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Research article

Incidence rate and risk factors of second primary neoplasms among older patients with hematological malignancies: Insights from a Chinese single-center experience (1997–2021)☆

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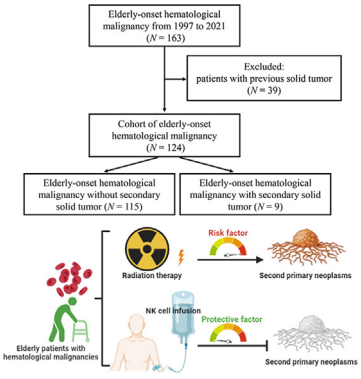
HIGHLIGHTS

- Older patients with hematological malignancies should be informed of the risk of developing secondary primary neoplasms.
- In older patients with hematological malignancies, the standardized incidence ratio (SIR) of second primary neoplasms was 0.81 in a Chinese center.
- Radiation therapy is a risk factor, whereas the regular infusion of natural killer (NK) cells protects against secondary primary neoplasms.

GRAPHICAL ABSTRACT



The study retrospectively analyzed 163 aged patients with hematological malignancies in a Chinese single center for incidence, risk factors, and outcome of secondary primary neoplasms. NK cell: Natural killer cell.

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ABSTRACT

Background: Patients with hematological malignancies face an increased risk of developing second primary neoplasms due to various factors, including immune system compromise and chemotherapy-related effects. However, the incidence and associated risk factors in older patients remain poorly understood. This study aimed to assess the incidence, identify risk factors, and evaluate their impact on survival outcomes among older patients with hematological malignancies.

Methods: This retrospective single-center study analyzed data from 163 patients, focusing on the occurrence of second primary neoplasms. Cumulative incidence rates were calculated, and risk factor analysis was conducted using a competing risk model.

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Results: Among 124 eligible patients with a total follow-up duration of 572.57 person-years, the incidence rate of second primary neoplasms was 15.72/1000 person-years. The standardized incidence ratio (SIR) was 0.81 (95% confidence interval [CI] [0.39–1.48], $P = 0.518$). History of radiotherapy emerged as a significant risk factor (subdistribution hazard ratio [SHR] = 21.61 [2.81–166.14], $P = 0.003$), whereas regular natural killer (NK) cell infusion was associated with reduced risk (SHR = 3.25 e−8 [9.81 e−9–1.08 e−7], $P < 0.001$).
Conclusions: These findings underscore the importance of informing older patients with hematological malignancies about the long-term risks of second primary neoplasms. Healthcare providers should carefully weigh risk factors when formulating treatment strategies. The results are valuable for investigating the fundamental principles underlying the occurrence and progression of second primary neoplasms.

Introduction

The prognosis of hematological malignancies has markedly improved due to iterative advancements in treatment modalities and novel drug development. Patients now experience significantly prolonged overall survival, approaching that of individuals without hematological malignancies. Consequently, there is a growing concern regarding the long-term complications associated with their treatment, particularly the emergence of second primary neoplasms. The literature extensively documents the tumor type, risk factors, and prognosis of second primary neoplasms after the treatment of hematological malignancies.[1–9] Standard therapeutic protocols have progressively evolved, with strategies such as dose reduction in radiotherapy and alkylating agents aimed at mitigating treatment-related toxicities.[2,3]

The risk of malignancy is significantly high in the older population, and >50% of the patients with hematological malignancies are old.[10] The incidence of tumors is higher in older patients than in young patients, and the risk of developing second primary neoplasms may increase when combined with hematological malignancies and treatment-related toxicities. Abnormal gene expression and immune microenvironment in patients with hematological malignancies may affect the occurrence of second primary neoplasms. Studies have found that some patients with myeloproliferative neoplasms exhibit *SOCS* overexpression. *SOCS* plays a regulatory role in the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathway and its overexpression promotes the occurrence and development of tumors.[11] Previous hematological malignancies have also been shown to increase the risk of developing second primary neoplasms.[5,12,13]

However, findings regarding the influence of hematological malignancies and their treatments on the development of second primary neoplasms are inconclusive. For instance, one study demonstrated a significantly elevated risk of second primary neoplasms among multiple myeloma patients undergoing maintenance therapy with lenalidomide post-hematopoietic stem cell transplantation, with an age range of 29–71 years.[14] Conversely, another study found no increased risk of second primary neoplasms with lenalidomide as a first-line treatment in multiple myeloma patients aged ≥65 years.[15] There is a paucity of data regarding the occurrence of second primary neoplasms in the aging population (≥60 years) with hematological malignancies. Moreover, physiological differences, metabolic efficiency, and life circumstances in older patients markedly differ from their younger counterparts. Therefore, investigating the incidence, risk factors, and survival outcomes of second primary neoplasms in older populations is imperative. Consequently, this study aims to ascertain the incidence rate (IR) of second primary neoplasms in older patients with hematological malignancies and analyze potential risk factors.

Materials and methods

Study design

Data were obtained from medical documents and telephone follow-up records of patients at the Second Medical Center of the Chinese People's Liberation Army General Hospital between January 1997 and December 2021. Patients were followed up until the occurrence of second primary neoplasms, death, or the end of the study.

Inclusion and exclusion criteria

The inclusion criteria were as follows. (1) According to the diagnostic criteria of the World Health Organization classification of myeloid and lymphoid tumors (fifth edition), patients with hematological malignancies were diagnosed using bone marrow aspiration or biopsy. (2) Age at diagnosis of hematological malignancy ≥60 years. (3) Chinese patients treated at the Second Medical Center of the Chinese People's Liberation Army General Hospital.

Exclusion criteria were as follows: solid tumors diagnosed before the diagnosis of hematological malignancies.

Data collection

The data collection encompassed variables such as sex, age at hematological malignancy diagnosis, type and stage of malignancy, white blood cell count at diagnosis, neutrophil count, lymphocyte count, neutrophil-to-lymphocyte ratio (NLR), medication history (including antibody preparations, cytotoxic drugs, demethylating drugs, small molecule targeted drugs, immunomodulatory agents, glucocorticoids, radiation therapy, erythropoietin, thymosin, immunosuppressant drugs, and regular natural killer [NK] cell infusion), comorbidities (including hypertension, diabetes, coronary atherosclerotic heart disease, dyslipidemia, chronic cardiac insufficiency, chronic kidney disease, and autoimmune disease), family history of tumors, smoking, and drinking history, outcomes of second primary neoplasms, age at diagnosis of second primary neoplasms, and time and cause of death.

Variable determination and screening strategies

To study the factors affecting the occurrence of second primary neoplasms, we calculated the time from the occurrence of hematological malignancies to second primary neoplasms, considering the baseline characteristics of the patients at the onset of hematological malignancies and treatment exposure as independent variables. The diagnosis of the second primary neoplasm was based on the pathological features. The date of diagnosis and histological type of the second primary neoplasm were also recorded. We included these independent variables in the competing risk model for the univariate analysis. Statistically significant clinical factors that may affect the occurrence of second primary neoplasms were included in the competing risk model for multivariate analysis.

Statistical analysis

The incidence of a second primary neoplasm was measured using the IR or incidence density, and standardized incidence ratio (SIR). The incidence density was calculated as the number of new second primary neoplasm cases divided by the sum of the total patient-years. The

cumulative incidence of second primary neoplasms in this study was defined as the ratio of the number of new cases of second primary neoplasms to the sum of the cohort. Statistical Package for Social Sciences (SPSS) (version 21.0) (International Business Machines Corporation [IBM], Armonk, NY, USA) and Stata (version 18.0) (Computing Resources Center, Santa Monica, CA, USA) were used for the data analyses. Data are presented as mean ± standard deviation (SD), median, interquartile ranges (IQRs), frequency, and percentage. Because the occurrence of a second primary neoplasm competed with death, the Fine–Gray model was used for competing risk analysis to compute the subdistribution hazard ratio (SHR) and 95% confidence intervals (CIs). Univariate and multivariate analyses were performed using competing risk analysis to study the risk factors related to second primary neoplasms. The cumulative incidence was calculated using Nelson-Aalen cumulative risk curves. Key confounding factors, such as age at diagnosis, sex, smoking, alcohol consumption, and treatment drugs, were included in the adjusted analysis. Results were considered significant when the P value was <0.05.

Results

Cohort description

Between January 1997 and December 2021, 163 patients were diagnosed with hematological malignancies in our institution and excluded 39 patients based on the exclusion criteria [Figure 1]. Hence, 124 patients with hematological malignancies were included in this study, with a total follow-up time of 572.57 person-years. Hematological malignancies covered in the study cohort included non-Hodgkin lymphoma (40/124, 32.25%), myelodysplastic neoplasms (21/124, 16.94%), multiple myeloma (19/124, 5.32%), myeloproliferative neoplasms (15/124, 12.10%), acute myeloid leukemia (10/124, 8.06%), monoclonal gammopathy of undetermined significance (7/124, 5.65%), chronic myelomonocytic leukemia (7/124, 5.65%), acute lymphoblastic leukemia (2/124, 1.61%), Hodgkin lymphoma (1/124, 0.81%), B cell chronic lymphoproliferative disorders (1/124, 0.81%), and myeloid neoplasms with eosinophilia and platelet-derived growth factor receptors A (PDGFRA) rearrangement (1/124, 0.81%). There were 12 patients with acute leukemia, including 10 with acute myeloid leukemia and two with acute lymphoblastic leukemia in this study. However, none of the patients with acute leukemia developed second primary neoplasms. Half of the study population was aged >80 years. Nine patients developed second primary neoplasms, whereas the remaining 115 had no second primary neoplasms. The follow-up durations for patients with and without second primary neoplasms were 55.50 and 517.07 person-years, respectively. The mean age at diagnosis of hematological malignancies, sex, smoking history, drinking history, family history of cancer, and comorbidities were not significantly different between the two groups [Table 1].

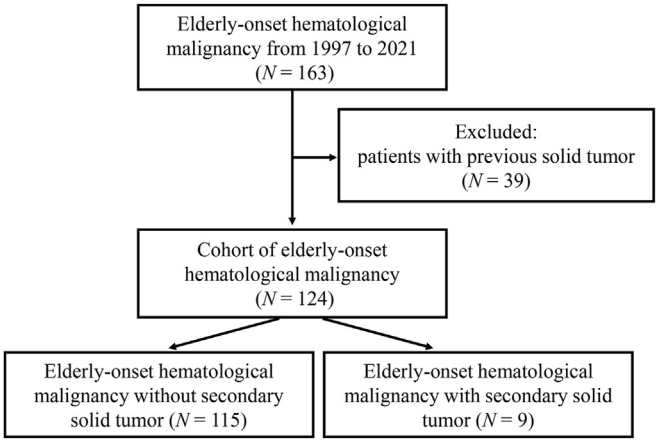

Figure 1. Cohort definition and flowchart of the study.

Table 1
Patient characteristics of the study.

Parameters	Second primary neoplasms	Non-second primary neoplasms	Statistical value	*P* value
Total patients	9 (100)	115 (100)	-	-
Sex			-	0.32
Men	8 (88.89)	111 (96.52)		
Women	1 (11.11)	4 (3.48)		
Age at hematological malignancy diagnosis (years)	75.44 ± 7.72	79.22 ± 9.64	1.14*	0.26
Smoking history (years)	6 (66.67)	49 (42.61)	1.10†	0.29
Alcohol consumption (mL)	2 (22.22)	38 (33.04)	0.09†	0.77
Family history of tumor	1 (11.11)	29 (25.22)	0.30†	0.58
Hypertension	4 (44.44)	80 (69.57)	1.40†	0.24
Diabetes mellitus	5 (55.56)	38 (33.04)	1.01†	0.32
Coronary heart disease	5 (55.56)	60 (52.17)	0.00†	1.00
Hyperlipemia	8 (88.89)	91 (79.13)	0.07†	0.79
Chronic heart failure	0 (0)	14 (12.17)	0.32†	0.57
Chronic liver failure	0 (0)	6 (5.22)	0.00†	1.00
Chronic kidney disease	1 (11.11)	19 (16.52)	0.00†	1.00
Autoimmune disease	1 (11.11)	4 (3.48)	-	0.32
Age at solid tumor diagnosis (years)	81.56 ± 7.67	-	-	-

Data are presented as n (%) or mean ± standard deviation. *: t value; †: χ^2 value;-: No data.

A total of 64 patients died in the study, including six patients in the second primary neoplasm group and 58 in the non-second primary neoplasm group. Respiratory failure due to infectious pneumonia was the most common cause of death in both groups. The causes of death are listed in Supplementary Table 1.

Incidence rate and characteristics of second primary neoplasms

Nine older patients with hematological malignancies developed second primary neoplasms and their hematological malignancies included one Hodgkin lymphoma, three non-Hodgkin lymphomas, two myelodysplastic neoplasms, one multiple myeloma, one monoclonal gammopathy of undetermined significance, and one chronic myelomonocytic leukemia. The incidence of second primary neoplasms was 15.72/1000 person-years, and the SIR was 0.81 (95% CI [0.39–1.48], $P = 0.518$). The mean age at the onset of the second primary neoplasm was 81.56 ± 7.67 years. The most common second primary neoplasm was lung cancer (4/9 [44.44%], IR = 6.98/1000 person-years), followed by genitourinary tumors (such as bladder and prostate cancer, 2/9 [22.22%], IR = 3.49/1000 person-years), liver cancer (1/9 [11.11%], IR = 1.75/1000 person-years), tongue cancer (1/9 [11.11%], IR = 1.75/1000 person-years), and

Table 2
Distribution and incidence rates of solid tumors among older patients with hematological malignancies.

Second primary neoplasms	ICD-11 code	Value	Per 1000 PYs
Lung cancer	2C25	4 (44.44)	6.98 (2.70–17.80)
Genitourinary cancer (bladder and prostate cancer)	(2C94, 2C82)	2 (22.22)	3.49 (1.00–12.70)
Liver cancer	2C12	1 (11.11)	1.75 (0.30–9.80)
Tongue cancer	2B62	1 (11.11)	1.75 (0.30–9.80)
Skin cancer	2C33, 2C3Y, 2C3Z	1 (11.11)	1.75 (0.30–9.80)
Total	–	9 (100)	15.72 (8.30–29.60)

Data are presented as n (%) or 95% CI. CI: Confidence interval; ICD: International Classification of Diseases; N: numbers; PY: Person-year; -: No data.

non-melanoma skin cancer (1/9 [11.11%], IR = 1.75/1000 person-years), as shown in Table 2.

Risk factors for second primary neoplasms in aged patients with hematological malignancies

Univariate and multivariate analyses of competing risk models were performed to identify risk factors for solid tumors secondary to elderly-onset hematological malignancies. Univariate analysis of the competing risk model showed that these two factors statistically influenced the cumulative incidence of second primary neoplasms, including a history of regular NK cell infusion and radiotherapy. However, there were no significant differences between the two groups in the use of medications, including monoclonal antibody preparations, cytotoxic drugs, demethylating drugs, small-molecule targeted drugs, glucocorticoids, immunomodulators, erythropoietin, or thymosin. Figure 2 shows the univariate analysis of the six representative factors of cumulative incidence under the competing risk model. The above six factors were included in the multivariate competing risk model analysis, and the results were consistent with those of the univariate analysis [Table 3]. Radiotherapy history (SHR = 21.61 [2.81–166.14], $P = 0.003$) was a risk factor for the development of second primary neoplasms, while regular NK cell infusion (SHR = 3.25 e−8 [9.81 e−9–1.08 e−7], $P < 0.001$) was a protective factor against second primary neoplasms, as shown in Figure 3.

Discussion

Patients with hematological malignancies may have a high risk of developing second primary neoplasms. However, whether this risk is high in older patients with hematological malignancies is controversial. We retrospectively analyzed the incidence and risk factors for solid tumors secondary to elderly-onset hematological malignancies and obtained the following results: first, the incidence of second primary neoplasms after elderly-onset hematological malignancies was 15.72/1000 person-years (SIR = 0.81), among which lung cancer was the most common. Second, a history of radiotherapy was a risk factor for the development of second primary neoplasms, whereas regular NK cell infusion was a protective factor against second primary neoplasms.

To further determine whether hematological malignancy increases the risk of developing solid tumors, we calculated age-SIRs. Advanced age may be a risk factor for malignant tumors in previous studies.[16] The SIR in our study was 0.81 (95% CI [0.39–1.48], $P = 0.518$), indicating that advanced age did not necessarily increase the risk of second primary neoplasms in older patients with hematological malignancies. The SIR was 0.92 for patients aged >80 years and 0.73 for those aged 60–80 years old in our study. We compared the relationship between the SIR and age in different studies [Supplementary Table 2]. Univariate and multivariate analyses using the competing risk model supported the finding that advanced age was not a risk factor for second primary neoplasms in patients with hematological malignancies. A multicenter study showed a high risk of second primary neoplasms in patients with Hodgkin lymphoma (SIR = 2.0).[9] Another study showed that patients with myeloproliferative neoplasms have a high risk of developing second primary neoplasms, and the SIR of solid tumors after essential thrombocythemia, polycythemia vera, and chronic myeloid leukemia was 1.2, 1.4, and 1.6, respectively.[5] In a study of 4676 patients with Waldenström macroglobulinemia, 681 developed second primary neoplasms, with an SIR of 1.49. Additionally, the SIR was 1.63 in the Waldenström macroglobulinemia population <65 years, while the SIR decreased to 1.13 for those ≥65 years.[12] In a Dutch study of 18,030 patients with multiple myeloma, 1334 developed second primary neoplasms with a cumulative incidence of 7.4%.[17] A German study that included 744 patients with multiple myeloma found a cumulative incidence of 4.3% for second primary neoplasms.[18] The cumulative incidence in our study was 7.26% (9/124), similar to that reported in previous studies.

One study reported that the most common second primary neoplasms were lung cancer, colon cancer, and breast cancer in women. Other types of cancers include oral, digestive tract, respiratory system, prostate, and

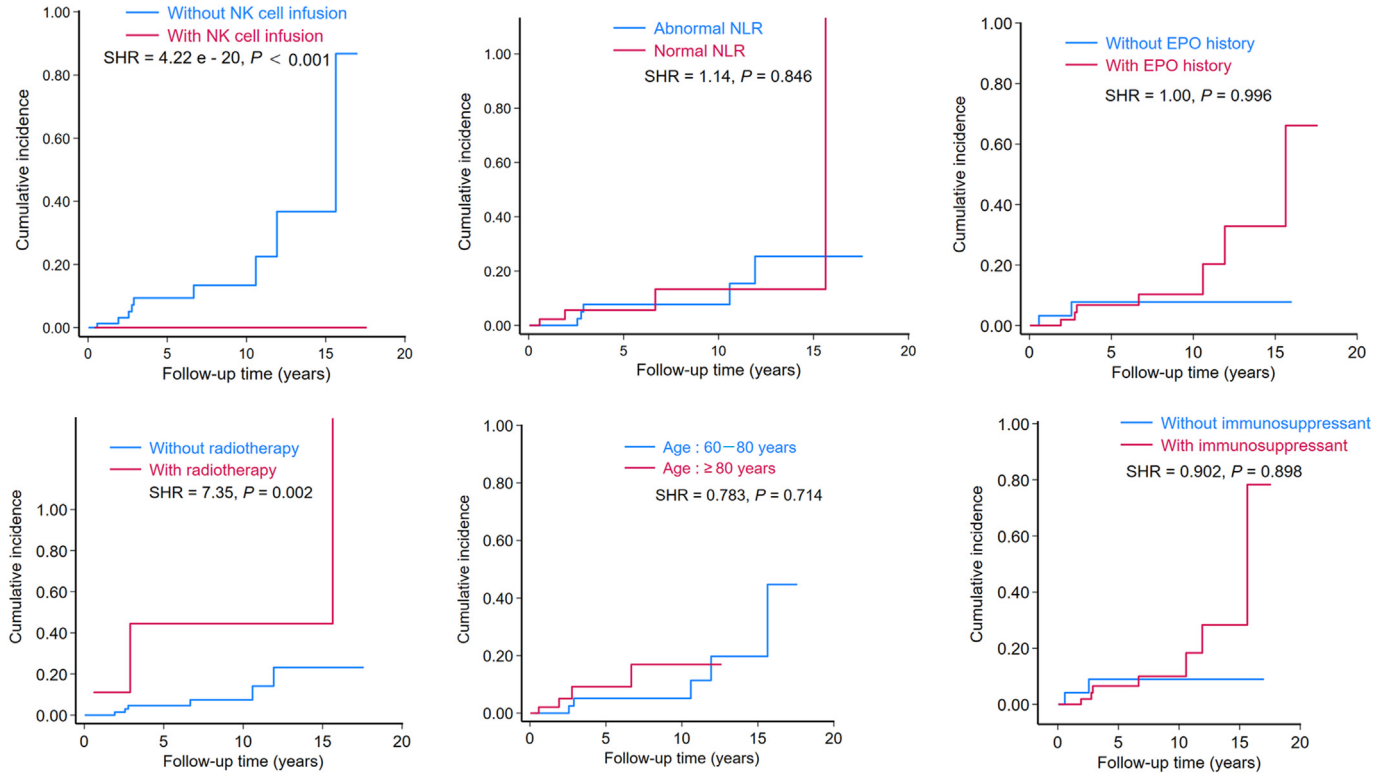

Figure 2. Competing risk regression of risk factors for second primary neoplasms in older patients with hematological malignancies. EPO: Erythropoietin; NK: Natural killer; NLR: Neutrophil-to-lymphocyte ratio; SHR: Sub-distribution hazard ratio.

Table 3
Univariate and multivariate analysis for second primary neoplasms in older patients with hematological malignancies.

Characteristics	Univariate analysis			Multivariate analysis		
	SHR	95% CI	*P*	SHR	95% CI	*P*
NK cell infusion yes *vs.* no	4.22e-20	2.01e-20–8.88e-20	<0.001	3.25e-8	9.81e-9–1.08e-7	<0.001
Radiotherapy history yes *vs.* no	7.35	2.08–25.95	0.002	21.61	2.81–166.14	0.003
NLR normal *vs.* abnormal	1.14	0.31–4.13	0.85	0.49	0.13–1.90	0.30
Immunosuppressant drugs yes *vs.* no	0.90	0.19–4.33	0.90	0.51	0.10–2.67	0.43
Age	0.78	0.21–2.89	0.71	1.86	0.28–12.27	0.52
60–80 *vs.* ≥80 years						
Erythropoietin history yes *vs.* no	1.00	0.21–4.72	1.00	1.26	0.33–4.87	0.74

CI: Confidence interval; HR: Hazard ratio; NK: Natural killer; NLR: Neutrophil-to-lymphocyte ratio; SHR: Sub-distribution hazard ratio.

bladder cancer.[9] In the Waldenström macroglobulinemia population, the most common second primary neoplasms are lung, prostate, and urinary tract tumors.[12] Our study identified lung cancer as the most common cancer, consistent with previous reports.

Few studies have analyzed the risk factors for second primary neoplasms in patients with hematological malignancies. A Swedish study found that the presence of a tumor in first-degree relatives increased the risk of second primary neoplasms in patients with Hodgkin lymphoma.[2] However, our study found that a family history of tumors did not affect the incidence of second primary neoplasms in older patients with hematological malignancies. This difference can be explained by genetic susceptibility, which usually occurs at a young age, whereas the age of our study population was 60–99 years old.

The reported risk factors for second primary neoplasms in patients with hematological malignancies include the use of immunomodulators, alkylating agents, and rituximab.[19,20] Our results showed that the use of medications, including monoclonal antibody preparations, cytotoxic drugs, demethylating drugs, small-molecule targeted drugs, glucocorticoids, immunomodulators, erythropoietin, and thymosin, is not a risk factor for second primary neoplasms in aged patients with hematological malignancies. This may be because the dose is typically lower in older patients. A Japanese study analyzed a patient population after allogeneic hematopoietic stem cell transplantation and found that patients with hematological malignancies who underwent systemic radiation therapy and bone marrow transplantation had an increased risk of second esophageal squamous cell carcinoma.[21] High-dose cyclophosphamide and age >65 years at diagnosis were independent risk factors for the occurrence of second primary neoplasms in patients with multiple myeloma undergoing stem cell transplantation.[22] Only one patient in our study received stem cell transplantation and did not develop second primary neoplasms. Studies have shown that radiation therapy increases the risk of secondary solid tumors in patients with Hodgkin lymphoma.[9,23,24] Radiotherapy was a risk factor for the development of second primary neoplasms in this study, which is consistent with the results of previous studies.

Several factors may affect the cumulative incidence of second primary neoplasms. We found that radiotherapy history was a risk factor for the development of second primary neoplasms, while regular NK cell infusion was a protective factor against second primary neoplasms. The count or function of NK cells deteriorates in patients with various hematological malignancies is deteriorative.[25–30] Decreased count or maturation disorder of NK cells provides an opportunity for the occurrence and development of hematological malignancies and solid tumors. In addition, clinical experience with adoptive infusion of NK cells over the past 20 years has demonstrated a minimal risk of adverse events. Therefore, adoptive NK cell immunotherapy has been applied in the treatment of a variety of hematological and solid tumors and has shown inhibitory effects on tumor cells.[31–33] In this study, 33 patients (33/124, 26.61%) patients received regular NK cell infusions. Our univariate and multivariate analyses suggested that regular NK cell infusion could reduce the risk of second primary neoplasms in older patients with hematological malignancies.

This study had limitations that need to be addressed. First, it was conducted at a single center, and the number of patients in the cohort was limited, which may have resulted in selection bias owing to the small sample size. Therefore, it is imperative to verify the relevant conclusions in a larger multicenter cohort study. Second, all patients in this study were older individuals, with half of them aged >80 years. As these patients generally have poor tolerance to treatment, the dose of drugs administered is lower than the standard dose. Furthermore, although some patients were prescribed the same drug, cumulative doses may have varied. This complexity cannot be clearly distinguished, and the long-term effects may differ. Third, the study subjects lacked homogeneity as hematological malignancies can vary greatly in their development, treatment, and prognosis. Despite our attempts to separate the three most common diseases (non-Hodgkin lymphoma, myelodysplastic neoplasms, and multiple myeloma) into subgroups, we were unable to find any significant results. In addition, our search for relevant data in the Surveillance, Epidemiology, and End Results Program (SEER) database was hindered by fragmented information, and we were unable to analyze the data according to disease type because of insufficient cases of second primary neoplasms. However, our study is significant in that it is the first to be conducted in an aged population (age ≥60 years) with hematological malignancies, establishing a link between these malignancies and second primary neoplasms.

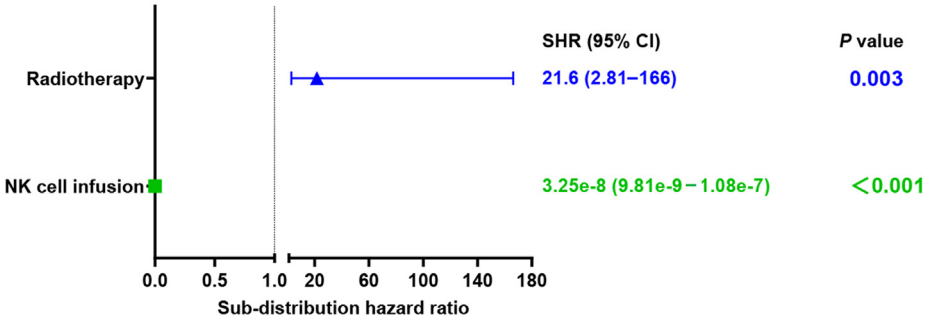

Figure 3. Risk factors for second primary neoplasms in older patients with hematological malignancies. CI: Confidence interval; NK: Natural killer; SHR: Sub-distribution hazard ratio.

In conclusion, this study conducted at our single center revealed that older patients with hematological malignancies have a higher probability of developing second primary neoplasms. Research has confirmed that a history of radiotherapy is a strong risk factor for the development of second primary neoplasms, while regular infusion of NK cells is a protective factor against them. Research indicates that older patients with hematological malignancies should be informed about the long-term complications of second primary neoplasms, and healthcare providers should carefully consider risk factors when making treatment decisions.

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Authors contribution

Yadi Zhong: conceptualization and writing - original draft preparation; Bing Zhai and Jing Zeng: methodology; Yadi Zhong, Bing Zhai, and Bo Yang: formal analysis and investigation; Bo Guo: writing - review and editing; Bo Guo and Xuechun Lu: funding acquisition and supervision. All authors reviewed and approved the submission of the final version of the manuscript.

Ethics statement

This study was conducted in accordance with the *Declaration of Helsinki* and approved by the Ethics Review Committee of the Chinese PLA General Hospital (Approval No. S2022-304-01, June 7, 2022). Written informed consent for participation was not required for this study, in accordance with national legislation and institutional requirements. The need for informed consent was waived by the ethics committee due to the retrospective nature of this study.

Data availability statement

Additional data can be obtained through a direct request to the corresponding author within the limits of what can be disclosed with respect to data protection related to ethical recommendations.

Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cpt.2024.06.001.

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