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Second Primary Malignancies in Patients with Hematologic and Solid Tumors: Risk Factors

Atakan Tekinalp[1], Oğuzhan Yıldız[2], Cengizhan Doğan[3], Sinan Demircioğlu[1], Mustafa Merter[1], Melek Karakurt Eryılmaz[2]

[1]*Necmettin Erbakan Univercity Faculty of Medicine, Department of Hematology, Division of Internal Medicine, Konya, Türkiye*
[2]*Necmettin Erbakan Univercity Faculty of Medicine, Department of Medical Oncology, Division of Internal Medicine, Konya, Türkiye*
[3]*Gürgentepe State Hospital, Clinic of Internal Medicine, Ordu, Türkiye*

ABSTRACT

Aim: This study aimed to evaluate time to second primary malignancy (SPM) development and associated clinical factors in adults with a PM.

Methods: This retrospective study included patients with hematologic malignancies (HM) and a prior history of solid organ malignancy (SOM) who had complete clinical data available. We recorded demographic characteristics; diagnoses of the PM and SPM; the interval between PM and SPM; treatments received; and survival outcomes. Time to SPM was calculated for the overall cohort and for predefined subgroups, and comparisons were performed according to demographic variables and treatment exposures.

Results: A total of 101 patients were included. Median age was 61 years (26-88). Median time to SPM was 42.9 months overall, longer in the primary hematologic malignancy than primary SOM (54.9 vs. 26.8 months, p=0.018). Patients <60 years had longer time to SPM than those ≥60 (66 vs. 21.4 months, p<0.001), a difference consistent across subgroups (<60: 96 vs. 37 months, p=0.001; ≥60: 41 vs. 8.9 months, p=0.036). Patients receiving chemotherapy (CT) and/or radiotherapy had longer SPM times than untreated patients (CT: 54.5 vs. 18.9 months, p=0.007). Among SPMs, the most frequent HM was chronic lymphocytic leukemia (chronic lymphocytic leukemia, 24.4%), while lung cancer (17.9%) was the most frequent solid tumor. In multivariate regression, the only independent predictor of shorter SPM time was age ≥60 years (odds ratio=0.34, 95% confidence interval: 0.12-0.88, p=0.023).

Conclusion: Advanced age is the main determinant of SPM development in adult cancer survivors, highlighting the need for closer surveillance in elderly patients.

Keywords: Chemotherapy, hematologic malignancies, medical oncology, onco-hematology

Introduction

In addition to conventional chemotherapy (CT), targeted therapies such as monoclonal antibodies, immunomodulatory drugs, tyrosine kinase inhibitors (TKIs), and checkpoint inhibitors have significantly contributed to the treatment of hematologic and solid cancers over the past two decades. With these agents, survival has improved [1-4], but attention to treatment-related adverse effects and secondary malignancies has also increased [5,6]. Drugs causing direct deoxyribonucleic acid damage, including alkylating agents, topoisomerase II inhibitors, and platinum compounds, are well recognized for inducing secondary cancers by affecting hematopoietic cells [7]. Data on targeted therapies are less consistent. Some studies suggest an increased risk of malignancy with imatinib in chronic myeloid leukemia (CML) and lenalidomide in maintenance therapy for multiple myeloma (MM) [8,9]. However, attributing secondary cancers solely to therapy may be misleading. These cases could represent therapy-related cancers or independent second primaries. Multiple factors, including age, genetic predisposition, radiotherapy (RT), hormone replacement therapy (HRT) and immune status, contribute to new cancer development [10].

This study evaluated clinical and treatment-related factors influencing the time to second cancer in patients with prior

Address for Correspondence: Atakan Tekinalp MD, Necmettin Erbakan Univercity Faculty of Medicine, Department of Haematology, Division of Internal Medicine, Konya, Türkiye

E-mail: atakantekinalp@hotmail.com **ORCID ID:** orcid.org/0000-0001-7937-4045

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malignancy. Understanding these risks is crucial for identifying high-risk groups and guiding individualized follow-up. Findings are expected to support improved management of secondary malignancies and inform future surveillance strategies.

Methods

This retrospective study involved review of the medical records of patients followed at the Necmettin Erbakan University Faculty of Medicine between 2002 and 2024. The medical documents were reviewed between 01.07.2023 and 01.07.2025. This study was conducted in accordance with the principles of the 1964 Helsinki Declaration and its subsequent amendments. The study was approved by the Non-interventional Research Ethics Committee of Necmettin Erbakan University (approval no: 177, date: 02.06.2023).

Patients diagnosed with hematologic malignancies (HM) who either had a prior diagnosis of solid organ cancer or who developed solid organ cancer during follow-up and for whom complete data were available were included in the study.

Demographic characteristics of the patients (age and sex), diagnoses of primary malignancy (PM) and second PM (SPM), interval between diagnoses, treatments received (CT, RT, HRT, TKI use, etc.), and survival times were recorded. For patients who received CT, the use of alkylating agents and topoisomerase inhibitors was specifically noted.

The time between diagnosis of PM and diagnosis of SPM was calculated. This duration was evaluated for all patients and separately for those with a primary HM (PHM) or primary solid organ malignancy (PSOM). The interval to SPM development was compared across PM diagnosis, demographic characteristics, and treatment modalities.

Statistical Analysis

Statistical analyses were performed using IBM SPSS version 25 (IBM Corp., Armonk, NY, USA). Descriptive data are presented as median (minimum-maximum). Continuous numerical variables were compared using the Mann-Whitney U test. Categorical variables were expressed as percentages (%) and analyzed with the chi-square test or Fisher's exact test. Survival analysis was conducted using the Kaplan-Meier method, and differences between groups were assessed with the log-rank test. A binary logistic regression analysis was performed to determine the factors influencing the development of second cancers. For this purpose, patients were divided into two groups based on the median time to the development of a SPM (42.9 months): early development (<43 months) and late development (≥43 months). Independent variables included age (<60 and ≥60), sex, diagnosis of PM, and treatment modalities. All variables were entered into the model using the Enter method. Results were reported as odds ratios (ORs) with 95% confidence intervals. A p value <0.05 was considered statistically significant.

Results

A total of 101 patients were included. The median age was 61 years (range, 26-88); 37 (36.6%) were women and 64 (63.4%) were men. Of the patients, 56 (55.4%) had PHM and 45 (44.6%) had PSOM. In these two groups, the numbers of females and males were 18 (38.1%)/38 (67.9%) and 19 (42.2%)/26 (57.8%) respectively, while the median ages were 60 years (range 26-82) and 63 years (range 34-88). No statistically significant differences in age or sex were observed between the groups (p=0.296 and p=0.672). The distribution of patients by PM and treatment characteristics is presented in Table 1.

Accordingly, the rates of CT administration differed significantly between the PHM and PSOM groups (87.5% vs. 37.8%; Pearson chi-square =27.240; p<0.001). Among patients who received CT, the rate of alkylating agent use was markedly higher in the PHM group (69.4%) than in the PSOM group (5.9%) (Pearson chi-square =20.435; p<0.001). Similarly, the rate of topoisomerase II inhibitor use was significantly higher among patients with PHM (30.6%) than among those with PSOM (Pearson chi-square =6.735; p=0.009).

No patients in the PHM group received RT or HRT. Regarding TKI use, 6 patients (10.7%) in the PHM group and 3 patients (6.7%) in the PSOM group received TKI therapy, reflecting similar rates between the groups. All patients in the PHM group were diagnosed with CML and treated with imatinib as first-line therapy. Among the PSOM patients, two had gastrointestinal stromal tumors (GIST) and were treated with imatinib, while one patient with lung adenocarcinoma received afatinib.

Table 1. Primary malignancy and characteristics of treatment

Treatment	PHM (n=56)	PSOM (n=45)	p
CT-treated patient, n(%)	49 (87.5)	17 (37.8)	<0.001[a]
Alkylating agent topoisomerase II inhibitors	34 (69.4) 15 (30.6)	1 (5.9) 0	<0.001[a] 0.009[a]
RT-treated patient, n (%)	0	6 (13.3)	0.006[b]
KT and/or RT-treated patient, n (%)	49 (87.5)	20 (44.4)	<0.001[a]
HRT-treated patient, n (%)	0	5 (11.1)	0.005[b]
TKI-treated patient, n (%)	6 (10.7)	3 (6.7)	0.727[b]

[a]: Pearson chi-square test
[b]: Fisher's exact test
PHM: Primary hematologic malignancy, PSOM: Primary solid organ malignancy, CT: Chemotherapy, RT: Radiotherapy, HRT: Hormone replacement therapy, TKI: Tyrosine kinase inhibitors

The median time to the development of SPM was 42.9 months (4-315.5) for all patients. This duration was significantly longer in the PHM group (54.9 months; range, 5.5-315.5) than in the PSOM group (26.8 months; range, 4-240) (p=0.018). When all patients were evaluated, the time to SPM development was longer in patients aged <60 years compared with those aged ≥60 years: 66 months (5-315.5) vs. 21.4 months (4-178.7), respectively (p<0.001). Similarly, in both the PHM and PSOM groups, patients younger than 60 years had a significantly time to development of SPM. In patients aged <60 years, the time was 96 months (6-315.5) vs. 37 months (5.5-169.9) (p=0.001), while in those aged ≥60 years, the time was 41 months (5-240) vs. 8.9 months (4-178.7) (p=0.036). When all patients were analyzed according to treatment status, the time to SPM development was significantly longer in patients who received CT and those who received CT and/or RT, compared with untreated patients. Among CT-treated and untreated patients, median times were 54.5 months (range 4.7-315.5) and 18.9 months (range 4-178.7), respectively (p=0.007). Similarly, among patients who received CT and/or RT compared with those who did not, the durations were 54 months (4-315.5) and 18.5 months (4-178.8), respectively (p=0.012). However, when patients were evaluated separately according to PM diagnosis, the time to SPM development was similar across treatment groups. The comparison of time to second cancer across PM, sex, and treatment groups is summarized in Table 2.

The median estimated overall survival (OS) for all patients was 178.3 months (113.2-243.5). In the PHM group, the duration was 283 months (41.6-524.4), whereas in the PSOM group it was 126.2 months (81.8-170.7), with no significant difference between the two groups (p=0.454).

Among SPMs, the most frequently reported HM was chronic lymphocytic leukemia (CLL, 24.4%), whereas the most common solid organ tumor was lung cancer (17.9%). The primary and secondary malignancy diagnoses of the patients are summarized in Table 3. Among the 34 PHM patients who received alkylating agent therapy, the most common second cancers were lung (20.6%), breast (14.9%), prostate (11.8%), bladder (8.8%), skin (8.8%), hepatocellular carcinoma (HCC, 5.9%), rectum (5.9%), endometrium (5.9%), and other tumors (Kaposi sarcoma, malignant melanoma, pleura, and

Table 2. Comparison of time to second primary malignancy

	All patients		PHM		PSOM	
Parameter	**Time to SPM (month)**	**p***	**Time to SPM (month)**	**p***	**Time to SPM (month)**	**p***
Sex						
Female	57.9 (5-315.5)	0.98	69.4 (5.9-315.5)	0.380	49.4 (5-240)	0.063
Male	36.7 (2-250)		53 (5.5-250.9)		13.9 (4-178.8)	
Age						
<60	66 (5-315.5)	<0.001	96 (6-315.5)	0.001	41 (5-240)	0.036
≥60	21.4 (4-178.7)		37 (5.5-169.9)		8.9 (4-178.7)	
CT						
Treated	54.5 (4.7-315.5)	0.007	56 (5.5-315.5)	0.408	39.9 (4.7-240)	0.122
Un-treated	18.9 (4-178.7)		37 (6.5-170.9)		14.9 (4-178.7)	
Alkylating agent						
Treated	54.9 (5.3-315.5)	0.07	55.4 (5.9-315.5)	0.540	-	0.771s
Un-treated	36.2 (2-250.9)		46 (5.5-250.9)		29.4 (4-240)	
Topo II inhibitor						
Treated	54.9 (6-315.5)	0.189	54.9 (6-315.5)	0.598	-	-
Un-treated	39.5 (4-250.9)		54.9 (5.5-250.9)		26.8 (4-240)	
RT						
Treated	32.5 (4-101.9)	0.464	-	-	32.4 (4-101.9)	0.961
Un-treated	47.1 (4-315.5)		54.9 (5.5-315.5)		26.8 (4-240)	
CT and/or RT**						
Treated	54 (4-315.5)	0.012	56 (5.5-315.5)	0.408	56.4 (4-240)	0.185
Un-treated	18.5 (4-178.8)		37 (6.5-170.9)		12 (4-178.7)	
HRT						
Treated	57.9 (5.4-89)	0.657	-	-	57.9 (5.4-89)	0.857
Un-treated	42.9 (4.0-315.5)		54.9 (5.5-315.5)		25.9 (4-240)	
TKI						
Treated	35.9 (5-250.9)	0.872	67.8 (23.9-250.9)	0.427	15.9 (5-26.8)	0.275
Un-treated	45 (4-315.5)		54.5 (5.5-315.5)		34.2 (4-240)	

*: Mann-Whitney U test
**: Three patients received both CT and RT. In the time comparisons, patients without treatment and those who received CT and/or RT were evaluated together
PHM: Primary hematologic malignancy, PSOM: Primary solid organ malignancy, CT: Chemotherapy, RT: Radiotherapy, HRT: Hormane replacement therapy, TKI: Thyrosine kinase inhibitors, SPM: Second primary malignancy

Table 3. Distribution of diagnosis

	Second primary malignancy	Primary malignancy
Hematological malignancies, n (%)		
CLL	11 (24.4)	15 (26.8)
MDS	8 (17.8)	4 (7.1)
AML	7 (15.6)	3 (5.4)
NHL	5 (11.1)	14 (25)
CML	5 (11.1)	6 (10.7)
MM	4 (8.9)	8 (14.3)
ALL	3 (6.7)	1 (1.8)
HL	1 (2.2)	2 (3.6)
PMF	1 (2.2)	-
ET	-	2 (3.6)
PV	-	1 (1.8)
Solid organ malignancies, n (%)		
Lung	10 (17.9)	5 (11.1)
Breast	9 (16.1)	10 (22.2)
Prostate	7 (12.5)	4 (8.9)
Skin	7 (12.5)	3 (6.7)
Bladder	4 (7.1)	-
Gastric	3 (5.4)	1 (2.2)
Pancreas	2 (3.6)	-
HCC	2 (3.6)	1 (2.2)
Colon	2 (3.6)	6 (13.3)
Rectal	2 (3.6)	3 (6.7)
Endometrium	2 (3.6)	4 (8.9)
Caposi's Sarcoma	2 (3.6)	-
Malignant melanom	1 (1.8)	1 (2.2)
Meningioma	1 (1.8)	-
Thyroid	1 (1.8)	-
Pleural mesothelioma	1 (1.8)	-
Larynx (SCC)	1 (1.8)	-
Timoma	-	1 (2.2)
Lip (SCC)	-	1 (2.2)

CLL: Chronic lymphocytic leukemia, MDS: Myelodysplastic syndromes, AML: Acute myeloid leukemia, NHL: Non-Hodgkin lymphoma, CML: Chronic myeloid leukemia, MM: Multiple myeloma, ALL: Acute lymphoblastic leukemia, HL: Hodgkin lymphoma, PMF: Primary myelofibrosis, ET: Essential thrombocythemia, PV: Polycythemia vera, HCC: Hepatocellular carcinoma, SCC: Squamous cell carcinoma

meningioma). Among patients treated with topoisomerase inhibitors, the most common second cancers were lung cancer (26.7%), breast cancer (20%), and HCC (13.3%). Of the 6 oncology patients who received RT, 3 (50%) developed acute myeloid leukemia (AML), 2 (33.3%) developed CLL, and 1 (16.7%) developed non-Hodgkin lymphoma. Among the 6 patients with CML treated with imatinib, 2 developed breast cancer, while the remaining four developed lung, skin, bladder, and thyroid cancers. AML and CLL developed in 2 patients with GIST treated with imatinib, whereas acute lymphoblastic leukemia (ALL) was diagnosed in a patient with lung adenocarcinoma treated with afatinib. Of the 5 solid-organ cancer patients who received HRT, 3 were female; the second cancers reported in these patients were CML, CLL, and myelodysplastic syndrome (MDS). ALL and MDS developed in the two male patients.

In the multivariable logistic regression analysis, factors influencing the time to SPM development (<43 months vs. ≥43 months) were evaluated. The overall model was found to be borderline significant (Omnibus test χ^2=18.1, p=0.053), with a classification accuracy of 69.7%. Among the analyzed variables, only age was statistically significant. Patients aged ≥60 years had a significantly lower likelihood of late SPM development (≥43 months) (OR=0.34, 95% CI: 0.12-0.88, p=0.023). This finding suggests that SPM may occur at an earlier stage in older patients. Gender (OR=1.99, p=0.156), PM type (PHM vs. PSOM, OR=1.27, p=0.733), topoisomerase inhibitor use (OR=1.72, p=0.490), CT (OR=0.88, p=0.943), RT (OR=0.35, p=0.451), CT+RT (OR=1.64, p=0.796), and TKI treatment (OR=0.64, p=0.596) were not significantly associated with early SPM development.

Discussion

In our study, the median age of the 101 patients was 61 years, and the majority were male (63.4%). These demographic characteristics are consistent with previously reported data on patients developed SPM in adult cancer populations [11]. Furthermore, the age and sex distributions were similar in the PHM and PSOM subgroups. In the large cancer survival cohort conducted by Kjaer et al. [12], the median age for SPM development was reported as 68.3 years, which is in line with our findings.

There are large-cohort epidemiological studies emphasizing that exposure to CT is one of the main factors increasing the risk of SPM [13]. In our study, follow-up without systemic therapy or surgical resection sufficed for most PSOM patients, and CT was unnecessary. In contrast, the markedly higher CT rate in the PHM group (87.5%) compared with the PSOM group (37.8%) aligns with the literature, suggesting that CT is a potential risk factor for SPM. Reviewing CT data, Pedersen-Bjergaard et al. [14] reported in the Danish cohort that after high cumulative etoposide doses, the 5.7-year cumulative risk of AML/MDS was 4.7%. Similarly, in the German cohort by Bokemeyer and Schmoll, the cumulative incidence of SPM was 1.0% in patients treated with regimens containing topoisomerase II inhibitors [15]. Notably, in our study, although no PSOM patients received topoisomerase II inhibitors, 17.8% developed MDS and 15.6% developed AML. Alkylating agents are also major chemotherapeutic culprits and significant risk factors, particularly for AML and MDS [16]. In our study, while most PHM patients received alkylating agents, only one PSOM patient was treated with this regimen. Despite the PHM-PSOM comparison and our cohort's relatively smaller size compared with that reported in the literature, our findings suggest that CT may not be the sole determinant of SPM. It has been demonstrated that RT is an important risk factor for the development of SPM in solid organ cancers [17]. However, in our study, only 6 PSOM patients received RT, which limits our ability to draw strong conclusions about this matter. Similarly, the number of patients receiving HRT was limited, making it difficult to draw inferences.

In CML, evidence on whether imatinib increases SPM risk remains conflicting, with some studies reporting elevated risk and others showing no difference from the general population [8,18]. In our study, the SPMs that developed in patients receiving imatinib were heterogeneous, whereas ALL was identified in the patient treated with afatinib.

When assessing the time to SPM development, the median duration in our study was 42.9 months (≈3.6 years), consistent with Halamkova et al. [19], who reported 1.7-5.2 years in an adult cancer survival cohort. A noteworthy finding in our study was that the time to SPM development was longer in the PHM group than in the PSOM group (54.9 vs. 26.8 months). In the Swiss cancer cohort, Feller et al. [20] reported that SPM risk became more pronounced after 5 years in PHM patients, whereas it could be observed earlier in PSOM patients. Although our dataset included fewer cases, our findings support these observations.

In the data reported by Wood et al. [21], SPMs occurred at a higher rate particularly within the first 2 years in patients aged ≥60 years, whereas this period was considerably longer in younger adults. In our study, time to SPM development was 66 months in patients aged <60 years and 21.4 months in those aged ≥60 years, consistent with this finding. Factors influencing time to SPM development were also evaluated using a regression model. The only factor associated with SPM duration <43 months was age ≥60 years.

In contrast, in the Swiss cohort, the risk of SPM was found to be higher in younger patients [20]. On the other hand, in our study, the longer time to SPM development in patients who received CT±RT may initially appear contradictory. However, large population-based data have also reported earlier SPM development in untreated groups [19,21]. This situation may be related to the higher mean age and shorter follow-up among untreated patients. In the elderly, more frequent genetic mutations and genomic instability, along with greater cumulative environmental exposures such as smoking and chemicals, are possible mechanisms explaining this difference [7,21]. Therefore, the shorter time to SPM development observed in older patients in our study may be attributable not only to the PM itself but also to age-related biological and environmental factors.

In the adult population, although survival in patients who developed SPM is somewhat shorter compared to those who did not, the 10-year OS remains 45-50%, and the median survival exceeds 10 years [20-22]. In our study, the median survival for all patients was 178.3 months and was similar in the PHM and PSOM groups.

A review of the literature shows that SPM diagnoses are highly heterogeneous. SPMs that develop after PHM have been particularly investigated in patients with MM. In one analysis of MM follow-up data, the most common solid organ cancers were reported as prostate (25%) and breast (13%) [23]. In a study evaluating patients who received chimeric antigen receptor T-cell therapy and had a median age of 66 years, the most common SPM was non-melanoma skin cancer. MDS and AML were identified as the most frequent hematologic SPMs [24]. In our study, the most common solid-organ SPM was lung cancer, which closely matched the 18% rate reported by Donin et al. [25]. The most frequently observed hematologic SPM was CLL. No data in the literature report CLL as the most common SPM. However, in our study, malignancy diagnoses were categorized into two distinct groups: SOMs developing after PHM and HMs developing after PSOM. Although this represents a limitation, it also provides a different contribution to the literature.

The main strengths of our study are the inclusion and comparison of solid-organ and HM, the broad age range of the study population, and the use of multivariable analysis.

Study Limitations

The limitations of our study include its single-center design, limited number of patients (n=101), retrospective design, lack of genetic data, and evaluation of cases in two separate groups.

Conclusion

Our study demonstrated that advanced age was an important determinant of the development of SPM, while the independent effects of other clinical and treatment-related parameters were limited. Our findings suggest that SPMs may occur at an earlier stage particularly in patients aged ≥60 years. These results highlight the need to consider age as a critical factor in follow-up care for adult cancer patients.

Ethics

Ethics Committee Approval: The study was approved by the Non-interventional Research Ethics Committee of Necmettin Erbakan University (approval no: 177, date: 02.06.2023).

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.T., O.Y., C.D., S.D., M.M., M.K.E., Concept: A.T., S.D., M.K.E., Desing: A.T., O.Y., C.D., S.D., M.M., M.K.E., Data Collection or Processing: A.T., O.Y., C.D., Analysis or Interpretation: A.T., M.M., Literature Search: A.T., O.Y., C.D., S.D., M.M., M.K.E., Writing: A.T., O.Y., C.D., S.D., M.M., M.K.E.

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