A REVIEW OF MANAGEMENT OUTCOME OF WILMS' TUMOUR IN KENYATTA NATIONAL HOSPITAL.

MANAGEMENT OUTCOME OF WILMS' TUMOUR IN KENYATTA NATIONAL HOSPITAL

(A TEN-YEAR RETROSPECTIVE STUDY)

BY:

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A DISSERTATION SUBMITTED IN PART FULFILLMENT OF MASTER OF MEDICINE IN SURGERY, UNIVERSITY OF NAIROBI
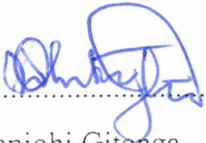
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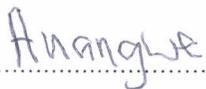
DECLARATION.

I hereby declare that this thesis is my original work and has not been presented for award of a degree in any other university.

Signed..

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This thesis has been submitted with my approval as a university supervisor.

Signed..

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DEDICATIONS

To my sons Ryan and Allan, my wife Leah and to my parents Mr &Mrs Gitonga for all their efforts and sacrifices that have made me what i am.

Lastly to all past, present and future Wilms' tumour patients for whom the work should benefit.

ACKNOWLEDGEMENTS

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ABBREVIATIONS

KNH	-	Kenyatta National Hospital
SPSS	-	Statistical Programmes for Social Services
IVU	-	Intravenous Urogram
CTScan	-	Compurized Tomogram Scan
U/S	-	Ultrasound
MRI	-	Magnetic resonance imaging
CXR	-	Chest X-ray
TNM	-	Tumour Node Metastasis
SIOP	-	International Society of Paediatric Oncology Studies
NWTS	-	National Wilms Tumor Study
FNAC	-	Fine Needle Aspirate Cytology
HBSAG	-	Hepatitis B surface antigen.
N	-	Total number of patients under consideration
VMA	-	Vanillyl mandelic acid
BM	-	Bone Marrow
USA	-	United States of America.
VAC	-	Vincristine, Adriamycin, Cyclophosphamide
CGY	-	Ciba Geigy

ABSTRACT

A total of 119 patients with Wilms tumuor were reviewed and analyzed. The ages at diagnosis varied from 4 months to 15 years. There were more male than female patients(male:female = 1.9:1). The age incidence decreased with increasing age. Patients were distributed from all over Kenya. Most of the patients presented with an abdominal mass (88.2%). Most of the patients took over 28 days before seeking medical attention. The tumuor affected the left kidney (55%) more than the right (42.3%). In 2.7% of the patients the tumuor was bilateral. Majority of the patients (64.8%) were in stage III and IV. At the end of the study, 25.4% of the patients were dead, with 28.8% still on follow up and 45.8% having been lost to follow up.

SUMMARY

This was a study to review the outcome of children managed for Wilms' tumor (Nephroblastoma) in Kenyatta National Hospital between January 1988 and December 1998.

All patients with histologically proven Wilms' tumor, managed and followed up in the clinic were reviewed. Factors contributing to morbidity and mortality pre-operatively, perioperatively and post operatively were looked for. The outcome was assessed as at the two-year follow up status. (Died,lost to follow up, still on follow up).

The evaluable parameters included age, sex, stage at diagnosis, chemotherapy use, radiotherapy, surgery, transfusion and any other conditions that may have contributed to morbidity and mortality. The data was collected and entered in a proforma questionnaire. The files were retrieved from the Records Department of the hospital.

The data was analyzed using SPSS programme.

INTRODUCTION AND LITERATURE REVIEW

Wilms' tumor (nephroblastoma) was first reported in 1814. It gained the name from a German's surgeon Max Wilms who defined its embryonic nature and histological features (1,2). It is one of the commonest intra-abdominal solid tumors of childhood. As with Burkitt's lymphoma and if managed appropriately, Wilms' tumor has comparatively better outcome relative to other childhood intra-abdominal malignancies.

Nephroblastoma is a malignant embryonic tumor of childhood arising in the kidney parenchyma (3). It comprises two percent (2%) of all malignancies in all age groups (4). Other parenchymal renal childhood tumors include renal cell carcinoma, oncocytoma, sarcoma, and angiomyolipoma.

Wilms' tumor is the commonest childhood renal tumor in all races and affects male and female children equally (1,5,6). It comprises ten percent (10%) of all malignancies in childhood. The incidence is 1:10000 live births in children under fifteen years (7). The peak incidence age bracket is two-four years (2-4 years). The median age at diagnosis being 39 months for unilateral tumors and 26 months for bilateral tumors. Few patients are seen after the age of seven years. The annual incidence being 7 per million children younger than 16 years and varies little from area to area (8).

In Kenya, there are no comprehensive statistics on pediatric tumors. A study done by Mwanda shows that the commonest childhood tumor in Kenya is Burkitt's lymphoma and

nephroblastoma is the commonest solid tumor (9). Overall it is second commonest

childhood tumour. Also he noted that the male female ratio was approximately 1.5:1 and

ratio is maintained in all age groups up to ten years and increases there after. He noted

that the above figures are different from the West where the commonest tumors are as

follows: leukemia (with acute lymphoblastic leukemia constituting 75% of childhood

malignancies) lymphomas and other reticuloendothelial neoplasms, sympathetic and allied

nervous system neoplasms; retinoblastoma and renal tumors, soft tissue sarcomas and

germ cell tumors in that order (9).

While Wilms' tumor is predominantly a childhood tumor cases have been documented

affecting adults. Akmansu et al (5) reported three cases of adult Wilms' tumor in 1997,

1998 , Biyani et al reported Wilms' tumor in a 76-year-old male in 1995 (10). Butler D. et

al reviewed 250 cases of adult Wilms' tumor reported in world literature (11). In Kenya,

there is no documented primary Wilms' tumor in adults, however Mwanda (in personal

communication) has observed three cases after the age of 17 years. These were all relapses

after more than 13-15 years disease free periods.

Nephroblastoma is primarily a renal tumor but extra-renal tumor has been documented.

Jiskout P. et al reported a case of 72-year-old female with uterine Wilms' tumor. He

reviewed literature and found five other documented cases of primary uterine Wilms'

tumor (12). In Kenya, there is no documented extra-renal Wilms' tumor, but again

Mwanda has noted two cases suspected to be mesenteric and splenic Wilms' (unpublished

data). Other sites where extra-renal tumor has been documented includes inguinal region and chest wall (3).

Aetiology of Wilms' tumor is unknown. There are postulated causes, but there has not been a direct association of factor and disease to certify Koch's postulate. Two forms of the disease are identified the heritable and non heritable. Heritable disease accounts for 15-20% of all Wilms' tumors (13). In these heritable ones this can be familial and bilateral case. In the familial cases (1%) it is postulated that there is a strong genetic influence and it fits with Knudson's two hit hypothesis (8). This applies more to the patient with tumor with associated congenital malformations. In these patients, predisposition occurs at an early age and there is usually bilateral involvement. The genetic defect is found in chromosome 11 where a tumor suppressor gene is located (Knudson first hit) . The defect is autosomal dominant with variable penetrance and affects band p13 in chromosome 11 (8). In 33% of Wilms' tumors associated with congenital malformations there are deletions involving more than 2 loci on chromosome 11. Hemizygous constitutional deletions 11p13 are associated with Wilms' tumor and WAGR syndrome (Wilms' tumor, aniridia, genital urinary tract malformations, mental retardation). Deletion 11p15 is associated with Beckwith Wiedemann syndrome (14). Beckwith 1998 showed presence of nephrogenic rests (abnormal persistence clusters of embryonal cells) that are known precursors of Wilms' tumor, but most of these embryonal cells are destined for eventual atresia (6).

Coppers' reviewed molecular characterization of Wilms' tumor and found that unlike
retinoblastoma that requires activation of one agent Wilms' involves several genetic loci
(15).

Environmental factors have been implicated for example paternal occupation and exposure
to hydrocarbon and lead (Kantos et al). Maternal vaginal infection, use of hair dyes and
tea consumption during pregnancy (Banin and colleagues). But in all above factors, none
has been conclusively identified (6).

Pathological features.

Nephroblastoma is a malignant embryoma of the kidney arising from primitive
mesoblastic stroma and nephroblastic epithelium, and metanephric blastoma gives rise to
both nephrons and stroma. Thus histologically one can have triphasic, biphasic or
monophasic patterns depending on which tissue predominates (16).

It is usually a large smooth mass with a fibrous pseudocapsule (compressed atrophic
normal renal tissue). It is sharply demarcated. With time as it grows cystic areas appear
due to necrosis and hemorrhage at the centre of the mass. Calcification occurs rarely. In
majority of the cases the tumor is unicentric i.e. arise form one focus in one kidney. Seven
percent (7%) of the cases are multicentric within one kidney. In five point four percent
(5.4%) there is bilateral renal involvement.

Histologically, it presents as a tubuloglomerular sea of nephrogenic cells in a background of undifferentiated somatogenic cells. The non-differentiated non-epithelial cells may rarely form striated muscle, adipose tissue cartilage or even bone.

Unfavourable histological type (anaplasia) is described as presence of cells that are three times the size of adjacent tumor cells and have hyperchromatic nuclei plus cells with abnormal mitosis.

Apart from anaplasia other histological factors that determine poor outcome include - biphasic/triphasic pattern, extension of tumor outside the renal capsule, inflammatory pseudocapsule, invasion of renal vein and local lymph node metastases.

Other renal childhood tumors that were in the past lumped together with Wilms' include renal cell sarcoma, rhabdoid kidney tumor and cystic nephroma.

Anaplasia changes prognosis little for children less than two years but thereafter the prognosis worsens with increasing age.

Clinical features.

Wilms' tumor usually presents clinically as an incidental abdominal mass on the flank in an otherwise healthy child. The mass is smooth, firm, and non-tender and rarely crosses the midline. Other signs and symptoms include malaise, anorexia, vomiting, abdominal

pain, weight loss, haematuria, hypertension. If the child presents at an advanced stage then metastasis signs and symptoms will be present.

For children with aniridia, hemihypertrophy, Beckwith- Wiedemann's syndrome, external genitalia anomalies and other congenital anomalies associated with Wilms' a high degree of suspicion may allow diagnosis to be made early.

Diagnostic work up in suspected Wilms' tumor patient.

In 1979, the frequency of incorrect pre-operative diagnosis was five percent (5%) on the basis of analysis of excretory urograms (17). Apart from history and physical evaluation the things to be done include; blood count, urine analysis, serum electrolytes determination and creatinine levels, urine catecholamines level to rule out neuroblastoma; liver function tests. Polycythaemia is rare but also occurs secondary to elevated erythropoeithin production (18). Bone marrow aspiration should be done early to rule out neuroblastoma. Cytogenetics studies should also be carried out.

Imaging

Imaging has improved precision with which diagnosis is made before surgery (19). It helps determine that the mass is solid, arising from the kidney, local extension, renal vein and or inferior vena cava involvement and distant metastases. Also it is of help in future follow up of patient.

The investigations include:

1. Plain abdominal x-ray film

2. Abdominal ultrasonography

3. Intravenous urogram (I.V.U)

4. Retrograde ureteropyelography

5. Computerized Tomogram Scan studies (CT Scan)

6. Magnetic Resonance Imaging (MRI)

7. Other investigations are determined by the stage of disease. signs and symptoms. These include skeletal surveys; chest x-rays (CXR) to rule out metastases; and arteriography.

8. Follow up studies are essential. They include;

   Those patients with tumor confined to kidney and favorable histology do chest x-ray 3 monthly for 2 years, then 6 monthly for 1 year, and yearly thereafter for 2 years. Abdominal U/S should be done yearly but more frequently if patient had nephroblastomatosis. Skeletal surveys are done annually till cessation of patient growth and then 5 yearly indefinitely to detect osteochondromas if radiation therapy was used. Anaplastic tumors require closer follow up with chest x-ray, abdominal U/S, clear cell sarcoma and rhabdoid tumor needs special brain CT scan or MRI and six monthly skeletal surveys for 10 years.

   NB: Patient follow up is dictated by clinical state.

Staging

Wilms' tumor classification is usually based on preoperative and intraoperative findings. Unlike other tumors, the TNM classification is not used. Garcia et al proposed the first detailed staging system in 1963 . The cooperative group studies NWTS and SIOP of America and Europe respectively made staging widely used and uniform. In Kenya, the American's staging system (NWTS) is used but it is not a hospital policy. The NWTS staging system is revised periodically and modified according to the outcome after treatment. The surgeon assigns the NWTS stage and is confirmed or modified by the pathologists (20).

Staging system NWTS-3 and NWTS-4 (13)

I   Tumor limited to kidney and completely excised. Renal capsule intact, no tumor rupture nor spillage during surgery, no residual tumor apparent at or beyond the margins of excision.

II.   Tumor extends beyond kidney but is completely excised. There is regional extension of that tumor into the peri-renal soft tissues. Vessels outside the kidney substance are infiltrated or contain tumor thrombus. The tumor has been biopsied or there have been local spillage of the tumor limited to the flank. There is no residual tumor apparent at or beyond the margins of excision.

III.   Residual non-hematogenous spread confined to abdomen.

Any one or more of the following may occur.

1. Lymph nodes on biopsy are found to be involved in the hilus, periaortic or beyond.

2. Diffuse peritoneal contamination by tumor such as by spillage of tumor beyond flank before or during surgery or by tumor growth that has penetrated through peritoneal surface

3. Implants are found on the peritoneal surface

4. The tumor extends beyond surgical margins either grossly or microscopically.

IV. Haematogenous metastases deposits beyond stage III

i.e. lungs, bone, liver, brain.

V. Bilateral renal involvement at diagnosis. An attempt should be made to stage each side according to criteria above on the basis of extent of disease before biopsy.

Treatment

Wilms' tumor treatment requires a multidisciplinary approach involving paediatrician, paediatric oncologist, paediatric surgeon, the pathologist and the radiologist. The NWTS and SIOP study groups have guidelines/protocols used in America and Europe respectively. In Kenya, Kasili's guideline exists but management differs from patient to patient even of the same stage depending on who is directing the management. Kasili had

drawn a chemotherapy guideline for management of nephroblastoma (KNH/STT/3/81) however, this is undergoing modification (21). While all the disciplines are needed for successful treatment of the tumor the surgeon plays a primary role in establishing the diagnosis, staging the tumor and in primary treatment.

The two major study groups on Wilms' NWTS and SIOP evaluate their protocols periodically with an aim of coming up with the optimum treatment strategies. SIOP study group lay emphasis on preoperative chemotherapy and radiotherapy while NWTS study group start radiotherapy or chemotherapy post operatively. For the NWTS group their main argument is that radiotherapy and chemotherapy distorts the staging while the SIOP group argue that since the therapies reduce the tumor mass and make some advanced tumors operable thereby reducing chances of tumor spillage.

Surgical management

Surgery provides the primary treatment role and establishes the diagnosis, stages the disease to enable future treatment considerations.

The approach is via a transverse transperitoneal approach incision that must be generous enough. This allows exploration of peritoneal cavity, easy access to both kidneys' beds, minimize chances of spillage and cutting through the tumor. Therefore the exposure is of paramount importance to avoid advancing the stage of tumor.

The incision involves division of ipsilateral rectus. Once in peritoneal cavity, the liver

paraortic nodes, inferior vena cava are assessed. The contralateral kidney bed is opened and assessed for any tumors and kidney inspected and suspicious area taken for biopsy (frozen section) (22). In KNH, frozen section biopsy is not available. Once one has ruled out multifocal bilateral disease then nephrectomy is considered in affected diseased kidney. NB: Wilms' tumor may occur in a horse shoe kidney and this may not be apparent pre-operatively (23).The retroperitoneal space is exposed by mobilization and reflection of colon medially taking care not to damage their blood supply. If possible, the renal vein is ligated first before tumor mobilization to avoid tumor embolisation but this does not affect outcome (24,25). The kidney tumor is mobilized laterally and inferiorly in a tissue plane outside of Gerota's fascia.

For advanced tumors preoperative radiotherapy and or chemotherapy reduce the size and thereby reducing risk of rupture (25). Also for large tumors it may entail adrenalectomy, en block removal of tumor plus parts of adjacent organs e.g. liver, diaphragm, mesocolon and lymph nodes. If the operation is going to be life threatening, then the surgeon takes enough tissue for diagnosis and stages the tumor and does surgery later after chemotherapy and or radiotherapy (26,27). Non-resectable tumor should be outlined with titanium clips for possible radiotherapy later.

Wilms' extension into inferior vena cava occurs in about four (4) percent of cases and is usually asymptomatic (28). The level of thrombus may even reach up to level of atrium. This is decided by real time ultrasonography, excretory urography may suggest renal vein

thrombus. Venography maybe used but results are hard to interpret. Renal vein

thrombosis is rarely diagnosed perioperatively but fortunately does not affect prognosis.

Free floating thrombosis even when extending to atrium can be extracted by cardiotomy

(classified as stage II). Tumor thrombus adherent to wall of inferior vena cava is removed

using Forgarty balloon catheter. Infiltration of the inferior vena cava wall requires

resection (stage III disease) and postoperatively requires radiotherapy. The main

complication of venous extension is hemorrhage. While preoperative chemotherapy

produce complete/marked shrinkage of tumor it increases difficulty in thrombus extraction

due to dense adhesions.

Intracardiac tumor extension does occur in around 0.7% of patients. Echocardiogram can

detect them, also CT scan and MRI are used to evaluate extension. Thus extra corporeal

circulation may be needed during surgery. Intracardiac extension does not adversely affect

life expectancy.

Lymph node involvement is a bad prognostic indicator (29, 30). Therefore, lymph node

sampling should be done with high degree of awareness. Complete lymph node removal is

not encouraged because of the side effects (2). The sites of lymph node removal should

be marked with clips in event of postoperative radiotherapy.

Sometimes situations arise that require a second look operation. These include where a

flank incision was used, abdominal recurrence, initially unresectable tumor treated by

chemotherapy.

Chemotherapy.

NWTS and SIOP studies have been looking at various modes of chemotherapy and radiotherapy in a view to come with the optimum therapy and best outcomes. Outcome involves best disease survival, minimal side effects from both radiotherapy and chemotherapy and shortest duration of course of treatment possible without affecting outcome.

The commonest chemotherapy regime used is Vincristine, actinomycinD and Cyclophosphamide and Adriamycin alternating with actinomycinD. Other drugs added depending on stage and response to above drugs.

National Wilms' Tumor Study (NWTS) groups

NWTS series were organised to provide answers to questions about optimum management of this tumor.

NWTS - 1 (29) started 1/10/69. The aim was to compare single agent actinomycin D therapy with single agent vincristine therapy and with both drugs combined. It also evaluates role of radiotherapy in stage I disease.

Outcome   - Radiotherapy did not change outcome in stage I and therefore not essential

      - Combined chemotherapy is superior to either agent alone

      - Children under 2 years did better compared to children over 2 years.

NWTS-2 - (31)

. The aim was to evaluate duration of chemotherapy (6 months versus 15 months in group I patients.

. The dosage of radiotherapy in stage II, III and IV

NB: stage I patients did not receive radiotherapy.

Outcome   -   6 months treatment of stage I disease was good as 15 months

          -      No difference in outcome according to age of patient at diagnosis as in NWTS –1 (due to combined chemotherapy)

          -      Combined chemotherapy eliminates need for radiotherapy in stage I

          -      Analysis of NWTS-1 and NWTS-2 showed that stage II did not benefit from radiotherapy

          -      Radiotherapy dose in excess of 2000cGy was no better than doses of 1000cGy.

          -      Addition of doxorubicin did not change prognosis of children with unfavourable histology except in clear-cell sarcoma of the kidney. It showed benefit in the stages II, III and IV disease with best benefit noted in stage IV disease. Disadvantage was that there was increased myelotoxicity and doxorubicin induced cardiomyopathy.

NWTS-3   The aim was to expand results from above two studies.

The study found out that:-

- Treating stage I disease for 10 weeks without radiotherapy versus 6 months revealed fewer relapses and deaths in the 6 month regime but no statistically significant difference.

- Stage I unfavourable histology can be treated as stage I favourable histology.

- Three drug regimens are not statistically better than two drug regimen but trend favour three-drug regimen in patients with stage III and favourable histology.

- Stage II disease with favourable histology showed no additional benefits with addition of radiotherapy.

- Radiotherapy in stage III disease with favourable histology showed that 1000cGy is effective as 2000cGy.

- In stage IV disease with unfavourable histology, there is no advantage adding a fourth cytotoxic drug (cyclophosphamide).

NWTS-4   Aims to refine optimal schedule and duration of chemotherapy, improve results in patients with unfavourable histology, stage IV disease at presentation and clear cell sarcoma.

*   See table for NWTS-4 treatment scheme

*   See table for chemotherapy schedule for NWTS-3

Dosage: Actinomycin D 15 mcg/kg/day I.V

Vincristine 1.5mg/m²/week I.V.

Doxorubicin (adriamycin) 20mg/m²/d (IV)

Cyclophosphamide 10mg/kg/day(IV)

International Society of Pediatric Oncology studies (SIOP)

This is the major cooperative study group in Europe and has conducted studies on Wilms'-
SIOP 1,2,5,6,9. Its major difference from NWTS is use of preoperative therapy i.e.

diagnosis is based on clinical characteristics rather than on cytopathology.

In SIOP-1-all the children received actinomycin D and randomised either to preoperative

radiotherapy or none. Shortcoming:- some children without Wilms' received radiotherapy

200cGy only to be found with some benign lesions.

Results: No statistically significant difference in the relapse free survival or overall

survival rates. Tumor size reduced and tumor altered leading to fewer tumors spillage and

total abdominal radiation dosage reduced. But it complicated anatomical staging.

SIOP-2 was to confirm SIOP-1 and NWTS results. SIOP-5 found out that preoperative

chemotherapy gave similar results to preoperative radiotherapy. SIOP-6 was aimed to

further reduce preoperative radiotherapy exposure. All children without recognisable

metastases received preoperative chemotherapy. The staging used by SIOP may not be an

accurate prognostic indicator.

SIOP-9 was designed to determine effectiveness of 4 versus 8 weeks of preoperative chemotherapy in down staging of patients to stage I. Also it was to evaluate the value of itosphamide and epiadriamycin.

Preoperative therapy is ideal in advanced tumors as it makes them operable. SIOP and NWTS results are almost similar.

Metastatic disease (stage IV disease) (31).

Lung metastases may occur in up to 11%-12% of children with Wilm's tumor. These metastases are detected by normal chest x-ray. NWTS recommended chest cage irradiation (1200cGy) and shields used only to protect the proximal humoral growth plates (19). CT scan improves chest metastasis detection rate (19). There are controversies regarding whether lung irradiation should be done without biopsy, but for multiple pulmonary metastasis the management is medical with chemotherapy and radiotherapy. Nodules that fail to regress may be removed surgically. Radiotherapy to chest may be deferred or even replaced by chemotherapy.

Liver metastasis responds poorly to chemotherapy. Therefore resection is advocated for the easily accessible or after chemotherapy and radiotherapy second look operation are done to excise the hepatic tumor. Non-resectable metastasis are responsive to radiation therapy of 108cGy to the total abdomen,1200cGy (maximum) to the whole lung fields and booster doses of 540-1080 cGy to bulk lesions. Bone and brain metastasis may be treated

with supplemental doses reaching 3060 cGy.

Bilateral stage V tumors (32)

Here the main aim is to eradicate the tumors and still remain with at least one functioning

kidney or both. Therefore in NWTS exploratory laparotomy is done and kidneys inspected

and either excisional biopsy done or incisional biopsy taken plus lymph node sampling,

then chemotherapy is given that shrinks the tumor and allow repeat operations and

resection of tumor. Nephrectomy is reserved for cases of failure to eradicate tumor in a

kidney. If all fails a bilateral nephrectomy is done and subsequent dialysis and renal

transplant considered.

Fortunately bilateral tumor occurs at an early age, have preponderance for favourable

histology and most are diagnosed at stage 3 disease and chemotherapy offer excellent

protection (23).

For large tumors and bilateral nephroblastoma, fine needle aspirate cytology (FNAC) is

occasionally done to enable diagnosis to be made. In bilateral tumors pre-operative

chemotherapy can be given after FNAC. Dimarcaptosuccinic acid scan (DMSA) is also

done to demonstrate the renal function. After chemotherapy repeat DMSA scan is done to

demonstrate the kidney with more residual function. Nephrectomy can then be considered

on kidney with poor residual function.

Side effects of radiation therapy.

Tumor is very susceptible to radiation but radiation has damaging effects for example on vertebral spine and may lead to scoliosis and kyphoscoliosis. Damage to muscles and soft tissues. Leukemias can develop years later after use of radiotherapy. Trends are to minimize use of radiotherapy.

Chemotherapy side effects

Side effects are multiplied by combination therapies. These side effects include:- hematological toxicity (Pancytopenia), (the use of half the normal dose in infants age less 12 months reduces these side effects). Doxorubicin side effects includes:- cardiomyopathy, neuropathy in those also receiving vincristine, relative infertility. Doxorubicin and actinomycin D potentiates radiotherapy induced toxicities for example enteritis, hepatotoxicity.

Years later patients who had received these drugs or radiotherapy may develop secondary malignancies e.g. osteochondroma, acute leukemia.

Prognosis.

Treatment of Wilms' tumor is an example of success of modern oncology. A combination of surgery, radiotherapy and chemotherapy is widely accepted as the efficacious treatment of nephroblastoma (33). Godzinki et al evaluated rates of nephrectomy-associated complications in patients who had received preoperative

chemotherapy. The results showed a low rate morbidity and this included small bowel occlusions, tumor ruptures but no deaths (34).

Effective diagnosis, staging and multimodality therapies have dramatically decreased the morbidity and mortality of children with Wilms' tumors. Increased awareness of the disease, biology, genetics and epidemiology have improved assessment of clinical syndromes and led to a more risk based treatment. Primary chemotherapy with delayed resection is the preferred approach for large inoperable, tumors, bilateral disease and those with extensive intravascular involvements (35).

The main prognostic factors are stage of disease at diagnosis, histology, age of patient at diagnosis. Other factors that may affect outcome now varies with other conditions that

patient may have and approach to the management. The four year survival rate is as follows (32):-

Favourable histology			Unfavourable histology		
Stage I	-	97%	Stage I	-	89%
Stage II	-	94%	Stage II-IV	-	54%
Stage III	-	88%			
Stage IV	-	82%			

In Kenya, the prognosis was poor according to Jumbi (1980) the 2 year survival was low at 10.42% and there was no 5 year survival in all stages. This is unacceptable high mortality rate (1). Currently there are no available figures.

RATIONALE.

In Kenyatta National Hospital an average of ten (10) children with Wilms' tumor are seen annually. There have not been a comprehensive review of nephroblastoma recently. The mortality and morbidity rate compared with other countries is relatively high (1), thus it was useful to conduct the study so that:-

1. Help form a data basis for future reference.

2. Also no study on outcome of management of Wilm's tumor has been done in Kenyatta National Hospital comprehensively.

3. Overview of current management of Wilms' tumor may assist in the revision of current practices for improved clinical outcome.

OBJECTIVES

Broad

To determine the factors that affect the morbidity and mortality of patients with Wilms'
tumour managed in Kenyatta National Hospital during the study period.

Specific

1. To determine pre operative factors that contributed to mortality and morbidity in
    the study population.

2. To determine intraoperative factors that affect outcome.

3. To determine postoperative factors that contribute to morbidity and mortality.

4. To make appropriate recommendations in order to reduce morbidity and mortality
    of Wilms' tumor patients.

MATERIALS AND METHODS

Study design

This was a descriptive retrospective study over a 10 years period from first January 1988 to thirty first December 1998.

Study population

All the persons who were managed and followed in KNH and a diagnosis of Wilms' tumor confirmed during the study period.

Study area : The study was carried out in KNH.It is situated in the capital of Kenya-Nairobi. It is the main referral and teaching hospital in Kenya. Kenya has a population of around 28 million by 1999 census.

Study methodology.

The study was carried out by the principal investigator under the guidance of supervisor from the Department of Surgery and Department of Haematoloty, University of Nairobi. A structured questionnaire was used to get information from the records of KNH and Cancer registry in the department of human pathology (University of Nairobi). The information that was retrieved included details of clinical examination, investigation i.e. radiological or otherwise, and operative and post-operative findings, follow up notes and complications. A data sheet was used to store the information . The information was reviewed and analyzed to enable answer the research questions.

ELIGIBILITY CRITERIA.

Inclusion

1. Patient records had a histological diagnosis of nephroblastoma

2. Two years had elapsed from time of diagnosis.

Exclusion.

1. Any patient without a histological proof of Wilms' tumor.

LIMITATIONS.

1. The records of some patients were incomplete with some of the clinical details missing.

2. There is no means of knowing the fate of the patients who are lost to follow up.

3. Some patients' records were not traced.

4. Some of the patient records may not have presented the correct findings due to incorrect documentation

Data management analysis and presentation

The results are presented in tabular, graphic bar and pie chart forms.

Ethical consideration.

This was a retrospective study. The data was collected from Kenyatta National Hospital medical record patient files. The information so gathered was treated with confidentiality.

Once the study was completed it was ensured that individual patients cannot be identified when findings were published. The study required approval by the Ethical and Research Committee of Kenyatta National Hospital.

Sample size.

The study population determined the sample size. This was based on the number of patients who presented to KNH with Wilms' tumor and fitted in the admission criteria. Approximately ten patients are seen every year, therefore at least a hundred patients were expected in the study.

To obtain 95% confidence interval for this proportion using a precision of 5%, the minimum size (n) is calculated to be 100 using the formula;

n $\qquad = \qquad$ $z_{1-\alpha/2}^2 \ p(p-1)/d^2$.

Where $\qquad$ $z_{1-\alpha/2}$ $\qquad$ is the standard normal deviation corresponding to the level of significance of $\alpha = 0.5$.

$\qquad\qquad$ P $\qquad$ Is the estimated proportion of patients who have nephroblastoma

$\qquad\qquad$ d^2 $\qquad$ is the width of confidence interval

RESULTS.

The study was carried between September 2000 and November 2000. One hundred and nineteen (119) patients fulfilled the inclusion criteria.

Study setting: Kenyatta National Hospital.

1.   HOME PROVINCE (N=119).

This was the place documented as the permanent address in the patient's file admission records. The patients were from all over Kenya with the exception of one patient referred from Uganda in early 90's for radiotherapy in KNH. Majority of the patients were from Central Province (31.6%). The other provinces had patients distributed as follows:- Rift Valley 19.7%, Eastern 17.1%, Nyanza 14.5%, Western 6.8%, Nairobi 3.4%, Coast 3.4% and North Eastern 2.6% (see pie chart below).

FIGURE 1:DISTRIBUTION OF PATIENTS BY HOME RESIDENCE (PROVINCE).
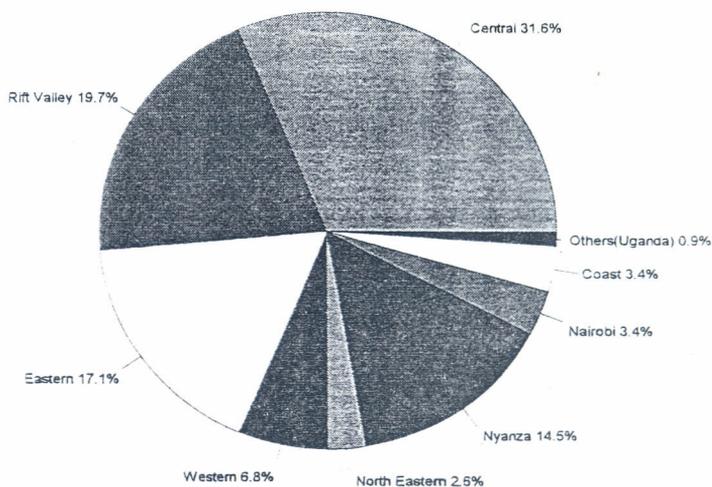
2.   SEX DISTRIBUTION (N=119).

There were more male patients than females. Males were 78 and females were 41.

TABLE 1:   SEX DISTRIBUTION.

Sex	Frequency	Valid percent
Male	78	65.5
Female	41	34.5
Total	119	100

FIGURE 2:   SEX DISTRIBUTION.

Female
34.5%

Male
65.5%
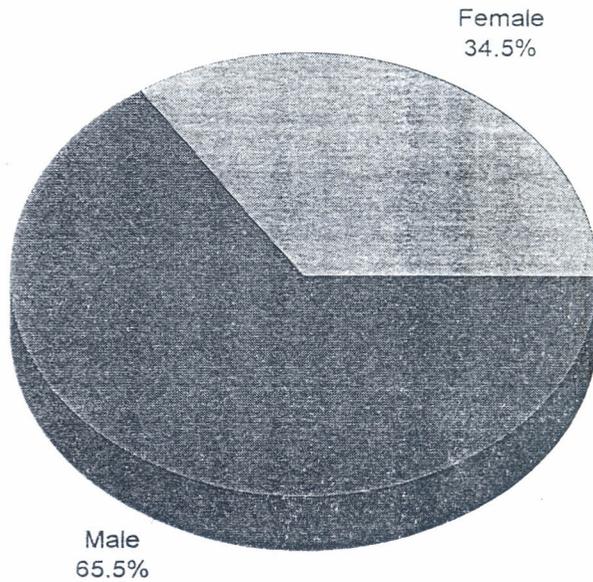
3.   AGE DISTRIBUTION.

The youngest patient at diagnosis was 4 months and the oldest was 15 years. Majority of

the patients were between 0 years and 4 years. There were only 3 patients seen after the

age of 10 years. The patient ages were distributed as follows (see bar graph below).

FIGURE 3:   AGE DISTRIBUTION.
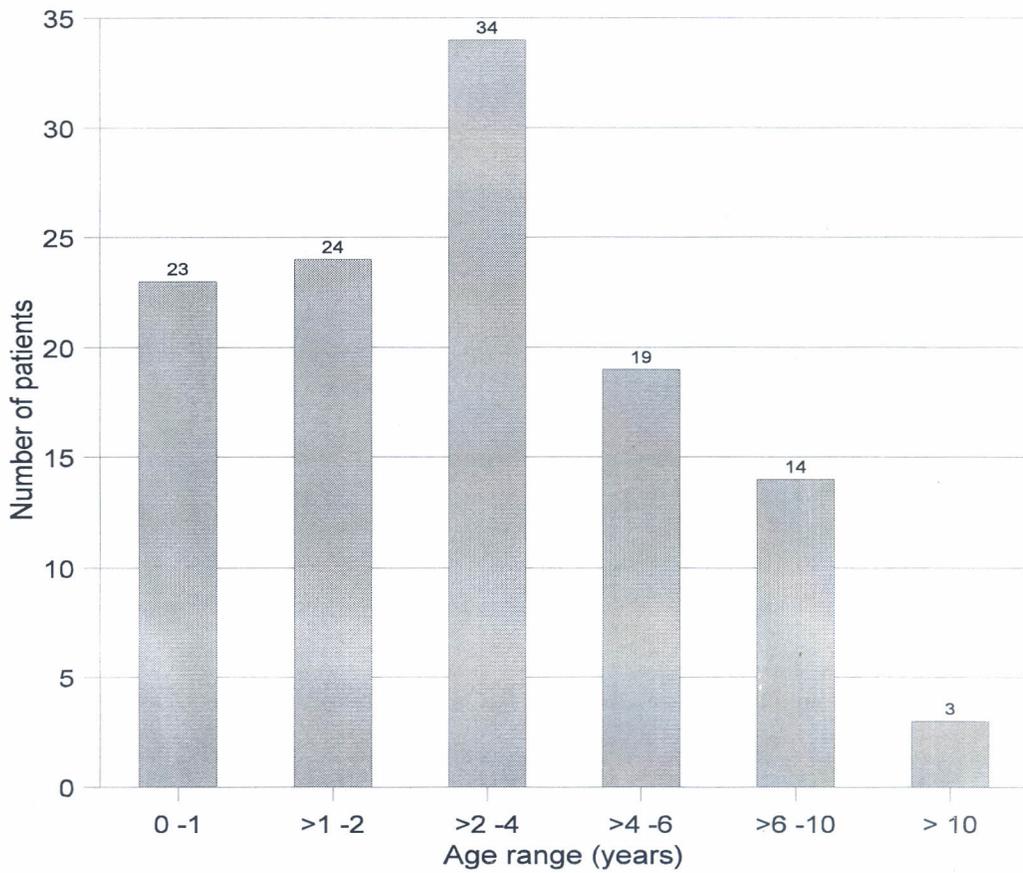
4 (A)   PRESENTING FEATURES TO HOSPITAL (N=119)

Most patients presented to hospital because of an abdominal mass (88.2%). Abdominal

pain was present in 13.4% of patients, hematuria in 10% and 21% of patients were

referred with a definitive diagnosis of Wilms' tumour from the peripheral hospitals.

TABLE 2:   PRESENTING FEATURES.

Presenting features	Number of patients	Percentage
Abdominal mass	105	88.2
Abdominal pain	16	13.4
Non specific features	25	21.0
Wilms' tumour as a diagnosis	23	19.3
Hematuria	12	10.1

NB: A patient presented with one or a combination of the above features.

4(B):   DURATION BETWEEN NOTICING PROBLEM AND TIME HELP WAS
        SOUGHT.

Most patients/guardians took more than 28 days after noticing the problem to seek

medical treatment (78.3% of patients). 9.6% of patients took 7-28 days and in only 5.2%

did they seek treatment within 7 days.

**FIGURE 4:   DURATION BETWEEN NOTICING PROBLEM AND SEEKING
            HELP.**
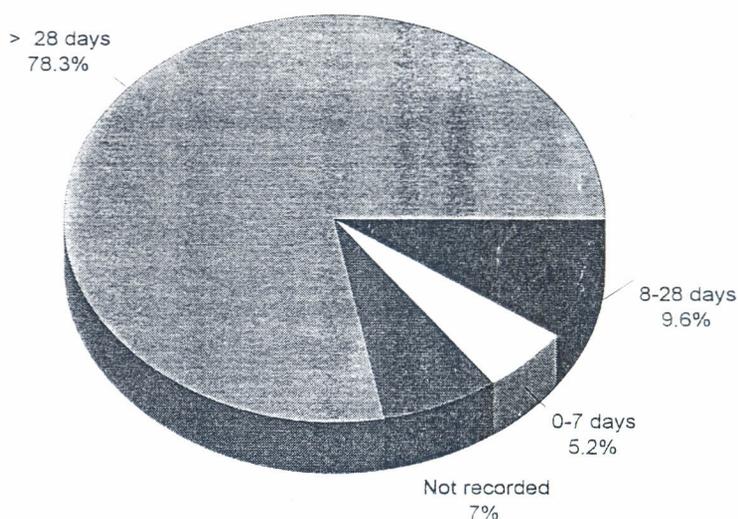
4(C): THE GENERAL STATUS OF PATIENTS.

Majority of the patients (48.3%) were assessed as fair general condition, 25% were

assessed as good, 24.2% as poor and in 2.6% of patients there was no record of the

general status.

5.   CONGENITAL MALFORMATIONS.

In only two patients (1.7%) were any congenital malformations noted. One patient had a

horse shoe kidney and the other had a spina bifida occulta.

6.   DIAGNOSTIC INVESTIGATIONS (N=119).

Intravenous urogram (IVU) was the commonest diagnostic investigation done. Other

investigations included urine analysis, VMA assessment, abdominal ultrasound, fine

needle aspirate cytology (FNAC), CT scan, plain abdominal x-ray, chest x-ray, bone

marrow biopsy, exploratory laparotomy and biopsy. The following table represents the

investigations done.

TABLE 3:   DISTRIBUTION OF DIAGNOSTIC INVESTIGATIONS.

Type of investigation	Number of patients	Percentage
I.V.U	99	83.2
Abdominal ultrasound	85	71.4
Urine analysis and microscopy	36	30.3
VMA assay	36	30.3
FNAC	42	35.3
CT scan	12	10.1
Plain abdominal x-ray	23	19.3
Chest x-ray	36	30.3
Laparotomy and biopsy	3	2.5
Other BM, HBSAg	16	14.2

NB: The number of investigations done increased if patient was initially admitted in

the paediatric medical wards compared to one admitted in the paediatric surgical ward.

7 (A)   HOSPITAL STAY BEFORE OPERATION (DURATION).

Seventeen patients (19.3%) had surgery within seven days of admission, 25 patients (28.4%) were operated between 7-28 days after admission, 46(52.3%) were operated after more than 28 days in hospital.

FIGURE 5:   HOSPITAL STAY BEFORE OPERATION(DAYS).
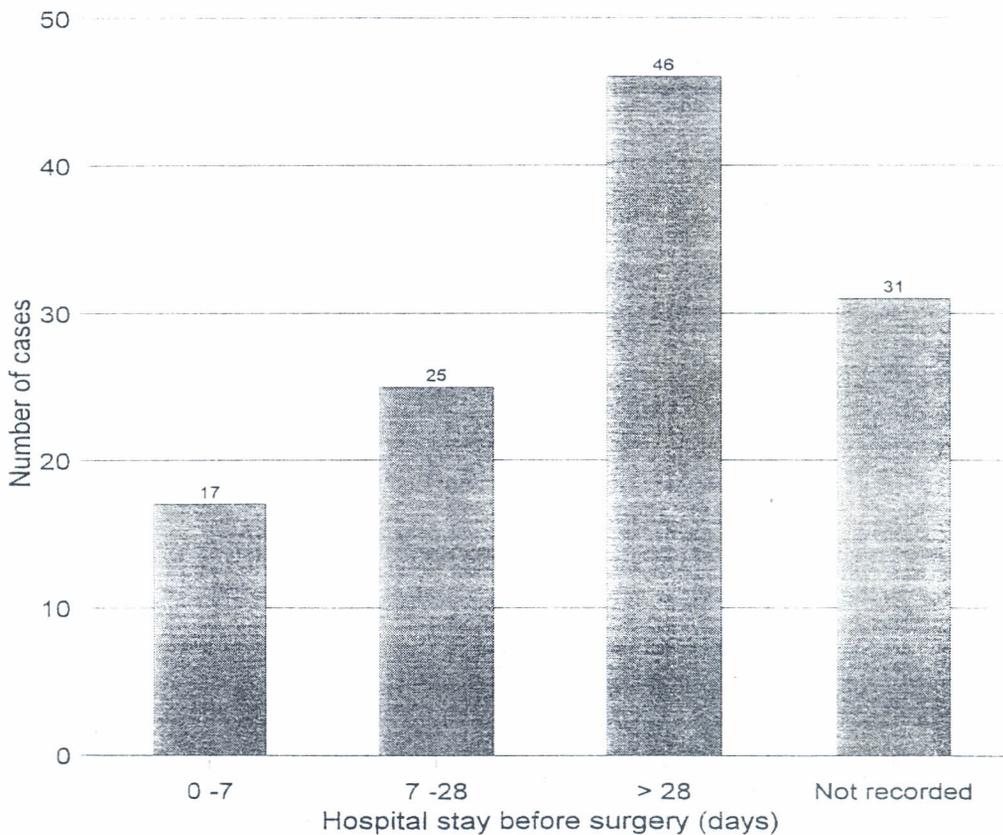
NB: Period generally was longer if patient was in a medical ward.

7 (B)   The reasons deduced from the patient file on why patients took more than 28 days before operation ranged from inability to do investigations on time (9.2%), patient needed pre-operative support - nutritional and anemia correction (16.8%), patient due to advanced tumour needed preoperative chemotherapy (25.2%). In 11 patients (9.9%) a wrong diagnosis was initially made. The wrong diagnosis made were abdominal Burkitts, neuroblastoma, hydatid cyst and splenomegally.

8.   PREOPERATIVE CHEMOTHERAPY/RADIOTHERAPY (N=45).

8(a)   Reason why patient was put on preoperative chemotherapy (N=42).

The commonest reason was that patient had an advanced tumour clinically (83.3%).

Other reasons included:- inability to withstand general anaesthesia (21.4%), wrong diagnosis (23.1%), surgery waiting period too long (7.1%), bilateral Wilm's tumour (2.4%) (see bar graph below).

FIGURE 6:   REASON WHY PATIENT WAS PUT ON CHEMOTHERAPY PRE-
OPERATIVELY.

Reasons why patient was put on chemotherapy
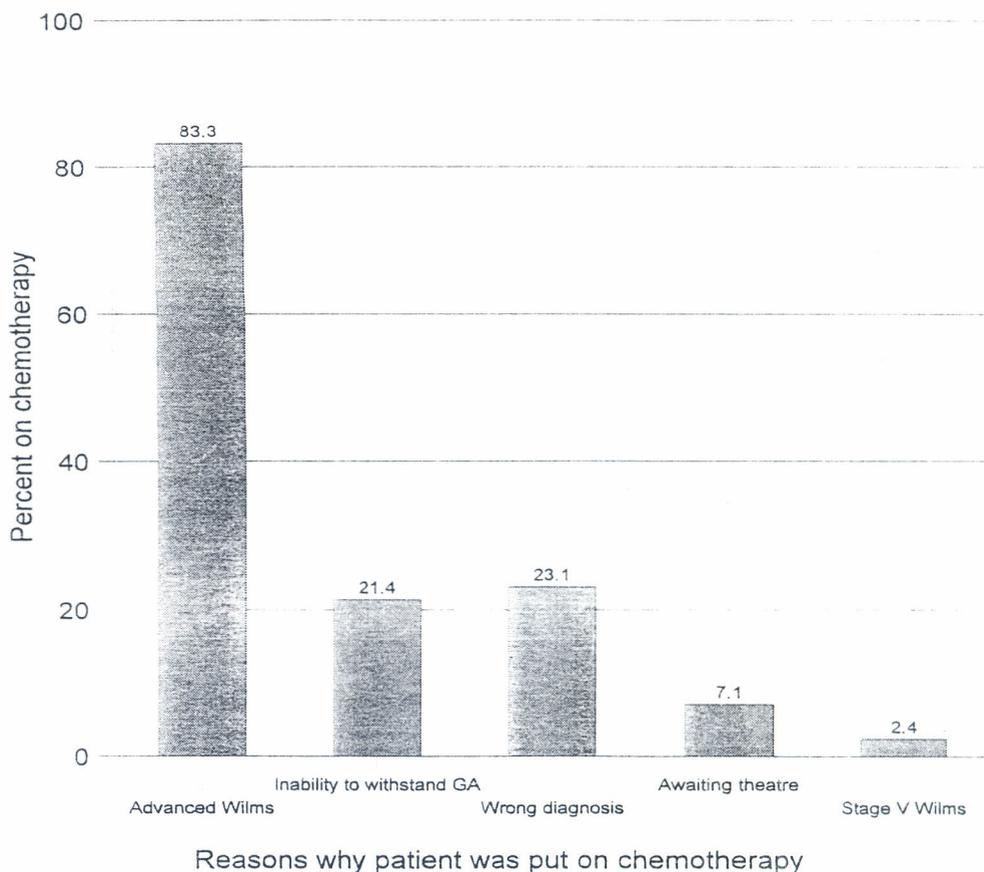
The chemotherapy regimen was VAC regime with adriamycin alternating with

actimomycin D. Occasionally and where there was no FNAC results one cytotoxic agent

was used. In the very sick patients, cis platinum was added. Those who had a wrong

diagnosis were put on chemotherapy specific to the wrong diagnosis made then.

In 61% of patients, chemotherapy regimen used pre-operatively was inconsistent. In only 39% of patients were there no interruptions. The main reason was due to unavailability of cytotoxics. Other reasons included:- patient too sick, either due to Wilms tumour, cytotoxics side effects or other medical disease.

Radiotherapy was used pre-operatively in 5 patients (11.1%) (n=45). In one patient both radiotherapy and chemotherapy were used preoperatively (had stage V disease).

9 (A)   WHICH KIDNEY WAS INVOLVED (N=108).

The tumour affected the right kidney in 47 patients and left kidney in 61 patients. In 3 patients, the tumour was bilateral.

FIGURE 7:   DIAGRAMMATIC REPRESENTATION OF WHAT SIDE WAS INVOLVED.

Left
55%

Bilateral
2.7%

Right
42.3%
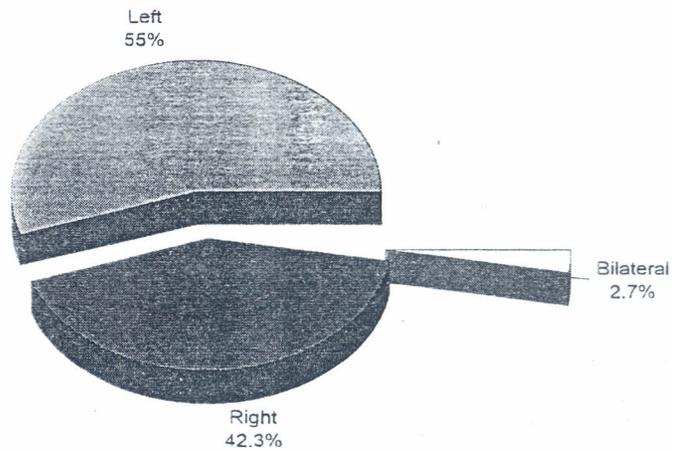
9 (B)   In 91.6% of patients, definitive surgery was performed while in 8.4% no surgery
was performed.

10.   INTRA-OPERATIVE FINDINGS.

STAGE AT SURGERY (N=108).

Most patients were in stage II, III and IV (23.1%, 35.2% and 29.6% respectively). See
bar graph below.

FIGURE 8:   STAGE AT SURGERY.
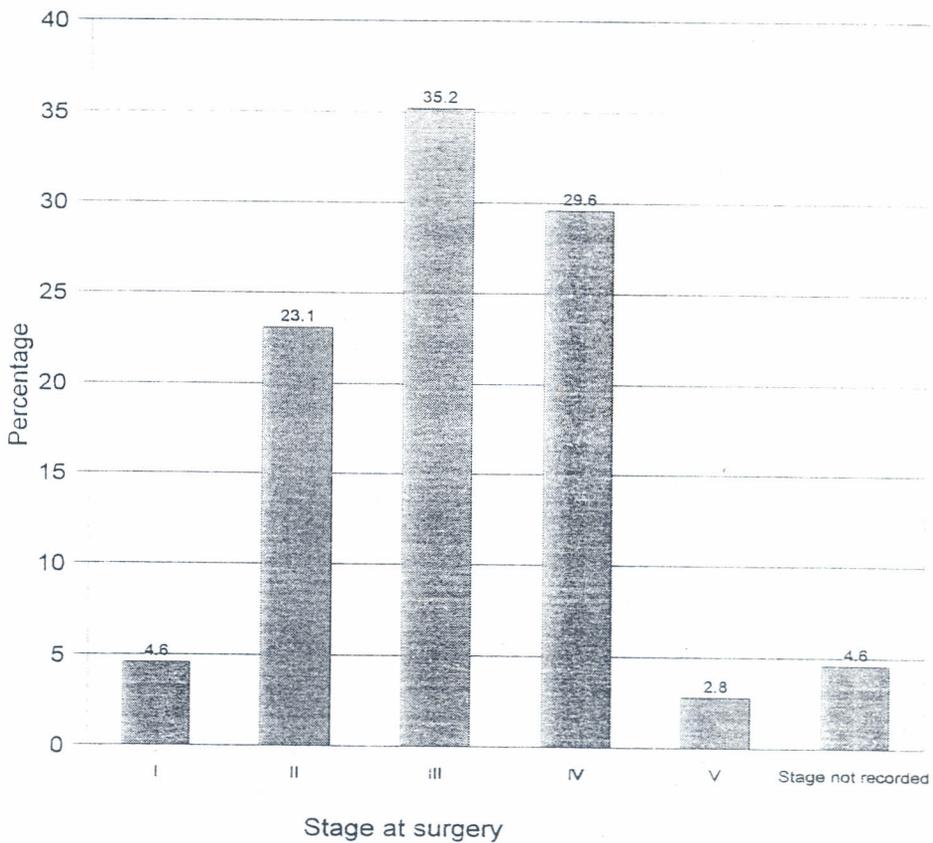
INTRA-OPERATIVE COMPLICATIONS.

Tumour spillage occurred in 12.6% of the patients intra-operatively, massive haemorhage in 18.0% of the patients, anaesthetic complications in 4.2% and in one (0.9%) patient, tumour was found extensive and patient died intra-operatively.

Transfusion intra-operatively occurred in 76 patients (70.4%). The amount of blood transfusion ranged from 200mls to four units.

Lymph node involvement occurred in 57 patients (52.8%). Majority had peri aortic nodes affected.

11.   CHEMOTHERAPY/RADIOTHERAPY USE POST OPERATIVELY (N=95).

11(A): Duration before chemotherapy was started post operatively.

Most patients were started on chemotherapy between 7-14 days (60%). 4.2% were started within a week of operation and 30.5% after 14 days. 5.3% had no chemotherapy at all.

TABLE 4:   DURATION BEFORE CHEMOTHERAPY WAS STARTED POST-

OPERATIVELY.

Day when chemotherapy was started	Number of patients	Valid percent
1-7	4	4.2
>7-14	57	60
>14 days	29	30.5
Not started	5	5.3
	95	100

11(B) CONSISTENCY OF CHEMOTHERAPY.

Chemotherapy was consistent in only 46.4% of patients. The reasons for inconsistency

included:- drugs not available, patient too sick, pancytopenia, inadequate follow up and

ignorance on part of the guardians.

FIGURE 9:   CONSISTENCY OF CHEMOTHERAPY.

Inconsistent
53.6%

Consistent
46.4%

11(C)   RADIOTHERAPY USE (POST OPERATIVELY).

Sixty five patients (68.4%) had radiotherapy use post operatively. In only 30 patients

(31.6%) was chemotherapy used exclusively.

The patients were put on radiotherapy as follows: (see table 5).

TABLE 5:   RADIOTHERAPY USE.

Stage	Number of patients	Percentage
I	6	9.2
II	17	26.2
III	21	32.3
IV	17	26.2
V	3	4.6
Not staged	1	1.5
	65	100

11(D) Complications of radiotherapy and chemotherapy were noted in 52 patients

(54.7%). The commonest complication was pancytopenia (all 52 patients) and gastritis.

Chicken pox occasionally made children oncology ward closed to avoid further spread t

the in patients of the ward.

12 (A) OUTCOME (N=118).

The outcome was assessed as to whether patient was still on follow up, lost to follow u

or deceased. Twenty five percent (25.2%) of patients died during treatment and follow

up. 28.8% of patients were still on follow up at end of study and 45.8% had been lost t

follow up.

NB: Two year had elapsed from time of diagnosis of the most recent patient.

TABLE 6:   OUTCOME.

Outcome	Frequency	Valid percentage
Died pre operatively	11	9.2
Died intra operatively	4	3.4
Died during follow up	16	13.4
Still on follow up	34	28.6
Lost to follow up	54	45.4

12 (B) WHAT TIME HAD ELAPSED FROM DIAGNOSIS TO DEATH.

All patients who died did so within four years after diagnosis. Most died within the first

12 months (see figure 9).

FIGURE 10: TIME FROM DIAGNOSIS TO DEATH.
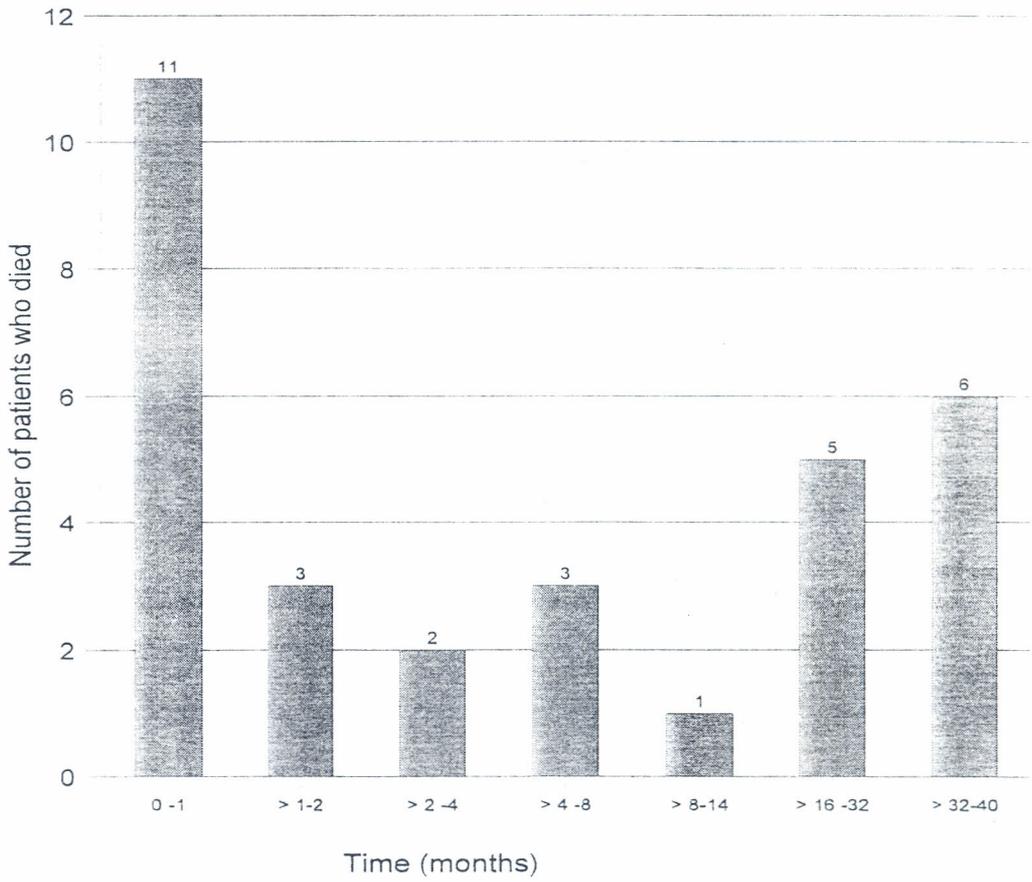
12(c)   TIME FROM DIAGNOSIS TO BEING LOST TO FOLLOW UP (N=54).

Most children were lost from follow up during the first 1 year (75%). 9 patients were lost

to follow up after 2 years of follow up (see figure 11).

FIGURE 11: TIME FROM DIAGNOSIS TO BEING LOST TO FOLLOW UP.
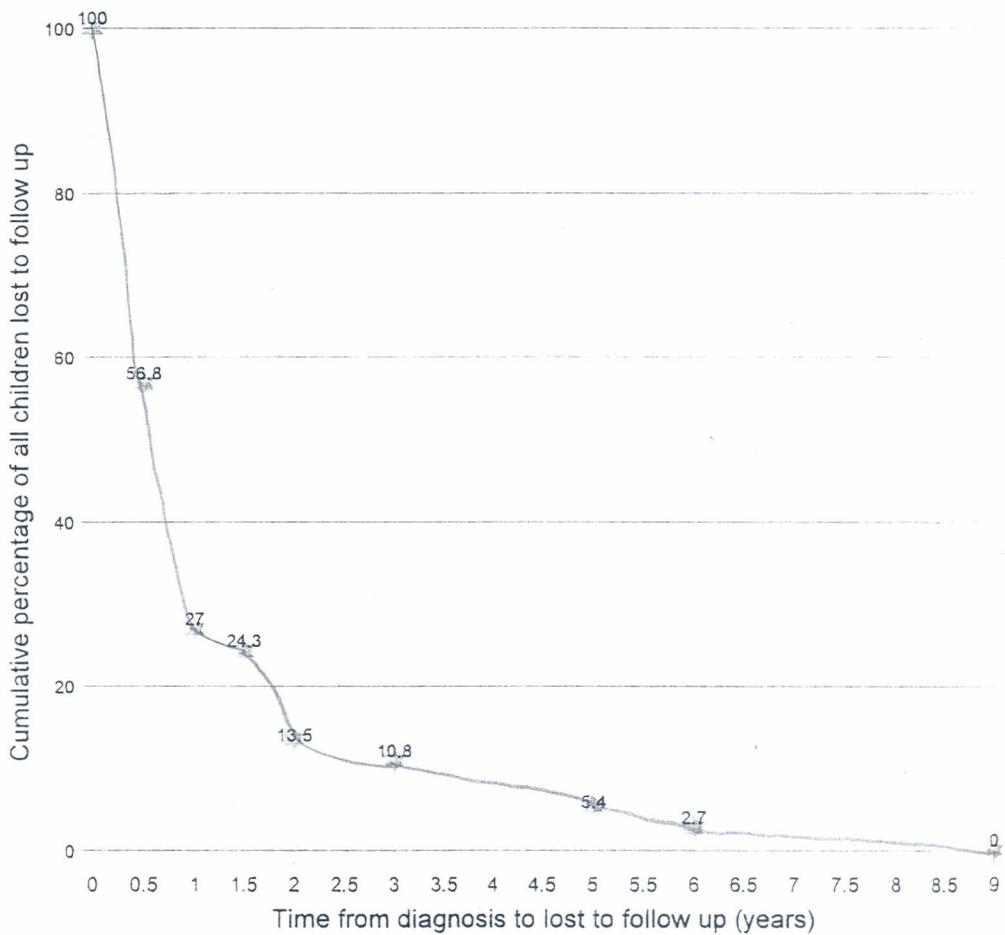
13.   TUMOUR RELAPSE (N=119).

Tumour relapsed in 26 patients (21.8%). Most of the patients relapsed within one year

(57.6% of all patients who had tumour relapse).

FIGURE 12: TIME FROM DIAGNOSIS TO TUMOUR RELAPSE.
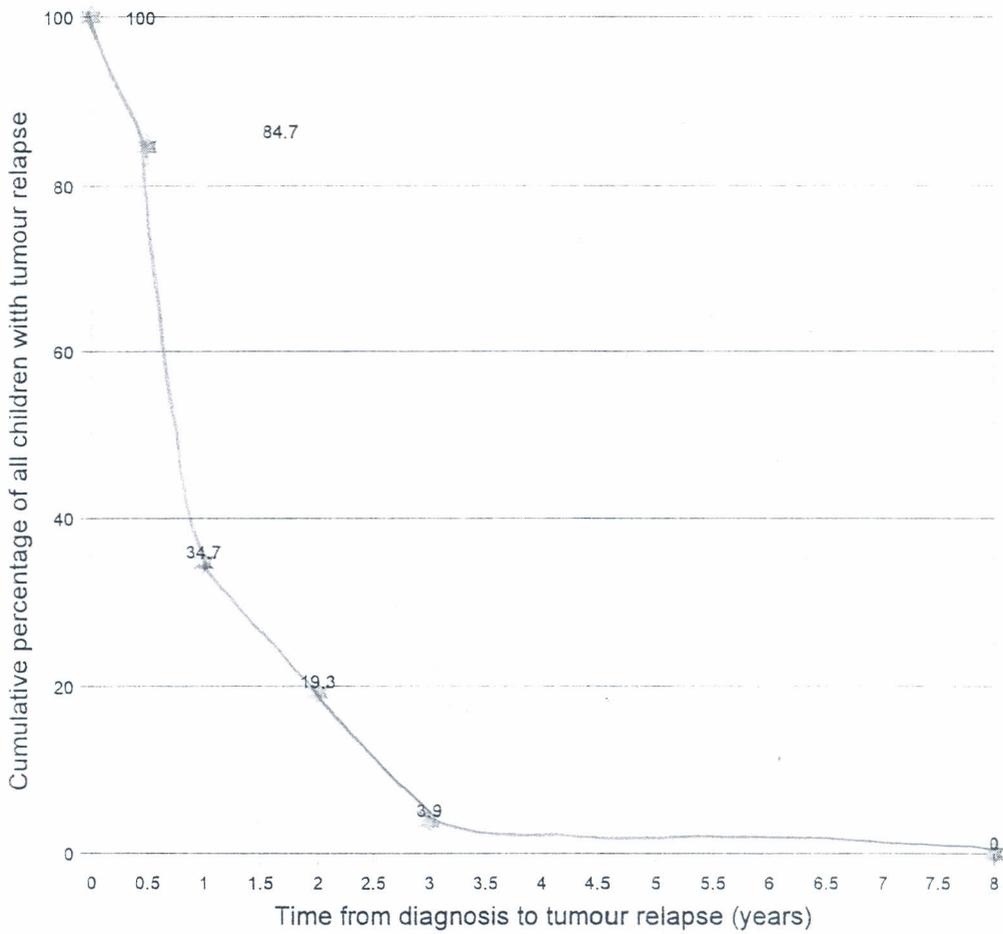
CROSS TABULATIONS.

1.   AGE VERSUS STAGE AT SURGERY.

All patients with stage I Wilms' tumour were within 0-2 years age bracket. Majority of patients were in stage III and IV and were distributed almost equally in all age brackets (see table 7).

TABLE 7:   AGE VERSUS STAGE AT SURGERY

Age(months)	Stage					Total
	I	II	III	IV	V	
0-24	5(12.5)	14(35)	14(35)	6(15)	1(2.5)	40(100)
>24-48		6(20.3)	10(34.5)	12(41.4)	1(3.4)	29(100)
>48-72		1(5.6)	8(44.4)	8(44.4)	1(5.6)	18(100)
>72-120		4(30.8)	3(23.1)	6(46.2)		13(100)
>120			3(100)			3(100)

NB: % in brackets.

All patients older than 6 years were in stage III.

2.   DURATION BEFORE SEEKING HELP AND STAGE AT SURGERY.

Majority of the patients (84.8%) took more than 28 days before seeking help and were

distributed in stage III and IV. All stage I patients presented after 28 days.

TABLE 8:   DURATION BEFORE SEEKING HELP AND STAGE AT

**   SURGERY.**

Days		Stage					Total
		I	II	III	IV	V	
0 - 7	Count X Y		1 25% 4.5%	1 25% 2.9%	2 50% 7.1%		4 100% 4.3%
>7 - ≤28	Count X Y		3 30.0% 13.6%	4 40% 11.8%	2 20% 7.1%	1 10.0% 33.3%	10 100% 10.9%
> 28	Count X Y	5 5.4% 100%	18 23.1% 81.8%	29 37.2% 85.3%	24 30.8% 85.7%	2 2.6% 66.7%	78 100% 84.8%
Total		5 5.4% 100%	22 23.9% 100%	34 37.0% 100%	28 30.4% 100%	3 3.3% 100%	92 100% 100%

X   -   % within how long patient was having symptoms before seeking help

Y   -   % within stage at surgery.

3.   PRE-OPERATIVE RADIOTHERAPY USE VERSUS STAGE AT SURGERY.

Only five patients were given pre-operative radiotherapy. One in stage III, two in stage

IV, and two who died before surgery and therefore not staged.

4.   TABLE 9:   PRE-OPERATIVE CHEMOTHERAPY USE BY STAGE.

		Stage					Total
		I	II	III	IV	V	
Pre-operative chemo-therapy use	Count % within stage % within count	1 20% 2.9%	6 24% 17.6%	11 29.7% 32.4%	15 46.9% 44.1%	1 33.3% 2.9%	34 33.3% 100%
No chemo-therapy use	Count % within stage % within count	4 80.0% 5.9%	19 78.0% 27.9%	26 70.3% 38.2%	17 53.1% 25%	2 66.7% 2.9%	68 66.7% 100%
Total	Count % within stage % within count	5 100% 8.8%	25 100% 24.5%	37 100% 36.2%	32 100% 31.3%	3 100% 2.9%	102 100% 100%

NB: Most patients who received pre-operative chemotherapy were in paediatric medical
wards.

5. **TABLE 10: DURATION BETWEEN PRESENTATION AND SURGERY VERSUS STAGE**

Days	Count	Stage					Total
		I	II	III	IV	V	
1 - 7	X	0.0%	41.2%	47.1%	11.8%	0.0%	100%
	Y	0.0%	33.3%	30.8%	7.4%	0.0%	21.8%
>7 - ≤28	X	0.0%	20.0%	36.0%	40.0%	4.0%	100%
	Y	0.0%	23.8%	34.6%	37%	33.3%	32.1%
> 28	X	2.8%	25.0%	25.0%	41.7%	5.6%	100%
	Y	100%	42.9%	34.6%	55.6%	66.7%	46.2%
Total	X	1.3%	26.9%	33.0%	0.0%	3.8%	100%
	Y	100%	100%	100%	100%	100%	100%

X - Percentage within duration before surgery
Y - Percentage within stage.

Most patients with stage IV took more than 28 days in the ward before surgery. The

same applied to stage I and V. Stage II and III were evenly distributed in the durations.

6. **TABLE 11: INTRA-OPERATIVE HEMORRHAGE VERSUS STAGE AT SURGERY.**

	Stage					Total
	I	II	III	IV	V	
% of those in stage with intra-operative haemorrhage	0.0%	4.3%	19.4%	34.5%	0.0%	18.9%
% of total of those with haemorrage	0.0%	5.6%	38.9%	55.6%	0.0%	100%

Most patients who had massive intra-operative haemorrhage were in stage IV. None of the patients was in stage I or V.

7.   **TABLE 12:   TUMOUR SPILLAGE DURING SURGERY VERSUS STAGE.**

	Stage					Total
	I	II	III	IV	V	
% within stage	0.0%	0.0%	13.9%	34.5%	0.0%	15.8%
% within those with tumour spillage	0.0%	0.0%	33.3%	66.7%	0.0%	100%

All those who had tumour spillage were within stage III and IV. Majority were within stage IV.

8.   TRANSFUSION AND STAGE.

All patients in stage IV and V were transfused. 93.5% of patients in stage III were transfused, 72.7% in stage II and 33.3% in stage I.

9.   STAGE VERSUS POST- OPERATIVE RADIOTHERAPY USE.

75% of patients with stage I disease did not receive any radiotherapy. The other patients

in stage II, III, IV and V received radiotherapy in 62.5%, 81.8%, 69.2% and 66.7% of

patients respectively. Overall, 70% of patients received radiotherapy.

TABLE 13:   STAGE VERSUS POST OPERATION RADIOTHERAPY USE

	Stage				
	I	II	III	IV	V
% within stage given radiotherapy	25%	62.5%	81.8%	69.2%	66.7%

TABLE 14: AGE VERSUS OUTCOME.

		Outcome					Total
(rs)		Died pre-op	Died intra-op. or immediate post op.	Died during follow up	Still on follow up	Lost to follow up	
	Count	2	1	2	13	28	46
	% within age	4.3%	2.2%	4.3%	28.3%	60.9%	100%
≤4	Count	5	1	6	14	8	34
	% within age	14.7%	2.9%	17.6%	41.2%	23.5%	100%
≤ 6	Count	1	2	2	5	9	19
	% within age	5.3%	10.5%	10.5%	26.3%	47.4%	100%
≤10	Count	1	0	5	0	8	14
	% within age	100%	0.0%	35.7%	0.0%	57.1%	100%
10	Count	0	0	1	2	0	3
	% within age	0.0%	0.0%	33.3%	66.7%	0.0%	100%

jority of the patients except those older than 10 years and those within > 2-4 years age

cket were lost to follow up.

11. **TABLE 15: SEX VERSUS OUTCOME.**

Sex		Outcome					Total
		Died pre-op	Died intra-op. or immediate post op.	Died during follow up	Still on follow up	Lost to follow up	
Male	Count	8	2	11	21	35	77
	% within sex	10.4%	2.6%	14.3%	27.3%	45.5%	100%
	% within outcome	80%	50%	68.8%	61.8%	64.8%	65.3%
Female	Count	2	2	5	13	19	41
	% within sex	49%	49%	12.2%	31.7%	46.3%	100%
	% within outcome	20%	50%	31.3%	38.2%	35.2%	34.7%
Total	Count	10	4	16	34	54	118
	% within sex	8.5%	3.4%	13.6%	28.8%	45.8%	100%
	% within outcome	100%	100%	100%	100%	100%	100%

Majority of patients who died pre-operatively were males (80%). Overall males performed poorly compared to females both by numbers and percentages - 27.3% of males had died by time of study compared to 21.9% of females. 45.5% of males were lost to follow up compared to 46.3% of females and 31.7% of females were still on follow up compared to 27.3% of males.

12.   GENERAL STATUS BY OUTCOME

88.9% of patients who died pre-operatively were classified as having poor general

condition. 66.7% of those who died immediately post operatively and intra-operatively

were also classified as poor.

NB: General status is defined as overall clinical appearance on initial examination

TABLE 16: GENERAL STATUS BY OUTCOME

General status		Outcome				
		Died pre-op	Died intra-op. or immediate post op.	Died during follow up	Still on follow up	Lost to follow up
Good	% within outcome	0.0%	0.0%	6.3%	51.6%	22.6%
Fair	% within outcome	11.1%	33.3%	62.5%	45.2%	54.7%
Poor	% within outcome	88.9%	66.7%	31.3%	3.2%	22.6%

13.   **TABLE 17: LYMPH NODE INVOLVEMENT VERSUS OUTCOME.**

Patients with lymph node involvement	OUTCOME				
	Died intra-op. or immediate post op.	Died during follow up	Still on follow up	Lost to follow up	Total
% within outcome	100%	86.7%	46.4%	70.3%	66.7%

14.   STAGE VERSUS OUTCOME.

Majority of the patients who died intra-operatively or immediate post-operatively (75%)

and during follow up (50%) were in stage IV. Most patients with stage I disease (60%),

stage II disease (52%) were still on follow up (see table 18) at the end of the study.

TABLE 18: STAGE VERSUS OUTCOME AT 2 YEARS AFTER DIAGNOSIS.

Stage at surgery		Died intra-op. or immediate post op.	Died during follow up after discharge	Still on follow up 2 years after discharge	Lost to follow up before 2 years	Total
I	Percentage within stage	0.0%	0.0%	60.0%	40.0%	100.0%
	Percentage within outcome	0.0%	0.0%	8.8%	4.2%	4.9%
II	Percentage within stage	0.0%	8.0%	52.0%	40.0%	100.0%
	Percentage within outcome	0.0%	12.5%	38.2%	20.8%	24.5%
III	Percentage within stage	2.7%	13.5%	32.4%	51.4%	100.0%
	Percentage within outcome	25%	31.3%	35.3%	39.6%	36.3%
IV	Percentage within stage	9.4%	25.0%	18.8%	46.9%	100.0%
	Percentage within outcome	75.0%	50.0%	17.6%	31.3%	31.4%
V	Percentage within stage	0.0%	33.3%	0.0%	66.7%	100.0%
	Percentage within outcome	0.0%	6.3%	0.0%	4.2%	2.9%
Total	Percentage within stage	3.9%	15.7%	33.3%	47.1%	100.0%
	Percentage within outcome	100.0%	100.0%	100.0%	100.0%	100.0%

DISCUSSION.

A total of 119 patients were seen in KNH between 1st January 1988 and 31st December 1998 with Wilms' tumour. Thus an average of twelve patients with Wilms' tumour were seen annually. Jumbi in 1980 had noted an average of ten patients annually between 1970 and 1979 inclusive (1). KNH being the biggest and main referral hospital in Kenya receives the bulk of most chronic diseases in the country that cannot be handled elsewhere. Thus these figures gives the magnitude of Wilms' tumour problem in Kenya.

The patients were distributed from all over Kenya except for one patient from Uganda. The patient was referred from Uganda in the early nineties because by then Uganda had no radiotherapy facilities. Central province provided more patients (31.6%), this was followed by Rift Valley (19.7%), Eastern (17.1%), Nyanza (14.5%), Western (6.8%) and rest of country (9.4%) in that order. The above distribution can be explained by nearness to Nairobi, population proportions, cost of transport and awareness of the population. Central province is near Nairobi, has a higher population density and a relatively higher percentage of literate people compared to the rest of the country. Whereas Coast, North Eastern are sparsely populated, they have low literacy levels and are far from Nairobi. Nyanza province on the other hand is far from Nairobi, densely populated and with a relative good literacy rate.

Sex distribution was as follows:- male:female ratio of 1.9:1. In the western world, the disease is equally distributed between the two sexes (1,5,6). In Kenya, in a period

between 1971-1978, Kyambi et al found a 1:1 sex ratio (37). In some series there is a slight female preponderance before age of two years (8).

The youngest patient at diagnosis was four months and the oldest was fifteen years. The peak incidence age group at diagnosis was between one and four years. Only three patients were older than ten years of age. In series reported in literature the peak incidence age group at diagnosis is 2-4 years (8). Fetal Wilms' tumour has been documented in stillborns but not in utero ultrasound diagnosis (38). In this study, there was no patient diagnosed with the tumour in the neonatal age group and after puberty.

Most patients (88.2%) presented to a health facility because of an abdominal swelling. Also in a majority (78.3%) the symptom had been there for more than 28 days. Also, 73.3% were assessed as being fair/good general condition. This is in conformity with what is found in literature-a healthy child with a mass being discovered accidentally in the abdomen (39). The only difference being the long duration taken before medical assistance is sought.

Hematuria occurred in 10% of patients. In only two patients (1.7%) were any congenital malformation noted. One patient had spina bifida occulta and the other had a horse-shoe kidney. Wilms' tumour is associated with congenital malformations in 7-10% of cases (41).

Diagnostic evaluation tools available in KNH included I.V.U., abdominal ultrasound, urine analysis and VMA assay, FNAC, CT scan and other radiological examinations. The investigations of choice were I.V.U and abdominal ultrasound. These were done in 83.2% and 71.4% of patients respectively. Chest x-ray done to rule out metastases in chest was done in 30.3% of patients. CT scan was done in 10.1% of patients and these were only the patients with what was judged clinically as an advanced tumour. In literature, abdominal ultrasound is a primary investigation to localise the tumour and assess presence or absence of tumour extension in the inferior vena cava. CT scan especially with contrast is also done. The role of I.V.U. is waning and is being replaced by above (17,19,40). FNAC is becoming increasingly common in KNH unlike in the eighties when it was not available (1).

Most patients (52.3%) were in hospital over 28 days before they were operated on. Only 19.3% of patients had surgery within seven days of admission. This is in contrast with what happens in western countries. It is recommended that in view of the high growth rate of the tumour, that investigations be done expeditiously, surgery done and chemotherapy started at earliest time possible (40). The reasons alluded to why patients took too long in the ward before any definitive treatment included:- an advanced tumour (25.2%), unavailability of investigations on time due to lack of money, machine breakdown and too many patients hence long booking (9.2%), patient too sick and needed pre-operative support (16.8%). 9.9% of patients were initially offered pre-operative chemotherapy on basis of a wrong diagnosis. The wrong diagnosis were made on the

basis of relying on a diagnostic tool results which were faulty - abdominal Burkitts (diagnosis made using FNAC), neuroblastoma (made on urine assessment for VMA), hydatid cyst (made using abdominal ultrasound).

Pre-operative therapy.

There was no protocol on which patient to put on what regimen. Most patients were started on chemotherapy because of lack of theatre space (7.1%), clinically were thought to have inoperable tumour (83.3%), could not withstand general anaesthesia and or had bilateral Wilms' tumour (2.4%). In NWTS series, chemotherapy was started post operatively as a protocol except in patients with stage V disease, while in SIOP series pre-operative chemotherapy was the rule to downgrade the tumour stage (29,31,40).

Pre-operative radiotherapy was used in 11.4% of patients. Only in one patient with stage V disease was chemotherapy and radiotherapy used together pre-operatively.

The chemotherapy regimen used was the standard solid childhood tumour regimen - vincristine, actinomycin D, cyclophosphomide and adriamycin alternating with actinomycin D (VAC). Occasionally, cisplatinum was used and the only reason alluded to was that patient was too sick. In a majority of patients (61%) pre-operative chemotherapy was inconsistent either due to lack of cytotoxics or side effects of cytotoxics leading to stoppage of their administration.

In U.S.A., Europe, Brazil patients are pooled together and put on treatment protocols, so as to come with best form of management with least deleterious effects immediate and long term, and with least cost (29,43).

The tumour affected the left kidney more times than the right kidney (1:1.3). Worldwide, the tumour affects any kidney with an equal probability (6).

Most patients were found to be in stage III (35.2%) and stage IV (29.6%) at surgery. Only 4.6% of patients were in stage I while 2.6% were in stage V. In NWTS-3 statistical reports of July 1989, patients were distributed as follows:- stage I (42%), II (19.3%), III (20.3%) and stage IV (9.1%)(3). Thus, in Kenya, most patients are seen late hence the advanced stage at surgery. Also, the delays that occur before the patients are taken to theatre and the inconsistency of preoperative chemotherapy are contributory to the late stages at surgery (see above). NWTS series record the incidence of stage V disease as between 4.4-7% (Bishop et al) (16). In this study stage V contributed 4.6% of all patients.

Peri-operative gross tumour spillage affects prognosis as intra-peritoneal spillage increases the risk of intraabdominal recurrences. In the population under study gross spillage occurred in 12.6% of patients. Roth et al reported a tumour spillage rate of 6% after pre-operative chemotherapy versus 11.5% in patients who had no chemotherapy before surgery (43). This correlates well with our figures where majority of our patients

do not receive pre-operative therapy. Most patients (83.5%) received blood transfusion but massive haemorrhage occurred only in 18% of patients.

Lymph node involvement occurred in 63.3% of patients. Lymph node involvement is a major adverse prognostic indicator (6).

Chemotherapy use and radiotherapy were consistent in only 46.4% of patients. This may contribute to the poor outcome. The contributory factors to inconsistency of chemotherapy and radiotherapy administration included - early loss from follow up, unavailability of cytotoxics, guardian ignorance, improper treatment documentation rendering treatment inconsistent and over booking in the radiotherapy department.

Radiotherapy use occurred in all stages and all age groups. This is unlike in NWTS and SIOP series where radiotherapy has been found not to be useful for stage I and II patients with favourable histology and stage I patients with unfavourable histology (29,31). In this study, it was found out that in almost all patients the pathologist does not grade the histology. They only report that the histology seen is in conforming with nephroblastoma.

The commonest chemotherapy/radiotherapy complication was pancytopenia. This was noted in more than 75% of all patients on chemotherapy/radiotherapy. These cytotoxics induced bone marrow suppression lead to episodes of chicken pox outbreak in the

paediatric oncology ward. Apart form hematological and enteral toxicities other side effects like growth deformities, fertility abnormalities, cardiomegally, neuropathy and secondary tumours were not documented. This may be because of the short duration of follow up, poor patient nutritional status, poor documentation and lack of facilities to screen for toxicities.

Outcome assessed as to whether patient was dead, lost to follow up or still on follow up showed that 25% of patients died during treatment and follow up, 45.8% of patients were lost to follow up even before two years had elapsed and only 28.8% were still on follow up for greater than two years. If you exclude those lost to follow up before two years are over, you get a mortality figure of 35.7%. This figure may be still be higher if the fate of those lost to follow up is known. Quite a number of those lost to follow up were discharged for palliative management at nearest home health facility and could therefore be deceased. All the dead even after two years were ascribed to Wilms' tumour. In western world the outcome is comparatively better. The five year survival rate being 97% for stage I, 94% stage II, 88% stage III and 82% stage IV (32). There were some improvement in outcome noted in this study. Jumbi (1980) had found no five year survivor (1), while in this study there were more than eleven patients (9.2%) who were still alive and still on follow up five years after diagnosis.

80.6% of all patients who died did so within the first 12 months from diagnosis and 75.6% of all patients lost to follow up did so within also the first 12 months. 57.6% of

patients had tumour relapse within the first one year. This implies that we need intensive management and counseling in the first one year so as to improve results. The only thing in common with western figures is that the patients have a high chance of dying, being lost to follow up and tumour relapse within the first year after diagnosis.

Age seemed to have a determined role in stage at diagnosis. All patients with stage I disease were below two years and all patients older than six years had stage III and IV Wilms' tumour. All patients older than ten years were in stage III. This can be explained by the fact that all children less than two years are with their mother almost always and are bathed by her hence early noting of the problem. Patients above ten years are also able to express themselves.

84.8% of patients took more than a month after noticing the problem to seek help. This may be a contributory factor to advanced stage at surgery (III and IV). Those who presented within the month of noticing the problem were in stage II and III but surprisingly all who had stage I disease presented after 28 days of noticing the problem. No explanation can be given but maybe they had tumour with favourable histology and therefore slow growth rate.

After admission in the ward, most patients were operated after more than a month. Only 21.8% were operated on within the week of admission. Surprisingly, patients with stage I, IV and V took longest duration in the ward before surgery. This can reflect on the

diagnostic evaluations being more in patients with stage I, IV and V. Also all patients who had what was thought to be inoperable tumours (stage IV) had pre-operative chemotherapy to downgrade the tumour stage at surgery.

Intra-operative complications were high in stage IV. This was as expected. Also the need and quantity of blood transfusions increased with advancing stage:- 100% transfusion rate in stage IV and V, 93.5% rate in stage III, 72.7% in stage III and 33.3% in stage I.

Post operative radiotherapy was used in all stages. This is unlike in the NWTS series where stage I and stage II favourable histology don't receive radiotherapy (32).

Age at diagnosis is usually a major prognostic factor (40). In this study, there was no correlation if one considered all patients, but exclusion of patients lost to follow up

produced an age correlation as found in other centres.

Age	% within age		N
	Died	On follow up	
0 - < 2years	27.8%	72.2%	18
> 2 - ≤ 4 years	46.2%	53.8%	26
> 4 - ≤ 6 years	50.0%	50.0%	10
> 6 - ≤ 10 years	100%	0.0%%	6
> 10 years	33.3%	66.7	3

The male patients had a relatively poor outcome. No reason could be infered although there were relatively more males than females.

The general status of patients was a good indicator of outcome. Most patients classified as or poor general status died either pre-operatively, intra-operatively or immediate post operatively. None of the patients classified as of good general status died pre-operatively and intra-operatively and most (51%) of them were still on follow up at end of study. In literature, general status is quoted as a prognostic indicator (40).

Lymph node involvement was a poor prognostic indicator and this concurs with what is found in other centres (32).

The late the stage at surgery the worse the prognosis. This was shown by the outcome that most patients who died were in stage IV disease.

CONCLUSION.

1. There have been a slight increase in incidence from an average of 10 patients annually (1971-1980) to 12 patients annually (1989-1998) as seen at Kenyatta National Hospital.

2. The patients seem to be distributed from all over Kenya with relatively more from adjacent areas to Nairobi

3. There are more males than females with a sex ratio of male:female ratio of 1.9:1. The tumour affects predominantly, children under 6 years with a peak incidence in the 1-4 years age group.

4. Most patients (78.3%) took more than 28 days after noticing problem before seeking help. The commonest presenting complaint was a painless abdominal swelling (88.2%). 23% of patients had a definitive diagnosis made in a peripheral hospital.

5. The commonest investigations done were I.V.U. (83.2%) and abdominal ultrasound (71.4%). FNAC of the mass and CT scan of the abdomen are becoming common investigations in patients with suspected Wilms' tumour.

6. Most patients took more than 28 days in hospital before any surgery was performed. This was largely due to investigations being delayed.

7. The left kidney was more affected than the right kidney (right:left ratio of 1:1.3). Most patients had advanced Wilms; tumour stage III and IV. Stage V contributed only 4.6% of all patients.

8.   Pre and post operative chemotherapy were erratic for 60% of patients. Also the pre-operative chemotherapy was not a standardized protocol.

9.   The major factors noted to contribute to morbidity and mortality were age at diagnosis, the male sex, general status of patient, stage at surgery, lymph node involvement, duration patient had problem before seeking help, radiotherapy and chemotherapy use.

10.   The commonest noted side effect of chemotherapy and radiotherapy was pancytopenia (bone marrow suppression) (75%).

11.   There was a high fall out rate from the clinic and especially after discharge from the ward (68.4% if you exclude those who had died).

12.   The first one year after diagnosis is critical in patients with Wilms tumour as shown by high morbidity rate, high relapse and high fall out rate from the clinic.

13.   At the end of two years from the time of diagnosis (at completion of study) 28.8% of patients were still on follow up against 25.8% dead and 45.8% lost to follow up.

RECOMMENDATIONS.

1. Health education is still needed to enlighten our people so as to improve outcome.

2. Peripheral hospitals (provincial hospitals) should be encouraged to manage these patients. Also there should be good correspondence with KNH so as to improve the outcome.

3. Ways of availing cytotoxics/radiotherapy to all patients at an affordable cost and accessibility should be looked at. This will improve consistency in therapy.

4. Any patient going to theatre for Wilms' tumour surgery in KNH needs blood to be grouped and cross matched and at least one unit kept ready.

5. A guideline is needed to decide on what modalities of treatment should be offered to each stage of disease and patient status. Also a multidisciplinary team involving the surgeon, paediatrician, oncologist, nutritionist, radiotherapist should be set up.

6. A prospective study should be carried out to determine the factors contributing to the poor outcome.

7. FNAC should be evaluated in view of the significance incidence of wrong diagnosis attributed to it's use in diagnosis of Wilms' tumour in Kenyatta National Hospital.

PROFORMA QUESTIONNAIRE.

1. Patient name: ....

    In-patient number......................

    Age...................................

    Sex...................................

    Geographical home region (residence province) ....

2.1 What brought the parent/patient to a health facility
    ☐ Abdominal swelling
    ☐ Abdominal pain
    ☐ Non specific symptoms
    ☐ Patient referred with Wilms' tumour

2.2 For how long has the patient been having the symptoms before seeking help?
    ☐ Days (up to 7 days)
    ☐ Weeks (> 7 days < 28 days)
    ☐ Months ($\geq$ 28) days
    ☐ Not recorded

2.3 Age at presentation
    ☐ Under 2 years
    ☐ 2-4 years
    ☐ 4-6 years
    ☐ 6-10 years
    ☐ Others (specify)......................................

2.4 General status of patient
    ☐ Good
    ☐ Fair
    ☐ Poor
    ☐ Not recorded

2.5 Any congenital malformation noted
    ☐ Yes
    ☐ No
    If yes, specify...

2.6   The definitive investigations done

(A)   ☐   Urine analysis, microscopy and
       ☐   Biochemistry (VMA)
       ☐   Plain abdominal x-rays
       ☐   Abdominal ultrasound
       ☐   Intravenous urogram
       ☐   Computerised tomography
       ☐   Others (specify)....................................

2.7 (a) What is the duration between presentation and surgery (specify)
       ☐   Days (1-7)
       ☐   Weeks (1-4 weeks)
       ☐   Months (more than 4 weeks)

  (b)   If above is more than four weeks, why?
       ☐   Inability to do investigations on time
       ☐   Require preoperative support e.g. correction of anaemia
       ☐   Preoperative radiotherapy and or chemotherapy
       ☐   Other (specify)..

3.   Preoperative chemotherapy and or radiotherapy
3.1   What is the criteria used to put patient on preoperative therapy
       ☐   Advanced tumour
       ☐   Patient inability to withstand general anaesthesia
       ☐   Others (specify)...

3.2   What preoperative therapy is used?
       ☐   Chemotherapy
       ☐   Radiotherapy
       ☐   Combined
       ☐   Supportive
       ☐   None

3.3   What drugs (cytotoxics) are used?
       ☐   V.A.C
       ☐   Others (specify)....................................

3.4   (a) Was there an interruption in schedule? No=0, Yes=1   ☐
       (b) If yes, specify......................................

4. Intraoperative findings

4.1 Which kidney was involved?
　　　[　　] Left
　　　[　　] Right

4.2 What is the stage at surgery? (Specify)....................................

4.3 Any intraoperative complications?
　　　[　　] Massive haemorrhage
　　　[　　] Tumour spillage into peritoneal cavity
　　　[　　] Anaesthetic complications (specify)..........................
　　　[　　] Others (specify)...

4.4 (a) Was patient transfused? No=0, Yes=1 　[　　]
　　　(b) How many units of blood used?.......................................

4.5 Lymph node involvement? No=0, Yes=1 　[　　]
　　　If yes, specify which..

5.1 Histology:　　Favourable=1, Unfavourable=2, Not stated=3 　[　　]

5.2 (a) Chemotherapy started after how many days from surgery?
　　　[　　] < 7 days
　　　[　　] 7-14 days
　　　[　　] Other (specify)...

5.2 (b) What chemotherapy regimen was used.............. duration...........................

5.3 (a) Radiotherapy use specify [　　] Yes [　　] No

5.3 (b) Who was put on radiotherapy?
　　　[　　] Stage I
　　　[　　] Stage II
　　　[　　] Stage III
　　　[　　] Stage IV
　　　[　　] Stage V

5.4 Any complications of radiotherapy and chemotherapy noted No=0, Yes=1 　[　　]
　　　If yes, specify...

6.   Follow up
6.1   Outcome
                Died preoperative
                Died intraoperative or immediate post operative period
                Died during follow up
                Still on follow up
                Lost to follow up

6.2   (a) If child passed away what time had elapsed from time of diagnosis
        (specify)..
        (b) If patient lost to follow up, what time has elapsed from time of diagnosis
        (specify)..

7.1   Tumour relapse   Yes ☐   No ☐
        If yes, specify after how long....................................

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