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The Time to Diagnosis in Childhood Lymphomas and Other Solid Tumors

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Background. There are few reports from developing countries on the factors that influence the time to diagnosis (TD) in childhood cancer. The purpose of this study was to investigate the determinants of the TD in Turkish cancer patients. ***Procedure.*** A retrospective analysis was performed on 329 children diagnosed with cancer, excluding leukemia. The TD, including parent/patient time and physician time, was defined as the interval between the onset of symptoms and the final diagnosis. ***Results.*** The median times for parent/patient, physician, and TD were 3, 28, and 53 days, respectively. For patient in the 1–9 years age group, physician time and TD were significantly shorter than in infants and those over 10 years. The longest median TD was recorded for children with germ cell tumors and retinoblastoma; the shortest was in children with renal tumors. When the first point of contact was a pediatrician, a private hospital or physician's office, a governmental educational hospital or a university hospital physician time was short. The longest TD was noted in patients who first contacted a non-pediatric specialist. The most significant predictors of parent/patient, physician time, and TD were metastases at diagnosis, first medical center, and first health professional contacted, respectively. ***Conclusions.*** The TD for childhood lymphomas and solid tumors was related to patient age, tumor type and location, the presence of distance metastases, first health professional, and center contacted. All physicians, especially other specialists seeing pediatric patients, need to be further sensitized to the signs and symptoms of childhood cancer. Pediatr Blood Cancer 2011;57:392–397. © 2011 Wiley-Liss, Inc.

Key words: cancer; childhood; delay; diagnosis; time

INTRODUCTION

Despite the important developments in therapy, cancer is the second leading cause of death among children 1–14 years of age in developed countries [1]. As a result of the improvement in child health and the reduction of the incidence and mortality from communicable diseases during the last decades in developing countries, the relative importance of cancer is rising [2]. However, timely diagnosis of childhood cancer is extremely important. Many pediatric malignancies are highly curable, and with some of them, earlier diagnosis can be associated with a better prognosis and diminished intensity of therapy. Patients with solid tumors diagnosed prior to metastatic spread, have better outcomes and require less aggressive treatment. Unfortunately, diagnosis of a childhood cancer is usually difficult in early stages of disease because of the rarity of disease and nonspecific presentation of symptoms [1]. The time between a patient's first symptom recognition to a diagnosis of cancer is defined as time to diagnosis (TD) [3,4]. This time period has also been called a prediagnostic symptomatic interval [5,6], symptom duration and/or interval [7–13], delay in diagnosis (or diagnostic delay) [14–17], lag time [18–22], or wait time [23,24] by different authors. The published data on the determinants and the impacts of TD in childhood cancer originates mostly from the studies conducted in developed countries [4–13,15,16,18–35]. There are only two reports in English from the developing countries [3,36]. The purpose of this study was to investigate the determinants of TD in Turkish children with cancer.

METHODS

A retrospective analysis was performed on 380 children (aged 0–19 years) diagnosed with cancer, excluding leukemia, at the Dokuz Eylul University Hospital, Department of Pediatric Oncology, from January 1999 to December 2009. We excluded patients with leukemia being diagnosed and treated by the Pediatric Hematology Department. A total of 329 patients were eligible for the study. Cases were categorized according to the International Classification of Childhood Cancer [37]. The patients diagnosed with Langerhans cell histiocytosis were included in this study. Clinicopathological data were collected from hospital records. The time of symptom onset was defined using the data in medical records. When the available data were not clear, parents/patients were contacted by phone to confirm the most accurate time for symptom onset. The TD was defined by the number of days between the onset of first symptom(s) associated with the cancer and the date of diagnosis. The TD consists of two time intervals, one from first symptoms associated with the cancer to the first contact with a physician (parent/patient time), and the other from the first contact with a physician to diagnosis (physician time). The time of diagnosis was mostly based on histopathological examination of biopsy or surgical specimen. It was based on clinical and radiological diagnosis only for pontine gliomas and Wilms tumors receiving preoperative chemotherapy. All diagnoses, excluding pontine gliomas, were confirmed by centralized pathologic review. Asymptomatic cases with incidental diagnoses were included in the study, and were assigned as having a parent/patient time of 0 days. Study variables were patient related factors (the age of the patient, the mother, and the father at the time of diagnosis, sex, number of siblings for the patient), disease related factors (type of neoplasm, symptom(s), cancer stage or grade, metastasis, tumor location), and healthcare system related factors (place of residence, the type of the health professional, and medical center initially contacted). Age at diagnosis was categorized into five groups: <1, 1–4, 5–9, 10–14, and 15–19. The times (parent/patient time, physician time, and TD) were used simply to represent a time interval, measured in days. They were classified into ''short'' when they are the same as or below the median value or ''long'' when they are above the median value.

Statistical analysis was carried out with the SPSS 16.0 statistical program. Correlation between the categorial parameters were evaluated with Pearson Chi-square, continuity correction (Yates

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Conflict of interest: Nothing to declare.

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Chi-square), or Fisher's exact test. The Chi-squared automatic interaction detection (CHAID), a method that uses Chi-squared statistics to identify optimal splits, was used in this study. A CHAID tree is a classification tree that is constructed by splitting subsets of the space into two or more child nodes repeatedly, beginning with the entire data set [38]. To determine the best split at any node, any available pair of categories of the predictor variables is merged until there is no statistically significant difference within the pair with respect to the target variable. This CHAID method naturally deals with interactions between the independent variables that are directly available from an examination of the tree. The final nodes identify subgroups defined by different sets of independent variables.

RESULTS

The median age at diagnosis was 8 years (1 month to 19 years). The male/female ratio was 1.25. Central nervous system (CNS) tumor was the most common diagnosis, followed by lymphomas and soft tissue sarcomas (STS). The distribution of times for each variable is summarized in Table I. The median parent/patient time, physician time, and TD was 3 (0–720), 28 (0–2,520), and 53 (0–2,520) days, respectively. The main symptoms presented were pain (35%) and mass (34%). Table II shows the results from the univariate analysis which were statistically significant. Physician time was shorter in patients with any preexisting congenital illness ($P = 0.004$). For patients presenting with metastatic disease, the parent/patient time ($P = 0.004$) and TD ($P = 0.008$) were significantly shorter than the patients with non-metastatic disease. Patients who were in the 1–9 year age group showed a significantly shorter physician time ($P = 0.031$) and TD ($P = 0.006$) when compared with infants (<1 year) and patients >10 years of age. Patients with hematuria/urinary obstruction had a shorter parent/patient time ($P = 0.013$) and TD ($P = 0.037$). When the patient had an abdominal tumor, physician time ($P = 0.003$) and TD ($P = 0.005$) were significantly shorter. Patients with cervical mass (or lymphadenopathy) had a longer physician time ($P = 0.010$). Parent/patient time was significantly

TABLE I. Median Times (Min–Max) in Days by Type According to Demographic Variables and Cancer Type

Characteristic	n (%)	Parent/patient time	Physician time	Time to diagnosis
Overall	329 (100.0)	3 (0–720)	28 (0–2,520)	53 (0–2,520)
Sex				
Female	146 (44.4)	3 (0–540)	28 (0–2,520)	46.5 (3–2,520)
Male	183 (55.6)	3 (0–720)	30 (0–810)	60 (0–813)
Age at diagnosis				
<1	17 (5.2)	3 (0–180)	45 (0–120)	73 (0–187)
1–4	86 (26.1)	3 (0–540)	21 (0–810)	33 (1–813)
5–9	80 (24.3)	3 (0–720)	25 (0–1,000)	38 (5–1,030)
10–14	75 (22.8)	3 (0–720)	30 (0–720)	60 (7–800)
15–19	71 (21.6)	10 (0–720)	28 (0–2,520)	83 (7–2,520)
Cancer type				
Lymphomas	57 (17.3)	3 (0–270)	30 (5–360)	60 (7–360)
CNS tumors	82 (24.9)	3 (0–720)	17.5 (0–2,520)	56.5 (7–2,520)
Neuroblastoma	28 (8.5)	3 (0–360)	32.5 (5–180)	48 (5–370)
Retinoblastoma	22 (6.7)	3 (0–360)	7 (0–810)	121 (0–813)
Renal tumors	24 (7.3)	3 (0–170)	10 (1–300)	25.5 (1–303)
Liver tumors	3 (0.9)	60 (10–210)	15 (10–50)	70 (60–225)
Bone tumors	27 (8.2)	7 (3–120)	30 (7–250)	48 (10–253)
STS	34 (10.3)	3 (0–360)	26.5 (3–180)	32 (6–385)
Germ cell tumors	20 (6.1)	52.5 (0–540)	29 (3–1,000)	125 (13–1,030)
Carcinomas	11 (3.3)	3 (3–350)	30 (10–540)	63 (33–543)
LCH	12 (3.6)	3 (3–360)	37.5 (10–320)	55.5 (13–500)
Others	9 (2.7)	3 (2–300)	25 (5–180)	33 (7–480)
Tumor location				
Intracranial	83 (25.2)	3 (0–720)	30 (0–540)	63 (1–735)
Head and neck	103 (31.3)	3 (0–720)	30 (0–1,000)	60 (0–1,030)
Thoracic	12 (3.6)	3 (0–32)	10 (5–150)	33 (8–153)
Vertebral/paravertebral	88 (26.7)	3 (0–360)	26.5 (0–810)	5 (0–813)
Abdominal/pelvic	22 (6.7)	5 (0–720)	25 (5–2,520)	52.5 (8–2,520)
Genitalia	11 (3.3)	3 (0–270)	7 (6–360)	27 (7–363)
Limbs	8 (2.4)	3 (3–330)	30 (5–360)	43 (10–363)
Cutaneous	2 (0.6)	55 (50–60)	20 (10–30)	75 (60–90)
FHPC				
GP/FP	60 (18.6)	3 (0–360)	33 (3–360)	45.5 (3–390)
Pediatrician	158 (48.9)	3 (0–720)	20 (0–1,000)	36 (0–1,030)
Other specialist	105 (32.5)	3 (0–720)	30 (0–2,520)	93 (3–2,520)

CNS, central nervous system; LCH, Langerhans cell histiocytosis; STS, soft tissue sarcomas; FHPC, first health professional contacted; GP, general practitioner; FP, family physician.

TABLE II. The Statistically Significant Variables Associated With Parent/Patient Time, Physician Time, and Time to Diagnosis

	Parent/patient time	*P*	Physician time	*P*	Time to diagnosis	*P*
Patient factor						
Age (year)[a]						
<1 and ≥10			↑	0.031	↑	0.006
1–9			↓	0.031	↓	0.006
Congenital illness[a]			↓	0.004		
Disease factor						
Symptom/finding						
Hematuria/UO[b]	↓	0.013			↓	0.037
Vomiting[c]			↓	0.037		
Servical mass[c]			↑	0.010		
Abdominal mass[c]			↓	0.003	↓	0.005
Testicular mass[b]	↑	0.03				
Diagnosis[a]						
Renal tumors	↓	0.006			↓	0.023
Neuroblastoma	↓	0.006			↓	0.023
STS	↓	0.006			↓	0.023
Germ cell tumors	↑	0.006			↑	0.023
Bone tumors	↑	0.006			↑	0.023
Metastatic disease[c]	↓	0.004			↓	0.008
Healthcare factor						
Physician[a]						
GP/FP			↑	<0.001		
Pediatrician			↓	<0.001		
Other specialist					↑	0.001
Medical center[a]						
PHCC	↓	0.02	↑	<0.001		
GEH	↑	0.02	↓	<0.001		
University hospital			↓	<0.001		
Private center	↓	0.02	↓	<0.001		

↑, Long time (parent/patient time >3 days, physician time >28 days, time to diagnosis >53 days); ↓, short time (parent/patient time ≤3 days, physician time ≤28 days, time to diagnosis ≤53 days); STS, soft tissue sarcomas; UO, urinary obstruction; GP/FP, general practitioner/family physician; PHCC, primary health care center; GEH, governmental educational hospital. [a]*P*-value is calculated using Pearson Chi-square; [b]*P*-value is calculated using Fisher's exact test; [c]*P*-value is calculated using Yates Chi-square (continuity correction).

longer for children with testicular tumors ($P = 0.030$). Children with renal tumors, neuroblastoma, and STS had significantly shorter parent/patient time and TD ($P = 0.006$ and 0.023, respectively). In children with germ cell and bone tumors, both the patient time and TD were longer ($P = 0.006$ and 0.023, respectively). The longest median TD was recorded for children with germ cell tumors (125 days) and retinoblastoma (121 days) while the shortest was in children with renal tumors (25.5 days) (Table I).

Univariate analysis revealed a significant association between the first health professional/medical center contacted and the times. Parent/patient time was short for patients who first contacted the primary health care center ($P = 0.02$). When the first point of contact was a pediatrician, a private hospital or physician's office, a governmental educational hospital, or a university hospital physician time was short ($P < 0.001$). When the first consultation was with a general practitioner physician time was long ($P < 0.001$). The longest TD was noted in patients who first contacted specialists in other branches (other than pediatricians) (Tables I and II) ($P = 0.001$).

Classification analysis (CHAID) was performed for parent/patient time, physician time, and TD (Figs. 1–3). The most significant predictor of parent/patient time was metastases at diagnosis. The presence of metastases at the time of diagnosis was associated with short parent/patient time. The other two most important variables for metastatic and nonmetastatic patients were primary location of the tumor and patient age at diagnosis, respectively (Fig. 1). It was determined that if the nonmetastatic patients were <10 years of age, the parent/patient time was short, but if they were >10 years of age, the time was long.

In metastatic patients, the parent/patient time was long if the primary location of the disease was CNS or genitourinary system. The first medical center contacted was the most significant determinant for physician time. Most of the patients (77.5%) who first contacted a primary health care center had longer physician time. The long physician time was detected at a rate of 95.5% for patients living in urban regions, with first physician contact in a primary health care center. Most of the patients (87.5%) with cervical mass (or lymphadenopathy) who first contacted a governmental hospital had longer physician time (Fig. 2). For the TD, best discriminator was the first health professional contacted (Fig. 3). In the 63.8% of patients who first contacted specialists other than pediatricians, TD was long. The TD was significantly longer for patients who first contacted other specialists, if the first health medical center contacted was a governmental hospital. In patients who contacted a general practitioner/family physician or a pediatrician, if there was an abdominal mass, the TD was short. If there was no abdominal mass, in patients who first contacted an Emergency Department the TD was short.

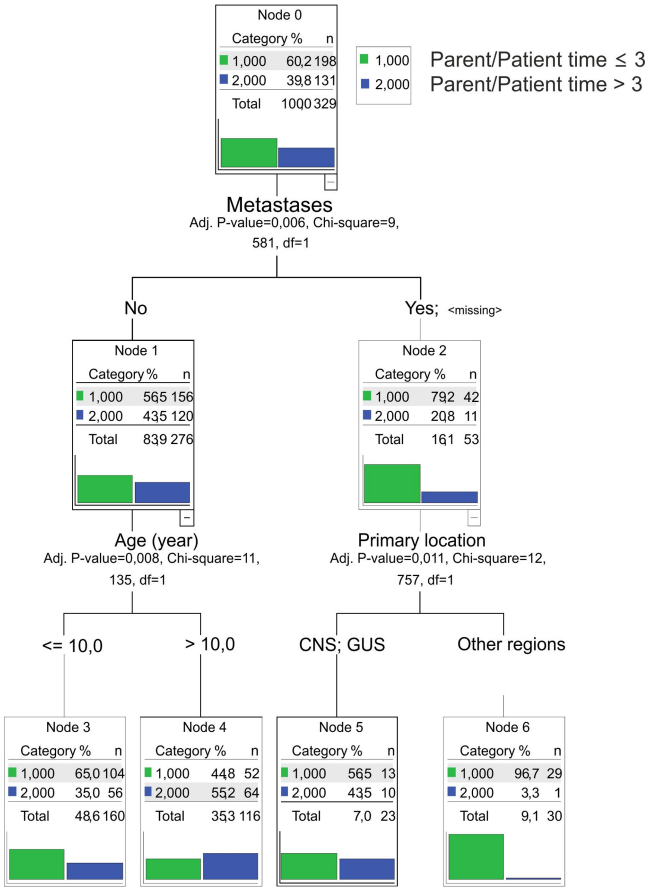

Fig. 1. CHAID analysis for parent/patient time. CNS, central nervous system; GUS, genitourinary system.

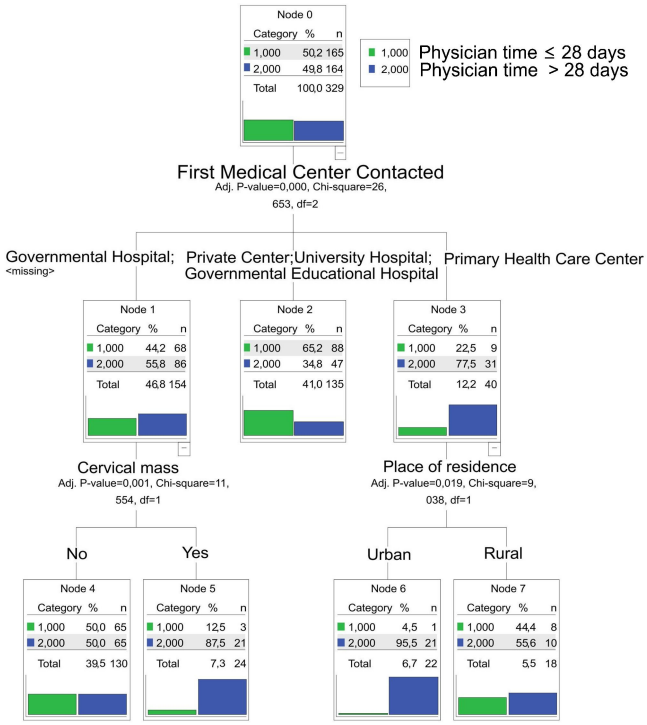

Fig. 2. CHAID analysis for physician time.

DISCUSSION

In this study, the TD for all cases was approximately 2 months (53 days). In general, compared to previous studies conducted in Israel and in Singapore, our study appeared to find a shorter TD than the median of 15.75 and 11.6 weeks reported by Haimi et al. [18] and Loh et al. [16], respectively. However, it appeared longer when compared to the Canadian study which reported approximately one month of the TD [15].

Several studies support the hypothesis that older patients are at higher risk of delayed TD than younger patients [3,5,6,8,12,15,16,18–21,32]. Our findings confirm these results. We observed a positive association between the patient age at diagnosis and physician time, and TD. In contrast, infants had the longest physician time (median 45 days) and longer TD than older children in our study. Dang-Tan et al. [15] reported that TD in infants was 18 days (7–36) and increased to 50 days among patients 15–19 years old. In Mexico, Fajardo-Gutierrez et al. [3] found that the highest risk for delayed the TD was in the 10–14 age group (OR = 1.8; 95% CI 1.4–2.3).

The age factor is influenced by some additional parameters such as the primary location of the malignant disease and symptom(s). Our study showed that cancer type was a significant factor related to patient and TD. The longest parent/patient time and TD was for germ cell tumors, retinoblastoma, and CNS. The shortest parent/patient time and TD was for renal tumors, STS, and neuroblastoma. Pollock et al. [19] reported that median TD ranged from 21 days for children with neuroblastoma to 72 days for those with Ewing sarcoma. Saha et al. [21] found that the mean TD varied from 2.8 weeks for nephroblastoma to 13.3 weeks for brain tumors. Dang-Tan et al. [15] reported that hepatic tumor and renal tumor patients had the shortest median TD at 13 and 14 days, respectively. Haimi et al. [18] reported that the greatest mean and median TD were in brain tumors, epithelial tumors, and especially astrocytoma and Ewing sarcomas; the shortest was in children with Wilms tumor. Some of the differences may relate to biology and clinical presentation, but they also relate to age [39].

The pattern of sign(s) and symptom(s) varied greatly for children with different tumors, which may account for some of the differences in TD among diagnostic groups. Whereas most of the presenting signs and symptoms of childhood tumors may be associated with other less serious causes, the discovery of an abdominal mass is a serious finding and is the most common presentation of a solid tumor. Although some abdominal masses may be benign, all require prompt and thorough work-up. A palpable abdominal mass is most common in children under the age of 5 and especially in children older than 1 year, and is often a more ominous sign. It is a readily observable and well-known symptom and may increase the likelihood of the child getting immediate medical attention, leading to a relatively shorter TD. Patients with nonspecific or common findings such as cervical mass (or lymphadenopathy) had a longer physician time. Patients with cervical mass (or lymphadenopathy) showed a longer physician time in our study. Cervical lymphadenopathy is a common complaint and a physical finding in children. A nodal mass, unlike an abdominal, pelvic, or mediastinal mass, is not always an indication for

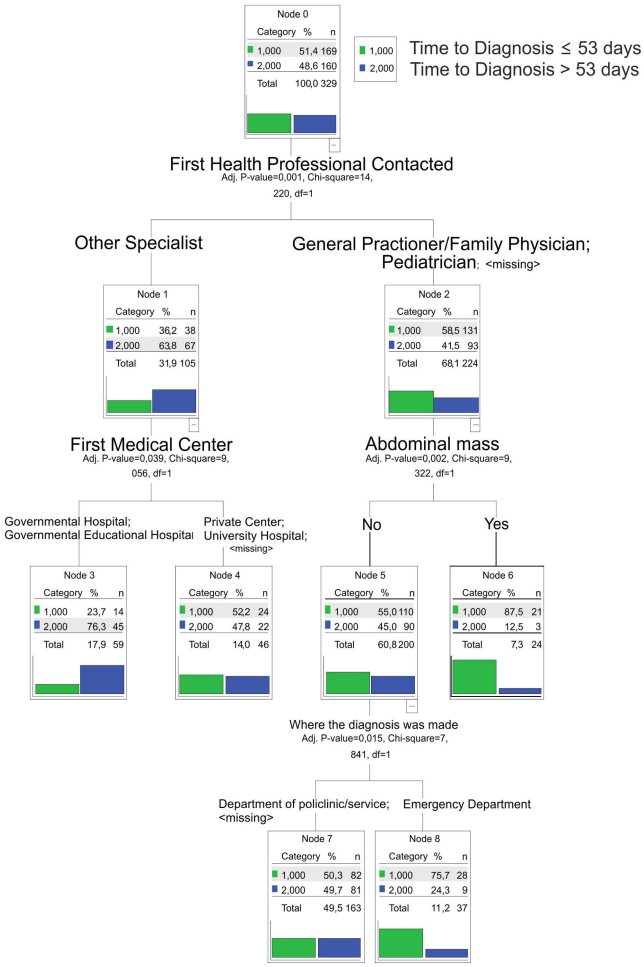

Fig. 3. CHAID analysis for diagnostic time.

detailed work-up or for a prompt surgical procedure to establish a diagnosis. However, the likehood of malignancy within the node will determine the urgency with which biopsy is undertaken. In this study, patients with hematuria/urinary obstruction had a shorter parent/patient time and TD. Frightening or more alarming complaints like hematuria or urinary obstruction may shorten parent/patient time. Parent/patient time was significantly longer for children with testicular tumors. Testicular mass, especially painless testicular mass may not be noticed by the patient, particularly adolescents, and may result in delayed parent/patient time.

The TD could be influenced by the rate at which tumor enlarges or spreads. Contrary to expectations, it is not obvious that short symptom interval correlates with early stage at diagnosis. In our study, parent/patient time and TD were inversely related to metastatic stage at diagnosis. More aggressive tumors may show rapid progression of symptoms which would lead parents to seek medical attention for their child. Indeed, rapidly progressive tumors (e.g., medulloblastoma and high grade gliomas) were reported to show shorter TD than slowly growing tumors [4–6,34]. In childhood STS, Ferrari et al. [12] reported that the symptom interval was found to be associated with tumor size, that is, longer symptom intervals coincided with larger tumors. Authors claim that tumor size should be seen as a chronological indicator and finding a large tumor may be indicative of a delayed TD. The tumor size and extent, relative to TD, might be due to the fact that some large tumors reflect neglect while others reflect tumor biology.

Physician time and TD may be influenced by health care-related factors such as access to medical centers, knowledge and recognition of the disease by health professionals, and availability of appropriate diagnostic capability and instrumentation [14]. In our study, the parent/patient time was shorter for patients who first contacted the primary health care center. Klein-Geltink et al. [24] reported that compared with an initial pediatrician's contact, patients who first visited a general practitioner had a lower risk of delayed patient time. This may be related to the reality that a general practitioner or a primary health care center is more accessible in our country. Our study showed that physician time was shorter when the first point of contact was a pediatrician. Haimi et al. [18] reported a shorter physician delay (time) and lag time (TD) for patients examined by pediatricians compared with family physician or another specialist. This may be attributed to rarity of childhood cancers. Only 1 in 650 children will ever develop cancer [39]. The average solo practitioner is likely to encounter one case every 20 years, and even in practices with multiple providers, one case will be diagnosed every 5–7 years [40]. Adding to these difficulties is the fact that once a cancer is diagnosed in a practice not only will there be a long lag time until the next case but that next case is likely to be a different entity with different presenting features. Thus, there is no learning curve and for the primary care physician or other specialists, the index of suspicion of cancer is low.

However, we did not take into consideration the number of symptom(s), especially during the assessment of the first health professional/medical center contacted, as in several previous studies. That is why the first health professional/medical center evaluating the child with cancer may have more barriers to an accurate diagnosis. In Turkish health care centers other than university hospitals, the patient burden is huge and a single physician may see more than 50 patients a day.

Our study has some limitations. First, its retrospective nature makes it difficult to ascertain the reliability and accuracy of the information collected. There may be considerable variation in the exact time course of certain symptoms, especially those symptoms that persisted for a long time before diagnosis. On the other hand, the date of onset of cancer symptoms might be earlier than it was noticed by patient or family. Second, this study was conducted in one pediatric oncology center, reflecting the results of a given setting only. Third, many other factors that might contribute to diagnostic delays such as family income, maternal education or occupation, and outcome of diseases could not be evaluated.

In conclusion, as with other studies, we found that the TD in childhood lymphomas and solid tumors were related to patient age, tumor type and location, the presence of distant metastases, first health professional, and center contacted. The findings from this study emphasize the importance of continuing medical education of childhood tumors for health care professionals who are likely to encounter childhood cancer cases, albeit rarely. All physicians, especially other specialists seeing pediatric patients, need to be further sensitized to the symptoms of childhood cancer. Given the limitations of the available data in developing countries, further prospective studies to elicit the contributors of TD and the outcomes associated with TD are definitely needed.

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