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2014

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A DESCRIPTIVE STUDY OF THE DISTRIBUTION AND RELATIVE FREQUENCY OF NEONATAL TUMOURS AT CHRIS HANI BARAGWANATH ACADEMIC HOSPITAL FROM 1 JANUARY 1988 – 31 DECEMBER 2012

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A research report submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, in partial fulfillment of the requirements for the degree of Master of Medicine in the branch

of

Paediatrics

Johannesburg, 2014.

DECLARATION

I, Dr Tanya Marie Schickerling, declare that this research report is my own work. It is being submitted for the degree of Master of Medicine in the University of the Witwatersrand, Johannesburg. It has not been submitted before for any degree or examination at this or any other University.

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ABSTRACT

Background: To describe the relative frequency and distribution of neonatal tumours; to determine the age at presentation to the oncology unit and to determine the extent of the delay in referral. To describe any associated syndromes in individual malignancies.

Material and methods: A retrospective case series was performed covering 24 years. Demographics, means of diagnosis, treatment and outcome details were reviewed.

Results: There were a total of 2626 patients that presented to the oncology department with suspected malignancies. Out of that, 2308 patients were diagnosed with a malignancy and 318 patients had benign tumours. Over the 24 year period 117 tumours were diagnosed in neonates (4,4%). Due to incomplete data 29 patients were excluded. Of the remaining patients, 61 were diagnosed with benign tumours and 27 with malignant tumours. The male to female ratio was 1: 1,5. The mean age at presentation was 16 days. The mean age at diagnosis was 36 days. Histology and radiology were diagnostic in 40,9% and 19,3% respectively. A combination of histology and radiology was used to make a diagnosis in 21,6% of patients, 11,4% of diagnoses were based on clinical examination and 6,8% on biochemistry and haematology. Malignant soft tissue tumours were the most common malignancy (25,9%) followed by renal tumours (18,5%), leukaemia (14,8%), neuroblastomas (11,1%) and retinoblastomas (11,1%). Teratomas (45,9%) and benign vascular tumours (44,3%) were the most common benign tumours. Chemotherapy was used to treat 22 neonates, while 50 underwent surgical removal of the tumour. Half (51,9%) of the patients diagnosed with a malignant tumour died, while 11,1% of patients were

lost to follow up. Just under 10% (8,2%) of the patients diagnosed with a benign tumour died, while 44,3% of patients were lost to follow up. The overall mortality amongst patients diagnosed with benign or malignant tumours was 21,6%.

Conclusion: There is a much higher incidence of benign tumours diagnosed in neonates (69,3%) compared to older children (12,1%). Only 1,2% of all childhood malignancies in our unit occurred in the neonatal period, which is slightly lower than the reported 2%. Two of the major issues that need to be addressed in the future management of neonatal tumours are prompt referral for prompt diagnoses and better follow up.

ACKNOWLEDGEMENTS

In the memory of a neonate diagnosed and treated at Chris Hani Baragwanath Academic Hospital who inspired me to do this study.

AND

To my supervisor Dr Diane Mackinnon for her patience, guidance and assistance with writing this research report.

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1.0 INTRODUCTION

A tumour is defined as a mass of new tissue which persists and grows independently of its surrounding structures and which has no physiological use.[1] It can be classified as benign or malignant. A benign tumour does not metastasize, invade or destroy adjacent normal tissue.[2] A malignant tumour is one that invades surrounding tissues and is usually capable of producing metastases.[2] It is likely to recur after attempted removal and can cause death of the host unless adequately treated.[2]

Neonatal tumours occur within the first 28 days of life.[3] These tumours are known to be very rare, with a prevalence of 1/12 500 to 1/17 300 total births.[4,5,6] It has been predicted that most neonatal units will see one case every one to two years.[4] The accuracy of this reported prevalence is unclear, as the majority of the studies reviewed were hospital based.[6,7,8] An ideal study would be a population based study where the overall incidence can be determined irrespective of government and private facilities.[3,6] A few studies considered stillborn babies and early neonatal deaths, however as postmortem examinations are not routinely performed in all institutions some tumours might be missed. A study done in 1987 in Toronto, Canada reported that 41% of neonatal tumours were evident on the first day of life, however, in 17% the diagnosis was made on autopsy.[6] The possibility of lab errors should also be taken into consideration due to the difficulty in distinguishing malignant tissue from normal neonatal tissue and it is reasonable to believe that the number of neonatal tumours are under reported. Lastly most case series reviewed did not leave room for late presentations or delayed referrals and used four weeks as a cut off age for patients they included in their studies.

Classification

Due to the uncommon behavior, neonatal tumours can be divided into four clinical groupings.[3]

Table 1. Tumour types.[3]

1. Benign tumours	a. Life threatening because of size and location (e.g. cervical teratoma) b. Have a known tendency towards malignant transformation (sacrococcygeal teratoma, giant naevus) c. Benign tumours, not life threatening or tending towards malignant transformation (mesoblastic nephroma)
2. Tumours demonstrating local invasiveness but no metastatic potential	(E.g. congenital fibrosarcoma, fibromatoses)

3. Malignant tumours	a. Behave more like those occurring in older children b. Behave better than expected (hepatoblastoma, neuroblastoma) c. Behave worse than expected (congenital alveolar rhabdomyosarcoma, leukaemia) d. Demonstrate unpredictable or uncertain behavior
4. Extremely rare tumours	Carcinoma, lymphoma, Hodgkins disease, Kaposi sarcoma

Aetiology

The aetiology of cancer in a child is multifactorial and includes both environmental factors and genetics.[3] Neonates are characterized as a separate entity as the environmental interference is minimal.[3] There are two groups of genetic abnormalities involved in the epidemiology of tumours in childhood.

The first comprises the constitutional chromosomal abnormalities resulting in an increased risk of malignancy, for example retinoblastoma on chromosome 13q and rhabdomyosarcoma on chromosome 11p.[9] Secondly, genetically determined syndromes, where an increased risk of malignancy exists. For example familial retinoblastoma with the gene RB1 and Down syndrome, which has been proven to have an increased risk of leukaemia and germ-cell tumours.[3] Other environmental

factors include ionizing radiation, infection or drugs taken during pregnancy.[3] Transplacental spread of maternal tumours have been reported with malignant melanoma, leukaemia and choriocarcinoma.[5,6]

Demographics

Gender predisposition seems to vary from study to study. Some studies reported a male predominance, while other studies reported an equal male to female ratio except for teratomas, which showed a female predominance.[6,3]

In the USA it was reported that Japanese children have the highest incidence of neonatal tumours while black African American children had the lowest reported cases.[3]

Distribution

The most common tumour in a neonate is a teratoma followed by benign vascular tumours. The most common malignant tumours are neonatal neuroblastomas, malignant soft tissue tumours and retinoblastomas.[6,7]

1.1 Germ-cell tumours (GCT)

Germ-cell tumours can be divided into seminoma/germinoma, embryonal carcinoma, yolk sac tumour, choriocaricnoma and mature or immature teratomas.[10] Malignant germ-cell tumours are rare tumours and the incidence varies according to the age and sex of the patient.[10]

TERATOMA: Teratomas are the most frequently diagnosed perinatal neoplasm accounting for one third of all cases.[5] It is very rarely malignant and the sacrococcygeal region is the most common site.[4,5] Teratomas can be classified into two groups according to histology, namely mature teratomas which are considered as benign tumours, and immature teratomas which may show clinical features of malignancy.[10] Numerous studies have shown a female predominance in teratomas.[11]

SACROCOCCYGEAL TERATOMA: It is considered to be the most common tumour in the newborn period with a reported incidence of approximately one in 35 000 – 40 000 live births.[12] It is composed of two or three germ cell layers, has multiple tissue types and can present in various shapes and sizes.[12] It is more common in females with a M: F ratio of 1: 3-4.[12,13]

Sacrococcygeal teratomas can present either prenatally or postnatally.[12,13] When the diagnosis is made before 30 weeks gestation there is a well documented association with high foetal morbidity and mortality.[12] Patients with external sacrococcygeal teratomas usually present at birth with a protruding mass from the sacrum.[13] The

overlying skin can have changes such as redundancy or patchy, dark discoloration, which can simulate a haemangioma or lymphangioma.[11]

The preferred treatment includes complete surgical excision (including resection of the coccyx).[12] The newborn with sacrococcygeal teratoma has an excellent prognosis depending on the timing of diagnosis, malignant potential of the tumour and the ease of surgical resection.[12] Chemotherapy and radiotherapy are indicated in malignant cases.[12] Strict follow up for the first three years of life is essential due to the high risk of recurrence early in life.[12]

1.2 Benign vascular tumours

The second most common tumours of infancy are benign vascular lesions.[14,15] Though histologically benign, certain unique presentations of vascular tumours may have serious consequences for the newborn.[14]

HAEMANGIOMA: Haemangiomas are one of the most common tumours of infancy with an incidence of 1 - 2,6% of all live births.[14] It is more common in the white population and an incidence as high as 10% has been recorded.[14] It is four times more common in female patients and is more commonly seen in premature babies.[14] Most infantile haemangiomas are benign and do not cause any morbidity or mortality.[15] Vascular neoplasms can incite a consumptive coagulopathy and may be life threatening (Kasabach-Merritt syndrome).[15]

Haemangiomas generally cease growing by the time the infant is 18 months old. Slow spontaneous involution then occurs over the next two to six years.[14] Medical intervention is often required for large ulcerative haemangiomas or those impinging on vital structures.[14]

HAEMANGIOENDOTHELIOMA: A haemangioendothelioma is a rare benign vascular tumour arising from mesenchymal tissue usually located in the liver.[16] Neonates often present with cardiac failure because of extensive arteriovenous shunting within the lesion.[16] Spontaneous involution normally occurs in the first 12 - 18 months of life thus asymptomatic lesions are generally managed conservatively.[16] If an infant presents with cardiac failure or anaemia they are normally treated with corticosteroids or interferon alpha-2a, to slow down the tumour growth.[16] In severe cases surgical resection, partial hepatectomy and embolization of afferent vessels should be considered.[16]

1.3 Malignant Soft Tissue tumours

The incidence of malignant soft tissue tumours varies greatly from study to study with an estimate of 10 – 30% of all neonatal malignancies.[6,7,8,17] These tumours include fibrosarcomas, rhabdomyosarcomas, leiomyosarcomas, liposarcomas, haemangiopericytomas and synovial sarcomas.[4,5]

FIBROSARCOMA: Infantile fibrosarcoma has an incidence of five per million infants.[18] It occurs more in males than females with a M: F ratio of 1: 0,2.[18] Most patients with infantile fibrosarcoma present with a tumour on the extremities, more

often the lower extremities than the upper extremities.[4,18] Other presentations include tumours on the head and neck, abdomen and pelvis.[18]

Fibrosarcomas are known to have an unpredictable clinical behavior. They are very chemosensitive, and may undergo spontaneous regression.[4,18,19] A Turkish study of 12 neonates with fibrosarcoma, showed a mortality rate of just 8%.[18]

RHABDOMYOSARCOMA (RMS): Rhabdomyosarcoma is a malignant mesenchymal neoplasm that exhibits striated muscle differentiation.[20] Two percent of all rhabdomyosarcomas are present at birth.[20] A third of all rhabdomyosarcomas are associated with at least one congenital anomaly.[21] In 20% of cases rhabdomyosarcoma presented on the extremities, more commonly the lower extremities than the upper extremities.[21] Other sites included the head and neck and the genitourinary tract.[20]

Optimal therapy has not been well established but neonatal rhabdomyosarcomas respond excellently to chemotherapy and surgery can even be avoided.[21] The prognosis of neonates with rhabdomyosarcoma is largely affected by: the immaturity of organs resulting in organ insufficiency during chemotherapy, low immunity in the neonatal period, the presence or absence of distant metastases, site, surgical resectability, histology, pre-treatment staging and clinical group staging.[21]

1.4 Renal tumours

Malignant neonatal renal tumours are very uncommon with an incidence of 4% of all neonatal malignancies.[6,17]

CONGENITAL MESOBLASTIC NEPHROMA (CMN): CMN is reported as the most common renal tumour in neonates with more than 80% of all CMN presenting in the neonatal period.[22,23,24,25] There are two pathological subtypes including the classic CMN and the atypical or cellular CMN.[23,24,25,26] About 10% of cases diagnosed are of mixed histology with a classic and cellular picture.[24] The natural histology of both variants are benign, but there have been reported cases of local recurrence and metastases.[4,22]

There is a strong male predominance with M: F ratio of 2: 1.[4,24] There is also a well documented association with mesoblastic nephroma and polyhydramnios.[22,23,25] The most common presentation is an asymptomatic abdominal mass.[22] The gold-standard imaging modality is MRI but it is limited in distinguishing between CMN and Wilms' tumour.[4] A histological diagnosis remains mandatory.[4]

The prognosis for patients with CMN is very good and treatment normally involves surgery alone.[24] In 95% of patients CMN's are benign and no further treatment is required.[31] The overall survival rate is reported to be as high as 95% - 98%.[4] Relapses were reported in 5% of patients, and are thought to be due to incomplete resection, older age and the cellular subtype.[22,24,26]

WILMS' TUMOUR (WT): Wilms' tumours normally present in an older age group but there have been reported cases of Wilms' tumours diagnosed in the neonatal period.[4] Unlike CMN, Wilms' tumours are more often seen in females of African descent.[4] Wilms' tumours are also more commonly associated with congenital anomalies and some studies show an association with syndromes in as many as 25% of cases.[4]

As for CMN, neonatal WT presents with a solid abdominal mass, which is difficult to distinguish from other renal tumours by radiological imaging alone.[4] Histology remains diagnostic.[4] Treatment for neonates with unilateral WT is a primary nephrectomy and the five year survival rate for neonatal WT has been reported to be around 90%.[4]

1.5 Congenital/Neonatal Leukemia

Congenital leukemia is very rare with a reported incidence of one in five million live births and represents approximately 8% of all neonatal malignancies.[6, 27] Unlike the paediatric population where lymphoid lineages predominate, myeloid lineages are reported more often in the neonatal period.[5,27,28,29]

The aetiology of congenital leukemia is unknown but it has been reported that maternal exposure to radiation, maternal dietary exposure to bioflavonoids, maternal use of tobacco and illicit drugs, and inherited conditions such as Down syndrome and Turner syndrome, increase the risk of congenital leukemia.[5,27,28] It has been shown

that patients with Down syndrome have a 20-fold increased risk of developing leukaemia in their lifetime.[30]

The criteria for diagnosing congenital leukaemia include: a) disease presentation within 30 days after birth, b) immature cell proliferation in myelomonocytic, lymphoid, or erythoid series, c) infiltration of these cells into extra hematopoietic tissue and d) the absence of any other conditions that mimics congenital leukaemia, together with the absence of transient abnormal myeloproliferative disorders typically seen in patients with Down syndrome.[28,31]

Transient myeloproliferative disorder is characterized by proliferation of abnormal myeloblasts in bone marrow and blood of infants with Down syndrome.[32] It is very difficult to distinguish it from AML morphologically and it resolves spontaneously without therapy.[32] It manifests in the first few days of life where AML is generally present after one year of age.[32] There have, however, been reported cases of AML at a younger age, but it is very rare.[32]

Patients with leukaemia present with anaemia, thrombocytopenia, high white cell count and organomegaly.[6,27,28,29] In 25% - 30% of cases, patients present with specific cutaneous infiltrates (leukemia cutis) which usually present as firm blue or red nodules ('Blueberry Muffin').[27] The disease is not always apparent at birth and signs may be evident after days and weeks. There may be an antecedent period of failure to thrive, diarrhoea and low grade fever.[29] Many neonates however present in respiratory distress secondary to pulmonary leukostasis and bronchopneumonia.[29,31]

Diagnosis of congenital leukemia is made on peripheral blood and / or bone marrow smears together with standard immunophenotypic and cytogenetic investigations, where possible.[33] The mainstay of treatment remains chemotherapy but unfortunately congenital leukemia has a very poor prognosis with 23% of patients surviving to the age of two years.[27,29]

1.6 Neuroblastoma

Neonatal neuroblastoma is the most common malignant tumour seen in the majority of studies, accounting for 30 – 50% of cases in most series. [3,4,5,6,7,34,35]

It was proposed in one study that there is an increased incidence in males with a M: F ratio of 2: 1, but other studies failed to confirm this gender preference.

Ultrasound remains the investigation of choice, while CT Scans and MRI Scans are of value in diagnosing the presence of metastases.[4] Urine catecholamine metabolites are considered as tumour markers, and vanillylmandelic acid (VMA) and homovanillic acid (HVA) are increased in 80% - 90% of neonates diagnosed with a neuroblastoma.[4,34] Histopathology is required to confirm the diagnosis.[34] Once the diagnosis is confirmed, the treatment will depend on the histology, cytogenetics and staging of the tumour. [34] Death resulting from tumour was seen in 23 – 34% of reported cases, while other studies showed spontaneous remission of stage 4S disease and an overall survival of 91%.[34,35]

1.7 Retinoblastoma

Retinoblastoma is a highly malignant intraocular tumour requiring an early diagnosis and immediate treatment.[36] The incidence is influenced by the policy of elective eye examination in children with a positive family history of retinoblastoma.[5] A series from Toronto, Canada reported an unusually high incidence of 25% of patients with neonatal retinoblastoma, which were diagnosed on elective eye examination because of high index of suspicion.[5,6,37]

It was shown in only one study that there appeared to be a female predominance in neonatal retinoblastoma with an M: F ratio of 1: 1,6.[37] The presenting symptoms included leucocoria (56,2%), strabismus (23,6%), poor vision (7,7%), family history (6,8%), proptosis, failure to thrive and heterochromia iridis.[6,37] Some studies revealed the majority of patients to have bilateral disease,[5,6] while other studies reported a higher incidence of unilateral retinoblastoma.[37,38]

The diagnosis is made by examining the fundus of the eye with indirect ophthalmoscopy.[38] Fundus imaging, MRI and ultrasonography are used to support the diagnosis and stage the tumour.[38]

Over the past five years, ophthalmic artery chemosurgery has been proven to be as effective as previous management with primary radiation or systemic chemotherapy, but without the unfortunate side effects.[39] The mortality rate in one series was 24%, where four out of the 17 neonates with retinoblastomas who received treatment consisting of enucleation, radiochemotherapy or both, died.[6]

1.8 Langerhans cell Histiocytosis (LCH)

The incidence of neonatal LCH is estimated to be approximately one to two per million live births.[40] A study from Chicago demonstrated a male predisposition where only six out of the 19 neonates investigated were female.[41]

Neonates most commonly present with vesiculopustular lesions that can easily be mistaken for an infectious process.[41] The clinical presentation can however vary from a single-organ to multiorgan invasion of the skin, bone, lymphatic system, liver, spleen, lungs and the central nervous system.[40] It is, however, not possible to predict the extent of the systemic involvement based on the morphologic characteristics of the skin findings, therefore it is of great importance to perform a series of baseline studies when a diagnosis of LCH is suspected.[41]

Treatment recommendations should be tailored according to the sites of involvement.[41] The prognosis depends entirely on the organs involved and the response to chemotherapy.[40]

1.9 Hepatic tumours

Hepatic tumours comprise about 4% of all tumours occurring in the neonatal period.[4] There is a largely unexplained but clearly recognized predominance in white, male patients, in preterm infants and those with low birth weight.[4]

HEPATOBLASTOMA: Hepatoblastoma is a very rare tumour and less than 10% of all hepatoblastoma cases are diagnosed in the neonatal period.[42] There is a slight male predominance with a M: F ratio of 1,4 - 2: 1.[42] A well documented association with hepatoblastoma and inherited syndromes include Hemi-Beckwith-Wiedemann syndrome and Intestinal Adenomatous Polyposis syndrome.[4]

The most common presentation includes an upper quadrant abdominal mass and generalized abdominal distention.[43] The first line of investigation is ultrasonography.[4] Approximately 90% of infants with hepatoblastomas will have an increased Alpha Feto Protein (AFP) level.[4,42,43]

Preoperative chemotherapy is considered the treatment of choice, followed by surgery.[4] The five-year survival rate in neonates diagnosed with hepatoblastoma is 25%.[4,7,8,17]

1.10 Central Nervous System tumours

Congenital brain tumours are rare with an incidence of 1,1 – 3,6 per 100 000 newborns.[44] About 1% of all childhood brain tumours occur in the neonatal period, with a prevalence of 8% of all neonatal malignancies.[5,6,45,46]

A study in Boston described medulloblastoma to be the most common CNS tumour seen in neonates, followed by ependymoma, astrocytoma and choroid plexus papilloma.[47] Overall it was reported that there is a slight male predilection with a M: F ratio of 1: 0,7.[46]

Congenital brain tumours have the propensity to bleed and intramural hemorrhage occurs in 14% - 18% of cases.[46] A CT scan is very useful to detect hydrocephalus and associated hemorrhage.[46]

MEDULLOBLASTOMA: In 1984 there was a study conducted in Boston which described 55 infants and stillborn babies with central nervous system tumours.[47] Medulloblastoma was by far the most common, with a prevalence of 13 out of the 55 patients, which accounted for 24% of all CNS tumours in the neonatal period.[47] Medulloblastoma is a malignant and invasive embryonal tumour of the cerebellum.[45] Common presenting features include increased head circumference, distended anterior fontanel and vomiting.[48]

Although numerous recent publications show an improvement in treatment, the prognosis of neonatal medulloblastoma remains very poor with a mean survival of only 6,8 months.[48] A combination of surgery, chemotherapy and radiation are regarded as the gold standard of treatment, but the controversy with radiating a developing brain persists, as the long term late effects can be devastating.[48]

PRIMITIVE NEUROECTODERMAL TUMOURS (PNET): Although PNET's are relatively common in the first year of life they constituted only 3,4% - 13,2% of foetal CNS tumours.[45] They are a heterogeneous group of highly malignant small-cell tumours thought to derive from the neural crest.[45]

2.0 MATERIAL AND METHODS

a. Study Design

A retrospective, descriptive study of the distribution and relative frequency of neonatal tumours presenting to Chris Hani Baragwanath Academic Hospital from 01 January 1988 to 31 December 2012.

b. Study Population

i. Inclusion Criteria

The sample population included all neonates up to 28 days of age who were born at or referred to Chris Hani Baragwanath Academic Hospital with a malignant or benign tumour.

ii. Exclusion Criteria

Patients with incomplete data were excluded.

c. Procedures

The clinical records of all patients with neonatal tumours presenting to Chris Hani Baragwanath Academic Hospital from 01 January 1988 through to 31 December 2012 were reviewed. Patients that presented up to three months of age were investigated and if they were symptomatic before 28 days of life they were included in the study. The clinical presentation, pathology, demographics, treatment and outcome were identified. For the purpose of this study, tumours were broadly divided into those considered to be malignant and those that seemed to be benign.

d. Data Handling and Collection

The data was collected and entered onto a prepared data collection sheet. The data sheet captured demographic information, birth and family history, classification of tumours, presenting complaints and duration of symptoms, any associated factors, treatment received and the outcome of the patients.

e. Data Analysis

The data was entered into a Microsoft Excel spread sheet. Appropriate descriptive statistical analysis using percentages, means, standard deviations, medians and ranges were used.

f. Ethical clearance

Ethical clearance was obtained from The Human Research Ethics Committee. Clearance certificate no. M130257 (See attached).

3.0 RESULTS

Over the 24 year period 2626 children (under 19 years of age) were referred to the Chris Hani Baragwanath Academic Hospital Oncology Department. A total of 346 patients were identified that were three months old and younger. Out of these, 117 patients were diagnosed with a malignant or a benign tumour and were symptomatic before 28 days of life. Due to incomplete data 29 patients were excluded. The study included 88 patients; 61 patients (69,3%) were diagnosed with a benign tumour and 27 patients (30,7%) were diagnosed with a malignant tumour. (See figure 3 pg 23)

Out of 2626 children referred to the Chris Hani Baragwanath Hospital Oncology Department, 2308 were diagnosed with a malignant tumour. (see table 2 pg 20)

Out of 2626 children that presented to Chris Hani Baragwanath Academic Hospital Oncology Department, 318 were diagnosed with a benign tumour. (see table 3 pg 21)

The overall M: F ratio in neonates included in this case series was 1: 1,5; however the M: F ratio in the patients diagnosed with a malignant tumour was 1: 0,8. The mean age at presentation was 16 days. The mean age at diagnosis was 36 days. In 82% of patients the tumours were evident on the first day of life. The data on stillborn babies was not collected. Although 74% of patients with malignant tumours had symptoms at birth, the mean age at presentation to the oncology unit was 15,8 days, and the mean age at diagnosis was 39,9 days. Eight of the patients with a malignant tumour, were born at CHBAH, and presented to the oncology unit at a mean age of 10 days, with a diagnosis made at a mean age of 43,1 days.

Table 2. Distribution and outcome of malignant neonatal and childhood tumours

Diagnosis	Total No of cases	No occurring in neonates	% of neonatal malignancies (nr 27)	% presentation in neonatal period	Mortality from malignancy (No (%))	Long-term survivors (No (%))	Lost to follow up (No pts)
Leukaemia	435	4	14,8	0,9	3 (75)	0	1
CNS tumours	336	1	3,7	0,3	1 (100)	0	0
Lymphoma	330	0	0	0	0	0	0
Malignant Soft Tissue tumours	292	7	25,9	2,4	3 (42.9)	3 (42.0)	1
Retinoblastoma	281	3	11,1	1,1	0	2 (66.7)	1
Renal tumours	255	5	18,5	2,0	2 (40)	1 (20)*	0
Neuroblastomas	104	3	11,1	2,9	1 (33.3)	0*	0
Bone tumours	89	0	0	0	0	0	0
Hepatic tumours	32	1	3,7	3,1	0	0	1
Langerhans cell Histiocytosis	21	2	7,4	9,5	0	2 (100)	0
Others	133	1	3,7	0,8	0	1 (100)	0
Total	**2308**	**27**	**100**	**1,2**	**10 (37)**	**9 (33.3)**	**4**

* Four neonates died due to unrelated causes

Of the patients diagnosed with a benign tumour 18 were born at CHBAH. The mean age at presentation to the oncology unit was 8,9 days and the mean age at diagnosis was 34,8 days. The referral time to the oncology unit was 5 days shorter for patients with a malignant tumour born at CHBAH. The age at diagnosis was similar in patients born at CHBAH and patients referred from other hospitals. This delay in diagnosing patients can be attributed to a shortage of medical and laboratory staff at CHBAH as well as a shortage of laboratory equipment.

Table 3. Distribution and outcome of benign neonatal and childhood tumours

Diagnosis	Total no of cases	No occurring in neonates	% of benign neonatal tumours (nr 61)	% presentation in neonatal period	Mortality from tumour (No (%))	Long term survivors (No (%))	Lost to follow up (no pts)
Benign vascular tumours	96	27	44,3	28,1	2 (2.4)	13 (48.1)	12
Teratomas	93	28	45,9	30,1	3 (10.7)	12 (28.6)	12*
Fibromas	30	2	3,3	6,7	0	0	2
Lymphangiomas	8	3	4,9	37,5	0	1 (33.3)	2
Others	91	1	1,6	1,1	0	0	1
Total	**318**	**61**	**100**	**19,2**	**5 (8.2)**	**26 (36.1)**	**29**

* one patient was referred back to the referral hospital.

Histology and radiology were diagnostic in 40,9% and 19,3% respectively. A combination of histology and radiology was used in 21,6% of the diagnoses, 11,4% was based on clinical examination and 6,8% on biochemistry and haematology.

Associated syndromes included Klippel Trenauny Weber syndrome, Kasabach-Merritt syndrome and Down syndrome. Associated abnormalities included cleft lip, ambiguous genitalia, partial aniridia, clubfoot and undescended testes.

A total of 22 neonates received chemotherapy and 50 of the neonates underwent surgical resection. Half of the patients (51,9%) diagnosed with a malignant tumour died while 11,1% of patients were lost to follow up. Death occurred in 8,2% of patients diagnosed with a benign tumour died, while 44,3% of patients were lost to

follow up. The overall mortality amongst patients diagnosed with benign or malignant tumours was 21,6%.

Figure 1. The distribution of the different malignant conditions in neonates

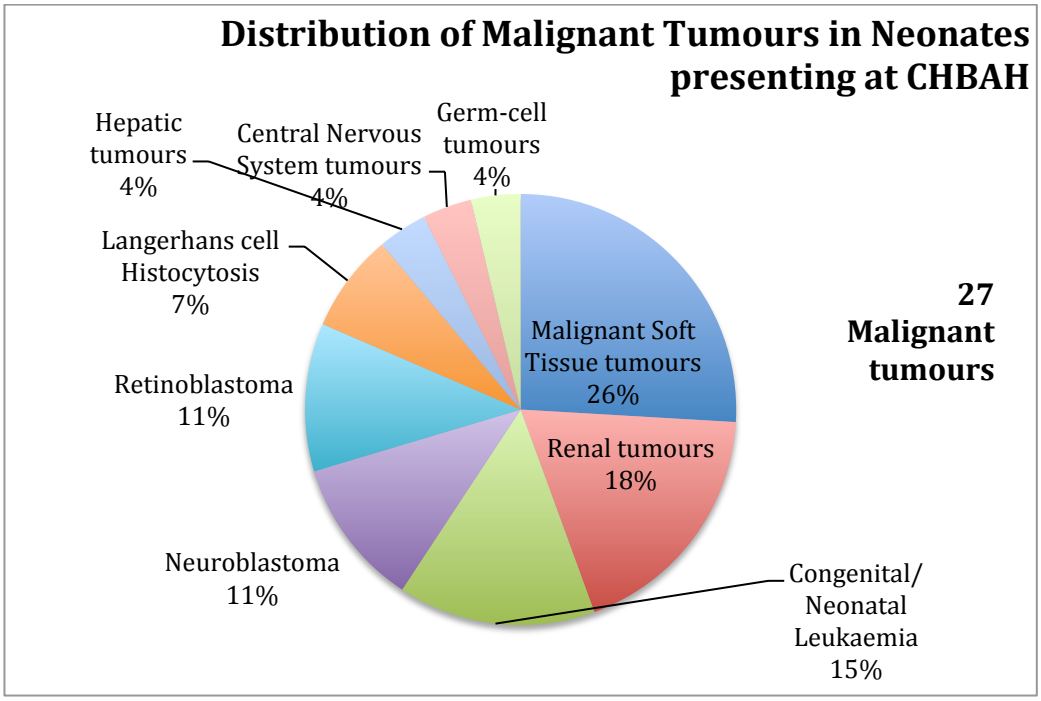


Figure 2. The distribution of the different benign tumours in neonates

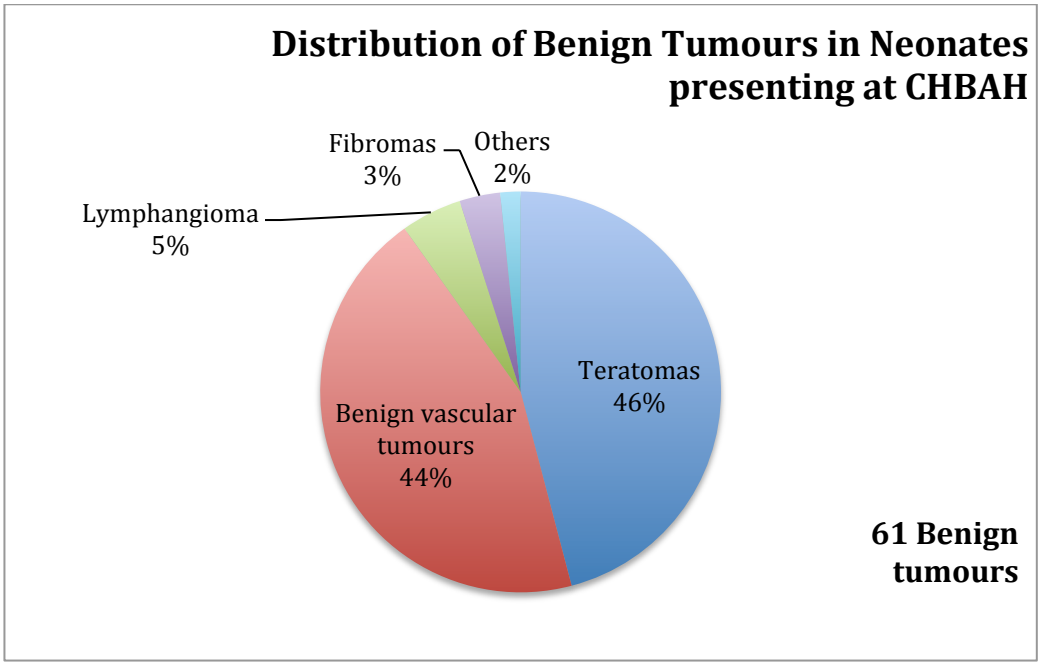
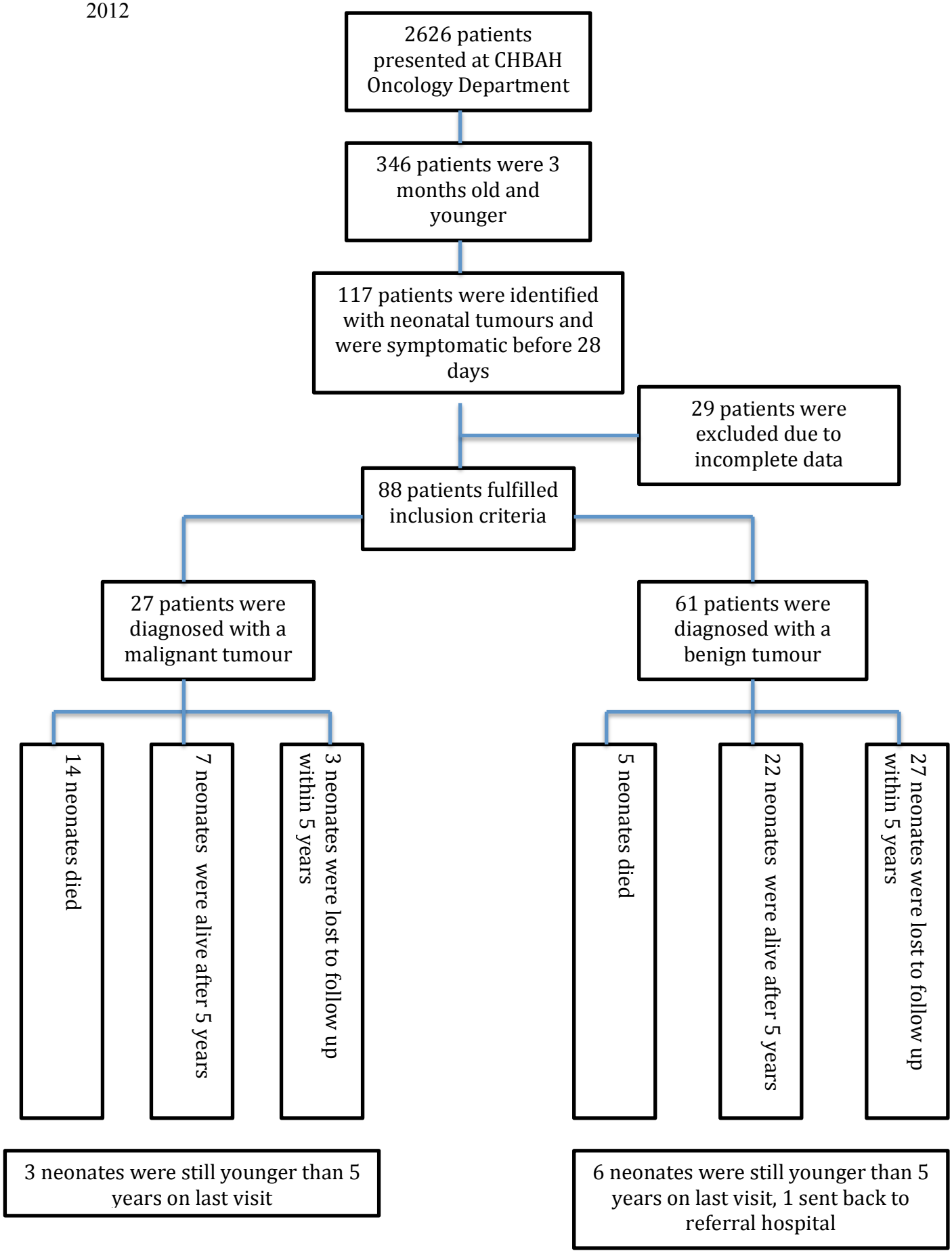


Figure 3. Flow chart of all oncology referrals to CHBAH from 1 Jan 1988 – 31 Dec 2012



Teratoma

There were 28 neonates diagnosed with teratomas (45,9% of neonatal benign tumours) of which 23 were sacrococcygeal. Of the neonates diagnosed with sacrococcygeal teratomas 17 were females, with a M: F ratio of 1: 2,8. The mean age at presentation was 10,6 days. All of the patients presented with a mass over the sacral area or buttocks. Associations included one patient with ambiguous genitalia, one patient with a haemangioma on her left ear, another patient with undescended testes and a clubfoot and one patient with abnormal looking thumbs. All but one patient underwent surgical removal. The patient that did not have surgery defaulted and was lost to follow up before surgery was performed. Five neonates received chemotherapy due to malignant histology or disease recurrence. One patient died due to disease recurrence. Ten patients were lost to follow up after five years. The mortality rate was 4,3% with the possibility of disease recurrence of 14,8%. The diagnoses were made on histology in 22 neonates. Alpha Feto Protein was elevated in 11 patients and radiological investigations were done in all patients to define the extent of the tumour for surgery. Investigations included CT scans and ultrasounds.

Five patients presented with teratomas elsewhere. Sites included the thyroid gland, neck, the pelvis, the brain and the abdomen. Four of the neonates were male and one was female. The average age at presentation was 24,2 days. The first baby with a teratoma of the thyroid gland presented with a lateral cystic neck mass, he underwent surgical excision; the diagnosis was made on histology and he was sent back to his referral hospital. The next baby was diagnosed with a teratoma of the neck. He presented with a cervical mass, underwent surgical excision; the diagnosis was

confirmed on histology but the patient died due to complications of surgery. The third patient presented with acute gastroenteritis and was diagnosed with a teratoma in the pelvis based on histology. He also underwent surgical excision and was discharged from oncology. The fourth patient presented with convulsions and hydrocephalus. He was diagnosed with an intracranial teratoma based on histology but died due to disease complications. The last baby was diagnosed with a teratoma in the abdomen. She presented with abdominal distention and had hydronephrosis secondary to compression of the mass on the genitourinary system. She had surgical excision and was discharged at eight years. Two out of the five patients died with a mortality of 40%.

Germ-cell tumours

There was one neonate diagnosed with a mixed germ-cell tumour at one month of age (3,7% of neonatal malignant tumours). She was a term neonate born via NVD and presented at one week of age with a history of a sacral mass present at birth. She had surgical resection and chemotherapy and the diagnosis was made on histology. She was last seen at 10 months of age and is alive and well.

Benign vascular tumours

Benign vascular tumours were diagnosed in 27 patients (44,3% of neonatal benign tumours), of which 22 patients were diagnosed with haemangiomas and five patients were diagnosed with haemangioendotheliomas. Of the 22 patients diagnosed with haemangiomas, 14 were female and eight were male patients with a M: F ratio of 1:

1,75. The average age at presentation was 25,1 days. The diagnosis was based solely on clinical examination in nine patients, three patients had biopsies or surgical excision, eight patients had symptoms together with radiological features and two patients had radiological and histological diagnoses. The most common site was on the extremities followed by the chest and the face. Associations included Klippel Trenauy-Weber syndrome, right heart failure and cleft lip. Five patients were treated medically, three patients underwent surgery and the other remaining patients had no treatment. Two patients died due to unrelated causes. Eleven patients were discharged and nine patients were lost to follow up.

Four out of the five patients with haemangioendotheliomas were females. The average age at presentation was 10,2 days. Three patients presented with abdominal distention and two patients presented with jaundice. One patient was diagnosed with Kasabach-Merritt syndrome and two patients had additional haemangiomas on their face and knee respectively. One patient also had Beckwith Wiedemann syndrome. Two patients underwent biopsy and four out of the five patients were treated medically.

Malignant Soft Tissue tumours

A total of seven malignant soft tissue tumours were diagnosed (25,9% of neonatal malignant tumours). Six out of the seven patients were males with a M: F ratio of 1: 0,2. The average age at presentation was 12,7 days and the average age at diagnoses was 51,9 days. Three out of the seven patients died from disease complications with an overall mortality rate of 43%.

Table 4. Patients with malignant soft tissue tumours and their outcome

Case no	Sex	Presenting age	Presenting symptoms	Diagnosis	Treatment	Outcome
1	M	3 days	Swelling and discoloration of right fore arm	Infantile fibrosarcoma	Surgery	Discharged at 20 years
2	F	1 day	Growth on the sole of her right foot	Embryonal rhabdomyosarcoma	Chemotherapy	Lost to follow up but still alive*
3	M	21 days	Lesion below right eye	Alveolar rhabdomyosarcoma	Chemotherapy, surgery and radiotherapy	Died at 1 year due to disease progression
4	M	21 days	Lump on left wrist	Infantile fibrosarcoma	Surgery	Lost to follow up but is still alive*
5	M	1 day	Cystic mass on left side of chest	Infantile fibrosarcoma	Chemotherapy, surgery and radiotherapy	Died at 13 months due to disease progression
6	M	21 days	Lump on sole of right foot	Embryonal rhabdomyosarcoma	Chemotherapy, surgery and radiotherapy	Defaulted for 2 years, had recurrence, then lost to follow up at 7 years
7	M	21 days	Left paranasal soft tissue mass	Embryonal rhabdomyosarcoma	Chemotherapy	Died at 4 months due to disease progression

*These patients were contacted and although they were lost to follow up at the clinic they were alive at the time of analysis.

Renal tumours

Five patients were diagnosed with congenital mesoblastic nephromas (18,5% of neonatal malignant tumours). Two were male patients and three were females with a M: F ratio of 1: 1,5. The average age at presentation was four days and the average age at diagnosis was 20,6 days. Four out of the five patients died before the age of three years. One died due to complications of prematurity, another patient died due to HIV related complications and two patients died due to disease recurrence. The tumours were inoperable and incompletely resected. One patient survived and was discharged from the clinic at nine years.

Table 5. Patients with renal tumours and their outcome

Case no	Sex	Presenting age	Presenting symptoms	Associated conditions /symptoms	Diagnosis	Treatment	Outcome
1	M	4 days	Abdominal distention and left flank mass	SGA	CMN	Surgery	Died at 3 months from complications of prematurity
2	F	3 days	Right flank mass	HIV positive	CMN	Surgery	Died at 3 years from complications of HIV
3	M	3 days	Right flank mass	Partial aniridia	CMN	Surgery	Discharged at 9 years
4	F	3 days	Abdominal mass	HIV positive	CMN	Surgery with incomplete resection	Died at 2 years 9 months
5	F	7 days	Abdominal mass	Nil	CMN	Surgery and chemo-therapy	Died at 10 months due to disease recurrence

Congenital/Neonatal Leukaemia

The clinical information of four patients with suspected congenital leukaemia was collected in this case series (14,8% of neonatal malignant tumours). One patient was a confirmed transient myeloid dysplasia. Three patients presented with acute myeloid leukaemia. All the patients were subsequently diagnosed with Down syndrome. The average age at presentation was 6,8 days and the average age at diagnoses was 23,3 days.

Table 6. Patients with Congenital/Neonatal leukaemia and their outcome

Case no	Sex	Presenting age	Presenting symptoms	Diagnosis	Treatment	Outcome
1	F	10 days	Features of Down syndrome and a raised WCC	AML	Chemotherapy	Died at 13 days
2	F	7 days	Hepatosplenomegally	TMD	Nil	Lost to follow up at 5 months
3	M	5 days	Respiratory distress and a raised WCC	AML	Nil	Died
4	F	5 days	Jaundice and pyrexia	AML	Chemotherapy	Died at 1 month

Neuroblastoma

Three out of the 27 neonates presenting with a malignant tumour were diagnosed with neuroblastomas (11,1% of neonatal malignant tumours). Two patients had stage IV disease and one patient stage IVS disease. All three patients presented within the first

week of life with abdominal distention and the diagnoses were confirmed on histology. There were two female patients and one male. The average age at presentation was 18 days and the average age at diagnosis was 39,7 days. All received chemotherapy and one patient received chemotherapy and radiotherapy. All three patients died within the first four months of life. The first two patients died from nosocomial sepsis and the third patient died from necrotic bowel secondary to abdominal compartment syndrome.

Retinoblastoma

There were three neonates diagnosed with retinoblastomas (11,1% of neonatal malignant tumours). Two patients had bilateral retinoblastomas and one patient had a unilateral retinoblastoma. Two were male patients and one was female patient, with a M: F ratio of 1: 0,5. The average age at presentation was 33,7 days and the average age at diagnosis was 34,3 days. Two patients had incidental findings of café-au-lait spots.

Table 7. Patients with retinoblastoma and their outcome

Case no	Sex	Presenting age	Presenting symptoms	Distribution	Treatment	Outcome
1	M	10 days	Discharge from eye (Brother with RBL)	Bilateral RBL	Chemotherapy	Alive and well
2	M	42 days	Leucocoria	Unilateral RBL	Surgery	Lost to follow up at 2 years
3	F	49 days	Swelling around eyes	Bilateral RBL	Chemotherapy, surgery and radiotherapy	Last seen at 2 years 2 months

Langerhans cell Histiocytosis

Two patients were identified with LCH (7,4% of neonatal malignant tumours). The average age at presentation was 51 days and the average age at diagnosis was 96 days. One was a male patient with a rash over his chest, back and genitalia, that was present from the age of one month. A biopsy confirmed LCH and the patient received chemotherapy. He was discharged at the age of 17 years. The second patient was a female who presented with erythematous papules on her face, body, arms and legs at birth. Histology confirmed LCH and this patient also received chemotherapy. She was last seen at two years six months and was well.

Hepatic tumours

One patient was identified with a congenital hepatoblastoma (3,7% of neonatal malignant tumours). He was a male infant, born at term via NVD and presented with an abdominal mass at birth. A hepatoblastoma was diagnosed on histology, the patient underwent surgery and received chemotherapy. Unfortunately the patient was lost to follow up at four and a half years.

Central Nervous System tumours

One patient in this series was diagnosed with a congenital brain tumour (3,7% of neonatal malignant tumours). The patient was a male patient, born at term via NVD and presented with macrocephaly. Radiological imaging confirmed hydrocephalus secondary to a space occupying lesion and a biopsy confirmed a medulloblastoma.

The patient received chemotherapy in a possible attempt to reduce the tumour size. Unfortunately the tumour did not respond to chemotherapy and the patient died at seven months of age.

Other benign tumours

The remaining benign tumours included three patients with lymphangiomas, two patients with fibromas and one patient with a hamartoma (4,9%, 3,3% and 1,6% of neonatal benign tumours). All three of the patients with lymphangiomas were females. The first patient presented with a left axillary mass. She underwent surgery but was lost to follow up. The second patient presented with a lump in her breast. She also underwent surgery but was lost to follow up. The third patient presented with a mass on the right chest wall, that extended anteriorly and posteriorly and down to the arm as well. She underwent surgical excision and was last seen at 16 years of age. Both the patients diagnosed with fibromas were males. One patient presented with a distal tibial mass, and the second had a right thigh mass. Both patients underwent surgery, and were subsequently lost to follow up. The patient diagnosed with a hamartoma presented with congenital pneumonia. The chest x-ray showed an enlarged thymus and a biopsy confirmed a hamartoma. Unfortunately this patient was also lost to follow up.

4.0 DISCUSSION

Tumour masses are fairly common findings in the neonatal period but are rarely malignant.[6] In our series malignant neonatal tumours comprised only 1,2% of all childhood malignancies. This study had a slightly lower incidence than the reported 2%, which can be attributed to the fact that a large number of tumours are diagnosed on post mortem examinations in reported series and not all of the early neonatal deaths or stillborn babies undergo post mortem examinations in our institution.[4,6] Unlike other series, we found a female predominance with a M: F ratio of 1: 1,5. Most case series report an equal M: F ratio with the exception of teratomas which have a strong female predominance.[3] When teratomas are excluded, this case series still reports a female predominance with a M: F ratio of 1: 1,3. There was however a male predominance in malignant tumours with a M: F ratio of 1: 0,8. We could not identify any race prevalence as almost all patients presenting to Chris Hani Baragwanath Academic Hospital were black patients.

As described in the literature, teratomas were the most common tumours diagnosed in this case series. Strong emphasis is placed on strict follow up for the first three years of life due to the high risk of disease recurrence early in life.[12] Our case series found similar results, that all 5 patients with disease recurrence, had recurrences within 3 years of diagnosis.

The second most common tumours described in neonates are benign vascular tumours and this was also found in this case series. The literature reports it to be four times more common in females. This case series also supported the female predominance

but not as strongly as in published data. Females had a 1,75 times higher risk of a benign vascular tumour compared to male patients. Literature also reports benign vascular tumours to be more common in premature babies but from the 27 patients with benign vascular tumours in our study only two neonates were born prematurely.

The most common malignant tumour in this case series was a malignant soft tissue tumour with an incidence of 25,9% of all neonatal malignancies. This correlates with the literature, which reports an incidence of between 10 – 30% of all neonatal malignancies. All three patients with fibrosarcomas were males, in keeping with the male predominance reported in the literature. Studies report a third of all patients diagnosed with rhabdomyosarcomas to have at least one congenital anomaly.[21] This is not supported in our study as all four patients diagnosed with rhabdomyosarcomas were otherwise normal. Half (50%) of the patients diagnosed with rhabdomyosarcomas had tumours on the extremities, which is higher than the reported 20%. At CHBAH 1,1% of the patients diagnosed with rhabdomyosarcomas were neonates, which is lower than the reported 2%.[20]

Renal tumours were far more common (18,5%) in this case series than the reported 4% in literature.[6,17] This case series demonstrated a female predominance which contradicts the male predominance in the literature.[2,24] Patients diagnosed with CMN are reported to have an excellent prognosis but in our case series 40% of patients died due to disease recurrence attributed to incomplete resection.

There was a higher incidence of congenital leukaemia in this case series with an incidence of 14,8% of all neonatal malignancies compared with the 8% reported in

literature.[6,27] Within the first month of life 75% of patients died and 25% were lost to follow up within five months. This poor prognosis is supported by the literature, which reports a 23% two-year survival.[27,29]

Neuroblastomas were one of the most common tumours present in neonates in many of the case series.[3,4,5,6,7,34,35] In our study, however, it only comprised 11,1% of all neonatal malignancies. In this case series there was a 100% mortality which contradicts the relatively good prognosis in the literature where death due to disease was only present in 23 -34% of patients.[34,35] However death did not occur solely due to the tumour; in two cases it was due to nosocomial sepsis and in the last case the patient developed abdominal compartment syndrome and died due to necrosis of the intestines.

The incidence of retinoblastoma in this case series was 11,1% of malignant tumours. This is much lower than the reported 25% in the Toronto, Canada series. It can be attributed to the fact that elective eye examinations are not performed frequently in our setting. Our series supports the higher incidence of bilateral disease similar to many studies done in neonates.[5,6]

Hepatic tumours were as prevalent in our series (3,7%) as the reported 4% in the literature reviewed of neonatal tumours.[4] The low frequency in the literature is supported in our study with only 3,2% of hepatoblastomas diagnosed at CHBAH being present in neonates.[42]

We found no evidence of heredity in congenital malignancies, with the exception of one case of familial retinoblastoma. Numerous series reported a clear association with certain neonatal tumours and congenital anomalies. In this series we found 6 associations including Klippel Trenauny-Weber syndrome and haemangioma, Beckwith Weidemann syndrome and haemangioendothelioma and all four leukaemia and transient myeloid dysplasia patients were diagnosed with Down syndrome.

Although 82% of patients were symptomatic at birth, the mean age at presentation was 16 days and the mean age at diagnosis was 36 days. Approximately three quarters (74%) of patients diagnosed with a malignant tumour were symptomatic at birth, with a mean age at presentation of 15,8 days and a mean age of 39,9 days at diagnosis. It appears that there is a significant delay in diagnosis, despite relatively early referral. Even though patients born at CHBAH with malignant tumours presented earlier to the oncology unit with a mean age at presentation of 10 days, there was still a clear delay in diagnosing these infants, with a mean age at diagnosis of 43,1 days. This can be attributed to a shortage of medical laboratory staff as well as laboratory services.

In this case series 22 babies received chemotherapy. Out of this 22, 11 babies died, two babies were lost to follow up within five years, five babies are still younger than five years of age and four babies were alive and well after 5 years. A quarter of patients (26%) diagnosed with a malignant tumour were alive and well after 5 years and 36% of patients with benign tumours were alive and well after 5 years. The documented survival rate in benign tumours may be much higher, as 44% of patients were lost to follow up within 5 years.

5.0 CONCLUSION

The neonatal period is identified as a time of rapid growth, development and maturation of all organs and tissue, especially the brain, liver, kidneys, bones and the lungs. This makes treating a neonate with a malignancy extremely difficult. The physician needs to balance treatment that has the best chance for cure, with the risk of causing irreversible damage to the rapidly growing organs.

Neonatal tumours are very rare and diagnosing a tumour in a neonate poses many difficulties. It has been shown that neonates diagnosed with a malignant tumour have a far better prognosis than cancer diagnosed in older children and a large percentage of patients can be successfully treated and cured with little impairment to future well being. At the moment patients present late to the oncology unit and diagnoses are delayed due to a shortage of medical staff and staff at laboratory services at public hospitals. People need to be educated and made aware that neonates can be diagnosed with tumours. In order to improve the outcome of these patients, 2 major issues need to be addressed promptly; timely referral for prompt diagnosis and improved follow-up of patients.

6.0 APPENDICES: DATA COLLECTION SHEET

STUDY NR	AGE AT PRESENTATION	AGE AT DIAGNOSIS	SEX	RACE	GESTATIONAL AGE	MODE OF DELIVERY	APGARS
				A			

STUDY NR	PLACE OF BIRTH	FAMILY HX OF CANCER	DIAGNOSIS	MALIGNANT / BENIGN	MODE OF DIAGNOSIS

STUDY NUMBER	PRESENTING SYMPTOM	DURATION OF SYMPTOMS	ASSOCIATIONEG. CONG ABN	TREATMENT	OUTCOME

7.0 REFERENCES

1. Dorland's Illustrated Medical Dictionary. 23rd ed. W.B. Sauders company; 1957. Tumor; p. 1482.
2. Stedman's Medical Dictionary. 22nd ed. Baltimore: Williams & Wilkins; 1972. Tumor: benign, malignant; p. 1342 – 1343.
3. Moore SW, Satge D, Sasco AJ. The epidemiology of neonatal tumours. Padiar Surg Int [serial online] 2003 Sept [Cited 2012 Dec 11]; 19: 509 – 519.
   Available from:
   URL: http://link.springer.com/article/10.1007/s00383-003-1048-8#page-1
4. Lakhoo K, Sowerbutts H. Neonatal tumours. Pediatr Surg Int [serial online] 2010 Sept – Oct [Cited 2012 Dec 10]; 26: 1159 – 1168. Available from:
   URL: http://www.springerlink.com/index/7W62862R46217X73.pdf
5. Stevens MC. Neonatal tumours. Archives of Disease in Childhood. [serial online] 1988; [Cited 2012 Dec 6]; 63: 1122 – 1125.
   Available from:
   URL: http://adc.bmj.com/content/63/10_Spec_No/1122.full.pdf
6. Campbell AN, Chan HSL, O'Brien A, Smith CR, Becker LE. Malignant tumours in the neonate. Archives of Disease in Childhood [serial online] 1987 [Cited 2012 Dec 9]; 62: 19 – 23.
   Available from:
7. URL: http://adc.bmj.com/content/62/1/19.full.pdf Hadley GP, Govender D, Landers G. Malignant solid tumours in neonates: an African perspective. Pediatr Surg Int [serial online] 2002 Sept [Cited 2012 Des 10]; 18: 653 – 657.
   Available from:
   URL: http://link-Springer.com/content/pdf/10.1007/s00383-002-0848-6.pdf#page-1
8. Davis CF, Carachi R, Young DG. Neonatal tumour: Glasgow 1955 – 86. Archives of Disease in Childhood [serial online] 1988 [cited 2012 Dec 11]; 63: 1075 – 1078.

Available from:
URL: http://adc.bmj.com/content/63/9/1075.full.pdf

9. Mueller RF, Young ID. Emery's Elements of Medical Genetics. 10th ed. Edinburgh, London, New York, Philidelphia, Sydney, Toronto: Churchill Livingstone; 1998. Chapter 13, The genetics of cancer; 189 – 207
10. Göbel U, Schneider DT, Calaminus G, Haas RJ, Schmidt P, Harms D. Germ-cell tumors in childhood and adolescence. Annals of Oncology [Serial online] 2000 [cited 2013 May 14]; 11: 263 – 271
Available from:
URL: http://annonc.oxfordjournals.org/content/11/3/263.full.pdf
11. Tapper D, Lack EE. Teratomas in Infancy and Childhood [Internet]. 1983 [cited 2013 May 13].
Available from:
URL:
http://www.ncbi.nim.nih.gov/pmc/articles/PMC1353316/pdf/annsurg00127-0168.pdf
12. Legbo JN, Opara EK, Legbo JF. Mature sacrococcygeal teratoma: case report. African Health Sciences [Serial online] 2008 March [cited 2013 May 13]; 8(1): 54 – 57
Available from:
URL:
http://www.ncbi.nim.nih.gov/pmc/articles/PMC2408549/pdf/AFH50801_0054.pdf
13. Sacrococcygeal teratoma [Internet]. 2012 [cited 2012 Dec 6].
Available from:
URL: http://en.wikipedia.org/wiki/Sacrococcygeal_teratoma
14. Metry DW, Adelaide A, Herbert MD. Benign Cutaneous Vascular Tumours of Infancy. Arch Dermatol [Serial online] 2000 July [cited on 2012 Nov 12]; 136: 905 – 914
Available from:
URL: http://archderm.jamanetwork.com/
15. Antaya RJ, James WD. Infantile Hemangioma [Internet]. 2012 [updated 2012 Jan 11; cited 2012 Dec 6];
Available from:

URL: http://emedicine.medscape.com/article/1083849-overview#showall

16. Infantile hemangioendothelioma. [Internet] 2012 [cited 2012 Dec 6] Available from: URL: http://en.wikipedia.org/wiki/Infantile_hemangioendothelioma
17. Moore SW, Kaschula ROC, Albertyn R, Rode H, Millar AJW, Karabus C. The outcome of solid tumours occurring in the neonatal period. Pediart Surg Int [serial online] 1995 [cited 2012 Dec 11]; 10: 366 – 370. Available from: URL: http://link.springer.com/article/10.1007/BF00182226#page-1
18. Akyüz C, Küpeli S, Varan A, Gedikoglu G, Yalçin B, Kutluk T, Büyükpamukçu M. Infantile fibrosarcoma: Retrospective Analysis of eleven patients. A Journal of Experimental and Clinical oncology [Serial online] 2011 [cited 2013 May 10]; 97(2): 166 – 169 Available from: URL: http://www.tumorionline.it/articoli.php?archivo=yes&vol_id=667&id=7778
19. Batcup G. Cancer in the very young child – pitfalls and problems for the pathologist. Br. J. Cancer [Serial online] 1992 [cited 2012 Dec 9]; XVIII: s5 – s7 Available from: URL: http://www.ncbi.nim.nih.gov/pmc/articles/PMC2149652/pdf/brjcancersuppl00076-0009.pdf
20. Garay M, Chernicoff M, Moreno S, Pizzi de Parra N, Olivia J. Apréa G. Congenital Alveolar Rhabdomyosarcoma in a Newborn. Eur. J. Pediat. Dermatol. [Serial online] 2004 [cited 2013 May 10]; 14: 9 – 12. Available from: URL: http://www.dermatologiapediatrica.com/volume14/rabdoing.pdf.
21. Khatami F, Bazrafshan A, Monajemzadeh M, Seyed M. Congenital Embryonal Rhabdomyosarcoma with Prenatal Onset. Iran J Pediatr [Serial online] 2008 March [cited 2012 Dec 12]; 18(1): 62 66 Available from:

URL: http://journals.tums.ac.ir/upload_files/pdf/_/6069.pdf

22. Khashu M, Osiovich H, Sargent MA. Congenital Mesoblastic Nephroma Presenting with Neonatal Hypertension. Journal of Perinatology [Serial online] 2005 April [cited 2013 May 12]; 25: 433 – 435
Doi: 10.1038/sj.jp.7211304

23. Al-Turkistani HK. Congenital Mesoblastic Nephroma: A Case Report. Journal of Family & Community Medicine. [Serial online] 2008 May – Aug [cited 2013 May 13]; 15(2): 91 – 93
Available from:
URL: http://www.ncbi.nim.nih.gov/pmc/articles/PMC3377027/

24. Surh JS, Hwang SA, Park HN, Jeon SJ, Kim SY. Prenatal diagnosis of mesoblastic nephroma: A case report. J Womens Med. [Serial online] 2011 [cited 2013 May 12]; 4(1): 11 – 14
Doi: 10.5468/jwm.2011.4.1.11

25. Ko S, Kim MJ, IM YJ, Park KI, Lee MJ. Cellular Mesoblastic Nephroma with Liver Metastasis in a Neonate: prenatal and Postnatal Diffusion-Weighted MR Imaging. Korean Journal of Radiology [Serial online] 2013 Mar – April [cited 2013 May 13]; 14(2): 361 – 365
Available from:
URL: http://kjronline.org/Synapse/Data/PDFData/0068KJR/kjr-14-361.pdf

26. Ozcan T. Prenatal diagnosis of congenital mesoblastic nephroma [Internet] 2013 April [updated 2013 Mar 22, cited 2013 May 13].
Available from:
URL: http://www.uptodate.com/contents/prenatal-diagnosis-of-congenital-mesoblastic-nephroma

27. Choi JH, Lee HB, Park CW, Lee CH. A Case of Congenital Leukemia Cutis. Ann Dermatol (Seoul) [Serial online] 2009 [cited 2013 May 12]; 21(1): 66 – 70
Available from:
URL: http://www.ncbi.nim.nih.gov/pmc/articles/pmc2883375/pdf/as-21-66.pdf

28. Prakash KP, Rau ATK, Bhat ST, Rau AR. Congenital leukemia – A Diagnostic Dilemma. Indian Journal of Medical & Paediatric oncology [Serial online] 2008 [cited 2012 Dec 12]; 29(4): 41 – 43
Available from:
URL: http://www.ijmpo.org/temp/IndianJMedPaediatrOncol29441-1459801_040318.pdf

29. Qureshi S, Khattak AZ, Yaqub N. Congenital Leukaemia presenting as Bilateral Renal Masses [Internet]. 2002 Oct [cited 2013 May 13]. Available from:
URL: http://www.jpma.org.pk/PdfDownload/3155.pdf

30. Ravindranath Y, Ginopolis G, Boulevard B. COMMENTARY Down Syndrome and Leukemia: New Insights Into the Epidemiology, Pathogenesis, and Treatment. Pediatr Blood Cancer [Serial online] 2005 [cited 2013 May 12]; 44: 1 – 7
Available from:
URL:
http://deepblue.lib.umich.edu/bitstream/handle/2027.42/35297/20242_ftp.pdf?sequence=1

31. Bargotra R, Suri J, Gupta Y. Congenital Leukemia. JK Science [Serial on online] 2010 Oct – Dec [cited 2012 Dec 13]; 12(4): 201 – 202
Available from:
URL:
http://www.jkscience.org/archive/volume124/Congenital%20%20Leukemia.pdf

32. Karandikar NJ, Aqråno DB, McKenna RW, Kroft SH. Transient Myeloproliferative Disorder and Acute Myeloid Leukemia in Down syndrome. American Society of Clinical Pathologists [Serial online] 2001 [cited 2013 May 25]; 116: 204 -210
Available from:
URL: http://ajcp.ascpjournals.org/content/116/2/204.full.pdf

33. Bajwa RPS, Skinner R, Windebank KP, Reid MM. Demographic study of leukaemia presenting within the first 3 months of lif in the Northern Health Region of England. Journal of Clinical Pathology [Serial online] 2004 [cited 2013

34. Dhir A, Wheeler K. Neonatal neuroblastoma. Early Human Development [serial online] 2010 [Cited 2013 May 9]; 86: 601-605.
Available from:
URL: http://www.sepeap.org/archivos/pdf/11583.pdf

35. Uzair M, Khan SJ. Neonatal Neuroblastoma. Gomal Journal of Medical Science [serial online] 2004 July – Dec [Cited 2012 Dec 11] 2(2).
Available from:
URL: www.gjms.com.pk/ojs786/index.php/gjms/article/download/33/33

36. Ungaro ABS, da Cunha SL, Santo RM. Congenital retinoblastoma – Report of a case. Arq Bras Oftalmol [Serial online] 2002 [cited 2013 May 11]; 65: 571 – 3
Available from:
URL: http://www.scielo.br/pdf/abo/v65n5/a/4v65n5.pdf.

37. Abramson DH, Du TT, Beaverson KL. (Neonatal) Retinoblastoma in the First Month of Life. Arch opthalmol [Serial online] 2002 June [cited 2012 Dec 12]; 120: 738 – 743
Available from:
URL: http://archopht.jamanetwork.com/

38. Lohmann DR, Gallie BL. Retinoblastoma [Internet]. 2013 [updated 2013 March 28, cited 2013 May 11]
Available from:
URL: http://www.ncbi.nim.nih.gov/books/NBK1452/?report=printable

39. Abramson DH, Marr BP, Brodie SE, Dunkel I, Palioura S, Gobin YP. Ophthalmic Artery Chemosurgery for Less Advanced Intraocular Retinoblastoma: Five-Year Review. PLoS ONE. 2012; 7(4): e34120. Doi: 10.1371/journal.pone.0034120
May 12]; 57: 186 – 188.
Doi: 10.1136/jcp.2003.12039

40. Yang TY, Chen SJ, Yan LY, Tang RB. Langerhans Cell Histiocytosis in a Newborn. J Chin Med Assoc [Serial online] 2009 Nov [cited 2013 May 13]; 72(11): 611 – 614
Available from:
URL: http://homepage.vghtpe.gov.tw/~jcma/72/11/611.pdf

41. Stein SL, Paller AS, Haut PR, Mancini AJ. Langerhans Cell Histocytosis Presenting in the Neonatal Period. Arch Pediatr Adolesc Med [Serial online] 2001 July [cited 2013 May 13]; 155: 778 – 783
Available from:
URL: http://archpedi,jamanetwork.com

42. Chattopadhyay S, Mukheruee S, Boler A, Sharma A, Biswas SK. Hepatoblastoma in the neonatal period: An unusual presentation. Journal of Cytology [Serial online] 2012 Oct [cited 2013 May 13]; 29(4): 252 – 254
Available from:
http://www.jcytol.org

43. Cömert S, Vitrinel A, Mutlu GY, Tokuç G, Bakir B. Abdominal Mass in a Neonate: Hepatoblastoma. Indian Journal of Pediatrics [Serial online] 2007 Oct [cited 2013 May 13]; 74: 956 – 958
Available from:
URL: http://medind.nic.in/icb.t07/i10/icbt07i10p956.pdf

44. Yamashita S, Tyu S, Miyata S, Uchinokura S, Yokogami K, Uehara H, Moriguchi S, Lwakirei T, Marutsuka K, Ikenoue M, Sawa D, Yamada N, Kodama Y, Takeshima H. A huge intraventricular congenital anaplastic astrocytoma: case report with histopathological and genetic consideration. Brain Tumor Pathology [Serial online] 2012 April [cited 2012 Dec 14]; 29(2): 107 – 112
Doi: 10.1007/s10014-011-0071-z

45. Severino M, Schwartz ES, Thurnher JJ, Rydland J, Nikas I, Rossi A. Congenital tumors of the central nervous system. Neuroradiology [Serial online] 2010 [cited 2012 Dec 13]; 52: 531 – 548
Doi: 10.1007/s00234-010-0699-0

46. Buetow PC, Smirniotopoulos JG, Done S. Congenital Brain Tumors: A Review of 45 Cases. AJR [Serial online] 1990 Sept [cited 2012 Dec 13]; 155: 587 – 593
Available from:
URL: http://61.186.173.202:8082/zywy/article/33.pdf

47. Jänisch W. Haas JF, Schreiber D, Gerlach H. Primary central nervous system tumors in stillborns and infants. Journal of Neuro-Oncology [Serial online] 1984 [cited 2012 Dec 14]; 2: 113 – 116
Available from:
URL: http://link.springer.com/article/10.1007/BF00177895#page-1

48. Kayama T, Yoshimoto T, Shimizu H, Skurai Y. Neonatal medullablastoma. Journal of Neuro-Oncology [Serial online] 1993 [cited 2012 Dec 14]; 15: 157 – 163
Available from:
URL:
http://link.springer.com/article/10.1007/BF01053963?LI=true#page-1