

The modalities included surgical procedures, radiotherapy, chemotherapy and a combination of any two.

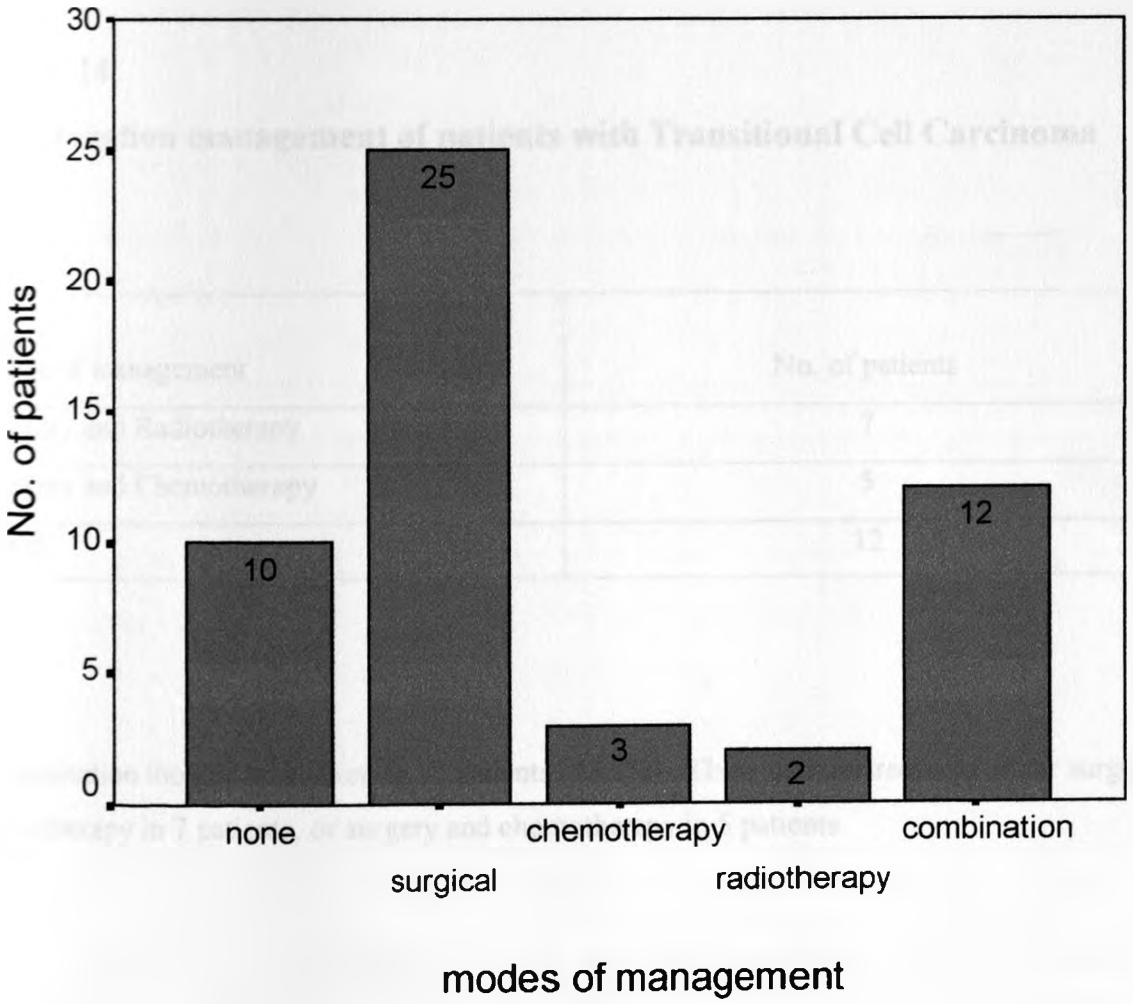
Table 13

The various modes of management of Transitional Cell Carcinoma patients

Mode of management	No. of patients	Percentage
Surgical	25	48.1
Combination	12	23.1
None/ palliation	10	19.2
Chemotherapy	3	5.8
Radiotherapy	2	3.8
Total	52	100.0

Figure 12

Management modalities employed



The commonest modality of management was surgery 48.1%, combination therapy 23.1% of the patients. Chemotherapy accounts for 5.8% of the patients and radiotherapy 3.8% of the patients.

Various chemotherapeautic agents were used. mainly in combination, they included vincristine (V), cyclophosphamide (C), doxorubicin (adriamycin-A), methotrexate (M), cisplatin (C).

Combination MVAC was used in one patient after recurrence following TURBT was done.

Systematic vincristine and adriamycin were given to one other patients.

Intravesical Doxorubicin was used in several patients.

Table 14

Combination management of patients with Transitional Cell Carcinoma

Mode of management	No. of patients
Surgery and Radiotherapy	7
Surgery and Chemotherapy	5
Total	12

Combination therapy was given to 12 patients (23.1%). These patients received either surgery and radiotherapy in 7 patients, or surgery and chemotherapy in 5 patients.

SURGICAL MANAGEMENT

Various surgical procedures were carried out on the patients of Transitional cell carcinoma seen over 10 years period. The following table summarises the procedures.

Table 15

Summary of surgical procedures done for Transitional Cell Carcinoma patients

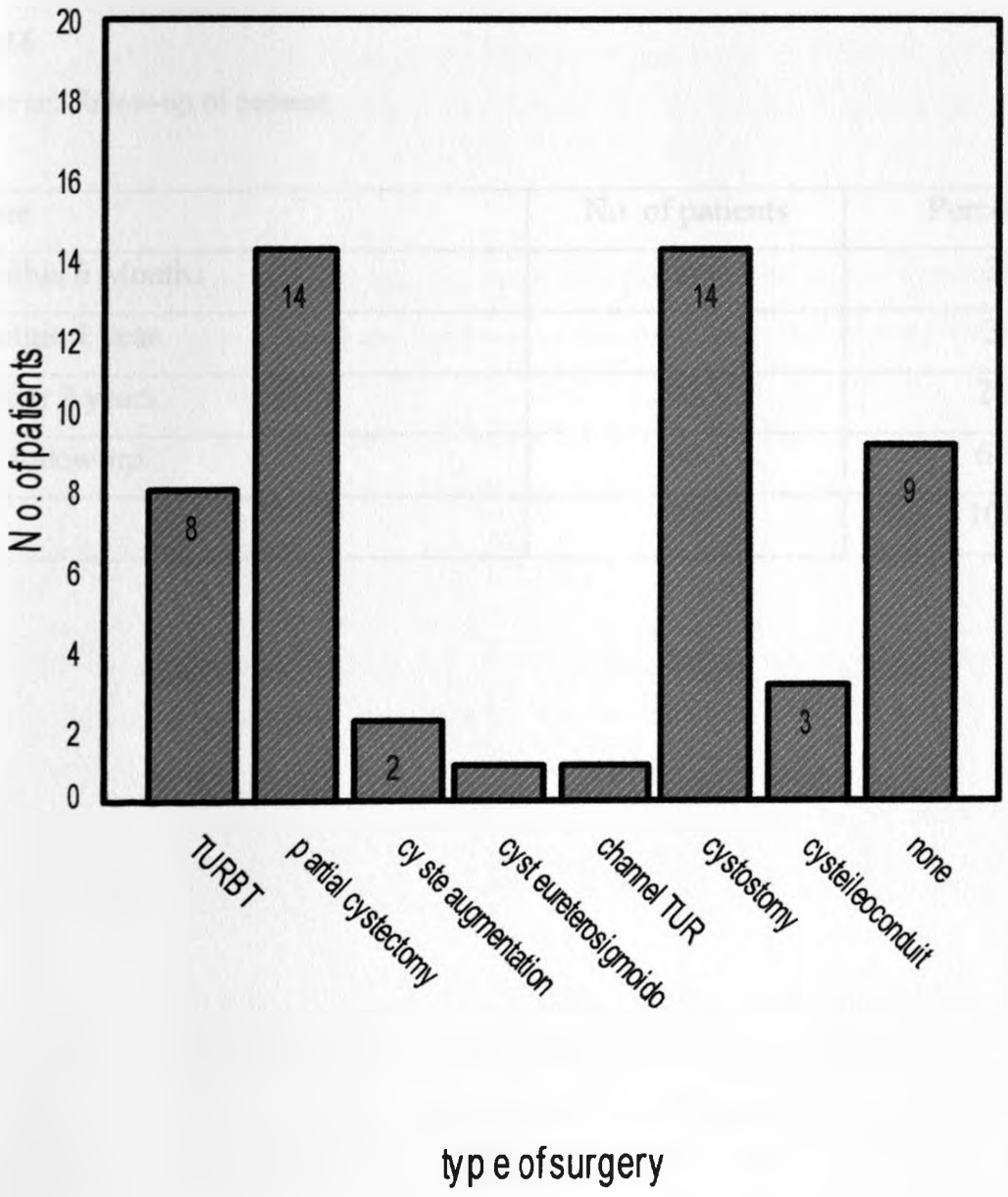
Surgical procedures	No. of patients	Percentage
Partial cystectomy	14	26.9
Cystostomy and excision	14	26.9
TURBT	8	15.4
Cystectomy and ileoconduit	3	5.8
Cystectomy and bladder substitution	2	3.8
Cystectomy and ureterosigmoidostomy	1	1.9
Channel TUR	1	1.9
None	9	17.3
Total	52	100.0

The commonest type of surgical procedure carried out was partial cystectomy in 14 patients (26.9%) and cystostomy and excision in 14 patients (26.9%). Others were transurethral resection in 8 patients (15.4%), cystectomy and ileoconduit in 3 patients (5.8%), cystectomy and bladder substitution in 2 patients (3.8%), channel transurethral resection to relieve urinary obstruction in 1patient (1.9%), and cystectomy and ureterosigmoidostomy were done in 1 patient (1.9%).

Nine (9) patients (17.3%) received no treatment or defaulted their appointments (lost to follow-up).

Figure 13

Surgical procedures carried out in patients with Transitional cell carcinoma



OUTCOME

MORTALITY AND FOLLOW UP OF PATIENTS

Within the ten- year period of study 67.4 % of the patients were lost to followup, 7.6 % of patients died within one year after diagnosis and another 25% were alive 2 years later.

Table 16

Outcome and follow-up of patients

Outcome	No. of patients	Percentage
Died within 6 Months	2	3.8
Died within 1 year	2	3.8
Alive after 2 years	13	25.0
Lost to follow-up	35	67.4
Total	52	100.0

DISCUSSION

Transitional cell carcinoma of the urinary bladder is a rare malignancy.

In this study covering a 10 year period only 52 patients of histologically proven transitional cell carcinoma patients were seen in Kenyatta National Hospital. This accounts for 67% of all bladder tumours. Over the same period of time total surgical admissions to the hospital were 99,028. Thus transitional cell carcinoma formed 0.06% of all surgical admissions in the hospital.

The average annual incidence of this condition over the 10 year period of study was 5.2 patients. These figures confirm that Transitional cell carcinoma is rare and seems to concur with other studies.[3]

The highest number of patients were seen and recorded in the period 1995-1998 constituting 69.2% of all the patients. The 1990-1993 period figures were low, this may be explained by the poor social economic situation prevailing in the country in this period, where most patients could not afford medical services and opted to stay away or seek medical advice from alternative sources. In the period of 1993-1994 there was a national doctors and University lectures strike and this affected the provision of medical services.

In 1995-1998 Introduction of cystoscopy as a routine diagnostic tool and transient improvement of the country's economy explains the increase in the number of patients at this time. In the year 1999 the number of patients reduced due to falling social-economic status and it may even be worse in the year 2000 (table1 and figure1). It is possible that there was better record keeping in the year 1996 to 1998.

AGE DISTRIBUTION

Peak age incidence of transitional cell carcinoma occurs between 67-70 years.

In this study, overall peak incidence occurred between 60-69 years age group accounting for 16 patients (30.8%) this compares with the peak incidence of 67-70 in the existing literature. The

youngest patient was 27 years and the eldest was 84 years with a mean of 57.19 and a median of 60 years. The majority of the patients were between 40 and 69 years (67.4%).

SEX DISTRIBUTION

In this study 78.8% of the patients were males and 21.1% were females giving a male to female ratio of 3.7:1 compared to 2-3:1 reported elsewhere.[4, 5]

REGIONAL AND ETHNIC PATTERN

There was a variation in provincial representation with 46.2% of patients coming from central province, 30.8% from Eastern province, 9.6% from Nyanza, 5.8% from Rift Valley while Nairobi, North Eastern, Western and Coast provinces had 1.9% each. The possible reason for this pattern is that KNH is in close proximity to patients from Central province and therefore easily accessible on logistic grounds. The other possible reason is because Central, Nyanza and Eastern provinces are areas where rice is grown and schistosomiasis is endemic (note that schistosomiasis is responsible for 10% of TCC).

In this study the ethnic distribution was Kikuyu 51.9%, Kamba 17.3%, Meru 7.7%, Luo 5.8% and other tribes 17.3%. The reason for this distribution is most likely as stated in the regional distribution.

PREDISPOSING FACTORS

Various aetiological factors have been identified in association with transitional cell carcinoma. In this study this correlation was studied by including relevant past medical and surgical history and relevant family history.

The result showed that most of the patients had no history of smoking and alcohol consumption i.e. 59.6%and 65.4% respectively. About 28.8% were smokers this accounts for about 1/3 of all patients with transitional cell carcinoma and is similar to existing literature.[14] One of the patient was using tobacco snuff and this is a known risk factor. [9, 13] None of the patients had a past history of surgery

(ureterosigmoidostomy or bladder substitution), chemotherapy or abdominal irradiation which are known risk factors in developing TCC.[5] There was no positive family history in any of the patients.

Farmers constituted 65.4 % of all the patients. It was not specified in the records the type of farming they were engaged in, but it is known that rice farming where schistosomiasis is endemic increases the risk of TCC.[16]

CLINICAL PRESENTATION

In this study out of the 52 patients haematuria was found in 51 patients (98.1%), lower abdominal pains in 37 patients (71.2%), pelvic mass in 19 patients (36.5%) and dysuria in 17 patients (32.7%). Pelvic mass was a sign of advanced disease.

Presentation of Transitional cell carcinoma depend on the clinical stage of the disease, presence or absence of metastases, haematuria being the commonest presentation.[31]

INVESTIGATIONS

These investigations were done in various combinations. The commonest investigative procedures for diagnostic purpose in this study were cystoscopy performed in 37 patients (71.2 %), ultrasonography in 24 patients (46.2%), IVU in 17 patients (32.7%), urine cytology in 7 patients (13.5%), plain abdominal x-rays in 1 patient (1.9%).

Open cystostomy and biopsy was done in 5 patients (9.6%) in other centres before admission to Kenyatta National Hospital.

Cystostomy and biopsy were done in other health centres before referral. This is only mentioned to be condemned for it encourages seeding and spread of tumour cells.[28, 29]

Urine cytology was not a favoured mode of investigation for it is not a cost effective means of screening for bladder cancer.[43]

HISTOLOGICAL DIAGNOSIS

In this study transitional cell carcinoma was the commonest urinary bladder malignancy accounting for 67% of the patients followed by squamous cell 15%, adenocarcinoma 8%, anaplastic 6% and rhabdomyosarcoma 8%.

Of the various stages of transitional cell carcinoma muscle invasive was the commonest accounting for 22 patients (42.3 %) followed by superficial 20 patients (38.5 %) metastatic 9 patients (17.3 %) and ca in situ 1 patient (1.9%). Many early stage tumours could be missed and many patients presented later.[6]

Muscle invasive histological stage accounts for the majority of patients of transitional cell carcinoma across the age spectrum.

A study done on the pattern of all urinary bladder tumours in Kenyatta national hospital by Ndagwatha, P.L.W, (1990) covering a period of 8years identified 75 cases of all urinary bladder cancers showed that transitional cell carcinoma comprises 53.3% of all histological type of bladder tumours. Others were anaplastic 17.3%, squamous cell carcinoma 13.5%.[3]

MANAGEMENT

Management of these tumours call for a multidisciplinary approach . Definitive management options depend on the stage and grade of the disease. For superficial tumours (early stage tumours Cis,Ta,T1) the main stage of treatment is TUR alone. In this study the most commonly mode of management employed was surgery in 25 patients (48.1%), combination in 12 patients (23.1%), chemotherapy in 3 patients (5.8%) and radiotherapy in 2 patients (3.8%).

Ten (10) patients (19.2%) received no treatment, they either did not comply, died before treatment or were lost to follow-up.

Immunotherapy with intravesical BCG, Interferons or megadose vitamins were not used on any of the patients.

OUTCOME

MORTALITY AND FOLLOW UP OF PATIENTS

The data on these was not found to be useful because of the fact that the follow-up of these patients was poor. Within the ten-year period of study 67.4 % of the patients were lost to follow-up, 7.6 % died within one year after diagnosis and another 25% were alive 2 years later. It is likely that the cost of travelling back to Nairobi may have hindered patients from coming back for follow up. Others may have died at home or the nearest health institution before coming back for their next appointment. This is despite the fact that they were discharged with instructions to have follow-up in both the radiotherapy and surgical outpatient clinic. Some patients were lost to follow-up when upon discharge from hospital were referred to the radiotherapy clinic.

CONCLUSIONS

The following conclusions can be drawn from this study of transitional cell carcinoma as seen in Kenyatta National Hospital over a 10 year period 1990-1999.

1. Transitional cell carcinoma is rare and constitutes only 0.06% of all surgical admission in Kenyatta National Hospital over the 10 year period.

2. Patients were seen from all over the country central province having the majority.

3. The commonest histological type of carcinoma of the urinary bladder was transitional cell carcinoma accounting for 67% of the patients, squamous cell 15%, adenocarcinoma 8%, anaplastic 6% and rhabdomyosarcoma 4%.

4. The commonest age group affected was 60-69 years accounting for 30.8% of all documented patients. The male to female ratio was 3.7:1.

5. None of the patients had a relevant past medical or surgical history.

6. Majority of the patients (98.1%) presented with haematuria, a finding consistent with reported literature.[31]

7. Most of the patients were farmers but the type of farming was not specified in the patients' records.

8. Cigarette smoking and alcohol use did not appear to be a major factor in causation of the disease but 1/3 of the patients had a history of smoking.

9. Majority of the patients (71.2%) underwent cystoscopy as a means of investigation or treatment. Cystoscopy was the most important diagnostic tool.

10. Urine cytology was not a favoured mode of investigation and was done in only 7 patients (13.5%).

11. The commonest histopathological stage was muscle invasive 42.3% followed by superficial stage.

12. In terms of management, most patients had surgery as a mainstay of treatment others received radiotherapy or chemotherapy or more than one mode of management.

13. Five (5) patients were done open cystostomy and biopsy in other centres before referral to Kenyatta National Hospital, this was probably done due to inexperience and lack of adequate consultation.

14. Follow-up of patients in the surgical outpatient clinic and radiotherapy clinics was poor. Check cystoscopies were not done routinely as they were supposed to have been done although patients compliance was also to blame.

RECOMMENDATIONS

As a result of this study, some recommendations can be made regarding various aspects of Transitional cell carcinoma. These includes;

1. That public awareness should be improved by public and community education, because though the condition is rare, if diagnosed early the prognosis is better. Medical fraternity should not be spared.

2. That more histopathologists, urologists and histopathological facilities and diagnostic equipment i.e. cystoscopes especially fibreoptic should be available in peripheral hospitals to increase early diagnostic index and shorten the distance to which the patient should travel to come to Kenyatta National Hospital.

3. Entry of patient information and data keeping should be improved. This study showed very clearly the inadequacy of information as regards history, physical examination findings investigation and management of the patient.

4. Multidisciplinary approach to the management of Transitional cell carcinoma is recommended. This involves cooperation of surgeons, radiotherapists, nurses etc.

5.. Cystoscopy is the most important diagnostic tool and should be done in all patients with haematuria and irritative bladder symptoms. If a mass is found intravesical, then its characteristics, site and configuration, are noted and biopsy done and taken for histology.

6. Clinico-pathological staging should be attempted in all patients for this improves management decisions.

7. Open cystostomy and biopsy is mentioned in this study just to be condemned. This should **NEVER** be done for it encourages seeding, implantation and upstaging of the tumour.

8. Urine cytology should be incorporated and used hand in hand with cystoscopy for diagnosis and follow-up.

9. Patients should be properly counseled and the importance of follow-up emphasized. Attempts should be made to write to patients who have been lost to follow-up and remind them to come back to the clinic. Unfortunately a number of patients can not afford the hospital fee and bus fare.

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APPENDIX

DATA COLLECTION FORMAT

(This format has been precoded to ease entry of data into the computer. Entering 0 against the appropriate box will indicate any missing data).

Study Code no.....

1. Name .....
2. Age..... [_][_]
3. Sex ..... MALE=1, Female=2 [_]
4. Tribe .....
5. IP / OP No .....[_][_][_][_][_][_][_]
6. District of residence .....
7. Date of admission .....
8. Date of discharge / death .....
9. Occupation .....
10. Family social history (Relevant). YES=1, NO=2
    - Smoking [_]
    - Alcohol [_]
11. Relevant past medical history YES=1, NO=2
    - None ..... [_]
    - Cystitis / UTI ..... [_]
    - Surgery (bladder substitution) ..... [_]
    - Chemotherapy ..... [_]
    - Others (specify) .....

12. History of lower abdominal irradiation. [ ] YES=1, NO=2

13. Clinical features YES=1, NO=2

Pelvic mass [ ]

Lower abdominal pain [ ]

Haematuria [ ]

Others (specify) .....

14. Investigations done YES=1, NO=2

Urine cytology [ ]

Ultrasound [ ]

KUB [ ]

IVU [ ]

Cystoscopy [ ]

CT Scan [ ]

MRI [ ]

Open cystostomy and biopsy [ ]

Others (Specify) .....

15. Histopathological diagnosis YES=1, NO=2

Superficial (pTa, T1) [ ]

Carcinoma in situ [ ]

Muscle invasive [ ]

Metastatic [_]

16. Management YES=1, NO=2

None [_]

Surgery (specify) .....

Chemotherapy ..... [_]

Immunotherapy ..... [_]

Radiotherapy ..... [_]

Surveillance ..... [_]

Combination ..... [_]

Others (Specify) .....