Research Article / Araştırma Makalesi

A Single-center Experience of Synchronous and Metachronous Hematologic and Oncologic Tumors

Senkron ve Metakron Hematolojik ve Onkolojik Tümörlerin Tek Merkez Deneyimi

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Abstract: The incidence of cancer is increasing in the world. With the developments in cancer treatment, the life expectancy of patients is prolonged and the incidence of secondary malignancies is increasing. We retrospetively patients with syncronous / metachronous oncological malignancies accompanying hematological malignancies in a newly established hematology center. Data were obtained from the medical records. Demographic data, treatments and overall survival of the patients were evaluated. Twenty eight (6%) of 433 patients hematological malignancies were included in the study. 12 patients (42.9) were diagnosed with syncronous and 16 (57.1%) patients with metachronous hematologic-oncologic tumors. Sixteen of the patients were male,twelve were female. In syncronous tumors, the most common hematologic malignancy was Non-hodgkın lymphoma (NHL), while the most common oncologic malignancies were thyroid papillary cancer and colon cancer. In metachronous tumors, the most common malignancies were NHL and breast cancer. The median time between diagnosis of metachronous tumors was 49.5 months (8-192 months). The median survival of patients with syncronous malignancies was 19 months (SE=12.19) (95% CI 0-42.89), with metachronous malignancies was 22 months (SE=14.0) (95% CI 0-49.44). There was no statistically significant difference in the comparison of survival curves of patients with syncronous and metachronous malignancies (p=0.382). Oncological malignancies accompanying hematological malignancies are not uncommon. There is no standart treatment for syncronous / metachronous hematologic malignancies. In the presence of syncronous multipl malignancies should be evaluated individually.
Keywords: Multipl primary neoplasms, syncronous neoplasms, hematologic malignancies

Özet: Dünyada kanser görülme sıklığı giderek artmaktadır. Kanser tedavisindeki gelişmelerle birlikte hastaların ortalama yaşam süreleri uzamakta ve sekonder malignitelerin görülme sıklığı artmaktadır. Yeni kurulan bir hematoloji merkezinde hematolojik malignitelere eşlik eden senkron / metakron maligniteleri retrospektif olarak inceledik.Veriler tıbbi kayıtlardan elde edildi.Hastaların demografik verileri, tedavileri ve genel sağ kalımları değerlendirildi. Hematolojik maligniteli 433 hastanın 28'i (%6) çalışmaya devam edildi. 12 hasta (%42,9) senkron, 16 (%57,1) hasta ise metakron hematolojik-onkolojik tümör tanısı almıştır. Hastaların 16'sı erkek, 12'si kadındı. Senkron tümörlerde en sık görülen hematolojik malignite non-hodgkın lenfoma (NHL), en sık görülen onkolojik maligniteler ise tiroid papiller kanseri ve kolon kanseri idi. Metakron tümörlerde en sık görülen maligniteler NHL ve meme kanseri idi. Metakron tümörlerin tanısı arasındaki medyan süre 49,5 aydı (8-192 ay). Senkron malignitesi olan hastalrın medyan sağkalımı 19 aydı (SE=12,19))%95 CI 0-42,89), metakron maligniteleri olan hastaların medyan sağkalımı 22 aydı (SE=14,9= (%95 CI 0-49,44). Senkron ve metakron maligniteleri olan hastaların sağkalım eğrilerinin karşılaştırılmasında istatistiksel olarak anlanmlı fark saptanmadı (p=0,382). Hematolojik malignitelere eşlik eden onkolojik maligniteler nadir değildir. Senkron / metakron hematolojik maligniteler için standart bir tedavi yoktur. Senkron multipl malignite varlığında, malignitelerin her biri ayrı ayrı değerlendirilmelidir.
Anahtar Kelimeler: Multipl primer tümörler, senkronize tümörler, hematolojik maligniteler

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Received 03.05.2023 ***Accepted*** 04.09.2023 ***Online published*** 05.10..2023

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1. Introduction

The incidence of cancer is increasing in the world. According to the world cancer statistics for 2020, it is estimated that there are 18.1 million cancer patients (excluding non-melanoma skin cancers). 9.3 million of them are men and 8.8 million are women (1). Despite the increasing incidence of cancer; with advances in cancer treatment, the life expectancy of patients' is prolonged. With the prolongation of the patients' life spans, the long-term effects of chemotherapeutics and radiotherapy may occur. Genetic susceptibility and exposure to environmental factors continue(cümlesi çıkarıldı). The incidence of cancer increases with age. Secondary or even tertiary malignancies may occur in these patients. If the time between the diagnosis of multiple cancers is less than 6 months, they are called syncronous tumors. If the time longer than 6 months, they are called metachronous tumors (2). The incidence of syncronous /metachronous tumors was found to be 0.73-11.7% in studies. The prevelance was found to be higher in the elderly (3-4).

In our study, we aimed to evalute the demographic characteristics of patients with syncronous / metachronous hematologic and oncologic malignancies diagnosed in a newly established hematology center, the treatments they received, the duration of diagnosis in patients with diagnosis of metachronous and overall survive.

2. Materials and Methods

We included patients with a diagnosis of syncronous / metachronous oncologic malignancy accompanying hematologic malignancy between 01.01.2017 and 01.01.2022 in the Department of Hematology of Afyonkarahisar Health Sciences University. In our study, patients under the age of 18 and patients with synchronous / metachronous solid tumors were not included in the study. The data of the patients were obtained by retrospectively scanning the medical records. The ages, genders, treatments they received, diagnosis times in metachronous tumors, and overall survival times were evaluated.

Statistical Analysis

PASW Statistics 18.0 package program was used for statistical analysis. In descriptive statistics, categorical data were evaluated as percentage frequency, continuous data as mean and standard deviation (mean±sd). Chi-Square Test was used for statistical analysis of categorical data. Kaplan-Meier Method was used to determine survival rates. Log Rank Test was used to compare survival curves. $p<0.05$ was accepted as the cut-off value for statistical significance. Overall survival (OS) was defined as the time from the date of diagnosis of the solid tumors or hematological malignancy, whichever was diagnosed first, and the last follow-up or death from any cause. All P values were two-sided, and P = 0.05 or less was considered to indicate statistical significance.

3. Results

Four houndred thirty three patients with hematological malignancies were evaluated. Twenty-eight patients with both hematologic and oncologic malignancies were included in the study. Sixteen (57.1%) patients were male and twelve (42.9%) were female. The mean age of hematological malignancy diagnosis was 66.5±11.5 (40-85). The mean age of oncological malignancy was 65.3±11.2 (37-84).

Metachronous malignancy diagnosis was made in 57.1% of the patients included in the study, and synchronous in 42.9%. Seventy five percent of patients with a diagnosis of metachronous were initially diagnosed with hematological malignancies. The median time between synchronous diagnoses was 2 months (1-6 months). The median time between metachronous diagnoses was 49.5 months, maximum 16 years and minimum 8 months. Eight (66.7%) of the synchronous patients and twelve (75.0%) of the metachronous patients were 65 years or older. There was no statistical difference between the synchronous and metachronous groups in the distribution of patients over 65 years of age (p=0.691) (Table 1). Hematological diagnoses and oncological diagnoses of synchronous and

metachronous cases are shown in Tables 2 and 3.

The median follow-up period of patients after hematological malignancy was 19.5 months (1-91 months). The median survival time after hematologic malignancy was 20 months (SE=8.56) (95% CI 3.21-36.78). The cumulative survival rate at 1 year after hematologic malignancy was 60.0±9.2%, and the 5-year cumulative survival rate was 31.2%±9.6% (Figure 1).

The mean life expectancy of patients with malignancies under the age of 65 was 46.06 months (SE=13.83) (95% CI 19.83-72.29). In patients younger than 65 years, the cumulative survival rate at 1 year after hematological malignancy was 75.0±15.3%, and the 5-year cumulative survival rate was 56.3%±19.9%. The mean life expectancy of patients with malignancies aged 65 and over was 28.53 months (SE=7.97) (95% CI 12.91-44.14). In patients aged 65 and over with malignancy, the cumulative survival rate at 1 year after hematological malignancy was 55.0±11.1%, and the 5-year cumulative survival rate was 21±10.0%. There was no statistically significant difference in the comparison of the survival curves of patients aged below 65 years and over 65 years of age with a diagnosis of hematological malignancy (p=0.183) (Figure 2).

The median survival of patients with synchronous malignancies was 19 months (SE=12.19) (95% CI 0-42.89). In patients with synchronous malignancy, the cumulative survival rate at 1 year after hematological malignancy was 58.3%±14.2%, and the 5-year cumulative survival rate was 13.0±11.7%. The median survival of patients with metachronous malignancies was 22 months (SE=14.0) (95% CI 0-49.44). In patients with metachronous malignancy, the cumulative survival rate at 1 year after hematological malignancy was 62.5%±12.1%, and the 5-year cumulative survival rate was 32.8%±13.3%. There was no statistically significant difference in the comparison of the survival curves of patients with synchronous and metachronous malignancies (p=0.382) (Figure 3).

Table 1. Distribution of synchronous and metachronous tumors under 65 years old and over 65 years

	Age <65		Age≥65		Total		p
	n	%	n	%	n	%	
Metachronous	4	25.0	12	75.0	16	100.0	0.691
Synchronous	4	33.3	8	66.7	12	100.0	
	8	28.6	20	71.4	28	100.0	

Table 2. Clinical characteristics of syncronous hematologic and oncologic tumors

	Sex	Age	Hematological malignancy	Treatment	Oncological malignancy	Treatment	OS	Cause of death
1	M	50	Small lymphocyctic lymphoma	Follow-up without treatment	Nasopharyngeal cancer	Radiotherapy	3 months	Oncological malignancy
2	F	67	Diffuse large B cell lymphoma	Chemotherapy (Rituximab, cyclophosphamide, doxorubucine, vincristine)	Thyroid papillary carcinoma	Surgical treatment	37 months	Cardiac event
3	F	53	Multiple myeloma	Chemotherapy Bortezomib, cyclophosphamide, dexametazone, lenalidomide AutoSCT	Thyroid papillary carcinoma	Surgical treatment	21 months	Alive
4	F	66	Multiple myeloma	Follow-up without treatment	Renal clear cell carcinoma,colon cancer	Surgical treatment -chemotherapy (oxaliplatin,flurourasil)	20 months	Oncological malignancy
5	F	66	Multiple myeloma	Follow-up without treatment	Uterin cancer	Surgical treatment -chemotherapy	19 months	Oncological

						(carboplatin paclitaxel)		malignancy
6	M	45	Castleman diasease	Surgical treatment	Squamosis cell carcinoma (Vocal cord)	Surgical treatment	13 months	Alive
7	M	72	Multiple myeloma	Chemotherapy (Bortezomib,dexametazone)	Lung cancer	Surgical treatment	2 months	Oncological malignancy
8	M	64	Hairy cell leukemia	Chemotherapy (Cladribine)	Colon cancer	Surgical treatment -chemotherapy (kapesitabin)	65 months	Alive
9	M	82	Acute myeloid leukemia	Chemotherapy (Azacytidine)	Prostate cancer	Surgical treatment	2 months	Hematological malignancy
10	M	84	Non- hodgkın lymphoma (Marginal zone lymphoma)	Follow-up without treatment	Skin squamosis cell carcinoma	Surgical treatment	4 months	Cardiac event
11	M	83	Non- hodgkın lymphoma (T cell, thyroid)	Chemotherapy (cyclophosphamide,vincristine, prednisolone)	Skin squamosis cell carcinoma	Surgical treatment	29 months	Cardiac event
12	F	73	Chronic lymphocytic leukemia	Follow-up without treatment	Rectal cancer	Surgical treatment	1 months	Oncological malignancy

Table 3. Clinical characteristics of Metachronous Hematologic and Oncologic Tumors

	Sex	Age	Primary malignancy	Treatment	Time interval	Secondary malignancy	Age	Treatment	OS after hematological malignancy	Cause of detah
1	F	63	Breast cancer	Operation, radiotherapy, hormone therapy(anastrazol)	54 months	NHL (Chronic lymphocyctic leukemia)	67	Follow up- without treatment	14 months	Alive
2	F	61	Endometrium cancer	Operation, Chemotherapy (paclitaxel,carboplatin)	66 months	T cell acute lymphoblastic leukemia	66	Chemotherapy (vincristine, dexametazone, doxorubicine)	1 months	Hematological malignancy
3	F	51	Breast cancer	Operation, radiotherapy	192 months	Chronic myeloproliferat ive disease	67	acetylsalicylic acid	28 months	Alive
4	F	55	Breast cancer	Operation, hormone therapy (anastrazol)	124 months	Multipl myeloma	65	Chemotherapy (bortezomibe, dexametazone)	1 months	Hematological malignancy
5	M	60	Renal cell carcinoma	Operation	120 months	NHL (Burkitt lymphoma)	70	Chemotherapy (rituximab, bendamustine)	1 months	Hematological malignancy
6	M	70	Renal cell carcinoma	Operation	12 months	NHL (Hepatic marginal zone lymphoma)	71	Operation	14 months	Alive
7	F	37	Cervix cancer	Operation, Radiotherapy, chemotherapy (cisplatin)	45 months	Aplastic anemia	40	Supportive treatment	1 months	Aplastic anemi
8	F	74	Breast cancer	Operation, Radiotherapy, hormone therapy (letrozol, anastrozol,eksemestan) Chemotherapy (gemcitabine, carboplatine, paxlitaxele)	42 months	NHL (Mantle cell lymphoma)	78	Chemotherapy (rituximab, bendamustine)	8 months	Hematological malignancy
9	M	67	Prostate cancer	Operation, hormone therapy (bikatulamide,loprolide)	9 months	Chronic myeloproliferat ive disease	68	Acetylsalicylic acid	61 months	Alive
10	M	82	Skin squamous cell carcinoma	Operation	37 months	Acute myeloid leukemia	85	Chemotherapy (azasitidine)	13 months	Hematological malignancy
11	M	74	Skin squamous cell carcinoma	Operation	8 months	Multipl myeloma	75	Chemotherapy bortezomibe, cyclophosphamide, dexametazone, lenalidomide)	22 months	Hematological malignancy
12	F	62	Breast cancer	Operation, Radiotherapy, hormone therapy(letrozole)	120 months	NHL (Diffuse large b cell lymphoma)	72	Chemotherapy(rituximab, cyclophosphamide, vincristine, doxorubicine,prednison)	1 months	Hematological malignancy
13	M	58	Multipl myeloma	Chemotherapy (bortezomibe, cyclophosphamide, dexametazone, lenalidomide, pomalidomide)	60 months	Hepatocelluer carsinoma	63	Operation	72 months	Oncological malignancy
14	F	53	NHL (Follicular lymphoma)	Chemotherapy (rituximab, doxorubicine, vincristine, cyclophosphamide,prednisolon)	30 months	Breast cancer	55	Operation, radiotherapy, hormone therapy (anastrazole) Chemotherapy (paklitaxel)	66 months	Alive
15	M	53	NHL (Mantle cell lymphoma)	Chemotherapy (rituximab, bendamustin, ibrutinib)	19 months	Lung cancer	55	Operation	27 months	Oncological malignancy
16	M	66	Chronic myeloproliferativ e disease	acetylsalicylic acid	63 moths	Skin squamous cell carcinoma	71	Operation	91 months	Alive

NHL: Non-Hodgkın Lymphoma
M: male
F: female
OS: Overall survival

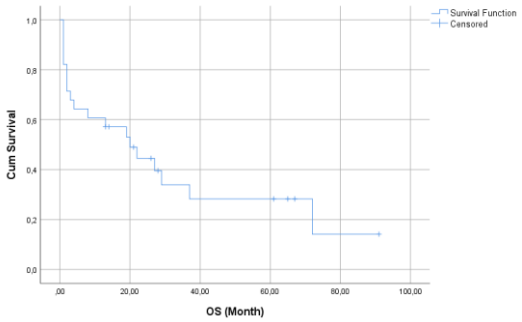

Figure 1. The cumulative survival rate after hematologic malignancy

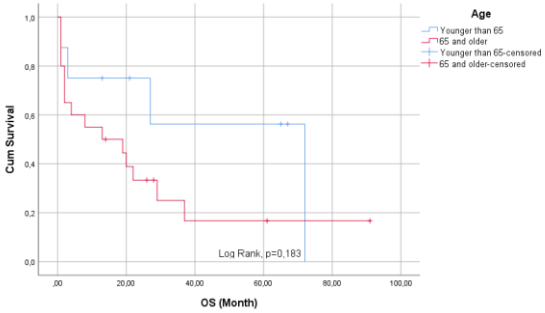

Figure 2. Graph of overall survival of patients under 65 and over 65 years of age

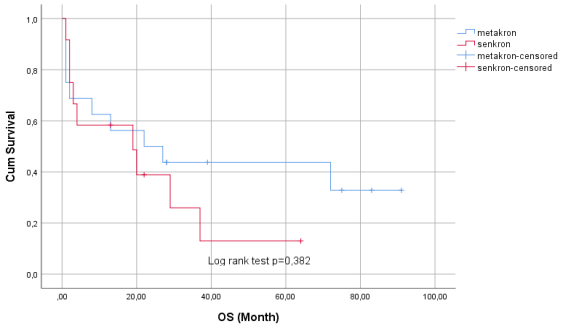

Figure 3. OS graph of patients with metachronous and syncronous tumors

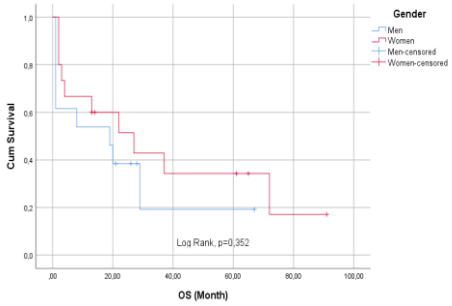

Figure 4. Os graph by gender

4. Discussion

Incidence of cancer continues to increase. With advances in cancer treatment, the life expectancy of patients is increasing. Prolonged life expectancy also increases the risk of second cancer. (5-6). Secondary or even tertiary malignancies may occur in these patients. If secondary malignancies are diagnosed in the first 6 months after the diagnosis of the primary tumor, they are called synchronous tumors, and if diagnosed after the first 6 months, they are called metachronous tumors (2). Synchronous / metachronous tumor pathogenesis is not completely clear. Familial cancer syndromes and genetic predisposition are thought to be effective in etiology. In addition, smoking, alcohol consumption, environmental factors, previous chemotherapy due to tumor, radiotherapy are other factors in the etiology. Genetic instability may play an important role in the development of multiple primary cancers. Studies have shown that genetic defects in the mismatch repair system carry a high risk for multiple primary tumors (7). Epidemiology studies show that approximately 20% of newly diagnosed malignancies have a previous history of malignancy (8).

The incidence of synchronous and metachronous tumors is increasing day by day. The prevalence was found to be higher in the elderly (4). The incidence of synchronous / metachronous tumors was found to be 1.4% in a study conducted in Turkey. Hematologic malignancies comprised 11.9% of this population (9). In another study from Turkey, the incidence of synchronous / metachronous malignancy was found to be 3.9% in patients with hematological malignancies (10). Our study is a cross-sectional study aiming to provide descriptive data on synchronous and metachronous oncological malignancies accompanying hematological malignancies. Although it is a newly established hematology center, the incidence of synchronous / metachronous oncological malignancy was found to be 6% in patients with hematological malignancies. The difference in this incidence might be attributable to differences in geography, environment, race, or various diagnostic criteria or, more importantly, the experience of the clinicians or the examination methods between studies.

In a study evaluating 649 hematological malignancies, syncronous malignant tumors were found in 19 patients. In this study, the most common hematological malignancy was non-Hodgkin lymphoma (NHL) (11). In a study from Turkey, the most common hematological malignancy was NHL (12). In a study evaluating 32 synchronous hematological malignancies and solid tumors, NHL was the most common hematological malignancy. The most common solid tumors are stomach and thyroid cancer (13). NHL was the most common hematological malignancy in both groups in our study. In our study, thyroid cancer and skin squamous cell carcinoma were the most common solid tumors in synchronous malignancies, while breast cancer in metachronous tumors. In the study of Burak Deveci et al., NHL and lung cancer are the most common malignancies in both synchronous and metachronous groups (12). In our study, the most common oncological malignancy was breast cancer (25%). The most common malignancy in the world is breast cancer (14).

There are studies showing an increased risk of second primary malignancy in patients with mantle cell lymphoma in population-based studies (15). In our study, we had 2 patients who were diagnosed with mantle cell lymphoma after breast ca and lung cancer .

Chronic lymphocytic leukemia (CLL) is the most common type of leukemia in adults. In CLL, the incidence of secondary malignancy has increased due to immune dysregulation, the treatments they have received, and environmental exposures (16). In our study, there were 2 CLL and 1 small lymphocyctic lymphoma (SLL) patients. The patient with SLL was diagnosed with synchronous nasopharyngeal carcinoma, 1 patient with rectal carcinoma synchronous with CLL, and 1 patient with metachronous CLL after breast cancer. Two of the patients with synchronous diagnosis died due to oncological malignancy.

In our study, unlike studies evaluating other synchronous / metachronous malignancies, one of our patients was diagnosed with Castleman syndrome and synchronized skin squamous cell carcinoma. One of our patients was diagnosed with aplastic anemia after cervical cancer.

Castleman disease is a rare lymphoproliferative disease characterized by hyperinflammation. In a study of 66 Castleman patients, one of the two most common causes of death was malignant cancer (17). In our study, a patient with stage 1 Castleman disease was cured by surgical treatment, and vocal cord squamoze squamous cell carcinoma was diagnosed 2 months after the diagnosis of Castleman. The patient, who was cured after radiotherapy, continues to live in good health.

Aplastic anemia (AA) complicated by a solid tumor is often found in hereditary bone marrow failure syndromes such as Fanconi anemia (FA), which is characterized by congenital malformations, bone marrow failure, and predisposition to cancer. (18). It is known that chemotherapy and radiotherapy are involved in the etiology of acquired aplastic anemia. In a study evaluating 25 patients with secondary aplastic anemia, only 5 patients (20%) were diagnosed with aplastic anemia secondary to cervical cancer. Of these patients, 4 received only chemotherapy, and 1 received both chemotherapy and radiotherapy (19). Our patient received chemotherapy and radiotherapy for cervical cancer and was diagnosed with aplastic anemia 3 years after the diagnosis of cervical cancer. Fanconi aplastic anemia was ruled out in the patient. And died due to sepsis.

Mutiple myeloma is the second most common hematological malignancy in the world. It constitutes 1-2% of all malignancies and 2% of malignancy-related deaths (20). With the prolongation of the life expectancy of myeloma patients, the incidence of secondary malignancies also increases. The etiology is multifactorial and different antimyeloma drugs pose varying risks for the development of secondary malignancy. In a study evaluating the malignancies accompanying multiple myeloma, the risk of developing secondary malignancy was found to be 2.19 times higher in the multiple myeloma population (21). In our study, 4 out of 7 (25%) patients were diagnosed with multiple myeloma as synchronous and 3 as metachronous. Of 7 patients, 2 patients died due to multiple myeloma and 4 patients due to concomitant solid tumor. Concomitant solid malignancy of 1 patient was synchronous thyroid papillary carcinoma. The patient underwent autologous stem cell transplantation and continues to live. Although it is known that the incidence of secondary malignancy increases in patients with multiple myeloma, there are few recommendations and guidelines for screening. Therefore, age-appropriate oncological screening of patients is required (22).

Acute myeloid leukemia constitute the majority of secondary acute leukemias. Secondary acute lymphoblastic leukemias are rare and the prognosis is poor. In our study, synchronous / metachronous acute leukemia was detected in 3 patients. Two of them were acute myeloid leukemia and one was T-cell acute lymphoblastic leukemia (ALL). In our study, there were two patients, one diagnosed with metachronous and one diagnosed with synchronous acute myeloid leukemia (AML). The overall survival time of two patients was less than 12 months. In a study evaluating patients with secondary AML, OS was 12.5 (3.8-48.0) months (23). Due to the low incidence of secondary AML, there is no standard treatment protocol. Induction, consolidation chemotherapy, hematopoietic stem cell transplantation, hypomethylating agents and supportive treatments used in the treatment of AML are among the treatments that can be applied (24). Treatment-related ALL accounts for 3-9% of adult ALL patients. Poor cytogenetic features are observed more frequently in treatment-related ALL and the prognosis is worse. In a study in which 1022 ALL cases were evaluated, 9.1% of the patients consisted of treatment-related ALL patients. Only 9% of treatment-associated ALL cases were of the T cell phenotype (25). Our patient was also diagnosed with T-cell ALL after the diagnosis of endometrial

cancer. However, the patient died in the first month of the diagnosis. All 3 of our patients diagnosed with acute leukemia had acute leukemia diagnoses that determined the surveys.

Studies conducted in recent years have shown that the incidence of secondary cancer is increased in patients with myeloproliferative disease. The cumulative incidence can reach 5-10% after the first 5 years of diagnosis. In our study, 3 patients had solid malignancy accompanying chronic myeloproliferative disease. None of these patients had myelofibrosis. Studies have shown that the development time of secondary cancer in primary myelofibrosis is shorter than in polycythemia vera and essential thrombocytosis (26). In our study, solid tumors accompanying chronic myeloproliferative disease were diagnosed as metachronous. Solid tumors of the patients were breast cancer, prostate cancer and skin squamous cell carcinoma. Studies have shown that 75% of patients with solid malignancies accompanying chronic myeloproliferative disease are over 50 years of age. In our study, all 3 of our patients were over 50 years old (27-28).

Studies have shown that synchronous multiple primary malignancies are associated with a significant reduction in overall survival compared to metachronous malignant tumors (29). However, there are also studies showing that overall survival is not different in synchronous / metachronous tumors (17). In our study, no statistical difference was found in terms of overall survival, whether synchronous or metachronous.

Multiple primary cancer is difficult to diagnose. A biopsy must be performed to confirm the diagnosis. After diagnosis, which malignancy will be treated first will depend on the patient and the biology of the accompanying tumors. Multifactorial evaluation of the patient and multidisciplinary follow-up is required. There is no standard treatment for synchronous / metachronous hematological malignancies. It is common practice to treat synchronous multiple primary malignancies as stand-alone malignancies and to begin treatment of the most aggressive cancer rather than treating the tumor with the least malignant potential (30-31).

Limitations

Our study includes a population with a small number of patients with a short follow-up period in a newly established hematology center. Due to its retrospective nature and the small number of non-randomized patients, it did not give us much information in terms of etiology. We think that this incidence will increase as the follow-up period of the patients increases and the awareness of synchronous / metachronous tumors increases. There is a need for more comprehensive studies that will also explain the etiologies of synchronous / metachronous hematological and oncological malignancies.

5. Conclusions

All systems should be evaluated in the presence of symptoms, physical examination, and laboratory findings that do not match clinically in an individual with an oncological / hematological malignancy. It is necessary to be suspicious in terms of secondary malignancy that may accompany. The presence of a second malignancy must also be confirmed by biopsy. Although there is no standard treatment, the patient should be evaluated multidisciplinary according to the biology and course of the disease, and malignancy with an aggressive course should be treated primarily.

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Ethics

Ethics Ethics Committee Approval: The study was approved by Afyonkarahisar Health Scıences University Ethical Committee (Approval Date/ Number: 07.01.2022 / 2011-KAEK-2)
Informed Consent:
Author Contributions: Idea/concept: F.Y, M.B.., İ.G.K.Y., Design: F.Y., Data Collection: F.Y., H.D., M.B., Data Processing: F.Y., Analysis/Comment: F.Y., Y.Ş., Literature research/review: F.Y., Writing: F.Y., All authors discussed the results and contributed to the final manuscript.
Conflict of Interest: No conflict of interest was declared by the authors.
Financial Disclosure: The authors declared that this study received no financial support.
Acknowledgment: The authors express their gratitude to the dental students who participated in the study by filling out the questionnaire.