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Role of surveillance screening in detecting tumor recurrence after treatment of childhood cancers

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What is already known on this topic?

- *Follow-up of recurrences after treatment of children with cancer is an important issue.*
- *Surveillance tests have disadvantages such as financial burden and radiation.*
- *The role of early recognition of recurrences on survival is controversial.*

What this study adds on this topic?

- *Recurrence was detected in almost half of the patients through surveillance tests in our study.*
- *In patients with recurrence, survival time was longer in those asymptomatic patients compared to symptomatic patients with recurrence.*
- *We need more studies demonstrating the importance of surveillance tests on survival time.*

ABSTRACT

Objective: As the survival rates in children with cancer reach up to 80%, this improvement in survival increases the number of patients under follow-up. After cancer treatment is completed, patients are taken to follow-up surveillance to ensure the early detection of recurrence and the late effects of treatments. The frequency and necessity of surveillance screening tests are controversial. This study aimed to assess the efficacy of surveillance screening in the detection of recurrence.

Material and methods: The files of 533 children who were diagnosed as having cancer at our pediatric oncology clinic between 2004 and 2013 were retrospectively evaluated. We looked at outcomes after recurrence, the timing and pattern of recurrence, the presence of symptoms during recurrence, physical examination findings, tumor marker levels, laboratory findings, and radiologic tests.

Results: Of the 63 patients with recurrence, 23 were symptomatic and 40 were asymptomatic at the time of the recurrence. Tumor location and time of the recurrence did not affect the post recurrence survival. The median post-recurrence survival for patients was 13 (range, 1–98) months. The median post-relapse survival was 10 (range, 1–73) months in patients with symptomatic recurrence, and 16 (range, 1–98) months in patients with asymptomatic recurrence. It was determined that patients in whom recurrence was identified with surveillance tests had longer post-relapse survival time. The 5-year survival rate of 23 patients with symptomatic recurrence was 12.2%; this rate was 49.5% in asymptomatic patients ($p<0.05$).

Conclusions: It should be considered that surveillance testing offers the benefit of prolonging post recurrence survival.

Keywords: Childhood cancer, follow-up, pediatric oncology, recurrence, surveillance screening

Introduction

Today, survival rates in children following cancer treatment reach up to 80% due to the advances in treatment and supportive care (1, 2). This improvement in survival leads to increased numbers of patients under follow-up. The reason for following up children with cancer after treatment is the early recognition of disease recurrence and the late effects of treatments (3). Recurrence of the primary tumor is still the most important cause of morbidity and mortality after treatment in children with cancer. In particular, the risk of recurrence is quite high in the first five years following treatment. Late effects such as malignant neoplasms, chronic cardiac and endocrine diseases, and functional disorders are also frequently encountered in patients after treatment (4, 5). The diagnosis of those late effects of cancer treatment is also very important in follow-up surveillance.

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Although frequent follow-up and regular investigations are almost routine in pediatric oncology departments, there is little evidence regarding the value of surveillance in the detection of disease recurrence. The frequency and necessity of surveillance tests following the treatment of pediatric cancers are controversial (4-6). The optimal surveillance for recurrent disease after treatment has not been well-defined (7-12). Excessive laboratory tests and imaging scans have disadvantages such as increasing the financial burden and exposure to radiation (9-13). To determine the optimal timing of surveillance and minimize unnecessary tests, data concerning risk factors associated with recurrence, recurrence time, and the methods that detect recurrence should be analyzed well. The aim of this study was to investigate how recurrence presented and the efficacy of surveillance screening performed in childhood cancers in detection of tumor recurrence.

Material and methods

A cohort of 533 patients who had been diagnosed as having lymphomas and solid tumors at our Pediatric Oncology clinic between March 2004 and May 2013 were retrospectively evaluated after the local ethics committee of Ankara Child Health Disease Hematology Oncology Hospital granted approval (No.: 2013-069, Date: 17.12.2013). The study was performed according to the Helsinki Declaration.

After reviewing medical files, 420 of 533 patients who completed treatment and were followed up were included to the study. The remaining patients who left or progressed during treatment were excluded. After treatment, our patients are followed up with a standardized schedule. Follow-up at our pediatric oncology department is conducted every 3 months in the first year, every 4 months in the second year, every 6 months for the next 2-5 years, and annually thereafter. Follow-up examinations include a physical examination, chest X-ray, tumor marker if available, abdominal ultrasonography, computed tomography (CT) or magnetic resonance imaging (MRI) according to the tumor type.

The recurrence of primary cancer was detected in 63 patients who were followed up after the cessation of treatment. They experienced recurrence after the end of treatment. Age, sex, date of diagnosis, tumor type, stage, tumor location, and response to treatment were recorded on a data form for patients with recurrence. We looked at outcomes after recurrence, the timing and pattern of recurrence, the presence of symptoms during recurrence, physical examination findings, tumor marker levels, laboratory findings, and radiologic tests. Medical files were reviewed according to how recurrence was detected (history and symptoms or routine surveillance scans).

The patients were classified as 'asymptomatic' if the recurrence detection method was a physical examination, imaging, and laboratory results, and were classified as 'symptomatic' if they were examined and tested after presenting to the clinic with symptoms such as headache, neck swelling, bone pain, and swelling anywhere on the body. Asymptomatic recurrence was defined as presenting a physical examination finding, abnormal laboratory values, and imaging study findings. Recurrence time was defined as the time after the end of treatment. Recurrence was investigated under three groups: less than 12 months, 12-24 months, and more than 24 months after the end of the treatment. The overall survival (OS) times of patients after diagnosis and their survival times after relapse (post recurrence survival, PRS) were recorded. The obtained data were recorded using the Statistical Package for the Social Sciences (SPSS version 18.0) software.

Statistical Analysis

Descriptive statistics are expressed in the form of mean±standard deviation or median (minimum-maximum) for discrete quantitative variables, and as the number of cases and (%) for categorical variables. Categorical variables were evaluated using Pearson's Chi-square or likelihood-ratio tests. Fisher's exact test was used as the first choice in distributions that were not suitable for Chi-square analysis. The presence of a statistically significant difference in OS rates based on categorical variables was investigated using the log-rank test with Kaplan-Meier survival analysis. The 5-year survival rates, expected average post recurrence survival (PRS) time, and 95% confidence intervals (CI) associated with this time were calculated for each variable.

Multivariate Cox's proportional hazard regression analysis was used to investigate the combined effects of the variables found to have an impact on OS in univariate statistical analyses and the risk factors thought to have a clinical effect. Results were considered statistically significant for a p-value <0.05.

Results

Tumor recurrence was identified in 63 (15%) of the 420 patients and these patients were enrolled in the study. Twenty-nine (46%) patients were female, 34 (54%) patients were male, and the mean age was 7.3 ±4.7 years. Recurrence time was less than 12 months after the end of treatment for 28 (44.4%) patients, 12-24 months for 22 (34.9%) patients, and more than 24 months for 13 (20.6%) patients. The recurrence site was local in 38 (60%) patients and distant in 25 (40%). When the tumor groups were investigated based on recurrence time, it was found that the tumors that recurred before 12 months (early recurrence) were non-Hodgkin lymphomas, Wilms tumors, and germ cell tumors, and recurrence after 24 months (late relapse) was encountered in Hodgkin lymphoma.

We analyzed the method of the diagnosis of recurrence. Of the 63 patients, 23 (36.5%) were symptomatic and 40 (64.5%) were asymptomatic when recurrence was detected. In the asymptomatic patient group, recurrence was detected in 35 (87.5%) patients using imaging methods and in 5 (12.5%) patients through laboratory tests. Table 1 presents the distribution of our patients with symptomatic and asymptomatic recurrence based on their tumor diagnoses. Pain was the most common symptom of recurrence. Swelling anywhere on the body, neurologic symptoms, and fever were among the other frequent symptoms.

Time of survival after recurrence (PRS) varied between 1 and 98 months. The median post recurrence survival was 13 (range, 1-98) months. Although 22 of 40 patients with asymptomatic recurrence were alive, only eight out of 23 patients with symptomatic recurrence were still alive. No statistically significant relationship was found between the tumor groups and age with symptomatic/asymptomatic recur-

Table 1. Distribution of recurrent patients based on recurrence detection method

		Symptomatic	Asymptomatic	p
Sex	Female	10	19	0.758
	Male	13	21	
Recurrence time	Less than 12 months	7	21	0.056
	12-24 months	7	15	
	24 months	9	4	
Tumor types	Non-hodgkin lymphoma	7 (46.2%)	6 (53.8%)	
	Hodgkin lymphoma	6 (54.4%)	5 (45.6%)	
	Neuroblastoma	4 (40%)	6 (60%)	
	Wilms tumor	1 (14.2%)	6 (85.7%)	
	Brain tumors	1 (16.6%)	5 (83.3%)	
	Germ cell tumor	0	5 (100%)	
	Rhabdomyosarcoma and soft tissue sarcomas	1 (25%)	3 (75%)	
	Other	3 (42.8%)	4 (57.2%)	
Recurrence location	Local	12	26	0.316
	Distant	11	14	
Recent follow-up	Alive	8	22	0.122
	Dead	15	18	

Table 2. Evaluation of factors that could have an effect on overall survival after recurrence

Variables	n	Survival rates %			Survival time * (95% Confidence interval)	Log-rank	p
		1-Year	3-Year	5-Year			
Recurrence time						**5.152**	**0.076**
Less than 12 months	28	65	47.3	37.8	46.8 (27.9-65.7)		
12-24 months	22	71.5	37.9	15.2	29.3 (20-38.5)		
More than 24 months	13	100	75	60	57.8 (44.2-71.3)		
Recurrence location						**0.016**	**0.899**
Local	38	77.6	49.6	34.7	48.2 (33.4-62.9)		
Distant	25	68.6	47.5	31.7	45.0 (26.4-63.6)		
Method of the recurrence detection						**4.532**	**0.033**
Symptomatic	23	63.9	36.5	12.2	29.7 (17.1-42.3)		
Asymptomatic	40	80.6	64.4	49.5	58.7 (43.5-74.0)		

Table 3. Identification of the most determinative factors of post recurrence survival based on the multivariate Cox's Proportional Hazard regression analysis

Variables		95%Confidence interval			
Diagnosis	**Relative risk**	**Lower limit**	**Upper limit**	**Wald**	**p**
Non-hodgkin lymphoma	18.327	3.565	94.204	12.124	<0.001
Hodgkin lymphoma	1.914	0.304	12.048	0.478	0.489
Neuroblastoma	6.266	1.371	28.650	5.600	0.018
Wilms tumor	0.625	0.062	6.276	0.159	0.690
Brain tumors	18.310	0.849	395.035	3.442	0.064
Other tumors	1.000	-	-	-	-
Recurrence detection					
Symptomatic	2.958	1.141	7.664	4.983	0.026
Asymptomatic	1.000	-	-	-	-
Relapse/recurrencetime					
Less than 12 months	2.380	0.335	16.907	0.752	0.386
12-24 months	2.961	0.475	18.450	1.352	0.245
24 months	1.000	-	-	-	-

rence detection (p>0.05). The 5-year survival rate of the 23 patients whose relapse was detected symptomatically was 12.2%, whereas this rate was 49.5% for asymptomatic patients (Figure 1). Tumor location and the time of recurrence did not affect the post recurrence survival. A statistically significant difference was found in post recurrence survival based on symptomatic/asymptomatic recurrence (p<0.05) (Table 2 and 3).

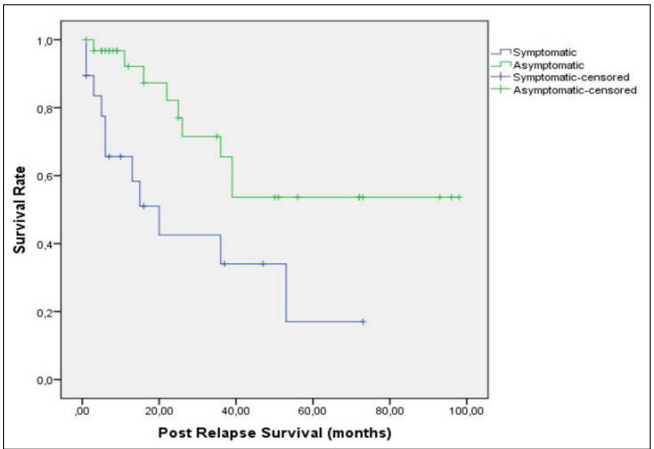

Figure 1. Post-recurrence survival analysis of cases based on the recurrence detection method

Discussion

Today, dramatic improvements in cancer treatments and prolongation of life in children with cancer have caused increasing numbers of patients under follow-up programs (1-4).

Surveillance radiologic imaging is used routinely to detect recurrence in children with various solid tumors in the absence of clinical signs and symptoms. The beneficial effect of early detection of recurrence is controversial (4-6). The optimal surveillance for recurrent disease after completion of therapy has not been well defined for many tumors (12-17). Pediatric oncologists usually feel obliged to perform frequent and thorough surveillance tests due to the consideration that early detection of recurrence could affect treatment positively. Numerous factors including sex, age at diagnosis, tumor type, stage, treatments used, and time of remission are involved in the identification of high-risk patients in follow-up surveillance (7). This follow-up process also allows the detection of secondary neoplasms and late toxicities after treatment as well as recurrence.

A standard follow-up scheme was used in our study group. Recurrence was identified in 63 of the 420 patients being followed up at our department after treatment in our study. Of the 63 patients with recurrence, 23 had recurrence diagnosed after presenting to the clinic with symptoms, whereas 40 patients who had no symptoms but had recurrence detected by examinations in the context of follow-up surveillance. Recurrence was detected through imaging methods in 35 of these patients who had no symptoms when they presented, and through laboratory tests in five patients. Asymptomatic patients who had recurrence detected through surveillance tests were found to have a longer survival time compared with symptomatic patients.

Biasotti et al. (12) recommended that clinical findings should be given priority in follow-up surveillance because clinical findings alone had a 75% effectiveness in detecting recurrences both in solid tumor and in lymphoma/leukemia tumor groups, and that laboratory tests and imaging methods should be used for the diagnosis of recurrence if patient history or a physical exam creates suspicion.

There are insufficient data regarding studies comparing differences of patients outcome between symptomatic and asymptomatic recurrence. For the majority of pediatric cancers, there is no evidence that early detection of recurrence on surveillance imaging is associated with improved salvage rates or impacts OS. The challenge for physicians is to determine a rational, cost-effective monitoring strategy that has a positive influence on disease outcome. On the other hand, surveillance radiologic imaging is burdensome to some patients and parents. Considering the adverse effects of lymphoma treatment and the additional imaging methods during follow-up, patients are thought to be exposed to unnecessary radiation (13).

In the present study, a slightly significant survival difference was observed. Overall survival was better in children whose recurrence was diagnosed on radiological surveillance than the patients diagnosed with recurrence based on the symptoms. The role of surveillance tests may change according to the primary tumor diagnosis. We suggest that surveillance imaging is more valuable for some tumor types such as Wilms tumor, brain tumors.

Rathore et al. (14) studied the surveillance tests of patients with Hodgkin lymphoma. They found that recurrence was identified in only 1.3% of all imaging tests, showing that recurrence was rarely detected in surveillance imaging tests, and patients were being exposed to cumulative radiation doses (14). In a similar study by Friedmann et al. (15), which included only patients with Hodgkin lymphoma, the authors found no difference between the post recurrence survival times of patients who had recurrence detected through surveillance tests and symptomatic patients. Many radiologic imaging or ionizing radiation modalities may result in more harm than benefit.

The studies that compared symptomatic and asymptomatic recurrence are scarcer when the literature reviewed. Howell et al. (16) showed that in more than half of their solid tumor group, the patients had symptomatic recurrence.

In accordance with these studies, recurrence was detected based on clinical findings in almost half of our patients. However, when we compared the patients with symptomatic and asymptomatic recurrence, we found that those who were diagnosed through surveillance tests had a longer survival time. This result may be explained by the detection of tumor at the early stage before the emergence of symptoms and the consequent start of treatment at an earlier stage.

Our study has certain limitations such as its retrospective nature and population size. It could have been better to investigate tumor groups separately, and could have even been more sensitive to consider stages based on tumor groups; however, we were unable to perform comparisons based on tumor groups due to the limited number of patients in our study. It should be taken into consideration that the presence or absence of symptoms is directly linked to the primary diagnosis. The optimal follow-up strategy should be determined based on the specific disease. We should review our data in view of the primary diagnosis and recurrence type. It is also possible that the patients who had a short recurrence time after remission had a less favorable prognosis, and the exclusion of patients who manifested recurrence within the first three months could have affected the results of the study.

In conclusion, history, clinical findings, laboratory tests, and imaging methods are all independently valuable for the detection of recurrence in follow-up surveillance. To obtain more certain results regarding the importance of surveillance tests for detecting recurrence, more comprehensive studies must be conducted. It should be considered that surveillance testing offers the benefit of prolonging post recurrence survival.

Ethical Committee Approval: The local ethics committee of Ankara Child Health Disease Hematology Oncology Hospital granted approval for the study (No.: 2013-069, Date: 17.12.2013).

Informed Consent: Written informed consent was obtained from the parents who participated in this study.

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Conflict of Interest: The authors have no conflicts of interest to declare.

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