RESEARCH ARTICLE

Epidemiologic Survey of Infantile Cancer in Iran based on the Data of the Largest Pediatric Cancer Referral Center (Ali-Asghar Children Hospital), 1996-2005

Gholamreza Bahoush-Mehdiabadi[1]*, Roshanak Habibi[2], Ahmad Shariftabrizi[3], Parvaneh Vossough[1]

Abstract

Background: Cancer in infants younger than one year of age represents a unique problem with distinct epidemiological, clinical and genetic characteristics compared with older age groups. No report is yet available from Iran regarding epidemiological and survival rate of cancers diagnosed in this age group. Materials and Methods: The population under study comprised of patients which were diagnosed and admitted to Ali-Asghar hospital between years 1996-2005. In total, 287 infants were included in the retrospective descriptive survey. Patient files were evaluated for age of patient at the time of diagnosis, sex, geographical residence, consanguinity of parents, histological diagnosis, site of cancer involvement, type of therapy, date of last follow-up and cause of death (if applicable). Results: The average age at the time of diagnosis was 7.2 months old. The most frequent malignancy was retinoblastoma (44%), followed by leukemia (19%) and neuroblastoma (10%), with five-year overall survival rates of 77.7%, 41% and 90%, respectively Parents of 40 infants (13.9%) had consanguinity relationships. Conclusions: Although we cannot make any conclusions regarding the incidence of infant cancer subtypes based on this study, survival rates for major types were similar to the developed countries, which signifies strict adherence to standards of care in Ali-Asghar hospital, the main infant cancer care centre in Iran. A Childhood Cancer Registry with high-resolution data collection and also advanced genetic testing is advocated for in-depth analysis of variation in incidence and survival.

Keywords: Infant cancers - epidemiology - pediatric cancer referral center - Iran

Asian Pac J Cancer Prev, **15 (3)**, 1211-1217

Introduction

Cancer among infants comprises 10 percent of all diagnosed malignancies in children under the age of 15 years old (Kliegman et al., 2007). Due to the unique clinical, genetic, and epidemiologic characteristics of cancers in infants (Dreyer et al., 2012; Gurney et al., 1997), it is increasingly recognized that the study of infant cancer may lead to further understanding of the mechanisms of carcinogenesis. The major types of embryonal tumor, i.e. neuroblastoma, retinoblastoma, nephroblastoma (Wilms' tumor), and hepatoblastoma, occur mostly in infants and young children. The same histologic subtype of cancer has a different outcome in infants and in older children. Infant leukemia may have a dismal prognosis in infants while most children with acute lymphoblastic leukemia (ALL) diagnosed beyond infancy can be cured. Infants with neuroblastoma have much better survival than older children with the same kind of cancer (Swaminathan et al., 2008). The probability of survival for a child with cancer has improved greatly over the last half century. In the early 1960s, approximately 30% of children with cancer survived their disease. By the mid 1980s, about 65% of children with cancer were cured; that rate increased to nearly 75% by the mid 1990s. Currently, survival for children with cancer approaches 80% (Davidoff, 2010).

We based this study on a similar valid survey in the United States called SEER Programs, which is widely referred to by pediatric oncology researchers and authors (Li et al., 2008). From 1975, the Surveillance Epidemiology and End Results (SEER-9) tumor registry program has collected information about all incident cancer patients from 9 geographic areas. Cancer incidence and survival among children and adolescents diagnosed between 1975 and 1995 and the epidemiology of cancer in older adolescents and young adults' ages 15 to 29 years diagnosed between 1975 to 2000 have been reported as two monographs (Gurney et al., 1997; Li et al., 2008). We also tried to compare results between different countries and centers to see how our results compare to the results of other centers\countries, especially regarding survival

*[1]Department of Pediatrics, Onco-Pathology Research Center, [3]General Medicine, Ali-Asghar Children Hospital, Iran University of Medical Sciences, [3]Farzan Clinical Research Institute, Tehran, Iran *For correspondence: bahoush04@eurocord.org*

which can be considered as a marker of the quality of the medical care provided.

Materials and Methods

The population under study comprised of patients which were diagnosed and admitted to Ali-Asghar hospital between years 1996-2005. In total, 287 infants younger than one year old age were included in the study. We used a non-randomized simple sampling for patient recruitment as this was a retrospective study and we planned to include all patients. Patients' files were evaluated for age of patient at the time of diagnosis, sex, geographical residency, consanguinity of parents, histological diagnosis, site of cancer involvement, type of therapy, date of last follow-up and cause of death (if applicable). The study was a retrospective descriptive survey.

Important data were transferred from original files to a standard checklist, one for each patient. Data were analyzed using SPSS 17.0 software. For epidemiological and descriptive analysis, central tendency indicators like Mean and also dispersion indicators such as confidence interval (CI) and Standard error of means (SEM) were used. Analytical tests such as Kaplan-Meier and Log rank were used for survival analysis.

During the entire study, patients' information was remained confidential. Research team members were aware of the details of Helsinki statement about ethic principles in medical research and were strictly committed to follow them in this research study.

Results

There were 287 infant (younger than one year of age) cancer cases admitted to Ali-Asghar Children Hospital between 1996-2005 and all of them had complete files for epidemiologic analysis. The sex distribution of these infants was almost equal, with 49.3% males and 50.7% females. The average age of infants at the time of diagnosis was 7.2 months old (95% CI= ± 6). Only 29% of patients were living locally in the Tehran province, which shows the referral nature of enrolled patients.

Overall picture

The most frequent malignancy was retinoblastoma accounting for approximately 44% of all infantile malignancies (see Figure 1).The second and third most frequent malignancies in this center were leukemia (19%) and Neuroblastoma (10%), respectively (Graph-2). The consanguinity status of parents for 187 infants could be determined; parents of 40 infants (13.9%) had consanguinity relationship with each other. Among 127 infants with retinoblastoma, 98 cases had complete files for parent's consanguinity status, where 23 of them (18%) had consanguineous parents. Also, among 30 infants with neuroblastoma, 20 infants had complete files for consanguinity determination, where 8 of them (26%) had consanguineous parents.Two major causes of death in this group of children were infection (51%) and disease complications (41%).

There was approximately 30% difference between male and female infants in 5-year overall survival rates. It seems that male infants had better survival rates than females (77% (SEM=6%) versus 51%(SEM=12%)). But the difference was not statistically significant (p=0.24) .

Survival for infants with retinoblastoma was favorable in our study (77.7% (SEM=8.3%)) (Figure 2). Fifty six percent of infantile retinoblastomas were bilateral. Frequency of retinoblastoma in female and male infants was almost equal. Most of the infantile retinoblastomas were diagnosed in stage 1 and 2 according to the pathologic staging. The 5-year overall survival rate for all infants with ALL was approximately 41% (SEM=8%). Acute Lymphoblastic Leukemia (ALL) was the most frequent type of Leukemia in infants (75.4% compared to 24.6% for Acute Myelogenous Leukemia (AML)). Approximately 53.5% of infants with ALL were female and 46.5% of them were male. Also, 78.6% of infants with AML were female and 21.4% of them were male. The 5-year overall survival rate for infantile neuroblastoma in our study was 90% (SEM=6%). The sex distribution for this cancer was equal. Most of the infantile neuroblastomas were in stage 4, at the time of diagnosis. 5-year event free survival (EFS) rates for retinoblastoma, ALL and neuroblastoma was 30%, 37% and 74%, respectively

Retinoblastoma

Retinoblastoma was the most frequent infantile malignancy in our study; accounting for approximately

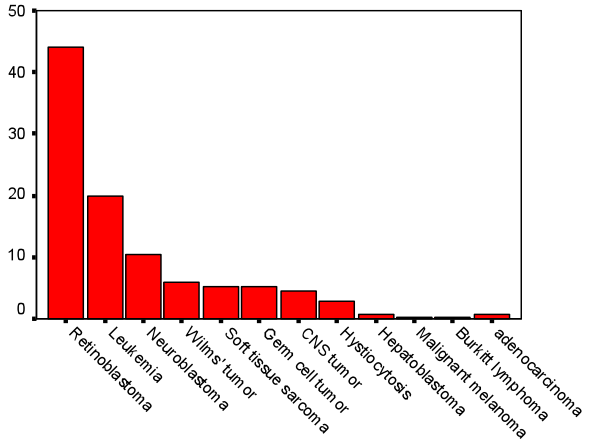

Figure 1. Histopathological Types of Tumors in Infants

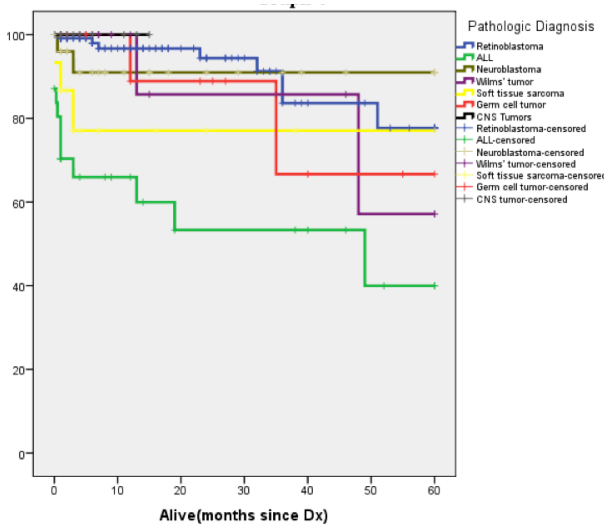

Figure 2. Cumulative Survival of Infant Cancer Cases

44.1% of cancers developing in the first year of life. Approximately 56% of infantile retinoblastomas were bilateral. Frequency of retinoblastoma in female and male infants was almost similar, as it was 49.6% and 50.4% respectively. The average age of infants with retinoblastoma at the time of diagnosis was 6.96 months (95% CI=6.36-7.56). Most of the infantile retinoblastomas were diagnosed in stage 1 and 2 (40.9% and 40.2%, respectively). Staging was based on surgical classifications. Over the ten year period of our study, frequency of retinoblastoma diagnosis remained relatively stable. In this period (1996-2005), the 5-year overall survival rate was 77.7% (SEM=8.3%, Graph-4).The 5-year overall survival rate for unilateral retinoblastoma was better than bilateral type, 92% (SEM=5) versus 68% (SEM=11). However this difference was not statistically significant (p=0.48). The 5-year overall survival rate for male infants with retinoblastoma was better than females (85% (SEM=5) versus 65% (SEM=2)) respectively, but the difference was not statistically significant (p=0.16). The 5-year event free survival rate was 30 % (SEM=8.4%).

Leukemia

Overall, 19.8% of cancer-diagnosed infants had Leukemia, making it the second most frequent infantile malignancy (Graph-2). Acute Lymphoblastic Leukemia (ALL) was the most the frequent type of Leukemia in infants (75.4%) as compared to the Acute Myelogenous Leukemia (AML) (24.6%). Approximately 53.5% of infants with ALL were female and 46.5% of them were male. Also, 78.6% of infants with AML were female and 21.4% of them were male. The average age of infants with Leukemia at the time of diagnosis was nine months old (95% CI=±6.36). In this period (1996-2005), 5- year overall survival rate in infants with ALL was 40.0% (SEM= 14.1%, Graph 4).The 5-year overall survival rate in female infants with ALL was 44% (SEM=20%) versus 41% (SEM=16%) in males, but the difference was not statistically significant (p=0.48). Because of too many lost-to-follow-up cases for AML and the small number of cases for this type of leukemia, we could not report any 5year survival rate for this type of leukemia. The 5-year event-free survival rate for infantile ALL was 37.3% (SEM=14.1%).

Neuroblastoma

During the 1996-2005 time period, 30 infants were diagnosed with Neuroblastoma (about 10.4 %), making it the third most frequent infantile malignancy in our study (Graph-2). As it was expected, neuroblastoma most commonly presented in the abdominal region (76%). Of infants with neuroblastoma, 53.3% of them were male and 46.7% of them were female (p=0.71). Most of patients with neuroblastoma were in stage 4 at the time of diagnosis (38%). The average age of infants with neuroblastoma at the time of diagnosis was 6.7 months (95%CI=6.7±7.8). The 5-year overall survival rate for infantile neuroblastoma in our study was 90.9% (SEM=6.2%). The 5-year event free survival for infantile neuroblastoma was 74.1% (SEM=12%.

Wilms' Tumor

In our study, all of the infant malignancies involving the kidney were Wilms' tumor. Seventeen infants were diagnosed with Wilms' tumor (5.9%), nine of them were female (52%) and 8 of them were males (48%). The average age of infants at the time of diagnosis was eight months old (95%CI=±6). At the time of diagnosis, the rate of unilateral kidney involvement was equal to bilateral involvement. The 5-year overall survival rate for infantile Wilms' tumor in our study was 57.1% (SEM=24.9%; Graph-4).The 5-year event-free survival rate for this tumor was 40.0% (SEM=19.9%; Graph 5).

Soft tissue sarcomas

Fifteen infants were diagnosed with Soft tissue sarcoma (STS), which was 5.2% of all malignancies in our study. The most common malignancy in this group was Rhabdomyosarcoma with 10 cases. Other tumors were Spindle cell tumor (4 cases) and Mucoepidermoid carcinoma (1 case). Nine infants with STS were female, and six of them were male. Head and neck was the major site of involvement. The 5-year overall survival rate for infants with STS in this study was 77% (SEM=12%).

Germ cell tumors

Fifteen infants were diagnosed with Germ cell tumor, which was 5.2% of all malignancies in this group. The two major malignancies in this group were Yolk sac tumor (9 cases) and immature Teratoma (6 cases). Nine of infants with Germ cell tumor were male and 6 of them were female. Pelvis was the major site of involvement. The 5-year overall survival rate for infants with Germ cell tumor in this study was 66.7 % (SEM= 20.8%).

Central nervous system tumors

Thirteen infants were diagnosed with CNS tumor, which was 4.5% of all malignancies in this group. Regarding the site of brain involvement, eight infants had supratentorial tumors and 5 of them had infratentorial tumors. Eight of infants with CNS tumors were male and 5 of them were female.The 5-year overall survival rate for infants with CNS tumor in this study was 100% and all of them were alive 5 years after diagnosis.

Discussion

The distribution of malignant disease in infants is quite different from that which is found in older children, adolescents, or adults. For instance, embryonal tumors such as neuroblastoma, Wilms' tumor, retinoblastoma, and hepatoblastoma are more prevalent in infants than other age groups. The descriptive epidemiologic data that is presented here may serve to stimulate ideas for further etiologic research into the multi-factorial nature of cancer occurrence. As evidence, the original two-hit theory for carcinogenesis was developed primarily from clinical observations of a higher frequency of bilaterality of retinoblastoma in infants than in older children (Knudson et al., 1971; Pollock et al., 2012). The study of infant cancer can aid in developing new hypotheses related to how aberrant genetic processes,

early developmental abnormalities and gene-environment interactions contribute to the carcinogenic process. The study of retinoblastoma, and later of Wilms' tumor, led to the discovery of two important tumor suppressor genes that are related to adult as well as pediatric malignancies (Malkin et al., 1994). Recent work has shown that hematologic malignancies manifest differently in infants than in older children (Pui et al., 2012). All these factors speak for the importance of further research into the epidemiology and biology of cancer in very young children.

Based on literature malignancies of infancy represented 10% of all cancers that was diagnosed among children younger than 15 years of age in United States of America (Li et al., 2008). Similar results were reported from Iran, such as a large epidemiologic evaluation performed in recent years in Ali-Asghar hospital by Dr Bahoush et al., in which the frequency of infantile malignancy was approximately 7% (Bahoush et al). The rate among females was essentially the same as that of males. The outlook in this age group depends mainly on the pathology diagnosis. Neuroblastoma and renal tumors have a better prognosis, whereas brain tumors and leukemias are very aggressive diseases with a very poor prognosis. Acute lymphoblastic leukemia (ALL) in infants is a unique disease comprising 3% of all children with ALL. Malignancies such as Neuroblastoma and Retinoblastoma have a very desirable survival rate in other countries (Bahoush et al., 2013; Li et al., 2008). Unlike the American and European studies in which CNS malignancies was the third most prevalent cancer among infants (Li et al., 2008), in our study CNS tumor was not a very frequent histological type in this age-group, accounting for only 4.5% of cases. In a similar study in Thailand, leukemia was the most prevalent cancer in infants followed by neuroblastoma (Wiangnon et al., 2011).

The frequency of infantile cancer varies geographically. It is higher in Japan (widespread screening for neuroblastoma may be the reason). That tumor is more common in Israel, while the prevalence of retinoblastoma is increased in Sweden. In Sweden, neuroblastoma is by farthe commonest type of cancer in children under 1 year of age followed by leukemia and renal tumors (Vasilatou-KoQsmidis et al., 2003) . According to the results of the Surveillance, Epidemiology, and End Results (SEER) program, incidence rate of all infant cancer combined was 233 per million infants, which was 12% higher than the age (2 years) with the next highest incidence. The rate among females (234 per million infants) was essentially the same as that in males (232 per million infants). Although neuroblastoma represented less than 8% of cancer cases among children younger than 15 years of age, neuroblastoma comprised 28% of infant cancer cases and was the most common malignancy among these young children (65 per million infants) in the SEER study results. The leukemias as a group (41 per million infants) represented the next most common type of cancer, comprising 17% of all cases (Li et al., 2008; Gurney et al., 1997) .It has been reported that in contrast to older children, acute lymphoblastic and acute non-lymphoblastic leukemia, Wilms' tumor and retinoblastoma are more common in female infants (Vasilatou-KoQsmidis et al., 2003; Gurney et al., 1997); we did not observe such a gender difference in our cases.

In our study, very few number of infant cancer cases were diagnosed in the first of month, i.e. neonatal cancer was a rare observation in our cases. While this is a very rough estimation, we can propose that actually neonatal cancer cases were much less frequent in the population as the Ali-Asghar hospital is one of very few referral centers for neonatal and pediatric cancer in Iran. In the Third National (US) Cancer Survey (TNCS), Bader and Miller estimated the prevalence of malignancy in the first month of life to be 36 per million live births, or about 1:27000, while a report from the British Pediatric Pathology Society estimated the prevalence of congenital neoplasia (benign and malignant) between 1:12500 and 1:17300 total births (Lakhoo et al., 2010; Moore et al., 2003). It appears noteworthy that the majority of tumors are sporadic mesenchymal and embryonic in nature (carcinomas being virtually absent), which is similar to reported tumors identified in newborn calves in Europe, suggesting similar causative mechanisms. A variety of tumor types are noted in the neonatal period. Teratomas, especially of the sacrococcygeal region, were most commonly reported followed by neuroblastoma and soft tissue tumors (Lakhoo et al., 2010; Moore et al., 2003).

Retinoblastoma was the most prevalent infantile malignancy (44% of cases) in our study, and the next most common cancer was leukemia with 19% of cases. Unlike our results, in the United States, Neuroblastoma comprised 28% of infant cancer cases and was the most common malignancy among these young children. The leukemias as a group represented the next most common type of cancer, comprising 17% of all cases, similar to other countries (Li et al., 2008). The high prevalence of retinoblastoma is an important point in cancer registry of this center. A possible explanation could be that fact that Ali-Asghar hospital is the major chemotherapy center for patients with retinoblastoma and in the years of study most of the Retinoblastoma cases referred to this center. So we can't generalize this statistical result for the cancer prevalence of infants in this country. Moreover, it can indicate the existence of unknown risk factors for development of this malignancy in Iran that should be surveyed in a separate genetics-directed study. Its peak age of incidence during infancy was in the middle part of the first year of life. The 5-year overall survival rate of retinoblastoma was favorable; it can be due to early detection of this disease by parents, earlier diagnosis in this center (most of the infantile Retinoblastomas were diagnosed in stage 1 and 2) and early enucleation of the involved eye. These results are the same as mentioned in the literature (Li et al., 2008; Aerts et al., 2006; Chung et al., 2007; Dimaras et al., 2012). Retinoblastoma is the most common intraocular malignancy of childhood, occurring at a rate of 1 in 20,000 live births. Iran has approximately 1,000,000 live births annually, this implies that Iran should have 500 new cases of Retinoblastoma in 10 years, so around 50% of the countries' new Retinoblastoma cases had been referred to this center. In 60% of cases, the disease is unilateral and the median age at diagnosis is two years. Of these

cases, 15% are hereditary. All bilateral and multifocal unilateral forms are hereditary. Vital prognosis, related to retinoblastoma alone, is now excellent in patients with unilateral or bilateral forms of retinoblastoma, with a cure rate of 95% in industrialized countries (Aerts et al., 2006). In the past two decades, the focus of therapy has shifted from preservation of life to preservation of sight through the development of focal therapies (Aerts et al., 2006). Regions with greatest prevalence have the highest mortality—40–70% of children with retinoblastoma in Asia and Africa die, compared with 3–5% in Europe, Canada, and the USA. In Canada, mean age at diagnosis is 27 months (SD 18) for unilateral retinoblastoma18 and 15 months for bilateral disease. A delay of more than 6 months from the first clinical sign to diagnosis is associated with 70% mortality recorded in developing countries (Dimaras et al., 2012). Our survival results from Ali-Asghar Hospital was comparable to United States and other industrial countries, which shows the success of screening and treatment programs established in Iran.

Neuroblastoma was the third most frequent infantile cancer in our study; however it is the most frequent type in SEER program reports (Li et al., 2008). In our center, most of the cases were diagnosed in the later stages of the disease. This could be explained by its late detection by parents. But the interesting point was that despite the late diagnosis, the survival rate was excellent (about 90% 5-year survival rate).In the literature, neuroblastoma is reported to be the most common extracranial solid tumor in infancy, accounting for 8–10% of all childhood malignancies. Annual incidence is 1 per 7000 live births. At diagnosis, 36% of patients are under age 1, 75% under age 4, and 90% under age 10 (Pizzo et al., 2012). In our study, 16% of infant neuroblastomas were diagnosed during the first month of life (i.e. neonatal) and 41% during the first 3 months.The most undifferentiated and aggressive neuroblastoma presents in young children (median age 2 years). Localized neuroblastoma and those arising in infants have a 90% survival rate except in cases with Myc-N amplification where survival is below 30% (Fisher et al., 2012; McHugh, 2007). In a retrospective study from our group covering 32 years, we had found similar results in Ali-Asghar hospital(Mehdiabadi et al., 2013) , which was showing much longer survival compared to the older children (only around 46%).

Acute lymphoblastic leukemia cases detected in our study were poor prognosis, with only 41% 5-year survival rate for this type of cancer. Based on SEER program reports, survival is usually poor for malignancies like Leukemia, Rhabdomyosarcoma and CNS tumor in infancy (Li et al., 2008). Acute lymphoblastic leukemia (ALL) in infants under 12 months of age is rare and biologically different from ALL in older children. ALL in infants accounts for about 4% of childhood ALL and differs from ALL in older children with respect to immunophenotypic, cytogenetic, and molecular genetic features. Compared with acute lymphoblastic leukemia (ALL) in older children, ALL in infants has a dismal outcome because rearrangements of the mixed-lineage leukemia (MLL) gene occur in about 80% of these patients, leading to an aggressive type of leukemia. With most recent therapies, about 50% long-term event-free survival is achieved, but early bone marrow relapse remains a major problem(Pieters, 2009; Pizzo et al., 2012).

Wilms' tumor is the second most common malignant retroperitoneal tumor. It is the most common primary renal tumor of childhood. It constitutes six percent of all childhood cancers and is the fourth most common childhood malignancy in the United States. It occurs in 1 out of 10,000 children less than 15 years of age. Nine new cases per million children are diagnosed annually in the United States(Pizzo et al., 2012).The 4-year overall survival rate, and presumed cure, ranges between 86% and 96% for stages I III disease, is up to 83% for stage IV and 70% for stage V disease (McHugh, 2007). In our study, the five year survival rate was lower than the above mentioned statistics, which can be attributed to the diagnosis of Wilm's tumor at higher stages and low clinical suspicion in routine well-child examinations.

Soft tissue sarcomas (STS) are a heterogeneous group of mesenchymal extra-skeletal malignant tumors. The overall incidence of STS is 5.9 per 100,000 persons/year, and this increases with age, rising from 1.6/100,000 in children aged <1 year to 18.2 for individuals aged >70 years. In a recently published study on data from the Surveillance, Epidemiology, and End Results (SEER),STS ranked as the fifth most prevalent malignancy in infants (7.3% of all tumors). Fibrosarcoma patients have the best outcome (5-year survival of 94%), rhabdoid tumors have the worst (5-year survival, 24%) (Ferrari et al., 2012). Rhabdomyosarcoma, a tumor of striated muscle, has the following epidemiologic characteristics: It is the most common pediatric soft-tissue sarcoma. Rhabdomyosarcoma is curable in the majority of children receiving optimal therapy (>70% survival 5 years after diagnosis (Pizzo et al., 2012).

In our study, rhabdomyosarcoma was the most prevalent STS observed in our study, with a favorable prognosis which was similar to the literature data mentioned above. Germ cell tumors accounted for approximately 2–3% of childhood malignancies. The incidence of germ cell tumors is 2.5 per million in white children and 3.0 per million in African-American children under 15 years of age. Germ cell tumors are more common in the ovaries and testes than extragonadal sites (Pizzo et al., 2012). In our study, most germ cell tumors were Yolk sac tumor (9 cases) and teratoma (6 cases), which is similar to that reported by other investigators.

Tumors of the central nervous system (CNS) are frequently encountered in children, brain tumors are the second most common group of malignant tumors in childhood, accounting for 20% of all childhood malignancies. In most children, brain tumors (60–70%) arise from glial cells and tend not to metastasize outside the CNS (Pizzo et al., 2012). Infants are just as frequently affected as older children. At present, a cure for CNS tumors can be achieved in more than 75% of children with a favorable constellation of risk factors. Average-risk medulloblastoma and other PNETs have a 5-year PFS of about 40% in those who received chemotherapy and delayed reduced craniospinal irradiation. This increases to 60% for patients with a gross total resection. Gliomas

may not do as well with this therapy. The 5-year PFS is between 0 and 43% in completely resected disease (Hwang et al., 2012; Magdum et al., 2010; Duffner et al., 1999). Although, we had 100% 5-year survival rate in our CNS tumor infant cancer patients, the low number of cases (10) makes any conclusion invalid.

Based on our results, a considerable number of our infant cancer patients had consanguineous parents, which was seen more in the case of retinoblastoma and neuroblastoma. It has been shown that parental consanguinity was significantly associated with the diagnosis of lymphoma and leukemia. The genetic isolation of coastal island populations living in middle Dalmatia, Croatia is likely to be a factor in the high incidence of cancer. Other investigators have linked the elevated levels of certain cancers among the Hutterites, Syrian Jewish community in Brooklyn, New York, Pakistanis, and Louisiana Acadians to high incidence of consanguinity within these groups. In Pakistan, daughters of parents who were first cousins were at approximately twice the risk of breast and ovarian cancer than were daughters of unrelated parents. An increased incidence of leukemia and tumors was found in consanguineous families. In an early study, an increased frequency of consanguinity was detected in Hodgkin lymphoma patients. Also for colorectal cancer, breast and ovarian cancer and thyroid cancert here is a striking evidence of familial aggregation (Denic et al., 2007; Feldman et al., 1976; Bener et al., 2009; Bener et al., 2009; Denic et al. , 2001).

High-density single nucleotide polymorphism (SNP) mapping arrays has shown that the genomes of normal somatic cells contain long homozygous stretches(autozygous), which may be raised from the common ancestry of the individual's parents. This can explain why consanguinity may be a factor in cancer predisposition. Also the presence of chromosomal regions of somatic uniparentaldisomy (UPD) in cancer genomes, characterized by loss of heterozygosity (LOH) can be a result of consanguineous parents. and a normal copy number (two) but which are not autozygous in the germ-line or normal somatic cell genome. Autozygosity also influences cancer predisposition by the increasing occurrence of certain chromosomal aberrations (copy number gain, LOH, and somatic UPDs) during carcinogenesis which depend on the germ-line genotypes of important cancer-related genes (oncogenes and tumor suppressors) found in those chromosomal regions (Bacolod et al., 2009). Constitutional genetic abnormalities present in all cells of the body that are hereditary or nonhereditary contribute to an estimated 10% to 15% of pediatric cancers. Thus, consanguinity also increases the probability of cancer by increasing the chance of cancer-predisposing syndromes such as Down syndrome (Davidoff, 2010). In future studies, we plan to compare the patients with consanguineous parents versus those with non-consanguineous parents regarding the genetic abnormalities and also compare these two groups based on survival.

Because childhood cancer is rare, it is difficult to describe its incidence accurately without having access to nationwide cancer data. In the United States the SEER program, administered by the National Cancer Institute, totally covers nine state cancer registries (Li et al., 2008). Specialized childhood cancer registries with national coverage exist in Germany, the UK and a few other countries. For example, in Switzerland, cancer registration for patients of all ages is done in 13 cantons covering 58% of the Swiss population (Michel et al., 2007).The registry analysis will respond to the need for a more comprehensive epidemiological support for health policy planning in the country. The necessity for a nation to have a National Cancer Registry is unquestioned; however, to have such a registry has been beyond the resources of most countries in the developing regions of the word. Because of this, most countries have to obtain their cancer data from hospital-based registries. A hospital-based cancer registry can serve the needs of the hospital administration, the hospital's cancer program, and above all, the individual patient (Davidoff, 2010). With all these shortcomings, single-centered cancer registries have been used to extrapolate the incidence rate of different cancer types for the whole-country, which is a potential application of our data.

Acknowledgements

The authors wish to thank Dr Asadi Lari (Head of Onco-Pathology Center) for his valuable advice on the manuscript. This work was supported in part by the Onco-Pathology Research Center.

References

Aerts I, Lumbroso-Le Rouic L, Gauthier-Villars M, et al (2006). Retinoblastoma. *Orphanet J Rare Dis*, **25**, 1:31.

Bacolod MD, Schemmann GS, Giardina SF, et al (2009). Emerging paradigms in cancer genetics: some important findings from high-density single nucleotide polymorphism array studies. *Cancer Res*, **69**, 723-7.

Bahoush GR, Arab E, Arjmandi KH, et al (2013). Neuroblastoma in Iran: an experience of 32 years at a referral childrens hospital. *Asian Pac J Cancer Prev*, **14**, 2739-42.

Bener A, Denic S, Al-Mazrouei M, et al (2001). Consanguinity and family history of cancer in children with leukemia and lymphomas. *Cancer*, **92**, 1-6.

Bener A, El Ayoubi HR, Chouchane L, et al (2009). Impact of consanguinity on cancer in a highly endogamous population. *Asian Pac J Cancer Prev*, **10**, 35-40.

Chung EM, Specht CS, Schroeder JW (2007). From the archives of the AFIP: Pediatric orbit tumors and tumorlike lesions: neuroepithelial lesions of the ocular globe and optic nerve. *Radiographics*, **27**, 1159-86.

Davidoff AM (2010). Pediatric oncology. *Semin Pediatr Surg*, **19**, 225-33.

Denic S, Frampton C, Nicholls MG (2007). Risk of cancer in an inbred population. *Cancer Detect Prev*, **31**, 263-9.

Denic S, Bener A (2001). Consanguinity decreases risk of breast cancer--cervical cancer unaffected. *Br J Cancer*, **85**, 1675-9.

Dimaras H, Kimani K, Dimba EA, et al (2012). Retinoblastoma. *Lancet*, **379**, 1436-46.

Duffner PK, Horowitz ME, Krischer JP, et al (1999). The treatment of malignant brain tumors in infants and very young children: an update of the Pediatric Oncology Group experience. *Neuro Oncol*, **1**, 152-61.

Feldman JG, Lee SL, Seligman B et al (1976). Occurrence

of acute leukemia in females in a genetically isolated population. *Cancer*, **38**, 2548-50.
Ferrari A, Orbach D, Sultan I, et al (2012). Neonatal soft tissue sarcomas. *Semin Fetal Neonatal Med*, **17**, 231-8.
Fisher JP, Tweddle DA (2012). Neonatal neuroblastoma. *Semin Fetal Neonatal Med*, **17**, 207-15.
Gurney JG, Ross JA, Wall DA, et al (1997). Infant cancer in the US: histology specific incidence and trends,1973 to 1992. *J Pediat Hematol Oncol*, **19**, 428-32.
Hwang SW, Su JM, Jea A (2012). Diagnosis and management of brain and spinal cord tumors in the neonate. *Semin Fetal Neonatal Med*, **17**, 202-6.
Knudson AG (1971). Mutation and cancer: statistical study of retinoblastoma. *Proc Natl Acad Sci USA*, **68**, 820.
Lakhoo K, Sowerbutts H (2010). Neonatal tumours. *Pediatr Surg Int*, **26**, 1159-68.
Li J, Thompson TD, Miller JW, et al (2008). Cancer incidence among children and adolescents in the United States, 2001-2003. Pediatrics, 121, :e1470-7 (& the website: http://www.mindfully.org/health/cancer-infants-SEER.75-79.html).
Magdum SA (2010). Neonatal brain tumours - a review. *Early Hum Dev*, **86**, 627-31.
Malkin D, Portwine C (1994). The genetics of childhood cancer. *Eur J Cancer*, **30A**, 1942-1946.
Mehdiabadi GB, Arab E, Rafsanjani KA, et al (2013). Neuroblastoma in iran: an experience of 32 years at a referral childrens hospital. Asian Pac J Cancer Prev, 14, 2739-42.
McHugh K (2007). Renal and adrenal tumours in children. Cancer Imaging. 7, 41-51.
Michel G, von der Weid NX, Zwahlen M, et al (2007). The Swiss Childhood Cancer Registry: rationale, organisation and results for the years 2001-2005. *Swiss Med Wkly*, 137, 502-9.
Moore SW, Satgé D, Sasco AJ, Zimmermann A, et al (2003). The epidemiology of neonatal tumours.Report of an international working group. *Pediatr Surg Int*, **19**, 509-19.
Pieters R (2009). Infant acute lymphoblastic leukemia: Lessons learned and future directions. *Curr Hematol Malig Rep*, **4**, 167-74.
Pizzo PA., Poplack DG., Pizzo I (2012). Principles and Practice of Pediatric Oncology(6th edition). Lippincott Williams & Wilkins.
Pollock BH, Tomlinson GE (2012). Preventing cancer in adulthood: advice for the pediatrician. In Pizzo PA., Poplack DG., Pizzo I (2012). Principles and Practice of Pediatric Oncology (6th edition). Lippincott Williams & Wilkins publications.
Pui CH, Mullighan CG, Evans WE, et al (2012). Pediatric acute lymphoblastic leukemia: where are we going and how do we get there? *Blood*, **120**, 1165-74.
Kliegman MD, Richard E. Behrman MD et al (2007). Nelson Textbook of Pediatrics(18th edition, chapter 491). Saunders Publications.
Dreyer Z, Indelicate DJ, Reaman GH, et al (2012). Infants and adolescents with cancer: special considerations. In Pizzo PA., Poplack DG., Pizzo I (2012). Principles and Practice of Pediatric Oncology(6th edition). Lippincott Williams & Wilkins publications.
Swaminathan R, Rama R, Shanta V (2008). Childhood cancers in Chennai, India, 1990-2001: incidence and survival. *Int J Cancer*, **122**, 2607-11.
Vasilatou-Koqsmidis H (2003). Cancer in neonates and infants. *Med Pediatr Oncol*, **41**, 7-9.
Wiangnon S, Veerakul G, Nuchprayoon I, et al (2011). Childhood cancer incidence and survival 2003-2005, Thailand: study from the Thai Pediatric Oncology Group. *Asian Pac J Cancer Prev*, **12**, 2215-20.