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DISSERTATION

The Incidence and Survival of Pediatric Malignancies with Focus on Ocular and Orbital Tumors

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von

Ahmed Samir Ahmed Alfaar

aus Damietta, Ägypten

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Abstract - English

Introduction: Childhood malignancies are rare cancers. We hypothesize that incidence and survival rates differ from those of adult cancers which can be the base of a treatment improvement of childhood cancers. This might be achieved by adapting supportive care and protocol-based managements to the needs of childhood cancers. Thus, we investigated childhood cancers in certain age groups, including those diagnosed in the neonatal period with focus on orbital cancers. Further, we analyzed ways of improvement of care after integration of multidisciplinary protocols in ocular tumors.

Methods: To study neonatal and orbital tumors, we acquired data from Surveillance, Epidemiology, and End-Results Program (SEER) of the National Cancer Institute, USA, for the period between 1973 to 2007 and 2009 respectively. To study the impact of protocols, we used data from the Children's Cancer Hospital, Egypt between 2007 and 2014. This time span was divided into periods to generate follow-up data. For neonatal and orbital malignancies, histology groups were identified and compared.

Results: Neuroblastoma followed by germ cell tumors represented the most common neonatal cancers. Although neonatal tumors showed a 5-year overall survival of 60%, brought down by leukemia and CNS tumors (39.1%, and 15% respectively), overall survival of patients with solid tumors reached 71.2%. Subgroup analysis of neonatal cancers revealed significantly worse outcome compared to older age group except for neuroblastoma. Cancer-specific survival rates showed no significant improvement over time.

Age-adjusted incidence of orbital tumors was 3.39 per million person-years (pMPY). Children were afflicted mostly by soft-tissue sarcomas (0.35 pMPY). In contrast, lymphomas, carcinomas and melanomas affected adults more than children, at 6.46, 2.65, and 1.39 pMPY respectively. Except for soft-tissue sarcomas and lymphomas, orbital tumors showed a male predilection. Whites apparently had higher incidences of all cancers except soft tissue sarcomas. Generally, the average incidence of orbital cancers showed a rising trend.

After implementation of protocols, decision making time especially enucleation, became faster, and the quality of documentation, safety of the surgery performed and the probability of survival all increased.

Discussion: Cancer therapy improvement requires special attention by deciphering uneven incidence and survival in specific groups and design of better supportive plans. Reaching this goal, subtypes need to be redefined, revision of topographical codes of head and orbit is required to better map orbital structures. Faster and more reliable indicators facilitating better cancer management can be acquired by the enactment of multidisciplinary protocols, data management, even without the acquisition of new therapies.

Abstract – German:

Einleitung: Maligne Erkrankungen des Kindesalters sind selten. Wir glauben, dass sich die Inzidenz und Überlebensrate von malignen Tumoren bei Erwachsenen unterscheidet und diese Unterschiede helfen, die Therapie durch unterstützende Betreuung und Protokoll-basiertes Management zu verbessern. Ziel dieser Arbeit war es, maligne Tumore im Kindesalter in bestimmten Altersgruppen zu untersuchen. Diese schließt Tumore ein, welche bei Neugeborenen diagnostiziert wurden, mit Fokus auf maligne Raumforderungen des Auges und der Orbita. Wir analysierten Möglichkeiten, die Therapie durch die Integration multidisziplinärer Protokolle für okuläre Tumore zu verbessern.

Methoden: Um orbitale Tumore bei Neugeborenen zu untersuchen, nutzten wir Daten des „Surveillance, Epidemiology, and End-Results Program“ (SEER) – Programms des „National Cancer Institute“ (USA) aus der Zeit von 1973-2007 bzw. 2009. Zur Evaluation des Einflusses der Protokolle nutzten wir außerdem Daten des „Children’s Cancer Hospital - Egypt“ zwischen 2007 und 2014. Dieser Zeitraum wurde in Intervalle unterteilt, um Daten im Zeitverlauf zu erhalten. Die neonatalen und orbitalen Raumforderungen wurden histologisch in Gruppen eingeteilt und verglichen.

Ergebnisse: Neuroblastome und Keimzelltumoren stellten die häufigsten malignen Tumoren bei Neugeborenen dar. Obwohl maligne Tumoren bei Neugeborenen eine 5-Jahresüberlebensrate von 60% aufweisen, welche durch Leukämie (39.1%) bzw. ZNS-Tumore (15%) vermindert wird, betrug die Überlebensrate bei soliden Tumoren 71.2%. Die Untergruppenanalyse der Neugeborenen zeigte signifikant schlechtere Überlebensraten als bei älteren Kindern, mit Ausnahme des Neuroblastoms. Das Krebs-bezogene Überleben zeigte keine signifikante Verbesserung über die Zeit.

Die altersabhängige Inzidenz von Orbitatumoren betrug 3.39 pro 1 Million Patientenlebensjahre. Kinder waren am häufigsten von Weichgewebssarkomen (0.35 pro 1 Million Patientenlebensjahre) betroffen. Im Gegensatz dazu traten Lymphome, Karzinome und Melanome häufiger bei Erwachsenen als bei Kindern auf (6.46 bzw. 2.65 bzw. 1.39 pro 1 Million Patientenlebensjahre). Mit Ausnahme der Weichteilsarkome und Lymphome waren Männer häufiger von Orbitatumoren betroffen. Abgesehen von Weichteilsarkomen wiesen Kaukasier ein höheres Risiko auf als andere Ethnien. Im Allgemeinen stieg die Inzidenz maligner orbitaler Raumforderungen.

Nach Einführung der Protokolle beschleunigten sich die Entscheidungsprozesse insbesondere bzgl. Enukleation signifikant, die Dokumentationsqualität und Operationssicherheit nahm zu und die Gesamtüberlebensrate stieg an.

Schlussfolgerung: Die Verbesserung der Therapie kindlicher Krebserkrankungen erfordert besondere Aufmerksamkeit gegenüber inhomogener Inzidenz und Kenntnis der Überlebensraten in Subgruppen, um unterstützende Maßnahmen zu entwickeln. Zu diesem Zweck müssen die Definitionen von Untergruppen revidiert werden; einschließlich der topographischer Merkmale von Kopf und Orbita, um orbitale Strukturen besser zu erfassen. Schnellere und verlässlichere Indikatoren, welche das Krebsmanagement erleichtern, können durch multidisziplinäre Protokolle und Datenmanagement, auch ohne Einführung neuer Therapien, erreicht werden.

Introduction

Childhood malignancies are relatively rare diseases where children (under 18 years of age) in the developed world constitute a small fraction of the population due to the narrow base of the population pyramid (Kaatsch 2010; Howard et al. 2008). The situation is assumingly different in the developing world where children constitute a much larger segment of the population (Moccia et al. 2005). Even though, investigation of the incidence of certain malignancies, survival outcome and factors contributing to outcome requires long duration of recruitment and large populations. We hypothesize that pediatric malignancies including orbital neoplasms are varying in incidence and outcome from adult cancers. Based on these differences, their survival outcomes can be improved by integrating better planning and supportive care. In this study, we wanted to study factors that affect special subpopulations of pediatric tumors and comparing them to related older patients when possible using population-based cancer registry in USA and a major referral center in Egypt.

Neonatal malignancies comprise 2% of pediatric malignant tumors and their early presentation suggests a continuation of an intrauterine process and underlying genetic alterations (Moore et al. 2003). Some studies suggested that these tumors can regress spontaneously or require minimal procedures to remove (Thompson and Kosnik 2005; Roosen et al. 1988). However, there is a lack of population-based studies to address the later point, and to discuss the distribution of the tumors or the discrepancy between survival due to cancer-related causes and those from other causes. This has encouraged us to study the distribution, characteristics and contributing factors that affect survival of patients with neonatal tumors through a population-based cancer registry.

Childhood orbital malignant tumors are rare in ophthalmologic practice and, thus, lack population-based studies that compare its incidence to adult ones. Some epidemiologic studies have focused on studying incidence of specific disease (e.g. orbital lymphomas) or within a single age group, and are mostly based on retrospective data accumulated in referral centers. The relative incidences of these tumors remained however unclear (Margo and Mulla 1998; Koopman et al. 2011; Teo et al. 2013; Gupta et al. 2012). We thus aimed to better identify the incidences of these tumors, their trends and characteristics through a population cancer registry and to discuss the possible reasons for the expected difference.

Retinoblastoma is a childhood malignancy that afflicts the retina. Chemoreduction in addition to local treatment is the standard treatment for the less advanced cases since the early twenty first century (C L Shields et al. 2012). Enucleation remains the ultimate treatment for advanced and progressive non-responsive cases. Careful examination of enucleated eyes is mandatory to detect any high-risk features or extra-ocular spread (Grossniklaus et al. 2011). Most treatment centers in

developing countries lack the knowledge of protocol-based management of the disease, resulting in possible incomplete diagnoses and unwarranted risks to patients' lives (Rodriguez-Galindo et al. 2013; H. ElZomor et al. 2015). To obtain a proof-of-principle for the effectiveness of protocol-based disease managements, we hypothesized that implementing systematic protocols for diagnosis, stratification and treatment beside implementing electronic data management and training will improve the survival outcomes of these patients. The lack of this systematic approach in many developing countries allowed us to compare the quality of reporting in major referral pediatric oncology hospital in a developing country before and after the implementation of protocols and including detailed studying of the features present in eyes after enucleation.

Methodology

Datasets

An agreement was signed with USA Surveillance, Epidemiology, and End Results (SEER) Program to access 17 US cancer registries for studying incidence and survival or neonatal tumors. The SEER program covers about 28% of the United States population. The accessed registries were: the Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, Utah, Los Angeles, San Jose-Monterey, Rural Georgia, the Alaska Native Tumor Registry, Greater California, Kentucky, Louisiana, and New Jersey registries (NCI's Division of Cancer Control and Population Sciences 2017). A special request was required to filter patient data according to the incidence of cancer in the first month of life.

For identifying incidence and trends of orbital, lacrimal gland and conjunctival tumors, we used only 9 registries from the USA SEER which joined the program in 1973-1974 to calculate incidence. These were the Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah registries. These represent about 10% of the United States population.

To study the impact of implementing multi-disciplinary protocols on quality and outcome, data were extracted from the Children's Cancer Hospital – Egypt (CCHE) Retinoblastoma Registry. Data collected belonged to 420 patients diagnosed between July 2007 and July 2014. Data were collected at CCHE retrospectively during the first year then prospectively thereafter.

Software

SEER*STAT version 8.2.1 software was used to access and analyze the SEER data. In addition, the IBM SPSS version 22 (NCI 2015; IBM Corp 2011) was used for further analysis. REDCap software was used for the collection and management of retinoblastoma patients' data.

Coding and Classification

In neonatal malignancies, tumor groups were classified according to the International classification of Childhood Cancers (ICCC) and further coded according to the International classification of Diseases for Oncology (ICD-O), 3rd edition (Steliarova-Foucher et al. 2005). Cancers were grouped according to demographic criteria and temporally, comparing the period between 1973 and 1990 with that between 1991 and 2007. After noting the need for further analysis, we reassigned the time periods compared into 1973-1985, 1986-1998 and 1999-2007. This was done to work out the effects of changes in treatment during these three periods.

For orbital tumors, we used ICD-O site codes C69.0, conjunctiva; C69.5, lacrimal gland and C69.6, orbit to filter the data for this study. We grouped the histology subtypes into five groups: carcinomas, melanomas, soft-tissue sarcomas, lymphomas and reticular malignancies and other rare and unclassified malignancies. We divided patients' data for the purpose of comparison into a 0-19, a 20-49 and a ≥ 50 years age group.

Diagnostic and treatment Protocols

Before the 2011, the aim of pathological examination was to discover extension of the tumor beyond the sclera and surgical resection margin. There was only one chemotherapy treatment regimen to treat intra-ocular retinoblastoma. During 2010, a retinoblastoma study team was formed, and treatment protocols for intra-ocular, high-risk and extra-ocular diseases were adopted. Also, the CAP pathology protocol for enucleated eyes and the COG guidelines for high risk disease were integrated in practice and both the International Intraocular Retinoblastoma Classification and the International Retinoblastoma Staging System and pathologic TNM (pTNM) came in use for the purpose of classifying disease (Grossniklaus et al. 2011; Ahmad Samir Alfaar et al. 2016; Sastre et al. 2009; Chantada et al. 2006; Carol L Shields et al. 2006). Prior to these changes at CCHE, further chemotherapy cycles (in the form of etoposide, carboplatin and vincristine) were offered to patients after failure of initial chemotherapy in disease groups B-E. New patients after 2011 were assessed for age, and intra-ocular retinoblastoma classification and assigned to a treatment group according to this assessment. Enucleation was offered initially to patients with eyes belonging to groups E, to group D who presented with disease after the age of one year and to other groups whose disease progressed in spite of chemotherapy, brachytherapy, and radiation therapy in combination with laser and cryotherapy. Adjuvant chemotherapy was given in cases with high-risk features such as an extensive separate choroid or optic nerve invasion (not to the level of the surgical margin) or any degree of combined choroid and optic nerve invasions. We compared patients' characteristics (e.g. age, delay of diagnosis and delay of enucleation) against levels of invasion and optic nerve length of their enucleation specimens' as well as the, quality of documentation and patients' survival before and after the implementation of protocols the beginning of 2011). The complete procedures conducted during the transitional period was described elsewhere (Ahmad Samir Alfaar et al. 2016).

Statistical methods

Student's T-test was used to compare the means of two groups (in case of normally distributed data), Mann–Whitney U test in case of Non-normally distributed data, and ANOVA and the Kruskal-Wallis test were used to compare ordinal measures distribution between categorical groups in cases of Normally and not-normally distributed data respectively. Significant relationship between

categorical variables was assessed using chi-squared test. Spearman's Correlation and Pearson's R tests were used to assess correlations. We used confidence intervals beside p-values to express significance with clinical relevance (du Prel et al. 2009).

For neonatal tumors, Frequencies, relative frequencies and survival rates were calculated. Survival stability for at least 6 months was labeled as a "survival plateau". Due to the limitations in accessing data, we compared cancers in two age groups only; those diagnosed in first month of life and those diagnosed within the period after the first to the 24th month of life (the latter labeled as "older age group"). For orbital malignancies, we calculated frequencies, incidence rates and annual percent changes (APC) to study trends. Survival analysis was presented in the form of Kaplan-Meier curves with log-rank tests to assess differences between curves.

Results

Aim 1: Identification of clinically relevant differences between neonatal and older age group malignancies.

- summarized from (Ahmad Samir Alfaar et al. 2017)

Among 615 patients presenting the disease in their first month of life, 310 were males, 454 had solid tumors, 93 leukemias/lymphomas, and 68 solid tumors. The five-year overall survival (OS) was 60.3% (95% CI: 56.2 - 64.4), pushed up by a 71.2% (95% CI: 66.9-75.5) survival of patients with solid tumors, but lowered by a 39.1% (95% CI: 28.3-49.9) survival of patients that had been afflicted by leukemias/lymphomas and a survival rate of only 15% (95% CI: 5.4-24.6) of cases that had suffered CNS tumors. Neonates afflicted with neuroblastoma were the only cases to have a survival rate not significantly lower compared to the group of patients at older ages. Non-cancer-related causes of death were significantly more frequent than cancer-related causes (37.9% compared with 16.4% consecutively, $P < 0.0005$). Lower mortality was noted in the older age group, whether due to cancer or non-cancer related causes. Survival has improved significantly over the years in older age group but not in neonatal patients.

Neuroblastoma was the most common histology followed by germ-cell tumors. Males represented the higher proportion of neonatal patients who suffered from neuroblastoma. The adrenal glands were the main affected sites. The 5-year overall survival rate reached 76.8% (95% CI: 70.3-83.3); with a survival plateau at 30 months. Neonates with retinoblastoma had a 91.7% 5-year OS (95% CI: 80.5–100) with a plateau at 6 months after presentation; representing the highest survival rate of all patients with the various tumors studied in the neonatal group. One patient out of the 27 developed later a secondary cancer. Neonates with nephroblastoma had a 62.5% 5-year OS (95% CI: 38.8–86.2) with a plateau at 6 months. In neonatal patients, rhabdomyosarcomas and fibrosarcomas affected head and neck and limbs respectively, and were the main soft-tissue sarcomas in this age group. Neonates who suffered from fibrosarcomas and rhabdomyosarcomas had a 76% (95% CI: 57.4-94.6) and a 36.3% (95% CI: 12.8-59.8) 5-year OS respectively. Females represented 62% of neonates who suffered germ-cell tumors. Neonates with extra-cranial – extra-gonadal germ-cell tumors had a 5-year OS of 74.5% (95% CI: 66.7-82.3) compared to 68.3% (95% CI: 60.7-75.9) for neonates afflicted by all the various germ-cell tumors and 84% (95% CI: 79.9-88.1) in older patients. Two out of 168 patients were diagnosed with secondary cancers. Acute myeloid leukemia comprised almost half of all leukemia diagnoses and patients afflicted showed higher survival rates than those who suffered acute lymphoblastic leukemia. Compared with other neonates who suffered various cancers, those

with CNS tumors had the worst survival rates at 15% (95% CI: 5.4-24.6) reaching a survival plateau after 24 months.

Aim 2: Identification of differences in incidence between pediatric and adult orbital cancers

- summarized from (W. M. Hassan et al. 2016)

We identified 2802 patients who had been afflicted with OCLG malignant tumors. The overall age-adjusted incidence rate was 3.39 per million person-years (pMPY) (95%CI: 3.27-3.52), with about 3-times higher this rate in the ≥ 50 age group (9.51; 95%CI: 9.11-9.92). Conversely, the 0-19 age group had an incidence rate of 0.56 pMPY (95%CI: 0.47-0.66). Generally, males and Caucasians had higher rates. Soft-tissue sarcomas represented the most common histology in the youngest age group (0.35 pMPY; 95%CI: 0.28-0.42) followed by lymphomas and reticular malignancies (0.09 pMPY; 95%CI: 0.06-0.14). Lymphomas and reticular malignancies characterized the second age group (20-49 years) malignancies with a combined rate of 0.72 pMPY (95%CI: 0.63-0.81) followed by carcinomas at 0.34 pMPY (95%CI: 0.28-0.4). Rates were higher in the older age group, reaching 5.74 pMPY (95%CI: 5.43-6.06) for lymphomas and reticular malignancies and 2.31 pMPY (95%CI: 2.11-2.51) for carcinomas. Carcinomas affected males, Whites and the ≥ 50 age group more frequently than in other groups. The same was true for melanomas. Soft-tissue sarcomas affected both genders and main ethnic groups equally but affected children more frequently than other age groups. Higher incidence rates were noted for orbital tumors than both conjunctival and lacrimal gland tumors (1.59 with 95%CI: 1.50-1.68, 1.37 with 95%CI: 1.30-1.46 and 0.43 with 95%CI: 0.39-0.48 respectively). Carcinomas and melanomas were more commonly found in the conjunctiva than other sites while lymphomas resided preferentially in the orbit.

Annual Percent Change in incidence rates over the period between 1975 and 2009 was 3.1 (95% CI: 2.61-3.61), mainly driven by the increase in lymphoma incidence (specifically mature B-cell non-Hodgkin's lymphomas, APC=5.82, p <0.01) and to a lower extent by a smaller increase in the incidence of melanomas and carcinomas. This trend did not show a gender difference.

Aim 3: Justification of implementing systematic approaches on survival and care of Retinoblastoma

- summarized from (Hossam ElZomor et al. 2016)

A total of 290 enucleation reports covering 276 patients were included into the analysis; 281(96.9%) for specimens and 9 (3.1%) for tissue paraffin blocks. Age at diagnosis did not differ before and after implementation of protocols (2007-2010: 24.1 ± 19.6 months compared to 2011-2014: 23.3 ± 15.9

months respectively). In the first period, patients with Unilateral disease was significantly older than those with bilateral one (33.7 ± 20.8 months compared to 26.9 ± 15.6 months, $p < 0.05$). Time between initial presentation and seeking medical advice decreased slightly from the first to the second period (11.7 ± 17.4 weeks compared to 10.0 ± 15.3 weeks in the later period, $p = 0.4$). This lag time was longer in patients with unilateral disease (13.6 ± 19.2 weeks compared to 6.8 ± 10.0 weeks in bilateral disease, $p < 0.05$). The time from decision to enucleation decreased significantly in both patients with unilateral disease who had not received neo-adjuvant chemotherapy (10.0 ± 27.2 weeks compared to 4.4 ± 12.7 weeks, $p <0.05$) and patients with bilateral disease who had received neoadjuvant chemotherapy (77.5 ± 48.5 weeks compared to 50.2 ± 28.7 weeks, $p < 0.05$).

The distribution of intra-ocular retinoblastoma classification was significantly different between the two periods ($p < 0.0001$); more patients presented with early A/B disease in the second period more than that in the first period (n=0 in first vs. 8 in the second) with almost equally high groups C/D and E (n= 107 and 106) in contrary to first period where 71.67%(n=43) of the patients was group C/D patients.

The mean optic nerve length increased significantly from 5.6 mm to 7.2 mm ($p =0.004$). Quality of reporting noted by the number of missing variables during documentation improved significantly presented by the disappearance of incomplete reporting fields. However, this improvement was coupled with increased time needed for reporting ($p <0.05$).

Degrees of choroid invasion and optic nerve invasion were strongly correlated (Pearson's R = 0.526; $p < 0.001$) in patients who did not receive chemotherapy in contrary to the case in those who received neoadjuvant chemotherapy (Pearson's R = 0.228; $p =0.082$).

Generally, survival increased significantly from the first to the second period (log-rank p = 0.018). Patients who presented with both intra-ocular and extra-ocular retinoblastoma at diagnosis in the second period showed better survival. Moreover, Patients who did not receive neoadjuvant chemotherapy showed significant increase of survival in the second period in contrary to that in the first period (93.6% vs. 79.2%, p=.008). Examining the relation between terms used before and after implementation of protocols revealed significant increase in survival between two periods associated with minimal choroid invasion, massive choroid with scleral invasion and pre-laminal optic nerve invasion (p=0.001, 0.009 and 0.024 respectively).

Discussion

Incidence of childhood malignancies differ from adult cancers. This difference is attributed to underlying genetic susceptibility, and environmental and medical exposure (Murphy et al. 2013). However, incidence of some cancers within pediatric age group is not homogeneous. Some cancers show tendency to affect younger children than other (Ward et al. 2014). One of these cancers is Retinoblastoma.

As little as only 28 neonatal cancers per one million live births, neonatal tumors were reported in the UK (Vormoor and Chintagumpala 2012). Similar to our findings, these patients had lower overall and individual disease outcome indicators compared with older patients. More patients died from causes other than cancer (congenital diseases and perinatal management) than those from direct cancer causes. This may be a reflection of the high rate of congenital anomalies associated with neonatal cancers and the possible underlying genetic mechanisms and abnormal intrauterine development. Such initial circumstances and associated cardiac and respiratory conditions enforces the managing physicians to treat these neonates in a neonatal ICU which is not likely to be part of or partnered with a pediatric oncology hospital. Such circumstances may result in depriving the patients from appropriate oncology care. Withholding treatment from some patients was reported (Isaacs 2009). These patients may be put under observation awaiting possible spontaneous regression or avoided treatment due to inability to deliver chemo- and radiation therapy because of the patient's young age. Surprisingly, some of these patients had a regressive course (Thompson and Kosnik 2005). Thus, there are strongly differing subgroups that need to be identified to develop appropriate treatment strategies. We believe that appropriate management of neonates requires an accurate consideration of the trade-off between the best possible outcome and the good long-term quality of life. Balancing benefit and risk, proper assessment would help us decide on the best management plan tailored to each neonate's needs. This integrative approach must be done hand-in-hand between oncologists, pediatricians, critical care physicians, nursing, nutritionists and other specialists. Previous studies have reported high incidences of mental retardation among neonates who had received treatment against CNS tumors (Oi, Kokunai, and Matsumoto 1990).

Although we found an overall improvement in outcomes of childhood tumor treatments over the years reaching about 85% of all sites together (Smith et al. 2010; Ma, Sun, and Sun 2015), this was not associated with a similar trend in the outcomes in neonatal tumors as shown in our study. We believe that the most likely explanation is the inability to formulate treatment plans and medications that are both safe and effective for this highly vulnerable age group and lack of systematic well-developed evidence-based protocols.

Neuroblastoma, the most common malignancy noted in this age group showed a 76.8% 5-year overall survival cohering with other studies (Gigliotti et al. 2009). On the other hand, results of treatment of germ cell tumors were hard to compare with those reported in the literature due to the fact that SEER mainly records malignant tumors. Our group of neonatal leukemia reported the worst survival rates, especially for cases of ALL. We noted also that ALL was less common than AML , an observation agreeing with those of previous studies (Vormoor and Chintagumpala 2012; Isaacs 2003; van der Linden, Creemers, and Pieters 2012; Sande, Arceci, and Lampkin 1999; Bresters et al. 2002). This may be due to the relationship between AML and transient myeloproliferative disorder.

The finding that neonatal cancer patients showed shorter survival times than patients presented with the cancer at later time-points is not due to specific cancer-causing factors but other associated benign diseases and related care differences should drive us to implement better initial supportive care plans. Moreover, a similar cancer-related OS survival at 30-year between the patients suffered from cancer in the neonatal age group and those diagnosed in older age may confirm such theory. One possible supportive care plan was delineated by Askin et. al (Askin 2000). The later paper recommends a scheme for combining the management of pain, nutrition, skin care, infection, respiratory status, fluid and electrolytes balance and body temperature in the integrated patient care plan. Our study provides evidence for the importance of investment in further nursing research in this area.

Further, we noted a higher incidence of OCLG malignancies in adults than in children, caused by the considerably high rates of lymphomas, carcinomas and melanomas in both the 20-50 age group and the above 50 group. On the other hand, embryonal rhabdomyosarcomas defined the 0-19 age group with no race or gender predilection as similarly observed in previous studies (Dutton, Sines, and Elner 2012; Ognjanovic et al. 2009). Moreover, we noted an ever increasing rate of OCLG malignancies as it reflected in positive annual percent changes similar to those noted in studies that have discussed incidences at other sites (Morton et al. 2006).

A Japanese study reported a high incidence of orbital lymphomas above the age of 40 - an observation possibly due to improvements in diagnostic technology, or due to environmental and racial causes (Choi, Kafkala, and Foster 2006). Other studies showed an ever-rising incidence of lymphomas over the last two decades. Such a trend has been attributed to the rise in numbers of immune-compromised patients, longer life-expectancies and to infections such as with the Epstein-Barr virus, Toxoplasma gondii or Chlamydia psittaci (that may trigger an antigenic affect causing B-cell proliferation) (Sagoo et al. 2014; Ferreri et al. 2004; Verma et al. 2008; Moslehi, Coles, and Schymura 2011; Moslehi et al. 2006). However, the incidence trend continued to increase despite of

the decrease in number of immunocompromised patients (Choi, Kafkala, and Foster 2006). Some of these studies initially attributed the rise to changes in diagnostic rules that reclassified what was previously known as “pseuolymphomas” as low-grade lymphomas. It was later noted however that the increase was real as it had involved all lymphoma subtypes (Howlader et al. 2016; Shiels et al. 2013). We have however calculated a recent reversal in the incidence of OCLG malignancies, seemingly dropping over the last few years. This may indicate a late effect of the drop in number of immunocompromised patients or a presence of a surrogate mechanism that take time to be reflected clinically in the population. Furthermore, our findings showed no significant difference in incidence by gender, agreeing with the results of other studies (Moslehi, Coles, and Schymura 2011; Moslehi et al. 2006).

Generally, SEER data is a valuable tool for revealing findings that require large population, however, it has limitations including the missing data, unrecorded variables and treatment reporting (Yu et al. 2009).

In addition to helping physicians to think systematically about the epidemiological patterns of OCLG malignancies, our study showed limitations of ICD-O-3 coding in representing the orbital anatomy and it has raised some questions that need further molecular and genetic correlation (Ahmad S. Alfaar, Bakry, and Ezzat 2014).

Treatment of retinoblastoma shows significant improvements in survival in the developed world but not in the developing world (Broaddus, Topham, and Singh 2009; Abramson et al. 1985). This may be attributed to the larger number of patients, the dissimilar rates of intra-ocular and extra-ocular disease and the lack of ability in the less developed countries to treat the patients in multidisciplinary settings (Howard et al. 2008). Thus, we compared quality of documentation and survival outcome before and after implementation of multi-disciplinary protocols in the largest pediatric oncology hospital in Egypt (opened in 2007). Before CCHE had opened, extra-ocular retinoblastoma was the most common presentation (S. A. Hassan, Massoud, and Hussain 1992). This could be due to the lack of specialized healthcare facilities in Egypt that manage pediatric malignancies, and inefficient public transportation network as few of many reasons resulting in lack of access to healthcare and lack of awareness about pediatric tumors all resulted in delayed diagnosis and poor management (Sethi et al. 2013). By the time of inauguration of the hospital most patients had either advanced intra-ocular disease or extraocular ones. Due to the challenges associated with managing such patients, the hospital had to design its own knowledge-based practices and form a trained multidisciplinary team. The transition phase involved encouraging the hospital staff to embrace the new approach, and showing them with evidence the importance of

each step towards our final goal (Ahmad Samir Alfaar et al. 2016). Initially, patients' families refused enucleation and avoided management sessions. This enucleation refusal behavior was observed more frequently from less developed countries (Olteanu and Dimaras 2016). Such denial and refusal resulted in a higher frequency of high-risk findings and metastases in older studies (Sitorus et al. 2009). High-risk features were increasing during the time-span of our study. This can be attributed to low reporting accuracy in the first period and couldn't allow us to infer relations. The delay of enucleation has been correlated in other studies with the degree of choroid invasion (Wang et al. 2001). The time needed for the analysis of pathology reports increased until the implementation of the protocols then started to decline. The increase attributes to increased burden of enucleations, as well as the time needed for the revision and interpretation of ocular samples. However, the decline resulted from established techniques and the well-defined criteria that pathologists identified. The lower survival rates in the earlier years at CCHE may be attributed to the high percentage of patients that presented with advanced disease (Elzomor et al. 2015). Other factors included the reluctance of physicians to support the enucleation decision due to their lack of knowledge about the prognosis, the unavailability of standardized protocols for diagnosis and treatment and the varied interpretations of how pathology reports should direct treatment. The relations between choroid and optic nerve invasion separately, and relation of both to delay of enucleation beside the contributing factors require extended follow-up as well as multi-factorial analyses to account for the effects of different variables. In our study, we cannot build conclusions from the difference between the two periods in choroid and optic nerve invasion apart from completeness of the data due to different techniques for evaluation of samples. The experience at CCHE has shown that any transition must be accompanied by continuous training and learning assessment to allow staff to adapt to the proposed new measures. We learnt that integrating the tools of information technology results in an acceleration of such a change and make it easier to monitor and follow-up on implementation. One of the benefits of continuous monitoring was the discovery of short optic nerve stumps after enucleation that require followup, and the re-evaluation of group E atrophic eyes that are indicated for enucleation in some patients (Taha et al. 2015). Short optic nerve stump was defined as a risk factor in some studies (Rubin et al. 1985; Coats et al. 2000). This finding resulted to move the ophthalmology team to adopt better techniques for obtaining longer optic nerve during enucleation procedure (Coats et al. 2000). Data became a learning tool after integration of the clinical and research systems, supplying real-time evidence that help provide timely improvement of management. We believe that these findings in retinoblastoma can be generalized on other pediatric and adult diseases and situation can be improved by applying systematic protocols for diagnosis, treatment and follow-up before adopting high-end expensive treatments.

Finally, our study has shown difference between incidence and survival of neonatal neoplasms and older age groups and between incidence of childhood and adulthood orbital malignancies. These differences can guide better understanding of childhood malignancies and designing better management plans including supportive care and in the recent information technology era, a better clinically-oriented intelligent information technology support.

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[The References were styled according to Chicago manual of style 16th edition]

Affidavit

I, Alfaar, Ahmed certify under penalty of perjury by my own signature that I have submitted the thesis on the topic [The incidence and survival of pediatric malignancies with focus on ocular and orbital tumors] I wrote this thesis independently and without assistance from third parties, I used no other aids than the listed sources and resources.

All points based literally or in spirit on publications or presentations of other authors are, as such, in proper citations (see "uniform requirements for manuscripts (URM)" the ICMJE www.icmje.org) indicated. The sections on methodology (in particular practical work, laboratory requirements, statistical processing) and results (in particular images, graphics and tables) correspond to the URM (s.o) and are answered by me. My contributions in the selected publications for this dissertation correspond to those that are specified in the following joint declaration with the responsible person and supervisor. All publications resulting from this thesis and which I am author of correspond to the URM (see above) and I am solely responsible.

The importance of this affidavit and the criminal consequences of a false affidavit (section 156,161 of the Criminal Code) are known to me and I understand the rights and responsibilities stated therein.

_____

Date August 29, 2017 Signature

Declaration of Contribution to Included Publications

Ahmed Alfaar had the following share in the following publications:

Publication 1:

Alfaar AS, Hassan WM, Bakry MS, Qaddoumi I.

Neonates with cancer and causes of death; lessons from 615 cases in the seer databases.

Cancer Medicine (IF: 2.915). 2017 Jul; 6(7): 1817–1826.

Alfaar AS- Contribution in detail: ASA shared designing the concept of the paper with IQ. ASA hypothesized the paper and designed the statistical tests accordingly. ASA signed the data access agreement with SEER and conducted the data collection using SEER*Stat, and initial data analysis then supervised and validated the extended data analysis. He performed the interpretation of results, and preparation of figures. ASA performed the literature review and drafting and writing the manuscript in collaboration with IQ. ASA managed the submission of the article to different journals including answering reviewers' comments and adjusting the article based on their comments. ASA is the first author of the paper.

Publication 2:

Hassan WM, Bakry MS, Hassan HM, **Alfaar AS**.

Incidence of orbital, conjunctival and lacrimal gland malignant tumors in USA from Surveillance, Epidemiology and End Results, 1973-2009.

Int J Ophthalmol (IF: 0.939). 2016 Dec 18;9(12):1808-1813. eCollection 2016.

Alfaar AS- Contribution in detail: ASA has designed the hypothesis and concept of the paper. ASA supervised and validated (repeated separately) the outcomes of data collection and analysis. ASA was responsible for the interpretation of results and wrote the first manuscript draft, supervised the team during the second draft then he finalized the manuscript for submission. ASA supervised WMH during the submission of the of the paper to the journals and ASA was responsible for preparing the answers to the reviewer's comments and preparing the manuscript. ASA was the last- and corresponding author of the paper.

Publication 3:

Elzomor H, Taha H, Nour R, Aleieldin A, Zaghloul MS, Qaddoumi I, **Alfaar AS**.
A multidisciplinary approach to improving the care and outcomes of patients with retinoblastoma at a pediatric cancer hospital in Egypt. Ophthalmic Genet (IF: 1.886). 2017 Jan 13:1-7

Alfaar AS- Contribution in detail: ASA has designed the concept of the paper and presented it in International Society of Genetic Eye Diseases and Retinoblastoma, Ghent. ASA designed the data collection tools, prepared the electronic system for data collection and maintained it. ASA shared the design of the clinical treatment protocols with team members and acted as a source for supporting evidence by literature search and building the team knowledge-base. ASA reviewed the patients' files beside phone follow-up with patients during the data collection phase. ASA conducted the data analysis, preparation of figures, interpretation of results and writing the manuscript. The manuscript was revised by the team leader, and other consultants. ASA prepared the manuscript according to journals styles and prepared the paper after reviewers' comments. ASA was the last- and corresponding author of the paper.

Signature, date and stamp of the supervising University teacher

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Signature of the doctoral candidate

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The Selected Publications

Publication 1:
Alfaar AS, Hassan WM, Bakry MS, Qaddoumi I.
Neonates with cancer and causes of death; lessons from 615 cases in the seer databases.
Cancer Medicine (IF: 2.915). 2017 Jul; 6(7): 1817–1826.

Publication 2:
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A multidisciplinary approach to improving the care and outcomes of patients with retinoblastoma at a pediatric cancer hospital in Egypt. Ophthalmic Genet (IF: 1.886). 2017 Jan 13:1-7

Cancer Medicine

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ORIGINAL RESEARCH

Neonates with cancer and causes of death; lessons from 615 cases in the SEER databases

Ahmad S. Alfaar[1], Waleed M. Hassan[2], Mohamed Sabry Bakry[2] & Ibrahim Qaddoumi[3,4]

[1]Ophthalmology Department, Charité - Universitätsmedizin Berlin (Charité - Berlin Medical University), Berlin, Germany
[2]Research Department, Children's Cancer Hospital Egypt, Cairo 57357, Egypt
[3]Departments of Oncology, St. Jude Children's Research Hospital, Memphis, Tennessee
[4]International Outreach Program, St. Jude Children's Research Hospital, Memphis, Tennessee

Keywords
Epidemiology, infancy, neonatal tumors, SEER, undertreatment

Correspondence
Ibrahim Qaddoumi, Department of Oncology, MS 260, St. Jude Children's Research Hospital, 262 Danny Thomas Place, Memphis, TN 38105-3678. Tel: 901 595 2365;
Fax: 901 595 9005;
E-mail: ibrahim.qaddoumi@stjude.org

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Abstract

Neonatal tumors are rare with no standard treatment approaches to these diseases, and the patients experience poor outcomes. Our aim was to determine the distribution of cancers affecting neonates and compare survival between these cancers and older children. We analyzed SEER data (1973–2007) from patients who were younger than 2 years at diagnosis of malignancy. Special permission was granted to access the detailed (i.e., age in months) data of those patients. The Chi-square Log-rank test was used to compare survival between neonates (aged <1 month) and older children (>1 month to <2 years). We identified 615 neonatal cancers (454 solid tumors, 93 leukemia/lymphoma, and 68 CNS neoplasms). Neuroblastoma was the most common neonatal tumor followed by Germ cell tumors. The 5-year overall survival (OS) for all neonates was 60.3% (95% CI, 56.2–64.4). Neonates with solid tumors had the highest 5-year OS (71.2%; 95% CI, 66.9–75.5), followed by those with leukemia (39.1%; 95% CI, 28.3–49.9) or CNS tumors (15%; 95% CI, 5.4–24.6). Except for neuroblastoma, all neonatal tumors showed inferior outcomes compared to that in the older group. The proportion of neonates who died from causes other than cancer was significantly higher than that of the older children (37.9% vs. 16.4%; $P < 0.0005$). In general, the outcome of neonatal cancers has not improved over the last 34 years. The distribution of neonatal cancer is different than other pediatric age groups. Although the progress in neonatal and cancer care over the last 30 years, only death from noncancer causes showed improvement. Studying neonatal tumors as part of national studies is essential to understand their etiology, determine the best treatment approaches, and improve survival and quality of life for those patients.

Introduction

Neonatal tumors occur during the first month of life and constitute 2% of all childhood cancers [1]. Understanding the distribution and behavior of these tumors will enable us to identify the underlying mechanisms, predict survival, and tailor clinical management of each disease. The timing of these neoplasms suggests a genetic origin [2, 3]. However, few studies have compared the incidence, survival, or treatment modalities for patients with neonatal tumors [4, 5]. The outcomes of neonatal tumors are diverse. Like some leukemias [6, 7], rhabdomyosarcoma [8], and brain tumors [9, 10], some neonatal tumors have poor prognoses; others (neuroblastoma [11] and fibrosarcoma [8]) have better ones. Some of the most aggressive tumors (diffuse pontine glioma or high-grade glioma) spontaneously regress or are cured by surgical resection only [12, 13], supporting Moore's theory that some congenital tumors mature into benign neoplasms [1]. Treatments vary according to center and pathology, and many infants with congenital tumors receive no therapy [9]. These

factors and the rarity of neonatal tumors make it difficult to determine the best treatment and factors influencing survival.

The SEER database provides a unique opportunity to study rare tumors. Thus, we obtained special permission from the SEER administration to analyze monthly data not annual data, as is their standard practice.

Materials and Methods

We accessed the 17 SEER databases and analyzed data of patients who were <2 years at diagnosis from 1973 to 2007. SEER administrators allowed us to access a custom database (i.e., with age in months) for patients who presented before 2 years of age. Only cases with known age and malignancy are included in the database. Only cases with malignant behavior were included. To extract and analyze data, we used SEER*STAT 8.2.1 and IBM SPSS version 20 software, respectively [14, 15]. The SEER registries' composition and statistical methods are described elsewhere (http://seer.cancer.gov/registries/terms.html). International Classification of Childhood Cancer (ICCC) was used to group the tumors [16]. Cancer types were coded using the *International Classification of Diseases for Oncology, 3rd Edition* (Table S1).

For each ICCC group, we calculated frequencies based on sex, race, year of diagnosis, and geographic region. Secondary cancers were extracted if available. To compare survival across eras, we grouped patients into two cohorts: 1973–1990 and 1991–2007. For more detailed analysis, we grouped patients into three cohorts: 1973–1985, 1986–1998, and 1999–2007 to account for changing in treatment eras. Relative frequencies (RFs) were calculated for each ICCC category; within each category, RFs were calculated for gender. Due to the fact that 17 registries did not join SEER at the same decade, these data do not reflect incidence or real change of frequency over time. Five-year overall survival (OS) was calculated for each ICCC category and subgroup, according sex, race, year of diagnosis, and region. To avoid statistical bias, no statistics were calculated for groups or subgroups with fewer than 10 patients. Although this study has the largest neonatal group of cancer patients, the subgroup analysis of survival should be considered with caution due to the small size of some groups. For this study, *survival plateau* was defined as, "the first point at which the cohort's OS did not change within the subsequent 6 months." The Chi-square Log-rank test was used to compare OS between neonates (<1 month) and older patients (>1 month to <2 years). For simplicity, we grouped intracranial teratomas with the other germ cell tumors in the solid tumors category per ICCC. $P < 0.05$ was considered significant.

Results

There were 615 (310 males) neonates registered with malignancies. The number of diagnosed patients decreased to 330 at 2 months and 346 at 3 months. The total number of patients registered older than 1 month and <2 years of age were 7804 patients. Solid tumors were the most common diagnosis ($n = 454$), followed by leukemias/lymphomas ($n = 93$), and CNS tumors ($n = 68$). Neuroblastoma was the most prevalent tumor (RF = 0.28), followed by germ cell tumors (RF = 0.27) (Table 1). About 25% of the cases were from the early era (1973–1990), and the rest were from the later era (1991–2007); 502 (81.6%) patients were white.

General outcome

The 5-year OS for all neonates was 60.3% (95% CI, 56.2–64.4). Patients with solid tumors had the highest 5-year OS (71.2%; 95% CI, 66.9–75.5), followed by leukemia (39.1%; 95% CI 28.3–49.9), and CNS tumors (15%; 95% CI, 5.4–24.6) (Fig. 1, Table 2, Figure S1 and S2). Except for neuroblastoma, all of the neonatal tumors showed significantly inferior outcomes compared to that in older patients. Lymphoma and hepatoblastoma data were removed from further analysis because those subgroups included fewer than 10 cases.

The proportion of neonates who died of noncancer causes was higher than that of older patients (37.9% vs. 16.4%; Chi–square $P < 0.0005$) (Tables S2–S4). Cancer–specific and noncancer-related OS was significantly better in older patients from the later era than in those from the earlier era; however, OS did not improve in neonates (Fig. 2). Most neonates died within 1 month of diagnosis, either from cancer (36.2%) or other causes (59.3%) (data not shown, Fig. 3, Table 3). Interventions across eras are presented in Figure S3.

Solid tumors

Neuroblastoma

Neuroblastoma was the most common neonatal tumor ($n = 174$, RF = 0.28) in the SEER database. Male neonates comprised 60% of patients. The 5–year OS was 76.8% (95% CI, 70.3–83.3), with a survival plateau after 30 months (Table S6). There was no difference in OS based on sex, race, era, or region (Table 2). In cases of neuroblastoma, there was no significant difference in survival between neonates and the older group (Log–rank $P = 0.062$) (Table 2).

The adrenal gland was the most common primary tumor site, occurring in almost 50% of neuroblastoma cases, followed by connective tissue, the retroperitoneum,

Table 1. Frequency and relative frequency of neonatal cancers according to broad grouping and ICCC categories.

		Gender (RF)		Race		Era		
ICCC Broad	Grouping	Male	Female	White	Non-White	1973–1990	1991–2007	Total (RF)
Leukemias and Lymphomas (*n* = 93)	I Leukemias, myeloproliferative & myelodysplastic diseases:	46 (0.54)[1]	39 (0.46)[1]	69	16	13	72	85 (0.14)[2]
	I(a) Lymphoid leukemias	12	8	15	5	3	17	20 (0.24)[1]
	I(b) Acute myeloid leukemias	19	23	36	6	7	35	42 (0.49)[1]
	I(c) Chronic myeloproliferative diseases	2	0	2	0	1	1	2 (0.02)[1]
	I(d) Myelodysplastic syndrome and other myeloproliferative	1	0	1	0	0	1	1 (0.01)[1]
	I(e) Unspecified and other specified leukemias	12	8	15	5	2	18	20 (0.24)[1]
	II Lymphomas and reticuloendothelial neoplasms	4 (0.50)[1]	4 (0.50)[1]	7	1	1	7	8 (0.01)[2]
	II(a) Hodgkin lymphomas	0	1	1	0	0	1	1 (0.13)[1]
	II(b) Non-Hodgkin lymphomas (except Burkitt lymphoma)	1	0	1	0	0	1	1 (0.13)[1]
	II(d) Miscellaneous lymphoreticular neoplasms	3	3	5	1	1	5	6 (0.75)[1]
CNS tumors (*n* = 68)	III CNS and misc intracranial and intraspinal neoplasms	35 (0.51)[1]	33 (0.49)[1]	58	10	22	46	68 (0.11)[2]
	III(a) Ependymomas and choroid plexus tumor	4	2	4	2	2	4	6 (0.09)[1]
	III(b) Astrocytomas	12	15	22	5	11	16	27 (0.40)[1]
	III(c) Intracranial and intraspinal embryonal tumors	13	13	25	1	7	19	26 (0.38)[1]
	III(d) Other gliomas	4	2	5	1	1	5	6 (0.09)[1]
	III(f) Unspecified intracranial and intraspinal neoplasms	2	1	2	1	1	2	3 (0.04)[1]
Other solid tumors (*n* = 451 + 3 patients were not classified by ICCC)	IV Neuroblastoma and other peripheral nervous cell tumors	103 (0.59)[1]	71 (0.41)[1]	143	31	58	116	174 (0.28)[2]
	IV(a) Neuroblastoma and ganglioneuroblastoma	103	70	142	31	58	115	173 (0.99)[1]
	IV(b) Other peripheral nervous cell tumors	0	1	1	0	0	1	1 (0.01)[1]
	V Retinoblastoma	13 (0.48)[1]	14 (0.52)[1]	21	6	7	20	27 (0.04)[2]
	VI(a) Nephroblastoma and other nonepithelial renal tumors	9 (0.56)[1]	7 (0.44)[1]	14	2	10	6	16 (0.03)[2]
	VII(a) Hepatoblastoma	4 (0.57)[1]	3 (0.43)[1]	6	1	3	4	7 (0.01)[2]
	IX Soft tissue and other extraosseous sarcomas	27 (0.53)[1]	24 (0.47)[1]	43	8	16	35	51 (0.08)[2]
	IX(a) Rhabdomyosarcomas	11	8	17	2	8	11	19 (0.37)[1]
	IX(b) Fibrosarcomas, peripheral nerve & other fibrous	9	13	17	5	7	15	22 (0.43)[1]
	IX(d) Other specified soft tissue sarcomas	7	3	9	1	1	9	10 (0.20)[1]
	X Germ cell & trophoblastic tumors & neoplasms of gonads	63 (0.38)[1]	105 (0.63)[1]	134	34	23	143	168 (0.27)[2]
	X(a) Intracranial & intraspinal germ cell tumors	7	13	17	3	0	20	20 (0.12)[1]
	X(b) Extracranial & extragonadal germ cell tumors	55	91	115	31	23	123	146 (0.87)[1]
	X(c) Malignant gonadal germ cell tumors	1	0	1	0	0	1	1 (0.01)[1]
	X(e) Other and unspecified malignant gonadal tumors	0	1	1	0	0	1	1 (0.01)[1]
	XI Other malignant epithelial neoplasms and melanomas	1 (0.25)[1]	3 (0.75)[1]	2	2	2	2	4 (0.01)[2]
	XI(d) Malignant melanomas	1	2	2	1	2	1	3 (0.75)[1]
	XI(f) Other and unspecified carcinomas	0	1	0	1	0	1	1 (0.25)[1]
	XII Other and unspecified malignant neoplasms	2 (0.50)[1]	2 (0.50)[1]	4	0	2	2	4 (0.01)[2]
	XII(a) Other specified malignant tumors	1	1	2	0	0	2	2 (0.50)[1]
	XII(b) Other unspecified malignant tumors	1	1	2	0	2	0	2 (0.50)[1]
	Not classified by ICCC	3	0	1	2	1	2	3
	Grand Total	310 (0.50)[2]	305 (0.50)	502	113	158	457	

RF, relative frequency; RTh, radiation therapy; Surg, surgery.

[1]Relative frequency was calculated as a fraction of the ICCC group.

[2]Relative frequency was calculated as a fraction of total cases.

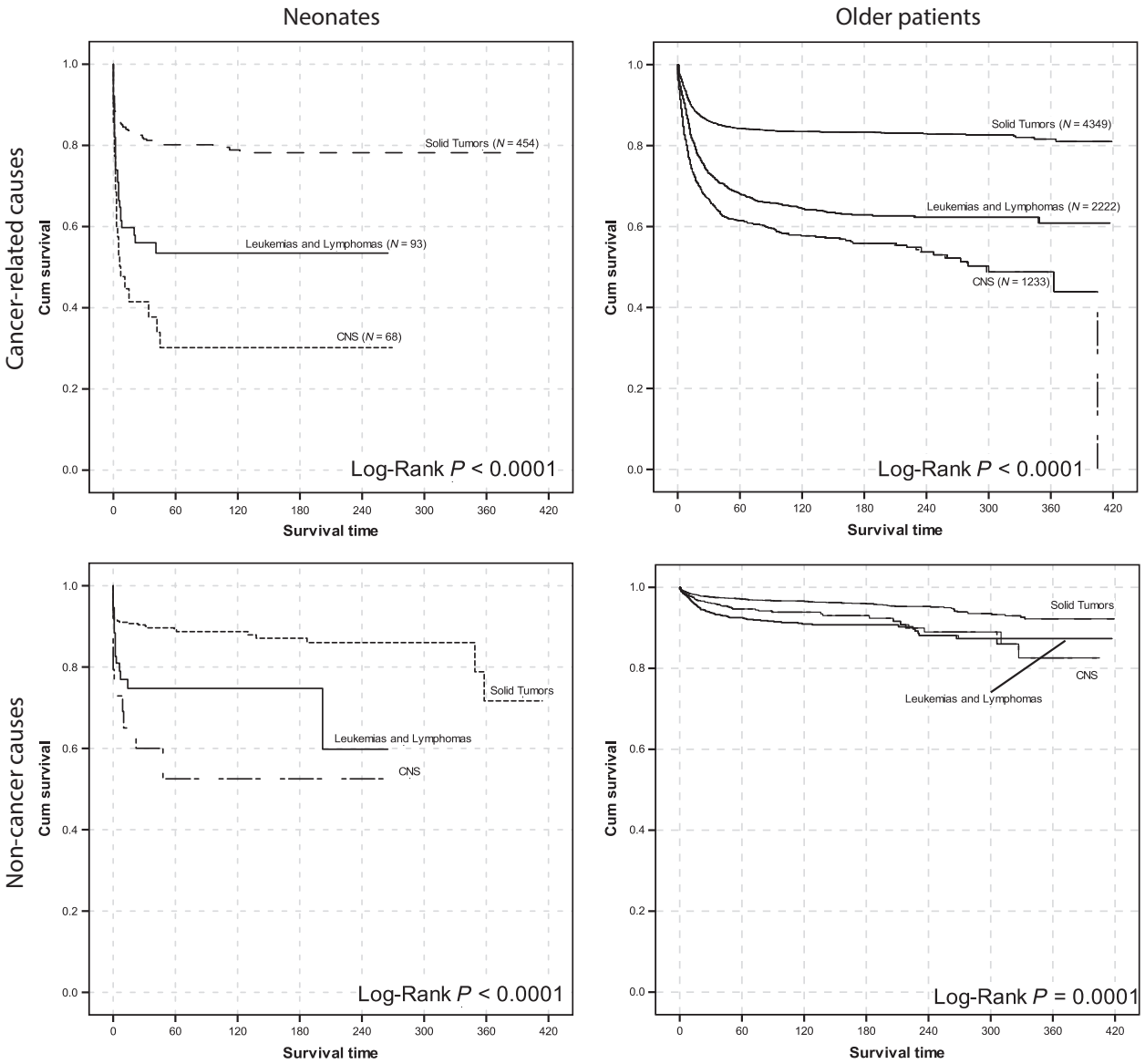

Figure 1. Survival of neonatal patients and older patients grouped based on ICCC categories. Cancer-specific and noncancer-related deaths are separated.

and the mediastinum. Adrenal gland tumors appeared to have the lowest 5–year OS (69.7%; 95% CI, 59.7–79.7), but the difference was not significant (Table S5). No secondary cancers occurred in neonates with neuroblastoma.

Retinoblastoma

The SEER records revealed 27 cases of retinoblastoma (RF = 0.04). The 5–year OS of neonates with retinoblastoma was 91.7% (95% CI, 80.5–100) (Table 2), with a survival plateau after 6 months (Table S6). This group experienced the highest OS among the neonatal disease subgroups. The OS of older patients who had retinoblastoma was significantly better than that of the neonates (Log-rank P = 0.043). Only one patient with retinoblastoma had secondary cancer.

Nephroblastoma

Renal tumors were also rare (n = 16; RF = 0.03). The 5–year OS for neonates with nephroblastoma was 62.5% (95% CI, 38.8–86.2) (Table 2), with a survival plateau after 6 months (Table S6). Older patients had a significantly higher OS (87.9%; 95% CI, 85.4–90.4; P < 0.001).

Table 2. Five-year overall survival of patients in each ICCC category with common subtypes having cases more than the predetermined cutoff and according to sex, race, era of diagnosis, geographic region and treatment received.

Broad Grouping	ICCC	Gender (95% CI)		Race (95% CI)		Era of diagnosis (95% CI)			
		Male	Female	White	Non - White	1973–1990	1991–2007	Total (95% CI)	>1 month–2 years
Leukemias	I Leukemias, myeloproliferative & myelodysplastic diseases:	41.6 (25.9–57.3)	37.7 (22.2–53.2)	39.9 (27.4–52.4)	36.5 (12.4–60.6)	43.3 (15.3–71.3)	38.4 (26.2–50.6)	39.1 (27.9–50.3)	62.8 (60.4–65.2)[1]
	I(a) Lymphoid leukemias							25 (2.9–47.1)	
	I(b) Acute myeloid leukemias							48.6 (33.1–64.1)	
	I(e) Unspecified and other specified leukemias							36.8 (13.7–59.9)	
CNS tumors	III CNS and misc intracranial and intraspinal neoplasms	17 (2.9–31.1)	12.4 (0–25.1)	19.3 (8.1–30.5)		9.1 (0–21.1)	19.1 (5.6–32.6)	15 (5.4–24.6)	58.5 (55.6–61.4)[1]
	III(b) Astrocytomas							22.9 (5.7–40.1)	
	III(c) Intracranial and intraspinal embryonal tumors							9.4 (0–21.6)	
Other solid tumors	IV Neuroblastoma and other peripheral nervous cell tumors	79.7 (71.7–87.7)	72.5 (61.9–83.1)	77.8 (70.9–84.7)	70.1 (52.7–87.5)	70.6 (58.8–82.4)	80.1 (72.7–87.5)	76.8 (70.3–83.3)	78.6 (76.4–80.8)[2]
	V Retinoblastoma	83.9 (63.5–100)	100	–	–	–	–	91.7 (80.5–100)	95.7 (94.1–97.3)[3]
	VI(a) Nephroblastoma and other nonepithelial renal tumors							62.5 (38.8–86.2)	87.9 (85.4–90.4)[1]
	IX Soft tissue and other extraosseous sarcomas	46.7 (25.7–67.7)	59.8 (39.2–80.4)	–	–	62.5 (38.8–86.2)	45 (25.6–64.4)	52.4 (37.5–67.3)	71.5 (67–76)[1]
	IX(a) Rhabdomyosarcomas							36.3 (12.8–59.8)	
	IX(b) Fibrosarcomas, peripheral nerve & other fibrous							76 (57.4–94.6)	
	IX(d) Other specified soft tissue sarcomas							31.1 (0–64)	
	X Germ cell & trophoblastic tumors & neoplasms of gonads	61.9 (48–75.8)	71.7 (62.7–80.7)	68.9 (60.5–77.3)	66.9 (49.7–84.1)	51.2 (30.4–72)	71.3 (63.3–79.3)	68.3 (60.7–75.9)	84 (79.9–88.1)[1]
	X(a) Intracranial & intraspinal germ cell tumors							25 (6–44)	
	X(b) Extracranial & extragonadal germ cell tumors	63.1 (47.6–78.6)	80.7 (72.1–89.3)	75.1 (66.5–83.7)	73.5 (56.3–90.7)	51.2 (30.4–72)	79.2 (71–87.4)	74.5 (66.7–82.3)	
	Grand Total	59.3 (53.4–65.2)	61.3 (55.6–67)	60.8 (56.3–65.3)	57.2 (47.2–67.2)	57.3 (49.5–65.1)	61.3 (56.4–66.2)	60.3 (56.2–64.4)	72.7 (71.7–73.7)[1]

RTh, radiation therapy; Surg, surgery.

[1]$P \leq 0.001$.

[2]No statistics were calculated because the group had fewer than 10 patients.

[3]$P = 0.043$.

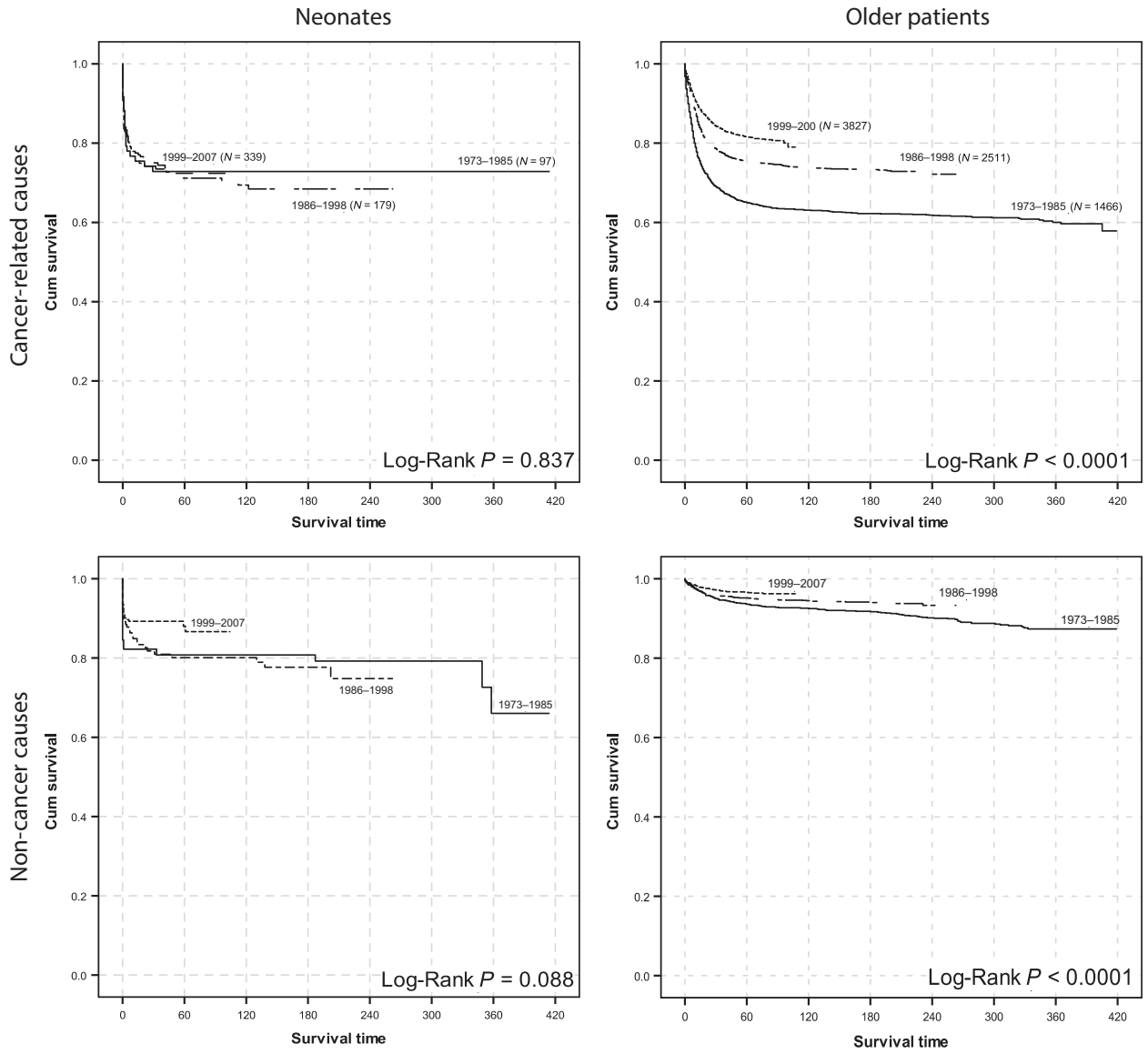

Figure 2. Survival of neonatal patients and older patients during the last three decades. Cancer-specific and noncancer-related deaths are separated.

Soft-tissue tumors

Fifty-one neonates had soft-tissue tumors (RF = 0.08) (Table 1). The 5-year OS for these patients was 52.4% (95% CI, 37.5–67.3), with a survival plateau after 18 months (Tables 2, S6). There was no difference in OS on the basis of sex, race, era, or region. Older patients with soft-tissue tumors had a significantly higher OS (71.5%; 95% CI, 67–76; P = 0.001).

Rhabdomyosarcomas and fibrosarcomas comprised the main histologies of soft-tissue tumors in this study. Patients with fibrosarcomas had a 5-year OS of 76% (95% CI, 57.4–94.6), which was significantly higher than that of patients with rhabdomyosarcomas (36.3%; 95% CI, 12.8–59.8) (Table 2). Connective tissue was the most common primary site of soft-tissue tumors. Fibrosarcomas occurred mainly in the limbs, and rhabdomyosarcomas occurred mainly in the head and neck (data not shown).

Germ cell tumors

Germ cell tumors were the second-most common neonatal tumors in the SEER database (RF = 0.27); 168 neonates had germ cell tumors, 20 of which were CNS tumors. Of the remaining 148 cases, two were gonadal and 146 were extragonadal. Female neonates comprised 62% of cases (Table 1). The 5-year OS of neonates with

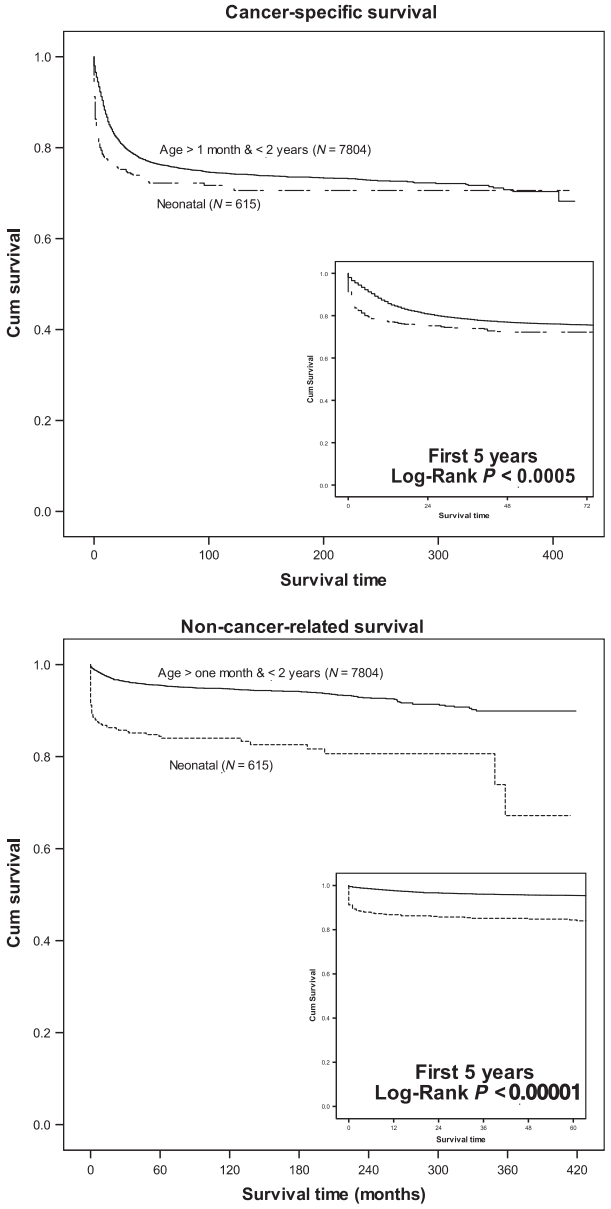

Figure 3. Comparison of cancer-specific and noncancer-related survival between neonates and older patients with cancer.

germ cell tumors was 68.3% (95% CI, 60.7–75.9), with a survival plateau after 12 months (Tables 2 and S6). The 5-year OS for neonates with extracranial or extragonadal germ cell tumors was 74.5% (95% CI, 66.7–82.3), which was significantly higher than that for neonates with CNS tumors (25%; 95% CI, 6–44) (Table 2). The 5-year OS did not differ based on sex, race, era, or region. Older patients had a significantly higher OS than did the neonates (84%; 95% CI, 79.9–88.1; $P < 0.001$). Two patients with germ cell tumors had secondary cancers.

Table 3. Proportion of patients who died of either noncancer- or cancer-related causes.

Age Group	Cause of death*		
	Noncancer *n* (%)	Cancer *n* (5)	Total
Neonate	91 (37.9)	149 (62.1)	240
Older	349 (16.4)	1780 (83.6)	2129
Total	440 (18.6)	1929 (81.4)	2369

*Pearson Chi-Square = 66, $P < 0.0005$.

Leukemias

Leukemias comprised 14% of our cohort, of which 49% were acute myeloid leukemia (AML), and 24% were acute lymphocytic leukemia (ALL) (Table 1). The 5-year OS for all leukemia cases was 39.1% (95% CI, 27.9–50.3), with a survival plateau after 24 months (Table 2 and S6). Patients with AML appeared to have a higher 5-year OS than did those with ALL, but the difference was not significant ($P = 0.403$). Survival of the older patients with leukemia was 62.8% (95% CI, 60.4–65.2), which was significantly higher ($P < 0.001$) than that of the neonates (Table 2). There was no difference in 5-year OS among neonates based on sex, race, era, or region. One patient suffered a secondary cancer.

CNS tumors

CNS tumors were the fourth-most common tumors affecting neonates in this study (RF = 0.11; Table 1, Table S7). Astrocytoma was the most common histology (40%), followed by intracranial and intraspinal embryonal tumors (38%). Of the 26 intracranial embryonal tumors, 17 were PNET, and seven were medulloblastomas (Table S1). The 5-year OS was 15% (95% CI, 5.4–24.6), with a survival plateau after 24 months (Tables 2, S6). Patients with astrocytomas had a 5-year OS of 22.9% (95% CI, 5.7–40.1), which appeared to be higher than that of those with intracranial or intraspinal embryonal tumors (9.4%; 95% CI, 0–21.6) (Table 1), but the difference was not significant. Survival of the older patients was 58.5% (95% CI, 55.6–61.4), which was significantly higher than that of the neonates ($P < 0.001$) (Table 2).

Discussion

Tumors rarely arise during the first month of life. In the U.K., only 303 neonates with cancer were reported over a 3–decade period [4]. To the best of our knowledge, this study represents the largest cohort of neonatal cancers ever studied. Nevertheless, the increasing number of patients over time is related to the fact that the 17

registries are enrolled in the SEER program over the period between 1973 and 2000 and pooled their patients gradually to the database [17].

Neonates with tumors experienced significantly inferior outcome compared with that of older patients who had the same disease, except for those with neuroblastoma. We believe the one cause of this difference could be treatment denial for newborns. This hypothesis is supported by the higher rate of death due to causes other than cancer among neonates in our study (Table S4). In our study 50.1% of children died of causes other than cancer (27% from congenital anomalies and 23.1% from perinatal conditions as defined in ICD-10-CM Guidelines [18]). This highlights another limitation of SEER data and our study and makes concrete conclusions difficult but it also underscores again our plea for further support and wider access to detailed data from patients reported on SEER.

Many neonates with tumors probably die of cardiac and/or respiratory dysfunction secondary to their untreated cancer. One possible explanation is that these infants are treated in neonatal intensive care units, and the decision to not treat their disease is occasionally made without consulting a pediatric oncologist. This explanation requires further investigation and conducting wider retrospective and prospective studies. Unfortunately, the SEER does not provide public access to information (to the time of writing this article) on chemotherapy regimens, so we cannot conclude anything about the prevalence of that approach to treating neonates.

Other studies have documented withholding therapy from neonates with cancer. In Isaacs' study [9] of 154 children with CNS tumors, 120 were not offered any treatment, but the 34 who received any kind of therapy experienced superior outcome. However, no quality-of-life data were provided.

We are not proposing aggressive treatment of all neonates, especially those with CNS tumors, without consideration of quality of life, or in patients with serious comorbidities or congenital anomalies (Table S4) as this may cause more harm than benefit. In a study from Japan, 76% of neonates who survived CNS tumors suffered mental retardation [10]. We propose that special attention be given to neonates to determine the optimal therapy with minimal toxicity (e.g., differentiating agents) that can be administered [1, 12, 13].

As reported by others [4], we found a disturbing lack of improvement in outcome over the last 34 years in all of the neonatal tumors we investigated. The fact that even with the major advances in medicine, oncologic treatment, supportive care, and neonatology care the outcome in the third period is not much different than 30 years earlier underscores that the major hindrance is related to age group and not other external factors. In older children, survival of every tumor type improved every decade. We believe the lack of outcome improvement, despite all the medical advancements, could result from depriving many neonates effective (or any) therapy. For each tumor group, the outcome of neonates was worse than that of older children. A similar observation was made in the U.K. neonatal cohort, even in cases in which the tumors were associated with a good prognosis [4].

In our study, neuroblastoma was the most common neonatal tumor. Most other neonatal cancer studies have reported teratomas as the most common neoplasm, followed by neuroblastoma [1, 5]. This difference may reflect the fact that the SEER registry does not report mature teratomas. The 5-year OS in our study was 76.8%, which is comparable to that in other studies (74% [19] and 88.3% [11]). In addition, Isaacs reported improved survival between cases before 1983 and those diagnosed thereafter. Era did not affect survival in our study.

The second-most common tumor in our study was germ cell tumors. The SEER database does not include mature or benign tumors before 2004; therefore, it is difficult to compare the outcome of those diseases with that of such tumors in other studies. Acute leukemias are rare in neonates, compared to their incidence in older children [20]. The distinction between congenital and neonatal leukemia is arbitrary, and most reports discuss congenital, neonatal, and infantile leukemias as a single group [6, 21]. Our study confirmed that patients with neonatal leukemias have a much poorer prognosis than older patients and less improvement in outcome, especially for those with ALL [4, 6, 7]. AML was the more common diagnosis than ALL in neonates, which was the case in earlier reports [21, 22]. The prognosis of neonates with AML was also better than that of neonates with ALL, which supports results from all other reports [7, 21] and contradicts what is seen in older children. This difference might reflect the fact that neonatal AML is closely related to transient myeloproliferative disorder, which shows spontaneous remission in most of cases.

Recently, an update for WHO Classification for Pediatric Brain Tumors has removed PNET as an entity from the classification and it was integrated in embryonal tumors. The diagnoses of this group became dependent on the presence C19MC amplification [23]. The new classification cannot be retrospectively implemented on the current SEER data without access to their histopathology and immunohistochemistry panels.

Neonates with cancer died faster than older children with cancer either from cancer or noncancer-related causes. However, noncancer-related deaths differentiated survival between neonatal and older patients. The 30-year OS of patients who experienced neonatal cancers equaled that of those who experienced cancer at an older age. Survival

plateaus can help researchers interpret the crucial periods for each tumor entity. We believe that some cancer-related deaths that occurred during the first month of life can be attributed to insufficient supportive care. Askin [24] outlined a supportive care plan for patients with neonatal cancer that we believe should be further investigated.

This research could not have been done without the SEER administrative team's approval. We believe that the SEER data is a crucial tool toward increasing our understanding of rare cancers, although its limitations [25]. For example, it would be interesting to investigate the incidence of second cancers and familial cancers in these children and their families because many believe neonatal tumors are indicative of genetic predisposition [2]. Previous studies have shown a correlation between congenital anomalies and childhood cancers [26–28]. We believe and propose that improving funding for SEER to acquire data on comorbidities, tumor biology, details of received treatments and even contacting surviving patients and their families for genetic testing or long term effects studies will open the flood gates of unlimited research opportunities. The concept of wider access to data will only enhance science [29, 30].

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Conflict of Interest

No conflict of interest to be disclosed by authors.

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Supporting Information

Additional supporting information may be found in the online version of this article:

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Supplementary Data

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Supplementary Table 1.

ICCC categories and ICD-O-3 codes used in the study and frequency of patients (n).

Leukemias and Lymphomas	**n**	**CNS Tumors**	**n**	**Other Solid Tumors**	**n**
I(a) Lymphoid leukemias	**20**	**III(a) Ependymomas and choroid plexus tumor**	**6**	**IV(a) Neuroblastoma and ganglioneuroblastoma**	**173**
9835/3: Precursor cell lymphoblastic leukemia, NOS	16	9390/3: Choroid plexus papilloma, malignant	2	9490/3: Ganglioneuroblastoma	3
9836/3: Precursor B-cell lymphoblastic leukemia	4	9391/3: Ependymoma, NOS	2	9500/3: Neuroblastoma, NOS	170
I(b) Acute myeloid leukemias	**42**	9392/3: Ependymoma, anaplastic	2	**IV(b) Other peripheral nervous cell tumors**	**1**
9861/3: Acute myeloid leukemia	21	**III(b) Astrocytomas**	**27**	9501/3: Medulloepithelioma, NOS	1
9867/3: Acute myelomonocytic leukemia	3	9380/3: Glioma, malignant	1	**V Retinoblastoma**	**27**
9872/3: Acute myeloid leukemia, minimal differentiation	2	9400/3: Astrocytoma, NOS	11	9510/3: Retinoblastoma, NOS	26
9874/3: Acute myeloid leukemia with maturation	1	9401/3: Astrocytoma, anaplastic	3	9511/3: Retinoblastoma, differentiated	1
9891/3: Acute monocytic leukemia	7	9420/3: Fibrillary astrocytoma	1	**VI(a) Nephroblastoma and other nonepithelial renal tumors**	**16**
9910/3: Acute megakaryoblastic leukemia	8	9421/3: Pilocytic astrocytoma, malignant	2	8960/3: Nephroblastoma, NOS	13
I(c) Chronic myeloproliferative diseases	**2**	9440/3: Glioblastoma, NOS	8	8963/3: Malignant rhabdoid tumor	3
9863/3: Chronic myeloid leukemia, NOS	2	9442/3: Gliosarcoma	1	**VII(a) Hepatoblastoma**	**7**
I(d) Myelodysplastic syndrome and other myeloproliferative	**1**	**III(c) Intracranial and intraspinal embryonal tumors**	**26**	8970/3: Hepatoblastoma	7
9946/3: Juvenile myelomonocytic leukemia	1	9470/3: Medulloblastoma, NOS	7	**IX(a) Rhabdomyosarcomas**	**19**
I(e) Unspecified and other specified leukemias	**20**	9473/3: Primitive neuroectodermal tumor	17	8900/3: Rhabdomyosarcoma, NOS	2
9800/3: Leukemia, NOS	8	9503/3: Neuroepithelioma, NOS	1	8910/3: Embryonal rhabdomyosarcoma	13
9801/3: Acute leukemia, NOS	9	9508/3: Atypical teratoid/rhabdoid tumor	1	8920/3: Alveolar rhabdomyosarcoma	4
9805/3: Acute biphenotypic leukemia	2	**III(d) Other gliomas**	**6**	**IX(b) Fibrosarcomas, peripheral nerve & other fibrous**	**22**
9930/3: Myeloid sarcoma	1	9380/3: Glioma, malignant	4	8810/3: Fibrosarcoma, NOS	4
II(a) Hodgkin lymphomas	**1**	9382/3: Mixed glioma	1	8813/3: Fascial fibrosarcoma	1
9663/3: Hodgkin lymphoma, nodular sclerosis, NOS	1	9430/3: Astroblastoma	1	8814/3: Infantile fibrosarcoma	11
II(b) Non-Hodgkin lymphomas (except Burkitt lymphoma)	**1**	**III(f) Unspecified intracranial and intraspinal neoplasms**	**3**	9150/3: Hemangiopericytoma, malignant	4
9729/3: Precursor T-cell lymphoblastic lymphoma	1	8000/3: Neoplasm, malignant	3	9540/3: Malignant peripheral nerve sheath tumor	1
II(d) Miscellaneous lymphoreticular neoplasms	**6**			9580/3: Granular cell tumor, malignant	1

9740/3: Mast cell sarcoma	1			**IX(d) Other specified soft tissue sarcomas**	**10**
9741/3: Malignant mastocytosis	1			8832/3: Dermatofibrosarcoma, NOS	2
9754/3: Langerhans cell histiocytosis, disseminated	4			8890/3: Leiomyosarcoma, NOS	1
				8963/3: Malignant rhabdoid tumor	4
				9130/3: Hemangioendothelioma, malignant	2
				9231/3: Myxoid chondrosarcoma	1
				X(a) Intracranial & intraspinal germ cell tumors	**20**
				9080/3: Teratoma, malignant, NOS	20
				X(b) Extracranial & extragonadal germ cell tumors	**146**
				9070/3: Embryonal carcinoma, NOS	2
				9071/3: Yolk sac tumor	4
				9080/3: Teratoma, malignant, NOS	134
				9081/3: Teratocarcinoma	3
				9085/3: Mixed germ cell tumor	3
				X(c) Malignant gonadal germ cell tumors	**1**
				9071/3: Yolk sac tumor	1
				X(e) Other and unspecified malignant gonadal tumors	**1**
				8631/3: Sertoli-Leydig cell tumor, poorly differentiated	1
				XI(d) Malignant melanomas	**3**
				8720/3: Malignant melanoma, NOS	3
				XI(f) Other and unspecified carcinomas	**1**
				8071/3: Squamous cell carcinoma, keratinizing, NOS	1
				XII(a) Other specified malignant tumors	**2**
				8936/3: Gastrointestinal stromal sarcoma	1
				8971/3: Pancreatoblastoma	1
				XII(b) Other unspecified malignant tumors	**2**
				8000/3: Neoplasm, malignant	2
				Not classified by ICCC or in situ	**3**
				8814/3: Infantile fibrosarcoma	1
				8963/3: Malignant rhabdoid tumor	1
				9364/3: Peripheral neuroectodermal tumor	1

Abbreviations: ICCC, International Classification of Childhood Cancer; *ICD-O-3, International Classification of Diseases for Oncology, 3rd edition*; NOS, not otherwise specified

Bold typeface indicates a category.

Supplementary Table 2.

Comparison of the causes of death across the age groups.

Age at Diagnosis (mos)	No. of patients	Cause of death		No. of living patients n (%)*
		Noncancer-related n (%)	Cancer-related n (%)	
<1	615	91 (14.8)	149 (24.2)	375 (61)
>1-2	330	20 (6.1)	75 (22.7)	235 (71.2)
>2-3	346	24 (6.9)	77 (22.3)	245 (70.8)
>3-<24	7128	305 (4.3)	162 (22.8)	5195 (72.9)
Total	8419	440 (5.2)	1929 (22.9)	6050 (71.9)

*The data reflect the number of living patients as of 8 August 2014.

Supplementary Table 3.

Comparison of the probabilities of survival of cancer or noncancer causes across the age groups

Cause of death	Age Group	Probability of survival at different times after diagnosis					
		1 mos	2 mos	3 mos	4 mos	1 y	5 y
Cancer	Neonates	.912	.863	.836	.824	.775	.722
Cancer	Older patients	.980	.966	.955	.945	.867	.762
Noncancer	Neonates	.912	.894	.886	.884	.868	.844
Noncancer	Older patients	.995	.992	.991	.988	.978	.955

Supplementary Table 4.

Comparisons of the causes of death (other than the primary cancer) between patients who were neonates at diagnosis and those who were older (>1 month and <2 years).

	Age at Diagnosis							
	Neonatal (<1 month)				Older (>1 month– <2 years)			
			Survival (mos)				Survival (mos)	
Cause of Death	Count	Col. (%)*	Mean	SD	Count	Col. (%)*	Mean	SD
State DC not available or state DC available but no COD	28	30.8	6	14	86	24.6	57	80
Congenital Anomalies	25	27.5	3	9	15	4.3	9	14
Certain Conditions Originating during the Perinatal Period†	21	23.1	0	0	11	3.2	7	12
Other Cause of Death	6	6.6	14	23	109	31.2	31	61
Diseases of the Heart	4	4.4	95	175	18	5.2	102	103
Accidents and Adverse Effects	2	2.2	106	115	9	2.6	92	118
Septicemia	2	2.2	244	149	11	3.2	33	93
Chronic Liver Disease and Cirrhosis	1	1.1	0	.				
Bones and Joints	1	1.1	130	.	4	1.1	131	41
Brain and Other Nervous System	1	1.1	202	.	2	0.6	49	60
Other Infectious and Parasitic Diseases including HIV	.	.	.	.	26	7.4	27	51
Pneumonia and Influenza	.	.	.	.	22	6.3	34	68
Symptoms, Signs, and Ill-Defined Conditions	.	.	.	.	8	2.3%	16	19
Cerebrovascular Diseases	.	.	.	.	7	2.0%	51	72
Acute Myeloid Leukemia	.	.	.	.	5	1.4%	28	28
Homicide and Legal Intervention	.	.	.	.	3	0.9	146	116
Other Diseases of Arteries, Arterioles, Capillaries	.	.	.	.	3	0.9	25	20
Other Endocrine Dysfunction, including Thymus	.	.	.	.	3	0.9	37	25
Soft Tissue, including Heart	.	.	.	.	2	0.6	245	125
Hypertension without Heart Disease	.	.	.	.	1	0.3	25	.
In Situ, Benign, or Unknown Behavior Neoplasm	.	.	.	.	1	0.3	2	.
Kidney and Renal Pelvis	.	.	.	.	1	0.3	7	.
Nephritis, Nephrotic Syndrome, and Nephrosis	.	.	.	.	1	0.3	4	.
Acute Lymphocytic Leukemia					1	0.3	166	.

=								
Total	91	100	19	62	349	100	44	74

*Percentages in columns were ordered and colored from highest (red) to lowest (blue).
†The perinatal period was defined as the period immediately before, during, or less than a month after birth.
Abbreviations: DC, Death Code; COD, cause of death; Col. (%), percentage of column total; SD, standard deviation; mos, months

Supplementary Table 5.

The relative frequency of neuroblastoma diagnoses and 5-year overall survival of patients with that disease.

Site of Neuroblastoma	Frequency	RF	5-year overall survival (95% CI)
Adrenal gland	86	0.49	69.7 (59.7-79.7)
Connective tissue	35	0.20	85.1 (72.9-97.3)
Retroperitoneum	20	0.12	90 (76.9-100)
Mediastinum	11	0.06	88.9 (68.3-100)
Other*	22	0.13	72.7 (54-91.3)

*Other sites included the kidney, vertebral column, nervous system, thorax, abdomen, and unknown.

Supplementary Table 6.

Survival plateaus* for each ICCC category in the neonatal group.

ICCC category	Probability of Overall Survival (SE) after Diagnosis*									
	6	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**
Leukemias	49.4 (5.6)	45.3 (5.6)	43.9 (5.6)	**41 (5.6)**	41 (5.6)	41 (5.6)	39.1 (5.7)	39.1 (5.7)	39.1 (5.7)	39.1 (5.7)
CNS tumors	34.7(6)	27.6 (5.7)	25.6 (5.6)	**23.6 (5.5)**	23.6 (5.5)	21.5 (5.4)	19.3 (5.3)	15 (4.9)	15 (4.9)	15 (4.9)
Neuroblastoma	80.2 (3.1)	79.5 (3.1)	78.2 (3.2)	77.6 (3.2)	**76.8 (3.3)**	76.8 (3.3)	76.8 (3.3)	76.8 (3.3)	76.8 (3.3)	76.8 (3.3)
Retinoblastoma	**96.3 (3.6)**	96.3 (3.6)	96.3 (3.6)	96.3 (3.6)	91.7 (5.7)	91.7 (5.7)	91.7 (5.7)	91.7 (5.7)	91.7 (5.7)	91.7 (5.7)
Renal tumors	**68.8 (11.6)**	68.8 (11.6)	62.5 (12.1)	62.5 (12.1)	62.5 (12.1)	62.5 (12.1)	62.5 (12.1)	62.5 (12.1)	62.5 (12.1)	62.5 (12.1)
Soft-tissue tumors	70.3 (6.4)	62.8 (7)	**57.8 (7.3)**	57.8 (7.3)	57.8 (7.3)	55.2 (7.5)	52.4 (7.6)	52.4 (7.6)	52.4 (7.6)	52.4 (7.6)
Germ cell tumors	75.6 (3.3)	**74.9 (3.4)**	74.9 (3.4)	74.1 (3.4)	73.3 (3.5)	71.5 (3.6)	70.5 (3.7)	69.5 (3.8)	69.5 (3.8)	68.3 (3.9)

*The point at which survival probability did not change during the following 6 months was used to determine the start of the survival plateau.

*Survival probabilities were calculated every 6 months for each ICCC group until 5-year survival. ICCC groups with fewer than 10 patients were removed to avoid small-sample bias. Time points are noted as months from diagnosis, and survival plateaus for each ICCC category are noted in bold.

Supplementary Table 7.

Common sites of primary disease identified by the WHO 2008.

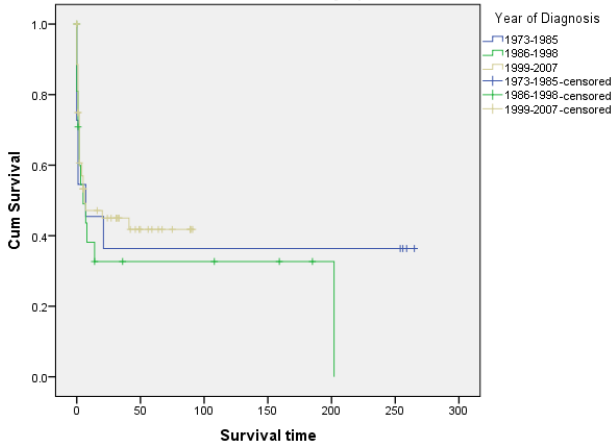
Sites	N
Soft tissue, including the heart	181
Other endocrine, including thymus	89
Brain	88
Blood	85
Miscellaneous	33
Eye and orbit	32
Retroperitoneum	25
Kidney and renal pelvis	21
Trachea, mediastinum, and other respiratory organs	17
Bones and joints	9
Liver	7
Cranial nerves and other nervous system	6
Tongue	3
Melanoma of the skin	2
Other, nonepithelial skin	2
Peritoneum, omentum, and mesentery	2
Urinary Bladder	2
Gum and other mouth	1
–Lymph node (Hodgkin)	1
Lung and bronchus	1
–Lymph node (Non-Hodgkin)	1
Oropharynx	1
Other oral cavity and pharynx	1
Ovary	1
Pancreas	1
Small intestine	1
Testis	1
Vulva	1
Total	615

Abbreviations: WHO, World Health Organization

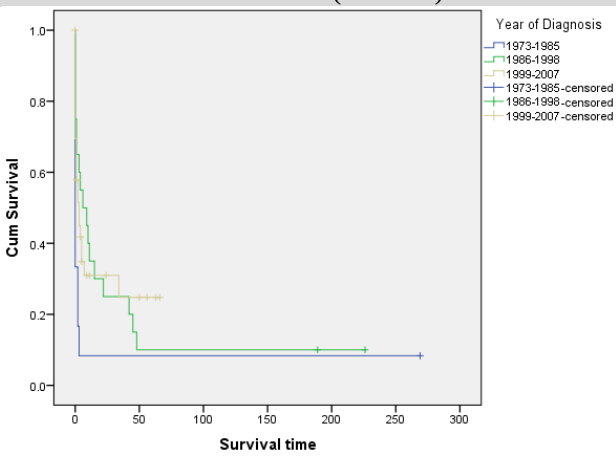
Supplementary Figure 1.

Survival by study groups by year of diagnosis. An “event” is defined as death due to cancer OR other causes.

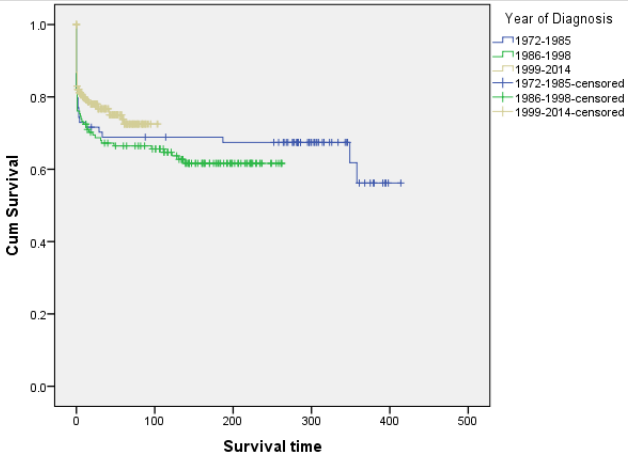
Leukemias and Lymphomas (P = 0.69)



CNS Tumors (P <0.005)

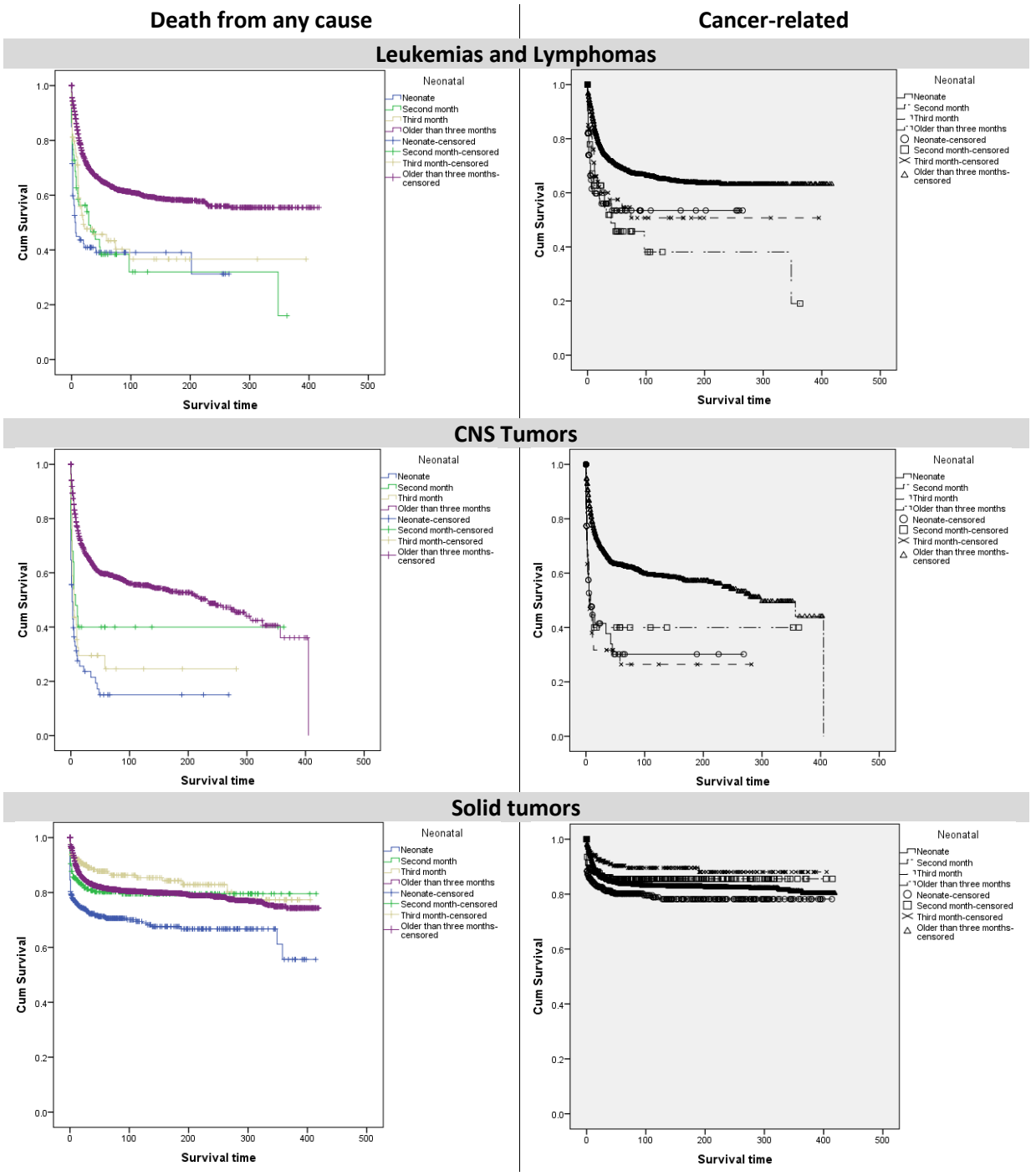


Solid Tumors (P >0.5)



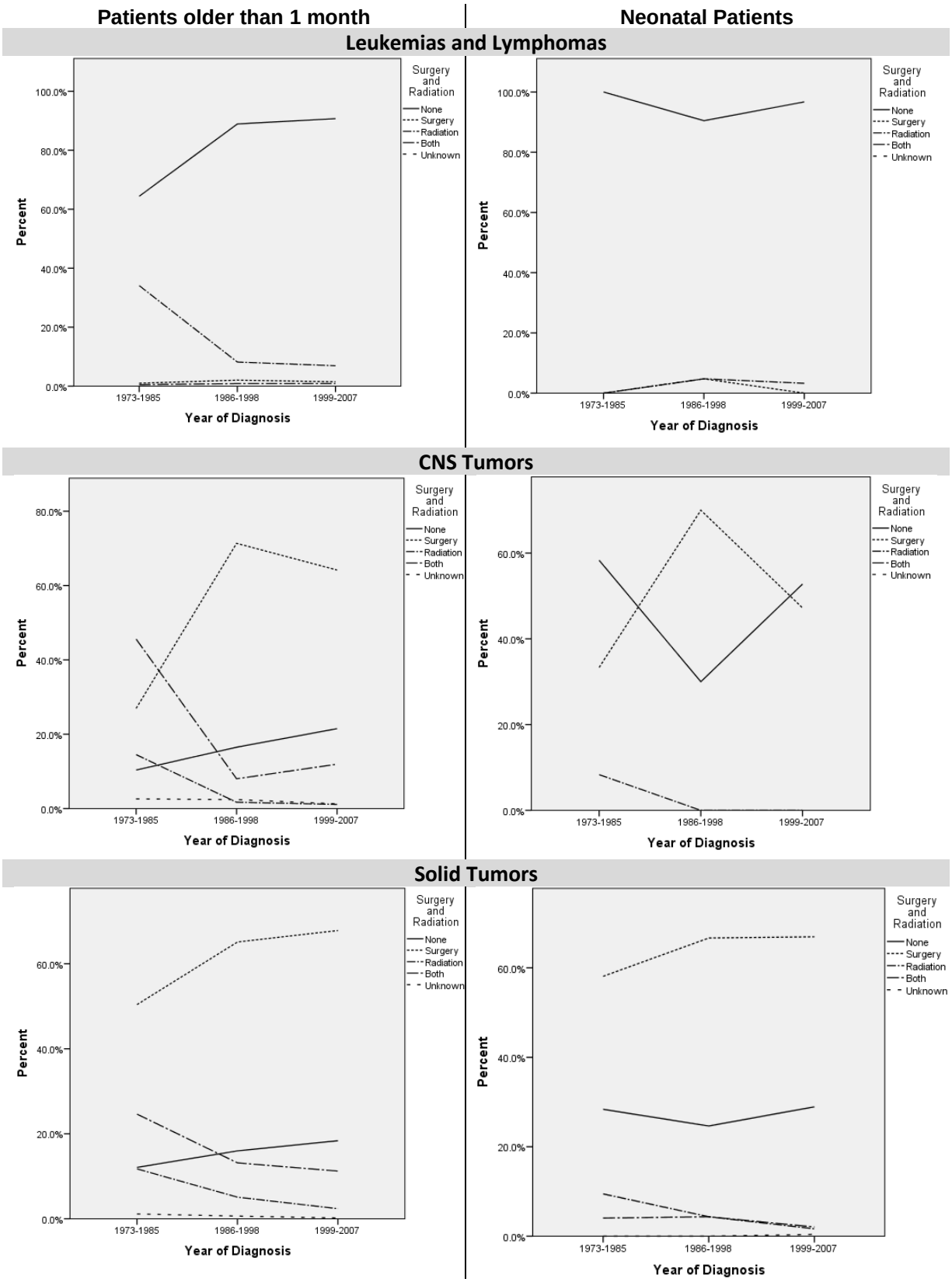
Supplementary Figure 2.

Comparison of cancer- vs. general survival on the basis of age at diagnosis and tumor category.



Supplementary Figure 3.

Comparisons of the pattern of intervention between neonatal and older patients over the last 3 decades.



·Clinical Research·

Incidence of orbital, conjunctival and lacrimal gland malignant tumors in USA from Surveillance, Epidemiology and End Results, 1973-2009

Waleed M. Hassan[1], Mohamed S. Bakry[1], Housam M. Hassan[2], Ahmad S. Alfaar[1,3]

[1]Research Department, Children Cancer Hospital Egypt 57357, Cairo 11441, Egypt
[2]Badr Hospital, Helwan University, Cairo 11795, Egypt
[3]Ophthalmology Department, Charité-Universtätsmedizin Berlin, Berlin 10117, Germany
Correspondence to: Ahmad S. Alfaar. Charité-Universtätsmedizin Berlin, Campus Virchow-Klinikum, Augenheilkunde-Forschung-CVK, Mittelallee 4, Room: 0030 0.1952, Augustenburger Platz 1, Berlin 13353 , Germany. ahmadsfar@gmail.com; ahmed.alfaar@charite.de
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Abstract

• AIM: To determine the types and incidence of tumors affecting the orbit, conjunctiva and lacrimal glands and to study the trend line of these tumors in the United States from 1973 to 2009.

• METHODS: We used the publicly available Surveillance, Epidemiology and End Results (SEER) database registries to determine the incidence rates. Age was adjusted to the 2000 US Standard Population. Patients were stratified according to age group, gender, race and histological grouping of tumor lesions. Three age groups were defined: 0-19, 20-49 and ≥50y. Annual percentage changes were calculated to examine trends.

• RESULTS: The overall age adjusted incidence rate was 3.39 (95% CI: 3.27-3.52) per million person-years. The tumors were more prevalent in age group ≥50 counting 9.51 (95%CI: 9.11-9.92) per million person-years. Most of the soft tissue sarcomas occurred in the young age with incidence rate of 0.35 (95% CI: 0.28-0.42) per million person-years. Lymphomas were the dominant subtype in the adult population with incidence rate of 5.74 (95%CI: 5.43-6.06) per million person-years. Incidence rates were higher in males than females with an overall rate ratio of 1.31 (95%CI: 1.21-1.41) mainly caused by the increase in carcinoma subtypes. White race had a higher tumor incidence with a rate ratio of 1.47 (95% CI: 1.25-1.73) driven by the higher incidence of most histological subtypes. Orbital tumors showed a higher incidence rate followed by conjunctival and lacrimal gland tumors with incidence rates of 1.59, 1.37 and 0.43 per million person-years respectively. The trend line of overall incidence of tumors showed a significant increase (APC=3.11, 95%CI: 2.61-3.61) mainly due to increase of lymphomas. This increase was higher than the increase of lymphomas at other sites.

• CONCLUSION: Orbital, conjunctival and lacrimal gland malignant tumors differ among children and adults. Over the years there has been a noticeable increase in incidence rates of orbital and lacrimal gland tumors mainly caused by an increase in lymphomas and an apparent increase due to advances in diagnostic techniques. ICD-O-3 topographical coding should be improved to consider the different orbital bones and ocular structures.

• **KEYWORDS:** orbital tumors; incidence; conjunctiva; lacrimal gland
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INTRODUCTION

Orbital lesions are frequently seen at ophthalmology clinics, but malignant forms of such lesions constitute a group of uncommon tumors. Many orbital, conjunctival and lacrimal gland (OCLG) malignant tumors are not at first suspected and thus initially misdiagnosed due to the lack of proper diagnostic methods, presentation to a general ophthalmologist and the lack of knowledge regarding the frequency of such tumors. This lack of knowledge is evident in paucity of literature covering the relative epidemiology and prognosis of these tumors. This study focused on incidence rates of OCLG malignant tumors. Only a few studies have discussed population-based pattern of orbital tumors incidence [1-2]. Most studies have focused on a special histological subtype or a particular age group. Other studies have investigated the population of a certain tertiary referral center-thus possibly showing referral bias[3-5].

In this study, we aimed at discovering the differences in incidence between malignant tumors originating from the OCLG, using data from the Surveillance, Epidemiology and End Results (SEER) Program database of the US National

Cancer Institute (NCI). Data analysis was carried out with a focus on incidence rates according to different histological categories-stratified by site, age, gender, and race.

SUBJECTS AND METHODS

The SEER database is a publicly available database covering cancer cases in the United States. This database collects patient information, including demographics, tumor site, morphology, and stage as well as treatment course and follow up survival data. In the database race is coded into three categories; White, African American, and "other" (American Indian native, Asian/Pacific). The "other" race category refers to a heterogeneous group of patients each comprising a small patient population and hence was removed during analysis. SEER data cover almost 28% of US inhabitants. Information from this data could be extrapolated from to make conclusions regarding the entire US population[6]. Cases in the current study were obtained from nine SEER registries collected over the period between 1973 and 2009. The SEER's nine registries are the Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound, and Utah registries. Data for cases diagnosed from 1973 and later are available in these registries with the exception of the Seattle-Puget Sound and Atlanta registries. These two joined the SEER program in 1974 and 1975, respectively. The nine registries used in this study cover approximately 10% of the US population. Population denominators used to calculate rates were extracted from the NCI data. NCI data modifies the population data produced by the US Census Bureau's Population estimate program based on a collaboration with the National Center of Health Statistics [7]. The SEER*Stat program was used to calculate frequencies, incidence rates and trends over time [7]. The database was accessed for data extraction in August 2013. Tumor sites of interest were identified and coded using the ICD-O3 codes as follows: C69.0, conjunctival; C69.5, lacrimal gland and C69.6, orbital. Similar histological subtypes were combined together into 4 groups in addition to a fifth group of rare and other unclassified malignant tumors. Only cases with known age and malignant behavior were included. Population was divided into 3 age categories: 0-19, 20-49 and ⩾50 years of age. Incidence rates were calculated per 1 000 000 person-years and age adjusted to the 2000 US Standard Population (single ages-Census P25-1130); confidence intervals (CIs) were set as 95% for rates and trends. Percentage changes were calculated using one year for each endpoint. Annual percentage changes (APC) were calculated using the weighted least-squares method. The APC were calculated based on the whole study duration. The principles outlined in the Declaration of Helsinki (2008) were followed.

RESULTS

The number of patients identified as having OCLG tumors were 2802 patients. The overall age-adjusted incidence rate for OCLG malignant tumors was 3.39 (95%CI: 3.27-3.52) per million person-years. The ⩾50 age group had the highest incidence rate of 9.51 per million person-years (95% CI: 9.11-9.92), while the 0-19 age group had the lowest incidence rate of 0.56 per million person-years (95% CI: 0.47-0.66). Incidence rates of different histological subtypes differed significantly between age groups. In the 0-19 age group, soft tissue sarcomas comprised the most common histological category with an incidence rate of 0.35 per million person-years (95%CI: 0.28-0.42). However, in the ⩾50 age group, the histological subtypes with the highest incidence rate were lymphomas at a rate of 5.74 per million person-years (95%CI: 5.43-6.06). Table 1 summarizes the more common histological subtypes found in each of the three age groups. Males had a statistically significantly higher rate ratio for the overall incidence of OCLG malignant tumors-compared to females of 1.31 (95% CI: 1.21-1.41). This increase was mainly caused by the increase in carcinoma subtypes in males [rate ratio 2.8 (95%CI: 2.36-3.32)].

There was a statistically significantly higher incidence rate among Whites compared to African Americans with a rate ratio of 1.47 (95%CI: 1.25-1.73). This higher incidence was noted in most histological subtypes, especially melanomas and carcinomas. The rate ratio for melanomas in the White population compared to African Americans was 3.75 (95% CI: 1.87-9.29), while that of carcinomas was 1.5 (95%CI: 1.08-2.14). Table 1 displays rate ratios of different histological subtypes according to gender and race.

The incidence rate was statistically significantly higher for orbital tumors at 1.59 per million person-years (95% CI: 1.50-1.68) compared with conjunctival tumors at 1.37 per million person-years (95%CI: 1.30-1.46) and lacrimal gland tumors at 0.43 per million person-years (95%CI: 0.39-0.48). When the incidence rate of each histological category was stratified according to site, carcinomas and melanomas were statistically significantly higher in conjunctiva than orbit and lacrimal glands. While for lymphomas, the orbit incidence rate was statistically significantly higher than the conjunctival and lacrimal gland rates. More details about the incidence rates according to site are available in Table 2.

The trend line of disease showed significant increase over the years. The annual percent change (APC) was a statistically significant 3.11 (95% CI: 2.61-3.61). This increase was mainly caused by an increase in lymphoma subtypes (APC=4.8, 95% CI: 3.8-5.82). APC was also statistically significant for melanomas and carcinomas but at lower percent increase. Trend analysis stratified according to gender showed that there was no statistically significant difference between both genders. When the trend was stratified according to race, APC could not be computed for African Americans due to the small sample size. Table 3

Table 1 Common histology according to gender, race and age groups

Histology	Statistic	Gender			Race			Age category			
		M	F	Rate ratio	White	African American	Rate ratio	0-19	20-49	⩾50	Total (all age groups)
Carcinomas	Rate[1]	1.27	0.45	2.8[a]	0.80	0.54	1.5[a]	0.02	0.34	2.31	0.79
	95%CI	1.15-1.4	0.39-0.52	2.36-3.32	0.74-0.87	0.38-0.74	1.08-2.14	0.01-0.05	0.28-0.4	2.11-2.51	0.73-0.85
	Count	439	209		554	41		6	126	516	648
Melanomas	Rate	0.48	0.39	1.22	0.47	0.13	3.75[a]	0.03	0.21	1.18	0.43
	95%CI	0.41-0.56	0.34-0.46	0.98-1.51	0.42-0.53	0.05-0.25	1.87-9.29	0.02-0.07	0.17-0.26	1.04-1.33	0.39-0.48
	Count	177	180		328	8		9	80	268	357
Soft tissue sarcomas	Rate	0.15	0.15	1.05	0.15	0.15	0.98	0.35	0.05	0.11	0.15
	95%CI	0.12-0.2	0.11-0.19	0.74-1.50	0.12-0.18	0.09-0.25	0.57-1.74	0.28-0.42	0.03-0.08	0.07-0.16	0.13-0.18
	Count	70	67		106	18		91	22	24	137
Lymphomas and reticular malignancies	Rate	1.92	1.94	0.99	1.90	1.46	1.31[a]	0.09	0.72	5.74	1.93
	95%CI	1.78-2.08	1.81-2.07	0.90-1.10	1.8-2.01	1.18-1.78	1.06-1.63	0.06-0.14	0.63-0.81	5.43-6.06	1.83-2.02
	Count	692	888		1307	103		25	261	1294	1580
Other rare and unclassified malignancies	Rate	0.12	0.08	1.52	0.1	0.07	1.47	0.06	0.07	0.17	0.09
	95%CI	0.08-0.16	0.05-0.11	0.94-2.43	0.08-0.13	0.03-0.14	0.66-3.59	0.03-0.1	0.04-0.1	0.12-0.24	0.08-0.12
	Count	44	36		68	8		16	27	37	80
Total	Rate	3.94	3.01	1.31[a]	3.43	2.34	1.47[a]	0.56	1.39	9.51	3.39
	95%CI	3.74-4.16	2.85-3.17	1.21-1.41	3.29-3.57	1.99-2.73	1.25-1.73	0.47-0.66	1.27-1.51	9.11-9.92	3.27-3.52
	Count	1422	1380		2363	178		147	516	2139	2802

[1]Rates are per 1 000 000 and age-adjusted to the 2000 US Standard Population (19 age groups-Census P25-1130) standard; Confidence intervals (Tiwari mod) are 95% for rates and ratios. [a]The rate ratio indicates that the rate is significantly different from the rate for the other comparison group (P<0.05).

Table 2 Incidence rates according to site and histological category

Site	Statistic	Carcinomas	Melanomas	Soft tissue sarcomas	Lymphomas and reticular malignancies	Other rare and unclassified malignancies	Total
C69.0-conjunctiva	Rate[1]	0.45	0.35	0	0.55	0.02	1.37
	95%CI	0.41-0.5	0.31-0.4		0.5-0.6	0.01-0.03	1.3-1.46
	Primary tumors	311	246	0	410	12	979
	Second tumors[2]	60	48	0	46	1	155
	Total count	371	294	0	456	13	1134
C69.5-lacrimal gland	Rate	0.18	0	0.01	0.24	0	0.43
	95%CI	0.15-0.21	0-0.01	0-0.02	0.21-0.27	0-0.01	0.39-0.48
	Primary tumors	137	3	8	166	3	317
	Second tumors	12	0	0	33	0	45
	Total count	149	3	8	199	3	362
C69.6-orbit, NOS	Rate	0.16	0.07	0.14	1.14	0.08	1.59
	95%CI	0.13-0.19	0.06-0.09	0.12-0.17	1.06-1.21	0.06-0.1	1.5-1.68
	Primary tumors	105	50	121	785	60	1121
	Second tumors	23	10	8	140	4	185
	Total count	128	60	129	925	64	1306
Total	Rate	0.79	0.43	0.15	1.93	0.09	3.39
	95%CI	0.73-0.85	0.39-0.48	0.13-0.18	1.83-2.02	0.08-0.12	3.27-3.52
	Primary tumors	553	299	129	1,361	75	2417
	Second tumors	95	58	8	219	5	385
	Total count	648	357	137	1,580	80	2802

[1]Rates are per 1 000 000 and age-adjusted to the 2000 US Standard Population (19 age groups-Census P25-1130) standard; Confidence intervals (Tiwari mod) are 95% for rates and ratios; [2]"Second tumors" means that they are the second neoplasms after a primary one (later primary neoplasms). The primary neoplasms for those second tumors might be of different histology and/or in different sites.

shows the APC for each histological category, with further analysis stratified by race and gender. Subgroup analysis of the trend in lymphoma subtypes was done. Table 4 shows a significant rise of mature B-cell non-Hodgkin's lymphoma over years (APC=5.82, P<0.01). Incidence rates of different histological subtypes and the overall incidence rates across the years are displayed in Figure 1.

DISCUSSION

OCLG malignant tumors are more predominant among adults. The 0-19 age group had the highest incidence rate of

Table 3 APC in each histological category stratified by gender and race

Histology	Statistic	Gender		Race white	Total
		M	F		
Carcinomas	APC[a]	0.66	0.89	1.02[b]	0.80[b]
	95%CI	-0.32 to 1.65	-0.14 to1.93	0.36-1.68	0.14-1.46
Melanomas	APC	-[c]	-[c]	1.41[b]	1.28[b]
	95%CI	-[c]	-[c]	0.35-2.49	0.19-2.39
Lymphomas and reticular malignancies	APC	4.45[b]	4.95[b]	4.60[b]	4.80[b]
	95%CI	3.25-5.66	3.77-6.15	3.63-5.59	3.80-5.82
Total	APC	2.61[b]	3.47[b]	3.03[b]	3.11[b]
	95%CI	1.9-3.33	2.83-4.12	2.51-3.55	2.61-3.61

[a]APC: Annual percent change is calculated using weighted least squares method; [b]The confidence interval indicates that the annual percent change is statistically significant different than zero; [c]Statistics could not be computed here beside soft tissue sarcomas, other rare and unclassified malignancies and African American race due to small sample size.

Table 4 Incidence rates of lymphoma broad groupings over years

Year of diagnosis	Lymphoma broad grouping (rate)		
	Malignant lymphomas, NOS or diffuse	NHL-mature B-cell lymphomas	Plasma cell tumors
APC	1.27 (P=0.12)	5.82 (P<0.01)	
1975-2009	0.44	1.51	0.02
1975-1984	0.27	0.39	0
1985-1994	0.49	1.03	0.01
1995-2004	0.58	2.19	0.03
2005-2009	0.31	2.39	0.03

APC: Annual percent change. Rates are per 1 000 000 and age-adjusted to the 2000 US Standard Population (19 age groups-Census P25-1130) standard. Malignant lymphomas as per codes 9590-9599, NHL-mature B-cell lymphomas as per codes 9670-9699 and plasma cell tumors as per codes 9730-9739.

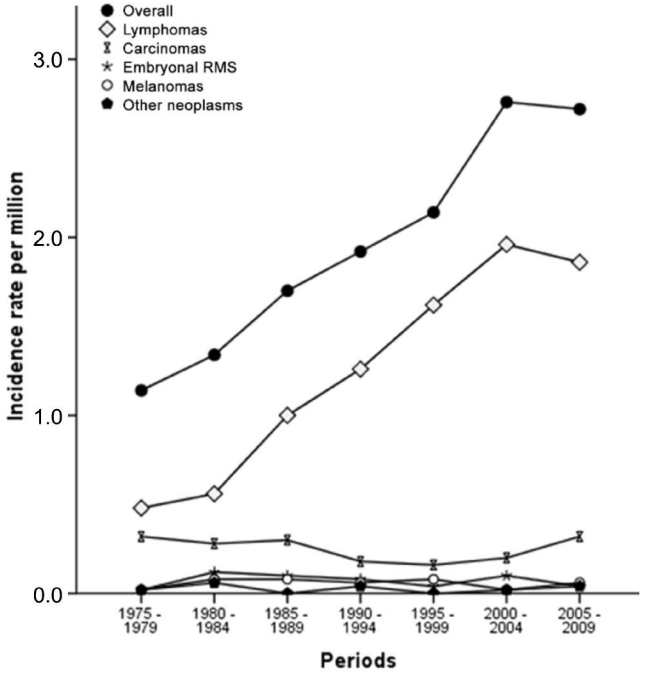

Figure 1 Incidence rates of different histological subtypes and the overall incidence rate across the years from 1975 to 2009
RMS: Rhabdomyosarcoma.

soft tissue sarcomas. This rate was mainly attributed to the high rate of embryonal rhabdomyosarcoma in this age group. According to the Cancer Incidence and Survival in Children and Adolescent Rhabdomyosarcoma the incidence rate is 4.3 cases per million child, with 10% of them being orbital in site (estimated to be 35 cases per year in US)[8].

Another longitudinal study of the years 1942-1959 highlighted 40 (73%) children were diagnosed with embryonal rhabdomyosarcoma (OER) out of a total of 55 children diagnosed with orbital tumors [9]. OER rise embryonically as other rhabdomyosarcomas from fibers imitating smooth muscles [10].

The results of this study are in alignment with others, enabling us to conclude that OER presents commonly in the younger age groups while being extremely rare in adults. Additionally, the results of this study suggest no statistically significant difference in incidence of OCLG soft tissue sarcomas based on gender or race.

Lymphomas have the highest incidence of orbital malignancies. We are able to note a rapidly rising trend with a rise in rate. According to one review of 244 cases of OCLG malignant tumors in Japan, malignant lymphoma was the most common tumor-at 31%- in the >40 age group [4]. This higher incidence rate was possibly due to environmental or racial differences, or due to different techniques of diagnosis of malignant lymphomas. Another study indicated that incidence had tripled within the last 15y [11]. It had been previously thought that this was due to an increase in immunocompromised patients. However the incidence has continued to increase whilst the number of immunocompromised patients have been recently decreasing[11]. Another hypothesis connected this increase to the increase in incidence of infections as with the Epstein Barr virus in HIV negative patients [12]. Moreover, Toxoplasma gondii and Chlamydia psittaci is often detected in cases of B-cell lymphoma [13]. This hypothesis suggests that an antigenic factor is the primary drive for B-cell expression. However, another study of 200 patients above the age of 60 showed that 28% of patients with orbital tumors had lymphoma [14]. The study connected the increased life expectancy in recent years to the higher incidence rates of lymphoma.

The increasing incidence of lymphoma could be partially attributed to new diagnostic methods which better diagnose low grade lymphomas which were previously diagnosed as pseudolymphomas [15]. But several other reviews have

confirmed the unexplained increasing incidence of all subtypes of lymphoma [16-17]. Our data show a steady annual increase of most subtypes of lymphoma in the OCLG which warrants further etiological studies. However, mature B-cell lymphomas showed the only significant increase over years. This is probably the subtype that leads the trends showed in other papers [18-19].

Our results indicate that there is no statistically significant difference in incidence rate of lymphomas according to gender comparable to two recent publications[15,19].

Carcinomas were the second most common histological type in our series. Most patients were above 50 years of age. The majority of cases suffered from squamous cell carcinoma, occurring predominantly in the conjunctiva. We noted that carcinomas show a statistically significantly higher incidence rate in males than females. These findings are inconsistent with the cancer statistics published by the American Cancer Society in 2010, which estimated the number of new cases of eye and orbital tumors to be the same-irrespective of gender [20]. However, Our results are consistent with a skin cancer study conducted at 2002 [21] and another study from the Netherlands [2]. The underlying reason for this may be due to higher sun exposure in males compared with females; possibly due to occupational differences [22]. Another recent study comparing gender impact on incidence of squamous cell carcinoma (SCC) in healthcare workers concluded that male incidence rates were higher than females [23]. It also noted that head and neck SCC were about 48%-60% of total SCC. In addition, it stated that the European standardized rates for male incidence was 22.2 to 35.4 per 100 000 and 7.8 to 20.5 for females. This was confirmed by other studies [24]. Conversely, one study studying association between ultraviolet ray exposure and squamous cell carcinoma showed a higher incidence in females compared to males in many anatomical sites [24]. The later study requires more correlation with demographics, pattern of work and sun exposure habits.

Carcinomas show a higher incidence rate in whites compared with African Americans. Other studies focused mainly on white populations[25].

Melanomas show its highest incidence rate in the ⩾50 age group, whites and in the conjunctiva. Melanomas show no statistically significant difference in incidence rate based on gender. A recent study identified the incidence of ocular melanoma to be 5.6 patients per million person-years-a very low value when compared with cutaneous disease. That study however did not discuss orbital affection [26]. In later study there was a lower age-adjusted incidence of cutaneous and ocular melanomas in women. The increasing incidence of conjunctival melanoma over years was noted by other studies[27] in contrast to ocular melanomas[26,28].

Examining the trend of OCLG malignant tumors reveals a significant increase across the years (Table 3). This increase has been brought about in the form of an increase in lymphomas subtypes. Other histological subtypes have also shown a statistically significant annual percent increase in incidence rates, but this was not as marked as in the case of lymphomas (Figure 1). Incidence rates of lymphomas are already shown to have been increasing at most sites across the years, but at lower rates[29]. A slight drop was observed in the last five years. The higher rates of increase of lymphomas in orbit and lacrimal glands compared with other sites should be further studied. We believe that this study will help ophthalmologists during diagnosis and patient counselling by considering all tumors that affect the ocular adnexa and comparing them together in standardized settings. Furthermore, our findings can be correlated with future systemic prospective studies. Our study carries the limitations of SEER data usage that were described else-where [30-31]. Moreover, ICD-O-3 coding has limited capability of representing eye lid, structures of the eye, adnexa and orbital bones[32].

In summary, primary malignant tumors at OCLG sites comprise numerous histological subtypes. They mainly affect adults, and do so with different histologies than those affecting children. This study concludes that lymphomas are the most common primary malignant orbital tumor in the US, followed by carcinomas, melanomas and rhabdomyosarcomas. The overall trend of orbital malignant tumors has been increasing and this is attributed mainly to the rising incidence rates of lymphomas. Incidence rates differences are observed between genders with a higher overall male incidence due to differences in incidence of carcinomas. There is also a significantly higher incidence rate among Whites compared with African Americans; predominantly due to increased incidence of melanomas and carcinomas among the former. We recommend further studies focusing on demographic and geographic factors, exposure to ultraviolet rays and to carcinogens, and the effect of habits and the role of genetics on incidence rates of OCLG malignant tumors.

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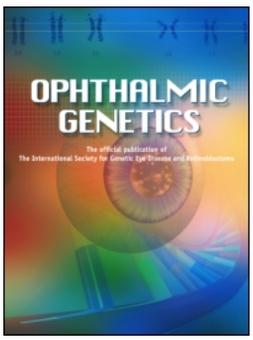

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A multidisciplinary approach to improving the care and outcomes of patients with retinoblastoma at a pediatric cancer hospital in Egypt

Hossam Elzomor, Hala Taha, Radwa Nour, Adel Aleieldin, M. Saad Zaghloul, Ibrahim Qaddoumi & Ahmad S. Alfaar

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Curriculum Vitae

Ahmad Samir Ahmad Alfaar, MD

Qualifications

2014 Oct.: **M.Sc. - Masters in Advanced Oncology**. Faculty of Medicine, Ulm University, Germany. **Thesis**: Ordinal Classification of Pediatric Tumors Samples (Computational Biology).

2012 Nov.: **M.Sc. - Masters in Ophthalmology**. Faculty of Medicine, Cairo University. **Thesis**: Molecular and Genetic Targeting of Retinoblastoma (Review).

2010 Jan.: **Diploma- Medical and Biomedical Informatics**. Faculty of Information and Computer Sciences, Helwan University. **Project**: Building Research-oriented Follow-up System for Cancer Patients.

2009 Oct.: **Certificate- Principles and Practice of Clinical Research**. Harvard Medical School. **Project**: Clinical Trial Protocol; Comparison of Bimatoprost with fixed combination of Bimatoprost and Timolol in adult patients with primary open angle glaucoma: an eight week, randomized, double blind, and parallel groups.

2009 Aug.: **Certificate- eLearning in Practice Course**. InWent/GIZ (Gesellschaft für Internationale Zusammenarbeit (GIZ)), DE/KE. **Project**: Online Training Module for Nurses on Leukemia.

2005 Nov.: **MB.BCh- Bachelor of Medicine and Surgery**. Faculty of Medicine, Cairo University, EG.

1999 Jul.: **Diploma- General Secondary Schools Certificate**. Damietta Military Secondary School. Damietta, EG.

Work Experience *(More in the extended part)*

2017 Jul – Aug: Pharmacovigilance consultant, Xendo Deutschland GmbH.

2015 Mar – Sep: **Visiting Physician.** Ophthalmology Department, Cairo University Hospitals

2014 Feb – now: **Cairo Site Director, Principles and Practice of Clinical Research Course.** Harvard Medical School

2011 Dec – 2014 Apr: **Head of Research Education Unit,** Research Department, Children's Cancer Hospital 57357 Egypt (CCHE-57357)

2008 Sep – 2014 Apr: **Researcher/ research coordinator**, Ocular and Renal Tumours, Research Department, CCHE-57357

2007 – Aug –2008: **Resident**, Ophthalmology Department, Cairo University

2007 Mar – Aug: **Primary Care Physician**, Ministry of Health and Population, Damietta

2006 – Feb – 2007: **House officer**, Cairo University Hospitals.

2002 Sep – 2008 Mar: **eLearning and Web Presence Administrator**, Cairo University School of Medicine

The complete curriculum vitae is available in the printed version

Complete List of Publications

Publications

Ahmed Samir Ahmed Alfaar - To June 15, 2017

Theses:

Thesis	Mentors	Year	University	Specialty
Genetic and Molecular Targeting of Retinoblastoma.	Hamza, H., AbouElnaga, S., & AbdelBaki, A.	2012	Cairo University, Cairo, Egypt	Ocular oncology – Review.
Using Computational Statistics for Ordinal Classification in Childhood Cancers.	Kestler, H. & Rodriguez-Galindo, C.	2014	Ulm University, Ulm, Germany	Oncology & Computational Biology.

Journal articles: - Published

Publication	IF
Alfaar AS, Hassan WM, Bakry MS, Qaddoumi I. (2017). "Neonates with Cancer and Causes of Death; Lessons from 615 Cases in the SEER Databases. Cancer Medicine. [Accepted 2012 May 3]	3.362
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Hassan WM, Bakry MS, Hassan HM, Alfaar AS*. (2016). Incidence of orbital, conjunctival and lacrimal gland malignant tumors in USA; Surveillance, Epidemiology, and end results 1973-2009. Int J Ophthalmol. 2016 Dec 18;9(12):1808-1813. doi: 10.18240/ijo.2016.12.18. eCollection 2016.	1.177
Alfaar AS*, Nour R, Bakry MS, Kamal M, Hassanain O, et al. (2016). A Change Roadmap Towards Research Paradigm in Low Resource Countries; Retinoblastoma Model in Egypt. Int Ophthalmol. 2017 Feb;37(1):111-118. doi: 10.1007/s10792-016-0233-4. Epub 2016 Apr 25.	1.132
Alfaar AS*, Hassan WM, Bakry MS, Ezzat S. (2016). Clinical Research Recession; Training Needs Perception among Medical Students. J Cancer Educ. 2016 Feb 5. [Epub ahead of print]	1.329
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Labib RM, Mostafa MM, Alfaar AS, Yehia D, Alaa M, Elzayat MG, Adel M, Ezzat S, Abo El-Naga S. (2015). Biorepository for Pediatric Cancer with Minimal Resources: Meeting the Challenges. Biopreserv Biobank. 2016 Feb;14(1):9-16. doi: 10.1089/bio.2015.0004. Epub 2015 Dec 21.	1.698

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Amgad, Mohamed, and Ahmad Samir Alfaar*. 2014. "Integrating Web 2.0 in Clinical Research Education in a Developing Country." Journal of Cancer Education: The Official Journal of the American Association for Cancer, 29(3), 536–540. Doi: 10.1007/s13187-013-0595-5. http://link.springer.com/10.1007/s13187-013-0595-5.	1.329
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Meselhy, G., Sallam, K., Elshafiey, M., Refaat, A., Samir, A., & Younes, A. (2012). Sonographic guidance for tunneled central venous catheters insertion in pediatric oncologic patients: guided punctures and guide wire localization. *The Chinese-German Journal of Clinical Oncology*, *8*(11), 484–490. Retrieved from http://link.springer.com/article/10.1007/s10330-012-1011-z	
AlFaar, A. S., Kamal, S., AbouElNaga, S., Greene, W. L., Quintana, Y., Ribeiro, R. C., & Qaddoumi, I. (2012). International Telepharmacy Education: Another Venue to Improve Cancer Care in the Developing World. *Telemedicine and e-Health*.	2.031

Book Chapters:

MUHAS (Muhimbili University of Health and Allied Sciences, Tanzania) Textbook of Oncology; Orbital and Adults' Ocular tumors. (In editing)

MUHAS Textbook of Oncology; Retinoblastoma. (In editing)

MUHAS Textbook of Oncology; Potential of Information and Communication Technologies in Oncology. (In editing)

Conference Presentations:

Presentation
Alfaar, A. S. Lausser, L., Rodrigeuz-Galindo, C., Kestler, H. (2016) Ordinal Classification of Microarray Data of Pediatric Tumors. European Molecular Biology Organization Meeting, Mannheim, Germany. (Poster and short oral)
Jomaa M., Gado N., Elgazawy H., et al. Assessment of breast cancer screening awareness among relatives of Egyptian breast cancer patients. In: Asia Congress of the European-Society-for-Medical-Oncology (ESMO). Singapore, SINGAPORE: OXFORD UNIV PRESS, GREAT CLARENDON ST, OXFORD OX2 6DP, ENGLAND; 2015. p. 26.
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Ahmad S. Alfaar. Ordinal Classification of Retinoblastoma (2014). Egyptian Ophthalmological Society meeting, Alexandria, Egypt
Wael Zekri, Mahmoud Hammad, Yasser ElBoraie et al. Adrenocortical Carcinoma In The Pediatric Age Group; Experience At Children Cancer Hospital Of Egypt (CCHE). In American Society of Pediatric Hematology/Oncology.
Ahmad S. Alfaar, Rania Labib, Sameera Ezzat et al. Telepathology to Improve Collaboration and Quality of Samples Annotation in Biorepository. In The International Society for Biological and Environmental Repositories Annual Meeting.
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Sameera Ezzat, Rania Labib, Mahmoud Mostafa, Ahmad Samir Alfaar, Mohamed Sabry, Khaled Shaaban, Hala Taha, Sherif Abou Naga. Building a State of Art Biorepository by Hybridizing Electronic Data Capture Systems in a Limited Resource Country. In "The International Society for Biological and Environmental Repositories" Annual Meeting.
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AlFaar AS, Bakry MS, Ezzat S. Childhood Orbital, Ocular and Optic nerve tumors in Egypt. In Association for Research in Vision and Ophthalmology.
Ahmad S. Alfaar, Iman Zaki, Hala Taha, et al. Accelerating innovation in outcomes and quality-of-care research through integrating clinical databases: Pediatric oncology experience in Egypt. In ASCO Conference.
Alei Eldin, A., Haddad, A., Elzomor, H., Medhat, Y., Taha, H., Saad, M., … Mohamed, S.. Evaluation of Retinoblastoma management in the first Multidisciplinary system in the Cancer children hospital in Egypt. In *International Society of Ocular Oncology Meeting*. Cleveland.
Alfaar, A. S., Nour, R., Kamal, M., Bakry, M. S., & Ezzat, S. Retinoblastoma Clinical Research in Egypt, 5 - year experience. In *International Society of Genetic Eye Diseases and Retinoblastoma meeting.* Gent, Belgium.
AlFaar, Ahmad S., Nour, R., Kamal, M., Ezzat, S., & Bakry, M. S. Automating clinical protocol monitoring; a model from developing countries. In *European Multidisciplinary Cancer Congress*. Amsterdam: Elsevier.
ElZomor, H., Nour, R., Alfaar, A. S., Aleieldin, A., Zaghloul, M. S., & Taha, H. High Risk Histopathologic features of Retinoblastoma in Egypt. In *International Society of Genetic Eye Diseases and Retinoblastoma meeting.* Gent, Belgium.

Elzomor, H., Nour, R., Alfaar, A. S., Aleieldin, A., Zaghloul, M. S., Taha, H., & Elhaddad, A. Presentation of Extra-Ocular Retinoblastoma In Egypt. In *International Society of Genetic Eye Diseases and Retinoblastoma meeting.* (p. 71). Gent, Belgium.

Taha, H., ElZomor, H., Aleieldin, A., Elhaddad, A., Nour, R., Zaghloul, M. S., & Alfaar, A. S. Pathological findings of Retinoblastoma in Egypt; implementing CAP protocol in developing countries. In *International Society of Genetic Eye Diseases and Retinoblastoma meeting.* Gent, Belgium.

Zekri, W., Alfaar, A., Yehia, D., Elshafie, M., Saad Zaghlol, M., Taha, H., … Younis, A. Clear Cell Sarcoma of The Kidney. In *European Multidisciplinary Cancer Congress*. Amsterdam: Elsevier.

ALFAAR, A., AlAsmar, M., AbdelHameed, M., Aamer, I., & Sabry, N.. Integrating Virtual Reality with eLearning in Medical Education: Cost Effective Model in Developing Countries. In *Online Educa*. Berlin.

Alfaar, A., Kamal, M., Hassanain, O., Sabry, M., Ezzat, S., & Abouelnaga, S. Advancing Clinical Oncology Practice in Developing Countries: Integrating Research Informatics for Continuous Process Improvement. In *European Society of Medical Oncology*. Vienna, Austria: Oxford.

Alfaar, A., Kamal, M., & Sabry, M. Next Generation Cancer Registry; Opportunities of web 3.0 and physician perspective. In *European Society of Medical Oncology*. Vienna, Austria.

Hanafy, N., & Samir Al-Faar, A. Developing A Specialized Central Venous Catheter Nursing Team In Pediatric Oncology Setting. In *International Conference on Cancer Nursing*. Prague, Czech Republic.

Hassanain, O., Adel, N., Kamal, M., Abouelnaga, S., & Samir AlFaar, A. (2012). Building the First ELearning Paediatric Oncology Clinical Pharmacy Program for Developing Countries. In *European Conference of Oncology Pharmacy*. Budapest, Hungary: European Journal of Oncology Pharmacy.

Kamal, M., Hassanain, O., AbouElNaga, S., Hosny, H., & Samir, A. Treatment Protocols' Monitoring Solution for Real-Time Tracking of Pediatric Cancer Patients: A Research Oriented System. In *21st Pediatric Pharmacy Conference and PPAG Annual Meeting.* Houston.

Kamal, M., Hassanain, O., AbouElNaga, S., Hussein, H., Hosny, H., Sabry, M., & Samir Alfaar, A. Integrating Treatment Protocol Monitoring System with Real-Time Statistics: A Research Oriented In-House developed Solution. In *International Society of Pediatric Neuro-oncology.* Toronto.

Taha, G., Sallam, K., ElShafie, M., A., S., Younes, A., & Refaat, A. Sonographic guidance for tunneled central venuos catheters insertion in pediatric oncologic patients: guided punctures and guide wire localization. In *5th Scientific Annual Conference of South Egypt Cancer.* Assiut, Egypt.

AlFaar, A. S. Teaching Clinical Research Leadership Skills for Undergraduate Medical Students and Impact on Public Health. . In *Washington DC: US Department of State Fellows Congress.*

Bakry, M. S., Kamal, M., Ezzat, S., & AlFaar, A. S. Integrating Web-based Real-time Analysis System with Clinical Research Database Facilitates Interim Analysis. In *European Multidisciplinary Cancer Congress* (p. p. 2.163). Stockholm: ElSevier.

Samir AlFaar, A., Ezzat, S., & AbouElNaga, S. "Bringing them together" – An essential role in retinoblastoma team; a disease coordinator. Two - year experience in a developing country. In *International Society of Genetic Eye Diseases and Retinoblastoma meeting.* (p. p. 62). Bangaluru, India.

Samir, A., & Kamal, S. Using hybrid solutions for maximizing the return on investment from telemedicine in pharmacy education. In *5th Annual Pediatric Telehealth Colloquium* (pp. 846–854). Baltimore, Maryland, USA: Mary Ann Liebert, Inc.,. Retrieved from www.americantelemed.org

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