

Evaluation of the Lag Time Between Onset of Symptoms and Diagnosis in Childhood Cancers

Çocukluk Çağı Kanserlerinde İlk Semptom ile Tanı Alma Süresinin Değerlendirilmesi

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Abstract

Introduction: Our aim was to evaluate the lag time between the first onset of symptoms and the final diagnosis in children with lymphoma and solid tumors.

Materials and Methods: This study was carried out by retrospectively scanning the records of 759 patients admitted to the Pediatric Oncology Department of Uludağ University between January 2005 and December 2014. Demographic data of the patients, first complaints, the time to apply to a physician after the first complaint, the first application center were determined, lag time to the center that established the oncologic diagnosis, the final diagnosis, time to diagnosis at the last center, total time elapsed from the first onset of complaints to the establishment of diagnosis and the last health state of the patient were obtained from the hospital records.

Results: The patients diagnosed with cancer firstly applied to a physician median 15 days. The physician who saw the patient for the first time referred to him/her to the center that established the final diagnosis after a median of 8 days. The median time to final diagnosis was 10 days minimum 1 days and total 55 days at the last center. In patients whose first symptom is fever, abdominal pain and seizures and in patients with a definitive diagnosis of germ cell tumor, neuroblastoma, kidney tumor and liver tumor, the time to the first admission was shorter than 15 days. In patients whose first symptom was a headache, and abdominal mass; in patients and central nervous system (CNS), and eyes, and in patients with the final diagnosis of CNS tumor germ cell tumor and retinoblastoma, the lag times for referrals were significantly shorter than 8 days. In patients whose first symptom was headache, nausea and vomiting, fatigue-weight loss, and visual disturbances and in patients with the final diagnosis of CNS tumors and neuroendocrine tumors, the time to diagnosis was significantly shorter than 10 days.

Conclusion: Delays in diagnosis are common in children with cancer. A sustained effort should be made to raise the level of awareness of childhood cancer among parents and to sensitize all physicians, especially those who treat pediatric patients infrequently, about the warning signs of the disease.

Keywords

Delay diagnosis, childhood cancer, early diagnosis

Anahtar kelimeler

Tanıda gecikme, pediatrik kanser, erken tanı

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Öz

Giriş: Bu çalışmada lenfoma ve solid tümör tanısı alan çocuklarda ilk yakınma ile kesin tanı konulması arasındaki geçen sürenin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: Bu çalışmada Uludağ Üniversitesi Tıp Fakültesi Pediatrik Onkoloji Bölümü' müze Ocak 2005 ve Aralık 2014 yılları arasında başvuran lenfoma ve solid tümör tanısı alan 759 hastalar retrospektif olarak değerlendirildi. Hastaların demografik özelliklerinin değerlendirilmesi, yakınmalarının başlamasından sonra ilk doktora başvuru süresi, doktora başvurduktan sonra tanı alma süresi ve toplam tanı alma süresinden oluşan semptomların başlangıcından kesin tanı konuncaya kadar geçen sürelerin tanımlanması amaçlandı.

Bulgular: Hastaların ilk doktora başvuru 15 gün, ilk başvuru doktorun asıl tanı merkezine sevk süresi 8 gün, tanı merkezinde tanı alma süresi 10 gün ve toplam tanı süresi 55 gün olarak saptandı. İlk belirtisi ateş, karın ağrısı ve nöbet olan hastalarda; kesin tanısı germ hücreli tümör, nöroblastom, böbrek tümörü ve karaciğer tümörü olan hastalarda ilk başvuru süresi 15 günden kısaydı. İlk semptomu baş ağrısı ve karında kitle olan hastalarda ve kesin tanısı SSS tümörü germ hücreli tümör ve retinoblastom olan hastalarda sevk gecikme süreleri 8 günden kısaydı ve anlamlı bulundu. İlk semptomu baş ağrısı, bulantı-kusma, yorgunluk kilo kaybı ve görme bozukluğu olan hastalarda ve kesin tanısı SSS tümörü ve nöroendokrin tümör olan hastalarda tanı süresi 10 günden kısa ve anlamlı bulundu.

Sonuç: Çocukluk çağı kanserlerinde tanı gecikmelerini azaltmak prognozu iyileştirmektedir. Bu nedenle toplumdaki çocuk ve erişkin tüm bireylerin ve bu hasta grubunu ilk gören hekimlerin farkındalığını ve bilgilerini artıracak eğitimlerin düzenli verilmesi uygun olacaktır.

Introduction

Cancer-related deaths are the first in disease-related child deaths in developed countries and third in our country (1,2). Today, with the advances in diagnosis and treatment methods, the survival rates in children's cancer have exceeded 80% (1). Because of the high survival rates and long life expectancy, it is aimed to keep the sequelae related to the disease and treatment to the lowest level. Making the diagnosis at an early stage may reduce treatment intensity and increase treatment success.

A child with cancer, usually with the initial findings of the disease, presents to the family doctor, pediatricians, internal medicine specialists or surgical departments. It has been reported that approximately 5-7% of patients apply to emergency services (3). Pediatric cancers are rare, as well as their signs and symptoms vary according to the type, and location of cancer, and the age of the patient, and similar findings are seen in common diseases of childhood. The fact that the same cancer can start with a different clinical manifestation in each patient makes early diagnosis difficult. In developed countries, it has been stated that parents are good observers; they notice abnormal manifestations in their children much faster than doctors. In countries with poor socioeconomic status, the most important task of early diagnosis falls to doctors (4,5).

This study aimed to evaluate the lag time between the first onset of symptoms and the final diagnosis in

children and adolescents with lymphoma and solid tumors.

Materials and Methods

Study Design

The study has been conducted by the principles of the Helsinki Declaration and approved by the Uludağ University Faculty of Medicine, Clinical Research Ethics Committee (approval no: 2015-21/13, date: 08.12.2015). This study was carried out by retrospectively scanning the records of 759 patients who were admitted to Pediatric Oncology Department between January 2005 and December 2014. Childhood leukemias are excluded from the study.

Outcome Parameters

Identity information and demographic data of the patients (date of birth, gender, and age of diagnosis), first complaints, the time to apply to a physician after the first complaint, and the first application center were determined. Tumor location of the patients, lag time to the center that established the oncologic diagnosis, the final diagnosis, date of the final diagnosis, time to diagnosis at the last center, total time elapsed from the first onset of complaints to the establishment of diagnosis and the last health state of the patient were obtained from the hospital records.

Statistical Analysis

Data were analyzed using the NCSS (Number Cruncher Statistical System) 2007 (Kaysville, Utah,

USA) program. Parametric tests were applied to data of normal distribution, and non-parametric tests were applied to data of questionably normal distribution. Pearson chi-square test and Fisher's Exact test were used to compare qualitative data. Correlations between continuous variables were determined nonparametrically using Spearman's rho. Statistical significance was assumed for $p < 0.01$ and $p < 0.05$. When the diagnostic stages of the children diagnosed with cancer were examined, since the range of distribution was greater regarding time to presentation to the physician and referrals, it was considered that the median value reflected the group better and the data were compared over median values.

Results

A total of 759 patients were included in the study. The mean age of the children 92.65 ± 67.11 months and the median age of 84 months (1 day- 216 months). While 10.8% (n=82) of the children were under one year of age, age ranges of the other patients were as follows: 1-4 years (n=196: 25.8%), 5-9 years (n=189: 24.9%), 10-14 years (n=158: 20.8%), 15-18 years (n=134: 17.7%). Of the children participating in the study, 54.2% (n=411) of them were male.

Two of the most common complaints were palpable mass and pain. The most common complaint

was discernible mass lesion in 39.8% (n=302) of the patients. In 11.5% (n=87) of these cases, swelling was located on the neck, and mass lesions were described in the abdomen (n=58: 7.6%), on the extremity (n=35: 4.6%), in the pelvis gluteal region, and other parts of the body (n=122: 16.1%). In 21.4% of the patients (n=163), the first complaint was pain. These patients had abdominal pain (n=99: 13%), bone pain (n=27: 3.6%) headache (n=23: 3%), and pain localized in other regions (n=14: 1.8%).

The specialties where the patients applied with the onset of their first symptoms were determined as follows: pediatricians (n=512: 67.5%), and its subspecialties (n=27: 3.5%). It was observed that 22.5% (n=171) of the patients were applied to various surgical branches. It was seen that 5.32% (n=40) of the patients had applied to general practitioners. The tumors were most frequently seen in abdomino-pelvic region (n=278: 36.5%), central nervous system (CNS), (n=144: 19.0%), and head and neck region (n=133: 17.5%) (Table 1).

The most frequently seen final diagnosis was lymphoma (non-Hodgkin lymphoma in 12.1% and Hodgkin lymphoma in 10% of the patients) in 22.1% (n=168), CNS tumors in 18.3% (n=139), germ cell tumors in 12.0% (n=91), and neuroblastoma in 10.8% (n=82) of the patients (Table 2).

Table 1. Distribution of final diagnoses

	n	%	
Lymphomas	Non-Hodgkin lymphomas	92	12.1
	Hodgkin lymphomas	76	10.0
Central nervous system tumors	139	18.3	
Germ-cell tumors	91	12.0	
Neuroblastoma	82	10.8	
Renal tumors	60	7.9	
Bone sarcomas	60	7.9	
Soft tissue sarcomas	58	7.6	
Other epithelial tumors	38	5.0	
Neuroendocrine tumors	17	2.2	
Thyroid carcinoma	12	1.6	
Retinoblastoma	12	1.6	
Liver tumors	9	1.2	
Langerhans-cell histiocytosis	9	1.2	
Malignant melanoma	4	0.5	
Total	759	100	

Table 2. Evaluation of the time intervals between onset of symptoms and application to a health care center according to the ages of the patients

		<15 days (n=361)	≥15 days (n=398)	^a p
		n (%)	n (%)	
Age (year)	<1 year	59 (72.0)	23 (28.0)	0.001**
	1-4 year	103 (52.6)	93 (47.4)	
	5-9 year	86 (45.5)	103 (54.5)	
	10-14 year	70 (44.3)	88 (55.7)	
	15-18 year	43 (32.1)	91 (67.9)	
Gender	Female	162 (46.6)	186 (53.4)	0.608
	Male	199 (48.4)	212 (51.6)	

^aPearson chi-square test
**p<0.01

Table 3. Evaluation of the time intervals between onset of symptoms and application to a health care center according to the ages of the patients

		<15 days (n=361)	≥15 days (n=398)	^a p
		n (%)	n (%)	
Age (year)	<1 year	59 (72.0)	23 (28.0)	0.001**
	1-4 year	103 (52.6)	93 (47.4)	
	5-9 year	86 (45.5)	103 (54.5)	
	10-14 year	70 (44.3)	88 (55.7)	
	15-18 year	43 (32.1)	91 (67.9)	
Gender	Female	162 (46.6)	186 (53.4)	0.608
	Male	199 (48.4)	212 (51.6)	

^aPearson chi-square test
**p<0.01

There was no statistically significant difference as for the lag time between onset of symptoms and their admission in children according to their gender ($p>0.05$). There was a statistically significant difference between the delay in admission times of children according to their ages ($p=0.001$; $p<0.01$) (Table 3). A significantly higher number of children aged between 15 and 18 years applied to our hospital more than 15 days after their onset of complaints. There was no statistically significant difference between the ages and gender of the children as for the time to application to our hospital ($p>0.05$).

In our study, the patients diagnosed with cancer firstly applied to a physician median 15 (range, 1-730) days after onset of their symptoms. The physician who saw the patient for the first time referred to him/her to

the center that established the final diagnosis after a median of 8 (range, 1-1050) days. The median time to final diagnosis was 10 (range, 1-223) days at the last center. Total time elapsed up to the establishment of the final diagnosis that encompasses the time interval between discernment of the first symptom by the patient to his/her presentation to a physician, the patient's referral to an oncology center and establishment of final diagnosis ranged between 3-1254 days (median 55 days).

The patients in our study were evaluated according to the first symptom, tumor location, and final diagnosis of the patients in terms of median lag time (15 days) to the first application to a physician. In patients whose first symptom was fever ($p=0.006$), abdominal pain ($p=0.001$), and seizure ($p=0.001$); in patients whose

tumors were localized in the abdomen ($p=0.001$); and in patients with the final diagnosis of germ cell tumor ($p=0.009$), neuroblastoma ($p=0.009$), renal tumor ($p=0.005$), and liver tumor ($p=0.016$), the lag time to the first admission was shorter than 15 days.

The patients in our study were evaluated according to the first symptom, tumor location, and final diagnosis of the patients in terms of the median 8-day period, which is the time elapsed for referral of the patients to the center that established the final diagnosis. In patients whose first symptom was headache ($p=0.009$), and abdominal mass ($p=0.006$); in patients whose tumors were localized in the abdomen ($p=0.003$), CNS ($p=0.012$), and eyes ($p=0.005$), and in patients with the final diagnosis of CNS tumor ($p=0.022$) germ cell tumor ($p=0.001$) and retinoblastoma ($p=0.005$), the lag times for referrals were significantly shorter than 8 days.

The patients in our study were evaluated according to their first symptom, tumor location, and final diagnosis of the patients in terms of median lag time to final diagnosis of 10 days. In patients whose first symptom was headache ($p=0.040$), nausea and vomiting ($p=0.037$), fatigue-weight loss ($p=0.009$), and visual disturbances ($p=0.004$); in patients whose tumors were localized in the CNS ($p=0.001$), and in patients with the final diagnosis of CNS tumors ($p=0.001$) and neuroendocrine tumors ($p=0.005$), the time to diagnosis was significantly shorter than 10 days.

When the final status of the patients was examined, it was seen that 77.2% ($n=586$) of them were still followed up, 3.7% ($n=28$) of them lost to follow-up, and 19.1% ($n=145$) of them died.

Discussion

In this study, we evaluated the diagnostic delays in children with lymphoma and solid tumors. 54.2% of the patients were male and 45.8% were female. The application period of the children between the ages of 15-18 was found to be longer than 15 days significantly higher than other age groups. There was no difference between the duration of patient admission according to the gender of children boys were found to have been shipped 8 days or more over girls. Diagnosis of Hodgkin's lymphoma in children with non-Hodgkin's lymphoma, bone sarcomas, soft tissue sarcomas, and thyroid ca The rate of admission time of 15 days or

more was significantly higher. The last diagnosis was germ cell tumors neuroblastoma, renal tumors and liver tumors, and the rate of admission was less than 15 days. In children with a final diagnosis of non-Hodgkin's lymphoma, Hodgkin's lymphoma, bone sarcomas and langerhans cell histiocytosis during the referral period, the rate of referral time of 8 days or more was significantly higher. In children with CNS tumor, germ cell and retinoblastoma, the incidence of referral time was less than 8 days. At the time of diagnosis, in children with the final diagnosis of Hodgkin's lymphoma, the rate of being diagnosed at or above 10 days was significantly higher. In children with final diagnosis of CNS and neuroendocrine tumors, the rate of diagnosis being less than 10 days is significantly higher.

The lag time to diagnosis in childhood cancers may vary depending on the population structure and conditions of the countries. In the study performed by Dang-Tan et al. (9) on patients with lymphoma in Canada, the mean time interval between the first symptom and diagnosis was found to be 39 days. In the study performed by Haimi et al. (10) on children with solid tumors, the median time interval of the patients from the onset of symptoms up to their application to a physician was found to be 4 weeks, and total time up to final diagnosis was median 7 weeks. In a study conducted by Abdelkhalek et al. (11) in Egypt in 2014 on children with solid tumors, they reported that the median time interval of 21 days had passed between the first onset of symptoms up to patients' referral to a physician, and additional 29 days elapsed till establishment of final diagnosis amounting to 50 days of total diagnostic process. In the study by Handayani et al. (12), the average time interval between first symptoms and patient admission was 5 days, and the mean duration of total diagnostic process was 58 days.

In a study, the median lag time to application to a physician, and time interval between the application and establishment of diagnosis were 20, and 23 days, respectively total diagnostic process totaling to 60 days (13). In a study conducted by Cecen et al. (14) in Izmir in 2012, the patients were referred to the physician, after a median of 3 days.

In their studies Fajardo-Gutiérrez et al. (15) (2002, Mexico), Dang-Tan et al. (9) (2008, Canada), Haimi et al. (16) (2004, Israel) found that the time to diagnosis increases with age. In the study of Begum et al. (17), it

was observed that children under 2 years of age were referred earlier to a diagnosis center than others. In our study, a statistically significant difference was found between the ages of children according to the age of diagnosis. The 72% of the patients under one year of age were referred to a physician a median of <15 days, while in older patients this period was prolonged. In 67.9% of the adolescents aged 15-18 years, the lag time for the first application to a physician was more than 15 days. Haimi et al. (10) reported that the time to diagnosis was shorter in patients who firstly applied to the pediatrician when compared with those who firstly consulted a family physician and other specialists. Dang-Tan et al. (9) found that the risk of prolonged diagnosis was lower in patients who first applied to the emergency department rather than a general practitioner. Cecen et al. (14) found that the diagnostic process was shorter among patients who first consulted a university hospital rather than a health institute. Araz and Güler (13) found that the diagnostic process lasted longer in patients who applied to non-pediatricians. In our study, it was determined that 10.7% of the patients made the first application to the pediatric emergency department.

In our study, the firstly applied medical specialties were examined. It was determined that 67.5% of the patients had applied to the pediatrician and 3.5% had applied to the subspecialties of pediatrics. The rate of patients who applied to the general practitioner was found to be 5.3%. It was found that the referral times were not different in patients who were mostly applied to pediatricians. There was a statistically significant difference between the lag time of diagnosis of the children according to the first referral center. The rate of being 10 days or over was found to be significantly higher among children who firstly applied to general practitioners, and branches of internal medicine which more frequently examine adult patients time to diagnosis was statistically significantly longer.

Similar to our study, Dobrovoljac et al. (19) found that the time to diagnosis of patients with increased intracranial pressure was shorter. Loh et al. (18) reported that tumors located in the abdomen were diagnosed within a shorter time. In their study, Araz and Güler (13) could not find a significant difference between the location of the tumor and the patient's referral to the physician. In the study of Cecen et al. (14), the mean time to application to the doctor was 55

days in the skin tumors, and the average time interval from presenting to a physician up to the establishment of final diagnosis was 20 days. Pratt et al. (20) reported that the patients diagnosed with rhabdomyosarcoma were diagnosed within a shorter period of time when the tumors were localized at eyes, and pharynx compared to those with head and neck tumors. In the study performed by Loh et al. (18), the time to diagnosis in cases with renal tumors was 39 days at the shortest, while the time intervals up to the diagnosis of lymphomas, CNS and soft tissue sarcomas were 110, 123 and 105 days, respectively.

Study Limitations

One of the limitations of our study is that it is a retrospective study based on data collected by scanning the file information. Factors such as the socioeconomic status of the patients' families, the educational level and occupations of the parents, the individuals who care for the patients, and the characteristics of the caregivers of the children could not be determined fully, and added to the study due to missing data in patient files.

Conclusion

Delays in diagnosis are common in children with cancer. A sustained effort should be made to raise the level of awareness of childhood cancer among parents and to sensitize all physicians, especially those who treat pediatric patients infrequently, with regard to the warning signs of the disease.

Ethics

Ethics Committee Approval: The study was approved by the Uludağ University Faculty of Medicine, Clinical Research Ethics Committee (approval no: 2015-21/13, date: 08.12.2015).

Conflict of Interest: No conflict of interest was declared by the authors.

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