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Factors Associated with Delayed Cancer Diagnosis in Egyptian Children

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ABSTRACT

BACKGROUND: Despite tremendous importance of early cancer diagnosis in children, few studies on this topic have been conducted in Egypt. Early stage diagnosis can have a positive effect on prognoses and the quality of life of children with cancer. We investigated delays in the diagnosis of childhood cancers in Egypt and determined the factors associated with these delays.

METHODS: This retrospective study included 172 children with cancer from two pediatric oncology units. The interval between symptoms onset and final diagnosis for each child was estimated and examined by univariate and multivariate analyses to determine correlations with the child's sex, age at diagnosis, type and site of malignancy, family residence, socioeconomic status, and parental educational level.

FINDINGS: The median total diagnosis delay period was 47 days caused by patients and/or parents (8 days) and diagnosis (28 days). Statistically significant patient factors associated with delayed diagnosis were age (<5 years), lower parental education, and socioeconomic status. Sex residence and family size were not significant. Malignancy type and tumor site significantly affected the time for diagnosis. The lowest median value was associated with germ cell tumors (GCTs) and leukemia, and the highest value was in children with brain tumor. Missed diagnoses were initially recorded in 39.5% of the patients and were associated with patient and tumor factors.

INTERPRETATION: Delayed diagnosis of childhood cancer is related to age, family, socioeconomic status and parental education, and cancer type and site. Efforts should be made to promote awareness, develop effective steps to eliminate possible contributing factors, and determine the best intervention method.

KEYWORDS: delayed diagnosis, cancer, children, Egypt

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Introduction

Despite tremendous advances in the field of pediatric oncology during the past two decades, cancer remains a leading cause of death in children.[1] Early diagnosis is fundamental for cancer management because it allows treatment of early stage disease, which results in better prognoses for these children and can also have a positive effect on their quality of life.[2,3] There are many published reports on children with cancer in developed countries;[3–5] however, few articles on this subject have been published in developing countries, particularly in Egypt. In South Africa, Stefan et al found a median total delay of 34 days in the diagnosis of childhood cancer.[6] In Nigeria,

James et al determined the median overall lag time in the diagnosis of childhood cancer to be 13.1 weeks. The shortest lag time was 8.1 and 8.7 weeks for patients with leukemia and Wilms' tumor, respectively, and the longest was 101.7 weeks for patients with Hodgkin's disease.[7]

A study examining the delays in childhood cancer diagnosis in Egypt would be particularly important because of the wide prevalence of poverty, cultural differences between people, and the economic differences that exist among Egypt's population. We investigated factors associated with delays in the diagnosis of childhood cancers in Egypt and discussed steps that are essential for shortening these delays in diagnosis.

Subjects and Methods

A predesigned questionnaire was used to collect data from parents or legal guardians of 172 children (0–15 years of age) diagnosed with cancer at two referral centers in Egypt between November 2010 and November 2012. Cases were collected from the Zagazig University Pediatric Oncology Unit, which is a regional referral center for children with cancer that serves the eastern Egyptian delta, the canal areas, and parts of the Sinai with approximately 5 million inhabitants. The Banha Pediatric Oncology Unit at the specialized children's hospital serves approximately 3 million inhabitants of the center of the delta. The sociodemographic characteristics of these two areas are representative of a larger Egyptian cohort that includes the entire delta. The ethics committees of both centers approved this study.

The patients' data, including age, sex, parental educational level, socioeconomic status, duration of illness at diagnosis, and type of malignancy were recorded. The first symptoms of the malady, first diagnosis by a health care professional, first doctor's notes, and any prescription given before the final diagnosis were also recorded. After a review of the available patients and their cancer types, the following most commonly observed malignancies were included in the analysis: leukemia (including acute lymphoblastic leukemia, acute myeloid leukemia, and chronic leukemia), lymphomas (including Hodgkin's and non-Hodgkin's lymphoma), Wilms' tumor, neuroblastoma, rhabdomyosarcoma, germ cell tumors (GCTs), brain tumors, histiocytosis, bone tumors (including Ewing's sarcoma and osteosarcoma), and other cancers, which included less common malignancies (eg, nasopharyngeal carcinoma, thymoma, and others).

A child with cancer was considered to be symptomatic starting at onset of unrelieved symptoms that were directly attributed to the malignancy. The term "patient delay," also called "parent delay" in some articles,[4–9] was defined as the interval between symptoms onset and the first visit to the primary doctor. We used the term "patient factors" to describe factors associated with delay attributed to the patient such as age, sex, family size, parental education, residence, and socioeconomic level. We used the term "diagnosis delay" (commonly referred to as "physician delay" or "health system delay" by other authors)[6] to describe the interval between the first contact with the primary doctor and diagnosis. "Tumor factor" denotes the type of tumor. The total delay was calculated from the date of symptoms onset until the date of diagnosis and the beginning of treatment. The term "misdiagnosis" was used when the malignant disease was not the first diagnosis and another benign disease was suspected.

Statistical analysis. The factors associated with total delays were identified by univariate analysis to assess the impact of each factor separately on total delays and to determine correlations between possible contributing variables and total delays. For comparison of two groups of categorical variables, independent t tests were used (as in sex variable). One-way analysis of variance (ANOVA) was used to compare more than two categorical variables (as in age groups, family size, parental education, residence, and socioeconomic level variables). Tamhane's T2 multiple comparison test is a post hoc test that was used to compare means of total delays between different group pairs after ANOVA. Frequency distributions of continuous data were compared by Pearson's correlation (bivariate). Variables that were statistically significant in the univariate analysis were included in the multivariate analysis using a linear regression model for continuous data to estimate independent factors associated with delays in cancer diagnoses. A P value of 0.05 was used to indicate the level of statistical significance. All analyses were performed using SPSS software (version 17.0). Data are presented as interval-scale data in means and standard deviations (SDs).

Results

A total of 172 children with different malignancies were included in this study [boys, 105 (61%); girls, 67 (39%); boy:girl ratio, 1.5:1; age range, 6 months–14 years; mean age, 5.3 years; median age, 5 years].

The median patient delay from the time of symptom appearance to seeking medical advice was 8 days (mean, 21 days), and the median diagnosis delay was 28 days (mean, 29 days). The median total delay period was 47 days (mean, 50 days) (Table 1).

We analyzed the risk factors associated with total delay of diagnosis in children. We determined correlations of these factors with the mean total delays in cancer diagnosis. The distribution of patients in each factor group and the associations with the mean total delays for each factor are shown in Table 2; a P value is given if there was a significant difference between the categories in each factor regarding the distribution of total delays in diagnosis.

Sex ($P = 0.901$), family size ($P = 0.519$), and residence ($P = 0.855$) were not significantly associated with total delay. On the basis of one-way ANOVA, we determined that there was a significant correlation between age and total delays ($P = 0.004$). The patients were then compared among the following three age groups: younger, <5 years; from 5 to 10 years; and >10 years. Application of Tamhane's T2 post hoc test showed a significant difference between the group of patients <5 years old and that between 5 and 10 years of age ($P = 0.01$).

Table 1. Length of delay in days for the total series.

DELAYS	DEFINITION	MEDIAN	MINIMUM	MAXIMUM
Patient delay	From appearance of symptoms to referral to a primary doctor	8 days	1	344
Diagnosis delay	From referral to a primary doctor to Day 1 therapy	28 days	1	157
Total delays	From appearance of symptoms to Day 1 therapy	47 days	3	372

Table 2. Patient factors associated with total delayed diagnosis of cancer in Egyptian children Characteristic.

	NO	%	*P* VALUE
Sex			
Male	105	61%	0.901
Female	67	39%	NS
Age At Diagnosis			
<5 years	85	49.4%	0.004
5–10 years	71	41.3%	S
>10–15 years	16	9.3%	
Family Size			
Small (3–4)	73	42.4%	0.519
Medium (5–6)	76	44.1%	NS
Large (>7)	23	13.5%	
Parental Education			
Illiterate	18	10.5%	<0.001
<6 years education	82	47.7%	S
Higher education	72	41.8%	
Residence			
Rural	52	30.2%	0.855
Suburban	39	22.8%	NS
Urban	81	47%	
Socioeconomic			
Low	29	16.8%	<0.001
Average	88	51.5%	S
Higher	54	31.7%	

Abbreviations: NS, non-significant; S, significant.

Greater total delay was found for the patients 5–10 years of age [mean, 25 days ($P = 0.01$)] than for the patients <5 years of age. Other statistically significant correlations were shown for lower parental education ($P < 0.001$) and socioeconomic status ($P < 0.001$) (Table 2).

For the factors associated with delayed diagnosis, the median total delay period was 47.5 days (mean, 49.85), which varied from 3 days to 372 days (Table 3).

A significant difference in total delays for different diagnoses was found ($P < 0.001$). Greater delay in diagnosis was observed in the patients with brain tumors from the start of symptoms until the time of diagnosis than in the patients with leukemia (mean difference, 66 days; $P = 0.029$) and in those with GCTs (mean difference, 81 days; $P = 0.005$). Greater delay from the start of symptoms until the time of diagnosis was observed in the patients with lymphoma than in those with GCTs (mean difference, 77 days; $P = 0.016$). The statistical difference between diagnoses lost significance when adjusted for the educational level and socioeconomic status in the multivariate analysis using linear regression (Table 4).

After performing univariate analysis to determine the factors that were significantly associated with total delays

Table 3. Length of delays (days) by type of malignancy.

TUMOR (NO)	MEAN	MEDIAN	MIN-MAX	STD. DEV
Leukemia (61)	29.31	16	3–120	25.266
Lymphoma (26)	92.65	55.5	8–372	94.312
Wilms' Tumor (15)	28.6	18	4–60	20.542
Neuroblastoma (8)	48.88	50	14–120	36.302
Brain Tumor (17)	96.24	75	15–247	65.236
RMS (12)	45.50	53.50	3–120	34.321
Bone tumors (11)	50.27	51	7–128	31.254
Histiocytosis (8)	52.25	57	3–120	36.201
GCT (9)	14.67	10	7–60	17.161
Others (5)	54.4	52	15–130	47.056
Total	49.85	47.5	3–372	54.892

Abbreviations: RMS, rhabdomyosarcoma; GCT, germ cell tumor.

in diagnosis, the statistically significant factors (diagnosis, socioeconomic level) were then included in a multivariate analysis using a linear regression model to identify the independent variables associated with total delays in cancer diagnosis. As shown in Table 4, socioeconomic level was identified as the only statistically significant and independent determinant of delayed cancer diagnosis ($P < 0.001$).

We analyzed the median patient delay from the first appearance of symptoms until referral to a primary physician and the median patient delay associated with the health system until final diagnosis. The comparison is illustrated in Figure 1.

Misdiagnosis was initially recorded in 68 patients (39.5%). Of the 61 children diagnosed with leukemia, 23% were initially misdiagnosed. Of the children diagnosed with Wilms' tumor, 33% were initially misdiagnosed. Of the children diagnosed with brain tumors and histiocytosis, 70 and 75%, respectively, were initially misdiagnosed. Initial misdiagnosis occurred in 42.3% of children with lymphomas, 50% of children with neuroblastoma, 45% of children with bone tumors, 50% of children with rhabdomyosarcoma, and 11% of children with GCTs (Fig. 2).

Discussion

This study is one among a few studies concerning delay of cancer diagnosis in Africa,[6,7] and to the best of our knowledge,

Table 4. Determinants of delayed cancer diagnosis obtained from multivariate analysis using a linear regression model.

| VARIABLE	RR	*P* VALUE	95% CONFIDENCE INTERVAL	
			LOWER BOUND	UPPER BOUND
Diagnosis	1.369	0.173	−0.786	4.343
Socioeconomic	−7.100	<0.001	−49.205	−27.795
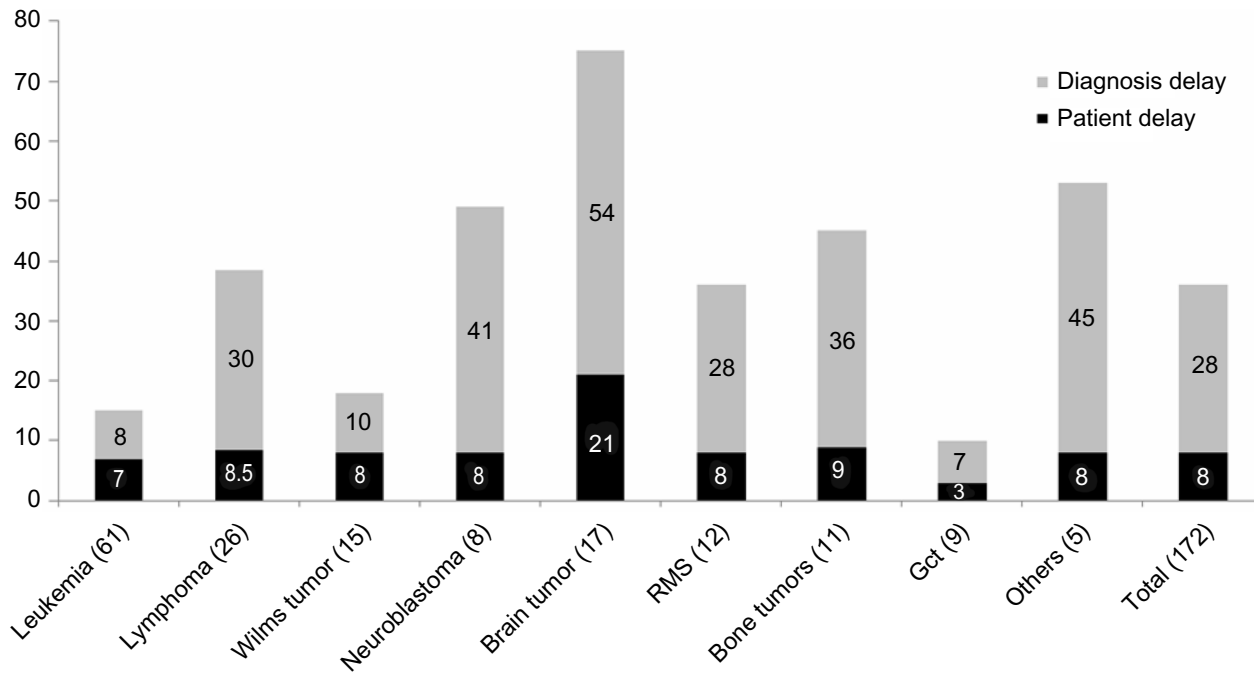
Figure 1. Median delay (days) associated with patient factors for different tumor types.

is the first in Egypt. In our series, the median total delay period was 47 days, diagnosis delay was 28 days, and patient delay was 8 days. A number of studies have investigated factors associated with delayed diagnosis in children.[3–8] In 2007, Dang-Tan and Franco published a review of 23 epidemiological studies that examined diagnosis delays in childhood cancer. They found that factors associated with diagnosis delays varied across studies[3] and included the child's age, level of parental education, type of cancer, presenting symptoms, and others.[3]

Our results are similar to the results reported in Israel, which is a geographically closed country. In 2004, Haimi et al reported similar values of 7 weeks, 4 weeks, and 1 week for the median total delay period, diagnosis delay, and patient delay, respectively. These similarities reflect the same milieu for two countries that are geographically close.[9] In contrast, the median total delays in a 2011 study conducted in South Africa reported a much shorter total delay of 34 days; this can be explained by the fact that this study was conducted at the
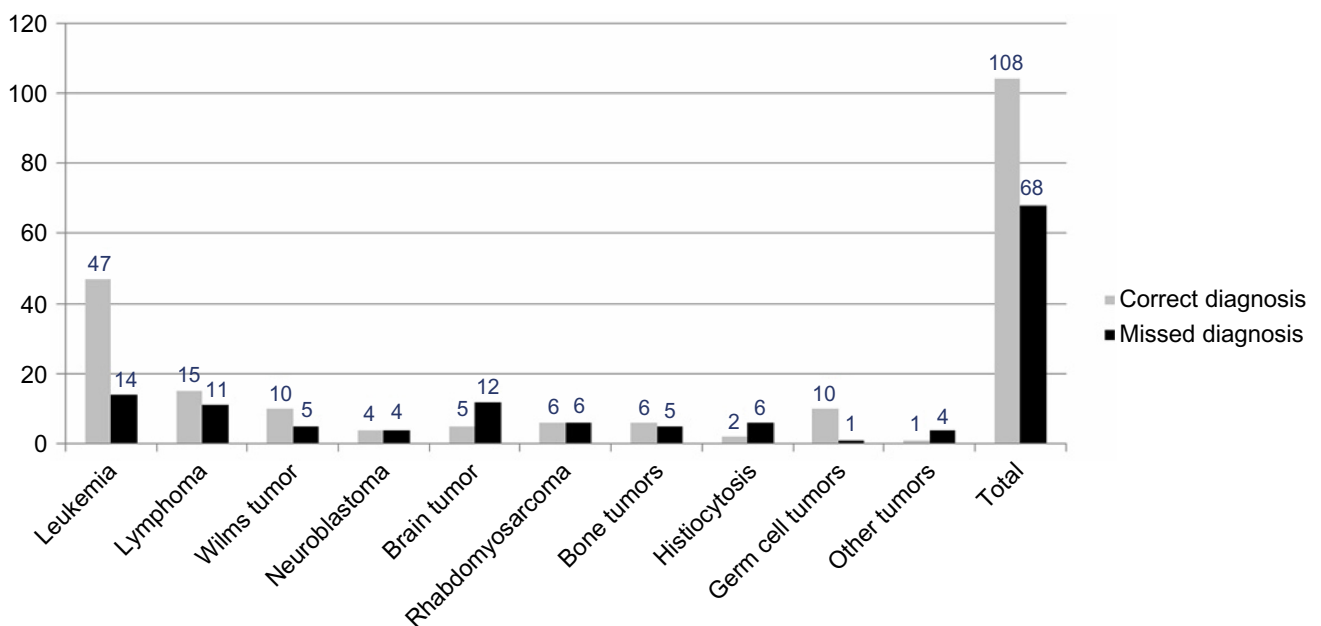
Figure 2. Numbers of cases misdiagnosed in our series by type of diagnosis.

Taygerberg Hospital, a center of excellence situated in a large urban area where all health services are readily accessible.[6] Approximately half of our results were reported in patients from Nigeria in 2010 with corresponding results of 13.1, 8.8, and 2 weeks for the median total delay period, diagnosis delay, and patient delay, respectively.[7] Differences in health attitudes and related socioeconomic and cultural factors between the two areas may have influenced our results.

There was no statistically significant difference in the total delayed diagnosis period between males and females ($P = 0.901$). This finding is consistent with those of most reports in the literature. Saha et al found no significant difference in the lag time between males and females with an estimated ratio of lag time, female to male, of 1.2 (95% confidence interval (CI) of 0–9 to 1–6, $P = 0–22$).[10] Our significant positive correlation of age with delay is in agreement with the findings of most previous series.[3–6] In a study in a large cohort of 2665 children, Pollock et al found that for all solid tumors except Hodgkin's disease, the total delayed diagnosis time increased with age.[11] In young children, the aggressive nature of their malignancies may lead to the rapid appearance of symptoms, which shortens the diagnostic delay period.[11]

Parental education and socioeconomic level, both of which are closely related, were determined to be important factors in suspecting and interpreting symptoms and signs of malignancies in our series. A statistically significant correlation ($P < 0.001$) was found between parental education and socioeconomic level and the total delayed diagnosis period. Families with higher levels of education and socioeconomic status tended to request private hospitals and clinics for care, which have higher levels of clinical expertise. This tendency most often leads to earlier suspicion and diagnosis of cancer and was also observed in a study conducted in Mexico, where children whose parents had the lowest level of education had longer delays in diagnosis than did the children whose parents had the highest level of education.[12] In Nigeria, the higher educational level of parents did not seem to provide any advantage with regard to delayed diagnosis.[7] This difference may reflect different sociocultural factors of the two areas.

In our series, the type of cancer clearly influenced diagnostic delay. Most patients diagnosed with GCTs had teratomas, sacrococcygeal tumors, and testicular tumors. Because these tumors were often visible from outside the body or present with a mass, diagnosis was often made early and treatment initiated earlier. Klein-Geltink et al reported patient and physician delays of 0.6 days and 1 week, respectively, for patients with GCTs.[4] In our series, a significant difference in total delays was found between different types of diagnoses ($P < 0.001$). More delay from the start of symptoms until the time of diagnosis was observed in children with brain tumors than in those with leukemia (mean difference, 66 days) and in those with Wilms' tumor (mean difference, 67.64 days). This observation is consistent with those of many authors who documented a shorter diagnosis period for patients with acute leukemia and Wilms' tumor than for those with brain and bone tumors.[13–15]

In our study, the median patient delay period (8 days) was also affected by the type of tumor, which was shortest with GCT, leukemia, and tumors presenting as masses (eg, Wilms' tumors, neuroblastoma, and bone tumors) and longest with brain tumors. This finding may be because the presenting features of these malignancies are more alarming to parents, whereas in those with brain tumors, the symptoms are often non-specific, vague, and misleading. In such patients, symptoms are often attributed to a more benign condition, such as fatigue, simple eye problems, or any another conditions. An increase in public awareness and authorization of young people to seek and obtain prompt help for any complaint would reduce delays in cancer diagnosis in children.

It is the authors' opinion that the problem with delay in diagnosis is not confined to the patient, and the initial contact of patient with a primary care physician has a considerable impact on early childhood cancer diagnosis. The ability of primary care physicians to recognize serious symptoms that may indicate cancer varies considerably. In our series, 39.5% of the patients were misdiagnosed. This issue was extensively discussed in South Africa, where misdiagnosis was reported in 58% of patients.[6] The type of cancer may also influence a physician's ability to make a correct diagnose. For example, young children with Wilms' tumor can have more identifiable signs at presentation than older children. In contrast, children with brain tumors, who often have a slower tumor growth rate than other cancers, present with less menacing symptoms to a general pediatrician. Therefore, efforts to further educate young physicians and general pediatricians about the presenting signs and symptoms of cancer in children will undoubtedly improve the diagnostic skills of the physicians and influence their index of suspicion and time of referral if presented with a child with possible cancer.

This study had certain limitations, including its retrospective nature, the relatively small sample size, and the fact that the patients mainly represented lower Egypt and the delta. Recall bias is a concern, particularly when addressing the beginning of symptoms. We overcame this by reviewing the initial referral letters and contacting the referring doctors when possible.

The influence of delayed diagnosis in children with cancer remains unclear, and more research is required to identify how delays affect morbidity and mortality.

Conclusion

The delay in diagnosis of childhood cancer in Egypt determined in this study was comparable with the findings published by other authors. In our study, delays in the diagnosis of childhood cancer were most influenced by the child's age, family's socioeconomic status and parental education, cancer type, and site of cancer. Every effort should be made to promote public and parental awareness of childhood cancer. Further

education of inexperienced physicians should improve their awareness of the signs of cancer, which will allow effective steps to be taken to eliminate possible contributing factors and to determine the best intervention methods.

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Author Contributions

Performed statistical analysis and interpretation of the data: RMS. Wrote the first draft of the manuscript: ERA, LMS, NMK. Agree with manuscript results and conclusions: ERA, LMS, NMK, RMS. Jointly developed the structure and arguments for the paper: ERA, LMS, NMK, RMS. Made critical revisions and approved final version: ERA, LMS, NMK, RMS. ERA and LMS had full access to all the study data and take responsibility for the integrity of the data and accuracy of the data analysis. All authors reviewed and approved of the final manuscript.

REFERENCES

1. Ribeiro RC, Pui CH. Saving the children–improving childhood cancer treatment in developing countries. *N Engl J Med*. 2005;352:2158–60.
2. Reaman GH. A national approach to evaluating delays in diagnosis and treatment: potential implications for age related and geo-political differences in access to care and outcome in children and adolescents with cancer. *Pediatr Blood Cancer*. 2008;51:447–8.
3. Dang-Tan T, Franco EL. Diagnosis delays in childhood cancer: a review. *Cancer*. 2007;110:703–13.
4. Klein-Geltink JE, Pogany LM, Barr RD, Greenberg ML, Mery LS. Waiting times for cancer care in Canadian children. Impact of distance, clinical and demographic factors. *Pediatr Blood Cancer*. 2005;44:318–27.
5. Eden T, Rogers M, Barker L, Morgan S, Smith S. Symptoms interval (SI) in teenage and young adults (TYA) with cancer. *Pediatr Blood Cancer*. 2007;49:575.
6. Stefan DC, Siemonsma F. Delay and causes of delay in the diagnosis of childhood cancer in Africa. *Pediatr Blood Cancer*. 2011;56:80–5.
7. James BO, Ajayi SO, Ogun OA, Oladokun RE. Factors influencing time to diagnosis of childhood cancer in Ibadan, Nigeria. *Afr Health Sci*. 2009;9:247–53.
8. Olesen F, Hansen RP, Vedseted P. Delay in diagnosis: the experience in Denmark. *Br J Cancer*. 2009;101:S5–8.
9. Haimi M, Peretz Nahum M, Ben Arush MW. Delay in diagnosis of children with cancer: a retrospective study of 315 children. *Pediatr Hematol Oncol*. 2004;21:37–48.
10. Saha V, Love S, Eden T, Micallef-Eynaud P, MacKinlay G. Determinants of symptom interval in childhood cancer. *Arch Dis Child*. 1993;68:771–4.
11. Pollock BH, Krischer JP, Vietti TJ. Interval between symptom onset and diagnosis of pediatric solid tumors. *J Pediatr*. 1991;119:725–32.
12. Fajardo-Gutierrez A, Sandoval-Mex AM, Mejia-Arangune JM, Rendón-Macías ME, Martínez-García Mdel C. Clinical and social factors that affect the time to diagnosis of Mexican children with cancer. *Med Peadiatr Oncol*. 2002;39:25–31.
13. Edeworth J, Bullock P, Baily A, Gallagher A, Crouchman M. Why are brain tumors still being missed. *Arch Dis Child*. 1996;74:148–51.
14. Halperin EC, Watson DM, George SL. Duration of symptoms prior to diagnosis is related inversely to presenting disease stage in children with medulloblastoma. *Cancer*. 2001;61:1444–50.
15. Bacci G, Ferrari S, Longhi A, et al. High grade osteosarcoma of the extremity: differences between localized and metastatic tumors at presentation. *J Pediatr Hematol Oncol*. 2002;24:27–30.