

T I T L E :

A REVIEW OF URINARY BLADDER CANCERS

AT KENYATTA NATIONAL HOSPITAL OVER 8 YEARS

PERIOD (JANUARY 1976 - JUNE, 1984).

- DISSERTATION SUBMITTED IN PART FULFILLMENT

FOR REQUIREMENTS OF THE DEGREE OF MASTER OF  
MEDICINE IN

SURGERY OF UNIVERSITY OF NAIROBI, JULY 1985.

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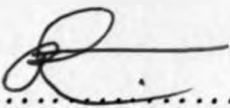
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DECLARATION

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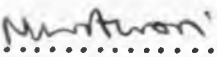
SIGNED:.....

DR. PETER LARRY WAWERU NDAGWATHA, MBChB(NRB)



SUPERVISOR

This dissertation has been submitted for examination with my approval as University Supervisor.

SIGNED:.....

PROFESSOR N.W. AWORI, FRCS  
Associate Professor in Surgery,  
Department of Surgery,  
University of Nairobi.

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(1)

S U M M A R Y:

A review of carcinomas of the bladder seen at Kenyatta National Hospital covering a period of 8 years (January, 1977 - June 1984) was undertaken. 113 patients were documented as having urinary bladder carcinomas, but only 75 cases were selected according to criteria used by the author. Total numbers of malignancies reported over this period was 14,495, hence the ratio of urinary bladder was found to be 0.75.

Males predominated over females by 4 times. The age peaks were overall at 6th and 7th decades though males were in 5th and 7th decades while females were at 6th decade. There was no clear cut aetiological agents although post ulates are presented. 81.3% of patients presented with haematuria, 65.3% of patients presented with irritative bladder symptoms, while 41.3% presented with bladder outlet obstruction.

The frequently seen histological variant of neoplasms were transitional cell carcinomas of all grade and/or stages, followed by anaplastic and then by squamous cell carcinoma. Bladder pheochromocytoma as well as embryonal rhabdomyosarcoma were also encountered. Squamous

cell carcinoma was frequently seen to be associated with *S. haematobium* in endemic areas, Coast and Lake regions.

Clinical, radiological, endoscopic examinations as well as biopsy and histology were used frequently as the diagnostic tools. A total of 32 patients underwent surgical intervention while 31 patients had non surgical intervention in form of chemotherapy and radiotherapy. 12 patients did not have any treatment offered as some refused treatment and some died before treatment could be instituted. Those that had surgical/nonsurgical intervention were 63 in all, 24 were recorded as alive and 20 as dead.

AIMS OF STUDY.

Carcinoma of the bladder is a world wide problem. European and North American series show about 2% of all neoplasms seen. In Kenya carcinomas of the bladder, overall form about 0.92% of all reported cancers as up to 1975 and shows two peak ages, 4th and 7th decades unlike in caucasians, where the peak age is seen at 6th decade (1). Though it is said to be a disease affecting old people; series elsewhere show young generations being affected, perhaps due to *S.hamatobium* infestation where squamous and transitional cell carcinomæ with schistosomiasis association, occur a decade and half earlier than their respective non bilharzial counterparts (1). Non Bilharzial cancers of the bladder occur twice as commonly in the first five decades of life of Kenya as in the white populations of Europe and North America (1).

Though carcinoma of the bladder is reported to be rare in Kenya unlike in Malawi where it is second commonest cancer, it is rather surprising to note, that while rotating in urologic wards, one is bound to see patients with features of carcinoma of bladder, filling about the whole room at one time or another.

It is with the above view, that I decided to look into those cases appearing in Kenyatta National Hospital urologic unit, and try to:-

- i) Find out age/sex distribution, and see if the distribution pattern is as reported by others.
  - ii) See if there is any associated aetiological link.
  - iii) See the mode of presentation of these patients.
  - v) See the diagnostic methods that are available in detecting, the cases.
  - vi) The distribution of this disease amongst the major ethnic groups seen here and their histological variants.
  - viii) See the treatment offered.
  - ix) See if there is effective follow up .
  - x) See if prognosis can be worked out.
  - xi) See if there is any link between squamous cell carcinoma and *S.haematobium* infection.
-

REVIEW OF LITERATURE

Bladder cancer is a disease of world wide distribution and is of varied incidence and histology. The vast majority of bladder cancers are carcinomas and with exception of predominantly squamous cell carcinomas in areas where *S. haematobium* is endemic, 90% of carcinomas are of the transitional cell (2).

Broadly the bladder epithelial tumours can be classified as:-

- (i) UROTHELIAL (transitional cell) papilloma which have a fine papillary processes with a delicate fibro-vascular stalk which is covered by urothelial layer which does not differ in any appreciable degree from normal bladder urothelium.
- (ii) Urothelial carcinoma.
  - Papillary, superficial
  - Solid, infiltrating
  - Papillary and solid infiltrating
  - Carcinoma in situ.
- (iii) Squamous Carcinoma
- (iv) Adenocarcinoma
- (v) Mixed forms, that is any combination of urothelial, squamous and glandular carcinoma.
- (vi) Undifferentiated carcinoma.



Empirical observations over the past century have revealed two basic types of bladder carcinomas i.e. superficial papillary and solid infiltrating, each having a rather distinctive histology and cytology. Papillary tumours comprise about 75% of bladder tumours (3) and show a certain special characteristics which remain unexplained;

i.e.:-

- They develop more frequently in the neighbourhood of ureteric orifices and posterolateral walls.
- They possess branching processes.
- They may be solitary or multiple with marked variations in size and shape but with the same histology or compounds as if two or more have coalesced to form one irregular mass.
- Local removal or diathermy destruction is curative, but tumours with identical histology appear either at the same site or at different sites in irregular intervals.
- The rest of the bladder epithelium frequently shows either diffuse or focal proliferation, cyst formation, lymphocytic infiltration and occasionally metaplasia.

Metaplasia of bladder transitional cell epithelium is thought to be the precursor of other non urothelial bladder neoplasms e. g. squamous cell carcinoma which is associated with *S. haematobium*; adenocarcinoma which is thought to occur from metaplastic changes of urothelium into glandular form, in calculus bladder, chronic infections of bladder especially due to *Esch. Coli*, in extrophy of bladder. Prior to adenocarcinoma transformation, there is urothelial hyperplasia which leads to epithelial down growth and Von Brun's nests formation which may be associated with cystic changes of urothelial wall (cystitis cystica). This neo epithelial layer behaves like a gland, producing mucus (cystitis glandularis). Any neoplastic change leads eventually to adenocarcinoma. Adenocarcinomas hence are frequently further associated to situations where urachus is persistent as well as in metaplastic bladder epithelium which is associated with cystitis glandularis and can be found at any site in the bladder, but commonest are in the basal and ureteric areas. Note cystitis cystica, Von Brun's nests are apparent in the surrounding mucosa in many cases. In urachal adenocarcinoma, bladder is involved at the vault and occasionally on the anterior wall in or near the midline and in the supravescical part of the urachus. It is thought to arise in pre-existing urachal cyst. The tumours show all grades of differentiation from mucous secreting papillary adenocarcinomas to poorly differentiated

colloid carcinomas of the signet ring types.

Recent studies in both human and experimental animals have indicated that most urothelial tumours arise in a generalised FIELD CHANGE, where the entire epithelium is involved in the carcinogenic process and endoscopically visible neoplasms, represent only the most florid components (4,5,6,7).

Whole bladders have been used to investigate field change in urothelium by means of giant sections (7). Field changes do not account for pathogenesis of all bladder tumours. Implantation of viable tumour cell after tissue injury for example in TUR, cystodiathermy may play a role (8,9). This field change phenomenon may lead on to hyperplasia and atypia precursor of carcinoma-in-situ which is generally multifocal and has the potential to involve any portion of the transitional epithelium (urothelium). There is a tendency of loss of cellular cohesion which is a characteristic feature of this lesion. Partial denudation may result, shedding neoplastic cells into the urine in large numbers, hence malignant cells of high grade can be identified in urine cytology in majority of cases. It used to be thought that carcinoma-in-situ progressed rapidly to invasive carcinoma, but the picture is changing in light of newer knowledge on carcinoma in-situ by many urologists. Treatment policy

in these cases has been, intravesical instillation of antineoplastic agent and monitor the patient closely with endoscopy, biopsy and cytology.

Bladder cancer accounts for about 2% of reported cancer cases in caucasians, the main histologic type being urothelial carcinoma i.e. transitional cell carcinoma. In areas infested with *S.haematobium*, the main histologic type seen is squamous cell carcinoma.

In Kenya, Carcinoma of the bladder is said to be rare unlike in Malawi where it is second commonest malignancy in women and third in frequency for men (10). In Malawi 80.1% of all bladder tumours, is squamous cell carcinoma, mainly of well or moderately differentiated types. Transitional cell type being rare (8.2%). Overall mean age at presentation in Malawi is about 44.9 years which is a decade later than the mean age at which benign bilharzial bladder lesions present. The typical bilharzial bladder cancer patient has chronic hilharzia for 10 years or more before the cancer manifestation.

In Kenya the incidence of bladder tumours has been reported as 0.92 of all neoplasms in the country (1). The highest prevalence reported is in the Coast Province where it is an area of hyperendemic for *S.haematobium*. It is noted that transitional and anaplastic carcinomas occur frequently, associated with *S.haematobium*; squamous cell carcinoma being the commonest type. Two age peaks are observed

at fourth and seventh decades, unlike in the Europe and North America population; the earlier peak being explained by the occurrence of bilharzial associated cancers (2).

The concept of a significant role for schistosomiasis in the aetiology of squamous cell carcinoma of urinary bladder has been supported by Lukas (12), but said that the link between schistosomiasis and cancer is likely to be chronic bacterial cystitis, which promotes the formation of carcinogens which act on the metaplastic bladder mucosa (squamous type). Association between carcinoma of the bladder and chronic urinary retention due to urethral stricture is now well recognised in Uganda. A study in Jamaica showed about 24% of patients with carcinoma of the bladder, had gonococcal urethral strictures, while in Uganda, it has been shown that 38% of patients with urinary bladder carcinoma had associated urethral strictures. In West Africa, 22% of urinary bladder cancers were associated with urethral strictures. Similar association has not been found in Europeans with chronic urinary retention due to either benign prostatic hyperplasia or urethral strictures. Recent work in Uganda, (13) showed that 4% of patients with urethral strictures attending urological clinic at Mulago Hospital bougie clinic developed tumours of the bladder within one to 33 years during the period of treatment at the clinic. Tryptophan metabolites in the urine were thought to contribute

to the urinary bladder carcinoma emergence in these Ugandan Africans.

A recent attempt has been made to estimate cancer incidence from proportional rate sources, throughout East and Central Africa (14). These estimated rates are comparable with figures from developed countries and demonstrated a weak positive correlation and the prevalence of *S. haematobium*. The difficulty in obtaining accurate local prevalence rates of infection undoubtedly affects the strength of the correlation.

The role of chemical carcinogens as the aetiological factors started with the work of Percivall Pott 1775 (15) who described the Chimney's Sweepers cancers of scrotum as due to the occupational hazards, on those people climbing the chimneys to dust the soot away. It was not until 1895 when it was noted that bladder cancers were mainly associated with synthetic dye stuffs which became linked later on with the Aromatic amines. Experimental and clinical evidence suggests that bladder carcinogenesis is a multifactorial and multistage process, which includes INITIATION, PROMOTION AND PROPAGATION. Some industrial chemicals particularly those in the dye, chemical and rubber industries, have been identified as powerful bladder carcinogens and may require relatively little interaction with other factors to induce bladder cancers. These chemicals are of:-

a) Aromatic polycyclic hydrocarbons:-

Cook and Kennaway in 1932 demonstrated that the active principle substance in experimental tar cancers was di-benzanthracene and that other derivatives of 1;2 -benzanthracene were almost equally active.

b) Aromatic Amines:-

( $\alpha$ -naphthylamine,  $\beta$ -naphthylamine, Benzidine).;

These are usually prone to affect workers in aniline dye, rubber and cable industries. (Naphthylamine was found in trace amounts in anti oxidants which used to be added to rubber to prevent it from perishing). -Naphthylamine applied locally, experimentally, is shown to have no effect, but effects are seen remotely from site of application, REMOTE CARCINOGENESIS PRINCIPLE. An intermediary metabolic product, 2-amino-naphthol, is a carcinogenic agent, and is produced in the liver from these aromatic amines. It is once detoxified by conjugation with glucuronic acid to give harmless 2-amino-1-naphthyl glucuronide which is excreted in the urine. - Glucuronidases found in the bladder mucosa split this compound to yield free carcinogenes. Saccharolectones are inhibitors to these

enzymes, and may be given to exposed workers. These urinary enzymes levels (-glucuronidases) are also seen to be elevated in bilharzial patients:-

- c) Azo compounds found in dyes for leather and in food stuffs  
-no definite proof in humans as aetiological agents.

During the past decade, a firm link has been established between bladder cancers and cigarette smoking. However, industrial exposure and cigarette smoking are unlikely to account for the majority of bladder cancers (2). Clearly these other factors together may be carcinogenic, although no one factor alone would produce bladder cancer. Evaluation of such factors therefore in man depends on epidemiological studies in which correlations can be difficult to interpret. Where there are positive correlations, it is upto the experimentalist to try to confirm causal significance. There are other factors apart from afore-mentioned ones i.e. occupational carcinogens, tobacco and smokings, dietary factors, drugs, endogenous factors, that have been incriminated.

General recent retrospective and prospective studies have found a dose response in terms of an increased risk of bladder cancer related to number of cigarettes smoked per day or to smoking index. The



duration of smoking has been hence taken as an important factor. Stoppage of smoking was coincident with low figure of Cancer bladder incidence (16).

Artificial sweeteners, sacharin or cyclamate have not as yet been proved to be carcinogenic, though thought to be so. Coffee drinking has not as yet been proved epidemiologically to be causative agent. Vit. A. as an aetiological agent is not conclusive as yet.

As for chemotherapeutic agents (cyclophosphamide, chlomaphazine), some work is required though they have been incriminated; phenacatin is an aniline derivative and its metabolites belong to a class of compounds which are bladder carcinogens in man. In view of the widespread use of these analgesics, further efforts are required to assess the degree of risk of bladder cancer to which large populations may be exposed, and excessive use should be discouraged.

Endogenous factors such as genetic factors, immune status, hormones, urine tryptophan, urinary tract infection have been thought of, and research on them is still on.

Several studies have documented familial incidences of bladder cancers, including more than one generation. One study done showed that blood group A was frequently encountered in patients with bladder

cancer than in controls. Their HLA profiles revealed an excess B5 antigen and CW 4 factors at the B and C loci. Estimated combined risk of developing bladder cancer in a person who is a blood group A, HLA B5 and HLA-CW 4 was 15 times greater than that of the mean population (17).

Data linking immunodepression with the development of malignant diseases have accumulated over the past two decades, but direct evidence in the development of urothelial neoplasia in man is lacking. However, a recent study suggests that immune recognition of bladder tumour antigens can occur before the development of overt malignancy (18), (Theory of immune surveillance). In immuno compromised patients such as those receiving azathioprine and steroids in renal transplant, have high chances of developing neoplasia of bladder. Whether it is the drugs that depress or interfere with immune surveillance, is not clear (19). Radiotherapy can cause marked depression of total lymphocyte counts, especially T cells (20). This depression can persist in recurrence free patients for up to 3 years post irradiation, hence the risk of pelvic irradiation in increasing bladder cancer development; by depressing immune response. Results so far, of expected improvement in prognosis of patients

at risk of recurrent urethelial enoplasia, that receive immunotherapy, have been equivocal (21,22).

The role of typtophan metabolites, though seen to be high in patients with bladder cancers, has not been conclusive as no data so far, exist which demonstrates that these compounds produce bladder cancers in man. Surprisingly, oestrogens have been shown to produce raised levels of urinary tryptophan metabolities, so the oestrogen therapy used for a long time may be a theoretical risk in bladder cancer development. Urinary tract infection has also been thought to be associated with bladder neoplasia—the bacteria present aid the formation of urinary nitrosamines which are strong carcinogens in animal studies (NITROSOAMINE STORY). Urinary calculi has not been linked with bladder cancer clearly, although urothelial hyperplasia and dysplasia are commonly observed (23).

So far there has been little evidence to implicate viruses in the aetiology of human bladder cancers.

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## MATERIALS AND METHODS

The patients selected included those seen from January 1977 upto June 1984 in Kenyatta National Hospital. The case histories were abstracted from hospital records this being a retrospective study. Only those patients who presented with clinical features, suggestive of carcinoma of urinary bladder, were selected. Those without supporting histological proofs were omitted. The proforma of study was as follows:-

### A. Patient identification:

- i) Name
- ii) Age
- iii) Sex
- iv) Ethnic origin
- v) Dietary habits
- vi) History of contact with radiation previously
- vii) History of smoking or drinking
- ix) History of cosmetic application
- x) History of schistosomal infestations Yes/No

### B. Presenting features:

- i) Irritative bladder symptoms (e.g. cystitis, dysuria, frequency).

- ii) History of haematuria Yes/No.
- iii) Inability to evacuate the bladder contents.
  - Acute.....
  - Chronic.....
- iv) Constitutional symptoms and signs
  - fever.....
  - general malaise .....
  - anaemia.....
  - weight loss.....

C. Investigative procedures:-

- i) Biochemical
  - BUN: Elevated.....
  - Normal.....
  - Electrolytes: Normal.....
  - Deranged.....
- ii) Microbiological
  - Urinalysis
  - Culture and Sensitivity of urine

i ii) Urinary cytology.....

iv) Radiological

i) Plain abd. x-rays, including pelvis.

Calcifications Yes.....

No.....

ii) IVP

iii) MCU.

v) Endoscopic examinations.

i) Cystoscopy

-ve.....

+ve.....

ii) Cystoscopic appearance, site of mass.

.....

vi) Bimanual Examination to give clinical staging of tumour,  
if tumour +ve endoscopically.

vii) Histopathological appearance or type of lesion

.....

staging.....

grading.....



R E S U L T S:

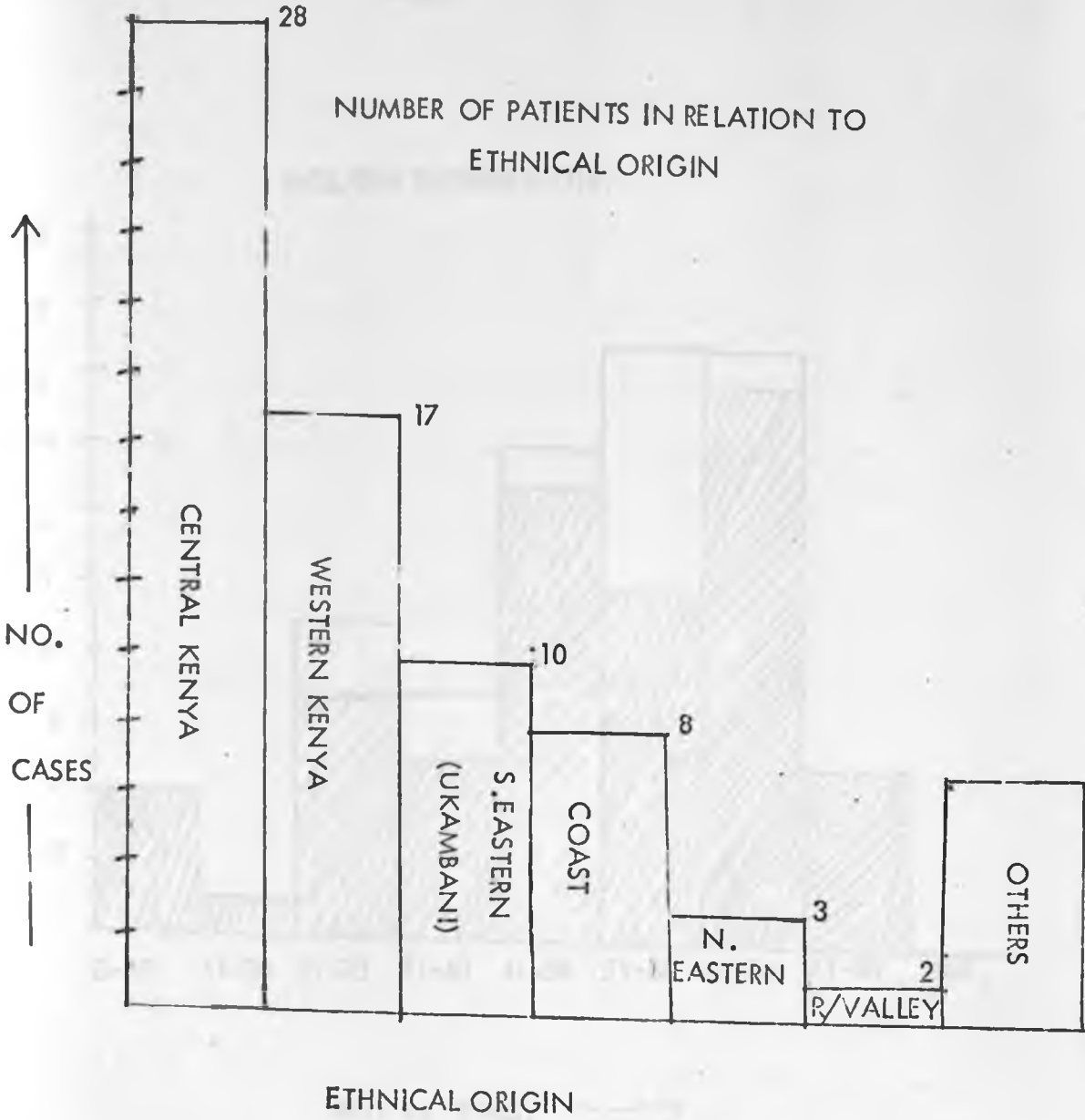
This is an 8 year period study of bladder cancer cases seen at Kenyatta National Hospital from January 1977 upto June 1984. The overall cases studied was 75 patients, those who satisfied the profoma. In all there were 113 patients reported as having carcinomas of bladder. Total number of malignancies reported over this period was 14,495.

REGIONAL ETHNIC GROUP	NO
CENTRAL KENYA (Kikuyu, Meru, Embu )	28
WESTERN KENYA, (Luos, Luhya, Kisii)	17
SOUTH EASTERN, KENYA (KAMBA)	10
COASTAL KENYA, (Giriama, Digos, Duruma)	8
NORTH EASTERN KENYA (Somali)	3
RIFT VALLEY (Kalenjins)	2
* OTHERS	7

- \*
  - 2 EUROPEANS
  - 3 ASIANS
  - 1 UGANDAN
  - 1 MALAWIAN

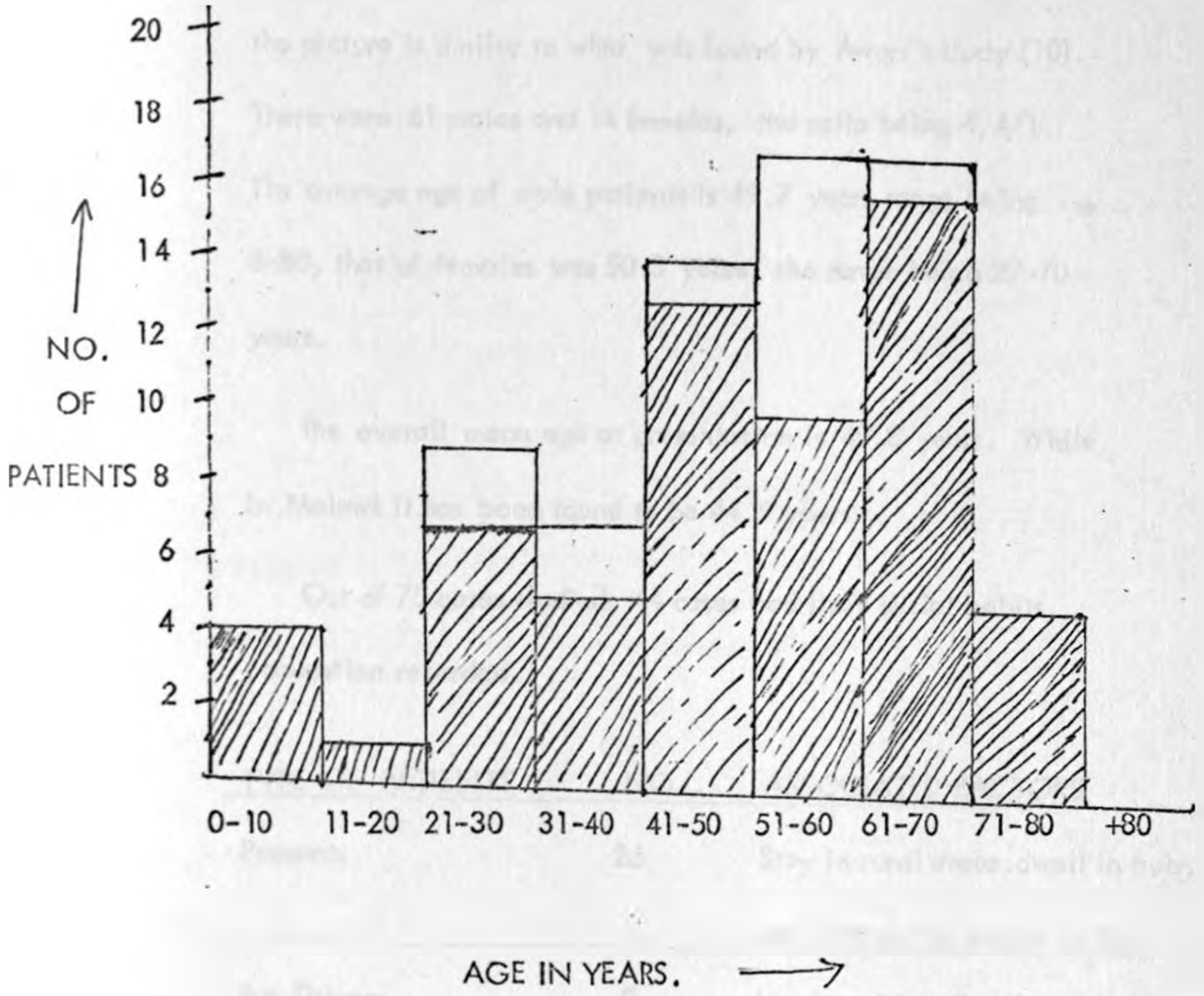
Table I







fig(i)

AGE/SEX DISTRIBUTION.



 MALES

 FEMALES

*fig(ii)*

The age peaks of incidence are at 6th and 7th decades. This is not as reported by Bowry (1) in 4th and 7th decade, but the picture is similar to what was found by Awori's study (10). There were 61 males and 14 females, the ratio being 4, 4/1. The average age of male patients is 49.7 years range being 6-80, that of females was 50.3 years, the range being 27-70 years.

The overall mean age at presentation is 49.8 years. While in Malawi it has been found to be 44.9 years.

Out of 75 cases studied, 44 cases had their social habits, occupation recorded.

TYPE OF PATIENTS	NO.	ASSOCIATED FACTORS
Peasants	26	Stay in rural areas, dwell in huts, use firewood as source of fuel
Bus Drivers	3	Used to drive diesel engined buses, which were emitting fumes near the drivers cabins.
Tanning Industry Works	2	Handling of chemicals used for tanning leather etc.

---

Sprayer technicians	1	Motor Vehicle paint sprayer
		5 years

---

Fire Fighters	1	Been in profession for over 20
		years

---

Gunner (Soldier)	1	Used to work with artillery
		guns for over 10 years

---

Watchman	1	Used to smoke 20 cigarettes
		a night while on duty

---

Prisoner	1	
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---

Teacher	1	
---------	---	--

---

Business	1	
----------	---	--

---

Pupils	4	
--------	---	--

---

TABLE II.

TABLE II

From above it can be seen that 26 patients out of 75 had contacts with smoke for most of their lives. These people live in huts which are very smoky especially during the wet seasons. Inside the roof, there is a lot of soot which keep on falling on to the floor. This could be a source of hydrocarbons. Refer to discussion chapter pg.54

The bus drivers inhale the fumes being emitted from the hot engines, while driving them.

There were two patients from the tanning industries and one fire fighter who has been in the profession for more than 20 years.

There was no record available for 31 patients.

PRESENTING FEATURES

1. Irritative bladder symptoms (cystitis, dysuria, frequency).

There were 49 positive cases for above i.e. 65.33% and 8 negative cases i.e 10.67%, 18 patients had not been recorded whether they had above or not (24.00%).

2. There were 61 positive cases with haematuria i.e. 81.33% and 5 negative cases 6.67%. Not recorded cases were 9 (12.00%).
3. There were 4 (5.33%) cases with acute retention of urine and 27 (36.00%) with chronic urinary retention. Overall there was 41.33% with retention of urine. The patients not recorded amounted to 58.67%.

4. Constitutional Symptoms/Signs:

Fever	13.33%
General malaise	42.67%
Anaemia	42.67%
Weight loss	29.33%

URINALYSIS = c/s

(a) 4 cases had ova of *S. haematobium* in urine.

(b) Urine culture.

28 samples of urine taken were +ve and grew various organisms, shown below in order of frequency.

<i>E. coli</i>	8
<i>Klebsiella</i>	8
<i>Proteus</i>	5

Pseudomonas	2
Staph aureus	2
Strept faecalis	2

Citrobacter	1
Salmonella chicao	1
Entero bacter	1
Aerobacter	1
These organisms are encountered frequently in urinary tract infections:-	

c) There was only one case of +ve cytology showing malignant cells. There was no other record of cytology.

Biochemically, it was found that not all patients had urea and electrolytes, done.

Those recorded showed:-

*Table IV*

	NORMAL	DERANGED	ELEVATED
BUN	20(26.7%)	-	12(16%)
ELECTROLYTES	20(26.7%)	12(16%)	-

20 Cases had normal urea, electrolytes, levels.

12 cases had elevated BUN and deranged electrolytes.

This group fell into those patients who presented with urinary obstruction, mainly chronic i.e. 12 out of 27 (44.4%) of chronic urinary obstruction.



RADIOLOGICAL FINDINGS:-

(i) Plain abdominal with pelvis, x-rays.

There were 4 cases with calcification of the bladder, indicating *S.haematobium* infestation. The bladder sizes were also found to be contracted.

(ii) I.V.P. FINDINGS:-

*Table IV*

	NO.OF PATIENTS	%
NORMAL	4	5.33
UPPER URINARY TRACT DILATATION		
UNILATERAL	5	6.67
BILATERAL	2	2.67
NON FUNCTIONING KIDNEYS	1	1.33
BLADDER FILLING DEFECTS	33	44.00

From above it is seen that 30 patients did not have IVP findings-  
this is because:-

- 1) Some were ordered but not done.
- 2) Others films could not be traced.
- iii) In Micturating cystograms, only 3 (4%) patients

had been done and showed filling defects in the bladder.

- iv) Angiogram - there was one flush selective hypogastric arteriogram done. This showed a tumour blush on (R) side of bladder with a large filling defect in the same area. IVP had shown earlier double density in the bladder on rt wall. The patient was 14 years Luhya boy being investigated for pheochromocytoma.

FINDINGS AT ENDOSCOPY

APPEARANCE OF TUMOUR	SITES						
	ANTERIOR	LATERAL RT	WALLS LT	POSTERIOR	VAULT	TRIGONE	NECK
1. PAPILLARY, POLYPOIDAL GROWTHS	-	7	4	6	-	4	3
2. INFILTRATIVE MASS, MARGINS WITH WITH NORMAL MUCOSA	-	1	2	1	-	1	-
3. SOLID, ULCERATIVE, FUNGATING, HAEMORRHAGIC	1	9	6	6	5	-	1

43 ENDOSCOPIES WERE DONE. 40 WERE POSITIVE AND 3 NEGATIVE.

*Table V*

Papillary, solid/papillary carcinomas were frequently seen involving the lateral, posterior, vault, walls and trigone of bladder. Lateral walls are more commonly affected.

It is interesting to note that four cases in vault were adenocarcinomas.

There were 11 open biopsies performed for reasons which are not clear. 6 were of infiltrative haemorrhagic lesions and 5 of papillary/solid growths. 4 of these were from a children aged 6 to 7 years.

Clinical stagings were done in 27 patients by bimanual examination under general anaesthesia.

Stage I	2	(2.7%)
Stage II	2	(2.7%)
Stage III	13	(17.3%)
Stage IV	10	(13.3%)

48 patients did not undergo EUA or bimanual examination under general anaesthesia after cystoscopy to ascertain the locality, configuration of intra vesical masses.

HISTOLOGICAL FINDINGS:-

There were:-

- i) 40 cases of transitional cell carcinomas (53.3%), only 1.3% were associated with bilharzia.
- ii) 13 cases of anaplastic carcinomas (17.3%) while 3 cases (4.0%) were associated with *S. haematobium*.
- iii) 10 cases of squamous cell carcinomas, 13.3% of total. Half of these were associated with *S. haematobium* infestation.
- iv) 4 patients (5.3%) with adeno-carcinomas.
- v) 4 patients who were young children with embryonal bladder rhabdomyosarcoma (5.3%).
- vi) 3 patients who had papillomas of the bladder (4.0%).
- vii) 1 patient who had bladder pheochromocytoma 1.3%.

RANGE AND AVERAGE AGES OF EACH NEOPLASM

TYPE OF NEOPLASM	RANGE OF YRS	MEAN AGE IN YRS
PAPILLOMA	21-46	33.3
SQUAMOUS CELL CARCINOMA	30-80	52.7 (BILHARZIAL 52.2) (NON " 53.2)
TRANSITIONAL CELL CA.	29-73	52.10 YRS
ANAPLASTIC CARCINOMA	27-70	55.8
ADENOCARCINOMA	40-78 YRS	47
EMBRYONAL RHABDOMYO- SARCOMA	6-7	6.5
PHEOCHROMOCYTOMA	14	-

Table VI

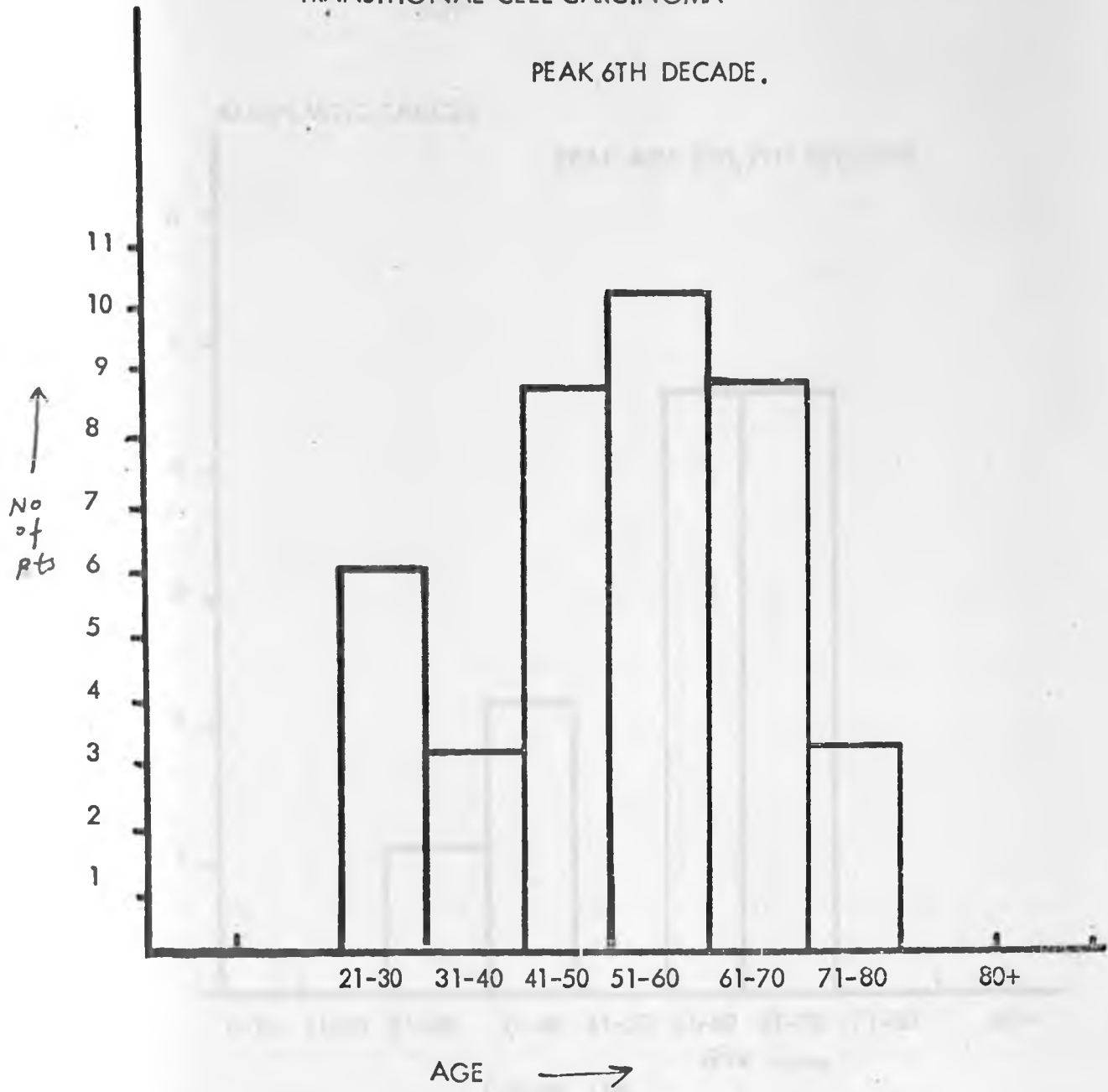
Bilharzial associated tumours have highest incidence in the 4th decade (1), lack of any case in this decade in the present study reflects perhaps the late presentation of patients or may be because of majority of patients are from non endemic area for Schistosomiasis. The peak shown in the 5th and 6th decades (see figure V) for squamous cell carcinoma.

Transitional cell carcinoma is shown to have a peak at 6th decade, but majority range from 5th to 7th decades. (Figure iv).



### TRANSITIONAL CELL CARCINOMA

PEAK 6TH DECADE.



(FIGURE 4).

### ANAPLASTIC CANCER

PEAK AGE 6TH, 7TH DECADES.

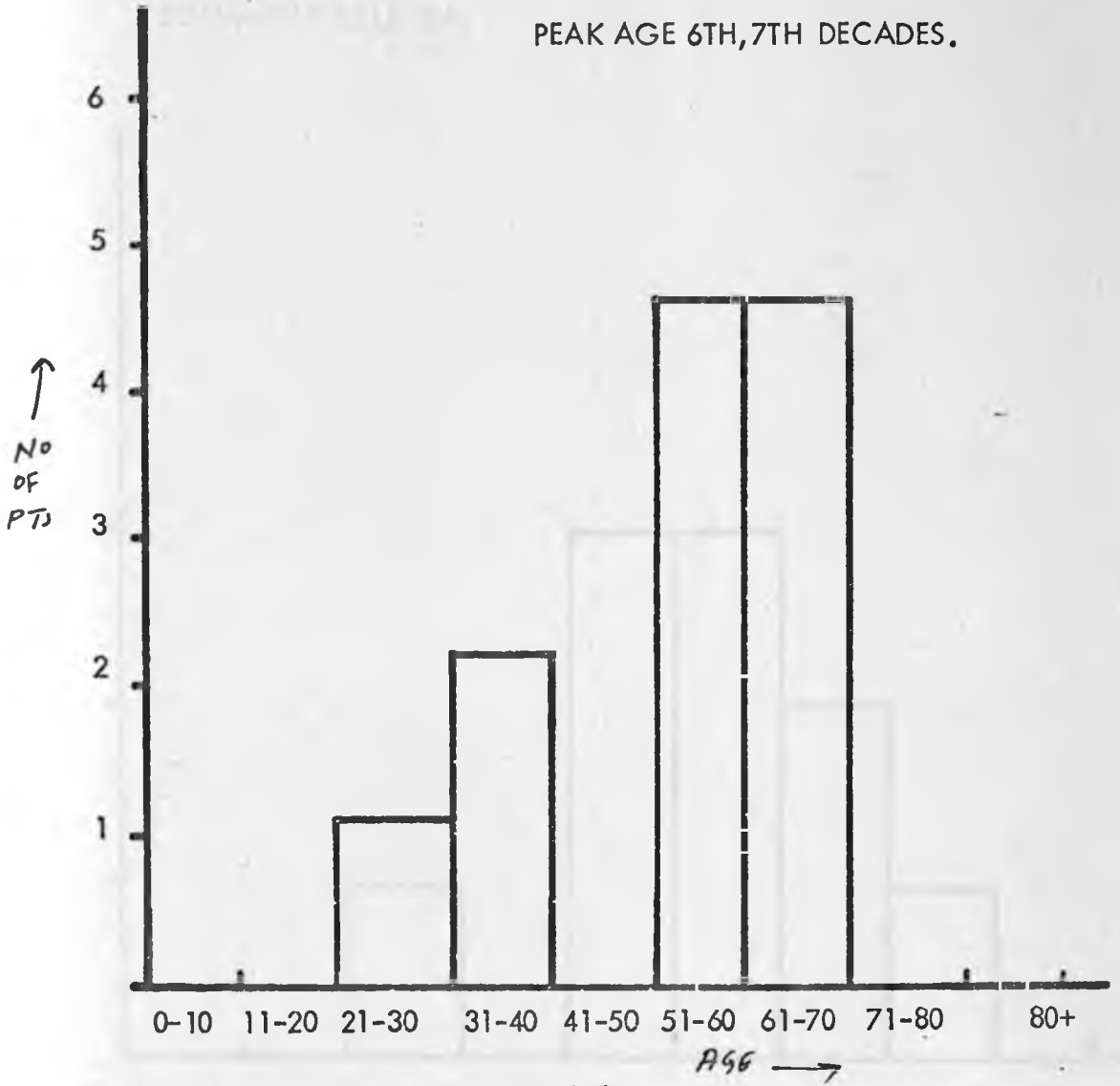


FIGURE (iv)

PEAK AGE 5TH, 6TH DECADES.

SQUAMOUS CELL CA.

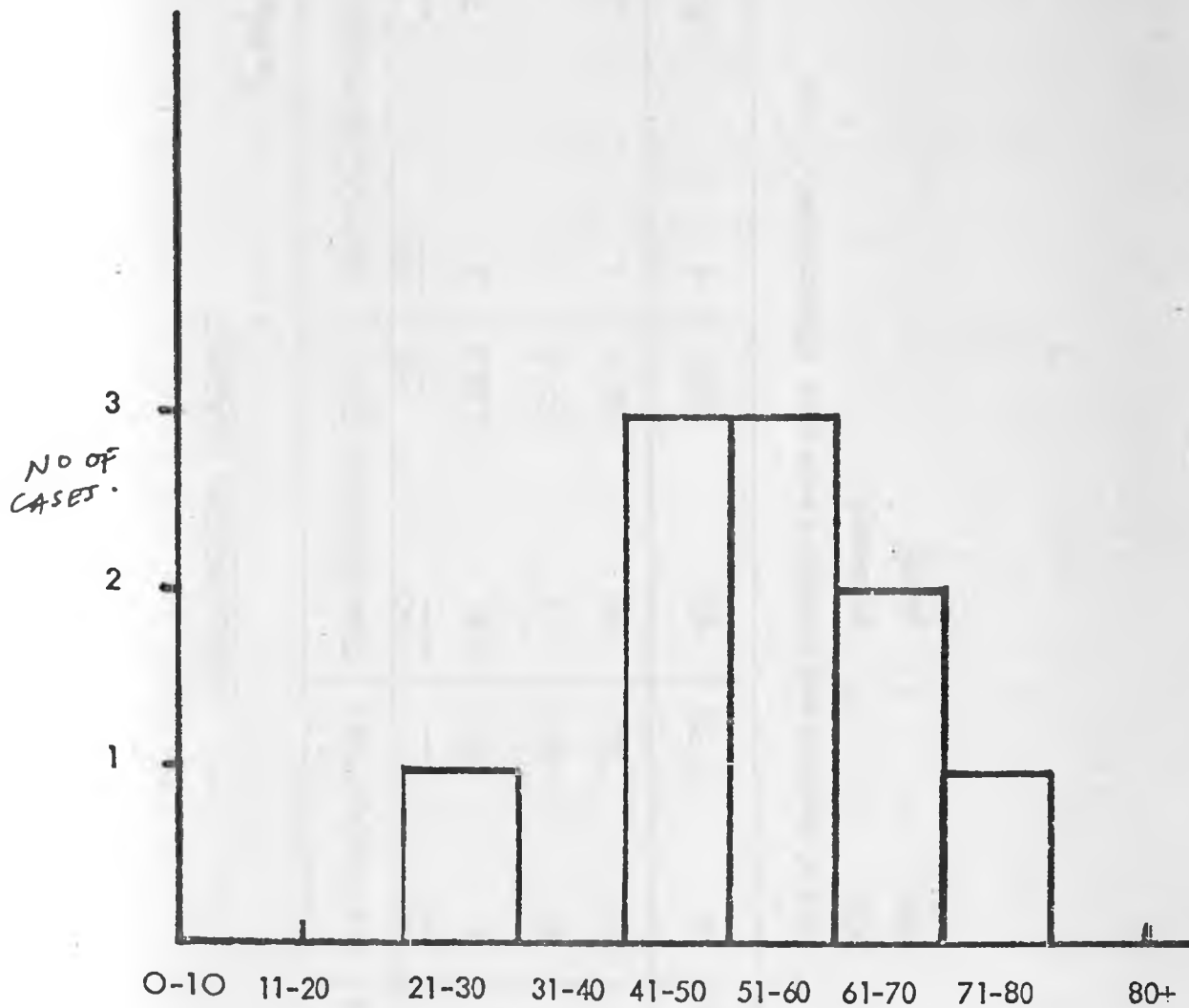


FIGURE (v)

AGE →

HISTOLOGICAL GRADING

*Table VII*

GRADE	SQUAMOUS CELL		TRANSITIONAL CELL		ADENOCARCINOMA	
	<u>NO.</u>	<u>%</u>	<u>NO.</u>	<u>%</u>	<u>NO.</u>	<u>%</u>
I	5	50	9	22.5	3	75
II	2	20	11	27.5	-	-
III	3	30	20	50.5	1	25
TOTAL	10	13.3%	40	53%	4	5.3%

- a)            50% of squamous cell carcinoma were well differentiated, Type  
                   20%    "            "    moderately                    "            "  
                   30%    "            "    poorly                         "            "

b) 22.5% of Transitional cell carcinoma were well differentiated type .

27.5% of transitional cell ca.were moderately differentiated type .

50.5% of transitional cell carcinoma were poorly differentiated type .

c) 75% adenocarcinomas were well differentiated type .

25% adenocarcinomas were poorly differentiated type .

TREATMENT OFFERED:A) RESECTIONS + ADJUVANTS:

TABLE VIII

MODE OF TREATMENT	NO.	NEOPLASM	DEAD	ALIVE
1. Local resection alone	3	Transitional Cell Carcinoma mean age 46.3 yrs	*	*
2. TUR plus Radiotherapy	1	Transitional Cell Carcinoma Grade II - III (Mean age 47 yrs)	-	1
3. Resection with Radiotherapy + Chemotherapy	4	All Transitional Cell Cas. (graded as well to poorly differentiated) (Mean age 46.8 yrs)	1	3
4. Resection with V.A.C. & Radiotherapy	4	Embryonal Rhabdomyosarcoma (mean age 6.5 yrs)	1	3
5. Cystodiathermy followed by Radiotherapy	2	Poorly differentiated superficial, Papillary Transitional cell. (mean age 32.0 yrs)	-	2
	14		2	9

\* NOT SPECIFIED. VAC- VINCRISTINE, ADRIAMYCIN, CYCLOPHOSPHAMIDE.

1. TUR - one patient aged 47 years with transitional cell carcinoma grade II - III, had localised lesion which was resected transurethrally, followed by radiotherapy. The patient is alive.

2. Local resection was done in 13 patients.

\* 3 had resection only, the patients were thought not suitable for radiotherapy, for tumours were too advanced.

Mean age 46.3 yrs. (see chart above).

\* 4 had resection combined with chemotherapy and radiotherapy.

They all had transitional cell carcinomas ranging from well differentiated to poorly types. There was 1 mortality.

Mean age of presentation was 46.8 years.

\* 4 children ranging from 6 years to 7 years. They all had embryonal rhabdomyosarcomas. They had local resections, followed by V.A.C. combination (Vincristine, adriamycin, cyclophosphamide) and radiotherapy.

3 are still alive and one died of status epilepticus

\* In cystodiathermy there were 2, whose mean age were 32 years. All were reported as alive.

B. PARTIAL CYSTECTOMY + ADJUVANTS

TABLE IX

	NO.	NEOPLASMS	DEAD	ALIVE
Partial cystectomy alone	3	1 pheochromocytoma 14 years		1
		2 well differentiated Transitional Cell Carcinomas MEAN AGE-67.5	1	1
Partial cystectomy with chemotherapy (methotrexate Adriamycin + Endoxan)	2	Anaplastic Carcinomas mean age - 65 years	1	1
Partial cystectomy + radiotherapy	8	Transitional cell Ca. age range 45-73 (mean 41.9 Yrs) -varied from Grade 1 -III	4	3(1*)
Partial cystectomy + Radiotherapy + Chemotherapy	2	Superficial poorly diff. transitional cell ca. with intravesical thiotepa	1	
		Anaplastic carcinoma (IV adriamycin) (mean age 49 yrs)	-	-
TOTAL	15		7	7

\* NOT SPECIFIED.



The operations were done mainly in patients whose age were mainly over 40 years with an exception of 1 boy of 14 years with pheochromocytoma. Total cystectomies were done in 3 patients, whose average age was 56.3 years one patient had poorly differentiated squamous cell carcinoma and died within 6 months of diagnosis. The other two had transitional cell carcinomas. They all had cystectomy and urinary diversions (ileo-conduct). One patient is up to date coming to the clinic for follow up, 8 years after diagnosis. In other patients, no follow up was done.

All in all patients underwent partial cystectomies either alone or with added forms of treatment as shown above in the chart. Note the survival from mortality cases, No marked differences.

TYPE OF TREATMENT	NO.	ALIVE	DEAD
Treatment with cystectomy	7	4	3
Treatment with partial cystectomy	24	1	23
Radical prostatectomy	20	1	19
Observation	1	1	0
Total	52	7	45

NON SURGICAL TREATMENT

Chemotherapy: - There were 6 patients  
3 with anaplastic carcinomas  
2 with transitional cell carcinomas  
1 with squamous cell carcinoma.

The mean age of presentation was 59.3 years (30-80 years)

3 patients died during the course of treatment

2 patients were not indicated.

1 patient among transitional cell carcinomas was alive but duration was not specified.

RADIOTHERAPY ALONE: There were 15 patients, whose ages ranged from 30 to 70 years, mean age 47.1 years.

TYPE OF TUMOUR	NO.	ALIVE	DEAD
Transitional cell carcinoma	9	3	1
Squamous cell carcinoma	3+	-	1
Adenocarcinoma	2+	-	1
Anaplastic carcinoma	1	-	1
TOTAL	15	3	4

TABLE 8

+It appears that transitional cell carcinomas are radiosensitive.

Lack of data in squamous cell carcinomas, adenocarcinomas in

patients who are alive, could suggest, their insensitivity to

radiotherapy. May be the patients died at home and did not

come for follow up where they would have been documented.

Data available show 33% mortality in squamous cell carcinomas,

50% adenocarcinomas, 100% in anaplastic and transitional cell

carcinomas 11%.

CHEMOTHERAPY + RADIOTHERAPY. Mean age 54.5  
(Range 40-78)

TABLE XI

TYPE OF NEOPLASM	NO.	ALIVE	DEAD
Squamous Cell Carcinoma	2	1	1
Anaplastic Carcinoma	2	-	1
Transitional Cell Carcinoma	3	1*	-
Adenocarcinoma	1	-	1
TOTAL	8	2	3

\* Poorly differentiated transitional cell carcinoma who had intravesical adriamycin.

3 patients were not specified whether, dead or alive.

Mortality in this treatment regimen was 50% for squamous cell carcinoma and 100% for adenocarcinoma. Probably in anaplastic carcinoma it was 100% as there was no record in one patient whether he was dead or alive. Two patients with transitional cell carcinomas were not accounted for.

NB 2 patients who were over 85 years with invasive, poorly differentiated transitional cell carcinomas had hyperthermic hydrostatic dilatation of bladders. They were free of symptoms until two years later. There was no follow up after that.

Those that did not have any form of treatment -were

12 whose mean age of presentation was 51.9 (range 27-70)

Histologically they were of:-

Papilloma	1
Anaplastic Carcinoma	2
Adenocarcinoma	1 (too advanced to benefit from any treatment)
Squamous cell carcinoma	2
Transitional cell carcinoma	6
2 patients refused treatment	
3 patient died.	

SURVIVAL AND MORTALITY OF PATIENTS  
WHO RECEIVED TREATMENT.

TABLE XII

TREATMENT	TOTAL	RECORDED		NOT RECORDED
		ALIVE	DEAD	
SURGICAL	32	18	10	4
NON SURGICAL	31	6	10	15
TOTAL OF ABOVE	63	24	20	19
NO ABOVE TREATMENT	12	-	3	9

KNOWN Total mortality - 23 ie 30.7% OF TOTAL

" Total survival - 24 ie 32.0% OF TOTAL

Total of 63 patients had treatment given as above and 44 of them were recorded as having either died or survived. The discrepancy of 19 patients that can not be accounted for, is because of lack of proper documentation and follow up. Mortality and survival recorded is almost equal indicating poor prognosis, for these patients. Those that did not receive any treatment were 9 whose fate was not known or given. Two

Bladder Cancer

patients had received hyperthermic hydrostatic dilatation

of bladder. They were followed up for two years only, hence their fate not known.

From 1977 to 1981

The present report includes all cases of carcinoma of bladder treated by hyperthermic hydrostatic dilatation between 1977 and 1981. The patients were followed up for a period of 2 to 5 years. The present study includes 15 patients, 10 males and 5 females, with a mean age of 65 years. The patients were followed up for a period of 2 to 5 years. The present study includes 15 patients, 10 males and 5 females, with a mean age of 65 years. The patients were followed up for a period of 2 to 5 years. The present study includes 15 patients, 10 males and 5 females, with a mean age of 65 years. The patients were followed up for a period of 2 to 5 years.

Hyperthermic hydrostatic dilatation is a treatment modality used in the management of bladder cancer. It involves the use of heat and pressure to dilate the bladder and destroy the tumor cells. The present study evaluates the effectiveness of this treatment modality in the management of bladder cancer.

## DISCUSSION

The age peaks were at 5th and 7th decades in males and in 6th decade in females. Males predominated (81.3%) by four times  $M/F = 4.1:1$ .

The mean age of males at time of presentation was 49.7 years ranging from 6-80 years, in females 50.3 years, (range 27.70 years). The overall mean age at time of presentation was 49.8 years. In Uganda mean age is 54.8 years, Europe 61.2 years, Malawi mean age 44.9 years. (11), which is the typical bilharzial bladder cancer period in patients who have had chronic bilharziasis for 10 years or more. Kenyatta National Hospital figures fall within this range. The histogram of age/sex distribution is shown in figure (ii).

One need not be alarmed by conflicting figures of incidences, as 0.75% is what is the problem at Kenyatta National Hospital and 0.92% as the country-wide problem.

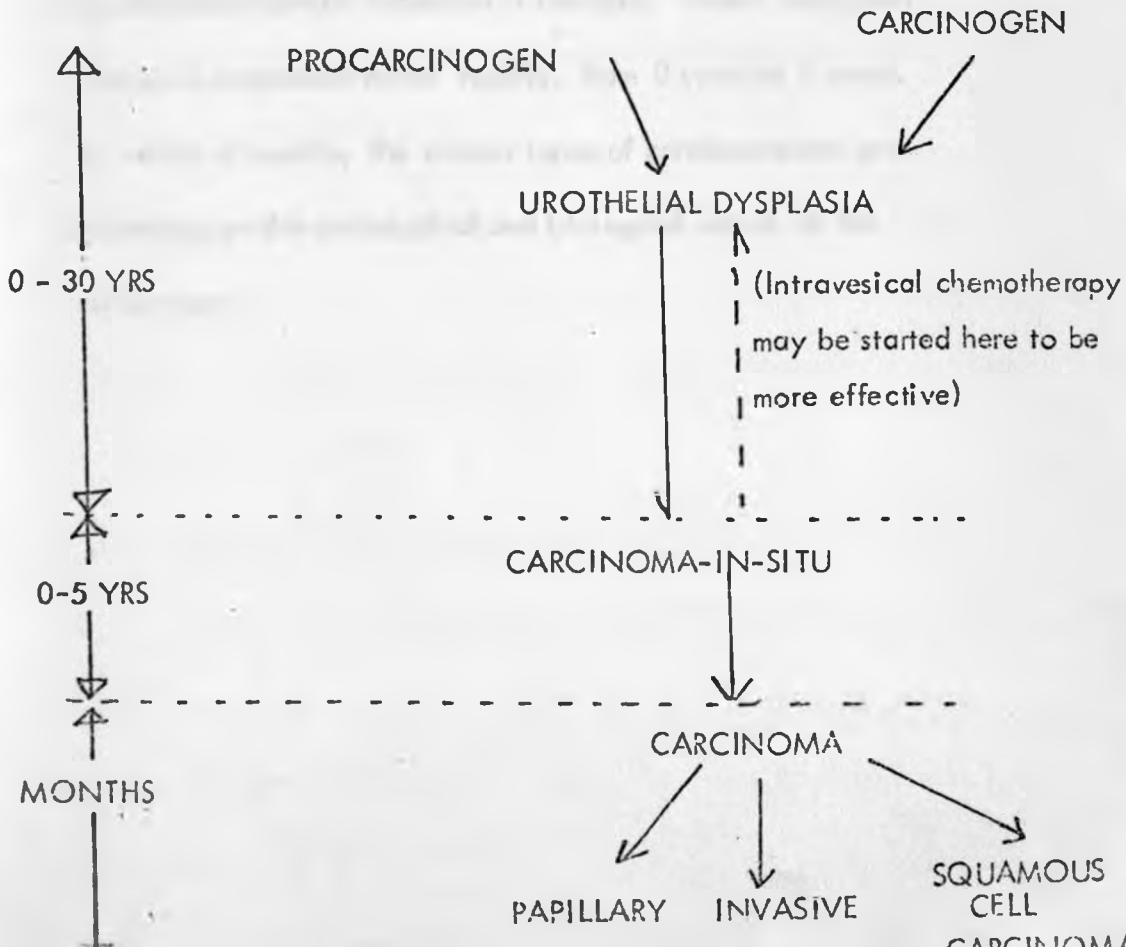


Aetiological factors were sought for in 44 patients who had records, of occupation, lifestyles, social habits. There was no record of irradiation, contact with any cosmetic usage, etc.

26 patients (34.7%) were peasants, living in huts, where they use firewood as source of fire. Inhalation of smoke from firewood is a possibility of causative agent.

3 patients (4.0%) were bus drivers.

The aetiological factors are thought to be mainly hydrocarbons which act on the target organs, as shown in the scheme below.



It would be difficult to say for sure whether aforementioned factors are contributory to bladder cancers. One would have to undertake a cohort (cases and controls) study so in our local situations further study is required as we have no much industrial, occupational hazards as in Europe and North America, in search of possible aetiological links. The *S. haematobium* infection as a possible link in squamous cell carcinoma is only conjectural. It is thought that interaction of procarcinogens and carcinogens do after a long time (range from 0-30 years) produce urothelial dysplasia which is a precursor to carcinoma in situ. This process may be reversible as experimentally it may be possible when intravesical chemotherapy is given, but more so the progression to carcinoma-in-situ formation is checked. Overt malignant change is progressed rather rapidly, from 0 years to 5 years. In matter of months, the various forms of carcinomas are seen depending on the aetiological and biological nature of the carcinomas.

### CLINICAL FEATURES:

65.3% of patients studied presented with cystitis, dysuria and frequency, while 10.7% were negative for above. Frequency and urgency occur sometimes because of reduced bladder capacity and pain by bladder tumour. This should be differentiated from bladder tuberculosis .

81.3% of patients presented with history of haematuria. Haematuria and frequency of urination not otherwise explained should suggest bladder carcinoma. Above figures are quite high which suggest that haematuria with irritative urinary tract symptoms should arouse one's mind to think about the possibility of having bladder cancer. It has been reported in literature that patients with Carcinoma in situ, 90% of them have irritative bladder symptoms i.e. frequency dysuria urgency, and haematuria (24).

Urinary retention was present in 41.3%, 5.3% having acute retention and 36.0% with chronic retention. Urinary retention, where evidence of enlarged prostate, urethral stricture obstruction is lacking should arouse the suspicion.

85.3% presented with general malaise and anaemia. This is the effect of haematuria and general features of tumours.

13.3% presented with fever, possibly due to superadded bacterial infection or release of pyrogenic emboli, by necrotic tumour cells.

29.3% presenting with weight loss is a reflection of systemic tumour effects, along with added urinary tract infections. In urinalysis -only four patients had ova of *S. haematobium* in urine, 3 cases were from Coast Province and one from Nyanza Province.

Culture and sensitivity of organisms was positive in 28 samples of urine. The pattern of frequency of organisms grown tally well with the work done by Clair et al (25) who reported almost the same pattern in order of frequency.

TABLE XIII

		KNH Serises
E. Coli	17.7%	10.7%
Aerobacter-Klebsiella	11.3%	10.7%
Intermediate coliforms	8%	-
Proteus species	6%	6.7%
Pseudomonas	6%	2.7%

Explanation for high rate of infection, is the effect of vesical neoplasm on the bladder defence mechanisms and possibly systemic defences as well. The principle determinant of infection is the conditions of the host and not the availability of bacteria i.e. suppression of immune response by the tumour to combat the infection. The high rate of enterococcal infections in these patients with vesical cancers is a reflection of reduced host defence

mechanisms as these organisms rarely infect individuals with good host resistance.

The high rate of haematuria encountered earlier can be explained partly by this high rate of infection and partly from the tumour itself. Cytology as a form of investigation was done only in one patient which showed malignant cells in the sample of urine.

Cytology is a valuable procedure in the detection and follow up of patients with bladder cancers. The early changes in the development of bladder cancer in those patients exposed to industrial carcinogenes could be detected if this procedure is routinely employed in those at risk. Recognition of fine often subtle cellular details requires meticulous attention to collection and processing methods. Recovery of cells can be in form of:- direct smears methods or Cyto-centrifuge of filtration .

The procedure used will depend on previous training and current experiences of laboratory personels, volume of material received, the cost of supplies and equipment. Sources of this cytological studies are got often from bladder washouts or morning specimens. Mainly the procedure is of value in those patients that are being screened and followed up. The stages of exfoliative cytological

screening will depend on:-

- i) Atypical urine cytology associated with histological evidence of transitional cell dysplasia.
- ii) Deteriorating cytological picture associated with carcinoma-in-situ.
- iii) Obvious malignancy.

In carcinoma -in-situ, cytology is superior to histology and even cystoscopy, hence the popularity. With topical and systemic chemotherapy, cytological alterations include multinucleation, nuclear hyperchromasia, and increased nuclear size, and cellular degeneration. These changes are largely confined to superficial cells and are sufficiently different from those cancer cells so as not be confounding factors in the diagnosis of neoplasia when performed by experienced pathologists. The cytological features are based on Papanicolau grading which is in five classes.

Class	I	(NORMAL) Normal transitional cells in sparse numbers.
Class	II	(ATYPICAL) - Urothelial cells are present in increased numbers, but of normal morphology or small transitional cells or increased numbers of leukocytes and histiocytes with or without bacteria indicating either infection or inflammation.
Class	III	(SUSPICIOUS) - Abnormal epithelial cells are present with enlarged and/or hyperchromatic nuclei not fulfilling malignant criteria.

Class IV (Probably malignant) - Abnormal epithelial cells, features resembling malignant cells (abnormal nuclei-cytoplasmic ratio, hyperchromatic nuclei).

Class V (Malignant) - cells are present in the urine with all the criteria of malignancy.

TABLE 4.101

UROTHELIAL CARCINOMA FEATURES IN CYTOLOGY

	Low grade	High grade
Cells	Occurrence - Papillary aggregate loose clusters	Isolated Loose clusters
	Size Increased Uniform	Increased Pleomorphic
Cytoplasm	Homogeneous	Variable
	Nuclear/ cytoplasmic ratio Increased	Increased
Nuclear	Position - size Morphology Borders Chromatin	Eccentric enlarged variable with aggregates Irregular Notches(Creases) fine-even
		Eccentric variable variable Irregular Notches(Creases) course-irregular
Nucleoli	small/absent	variable

Of the patients whose biochemical records were available, they were 32 and showed that 26.7% had normal urea and electrolytes while 16.0% showed deranged electrolytes and raised BUN respectively.

RADIOLOGICAL FINDING:

4 patients (5.3%) had positive calcifications of the bladder, indicating *S. haematobium* infection. 7 patients (9.3%) had upper urinary tract changes of hydronephrosis, 5 cases showing unilaterally while 2 cases were bilateral, thus indicating high frequency of cancers unilaterally while 2 cases were bilateral, thus indicating high frequency of cancers unilaterally. One patient had unilateral non functional kidney showing total affection by the neoplasm. 33 patients (44.0%) showed filling defects in the bladder; 1.3% being contributed by a case investigated for bladder pheochromocytoma, while 42.7% were shown by I.V.U.

M.C.U. done, revealed 3 cases as positive (4.0%) for bladder filling defects.

It is interesting to note that the pyelographic changes in the upper urinary tracts are seldom seen in the presence of the bladder tumours (26) however the following occur:-

- Non functioning of one or other kidney.
- Dilatation of the ureters and possibly the pelvicalyceal system.



These changes are most commonly seen in association with tumours of the region of ureteric orifices. Such changes are infrequent in the presence of the common exophytic type of growths.

- A filling defect in the pelvis or calyces indicating the presence of a urothelial tumour.

However in lower renal tract, the cystographic changes are dependent upon the pathological variety of the tumour such as in a:-

- a) Common exophytic type of growth - a well circumscribed filling defects or defect are or is seen. However large the tumour, a thin layer of contrast medium always surrounds the mass and outlines the bladder wall. The filling defect may have a mottled appearance because the dye flows between the fronds of the tumour.
- b) The less common infiltrative endophytic type of growth causes a similar positive filling defects on the cystogram but it is usually flatter. Infiltration causing rigidity of the bladder wall may lead to an unnatural asymmetry of the bladder shadow.

Other diseases or conditions that may be mistaken for bladder tumours or may complicate the urographic picture if a tumour is present, are ureterocoele, bladder diverticulum, asymmetry without other vesical abnormality, oedema of the trigone resulting from a low ureteric calculus, friction of the bladder wall by an indwelling catheter or from acute cystitis radiolucent calculus or compression of the bladder e.g. prostate.

The bladder tumours that are likely to be missed in cystogram are those that are nonpapillary, non sessile, less than 1 cm in diameter, situated close to the prostate so that they may merge into filling defects they cause or in bladders that sag into the pelvis because of cystocoele formation and obscured by the pubic bone (27).

N.B. Tumours in a bladder, where the diverticular can be seen only in an oblique view of the bladder, where the diverticular is (filled with contrast medium) is filled with contrast medium (27).

Flush angiogram was done on one boy of 14 years who showed features of pheochromocytoma and this turned out to have a filling defect in the bladder/will ne explained later.

## CYSTOSCOPY

The frequency of distribution was mainly on the lateral and posterior walls of the bladder. Fewer frequencies in infiltrative masses could be due to their being missed and passed as cystitis. The mucosæ are roughened, thickened irregular, indurated and haemorrhagic generally (28) in early cases of neoplasms e.g. carcinoma-in-situ.

The cystoscopy enables one to observe:-

- i) Position and number of tumours present.
- ii) The degree of fronding e.g. a high fronded papillary growth indicates an exophytic non infiltrating tumour.
- iii) The presence of ulceration and associated infection; these changes indicate a malignant infiltrative or endophytic type of tumour.
- iv) Solidity of the tumour; indications of endophytic types.
- v) Roughening, thickening and irregularity of the intervening mucosa-indication of probable carcinoma-in-situ.

### STAGING:

The staging was not done in all patients. Bimanual examination (palpation) of bladder masses were done under general anaesthesia soon after cystoscopy in 27 patients (36.0%). Bimanual examination if done hurriedly can miss tumours at vault, anterior wall immediately behind the symphysis pubis (28). Palpation is open to considerable observer variation. Ultrasonic scanning where available is said to aid in correct staging (29).

Added methods to assist the assessment of the degree of bladder involvements are radiological, arteriography, lymphangiography.

Radiologically, one could employ the:-

- Double contrast cystography or
- Triple contrast cystography.

Double contrast cystography involves the insufflation of bladder with gas approximately 200ml or until the desire to void occurs. The bladder will have had contrast medium introduced into it to coat the tumour.

X-ray films are taken in different views after the patient has been rotated several times in order to ensure complete coating of the tumour. Tumours not readily apparent in the cystogram, following IVU are demonstrated (30). In addition rigidity and irregularity of the bladder wall is recognised.

Triple contrast cystography technique involves the above with the perivesical insufflation with air. Here sharper contrast, details of vesical wall thickness are demonstrated.

In arteriography, the vascular pattern very according to the tumour. The pathological vessels which supply a bladder tumour possess a convoluted appearance, and arterio-venous shunting is common place, leading to early venous filling. Extension of the tumour beyond the bladder wall leads to the presence of the abnormal vascular changes in the perivesical tissues. It has been shown to furnish very accurate information with regard to staging (31).

In lymphangiography, correlation of the lymphangiogram with histologic examination of the surgically excised pelvic and para-aortic nodes is reported to be less than 50%, this suggests limited applicability of this diagnostic technique in staging bladder cancers (32), but the accuracy of lymphangiography and arteriography (bilateral selective hypogastric) is said to be about 78.8%.

With the above procedures the staging can be done adequately, see chart.

T. - Primary tumour

The suffix (m) may be added to the appropriate T category to indicate multiple tumours, e.g. T2 (m):

- TIS Pre-invasive carcinoma (carcinoma in situ)
- TX The minimum requirements to assess fully the extent of the primary tumour cannot be met.
- TO No evidence of primary tumour.
- T1 On bimanual examination a freely mobile mass may be felt; this should not be felt after complete transurethral resection of the lesion and/or microscopically the tumour does not extend beyond the lamina propria.
- Note: This category includes papillary tumours.
- T2 On bimanual examination there is induration of the bladder wall which is mobile. There is no residual induration after complete transurethral resection of the lesion and/or there is microscopic invasion of superficial muscle.
- T3 On bimanual examination induration or a nodular mobile mass is palpable in the bladder wall which persists after transurethral resection of the exophytic part of the lesion and/or there is microscopic invasion of deep muscle or of extension through the bladder wall.
- T3a Invasion of deep muscle.
- T3b Extension through the entire bladder wall.

T4 Tumour fixed or invading neighbouring structures and/or there is microscopic evidence of such involvement.

T4a Tumour fixed to the pelvic wall and/or infiltrating the abdominal wall.

#### N-Regional and Juxtaregional Lymph Nodes.

The regional lymph nodes are the pelvic nodes below the bifurcation of the common iliac arteries. The juxtaregional nodes are the inguinal nodes, the common iliac and para-aortic nodes.

NX The minimum requirements to assess the regional lymph nodes cannot be met.

NO No evidence of involvement of regional lymph nodes.

N1 Involvement of single homolateral regional lymph nodes.

N2 Involvement of contralateral or multiple regional lymph nodes.

N3 There is a fixed mass on the pelvic wall with a free space between this and the tumour.

N4 Involvement of juxtaregional lymph nodes.

Subsequent information regarding the histological assessment of the regional lymph nodes may be added to the clinical N category thus: N-(minus) for nodes with no microscopic evidence of metastases; or N+ (plus) for nodes with microscopic evidence of metastases, e.g. N0+, N1-

M-Distant Metastases

MX The minimum requirements to assess the presence of distant metastases cannot be met.

MO No evidence of distant metastases.

MI Distant metastases present.

MIa Evidence of occult metastases based on biochemical and/or other tests.

MIb Single metastases in a single organ site.

MIc Multiple metastases in a single organ site.

MI d Metastases in multiple organ sites.

Note: the location of metastases should be specified. The lymph nodes beyond the regional and juxtaregional nodes, and bone are regarded as single organ sites.

P Histopathological categories.

Assessment of the P categories is based on evidence derived from surgical operation and histopathology - i.e. where tissue other than biopsy is available for examination.

The suffix (m) may be added to the appropriate P category to indicate multiple tumours, e.g. P2(m).

PIS Pre-invasive carcinoma (Carcinoma in situ).

PX The extent of invasion cannot be assessed.



- PO No tumour found on examination of specimen
- P1 Tumour not extending beyond the lamina propria
- P2 Tumour with infiltration of superficial muscle  
(not more than half-way through muscle coat).
- P3 Tumour with infiltration of deep muscle (more  
than half way through muscle coat) or infiltration  
of perivesical tissue.
- P4 Tumour with infiltration of prostate or other  
extravesical structures.

G-Histopathological Grading .

- GX Grade cannot be assessed .
- GO No evidence of anaplasia .
- G1 Low grade malignancy .
- G2 Medium grade malignancy.
- G3 High grade malignancy.

L- Invasion of Lymphatics .

- LX Lymphatic invasion cannot be assessed.
- LO No lymphatic invasion .
- L1 Superficial lymphatics invaded.
- L2 Deep lymphatics invaded.

**Note:** The histopathological categories and grading confirm to the recommendations of WHO ref: **Histological Typing of Urinary Bladder Tumours WHO 1973, Geneva.**

HISTOLOGICAL FINDINGS:

The histological classifications seen in the study were in order of frequency.

Transitional cell carcinoma	53.3%
Anaplastic Carcinoma	17.3%
Squamous cell carcinoma	13.3%
Adenocarcinoma	5.3%
Embryonal bladder rhabdomyosarcoma	5.3%
Bladder pheochromocytoma	1.3%
Bladder papilloma	4.0%

Those tumours that were found to be associated with *S. haematobium*.

Squamous cell carcinoma	6.7% of total cancers
Anaplastic carcinoma	4.0% of total cancers
Transitional cell carcinoma	1.3% of total cancers.

Squamous cell carcinoma showed high association as reported earlier (1). Transitional cell carcinoma was encountered frequently. This is not surprising, as the majority of patients seen are from non endemic area again tallying with previous reports (1), and has the least association with *S. haematobium*. Those cases associated with bilharziasis are mainly from the Coast and Western Kenya with a few pockets scattered among the Kambas (Ukambani) and Somalis (North Eastern).

The histological development of squamous cell carcinoma may be either, the normal transitional epithelium undergoing abnormal transitional epithelium which undergoes metaplastic change into squamous epithelium, which in turn develops into squamous cell carcinoma or normal transitional cell epithelium, undergoing abnormal transitional epithelium, and then onto transitional cell carcinoma, to squamous cell carcinoma by metaplasia. There is no evidence that transitional cell carcinomas regularly undergo metaplasia with lengthening history, but it has been suggested that the typically late presentation; of bilharzial bladder cancer patients allowed time for cancer, initially transitional cell, to undergo squamous metaplasia and result in squamous cell carcinoma (33).

The actual pathogenesis is not known in man but the postulates in man include:-

The effects of chronic inflammation on reducing the mucosal barrier to carcinogens, the bladder stasis resulting from bilharzial fibrosis permitting layer contact between mucosa and carcinogens, reduced immune surveillance through chronic infection having a permissive effect, elevated urinary  $\beta$  glucuronidase levels in bilharzial patients liberating carcinogenic amines from glucuronides in the urine, disordered tryptophan metabolism with

Increased production of carcinogenic metabolites; the effects of the chronic foreign-body reaction in the bladder to schistosome eggs (foreign body tumorigenesis). The most attractive hypothesis is the role of secondary bacterial infection in the bladder (cystitis) as a result of the poorly functioning fibrotic bilharzial bladder. Nitrosamine levels have been found to be high in urine of Egyptian *S. haematobium* infected patients with bladder cancer. They are formed by bacterial catalysis of the nitrosation of secondary amines with nitrates or nitrites (12).

Embryonal rhabdomyosarcoma of the bladder, though not reported previously in Kenyatta National Hospital was seen in 5.3%. Interest has grown recently with embryonal rhabdomyosarcomas, not necessarily those involving the bladder, with the set up of paediatric surgical unit, which picks such cases early before it is too late. This is evidenced by 4 cases reported in 1982.

Pheochromocytoma of the bladder form the least incidence. This is the first case reported in Kenya. Existence of paraganglia associated with the urinary tract was illustrated by Kohn in 1903 (2), other reports say that it is a constant feature, of the adult bladder, usually, found between muscle cells, but also present in the submucosa and adventitia (34). The case reported in Kenyatta National Hospital was transmural. Besides pheochromocytoma in these rests, non

chromaffin paraganglioma (chemodectoma) and mixed pheochromocytoma-chemodectoma, are also on record (35). Work on bladder tumours has shown the frequency of pheochromocytoma of bladder to be in the order of 0.3% of all bladder tumours (36). High frequency seen here (1.3%) on the study, could be due to small samples or may be it could be of high frequency if looked around.

By 1981, 68 cases of bladder pheochromocytoma had been on record in literature, and 10.3% of them were malignant as evidence by local or distant metastasis. The malignant potential of the bladder pheochromocytoma is thus similar to other extra pheochromocytomas. The tumour might occur anywhere in the bladder, lateral wall being the highest. Painless haematuria is said to be present in 45% and hypertension in 77%. The youngest reported patient was 11 years. In my series the patient was a 14 year old boy.

Individual variations in paroxymal attacks may occur for a part from producing catecholamines, a number of hormonal peptides are found, e.g. somatostatin, methionine-enkephalins, calcitonins which have been found in the bladder.

It is thought that some remains of foetal paraganglia might persist through adult life, even in such anomalous places as the bladder wall.

The paranglia are only sparsely distributed in the midterm of human foetal bladder. A tremendous increase in their number must occur during later stages of development, it is probable that the differentiation of the primitive sympathicoblasts which are known to be distributed along the sympathetic chain, leads to the development of the intramural ganglia located in the bladder wall.

### HISTO-PATHOLOGICAL GRADING/STAGING

Histological grades show that transitional cell carcinoma has high rate of poorly differentiated types (50.5%) followed by squamous cell carcinoma (30%). This grading is dependent upon, increased degree of nuclear pleomorphism, increased nuclear-cytoplasmic ratio; increased chromatin clumping, mitotic activity; cytoplasmic differentiation into well, moderately well or poorly differentiated into well, moderately well or poorly differentiated categories.

Histopathological staging was not given. Tumour invasion and/or presence of lymphatic or vascular permeation is possible, or easily seen on cystectomy specimens, but is not so and is less accurate on biopsy material. The main problem stems from sampling errors by the cystoscopist and the necessarily superficial nature of most biopsies.

The above high rate of poorly differentiated type of carcinomas could have a bearing in the survival rate of the patients in that the majority of patients have poor prognosis. This could be explained

by the fact that the patients present late.

TREATMENT OFFERED:

Patients that underwent surgical intervention were 32 i.e. 42.7% out of whom the reported mortality was 31.3% or 13.3% of total patients under review. This mortality figure is not a true reflection of the problem, as there was no proper recording of patient follow up. It appears that patients who had continued therapy - surgical/chemotherapy and radiotherapy did better than those with surgical excision only provided that the tumour is not advanced. Local resection and partial cystectomy cases do not seem to do well than when surgical treatment is coupled with adjuvant therapy.

One patient with superficial poorly differentiated carcinoma besides partial cystectomy and DXT, had intravesical adjuvant chemotherapy (Thiotepa). Thiotepa is a tumour inhibiting agent which has the theoretical advantage of being poorly absorbed through the bladder mucosa, due to its high molecular weight (37). Intracavitary instillation of bladder cancer principles are that the ideal agent used should have:-

- i) Minimal if any systemic toxic effects.
- ii) Minimal if any local symptomatic reaction in the bladder.



- i ii) Simplicity of treatment enabling many patients to be treated simultaneously.
- v) Satisfactory therapeutic response.
- vi) Repetitive treatment possible, due to absence of damage to normal bladder wall.
- vii) No risk of inducing metastases.

Therefore the rationale for intravesical bladder chemotherapy is necessary where the recurrence rate is high even with complete surgical resection hence adjuvant therapies are utilised for sometime because:-

- i) Antineoplastic agents instilled into the bladder would allow a high concentration of drug to come into contact with urothelium for a relatively long period of time.
- ii) This route might allow a reduced likelihood of tumour recurrence by destroying viable tumour cells in the bladder following surgical intervention and this prevent tumour implantation.
- iii) It might also exert cytotoxic activity on residual carcinoma or carcinoma-in-situ adjacent to primary site of tumour.
- iv) It might minimise the systemic toxicity of the agent.

- v) It might delay or abort the need for cystectomy and attendant loss of urinary and sexual function in what may be an asymptomatic patient.

Transurethral resection is gaining popularity in Europe and hence is used extensively in superficial tumours with no muscle invasion. It is usually accompanied by endoscopic coagulation which is with hazards or disadvantages such as:-

- a) Ureteric orifices stenosis or refluxing.
- b) Perforation which may be immediate (acute) or delayed.
- c) Bladder contracture as a result of diathermy.
- d) Chronic infection.
- e) Implantation of clumps of tumour cells in deeper biopsies in possible.
- f) Some tumours in saccules or diverticulae are in accessible to cystoscopic treatment.

Besides the control of e and f, intravesical chemotherapy especially Thiotepa is warranted and is advantageous in:-

- failure of control of multiple recurrences by local means (cystodiathermy or TUR) including inaccessibility,

- inadequate diathermy
- uncontrolled haematuria; massive tumour.

Provided that the hazards of bone marrow depression are recognised, intravesical thiotepa therapy appears to have a place in the management of low grade tumours, where direct treatment by cystodiathermy has failed (38).

Recent work on blood group iso antigens on urothelial epithelium can determine whether intravesical therapy is warranted (39). Deletion of blood group antigens is not correlated with histologic grade, stage or survival rates in patients with transitional cell carcinoma of bladder. However the presence or absence of the blood group antigens may be an important parameter in segregating patients who will and will not have subsequent intravesical recurrences. Absence of blood group antigens represent a future malignant potential of transitional cell carcinoma of the bladder such as subsequent intravesical recurrence and later invasion into deep muscles. Deep infiltration or advanced bladder tumour can be sought for by assaying urine immune complexes, found more frequently in urine than in serum, which have a better correlation with the presence of infiltrating bladder cancer.

The natural and therapeutic history of any superficial bladder cancer will depend on grade, multicentricity (polychromotopicity)

the variable nature of of Carcinoma-in-situ, tumour implantation (37). The grade provides the clinician with an estimate of potential for growth and subsequent invasion of the bladder wall, the probability of which increases with increasing tumour grade. Carcinoma-in-situ, is a different biologic entity in that it probably represents a spectrum of neoplasia. At least there are 4 different clinical situations which may have different biologic outcome,

- a) Small foci of carcinoma-in-situ immediately adjacent to a papilloma of the bladder.
- b) A number of areas on random biopsy which show carcinoma-in-situ at the time of TUR of the papilloma.
- c) Total or near total involvement of the urothelium with carcinoma-in-situ with or without papillary tumours.
- d) Symptomatic (irritative bladder symptoms) carcinoma-in-situ which is associated with total or near total mucosal involvement.

Tumour implantation, evidenced by wound recurrences rate is higher following segmental resection as against transvesical fulguration, a factor being may be the traumatised urothelium. Infact one patient in the series was noted to have this phenomenon after local resection of pillary tumour; tumour growths were seen in surgical wound 2 weeks after surgery. Prevention of tumour implantation has been attempted by Bumard et al (40) who noted a decrease in recurrence rate after 1 year between a treatment group receiving 40mg thiotepa intravesically for  $\frac{1}{2}$  hour following TUR versus a non chemotherapy control group. Radium implants to control large superficial turn over locally have been used elsewhere and reported recurrence rates was 12% in contrast to 50% recurrence rate in patients having TUR alone.

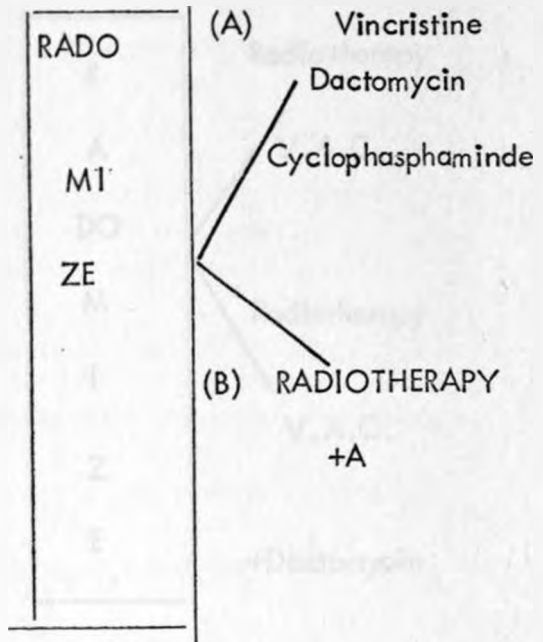
In embryonal rhabdomyosarcoma, the treatment depends upon the group at which the tumour lies.

The Rhabdomyosarcoma intergroup study committee or Institute (I.R.S.I.) has classified them and randomised the treatment depending on the group.

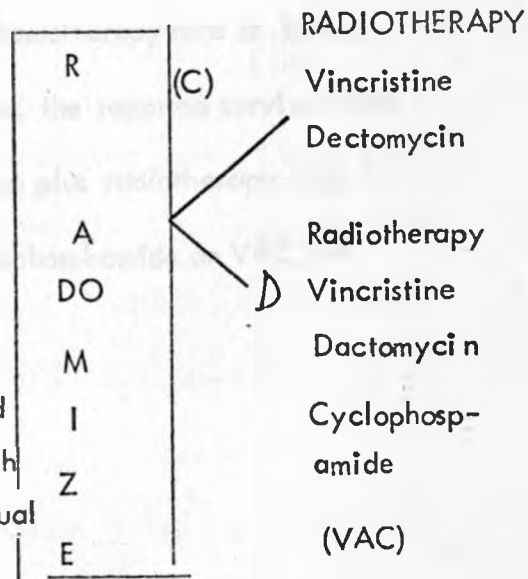
In our series the cases of embryonal rhabdomyosarcoma fell into group 1: the treatment policy adopted is as shown in the flow chart below.

Table XV

- Group 1 Localised disease, completely resected (Regional nodes not involved)
- a) Confined to muscles or organ of origin.
  - b) Continuous involvement - infiltration outside the muscle or organ of origin as through fascial planes.

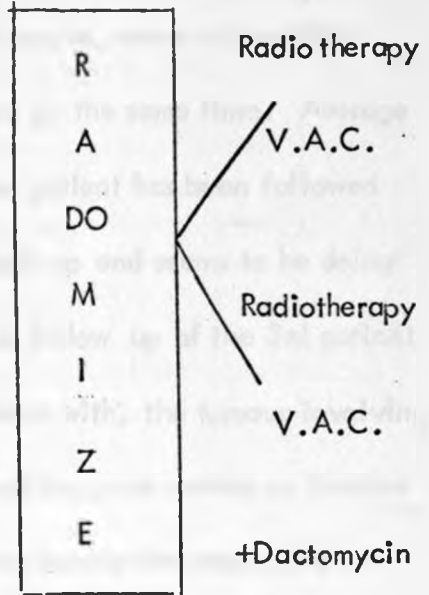


- Group II
- a) Grossly resected tumour with microscopic residue disease (nodes negative)
  - b) Regional disease completely resected (nodes +ve or -ve)
  - c) Regional disease with involved nodes, grossly resected but with evidence of microscopic residual disease.



Group III Incomplete resection or biopsy with gross residual disease.

Group IV Metastatic disease present at onset.



Partial cystectomy or simple tumour excision leads to local recurrences and dissemination but with chemotherapy rate of local recurrence is low. In pelvic exenteration, the reported survival rates is low (10-40%) while pelvic exenteration plus radiotherapy plus 1 or 2 year treatment with vincristine cyclophosphamide or VAC, the survival rate is high (41).

The patients who had total cystectomy had tumours involving the trigone of bladders hence partial cystectomies, were not possible. Diversion of urine was (ileal conduit) done at the same time. Average age in these 3 cases was 56.3 years. One patient has been followed up for 8 years, he comes regularly for check up and seems to be doing well. One patient died while there was no follow up of the 3rd patient. Total cystectomy is therefore done in patients with, the tumour involving the trigone or internal meatus, tumour involving both ureters or involve one and extends to within 2 cm of the other tumour has destroyed a wide extent of bladder wall, tumour is of infiltrating type, tumour is associated with septic cystitis which does not respond well to chemotherapy.

#### CHEMOTHERAPY ALONE

Six patients, half with anaplastic carcinomas and one with squamous cell carcinoma died during the course of the disease. One with transitional cell carcinoma was not specified whether dead or alive. Surgery was not indicated as the tumours were for too advanced. Chemotherapy was only palliative, as their mean age was going into the six decade. It can be seen that mortality for anaplastic cell carcinoma is high (66.6%) though also, one with squamous cell died due to old age (80 years) plus pneumonia. The uncounted two patients, could have died at home. Only one survivor recorded, indicating that systemic chemotherapy is probably of no value in very advanced neoplasms of the bladder.



### RADIOTHERAPY ALONE:

15 patients underwent radiotherapy for palliative purposes. Their ages ranged from 30 to 70 years. Mean age being 47.1 years. Radiotherapy was chosen because of degree of spread of tumour or the age factor. Records show 4 mortalities and 3 survivors. One cannot account for other 8 patients. Data available show the mortality on anaplastic carcinomas to be 100%, Adenocarcinomas 50%, squamous cell carcinomas, 33% and transitional cell 11%. Lack of information in squamous cell carcinoma, (two thirds of patients) and half of adenocarcinoma, indicate that perhaps the patients died at home as their prognostic documentation was not available. The inference is that perhaps they are radio-resistant, unlike transitional cell carcinoma. The unaccounted eight patients might mean that they were missed on their follow up or perhaps died at home.

### RADIOTHERAPY & CHEMOTHERAPY:

Combined chemotherapy and radiotherapy were done in 8 patients. One patient with superficial poorly differentiated transitional cell had intravesical chemotherapy and is alive. Intravesical adriamycin in varying concentration on frequency of instillation has been reported to be of value in the management of superficial papillary bladder tumours

and carcinomas-in-situ. It has been advocated both for treatment of residual bladder tumours and in the prevention of recurrences. It has also been shown that plasminogen activators enhance the penetration of cytotoxic drugs into tumour cells and these promote the intracellular release of cytosomal hydrolases which destroy the internal cellular structure. If this mode of treatment is adopted then it should be given one month after tumour resection to avoid systemic side effects. Its limitation is the cost (42). Mortality rate was 50% for squamous cell carcinoma, 100% for adenocarcinoma. Probably it was 100% for mortality in anaplastic carcinoma as there was no record in one patient whether he was alive or dead.

This indicates poor prognosis for anaplastic carcinomas and relative insensitivity to radiotherapy of large squamous cell carcinomas. Whether this is due to their size, lack of vascularity or an inherent property of squamous cell carcinoma is unclear.

#### HELMSTEIN THERAPY:

Two patients over 65 years of age had massive haematuria and so weak to stand any operation. They had transitional cell carcinomas, and underwent hyperthemic hydrostatic dilatation of the bladder. Their symptoms subsided but recurred after 2 years. It is not indicated what happened to them. This demonstrates that it is possible to have a clinical cure for patients with transitional cell

carcinoma if they present early to treatment.

PROGNOSIS:

It was not possible to quantify the extent of prognostic magnitude as the documentation of patients were quite difficient in as to:-

- When the patient died, after the problem was diagnosed.
- The follow up
- Staging (clinical) which was not done in all the patients

Generally it is known that the potential curability progressively decreases with the degree of infiltration of the tumour i.e. curability is better in situation where infiltration even more so in perivesical connective tissue involvement (43). The potential curability is much lower when the cancer cells have invaded the whole muscle wall, than when they are half way level i.e. in superficial muscle only. The exact depth of the infiltration can be assessed only in an excised bladder segment or in the excised whole bladder, but cystectomy is not the only procedure when dealing with vesical neoplasm. TUR are gaining importance and one can not be sure that the separate pieces of superficial and deep muscle layers can be obtained in every patient.

It has been noted that the prognosis of a neoplasm especially superficial non invasive tumours of the bladder can be assessed by identifying the blood group isoantigens (39,44,45) loss of this isoantigens on mucosal surface of surgical specimens signifies the likelihood of recurrence, or increased invasiveness. On the same token, it had also been observed that advanced bladder carcinoma associated with schistosomiasis frequently maintain respective blood group isoantigens, unlike those not associated with schistosomiasis in whom isoantigens almost are always lost hence better prognosis (46). Further work has shown that presence of isoantigens correlates best with squamous differentiation rather than schistosomiasis, as it has been observed that tumours with secondary degenerative changes or schistosomiasis unrelated squamous or glandular differentiation (as often occurs after radiation or chemotherapy) usually are positive for respective isoantigens (46).

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## CONCLUSION

1. The age sex distribution of the urinary bladder neoplasm:-
  - The peak ages are double, 1st on 6th decade, 2nd on 7th decade but peak age range 50-70 years, but males were majority whose peaks were in 5th and 7th decades, while in female it was in the 6th decade.
  - The males predominated in all age groups. There were no patients encountered above 80 years, perhaps our population with this condition do not live this long.
2. There was no clear cut aetiologic link.
3. Most patients present with irritative bladder symptoms in 65.3% while 81.3% present with haematuria and 41.3% with bladder outlet obstruction or inability to pass urine with easy, 85.3% with general malaise, 29.3% with weight loss. It has been suggested that frequency, urgency, haematuria and sometimes reduced bladder capacity and suprapubic pain is suggestive of bladder cancer which requires investigations (47).
4. Immuno compromised patients with carcinoma of bladder have high rate of urinary tract infection more so with enterococcal microbes.

5. The patients with bilharzial bladder involvement with carcinomatous changes do not necessarily have ova of *S-haematobium* in urine. The ova could have been eliminated prophylactically long before the bladder cancer symptoms start.
6. Cytological study if done well by well trained personnel is the best tool both for diagnosis and follow up. It has the advantage of being quicker and less time consuming.
7. Derangement of urea/electrolytes seem to tally with extent of renal damage by the tumour effects.
8. Radiological examination to see the state of kidney function as well as lower urinary tract is essential. It is useful pre-operatively as well as follow up as a measure of surgical/non surgical treatment effectiveness. I.V.U. is the most single important investigation, which apart from above can also be used as a complement to clinical staging of bladder tumour invasiveness (27.30).
9. Cystoscopy is the most important diagnostic tool. It should be done in all patients with irritative bladder symptoms plus haematuria to ascertain their causes. If the mass is found intravesically, then its characteristics, site, configurations are noted.

It should be followed up by biopsy of the mass seen or multiple blind punch biopsies which are taken to histology. Staging of the tumour clinically, follows above procedures.

10. The frequently seen histological variant of the tumour is transitional cell carcinoma of all stages and/or grades. It is followed by anaplastic, and then by squamous cell carcinoma. The least found was a bladder pheochromacytoma. High grade and advanced stage of transitional cell and poor prognosis of anaplastic could explain high mortality that is noted.

For histopathological staging, adequate tissue biopsies are necessary.

11. The frequently seen tumour associated with *S. haematobium* was squamous cell carcinoma followed by anaplastic carcinoma. These were cases mainly from the Coast and Lake regions.
12. In paediatric practices, the role of embryonal rhabdomyosarcoma involving the pelvic organs should be emphasized in a child who is found to have pelvic mass. Four cases were picked up on time. A case of bladder pheochromocytoma is also presented.

13. Surgery alone, without adjuvant therapy in form of chemotherapy and/or radiotherapy is not effective in advanced cases of neoplasia.
14. Non invasive lesions (single or multiple) of the bladder can be treated with endoscopic resection or diathermy which may be followed by intravesical chemotherapy which should not be immediate to avoid absorption through the raw areas and cause systemic side effects. Alternative to chemotherapy, the Helmstein therapy, may be used which consists of inserting, a balloon into the bladder and raising pressure to above the diastolic pressure (48). In multiple bulky fronded bladder tumours in which there is a narrow pedicle, this form of therapy may, by cutting off blood supply of tumour, produce necrosis and subsequent tumour regression. In advanced cases this hydrostatic pressure can be used to control haemorrhage and pain as evidenced by two cases reported in the study.
15. Radiation for non invasive tumour is not recommended since although regression may occur, radiation changes or radiation haemorrhage may be produced. Recurrences may occur after



radiation and subsequent diathemy of heavily radiated bladder can precipitate necrosis of the bladder wall, hence reserved for more serious infiltrating type of lesions.

16. The average age of the patients undergoing surgery were all below 60 years except for one instance where average ages was 65 years, but mortality here was high.
17. In the present series, it was not pointed out what therapeutic criteria was used except for very few patients under study.
18. Provided the patients seek medical advise early perhaps some of these patients can be helped and survival rates improved.

RECOMMENDATIONS

1. Adequate documentations of the patients is necessary.
  2. Close follow up of the patients is necessary if proper records for prognosis is to be made in terms of patients survival rates with different treatment regimens.
  3. In follow up, a clear policy should be made, repeat cystoscopy at three monthly intervals in the first instance and then at gradually increasing intervals, but never less than yearly. Intervention will depend on these findings.
  4. All patients with history of irritative bladder symptoms, haematuria or any evidence of urinary retention should have pre cystoscopy, I.V.U. followed by cystoscopy to rule out any bladder malignancy .
  5. Awareness should be made to the general population and indeed to medical personnel, the value of early diagnosis to avoid late cases which have gone beyond remedial measure.
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