Original Study

Impact of Synchronous Multiple Primary Malignant Tumors on Newly Diagnosed Hematological Malignancies

Satoshi Nishiwaki,[1,2] Shingo Okuno,[1] Kotaro Suzuki,[1] Shingo Kurahashi,[1] Isamu Sugiura[1]

[1]Division of Hematology and Oncology, Toyohashi Municipal Hospital; [2]Center for Advanced Medicine and Clinical Research, Nagoya University Hospital

Corresponding author: Satoshi Nishiwaki, MD., PhD.

Center for Advanced Medicine and Clinical Research, Nagoya University Hospital,

65 Tusukami-cho Showa-ku, Nagoya, 4668560, Japan.

TEL: 81-52-744-2942, FAX: 81-52-744-1303

e-mail:n-3104@tf7.so-net.ne.jp

Running title: **Impact of sMPMTs on hematological tumors**

Text pages: 25 pages

Table/Figure count: 3 tables/ 1 figure

FUNDING SUPPORT

This study was supported in part by the Japan Leukemia Research Fund grant and Kudo Academic Foundation to Satoshi Nishiwaki.

ABSTRUCT

Existence of synchronous multiple primary malignant tumors was not a significant risk factor for patients with newly diagnosed hematological malignancies. It is important to provide adequate treatment for both hematological malignancies and solid tumors appropriately.

Background: Hematological malignancies are occasionally observed with synchronous multiple primary malignant tumors (sMPMTs) at diagnosis. We aimed to clarify the impact of sMPMTs on newly diagnosed hematological malignancies and consider optimal treatment strategies. **Patients and methods:** We analyzed the outcomes of 649 hematological malignancy patients, including 19 patients with sMPMTs (2.9%), and compared the outcomes between patients with and without sMPMTs. **Results:** The overall survival (OS) and disease-free survival (DFS) rates of patients with sMPMTs were 77% and 70%, respectively, at 2 years; these rates were not statistically different from those of patients without sMPMTs (*P* = .17 and *P* = .64, respectively). Multivariate analysis showed that the presence of sMPMTs was not a significant prognostic factor for OS, DFS, or relapse [Hazard ratio (HR) 1.48 95%CI (0.65–3.38), *P* = .35; HR 0.97 95%CI (0.46–2.10), *P* = .97; HR 0.79 95%CI (0.29–2.14),

P = .65]. In patients with sMPMTs, the order of treatment was not a significant prognostic factor. However, discontinuation of treatment was a marginal favorable factor and may reflect a selection bias. **Conclusion:** Existence of sMPMTs was not a significant risk factor for patients with newly diagnosed hematological malignancies. It is important to provide adequate treatment for both hematological malignancies and solid tumors at the physician's discretion.

Keywords: Synchronous multiple primary malignant tumors, Hematological malignancies, Solid tumors, Order of treatment, Treatment discontinuation

Introduction

Synchronous multiple primary malignant tumors (sMPMTs) are occasionally diagnosed during screening tests of patients with newly diagnosed malignant neoplasms.[1,2] Although it has been reported that special attention should be given to MPMTs, especially for head and neck cancer and urinary tumors,[1] their prevalence is generally very low. Only sporadic case reports exist concerning hematological malignancies with sMPMTs.[3-5]

Because multiple cycles of combination chemotherapy are the standard treatment, at least several months are necessary for the treatment of newly diagnosed hematological malignancies such as acute leukemia, malignant lymphoma, and multiple myeloma.[6-10] Therefore, deciding when to treat the sMPMTs can be difficult. The physician must balance the risk of re-exacerbating the hematological disease due to insufficient treatment with the risk of exacerbating the untreated sMPMTs. No optimized treatment policy exists for hematological malignancies with sMPMTs.

In this study, we analyzed the prognostic impact of sMPMTs on patients with hematological malignancies. We also assessed the impact of treatment strategies on the outcome.

Patients and methods

Patients

sMPMTs were found in 19 patients with newly diagnosed hematological malignancies at Toyohashi Municipal Hospital between 2009 and 2015. Because these hematological diseases were non-Hodgkin lymphoma (NHL) and multiple myeloma (MM), a total of 649 patients diagnosed with those diseases during the same period were included in this study. The therapeutic strategies for patients with sMPMTs were according to physician choice. The study protocol was approved by the hospital's institutional review board.

Definitions

sMPMTs were defined as solid tumors within 6 months of the diagnosis of hematological disease.[11] Indolent NHL was defined as follows by reference to previous classifications[12,13]: follicular lymphoma, mucosa associated lymphoid tissue lymphoma, marginal zone lymphoma, or hairy cell leukemia. Other NHLs were defined as aggressive NHLs. Low-risk disease was defined by an international prognostic index (IPI) of low or low-intermediate NHL,[14] and other

conditions were defined as high-risk disease.

Statistical Analysis

The primary endpoint of this study was the 2-year overall survival (OS) rate of patients with sMPMTs. The secondary endpoint was the comparison of the survival and relapse rates between patients with and without sMPMTs and the prognostic significance of sMPMTs. The two–sided χ^2 test was used for categorical variables, and the Mann-Whitney U test was used for continuous variables. OS and disease-free survival (DFS) were estimated by the Kaplan-Meier method, and *P* values were calculated using a log-rank test.[15,16] Cumulative incidence of relapse was calculated by Gray's method.[17,18] Death without relapse was considered as a competing event for relapse. Univariate and multivariate analyses were performed using a Cox proportional hazard regression model.[19] The covariates included in the multivariate analyses were age at diagnosis (≦ 75 vs. > 75), sex, disease diagnosis, grade of lymphoma, IPI, international staging system (ISS),[20] disease risk, and presence or absence of sMPMTs. A significance level of $P < 0.05$ was used for all analyses. The STATA statistical software (Stata Corporation, College Station, TX, USA) was used for

the analyses, which were based on all data available as of March 2016.

Results

Patient Characteristics

The characteristics of the patients are shown in Table 1. sMPMTs were diagnosed in 16 of 505 NHL patients (3.2%) and 3 of 144 MM patients (2.1%). Among the 505 NHL patients, aggressive disease accounted for 77% (391/505) of cases and high-risk disease for 36% (184/505). No differences of distribution were observed between patients with and without sMPMTs regarding age, diagnosis, and disease risk.

Survival

The median follow-up period for survivors was 30 months (range, 0.6 to 79 months). The OS of patients with sMPMTs was 77% at 2 years, and the OS of all patients was 80%. No statistically significant difference was observed between patients with and without sMPMTs (P = .17) (Figure 1A). Multivariate analysis showed that age (> 75), male sex and high-risk disease were significant risk factors for OS, whereas the presence of sMPMTs was not a significant risk factor

(Table 2).

The DFS of patients with sMPMTs was 70% at 2 years, and the DFS of all patients was 65%. No statistically significant difference was observed between patients with and without sMPMTs (*P* = .64) (Figure 1B). Multivariate analysis showed that age (> 75) and high-risk disease were significant risk factors for DFS, whereas the presence of sMPMTs was not a significant risk factor (Table 2).

Relapse

The cumulative incidence of relapse was 24% at 2 years, and no statistically significant difference was observed between patients with and without sMPMTs (*P* = .84) (Figure 1C). Multivariate analysis showed that high-risk disease was a significant risk factor for relapse and the presence of sMPMTs was not a significant risk factor (Table 2).

Details of patients with sMPMTs

The disease status and treatment outcomes of patients with sMPMTs are summarized in Table 3. Regarding hematological malignancy, diffuse large

B-cell lymphoma was the most common disease (53%), and 11 of 19 patients (58%) had a high-risk disease. Most patients (84%) received chemotherapy as an initial treatment, and treatment was discontinued in 11 of 16 patients (69%) for a median of 60 days (rang, 36–113) for treatment of the comorbid solid tumor. Regarding solid tumor, gastric cancer was the most common concomitant solid tumor. Most patients (84%) were in a limited stage, and stage III or IV TNM classification was observed in only three patients. Of the six deceased patients, the solid tumor was the cause of death in four.

Treatment strategy for patients with sMPMTs

Treatment was initiated for the earlier-diagnosed disease in all except one of the patients with sMPMTs. Treatment priority was given to the hematological malignancy when its risk was high at diagnosis (P = .046). DFS was not significantly different according to the disease treated earlier (hematological malignancy earlier vs. solid tumor earlier: 83% vs. 53% at 2 years, P = .38).

After a median of four cycles of chemotherapy, treatment for the hematological malignancy was discontinued in 11 patients. The DFS of patients whose treatment was discontinued tended to be superior to that of those without

interruption of treatment (88% vs. 50% at 2 years, *P* = .05).

Discussion

This study collected the outcomes of hematological malignancy patients with sMPMTs, and analyzed the impact of sMPMTs. The survival of patients with sMPMTs was not significantly different from that of patients without sMPMTs. Because the presence of sMPMTs was not a significant prognostic factor, it is important to appropriately treat both the hematological malignancy and concomitant solid tumor.

To our knowledge, this report is the first to examine the influence of sMPMTs on patients with hematological malignancies. The number of patients with sMPMTs at the diagnosis of a hematological malignancy appears to be increasing. Two possible causes may account for this increase: the aging of patients and improvement of screening tests. Although the median age was the same between patients with and without sMPMTs, the age of the youngest patients with sMPMTs was older than that of patients without sMPMTs (60 years vs. 20 years).

A systematic full-body check has been performed as a screening test on the

diagnosis of hematological malignancies, especially for staging.[21-23] Many sMPMTs have been detected through this process. Considering that the cancer incidence rate in Japan is 666 per 100,000 population (0.67%),[24] the observed incidence of sMPMTs (19/649 = 2.9%) was high. This result indicates that more cancer was detected in patients with hematological malignancies than in the general population due to screening tests. The percentage of advanced-stage (stage III or IV TNM classification) was lower in this study (4/19 = 21%) than in patients at designated cancer care hospitals in Japan (33.7%)[24], which also supports the efficacy of screening: tests at the diagnosis of hematological malignancies detected more early-stage cancer. The diagnosis of sMPMTs can therefore contribute to the early detection of an asymptomatic cancer.

The order of treatment is not associated with the prognosis of patients with sMPMTs. All but one of the patients were first treated for the disease that was detected earlier. Because this study was retrospective, the treatment strategies for each patient were according to physician choice. In a clinical situation, it is helpful to know that treatment policy based on the disease condition of the patient is acceptable for hematological malignancy patients with sMPMTs.

Surprisingly, the DFS of patients who experienced interruption of treatment

tended to be higher than that of patients without treatment interruption. This result may reflect a bias for interrupting treatment in patients whose prognosis was judged good, even if their treatment was discontinued. No data show a negative impact of treatment discontinuation for the other cancer at the doctor's discretion.

This single-center study was limited by the small number of patients with sMPMTs. Although excellent databases of hematological disease exist for many countries and regions, these registries are often focused on the background and outcome of primary hematological diseases.[25-28] Therefore, limited information is often available about comorbidities in such databases. Because we were able to access the medical records of our hospital, we could obtain details for both the hematological malignancies and solid tumors in this study.

Conclusion

In conclusion, the presence of sMPMTs was not a significant prognostic factor in newly diagnosed hematological malignancy patients. No specific order no optimal timing was identified for discontinuation of treatment. It is important to treat both hematological malignancies and solid tumors appropriately at the

physician’s discretion.

Clinical Practice Points

· sMPMTs were observed in 2.9% of patients with newly diagnosed hematological malignancies.

· Survival were not significantly different between patients with and without sMPMTs.

· Treatment order was not a significant prognostic factor for patients with sMPMTs.

· Discontinuation of treatment did not have unfavorable effect on survival of patients with sMPMTs.

Disclosure

The authors declare that they have no competing interests.

References

1. Liu Z, Liu C, Guo W, Li S, Bai O. Clinical analysis of 152 cases of multiple primary malignant tumors in 15,398 patients with malignant tumors. *PLoS One*. 2015;10(5):e0125754.
2. Yoshida N, Tamaoki Y, Baba Y, et al. Incidence and risk factors of synchronous colorectal cancer in patients with esophageal cancer: an analysis of 480 consecutive colonoscopies before surgery. *Int J Clin Oncol*. 2016;21(6):1079-1084.
3. Vennepureddy A, Motilal Nehru V, Liu Y, Mohammad F, Atallah JP. Synchronous Diagnosis of Multiple Myeloma, Breast Cancer, and Monoclonal B-Cell Lymphocytosis on Initial Presentation. *Case Rep Oncol Med*. 2016;2016:7953745.
4. Kader I, Leavers B, Shashinder S, Wylie B, Chi KK, Sundaresan P. Synchronous or metachronous lymphoma and metastatic cutaneous squamous cell carcinoma in the head and neck region: a diagnostic and management dilemma. *J Laryngol Otol*. 2016;130 Suppl 4:S45-49.
5. Zuo W, Zhu X, Yang J, et al. Bortezomib combined with lenalidomide as the first-line treatment for the rare synchronous occurrence of multiple

myeloma and pulmonary adenocarcinoma: A case report. *Medicine (Baltimore)*. 2017;96(1):e5787.

6. Miyawaki S, Ohtake S, Fujisawa S, et al. A randomized comparison of 4 courses of standard-dose multiagent chemotherapy versus 3 courses of high-dose cytarabine alone in postremission therapy for acute myeloid leukemia in adults: the JALSG AML201 Study. *Blood*. 2011;117(8):2366-2372.

7. Fisher RI, Gaynor ER, Dahlberg S, et al. Comparison of a standard regimen (CHOP) with three intensive chemotherapy regimens for advanced non-Hodgkin's lymphoma. *N Engl J Med*. 1993;328(14):1002-1006.

8. Coiffier B, Lepage E, Briere J, et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. *N Engl J Med*. 2002;346(4):235-242.

9. Harousseau JL, Attal M, Avet-Loiseau H, et al. Bortezomib plus dexamethasone is superior to vincristine plus doxorubicin plus dexamethasone as induction treatment prior to autologous stem-cell transplantation in newly diagnosed multiple myeloma: results of the IFM

2005-01 phase III trial. *J Clin Oncol*. 2010;28(30):4621-4629.

10. Sugiura I, Terabe S, Kinoshita T, et al. Phase I dose-escalation study of cyclophosphamide combined with bortezomib and dexamethasone in Japanese patients with relapsed and/or refractory multiple myeloma. *Int J Hematol*. 2015;102(4):434-440.

11. Warren S, Gates O. Multiple primary malignant tumors: survey of the literature and a statistical study. *Am J Cancer*. 1932;16:1358-1414.

12. Armitage JO, Weisenburger DD. New approach to classifying non-Hodgkin's lymphomas: clinical features of the major histologic subtypes. Non-Hodgkin's Lymphoma Classification Project. *J Clin Oncol*. 1998;16(8):2780-2795.

13. Swerdlow SH, Campo E, Harris NL, et al. WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues, Fourth Edition. Lyon: IARC; 2008.

14. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. A predictive model for aggressive non-Hodgkin's lymphoma. *N Engl J Med*. 1993;329(14):987-994.

15. Kaplan E, Meier P. Nonparametric estimation from incomplete

observations. *J Am Stat Assoc*. 1958;53:457-481.

16. Peto R, Peto J. Asymptotically efficient rank invariant test procedures. *J R Stat Soc A*. 1972;135:185-207.

17. Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med*. 1999;18(6):695-706.

18. Scrucca L, Santucci A, Aversa F. Competing risk analysis using R: an easy guide for clinicians. *Bone Marrow Transplant*. 2007;40(4):381-387.

19. Cox DR. Regression models and life tables. *J R Stat Soc B*. 1972;34:187-220.

20. Greipp PR, San Miguel J, Durie BG, et al. International staging system for multiple myeloma. *J Clin Oncol*. 2005;23(15):3412-3420.

21. Iwamuro M, Kondo E, Takata K, Yoshino T, Okada H. Diagnosis of follicular lymphoma of the gastrointestinal tract: A better initial diagnostic workup. *World J Gastroenterol*. 2016;22(4):1674-1683.

22. Johnson SA, Kumar A, Matasar MJ, Schoder H, Rademaker J. Imaging for Staging and Response Assessment in Lymphoma. *Radiology*. 2015;276(2):323-338.

23. Raza S, Leng S, Lentzsch S. The Critical Role of Imaging in the Management of Multiple Myeloma. *Curr Hematol Malig Rep*. 2017.

24. The Editorial Board of the Cancer Statistics in Japan. CANCER STATISTICS IN JAPAN 2015. Tokyo: Foundation for Promotion of Cancer Research; 2015.

25. Atsuta Y, Suzuki R, Yoshimi A, et al. Unification of hematopoietic stem cell transplantation registries in Japan and establishment of the TRUMP System. *Int J Hematol*. 2007;86(3):269-274.

26. Ocias LF, Larsen TS, Vestergaard H, et al. Trends in hematological cancer in the elderly in Denmark, 1980-2012. *Acta Oncol*. 2016;55 Suppl 1:98-107.

27. Rihani R, Bazzeh F, Faqih N, Sultan I. Secondary hematopoietic malignancies in survivors of childhood cancer: an analysis of 111 cases from the Surveillance, Epidemiology, and End Result-9 registry. *Cancer*. 2010;116(18):4385-4394.

28. Kuwatsuka Y. Quality control and assurance in hematopoietic stem cell transplantation data registries in Japan and other countries. *Int J Hematol*. 2016;103(1):20-24.

Table 1 Characteristics of Patients with Newly Diagnosed Hematological Malignancies according to the Existence of sMPMTs.

	sMPMTs			Total
	−	+	*P*	
No. of patients	630	19		649
Median age at diagnosis, y (range)	69 (20–99)	69 (60–86)	0.40	69 (20–99)
Sex Male/Female	347/283	9/10	0.51	356/293
Diagnosis			0.94	
FL	73	5		78
MALT	21	0		21
MZL	14	0		14
Hairy cell	1	0		1
DLBCL	310	10		320
AITL	17	1		18
PTCL	12	0		12
MCL	8	0		8
BL	6	0		6
Extranodal NK/T	5	0		5
EBV-LPD	4	0		4
Plasmablastic lymphoma	4	0		4
Other B-cell lymphoma	10	0		10
Other T-cell lymphoma	4	0		4
MM	141	3		144
Grade of lymphoma			0.40	
Indolent	109	5		114
Aggressive	380	11		391
IPI			0.52	
Low	173	4		177
Low-intermediate	139	4		143
High-intermediate	107	6		113
High	69	2		71
Missing	1	0		1
ISS			0.86	
I	28	1		29
II	53	1		54
III	56	1		57
Missing	4	0		4
Risk			0.52	
Low	312	8		320
High	317	11		328
Missing	1	0		1

sMPMTs indicates synchronous multiple primary malignant tumors; FL, follicular lymphoma; MALT, mucosa associated lymphoid tissue; MZL, marginal zone lymphoma; DLBCL, diffuse large B-cell lymphoma; AITL, angioimmunoblastic T-cell lymphoma; PTCL, peripheral T-cell lymphoma; MCL, mantle cell lymphoma; BL, Burkitt lymphoma; EBV-LPD, Epstein-Barr virus-associated lymphoproliferative disease; IPI, international prognostic index; ISS, international staging system.

Table 2 Impact of sMPMTs among Patients with Newly Diagnosed Hematological Malignancies: Multivariate Analyses.

Covariates	Multivariate		
	HR	95%CI	*P*
Overall survival			
Age at diagnosis, y			
≦ 75	1.00		
> 75	1.71	(1.22–2.39)	0.002
Sex			
Female	1.00		
Male	1.57	(1.12–2.21)	0.01
Risk			
Low	1.00		
High	3.10	(2.13–4.50)	<0.001
sMPMTs			
(–)	1.00		
(+)	1.48	(0.65–3.38)	0.35
Disease-free survival			
Age at diagnosis, y			
≦ 75	1.00		
> 75	1.33	(1.01–1.73)	0.04
Risk			
Low	1.00		
High	2.61	(1.98–3.44)	<0.001
sMPMTs			
(–)	1.00		
(+)	0.97	(0.46–2.10)	0.97
Relapse			
Risk			
Low	1.00		
High	2.41	(1.75–3.32)	<0.001
sMPMTs			
(–)	1.00		
(+)	0.79	(0.29–2.14)	0.65

sMPMTs indicates synchronous multiple primary malignant tumors.

Table 3 Details of Patients with sMPMTs.

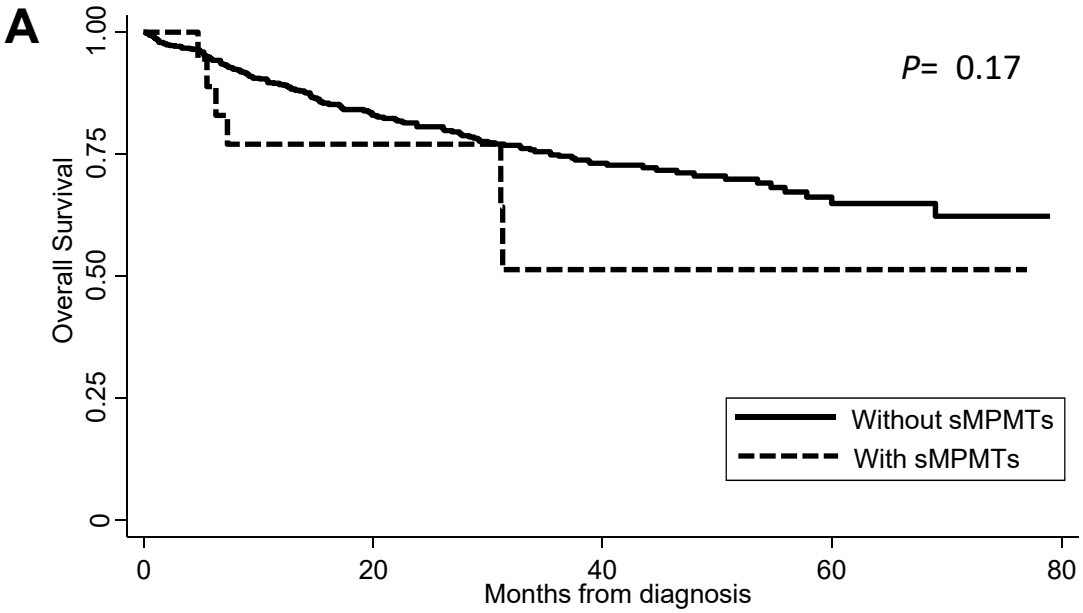
Hematological malignancy											Solid tumor											
Disease	Age	PS	IPI/ISS	Risk	Initial treatment	First evaluation	Discontinuation (d)	Relapse	DFS (mo)	Last evaluation	Site	Stage (TNM)	Treatment	First evaluation	Discontinuation (d)	Relapse	Last evaluation	Diagnosed earlier	Treated earlier	Last state	OS (mo)	Causes of death
DLBCL	78	1	H-I	High	Chemo	CR	Y (70)	N	60	CR	Colon	IIA	Ope	CR	N	N	CR	Hemato	Hemato	Alive	60	
FL	66	0	H-I	High	Chemo	CR	Y (113)	Y	25	PD	Stomach	IA	Ope	CR	N	N	CR	Hemato	Hemato	Alive	44	
DLBCL	65	0	H-I	High	Chemo	CR	Y (79)	N	31	CR	Stomach	IA	ESD	CR	N	N	CR	Hemato	Hemato	Dead	31	Pneumonia
FL	66	0	L-I	Low	Ope	CR	N	N	30	CR	Rectum	I	Chemo-Ope	CR	N	N	CR	Solid	Solid	Alive	30	
DLBCL	86	1	L-I	Low	Chemo	PR	Y*	N	18	CR	Liver	I	RFA	CR	N	N	CR	Hemato	Hemato	Alive	18	
DLBCL	60	1	Low	Low	Chemo	CR	N	N	7	CR	Colon	II	Ope	CR	N	N	CR	Solid	Solid	Alive	7	
DLBCL	83	2	H-I	High	Chemo	PR	N	N	6	PR	Stomach	IB	None	PD	NA	NA	PD	Solid	Hemato	Dead	6	Gastric cancer
FL	73	2	L-I	Low	None	SD	NA	NA	6	SD	Lung	IA	Chemo-Ope	CR	N	N	CR	Solid	Solid	Alive	6	
DLBCL	69	2	Low	Low	Chemo	CR	N	N	6	CR	Pancreas	III	Ope	PR	N	Y	PD	Solid	Solid	Dead	6	Pancreas cancer
DLBCL	66	3	High	High	Chemo	CR	Y (36)	N	48	CR	Stomach	IA	ESD	CR	N	N	CR	Hemato	Hemato	Alive	48	
DLBCL	68	1	H-I	High	Chemo	CR	Y*	N	8	CR	Tongue	II	Ope	CR	N	N	CR	Hemato	Hemato	Alive	8	
FL	86	0	H-I	High	Chemo	PD	N	NA	7	PD	Stomach	IA	None	SD	NA	NA	SD	Hemato	Hemato	Dead	7	Lymphoma
DLBCL	67	0	High	High	Chemo	CR	N	Y	53	CR	Lung	IV	Chemo-RT	PR	N	N	CR	Solid	Solid	Alive	76	
DLBCL	74	0	Low	Low	Chemo	CR	Y (38)	N	3	PR	Stomach	IA	ESD	CR	N	N	CR	Hemato	Hemato	Alive	3	
FL	68	0	L-I	Low	Chemo	PR	Y*	N	32	PR	Stomach	IIIA	Ope-Chemo	PD	Y (137)	NA	PD	Solid	Solid	Dead	32	Gastric cancer
AITL	75	0	Low	Low	Chemo	CR	Y (50)	N	19	CR	Stomach	IA	ESD	CR	N	N	CR	Hemato	Hemato	Alive	19	
MM	62	0	I	High	None	SD	NA	NA	4	SD	Pancreas	IV	None	PD	NA	NA	PD	Hemato	NA	Dead	4	Pancreas cancer
MM	75	0	II	High	Chemo	PR	Y (50)	N	11	PR	Stomach	IB	Ope	CR	N	N	CR	Hemato	Hemato	Alive	11	
MM	79	1	III	High	Chemo	SD	Y (82)	N	15	SD	Colon	I	Ope	CR	N	N	CR	Hemato	Hemato	Alive	15	

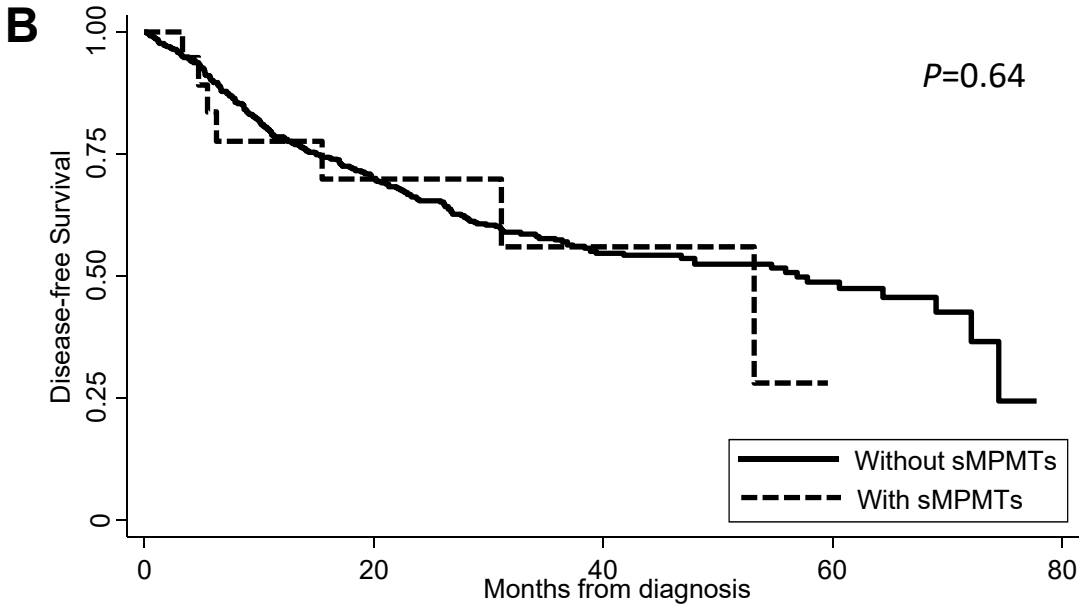
PS indicates performance status; IPI, international prognostic index; ISS, international staging system; DFS, disease-free survival; OS, overall survival; DLBCL, diffuse large B-cell lymphoma; FL, follicular lymphoma, AITL, angioimmunoblastic T-cell lymphoma; MM, multiple myeloma; Chemo, chemotherapy; Ope, operation; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; NA, not applicable; ESD, endoscopic submucosal dissection; RFA, radiofrequency ablation; RT, radiotherapy; Hemato, hematological malignancy; Solid, solid tumor.
*Treatment was not restarted after treatment of the solid tumor.

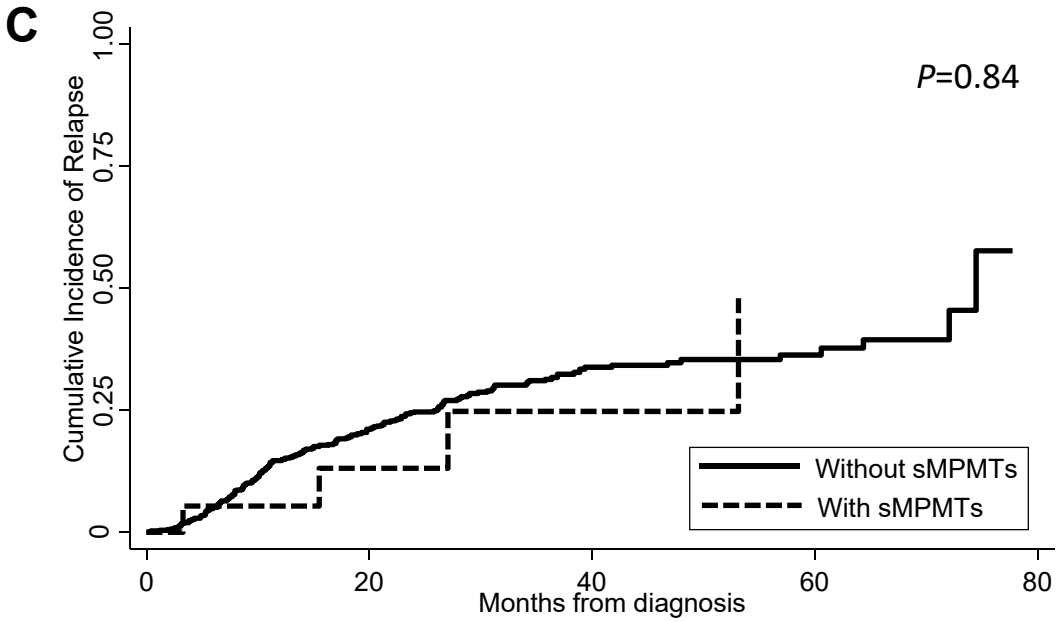
Titles and legends to figures

Figure 1 Outcomes according to the Existence of sMPMTs.

(A) Overall survival; (B) Disease-free survival; (C) Cumulative incidence of relapse.


A
P= 0.17
Overall Survival
0
0.25
0.50
0.75
1.00
0
20
40
60
80
Months from diagnosis
Without sMPMTs
With sMPMTs


B
P=0.64
Disease-free Survival
0
0.25
0.50
0.75
1.00
0
20
40
60
80
Months from diagnosis
Without sMPMTs
With sMPMTs


C
P=0.84
Cumulative Incidence of Relapse
0
0.25
0.50
0.75
1.00
0
20
40
60
80
Months from diagnosis
Without sMPMTs
With sMPMTs