

**Benghazi University – faculty of medicine Department of  
Paediatrics**



***Patterns of malignancies in childhood : A thirteen year study in the  
Eastern part of Libya (2001-2013).***

***أنماط الامراض السرطانية في الاطفال: دراسة علي مدي ثلاثة عشر سنة في منطقة ليبيا  
الشرقية***

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***In loving memory of my father***

***Mohamed S Bibtana***

***Who always encouraged me to reach for the stars***

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## ABBREVIATIONS

<b>AAPC</b>	Approximate annual percent change	<b>MC</b>	Mixed cellularity
<b>ALL</b>	Acute lymphoblastic leukemia	<b>N</b>	Number
<b>AML</b>	Acute myeloblastic leukaemia	<b>NB</b>	Neuroblastoma
<b>APC</b>	Annual percent change	<b>NHL</b>	Non-Hodgkin's lymphoma
<b>BL</b>	Burkitt's lymphoma	<b>NHNBL</b>	Non Burkitt's non Hodgkin's lymphoma
<b>BT</b>	Brain tumour	<b>No.</b>	Number
<b>CML</b>	Chronic myeloid leukaemia	<b>NPC</b>	Nasopharyngeal carcinoma
<b>CNS</b>	Central nervous system	<b>NS</b>	Nodular sclerosing
<b>F</b>	Female	<b>RB</b>	Retinoblastoma
<b>GC</b>	Germ cell tumour	<b>RMS</b>	Rhabdomyosarcoma
<b>HCC</b>	Hepatocellular carcinoma	<b>SD</b>	Standard deviation

<b><i>HL</i></b>	Hodgkins lymphoma	<b><i>WT</i></b>	Wilm's tumour
<b><i>LD</i></b>	Lymphocyte depletion	<b><i>Yrs</i></b>	Years
<b><i>LP</i></b>	Lymphocyte proliferative		
<b><i>M</i></b>	Male		



# 1. ABSTRACT

## OBJECTIVE

- To measure the types and trends of the childhood cancer.
- To describe the demographic profile of childhood malignancy in relation to epidemiological variables.

## PATIENTS AND METHODS

A retrospective cross sectional study, was carried out between 2001 and 2013, where data was obtained either from medical records of all patients who were admitted over the study period to the Haematology/oncology department of Benghazi children's hospital or from the statistics dept. Data included; Patients demographics, physical examination and investigations.

## RESULTS

The most common tumour in the Eastern part of Libya was leukaemia (38% 219/568), this was followed by lymphoma (14% 78/568) and brain tumours (12% 67/568) respectively. The number of patients admitted increased over the study period. Malignancy cases peaked around the age of 2 years with a major portion in the preschool age group. Leukaemia and neuroblastoma were the most common tumours in patients less than 1 year old. There was male to female ratio of 1.4:1 showing a male predominance. A slightly higher number of cases resided in suburban and rural areas (53.7%). A large percentage of solid tumours presented in late stages (III, IV).

## CONCLUSION

We can conclude that Leukaemia, lymphoma and brain tumours are the most common malignancies in children, of these solid tumours may have been underestimated. There was an obvious increase in the total number of annual cases diagnosed per year, with the highest frequency of cases in the pre-school age group. Male cases outnumber females and most of the solid tumour patients present at late stages.

## 2. INTRODUCTION

*Childhood cancer is defined as tumours affecting those in the population under 15 years of age. Unlike in adults, it is relatively rare in children and although cancer is rare in childhood, it has a tremendous impact on the families affected and is an important concern for public health, medical care and society. It is the main cause of disease-related death in childhood. The majority of childhood cancers are malignant (93%), with the remainder being non-malignant tumours of the brain and CNS. The most common paediatric cancer is acute lymphoblastic leukaemia [ALL] followed by brain tumours. Leukaemia, brain, other CNS and intracranial tumours and lymphomas account for more than two-thirds of all cancers diagnosed in children (1).*

*Incidence and mortality rates of childhood cancers differ worldwide. The differences depend on how extensively data are reported. Incidences vary from as high as 155 per million persons in Nigeria to 40 per million persons in the Indian population of Fiji. In the United States, the incidence of childhood cancer overall is approximately 125 per million persons, with slightly increased rates in males and white children. Increases in childhood cancer incidence since the 1960s and 1970s have been reported in Europe and the rest of the world. In Great Britain, the World age-standardised incidence rate has increased by more than two fifths (43%) since the late 1960s, from 107 cases per million children in 1966-1970 to 152 cases per million in 2001-2005. Between 1966 and 2000 there has been a statistically significant average annual increase of almost 1% per year, though this varies between 0.5% and 2.5% per year by tumour type (2,3,4,5,6,7,8). The decreased mortality rate of paediatric cancers has been one of the major success stories of medicine in the last 30 years. Improvements in the survival rates of leukaemia, Hodgkin disease, and sarcomas have been notable successes. Most of these improvements can be traced to the use of aggressive multimodal therapy and the judicious use of blood products, use of cytokines, and improved supportive care to prevent and treat infections (2).*

*This retrospective study was designed primarily to achieve the following dual objectives; firstly to measure the types and trends of childhood malignancies over*

*the study period and secondly to describe the demographic profile of the 12 major diagnostic groups of the international classification of childhood cancer in relation to the epidemiological variable. It includes all cases of childhood cancer, aged 0 to 15 years who were diagnosed in, receive treatment or follow up in the Haematology/ Oncology department, Children's hospital, Benghazi as well as, the deaths registered with the statistics department of the hospital.*

### 3. LITERATURE REVIEW

*Childhood cancer patterns and trends vary depending on the geographical area around the world. In the developed countries leukemia is the most common cancer by far forming about one third of the total childhood cancers, with brain tumours (e.g., gliomas and medulloblastomas), representing the second most common tumour, as well as, the most common solid tumour. Together, these form more than half the cases occurring in children (9,10,11). Lymphoma, with other solid tumors (e.g., neuroblastomas, Wilm's tumours, and sarcomas such as rhabdomyosarcoma and osteosarcoma), being less common.*

*Childhood acute lymphoblastic leukemia (ALL) is said to have lower incidence in developing countries, some of these developing countries are characterized by a high incidence of lymphoma (12).*

*The overall incidence rate for childhood cancers has increased significantly by almost 33% during the period 1975 to 2001, although, in more recent years, the rate has been levelling off (13,14). In Great Britain childhood cancer incidence rates have increased by more than 40% since the late 1960s. The reasons for this are poorly understood, though improvements in diagnosis and registration are likely to have played a part (15).*

*An Italian study in 2012, described up-to-date cancer incidence and survival in Italian paediatric and adolescent patients in the period 2003-2008, covering 47% of the Italian population below age 20 years. During the period mentioned, 31 cancer registries reported 4,473 incident malignant neoplasms, 2,855 in children and 1,618 in adolescents. Cancer incidence rates were 164 cases per million in children aged 14 years or below. In children (0-14 years) a significant increase in malignant cancer incidence was observed until 1997 (APC: +3.2%), followed by a plateau (APC: -1.1% not statistically significant). Until the late Nineties, a statistically significant increase was also observed in the incidence of all leukaemias in males (APC: +5.7%), lymphoid leukaemias (APC: +5.6%), representing 80% of all leukaemias, Hodgkin and non-Hodgkin lymphomas (APC: +6.3%). A significant decrease emerged for lymphoid leukaemia starting in 1995 (APC: -1.9%), while no substantial change in cancer incidence rates was observed in the last decade of observation for all malignant neoplasms and lymphomas. In addition, no variation emerged for malignant (according to the most recent classification) central nervous system (CNS) neoplasms, while an annual increase*

of 1.8% (significant) was observed in the period 1988-2008, when non-malignant tumours were included.

Increases in cancer incidence were observed throughout the study period for neuroblastoma (APC: +1.9%) and epithelial tumours or melanoma (APC: +4.1%). In the period 1998-2008, in addition to lymphoid leukaemias, a significant decrease was observed for all malignant neoplasms, lymphomas in girls, CNS tumours (males and females), and renal tumours in girls, while no increases were observed in this age group. Recent trends (1998-2008) confirmed the long-term increases only for all malignant neoplasms in girls and thyroid cancer (APC: +7.9%, boys and girls), while a decrease in bone tumour incidence emerged in girls, albeit based only on 46 cases. Cancer mortality in children showed a persistent decrease for all neoplasms and even for more frequent cancer sites or types and mortality rates for cancer were three-fold higher in the early Seventies than in 2008. In addition, five-year survival after cancer diagnosis increased in the last three decades and still was increasing in the period 2003- 2008, reaching 82% in children. The results also showed that the significant increase in cancer incidence observed until the end of Nineties has halted. Efficacy of therapeutic protocols has improved constantly since the Seventies, and recent findings confirm this trend in all age groups and, in particular, for rarer tumours and cancer types that have very poor prognosis<sup>(16)</sup>.

Another study done in Aden, Yemen, from 1997 to 2006 concerning childhood cancer showed that out of a total of 483 childhood cancers <15 years age comprising 12.7% of all registered malignancies with a male to female ratio of 1.5:1. The predominant age affected was 5–9 years in (38.3%) children. The most frequent cancer among Yemeni children was leukaemia 160 (33.1%) followed by lymphoma 152 (31.5%), CNS tumors 35 (7.2%) and bone tumours 25 (5.2%). An interesting and unusual finding was the frequency of acute myeloid leukaemia twice more common in female (66.7%) than male (33.3%). Lymphoma was the most common cancer in children >5 years. An interesting comparison was the preponderance of non-Hodgkins's lymphoma over Hodgkin's disease (1.6:1) stronger in female (3:1) than male (1.25:1). Medulloblastoma was the most common CNS tumour followed by astrocytoma, an infrequent finding in childhood cancer. Osteosarcoma was the most frequent bone tumour (male:female ratio of 1.8:1). A female preponderance was noticed in chondrosarcoma that was not yet documented. The blastoma group was common in younger age group. Retinoblastoma and nephroblastoma predominated in female while neuroblastoma, hepatoblastoma and soft tissue sarcomas in male.

It is concluded that there is a lower frequency of childhood cancer in Aden when compared with developed countries. It may explained by the fact that a large

number of childhood cancers remain undiagnosed due to limitations of diagnostic facilities or under registration. Central paediatric hospitals should be provided with essential diagnostic and therapeutic services that should be freely available to all children with cancer <sup>(17)</sup>.

In Australia, data from the population-based Australian Paediatric Cancer Registry were used to calculate incidence rates during the 10-year period (1997–2006) and trends in incidence between 1983 and 2006 for the 12 major diagnostic groups of the International Classification of Childhood Cancer. It was found that there were 6184 childhood cancer (at 0–14 years) cases in Australia (157 cases per million children). The commonest cancers were leukaemia (34%), that of the central nervous system (23%) and lymphomas (10%), with incidence the highest at 0–4 years (223 cases per million). Trend analyses showed that incidence among boys for all cancers combined increased by 1.6% per year from 1983 to 1994 but remained stable since. Incidence rates for girls consistently increased by 0.9% per year. Since 1983, there were significant increases among boys and girls for leukaemia, and hepatic and germ-cell tumours, whereas for boys, incidence of neuroblastomas and malignant epithelial tumours decreased. For all cancers and for both sexes combined, there was a consistent increase (+0.7% per year, 1983–2006) at age 0–4 years, a slight non-significant increase at 5–9 years, and at 10–14 years, an initial increase (2.7% per year, 1983–1996) followed by a slight non-significant decrease <sup>(18)</sup>.

In a fourth study in 2009 by A. Mohammed and H. O. Aliyu to determine the relative frequencies of childhood malignancies and their age – sex distribution in northern Nigeria. A total of 329 children aged  $\leq 15$  years, with confirmed malignant disease, were recorded. This constituted 8.44% of all malignancies diagnosed in the same period with a Male : Female ratio of 1.5:1. Burkitt's lymphoma accounted for 27.01% of the cases followed by retinoblastoma (17.02%), non-Hodgkin's non-Burkitt's Lymphoma (9.42%), and Rhabdomyosarcoma (9.42%). Others were Nephroblastoma (8.81%), Hodgkin's lymphoma (6.69%), Neuroblastoma (3.34%), Colorectal carcinoma (2.43%), Osteosarcoma (2.13%), and Unspecified lymphomas (1.82%). Burkitt's lymphoma was most prevalent in the 5–9 and 10–15 year age groups, retinoblastoma in the 0–4 year age group, and Non-Hodgkin's lymphoma, Hodgkin's lymphoma, and unspecified carcinomas were more prevalent in the 10–15 year age group <sup>(19)</sup>.

In a retrospective analysis of childhood cancer patients presenting for treatment in Western Kenya carried out by Saskia Mostert, Festus Njuguna, et al, between January 2006 and January 2010 using information from three separate databases at the Moi Teaching and Referral Hospital in Eldoret. A total of 436 children with cancer between the ages of 0-15 were registered during the period. There were

256 (59%) boys and 180 (41%) girls with a male/female ratio of 1.4:1. The group aged 6–10 years contained most children (29%). Median age at admission was 8 years. Non-Hodgkin's lymphoma was the most common type of cancer (34%), followed by acute lymphoblastic leukaemia (15%), Hodgkin's lymphoma (8%), nephroblastoma (8%), rhabdomyosarcoma (7%), retinoblastoma (5%) and Kaposi's sarcoma (5%). Only four (1%) children with brain tumours were documented. Ewing's sarcoma was not diagnosed.

This study provided an overview of childhood cancer patients presenting for treatment in Western Kenya. The distribution of malignancies was similar to findings from other equatorial African countries but differed markedly from studies in high-income countries (20).

Another study done at the Institute for Medical Biostatistics, Epidemiology and Informatics, University of Mainz, Germany, reported on childhood cancer incidence and survival rates as well as time trends and geographical variation. According to the data, which referred to the International Classification of Childhood Cancer, leukemia, at 34%, brain tumors, at 23%, and lymphomas, at 12%, represented the largest diagnostic groups among the under 15-year-olds. The most frequent single diagnoses were: acute lymphoblastic leukemia, astrocytoma, neuroblastoma, non-Hodgkin lymphoma, and nephroblastoma. There was considerable variation between countries. Incidence rates ranged from 130 (British Isles) to 160 cases (Scandinavian countries) per million children.

Incidence rates showed an increase over time since the mid of the last century. In Europe, the yearly increase averaged at 1.1% for the 1978-1997 period and ranged from 0.6% for the leukemias to 1.8% for soft-tissue sarcomas. The probability of survival rose considerably over the past decades, with the EURO CARE data showing an improvement of the relative risk of death by 8% when comparing the 2000-2002 time span to the 1995-1999 period. Regarding the years 1995-2002, the data showed an overall 5-year survival probability of 81% for Europe and similar values for the USA (21).

In a study to investigate the characteristics and incidence trends of childhood cancer in Beijing, China, from 2000 to 2009 by Yang L, Yuan Y et al, of a total of 1,274 cases with childhood the crude incidence rate was 106.47 per million [age-standardized rate (ASR) 113.34], with the most common diagnoses, leukemia (N=505, 39.64%, ASR 45.20), followed by central nervous system (CNS) tumors (N=228, 17.90%, ASR 19.28) and lymphoma (N=91, 7.14%, ASR 6.97). The incidence for all childhood cancers combined increased during the study period, with an APC

of 5.84% [95% confidence interval (95% CI): 1.0-10.9] after adjusted by world population. The ASR of all combined cancers in boys showed a slight, but no significant increase, with an APC of 5.33% (95% CI: -0.6-11.6); for girls, the trends increased significantly, with an APC of 6.54% (95% CI: 1.5-11.8).

This concluded that the incidence rate of childhood cancer in Beijing was higher than the average level of China and lower than that of western countries. The incidence trends of childhood cancer, especially leukemia among girls showed a significantly increase from 2000 to 2009. While among boys, no substantially change was seen during the observed time period <sup>(22)</sup>.

In a study done in eastern Nigeria the clinical records of 257 children admitted with malignant disease to the University of Nigeria Teaching Hospital, Enugu between January 1978 and December 1982 were studied retrospectively to determine the pattern of malignant diseases amongst these children. The lymphomas were the commonest tumours, constituting nearly 40% of the total, followed by Wilm's tumour (14.0%), leukaemia (12.9%) and CNS tumours (9.7%). However, the incidence of lymphoma was lower while the incidence of leukaemia was higher than in previous reports from other parts of Nigeria and Africa. The rarity of Ewing's tumour, histocytosis-X and testicular tumours in African children was confirmed in the study.

The study concluded that the pattern of childhood malignancies in the developing countries of Africa was characterized by a high incidence of lymphoma and a low incidence of leukaemia which has been associated with poor living standards. The converse is the case in the developed countries of Europe and North America <sup>(23)</sup>.

### **3-1.Leukaemia:**

Leukaemia form the most commonly diagnosed cancer in children, accounting for around a third (30%) of all cases <sup>(24)</sup>. Acute lymphoblastic leukaemia (ALL) is the most common type of childhood leukaemia by far. ALL accounts for around four-fifths (78%) of all leukaemia diagnosed in children, and as such largely determines the age and sex pattern for childhood leukaemia overall.

The next most common leukaemia diagnosed in children is acute myeloid leukaemia (AML). AML accounts for 15% of childhood leukaemia; incidence rates are highest in infants (under one-year-olds) and show little variation with age from three onwards <sup>(25)</sup>.



Hjalgrim LL, Rostgaard K et al; studied the Age- and sex-specific incidence of childhood leukemia during the period between, January 1, 1982, and December 31, 2001, Studies from various countries found an increasing incidence of childhood leukemia in recent decades. To characterize time trends in the age- and sex-specific incidence of childhood acute leukemia during the last 20 years in the Nordic countries, a large set of population-based data were analyzed from the Nordic Society of Paediatric Haematology and Oncology (NOPHO) in their acute leukemia database covering a population of approximately 5 million children aged 0-14 years. 1595 girls and 1859 boys diagnosed with acute lymphoblastic leukemia between January 1, 1982, and December 31, 2001, and 260 girls and 224 boys diagnosed with de novo acute myeloid leukemia between January 1, 1985, and December 31, 2001. No statistically significant change was seen in the overall incidence rate for acute lymphoblastic leukemia during the 20-year study (annual change = 0.22%, 95% confidence interval [CI] = -0.36% to 0.80%). The incidence rate of B-precursor acute lymphoblastic leukemia remained unchanged (annual change = 0.30%, 95% CI = -0.57% to 1.18%) from January 1, 1986, through December 31, 2001. A somewhat lower incidence in the first years of the study period indicated an early increasing incidence of B-precursor acute lymphoblastic leukemia that corresponded to a simultaneous decreasing incidence of unclassified acute lymphoblastic leukemia. Incidences of T-cell acute lymphoblastic leukemia (annual change = 1.55%, 95% CI = -1.14% to 4.31%) and acute myeloid leukemia (annual change = 0.58%, 95% CI = -1.24% to 2.44%) were stable during the study period. The study concluded that the incidences of acute myeloid leukemia overall, acute lymphoblastic leukemia overall, and specific acute lymphoblastic leukemia immunophenotypes have been stable in the Nordic countries over the past two decades (26).

### **3-2. Brain and central nervous system (CNS) tumours:**

Brain and CNS tumours form the second most common group of cancers in children, accounting for a more than a quarter (27%) of all childhood cancers overall (24).

The largest subgroup is astrocytoma and these constitute over two-fifths (43%) of all brain and CNS tumours in children. Astrocytoma is diagnosed throughout childhood and there is no strong pattern by either sex or age. Around three-quarters (76%) of astrocytomas are diagnosed as low grade and 15% as high grade. (25,27).

In a study based on records of the Department of Pathology, Al-Sabah Hospital, which examined all brain tumor biopsies done in the (0-14) and (15-19) age groups

*in Kuwait between 1995 and 2011, by Chukwuka Katchy et al; it was found that during this period, 75 boys (49%) boys and 77 (51%) girls had histologically confirmed primary brain tumors (PBT). They comprised 122 children (0–14 years) and 30 adolescents (15–19 years). The boys/girls ratio was 1.03 in childhood and 0.76 in adolescence. The age-adjusted incidence rate was 11.2/ million person-years. Early childhood (0–4 years) had the peak frequency of tumors (33%), highest adjusted age-specific incidence rate (3.8/million person-years) of all tumors and the least boys/girls rates ratio (0.38) for astrocytic tumors. Low grade and high grade tumors peaked in 5–9 and 0–4 years respectively.*

*Risk factors (hereditary syndromes or previous radio-therapy) were identified in three patients. Three (2%) tumors were congenital. High grade tumors comprised 47% of childhood and 23% of adolescence PBT. The most common tumors in childhood were astrocytoma (37%), embryonal tumors (31%),ependymoma (8%), and in adolescence astrocytoma (27%), pituitary adenoma (23%) and glioblastoma (13%).*

*Embryonal tumors formed 44% of PBT in early childhood. Gliomas constituted 54% and 43% of all PBT, but 25% and 57% of high grade tumors in childhood and adolescence respectively. Most common tumor locations were cerebellum (47%), ventricles (19%) and cerebral lobes (17%) in childhood and pituitary (30%), cerebellum (27%) and 13% each for cerebral lobes and ventricles in adolescence. Approximately 57% of childhood and 23% of adolescence PBT were infratentorial.*

*In conclusion, despite the high relative frequency of PBT before the age of 20 years in Kuwait, its incidence rate was found to be apparently low. Compared with Western countries, Kuwait had a lower incidence of malignant gliomas, but a higher frequency of cerebellar and intraventricular tumors. Embryonal tumors were remarkably common in early childhood <sup>(28)</sup>.*

*In Beijing Tiantan Hospital, from 2001 to 2005, a retrospective study was done by Zhou D. Zhang Y. et al, to describe the epidemiology of nervous system tumors in children based on the clinical data obtained from a neurosurgical center in Beijing. During a 5-year period, from January 2001 to December 2005, 1,485 primary brain and spinal tumors in children up to 17 years of age were diagnosed histopathologically according to the World Health Organization 2000 nervous system tumor classification. The sex predilection, tumor location, and histological grade in relation to age were investigated, and the epidemiological characteristics of the 5 most common brain tumors were discussed. Results showed that of the*

1,485 cases evaluated, brain and spinal tumors comprised 92.3% (1,371) and 7.7% (114), respectively, with a predominance of low-grade tumors (65.1 and 78.9% for brain and spinal cord, respectively). For all tumors, the overall sex ratio (male to female) was 1.6:1. 61.9% of the brain tumors were supratentorial, whereas an infratentorial location was slightly more common in the 872 brain tumors of neuroepithelial tissue (53.7%). The 5 most common brain tumors were astrocytic tumors (30.5%), craniopharyngiomas (18.4%), medulloblastomas (14.6%), germ cell tumors (GCTs, 7.9%) and ependymal tumors (5.6%). The highest preponderance of boys was observed in GCTs followed by medulloblastomas. The most common types of spinal tumors were ependymal tumors (19.3%), neurilemmomas (16.7%) and astrocytomas (14.9%)<sup>(29)</sup>.

In a second retrospective study which was performed in the Departments of Pediatric Neurosurgery of the Cairo University Hospitals from 2005 to 2008. The characteristics of 451 Egyptian children (aged 0–14 years) with primary intracranial neoplasms were investigated for demographic, clinical, topographical and pathological features using the most recent 2007 Classification of Central Nervous System Tumors. There was a slight male predominance (51.4%) observed in the study, and the most affected age group was 5–9 years old (43.2%). Most of the tumors were confined to a single compartment (infratentorial in 49.7%, supratentorial in 46.6%), while 3.8% of the tumors involved multiple compartments. The most common intracranial tumors were astrocytomas (35%), medulloblastomas (18.8%), craniopharyngiomas (11.3%) and ependymomas (10%). Pilocytic astrocytomas constituted 55% of all astrocytomas and 19.3% of all brain tumors, only slightly ahead of medulloblastomas. Less common types were primitive neuroectodermal tumors (2.7%), followed by meningiomas, germ cell tumors and choroid plexus tumors (2.4% each). According to the International Classification of Diseases for Oncology Coding (ICD-O-4), benign, borderline and malignant tumors constituted 7.54, 36.14 and 56.32%, respectively. Conclusion: The characteristics of pediatric intracranial tumors in Egypt are generally similar to those reported in the literature, with only minor differences<sup>(30)</sup>.

Another study done on brain tumor demographic Pattern over a Ten-Year Period in the Kashmir Valley in children between 2000-2009, showed that; brain tumours represent the second most frequent tumors in this age group after hematologic

malignancies. It highlighted the demographic pattern after retrospective analysis of brain tumors in children from geographically and ethnically distinct Kashmir Valley managed the center between 2000 and 2009. A total of 248 pediatric patients with brain tumors were analyzed for age, gender, location of tumors and histopathological subtypes as well as WHO grade of tumor. A comparison was made between the frequencies of common varieties of tumor in the first and second 5-year periods. It was found that 111 tumors (44.75%) were supratentorial, and 137 (55.25%) were infratentorial. The male-to-female ratio was 1.4:1. The proportions of low-grade and high-grade tumors were 60 and 40%, respectively. The most common tumor in the series was astrocytoma. The most common tumors in the supratentorial and infratentorial compartments were craniopharyngioma and medulloblastoma, respectively. This reflects a different demographic profile of pediatric brain tumors as compared with other regions of the world <sup>(31)</sup>.

### **3-3.Lymphomas:**

These account for 11% of all cancers diagnosed in children and more than twice as many cases are diagnosed in boys as in girls. Lymphomas are rare before the age of two and incidence increases with age thereafter such that lymphomas account for nearly a fifth (19%) of all childhood cancers diagnosed in 10-14 year-olds <sup>(24)</sup>.

In a study done in 2006 in Aga Khan university- Karachi a slow upward variation in the annual incidence of NHL was observed between 1999 and 2006. The increase in the incidence affected all age groups in both genders. During this period, the mean age of childhood lymphoma was 7.9 years (95% CI 6.3; 9.4) in males and 8.4 years (95% CI 6.1; 10.6) in females. The youngest male patient was 2 years and the youngest female patient was 3 years; the oldest male and female children were 14 and 13 years respectively. The component of childhood NHL was 10.4% and 9.3% in males and females respectively. The adult to childhood ratio (A:C) was 8.6 in males and 10.7 in females.

Children and adolescents were at the highest risk of developing NHL, 0-4 years OR 4.5 (95% CI 0.3; 6.7) in males, 5.4 (95% CI 0.3; 9.8) in females; 5-9 years, OR 8.9 (95%CI 0.2; 12.2) in males, 10.1 (95% CI 0.2; 16.4) in females and 10-14 years, OR 5.0 (95% CI 0.3; 6.7) in males, 5.8 (95% CI 0.3; 8.2) in female <sup>(32)</sup>.

### **3-4.Neuroblastoma:**

*Neuroblastoma is the most common extracranial solid tumor of infancy. It is an embryonal malignancy of the sympathetic nervous system arising from neuroblasts (33). The incidence in developed countries is greater than that in developing countries. NB represents between 8–10% of the total cancers in children (0–14 years) in countries such as the United States of America (USA), Australia, and those in Europe, whereas the frequency is generally lower (3%) in Latin-American countries and in some cities in Asia, such as Tianjin, China, and Delhi and Madras, India. In some of these countries, NB occupies fourth place in incidence (34, 35). Approximately 70-80% of patients older than 18 months present with metastatic disease, usually in the lymph nodes, liver, bone, and bone marrow. Less than half of these patients are cured, even with the use of high-dose therapy followed by autologous bone marrow or stem cell rescue (33).*

*In a study, published in the BMC cancer 2009, showing the epidemiology of NB in Mexican children during the period from 1996–2005. A population-based, prospective study, with data obtained from the Childhood Cancer Registry of the Instituto Mexicano de Seguro Social. Statistical analysis: The simple frequencies of the variables of the study and the annual average incidence (per 1,000,000 children/years) by age and sex were obtained. The trend was evaluated by calculating the annual percentage of change. The curves of Kaplan-Meier were employed for the survival rate and the log-rank test was used to compare the curves.*

*Of a total of 2,758 children with cancer registered during the period from 1996–2005, 72 (2.6%) were identified as having Group IV, defined according to the International Classification of Childhood Cancer. The incidence for NB was 3.8 per 1,000,000 children/year; NB was highest in the group of children under one year of age, followed by the group of children between the ages 1–4 years (18.5 and 5.4 per 1,000,000 children/years, respectively). The male/female ratio was 1.1 and there was no trend toward an increase. The time of diagnosis was 26 days (median), but varied according to the stage at diagnosis. Stages III and IV were presented in 88% of the cases. There was no association between the stage, the age at time of diagnosis, or the histological pattern. The overall five-year survival rate was 64%; the patients with stage I, II, III, or IVs did not die; and the five-year survival rate of cases in Stage IV was 40%.*

*It is possible to conclude that the low incidence of neuroblastoma in Mexican children was due to the difficulty in diagnosing the cases with the best prognosis, some of which could have had spontaneous regression. There was no trend to an*

*increase; the majority of the cases were diagnosed in the advanced stages; and the overall five-years survival rate was similar to that for developed countries (34).*

*In another study on the international variations in the incidence of neuroblastoma, by Stiller CA and Parkin DM in the department of Paediatrics, University of Oxford, UK, it was found that, in predominantly white Caucasian populations the age-standardized rate was 7-12 per million, and 6-10% of all childhood cancers were neuroblastomas. Rates were highest in the first year of life (25-50 per million, 30% of total neuroblastoma incidence), and decreased with age to 15-20 per million (50% of the total) at age 1-4, 2-4 per million (15%) at 5-9 and 1-1.5 per million (5%) at 10-14. In the United States, black children had an incidence of 8.5 per million compared with 11.5 among Whites; Blacks tended to be older than Whites at diagnosis. The highest rate in Africa was in Bulawayo, Zimbabwe (8.0 per million) and the lowest in West Nile, Uganda, with no cases registered. In other parts of West Asia neuroblastoma had a low relative frequency, suggesting that incidence is low. Rates were also low throughout much of southern and eastern Asia, including India and China. Incidence in Japan was somewhat higher, though less than in Western countries, with the deficit most pronounced in the first year of life; these data related to the period before mass screening of infants for neuroblastoma in the regions concerned. Incidence was generally higher in regions and among ethnic groups enjoying a higher standard of living, though previous studies within single countries had suggested that neuroblastoma was more common among less affluent groups. Blacks in Africa and the United States may have a weaker genetic predisposition to neuroblastoma, but some of the deficit in many developing countries is likely to be due to under-diagnosis (35,36).*

## **4. OBJECTIVE**

- *To measure the types and trends of childhood malignancy over the study period.*
- *To describe the demographic profile of childhood malignancy in relation to epidemiological variables.*

## **5. PATIENTS AND METHODS**

### **5-1.Study design:**

*This study is a cross sectional study, with retrospective timing of data collection where patients diagnosed with various types of cancers were followed to achieve the objectives.*

*The study period was 4 months for data collection, 2 months for literature review, and 2 months for analyzing the data and thesis writing.*

### **5-2.Study settings:**

*The study was undertaken at the Benghazi children's hospital, which is a government hospital that came into existence in the year 1966. The haematology unit opened in 1983 and within this unit the oncology department was established in the same year forming the only available centre for the diagnosis and treatment of children with all types of cancer from Benghazi and the Eastern zone of Libya.*

### **5-3.Source of data:**

*Medical records of all cancer patients clinically diagnosed and confirmed by investigations who were admitted during the period 2001 to 2013 with various cancers including solid tumours and haematological malignancies; where records of patients who died in the hospital were made available by the statistics dept.*

*Data collected included; Patients demographics including; age, gender, residence, date of admission, age at diagnosis, we also used the patients physical examination and investigations including; complete blood count, bone marrow, CSF cytology, ultra sound scans and bone marrow report forms and histopathology report forms, to assist in the diagnosis, sub-typing and staging where available and to identify the site of the tumour.*

### **5-4.Exclusion criteria:**

- *6 patients were found to be from Misrata and one from Tripoli.*



- *Patients had missing data in their files these cases were excluded only from the section for which their data was unavailable, they were included into the overall case count, yearly distribution and any other section for which their data was available.*

### **5-5.Data analysis:**

*Data was analyzed manually and interpreted in term of percentage, mean and median.*

*The annual percent change*

$$\text{Percent change} = [(V_{\text{present}} - V_{\text{past}}) / V_{\text{past}}] * 100$$

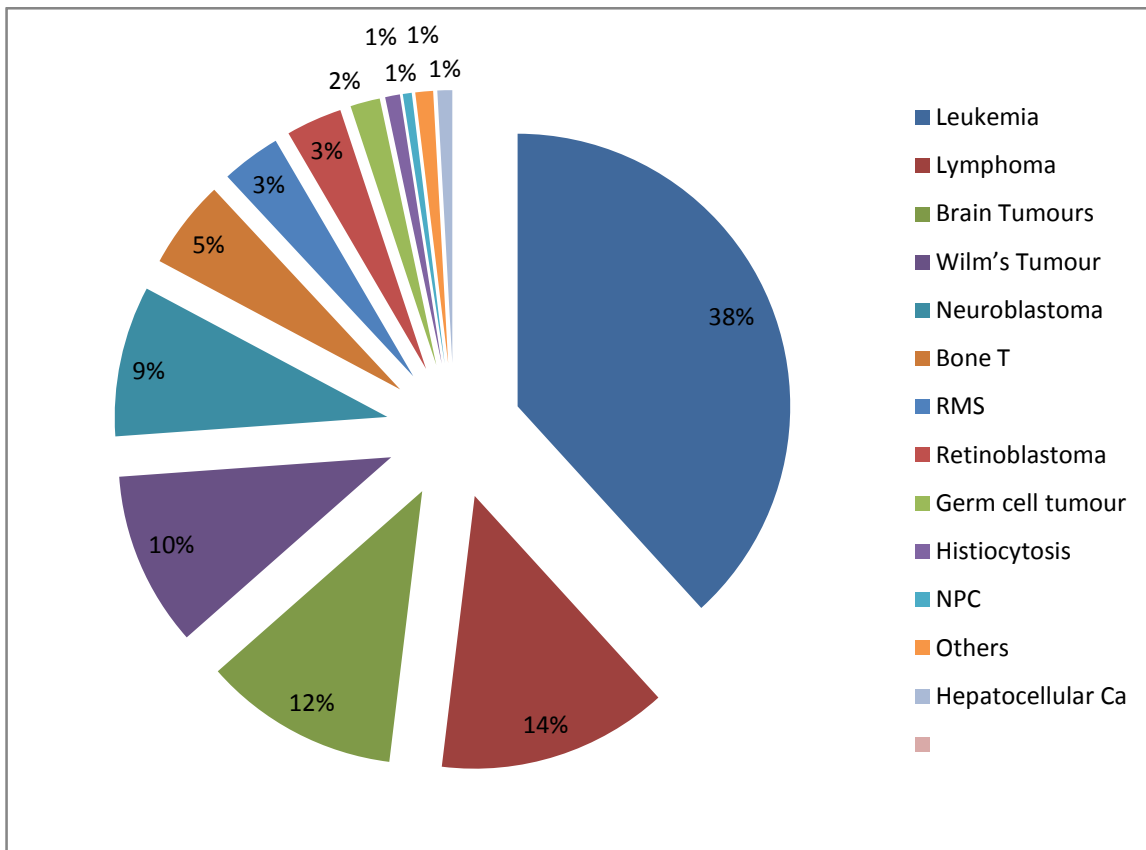
*In this formula:*

*V present = present or future value*

*V past = past or present value*

## 6. RESULTS

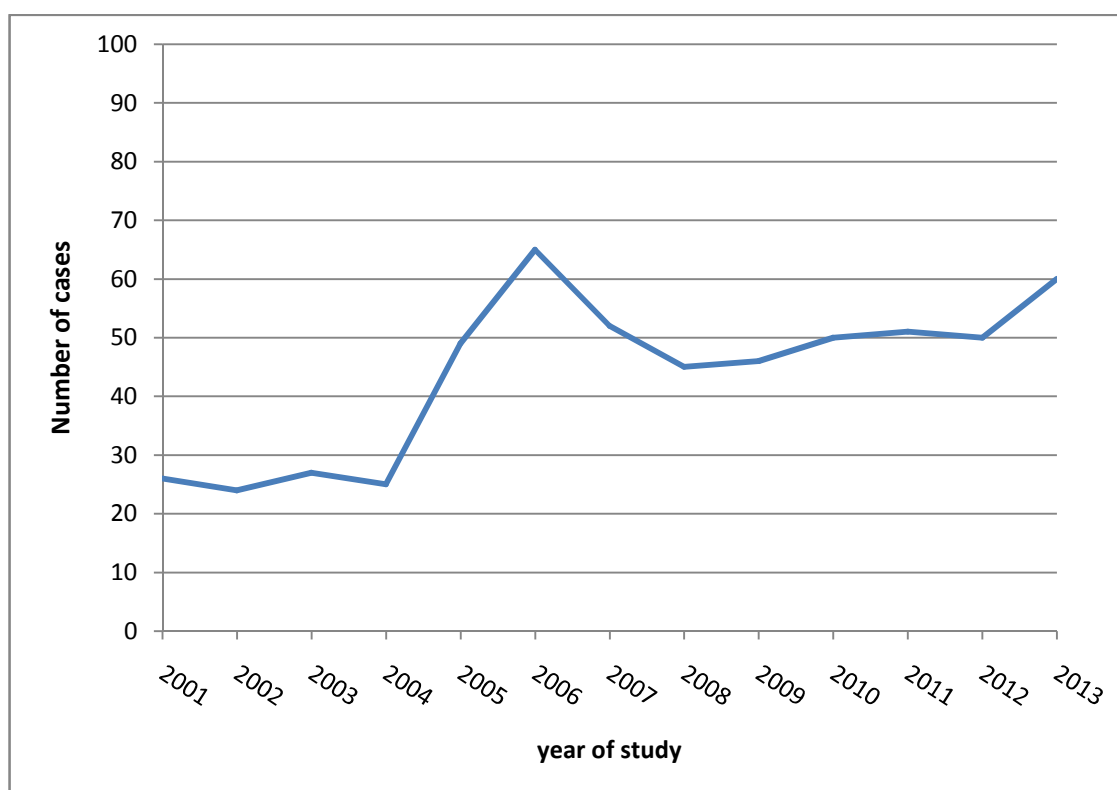
- A total of 568 patients between birth and 15 years of age were diagnosed with some form of childhood malignancy over the period between 2001 and 2013.
- Out of the 568, leukaemia, lymphoma, brain tumours, WT and NB represent the majority of cases, with 219, 78, 67, 58 and 49 cases respectively.
- While the remaining cases were bone tumours, RB, RMS, germ cell tumours, others, histiocytosis, hepatoblastomas and NPC, with 30, 19, 19, 10, 6, 5, 5 and 3 cases respectively.



**Graph -1: Distribution of patients according to the type of malignancy**

### 6-1: Annual changes in malignancy admissions

- Out of a total of 171627 admissions during the 13 years a total of 568 (0.33%) were admitted with malignancy.
- Over the study period the number of yearly cases more than doubled from 26 in 2001 to 60 cases in 2013, this represents a percentage increase of 130%.
- The average annual percentage change (AAPC) was not constant; it showed a very fluctuating course with an annual percentage change (APC) of 96% between 2004 and 2005 and an APC of -25% between 2006 and 2007.
- The average APC over the 13 years of the study was 10%.
- In 2013 there were 60 admissions in total rising 20% from a total of 50 cases in 2012.
- The percentage of malignancy cases to total admissions started in 2001 at 0.31% and rose marginally to 0.34% in 2013.
- Graph -2 and table -1 illustrates the number of malignancies by year of diagnosis and the percentage of malignancy admissions to total hospital admissions respectively.



**Graph -2: Distribution of patients (n=568) by year of diagnosis**

**Table -1: Distribution of patients (n=568) by year of diagnosis.**

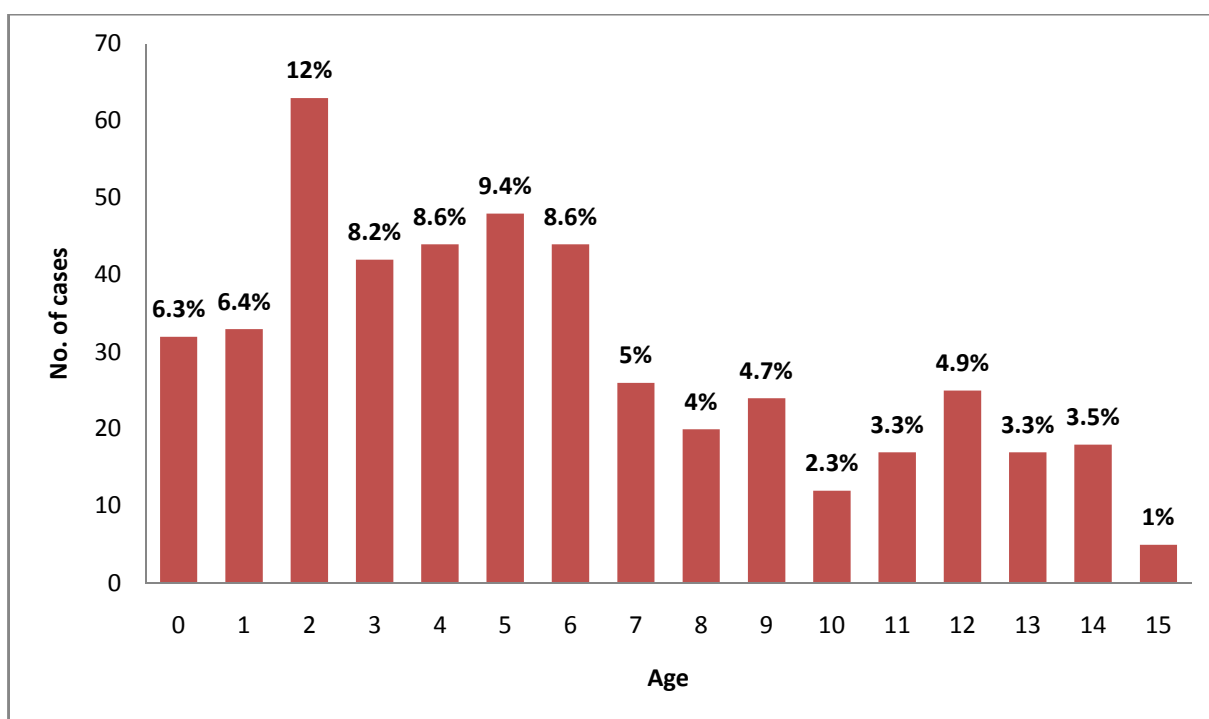
<b>Year</b>	<b>Total admissions</b>	<b>No. of cases</b>	<b>%</b>	<b>APC</b>
<b>2001</b>	8298	26	0.31%	
<b>2002</b>	9093	24	0.26%	-7.7%
<b>2003</b>	8928	27	0.30%	12.5%
<b>2004</b>	9274	25	0.26%	-7.4%
<b>2005</b>	9445	49	0.51%	96%
<b>2006</b>	12937	65	0.50%	32.6%
<b>2007</b>	13099	52	0.39%	-25%
<b>2008</b>	15140	45	0.29%	-13.5%
<b>2009</b>	15360	46	0.30%	2.2%
<b>2010</b>	17051	50	0.29%	8.7%
<b>2011</b>	16242	51	0.31%	2%
<b>2012</b>	19445	50	0.26%	-2%
<b>2013</b>	17315	60	0.34%	20%

APC: Annual percent change

## 6-2. Demographic characteristic (n=568)

### 6-2-1. Age

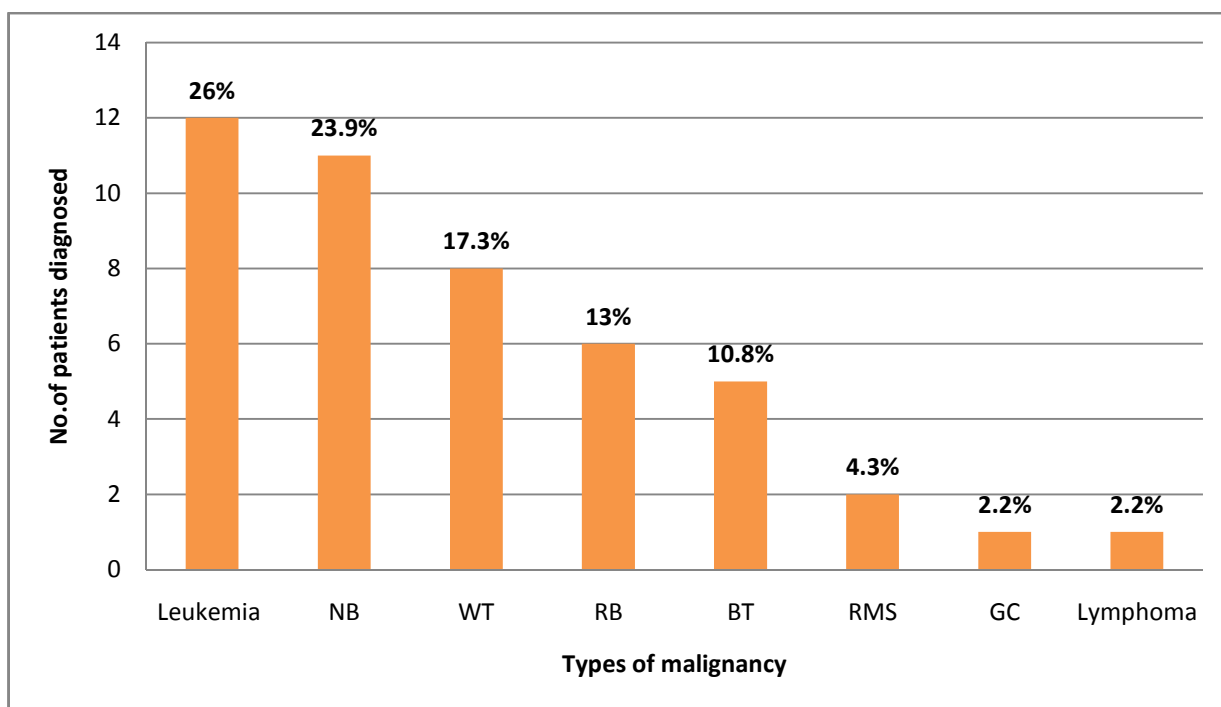
- Our study covered patients from 0-15 years of age.
- The peak age for the diagnosis of malignancy in children in the Eastern parts of Libya is 2 years of age.
- Around 60% of patients are aged 0-6 years.
- Only 5 patients (less than 1%) are 15 years old.
- The following (graph -3), shows the number of patients that presented at each age and their corresponding percentages.



**Graph -3: Distribution of patients (n=568) by age at diagnosis**

## 6-2-2. Analysis of malignancies in the first year of life:

- Out of the total 568 cases, there were 46 cases (8%) diagnosed at less than one year old.
- Leukaemia and NB are the most common tumours diagnosed in patients less than one year of age, with 12 and 11 cases respectively.
- This age group forms just over 1/5<sup>th</sup> of the total NB cases (21.5%)
- Bone tumours, NHL, NPC and hepatocellular carcinoma were removed from the table as no cases under 1 year were registered.



**Graph 4: Distribution of patients under one year of life (n=46) according to their diagnosis**

NB: Neuroblastoma WT: Wilm's tumour RB: Retinoblastoma BT: Brain tumours RMS: Rhabdomyosarcoma GC: Germ cell tumour.

### **6-2-3. Analysis of leukaemia patients by age:**

- The ages of patients ranged from 2 months to 15 years, with a peak age for leukaemia of 2 years.
- Patients had a mean age of  $5.8 \pm 3.9$  and a median of 5.
- The following table gives us the leukaemia patient subtypes according to age.

**Table -2: Distribution of leukemia patient subtypes according to age.**

<i>Type of leukaemia</i>	<i>Range of age</i>	<i>Median</i>	<i>Mean-+SD</i>	<i>Peak age</i>
<i>ALL</i>	<i>2m-15yrs</i>	<i>5yrs</i>	<i>5.8±3.9</i>	<i>2 yrs</i>
<i>AML</i>	<i>3m-14yrs</i>	<i>5yrs</i>	<i>6±4.2</i>	<i>2 yrs</i>

### **6-2-4. Analysis of Lymphoma patients by age:**

- The patients' ages ranged from 6 – 15 years, with a peak age of 6 years at diagnosis.
- Lymphoma patients had a mean age of  $7.7 \pm 3.4$  and a median of 7.
- HL, NHL and BL showed a median age at diagnosis of 9, 6.5 and 5.5 years old respectively. Table-3 displays the differences between the mean, median, peak age and standard deviation of the lymphoma subtypes.

**Table -3: Distribution of lymphoma patient (n=78) subtypes according to age**

<b>Type of malignancy</b>	<b>Range of age</b>	<b>Median</b>	<b>Mean-+SD</b>	<b>Peak age</b>
<i>HL</i>	<i>4-14 yrs</i>	<i>9</i>	<i>9.1±3.1</i>	<i>7 yrs</i>
<i>NHNBL</i>	<i>1-14 yrs</i>	<i>6.5 yrs</i>	<i>7.3±3.5</i>	<i>8 yrs</i>
<i>BL</i>	<i>1-11 yrs</i>	<i>5.5 yrs</i>	<i>5.8±2.5</i>	<i>5.5 yrs</i>

*HL: Hodgkin's lymphoma NHNBL: Non Hodgkins Non Burkitt's lymphoma BL: Burkitt's lymphoma.*

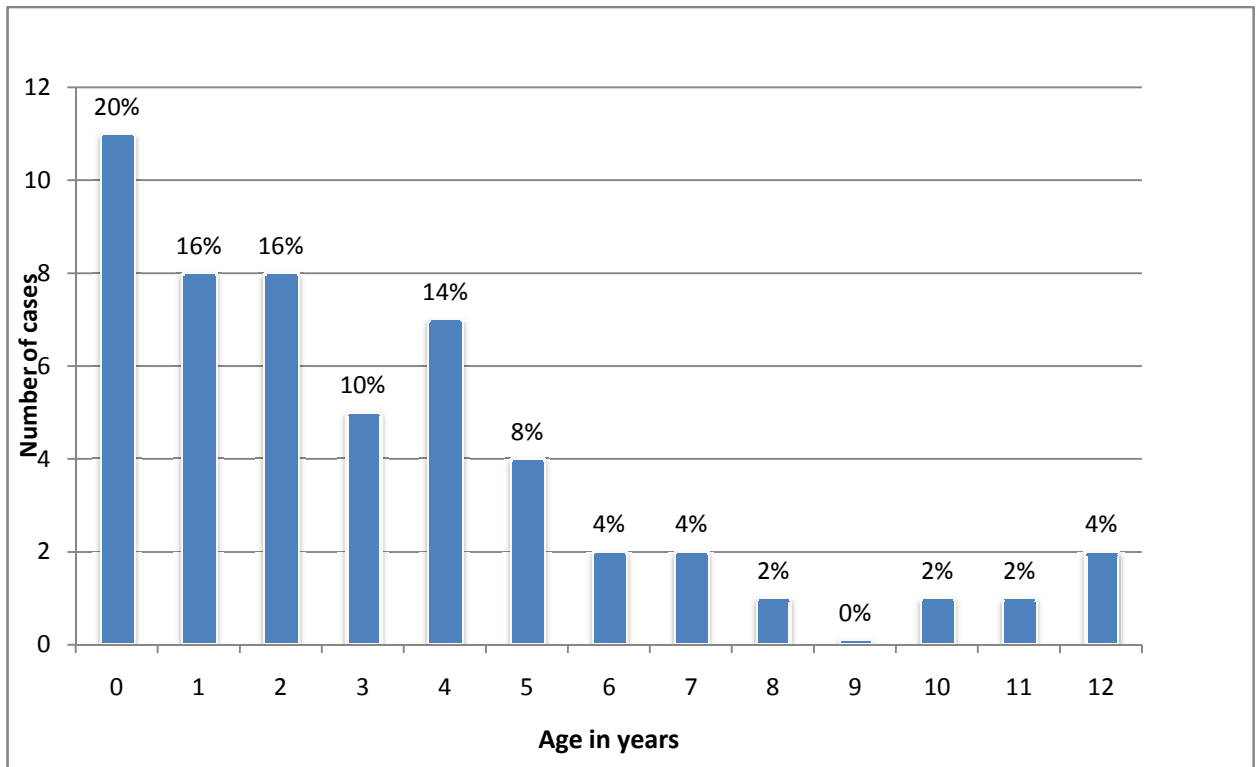
**6-2-5. Analysis of Brain tumour patients by age:**

- *The ages of patients ranged from 2 months to 15 years, with a peak age of 2 years.*
- *Patients had a mean age of 6.*



### 6-2-6. Analysis of Neuroblastoma patients by age:

- NB was highest in the group of children under one year of age (20%) followed by the group of children between the ages 1–5 years with 84% of the patients under 5 years old.
- Graph –5 displays neuroblastoma patients by age.



**Graph -5: Distribution of neuroblastoma patients by age**

**6-2-7. Analysis of Wilm’s tumour, Bone tumours, RMS, retinoblastoma, germ cell tumours and others by age:**

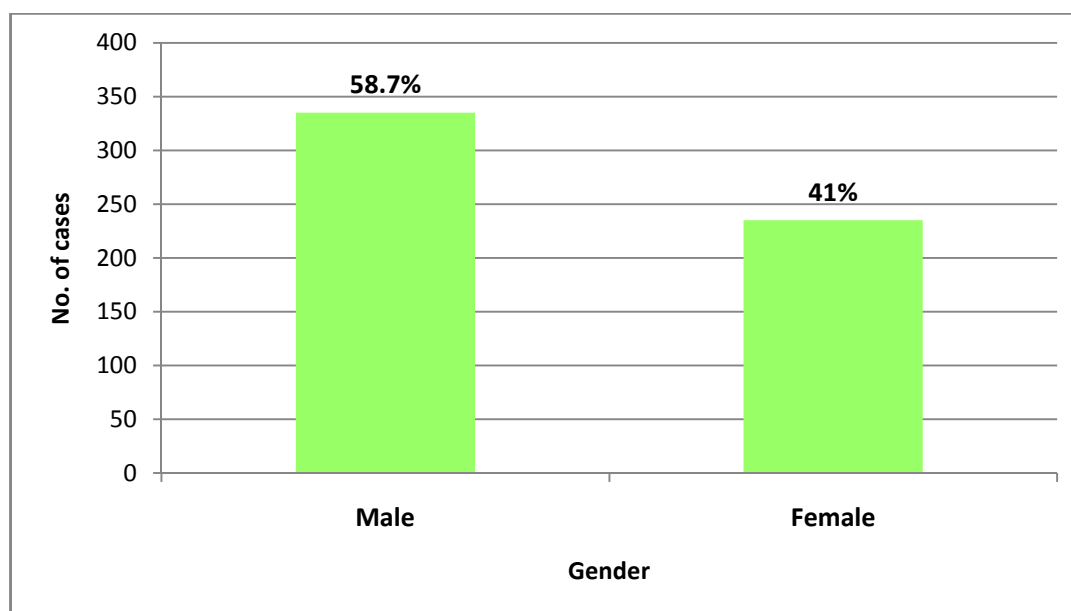
- 15% of Wilm’s tumours were diagnosed at under one year old.
- 93% of Wilm’s tumour patients were 6 years old and under.
- Nasopharyngeal carcinoma more common in second decade of life.
- The following table shows the range of age, mean, median and standard deviation of Wilm’s tumour, Bone tumours, RMS and retinoblastoma, germ cell tumours and others.
- Due to the small number of patients in HCC, Histiocytosis and NPC it was not possible to measure the peak age.
- Others include liposarcoma, desmoids tumors, adrenal carcinoma, ameloblastic carcinoma and epitheloid sarcoma.

**Table -4: Distribution of Wilm’s tumour, Bone tumours, RMS and retinoblastoma, germ cell tumours and others according to age**

<i>Type of malignancy</i>	<i>Range of age</i>	<i>Median</i>	<i>Mean-+SD</i>	<i>Peak age</i>
<i>Neuroblastoma</i>	<i>2 days-12yrs</i>	<i>2</i>	<i>3.3±3</i>	<i>0-1 yrs</i>
<i>Wilm`s</i>	<i>6m-14 yrs</i>	<i>3</i>	<i>3.6±2.6</i>	<i>6m-4yrs</i>
<i>Bone tumors</i>	<i>2-14 yrs</i>	<i>12</i>	<i>10.6±3.4</i>	<i>10-14 yrs</i>
<i>Rhabdomyosarcoma</i>	<i>3m -12yrs</i>	<i>3</i>	<i>4.1±3.7</i>	<i>2 yrs</i>
<i>Retinoblastoma</i>	<i>10 days-9 yrs</i>	<i>2</i>	<i>2.5±2.5</i>	<i>0-2 yrs</i>
<i>Germ cell tumours</i>	<i>10m-11 yrs</i>	<i>2</i>	<i>4±4.7</i>	<i>0-2 yrs</i>
<i>HCC</i>	<i>6m-14yrs</i>	<i>2</i>	<i>4.4±5.5</i>	<i>—</i>
<i>Histiocytosis</i>	<i>8m-10yrs</i>	<i>3</i>	<i>4.4±3.6</i>	<i>—</i>
<i>Nasopharyngeal carcinoma</i>	<i>8yrs-15yrs</i>	<i>10</i>	<i>11±3.6</i>	<i>—</i>
<i>Others</i>	<i>6m-15 yrs</i>	<i>4</i>	<i>6.2±4.8</i>	<i>2 years</i>

### 6-3. Gender:

- A male predominance was found in malignancies.
  - 335 cases being male (58.7%)
  - 233 female (41.3%).
- This formed a ratio of 1.4:1.
- 3 patients with CML and 5 with hepatocellular carcinoma were all male so they were not included in table -3.
- Graph (6) below illustrates the gender of patients included in the study and table -4 shows the M:F ratio of each type of malignancy.
- Male to female ratios in leukaemia patients are nearly equal with a ratio of 1.2:1 and 1.1:1 in ALL and AML respectively.
- Lymphoma males patients are double that of the female patients with a ratio of 2.15:1.
- Nasopharyngeal carcinoma patients showed a male predominance with a M:F ratio of 2:1.
- In Histiocytosis patients the female patients outnumbered the male ones with a male to female ratio of 1:1.5.



**Graph -6: Distribution of patients (n=568) according to gender for all malignancy types.**

**Table-5: Distribution of patients according to M:F ratios in each type of malignancy.**

	<b>Male</b>	<b>Female</b>	<b>Ratio</b>
<b>ALL</b>	94	76	1.2:1
<b>AML</b>	24	22	1.1:1
<b>HL</b>	27	12	2.3:1
<b>NHL</b>	26	13	2:1
<b>Brain T</b>	40	27	1.5:1
<b>Neuroblastoma</b>	31	18	1.7:1
<b>RMS</b>	11	8	1.5:1
<b>Retinoblastoma</b>	11	8	1.4:1
<b>Bone T</b>	16	14	1.14:1
<b>Germ cell ca</b>	6	4	1.5:1
<b>Wilm's T</b>	33	25	1.3:1
<b>Histiocytosis</b>	2	3	1:1.5
<b>Others</b>	4	2	2:1
<b>NPC</b>	2	1	2:1
<b>Total</b>	327	233	1.4:1

**6-4: Analysis of patients by types of malignancies and their residence:**

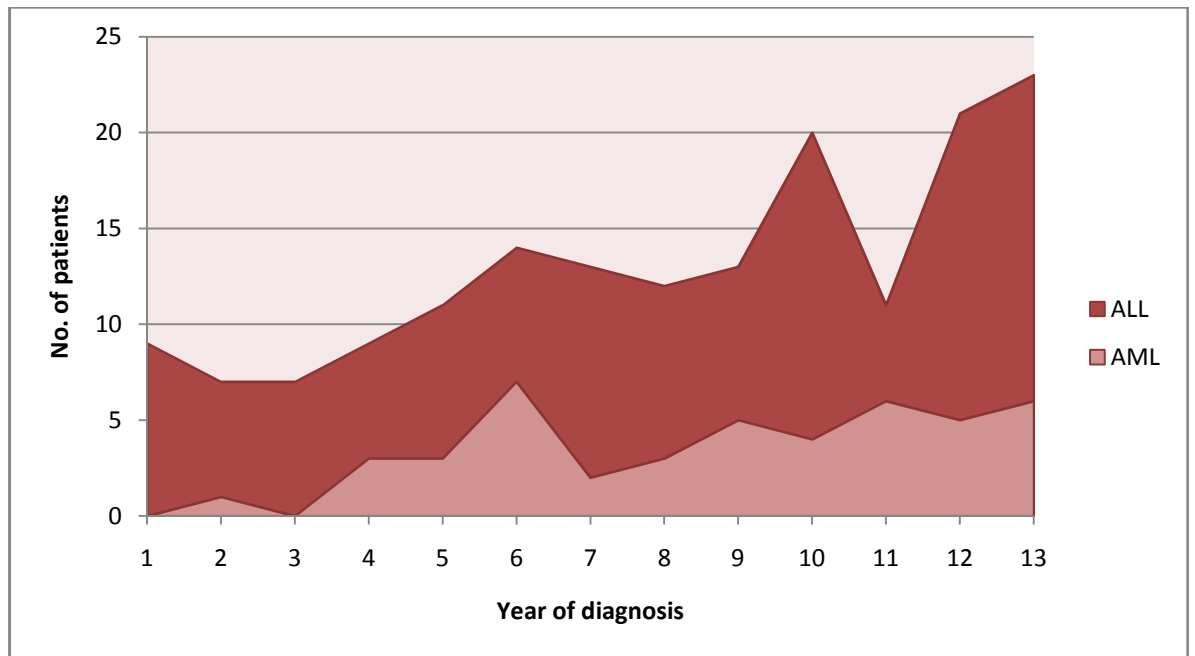
- The studies residence results have been divided by location in relation to Benghazi; either within Benghazi, East of the city, west, or south of it.
- Suburban and rural areas have just slightly more cases of malignancies with 53.7% of patients residing outside Benghazi (299).
- Nearly 56% of solid tumours were from outside Benghazi.
- In Benghazi leukemia cases are equal to those in the rural areas.
- Both HL and NHL were more common outside Benghazi than in the city, with a percentage of 59% and 61.5% respectively.
- Neuroblastoma patients were more common in suburban and rural areas with just over 67% of cases outside Benghazi.
- Nearly 58% of WT patients were located outside Benghazi.
- 2 cases of leukaemia were excluded from this due to unavailable data. 2 cases of NHL, 2 WT patients 1 histiocytosis patient and 1 Germ cell tumour patient were not included for the same reason.

**Table -6: Distribution of malignancies by residence of the patients**

Residence	Type of malignancy					
	Leukaemia		Solid tumour		Total	
	No	%	No	%	No	%
Benghazi	109	50.2%	151	43.8%	260	46.4%
East	75	35.4%	129	37.5%	204	36.5%
West	26	11.5%	48	14%	72	13%
South	7	28.7%	16	4.7%	23	4.1%
	217	100%	344	100%	561	100%

### 6-5. Leukemia:

- Forms 38.3% of all tumours in the study, this corresponds to 219 patients.
- Of these, 170 (78%) are ALL.
- Table (4) shows leukaemia and its distribution according to subtypes.
- Over the study period the number of leukemia patients showed a steady rise; this is seen in both ALL and AML as shown in the graph below.
- From 9 in 2001, ALL peaked dramatically in 2010 and then again in 2013 reaching 23.



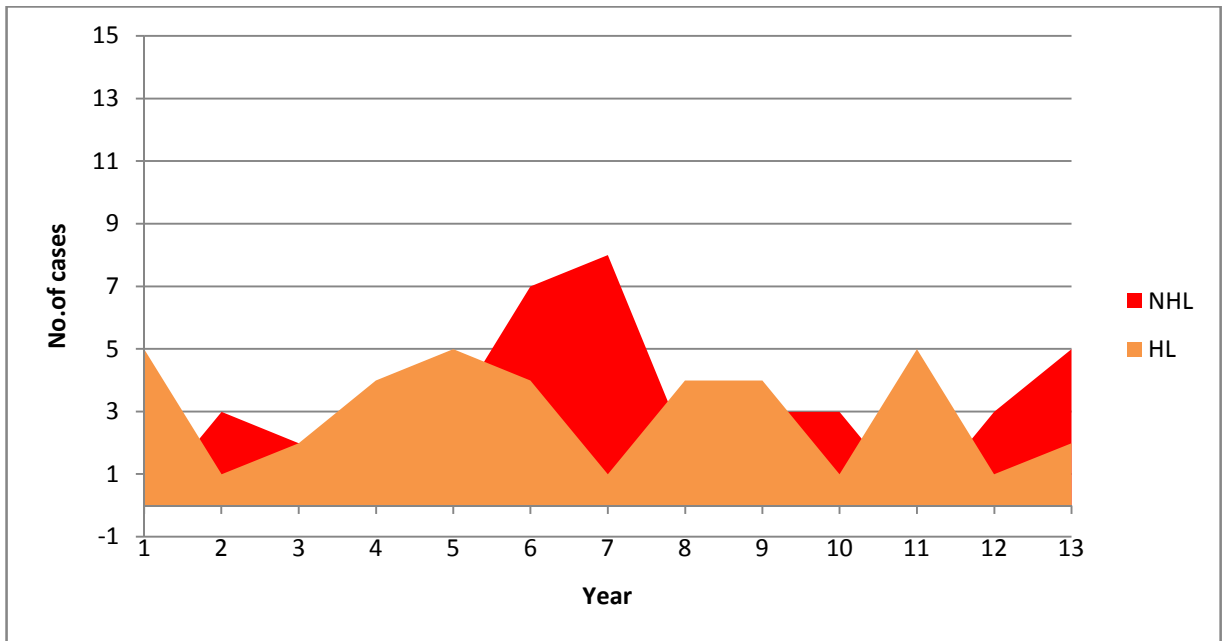
**Graph -7: Distribution of leukemia patients by year of admission**

**Table-7: Distribution of leukaemia patients according to subtypes**

<b>Type of leukaemia</b>	<b>Gender</b>		<b>Total</b>	<b>Percent</b>
	<b>M</b>	<b>F</b>		
<b>ALL</b>	94	76	170	78%
<b>AML</b>	24	22	46	21%
<b>CML</b>	3	0	3	1%
<b>Total</b>	120	98	218	100%

## **6-6. Lymphoma**

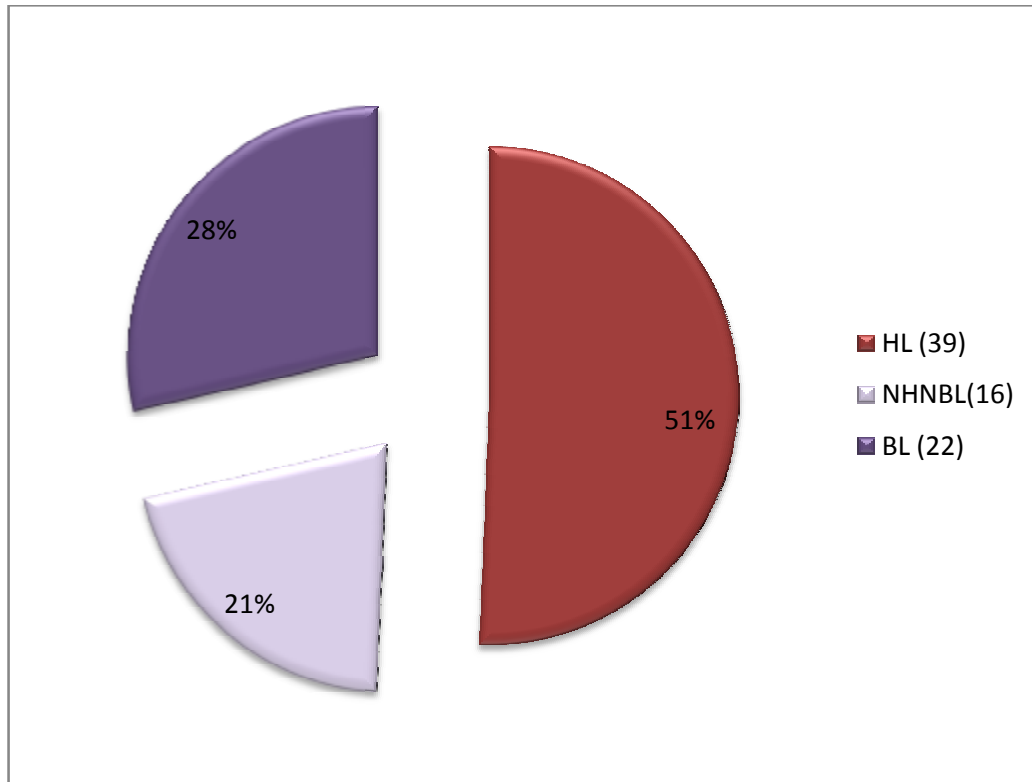
- *Lymphoma was found in this study to be the second most common tumour in childhood. It formed 14% of the cases, coming to a total of 78 cases.*
- *Lymphoma is classified into:*
  - *Hodgkin's (50%)*
  - *Non-Hodgkin's (50%)*
    - *Burkitt's lymphoma (56%)*
    - *Non Burkitt's non Hogkin's lymphoma (41%)*
- *The percentages of lymphoma subtypes are seen displayed in graph -9.*
- *Both NHL and HL show a very fluctuating course over the study period but has no significant overall increase in either as illustrated in graph -8.*
- *Over the thirteen years of the study the number of patients diagnosed each year has fluctuated; reaching its peak of 11 in 2006 and dropping down to 2 in the year 2012.*
- *There were 7 cases of lymphoma recorded in the year 2013.*



**Graph -8: Distribution of lymphoma patients (n=78) by year of diagnosis**

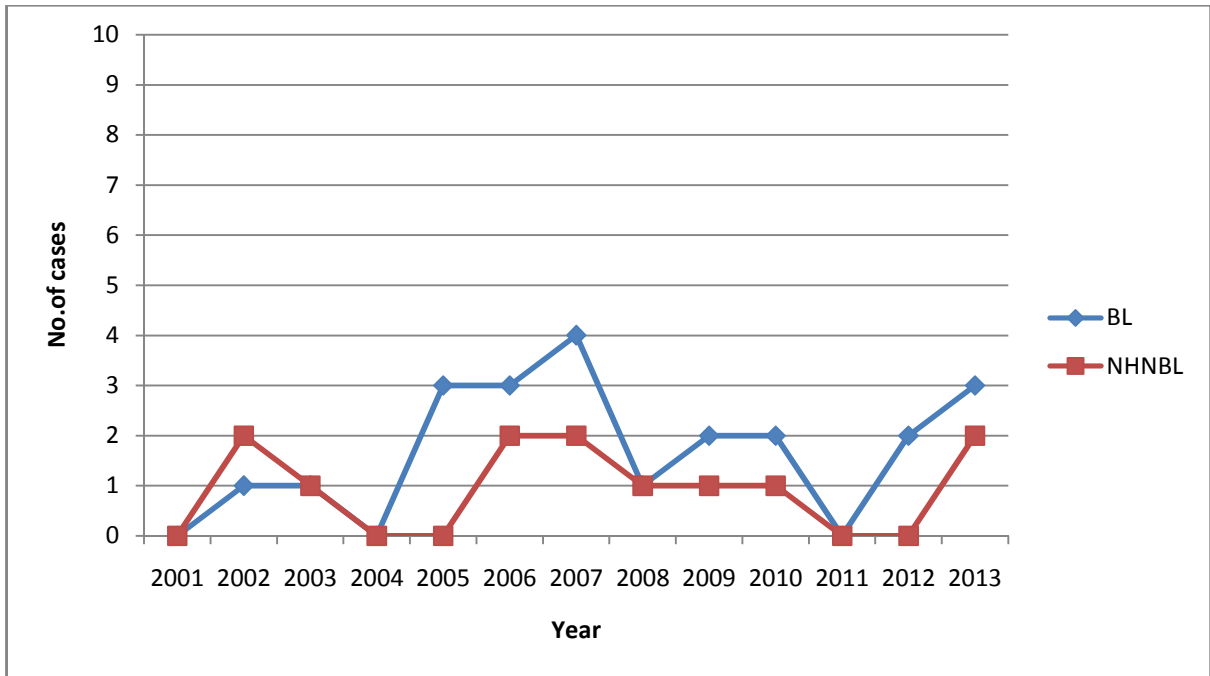
*NHL: Non Hodgkin's lymphoma HL: Hodgkin's lymphoma*





**Graph -9: Distribution of lymphoma patients (n=78) according to subtypes**

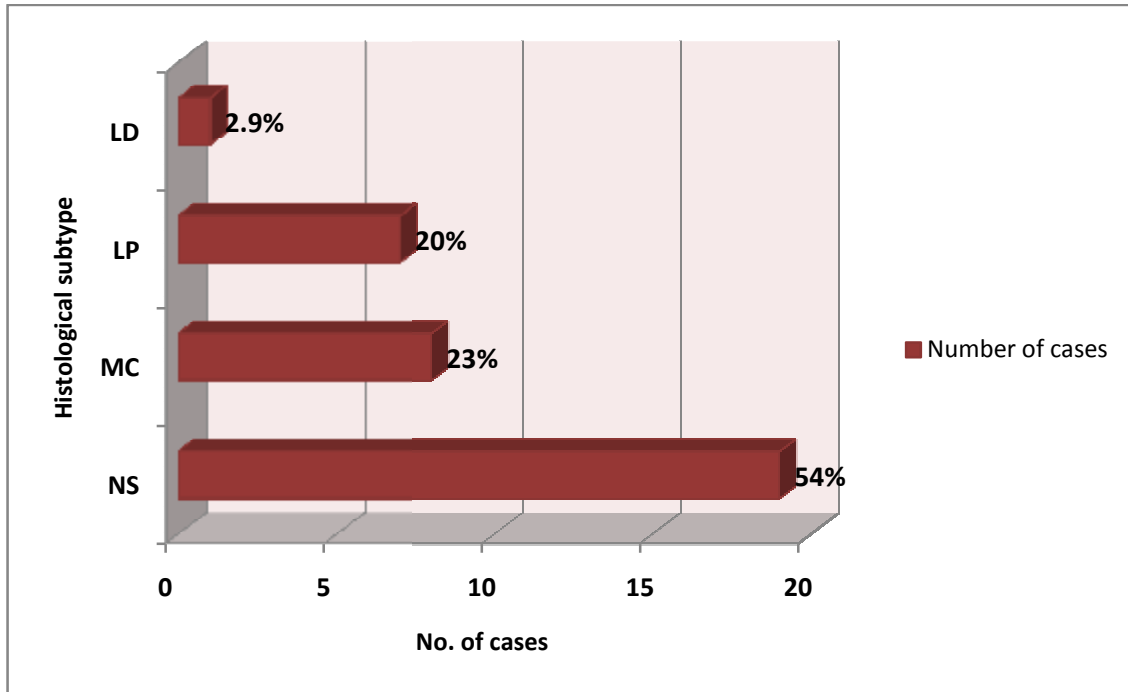
- *Burkitt's lymphoma cases showed a rise in numbers from 2004 to 2007, only to decrease over the next 4 years. There were 3 cases diagnosed in 2013.*
- *Graph-10: Compares BL with Non Hodgkin's non Burkitt's lymphoma over the period between 2001 and 2013.*



***Graph -10: Distribution of NHL subtypes by year of diagnosis.***

***NHNBL: Non Hodgkin's non Burkitt's lymphoma, BL: Burkitt's lymphoma***

- Nodular sclerosis formed over half the total number of cases with 19 cases, followed by mixed cellularity with 8 cases. Graph -10 shows the percentages of each type.
- 4 cases had limited data in their files and so were removed.

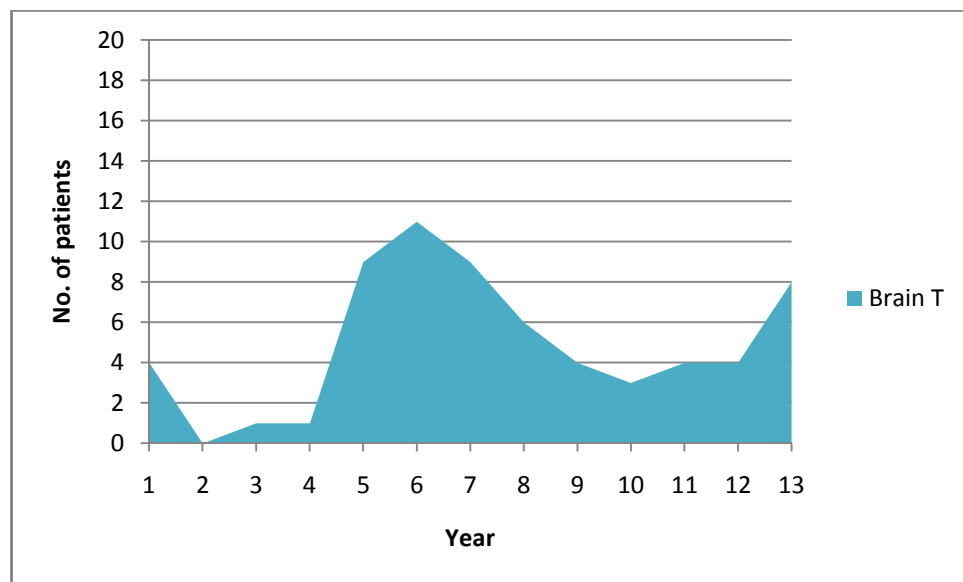


**Graph -11: Distribution of HL cases (n=35) according to histopathology.**

NS: Nodular sclerosis MC: Mixed cellularity LP: Lymphocyte predominant LD: Lymphocyte depletion.

## 6-7. Brain tumours

- Brain tumours are the third most common tumour in our study, 67 cases (12%).
- The pattern of brain tumours, as shown in graph -12, rises significantly to reach a peak of 11 cases in the year 2006, descends to 3 in 2010 and ends at 8 in 2013.



**Graph -12: Distribution of brain tumours (n=67) by year of diagnosis**

### **Histopathological classification of brain tumours:**

- Medulloblastoma is the most common type of brain tumour 38% (25), the second most common tumours are astrocytomas 26% (17).
- Others include; ependymoma, unspecified glioma and ganglioneuroma.
- Gliomas include; optic gliomas, pontine and unspecified glioma are highly malignant brain tumours that are undifferentiated into either astrocytomas or medulloblastomas.
- 5 of brain tumours were not histopathologically classified.

**Table -8: Histopathological classification of brain tumours.**

<b><i>Histopathological type</i></b>	<b><i>No</i></b>	<b><i>%</i></b>
<i>Medulloblastoma</i>	<i>25</i>	<i>38%</i>
<i>Astrocytoma</i>	<i>17</i>	<i>26%</i>
<i>Ependymoma</i>	<i>9</i>	<i>14%</i>
<i>Craniopharyngioma</i>	<i>1</i>	<i>1.5%</i>
<i>Glioma</i>	<i>6</i>	<i>9%</i>
<i>Ganglioneuroma</i>	<i>2</i>	<i>3%</i>
<i>pinealblastoma</i>	<i>2</i>	<i>3%</i>
<i>Unclassified</i>	<i>5</i>	<i>7%</i>
<i>Total</i>	<i>42</i>	<i>100%</i>

### **6-8: Neuroblastoma**

- *A total of 49 cases (9% of malignancy) of neuroblastoma were recorded in our study.*
- *80% of neuroblastomas presented with abdominal tumours.*

### **6-9: Wilm's tumour, Osteosarcoma, Retinoblastoma and others:**

- *Wilm's tumour represents 10% of the total cases (58 cases).*
- *55% of bone tumour were Osteosarcomas*
- *10% of Retinoblastoma patients had bilateral tumours.*
- *Cases of hepatocellular accounted for 1% of this study.*

### **6-10 .Analysis according to site:**

- *The most common site for tumours to arise from is the head and neck with around 39% of the sites (144/368). It is the most common site for lymphoma; with 64% of HL 25/39 and 49% of NHL cases presenting with head & neck tumours.*
- *The second most common site of tumours is the abdomen with 34.5% (127/368)*
- *49% of abdominal tumours were Wilm's tumours and 30% were Neuroblastomas.*
- *Nearly half of pelvic tumours were germ cell tumours (10 of 21).*

**Table -9: Distribution of solid tumours by their site.**

<b>Type</b>	<b>Head &amp; Neck</b>	<b>Chest</b>	<b>Abdomen</b>	<b>Pelvis</b>	<b>Limb</b>	<b>Total</b>
<i>Hodgkin's</i>	25	14	8	4	0	51
<i>Non-Hodgkin's</i>	19	7	11	1	0	38
<i>Wilm's tumor</i>	0	0	58	0	0	58
<i>Brain tumors</i>	67	0	0	0	0	67
<i>Neuroblastoma</i>	4	8	42	1	0	55
<i>Bone tumours</i>	0	9	0	1	27	37
<i>Retinoblastoma</i>	19	0	0	0	0	19
<i>Rhabdomyosarc.</i>	6	2	2	5	5	20
<i>Germ cell tumors</i>	0	0	0	10	0	10
<i>Hepatoblastoma</i>	0	0	5	0	0	5
<i>Nasopharyngeal Ca</i>	3	0	0	0	0	3
<i>Others</i>	1	0	1	1	2	5
<b>Total</b>	<b>144</b>	<b>40</b>	<b>127</b>	<b>23</b>	<b>34</b>	<b>368</b>

*Others include: Liposarcoma, Desmoid tumour, Epitheloid sarcoma, Adrenal carcinoma and Ameloblastic carcinoma.*

### 6-6-2. Analysis according to stage

- A third of WT patients were diagnosed at stage III
- 64% of neuroblastoma cases are discovered at stage IV
- The stage of 1 neuroblastoma case was not registered in the files.

**Table- 10: Distribution of patients by stage of malignancy.**

Type of malignancy	stage								Total
	I	%	II	%	III	%	IV	%	
Lymphoma	5	6%	24	31%	29	37%	20	26%	78
Wilm`stumor	8	13.8 %	16	27.6%	20	34%	14	24%	58
Neuroblastoma	2	2%	5	11%	10	23%	30	64%	47



## **7. DISCUSSION**

The trend of childhood cancers around the world is different for developed countries than the developing ones. Developed countries show Leukaemia to be the most common childhood cancer followed by brain tumours and then lymphomas (37,38). In developing countries a high incidence of lymphoma has been noted, making it the second most common tumour after leukaemia or in some studies in Africa it was even found to be the commonest tumour.(58)

The distribution of the various haematological malignancies in Australia corresponded to the picture described for developed countries with leukaemia forming (34%), central nervous system tumours (23%) and lymphomas (10%) (18). Also following this pattern were childhood cancer statistics in China where between 2000 and 2009 in Beijing the most common diagnoses were leukaemia (39.64%), followed by central nervous system (CNS) tumours (17.90%) and lymphoma (7.14%)(22). This was also true in correspondence with a German study of Europe that showed; leukaemia, at 34%, brain tumours, at 23%, and lymphomas, at 12%, represented the largest diagnostic groups among the under 15-year-olds (21).

A Yemeni study followed the pattern of developing countries where, the most frequent cancer among Yemeni children was leukaemia (33.1%) followed by lymphoma (31.5%), CNS tumours (7.2%) and bone tumours (5.2%) (17).

In our study, although Leukaemia corresponded with the pattern of being the most common tumour, at (38%) its incidence was higher than that registered in Australia, Europe and Yemen but was similar to the findings in China (18,21,17,22) . We also found that Lymphoma at 14% (n=78), formed the second most common cause of cancer in under 15 year olds. It shows similarity in the order of the diagnostic groups to that of Yemen's but forms a much lower percentage of the overall.

In contrast to Europe and Australia where Brain tumours formed the second most common malignant tumour in childhood at 23% (21,18), our study showed it to come

third in order with a much smaller percentage (12%). It is possible that these cases, as with other solid tumours that require specialized surgery, are most likely underestimated as they are likely to travel abroad or require surgery provided in other hospitals and are therefore not included in the full count.

In a previous study performed in our hospital between 1996 and 1999 it was found that the most common malignancies were, in order: leukaemia, lymphoma and brain tumours.<sup>(59)</sup>

Data suggests an increase in cases of childhood cancer in general <sup>(39,40)</sup>. All childhood cancers combined increased during a Chinese study with an Annual Percent Change (APC) of 5.84% <sup>(22)</sup> In children (0-14 years) an increase in malignant cancer incidence was observed until 1997 (APC: +3.2%), followed by a plateau (APC: -1.1%) <sup>(22)</sup>. In our study however, the average annual percentage change was much higher at (10%), the APC varied greatly over the study period from an APC of (96%) between 2004 and 2005 to an APC of (-13.5%) between 2007 and 2008.

There was more than a 2 fold increase in the number of patients from the beginning of the study to the end in 2013. From 26 cases diagnosed in the year 2001 to 60 in 2013. This is an increase of 130% in total. Although the number of admissions showed a significant rise in general, in proportion to the total number of cases admitted to the hospital each year there was very little change from 31% in 2001 to 34% in 2013.

In relation to age, studies showed that the highest incidence of malignancies occurs in children < 5 years old <sup>(42,43,44,45)</sup>. A study in Australia found that the highest incidence was at 1-4 years old <sup>(18)</sup>. In agreement with this, our results gave use a peak age of 2 years old with 12% of cases presenting at that age and more than half of the patients of ages between 0-5 years. This also runs in accordance with a previous study done in our hospital where most of the cases were in the preschool age group, nearly 43% were below the age of 4 years.<sup>(59)</sup> Whereas in contrast to these findings a study in west Kenya showed the group aged 6–10 years contained most children (29%)<sup>(20)</sup>. The small number of patients in the 15 year old age group may be due to the patients following up in other hospitals with physician rather than paediatricians.

6.3% of the patients were diagnosed with cancers in the first year of life, this is slightly lower than the finding of the previous study which showed 8.5% in this age group <sup>(59)</sup>.

Studies on childhood cancers in the first year of life showed that neuroblastoma was the most commonly diagnosed neoplasm in the US and in Spain <sup>(46,47)</sup> . In contrast, this study, as well as, a study done in Taiwan gave the top cancer subtype in the first year of life as leukemia <sup>(48)</sup>.

The top five cancer subtypes in infancy in our study were: leukemia in 12 infants (26%), neuroblastoma in 11 (23.9%), wilm's tumour 8 (17.3%), retinoblastoma in 6 (13%), brain tumor in 5 (10.8%), rhabdomyosarcoma 2 (4.3%) and germ cell tumors as well as lymphoma each with 1 case each (2.2%).

According to several studies acute lymphoblastic leukemia peaks in children aged 1-4 years <sup>(45,49,61)</sup>. The incidence of ALL among 2-3 year olds is approximately 4-fold greater than that for infants <sup>(45)</sup>. Similar findings were found in our results with a peak age for leukemia patients at 2 years, 15.5% of cases.

In this study, lymphoma patients ranged from 6-15 years with a mean age of 7.7. NHL patients had a mean age of 7.3 and 5.8 for Non-Hodgkins Non-Burkitt's lymphoma and Burkitt's lymphoma respectively and also a peak age of 8 years and 5.5 years respectively. It was observed in a Karachi study that the mean age of childhood lymphoma was 7.9 years in males and 8.4 years in females <sup>(32)</sup>. The risk for non-Hodgkin's Lymphoma had a high peak in the 5-9 year age group. Again in Karachi the youngest male patient was 2 years and the youngest female patient was 3 years; the oldest male and female children were 14 and 13 years respectively <sup>(32)</sup>. Similarly in this study the youngest non-Hodgkin's lymphoma patient was 1 and the oldest 14 years old.

Studies showed that that highest frequency for brain tumours occurred from 0-4 years old. The general age distribution in Kuwait was as follows: 0-4 years (32.89%), 5-9 years (30.26%), 10-14 years (17.11%) <sup>(28)</sup>. Contrary to that the most affected age group in a Cairo study was 5-9 years old (43.2%) <sup>(30)</sup>. Our findings agreed with the Kuwait with the 0-4 year olds representing 39% of cases, followed closely by 5-9 year olds with 35%, the 10-14 year olds with 24 % of cases and only 1.5% of cases at age 15 years.

A UK study showed that NB was highest in the less than 1 year old age group, followed by the group of children between the ages 1–4 years <sup>(27)</sup>. Following the findings of the UK study, we found that the highest age group was that of children under one year of age (21.5%) with (84%) of cases 5 years old or less.

In this study bone tumours had a peak age of between 10-14 years, malignant bone tumours in the UK were also mainly diagnosed in 10-14 year-olds. Similarly, other studies showed a peak age of 13 years. This maybe due to a correlation between bone tumours and pubertal development <sup>(54, 55, 56)</sup>.

Overall cancer is more common in males than in females. In studies done in both Yemen and Nigeria the M:F ratio was found to be 1.5:1 <sup>(17,19)</sup>. In another study done in Western Kenya the M:F ratio was 1.4:1<sup>(20)</sup>. Similarly, in our study the ratio was 1.4:1 with 335 males (58.7%) and 233 females (41.3%).

An unusual finding in a Yemeni research was the frequency of acute myeloid leukaemia being twice more common in female than male <sup>(17)</sup>, while in our study there was a slight male preponderance at 1.1:1.

According to a study in Kuwait the brain tumour boys/girls ratio was 1.03 in childhood <sup>(17)</sup>. Whereas in another study done on brain tumour demographic pattern over a ten-year period in the Kashmir Valley in children (2000-2009) the male-to-female ratio was 1.4:1 <sup>(31)</sup>. Our study was similar to the findings in the Kashmir valley with 40 male and 27 female, giving a ratio of 1.5:1.

Female predominance was found in Histiocytosis with a M:F ratio of 1:1.5 albeit in only 5 patients.

In retinoblastoma and wilm's tumour, Kuwait reported a predominance in females whereas in neuroblastoma, hepatoblastoma and soft tissue sarcomas in male <sup>(17)</sup>. This is in contrast to our study where retinoblastoma males outnumber females with a ratio of 1.4:1 and wilm's tumour with a ratio of 1.3:1. In this study, the males also outnumber females in neuroblastoma, hepatocellular carcinoma, nasopharyngeal carcinomas and germ cell tumours.

We found a slightly larger proportion of patients came from sub-urban and rural areas with (53.7%). This is seen even more pronounced in a report done in central

Sudan where most of the children admitted with cancer came from the rural areas (66.1%) compared to 33.9% from urban areas <sup>(41)</sup>.

Leukemia in our study had an almost equal urban to rural distribution, with 50.2% of cases coming from Benghazi. This is slightly lower than shown in a previous study performed in the Benghazi children's hospital which covered the period between 1994 – 2001. Their results showed that 53.5% of the patients diagnosed with leukaemia were from Benghazi <sup>(60)</sup>.

In a recent study in Mexico acute lymphoblastic leukemia (ALL) was the most frequent type of leukemia, constituting 85.1% of the cases, followed by acute myeloblastic leukemia at 12.3% and chronic myeloid leukemia at 1.7% <sup>(49)</sup>. Similarly we found that ALL formed just less than 80% of the total leukaemia patients, although AML constituted a higher percentage with 21% of the overall and CML at 1%. This corresponds also to the study performed in this hospital between 1994-2001<sup>(61)</sup>.

Incidences of acute myeloid leukemia overall, acute lymphoblastic leukemia overall, and specific acute lymphoblastic leukemia immunophenotypes have been stable in the Nordic countries <sup>(26)</sup>. In contrast we found that the number of ALL and AML patients rose greatly over the last 13 years; from 9 cases diagnosed in 2001 to 30 in 2013.

In contrast to other studies <sup>(50)</sup> in this study, Hodgkin's lymphoma and Non Hodgkin patients were equal with 39 cases each (50%). It was observed in a Karachi study that there was a slow upward variation in the annual incidence of NHL <sup>(32)</sup>. Whereas in our findings there was no obvious pattern to the number of NHL cases.

In northern Nigeria, Burkitt's lymphoma accounted for the number one cause of malignancy with 27.01% of the cases and non-Hodgkin's non-Burkitt's Lymphoma (9.42%) <sup>(19)</sup>. In contrast, our cases showed lymphoma in general to form the second most common cause with (14%) of these (21%) only was Burkitts lymphoma, (28%) non-hodgkins non-Burkitt's lymphoma and (51%) was Hodgkin's lymphoma.

A relatively high frequency of primary brain tumours was observed in childhood and adolescence in Kuwait, of these, the most common brain tumors were

astrocytoma (37%), embryonal tumours (31%), ependymoma (8%)<sup>(28)</sup>. Also in the Departments of Pediatric Neurosurgery of the Cairo University Hospitals finding showed the most common intracranial tumours to be astrocytomas (35%), medulloblastomas (18.8%), craniopharyngiomas (11.3%) and ependymomas (10%)<sup>(30)</sup>. In contrast to this our results found that the most common brain tumour was medulloblastoma with 25/67 forming (38%); this was followed by astrocytomas (26%), ependymoma (14%).

A UK study showed 6-10% of all childhood cancers were neuroblastomas <sup>(27)</sup>. This confirms the findings of our study where NB formed 9% of the overall cancers recorded.

Bone tumours formed 5% of our cases; the most common type being osteosarcoma 55% with Ewing's and other bone sarcomas forming the remaining percentage. Malignant bone tumours in the UK account for around a tenth (9%) of all cancers diagnosed in 10-14 year-olds. This is slightly higher than our study's findings. There study also showed the most common types of malignant bone tumours to be osteosarcoma (55%) and Ewing tumour and related bone sarcomas (39%) <sup>(54)</sup>.

Primary hepatic neoplasm are a rare embryonal tumor it account only 1-2% from all childhood cancer with two third Hepatoblastoma and one third Hepatocellular carcinoma (HCC) 85% diagnosed before 5th year of age <sup>(57)</sup>. In agreement with this our cases of hepatocellular accounted for 1% of our total case.

The most frequent sites for tumours to develop in the body were the head and neck 144/368 followed by the abdomen 127/368. Over half of lymphoma patients presented with head and neck tumours (56%), just over a quarter with chest tumours (26%) and only (15%) presented with either abdominal or pelvic tumours.

In both of subtypes of lymphoma the most site of lymph node involvement was cervical with 25/39 patients and 19/39 patients respectively while the mediastinal lymph node involvement was more in Hodgkin lymphoma with 14/39 patients in contrast to NHL were only 7/39 of cases had mediastinal lymph node involvement .

Others found the most frequent anatomical site for neuroblastoma was abdomen (60%), pelvis (6%), neck (2%) and chest (15%) <sup>(51)</sup>. In our study however neuroblastoma's most frequent site was the abdomen (85%), followed by the chest (16%), the head and neck (8%), the pelvis (2%).

Around the world it is estimated that 90000 children die from cancer each year due to parental ignorance and poverty as well as poor health facilities. It has also been estimated that more than 85% of childhood cancers occur in resource poor countries <sup>(52)</sup>. Most patients with solid tumours in this study presented late at either stage III or IV. 63 % of Lymphoma patients, 58% of Wilm's tumours and 87% of neuroblastoma patients presented in stage III or IV at the time of diagnosis, this was also seen in a Mexican study where 88% of neuroblastoma patients presented in stages III and IV while in other studies just one third of their patients presented at this stage <sup>(50, 53)</sup> .

## ***8.CONCLUSION***

- Leukaemia, lymphoma and brain tumours are the most common malignancies in children.
- There was an obvious increase in the total number of annual cases diagnosed per year.
- Brain tumours and other solid tumours may have been underestimated due to patients travelling abroad and following surgical departments.
- The pattern of childhood malignancies showed the pre-school age group to have the highest frequency of cases.
- The number of male patients outnumbered females.
- More than half of patients were from outside Benghazi.
- Most of solid tumour patients presented at late stages.



## ***9. RECOMMENDATION***

- Establishment and maintaining a national registry of childhood malignancies for conducting further studies in the whole country is paramount.
- Updating the haematology department with an electronic database and networking it with the clinic is an essential step.
- Establishment of Haematology Oncology Centres in the east to give good health serves in those areas.
- Providing all the up to date and essential laboratory investigations needed for proper diagnosis.
- Updating laboratory technicians on the needed tests and techniques is of vital importance.
- Educating the population concerning how to know the signs of malignancy for early detection to improve the outcome.

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## 11. الملخص

### ■ الأهداف

- لقياس أنواع واتجاهات السرطان في مرحلة الطفولة.
- لوصف الوضع الديموغرافي لسرطانات الأطفال من حيث المتغيرات الوبائية.

### ■ المرضى والطرق

دراسة مقطعية بأثر رجعي، أجريت بين عامي 2001 و 2013، حيث تم الحصول على البيانات إما من السجلات الطبية لجميع المرضى الذين تم إدخالهم خلال فترة الدراسة لقسم / الأورام وأمراض الدم في مستشفى الأطفال في بنغازي أو من قسم الإحصاء. وشملت البيانات؛ (المرضى التركيبية السكانية، والفحص البدني والمعملي).

### ■ النتائج

كان الورم الأكثر شيوعا في الجزء الشرقي من ليبيا سرطان الدم (38%) (568/219)، وتبع ذلك سرطان الغدد الليمفاوية (14%) (568/78) وأورام الدماغ (12%) (568/67) على التوالي. لوحظ ارتفاع عدد المرضى خلال فترة الدراسة. حالات الأورام الخبيثة بلغت ذروتها في سن السنتين ولوحظ جزء كبير من المرضى هم من الفئة العمرية ( سن ما قبل المدرسة). كان سرطان الدم ( Leukaemia ) والأورام العصبية (Neuroblastoma) الأورام الأكثر شيوعا في المرضى أقل من عمر السنة الواحدة . نسبة الذكور إلى الإناث 1.4: 1 يدل على غلبة الذكور . لوحظ نسبة أعلى قليلا من الحالات التي تقيم في مناطق الضواحي والمناطق الريفية (53.7%). كما ان هناك نسبة كبيرة من الأورام الصلبة شخّصت في المراحل المتأخرة (III، IV).

### ■ الإستنتاج

يمكننا أن نستنتج أن سرطان الدم، سرطان الغدد الليمفاوية وأورام الدماغ هي الأورام الخبيثة الأكثر شيوعا في الأطفال، من هذه الأورام الصلبة ( Solid Tumours ) قد تم التقليل من شأنها. كان هناك زيادة واضحة في عدد الحالات السنوية التي يتم تشخيصها سنويا، حيث كان أعلى تواتر للحالات في الفئة العمرية ما قبل المدرسة. الحالات من الذكور يفوق عدد الإناث، ومعظم مرضى الأورام الصلبة تم تشخيصها في مراحل متأخرة من المرض.