Changing trends in the risk factors for second primary malignancies after autologous stem cell transplantation for multiple myeloma before and after the introduction of proteasome inhibitors and immunomodulatory drugs

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Abstract

The incidence of second primary malignancies (SPM) in long-term survivors of multiple myeloma (MM) is increasing because of increased life expectancy. We retrospectively analyzed the risk factors for SPM in patients with MM after autologous stem cell transplantation (ASCT) before and after the introduction of proteasome inhibitors and immunomodulatory drugs (IMiDs). In total, 2,340 patients newly diagnosed with MM who underwent ASCT between 1995 and 2016 were enrolled in this study. Forty-three patients developed SPM (29 solid, 12 hematological, and 2 unknown tumors), with cumulative incidence rates of 0.8% and 2.5% at 24 and 60 months, respectively. The cumulative incidence rates of hematological and solid SPM at 60 months were 0.8% and 1.8%, respectively. The overall survival (OS) rate at 60 months after ASCT was 62.9% and the OS rates after the diagnosis of SPM at 24 months were 72.2% for hematological SPM and 70.9% for solid SPM. Multivariate analysis revealed that the use of IMiDs (P=0.024) and radiation (P=0.002) were significant independent risk factors for SPM. The probabilities of developing SPM and death due to other causes (mainly MM) at 60 months were 2.5% and 36.5%, respectively, indicating that the risk of SPM was lower than that of death from MM. Furthermore, SPM between the pre-novel and novel agent eras (ASCT between 2007 and 2016) groups significantly increased (1.9% *vs*. 4.3% at 60 months; P=0.022). The early occurrence of SPM after ASCT should be monitored cautiously.

Introduction

Despite the development of various novel agents, such as proteasome inhibitors (PI) and immunomodulatory drugs (IMiDs), autologous stem cell transplantation (ASCT) is the gold standard treatment for transplant-eligible (TE) patients with multiple myeloma (MM).[1-4] Because patients with MM survive longer, the incidence rate of second primary malignancies (SPM) in long-term survivors of MM is increasing. To date, only a few studies have evaluated SPM in real-world patients,[5-9] particularly in Asian patients with MM.[10-12] In this study, we analyzed Japanese patients with MM who underwent ASCT using large registry data.

Methods

Data source

In this retrospective observational study, ASCT data from the Registry of the Japanese Society for Transplantation and Cellular Therapy (JSTCT) and the Japanese Data Center for Hematopoietic Cell Transplantation were collected and analyzed. More than 99% of all transplant centers in Japan report and update their outcomes annually. As the registry data comprised anonymized clinical information, patient consent was not required for registration. This study was approved by the Data Management Committee of the JSTCT and the Institutional Review Board of Kanazawa University (no. 2019-118 [3163]). In total, 2,340 patients with newly diagnosed MM who underwent ASCT between 1995 and 2016 and whose clinical data were sufficient for this analysis were enrolled in this study. Patients with a history of solid tumors were excluded from the analysis. Cancer incidence and survival data in the Japanese general population were estimated using population-based cancer registries through the Monitoring of Cancer Incidence in Japan project conducted by the Japan Cancer Surveillance Research Group.[13] Cancer type was classified according to the International Classification of Diseases, tenth revision.

Statistical analyses

Categorical and continuous variables were compared using Fisher's exact test and the Mann–Whitney U test, respectively. Overall survival (OS) was calculated from the time of ASCT or diagnosis of SPM using the Kaplan-Meier method and compared between groups using a log-rank test. The probabilities of SPM and death were estimated based on cumulative incidence methods and compared between groups using the Gray test, considering death without SPM or SPM without death as competing events.[14,15] Multivariate analysis for OS was performed using the Cox proportional hazards model, whereas multivariate analysis for SPM was performed using the Fine-Gray regression model.[16] The Cox proportional and Fine-Gray proportional hazards models were used to calculate hazard ratios (HR) with 95% confidence intervals (CI) for all variables. Multivariate analyses were performed by entering all variables associated with survival into the Cox proportional hazards model or variables associated with SPM into the Fine-Gray proportional hazards model. Owing to the small incidence rate of SPM, the factors of *P* value <0.1 were entered into multivariate analysis. All statistical analyses were performed using the EZR software package (Saitama Medical Center, Jichi Medical University, Saitama, Japan),[17] which is a graphical user interface for R version 3.4.0 (R Foundation for Statistical Computing, Vienna, Austria). $P<0.05$ was considered statistically significant.

Results

Patients' characteristics

A total of 2,340 (males, 1,329 [56.8%]; females, 1,011 [43.2%]) patients newly diagnosed with MM were extracted from the database. The median age of the patients was 58 (range, 22–72) years at ASCT. Immunoglobulin (Ig) G, IgA, IgD, IgE, IgM, Bence Jones protein, non-secreting, and unknown antibodies were observed in 1,340 (57.3%), 452 (19.3%), 63 (2.7%), three (0.1%), six (0.3%), 416 (17.8%), 38 (1.6%), and 22 (1.0%) patients, respectively. International Staging System (ISS) stages 1, 2, and 3 were observed in 774 (33.1%), 825 (35.3%), and 455 (19.4%) patients, respectively. ISS staging was not assessed in 286 (12.2%) patients. In total, 1,908 (81.5%) and 432 (18.5%) patients received single melphalan 200 mg/m^2 (MEL 200) and double MEL 200, respectively, as a conditioning regimen before ASCT. Moreover, 771 (32.9%) and 1,569 (67.1%) patients underwent ASCT between 1995 and 2006 (pre-novel agent era) and between 2007 and 2016 (novel agent era), respectively. In total, 1,562 (66.8%), 977 (41.8%), and 904 (38.6%) patients received PI (bortezomib [n=1562], carfilzomib [n=14], and ixazomib [n=11]), IMiDs (thalidomide [n=185], lenalidomide [n=852] and pomalidomide [n=41]), and both PI and IMiDs, respectively. Meanwhile, 131 (5.6%) patients received radiation treatment, and 50 (2.1%) received allogeneic stem cell transplantation post-ASCT. The disease statuses at ASCT were as follows: 366 (15.6%), stringent complete response (CR)/CR; 608 (26.0%), very good partial response; 1,122 (48.0%), partial response; 164 (7.0%), stable disease; 55 (2.4%), progressive disease; and 25 (1.1%), unknown (Table 1).

Incidence rates and types of second primary malignancies

The median follow-up period after ASCT was 24 (range, 0–218) months (*Online Supplementary Figure S1*). Forty-three patients in this cohort developed SPM, with cumulative incidence rates of 0.8% (95% CI: 0.4-1.2) and 2.5% (95% CI: 1.7-3.6) at 24 and 60 months, respectively, and

Table 1. Baseline characteristics and outcomes of 2,340 transplant-eligible patients.

	Patients with SPM N=43 unknown type, N=2		Patients without SPM N=2297	*P**
	Hematologic malignancies, N=12	Non-hematological cancers, N=29		
Median age in years (range) at ASCT	60.5 (54-69)	58 (42-70)	58 (22-72)	0.094
>65 years of age at diagnosis, N (%)	1 (8.3)	3 (10.3)	220 (9.6)	1.000
Male, N (%)	5 (41.7)	18 (62.1)	1304 (56.8)	0.878
M-protein isotype, N (%)				0.878
IgG	11 (91.7)	17 (58.6)	1312 (57.1)	
IgA	1 (8.3)	7 (24.1)	444 (19.3)	
IgD	0	0	63 (2.7)	
IgE	0	0	3 (0.1)	
IgM	0	0	6 (0.3)	
Light chain only	0	4 (13.8)	410 (17.8)	
Non-secreting	0	1 (3.4)	37 (1.6)	
Unknown	0	0	22 (1.0)	
Light chain type, N (%)				0.173
κ	9 (75.0)	21 (72.4)	1384 (60.3)	
λ	3 (25.0)	6 (20.7)	828 (36.0)	
Unknown	0	2 (6.9)	85 (3.7)	
ISS at diagnosis, N (%)				0.154
I	5 (41.7)	10 (34.5)	759 (33.0)	
II	2 (16.7)	10 (34.5)	813 (35.4)	
III	3 (25.0)	3 (10.3)	449 (19.5)	
Unknown	2 (16.7)	6 (20.7)	276 (12.0)	
Conditioning regimen				0.071
Single melphalan 200 mg/m^2	10 (83.3)	20 (69.0)	1878 (81.8)	
Tandem melphalan 200 mg/m^2	2 (16.7)	9 (31.0)	419 (18.2)	
ASCT year				0.005
between 1995 and 2006	3 (25.0)	18 (62.1)	748 (32.6)	
between 2007 and 2016	9 (75.0)	11 (37.9)	1549 (67.4)	
PI and/or IMiDs Tx during induction and post-ASCT, N (%)	9 (75.0)	13 (44.8)	1612 (70.2)	0.028
PI without IMiDs based	5 (41.7)	3 (10.3)	650 (28.3)	0.175
IMiDs without PI based	0	5 (17.2)	67 (2.9)	0.002
PI + IMiDs based	4 (33.3)	5 (17.2)	895 (39.0)	0.017
Radiation Tx	2 (16.7)	4 (13.8)	125 (5.4)	0.030
Allo-SCT post-ASCT	0	1 (3.4)	49 (2.1)	0.608
Pre-ASCT response, N (%)				0.596
sCR/CR	0	4 (13.8)	362 (15.8)	
VGPR	3 (25.0)	7 (24.1)	597 (26.0)	
PR	8 (66.7)	13 (44.8)	1100 (47.9)	
SD	1 (8.3)	3 (10.3)	160 (7.0)	
PD	0	1 (3.4)	54 (2.4)	
Unknown	0	1 (3.4)	24 (1.0)	
Cause of death, N (%)	3 (100)	14 (100)	583 (100)	<0.0001
MM	0	5 (35.7)	495 (84.9)	
SPM	3 (100)	8 (57.1)	0	
Others	0	1 (7.1)	88 (15.1)	

SPM: second primary malignancy; ASCT: autologous stem cell transplantation; ISS: International Staging System; Tx: therapies; PI: proteasome inhibitor; IMiDs: immunomoduratory drugs; sCR: stringent complete response; CR: complete response; VGPR: very good partial response; PR: partial response; SD: stable disease; PD: progressive disease; MM: multiple myeloma. *Patients with SPM *vs*. without SPM.

these patients had no history of solid cancer before ASCT. Twenty-nine solid (7, lung; 4, stomach; 3, breast; 2, liver; 2, pancreas; 2, colon; 1, uterus; 1, thyroid gland; 2, bladder; 1, tongue; 2, sarcoma; 1 vulvar; and 1, basal cell carcinoma [BCC]), 12 hematological (8, myelodysplastic syndrome [MDS]; 1, acute leukemia; and 3, lymphoproliferative disorders), and two unknown tumors were observed (Table 2). The cumulative incidence rates of hematological and solid SPM at 60 months were 0.8% and 1.8%, respectively.

Risk factors for second primary malignancy

The risk factors for SPM were analyzed (Figure 1; Table 3), including age at ASCT (≤65 or >65 years), sex, PI/IMiD treatment, use of radiation, single/double ASCT, and period of ASCT (1995–2006 or 2007–2016). Because bortezomib, thalidomide, and lenalidomide were released for relapsed/refractory MM treatment in Japan in December 2006, February 2009, and July 2010, respectively, we categorized the patients into two treatment cohorts: the pre-novel (1995–2006) and novel (2007–2016) agent eras. Univariate analysis showed that the risk of SPM was increased in the novel agent era (Figure 1A; 1.9% *vs*. 4.3% at 60 months; *P*=0.022), and IMiDs without PI treatment (Figure 1E; Table 3; *P*=0.029) and the use of radiation (Figure 1F; Table 3; *P*=0.003) were also significant risk factors for SPM. Multivariate analysis also revealed that IMiDs without PI treatment (HR=2.738; 95% CI: 1.142–6.568; *P*=0.024) and the use of radiation (HR=4.151; 95% CI: 1.687–10.210; *P*=0.002) were significant independent risk factors for SPM. In contrast, PI without IMiD treatment were not a risk factor for SPM (Figure 1D; Table 3).

Survival rates and causes of death after autologous stem cell transplantation and diagnosis of second primary malignancies

The OS rate at 60 months after ASCT was 62.9% (Figure 2A), and the OS rate between the pre-novel (1995-2006) and novel agent (2007-2016) era groups significantly improved (59.2% *vs*. 69.5% at 60 months; *P*<0.0001; Figure 2A) after ASCT. Furthermore, the use of PI and/or IMiDs improved OS (*Online Supplementary Figure S2C*). However, there were no differences in OS regarding age, sex, and single/tandem ASCT (*Online Supplementary Figure S2A, B, D*). Multivariate analysis revealed that the use of PI and/or IMiDs and tandem ASCT significantly improved OS (Table 3). The probabilities of developing SPM and death due to other causes (mainly MM) at 60 months were 2.5% and 36.5%, respectively (Figure 1A), indicating that the risk of SPM was lower than that of death from MM. Furthermore, Figure 2B shows a comparison of the OS rates between patients with and without SPM. There were no significant differences in the OS rates among hematological SPM, solid SPM, and no SPM cases.

Table 2. Second primary malignancy by type (N=43).

Variable	N
Hematologic malignancy	12
Myelodysplastic syndrome	8
Acute leukemia	1
Post-transplant lymphoproliferative disorder	2
MTX-related lymphoproliferative disorders	1
Solid tumor	29
Lung	7
Stomach	4
Breast	3
Bladder	2
Colon	2
Liver	2
Pancreas	2
Sarcoma	2
Uterus	1
Thyroid gland	1
Tongue	1
Vulvar	1
Basal cell carcinoma	1
Type not reported	2

MTX: methotrexate.

The OS rates after the diagnosis of SPM at 24 months were 72.2% for hematological and 70.9% for solid SPM (median follow-up period, 23 months; Figure 2C). There was no significant difference in the OS rates post-SPM diagnosis between solid and hematological cancers (*P*=0.762).

Comparison of adjusted survival probabilities of solid and hematological cancers between patients with second primary malignancy post-autologous stem cell transplantation and the general population in Japan

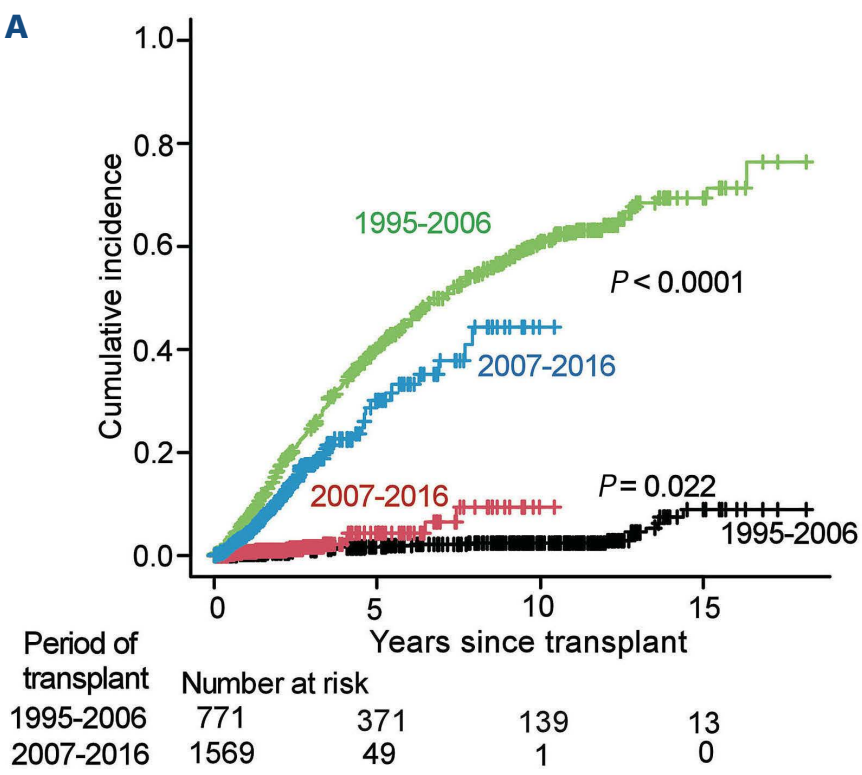
In order to compare the OS rates between SPM post-ASCT and primary solid cancers (PSC) and primary hematological cancers (PHC) in Japan's general population, we conducted a study where patients with PSC or PHC were matched with patients with SPM post-ASCT at a 20:1 ratio based on sex, age, and cancer type. We analyzed the OS rate following the diagnosis. Lymphoproliferative disorders and carcinoma *in situ* were excluded because there were no data in the population-based cancer registries. The OS rate in patients with solid SPM post-ASCT was comparable with that of PSC in the general Japanese population (Figure 2C, D). Owing to the small number of hematological SPM, it was difficult to compare the OS rates between hematological

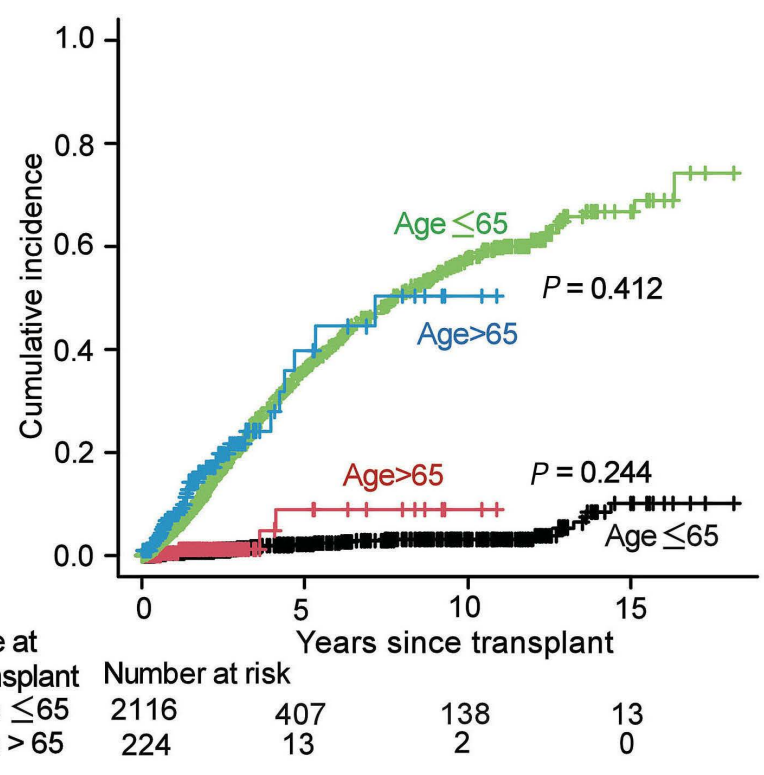
SPM and PHC. Five primary MM, 13 SPM, and one bacterial infection were identified as the causes of death in 19 patients with SPM in this cohort.

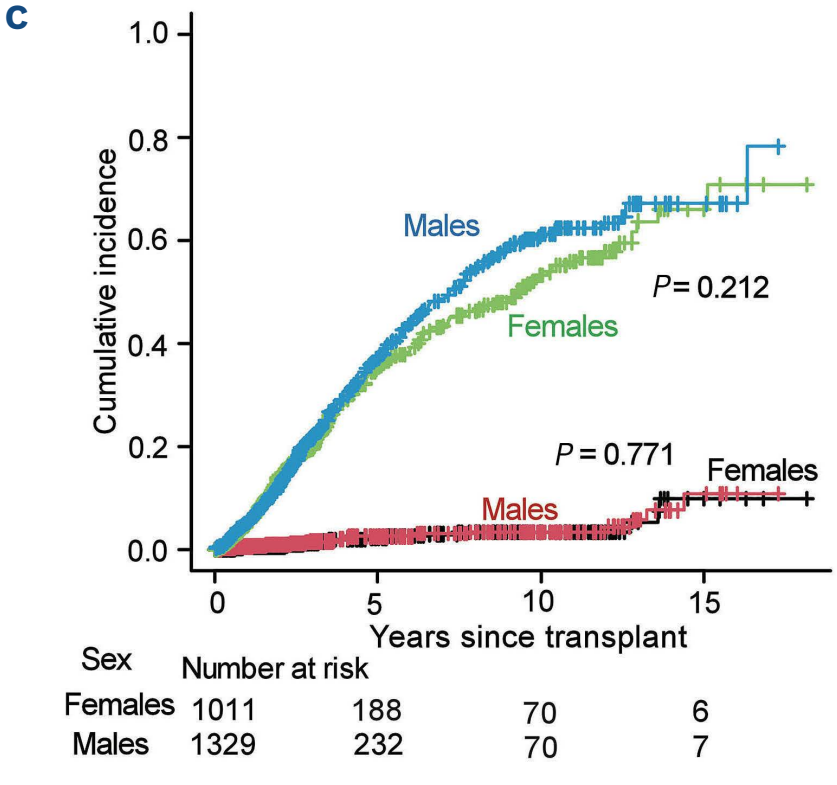
Discussion

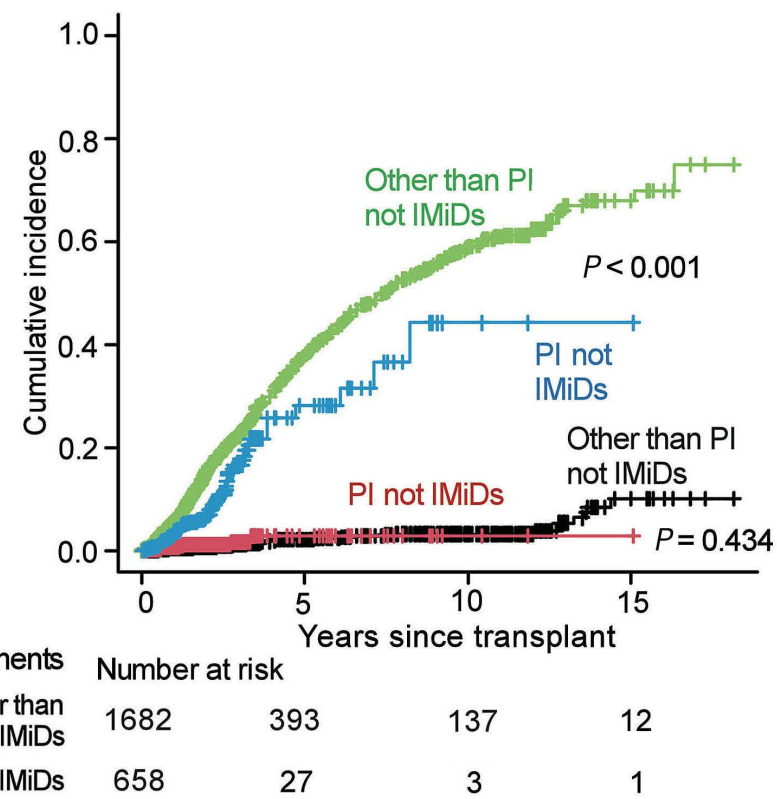
The incidence rate of SPM in patients with MM in Japan in our study (0.8% [95% CI: 0.4-1.2] and 2.5% [95% CI: 1.7-3.6] at 24 and 60 months) was somewhat lower than that (5.3% [95% CI: 4.4-6.3] at 72 months post-ASCT) reported by Sahebi *et al.*[6] Although the risk of SPM increased in the novel agent era group, the mortality rate of SPM was lower than that of other causes (primarily MM). Considering the increase in the number of long-term survivors of MM, the occurrence of SPM should be monitored cautiously.

Our multivariate analysis revealed that IMiDs without PI treatment (P=0.024) and the use of radiation (P=0.002) were significant independent risk factors for SPM. To the best of our knowledge, no studies have demonstrated that the use of radiation is a significant risk factor for SPM. However, radiation is a risk factor for cancer. Data on atomic bomb survivors demonstrated a linear relationship between cancer development and radiation dose,[18] and patients with Hodgkin lymphoma usually receive chemotherapy and/or radiation therapy, which induce secondary cancer.[19] Therefore, our result of radiation on SPM seems to be reasonable. However, to date, several reports have









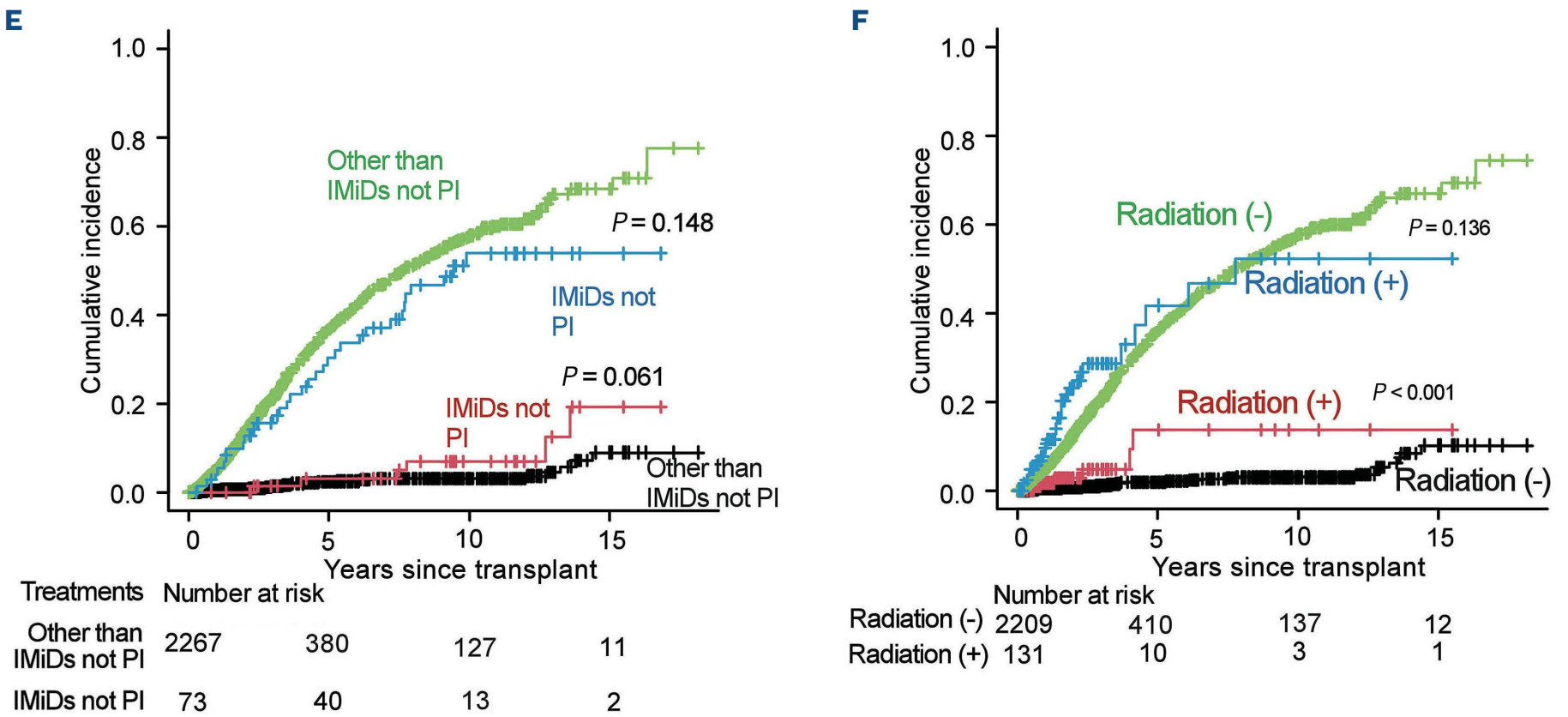


Figure 1. Cumulative incidence rate of developing second primary malignancies (SPM) (black and red curves) *versus* death from all causes without occurrence of SPM (green and blue curves). According to (A) years of transplant, development of SPM: 1.9% (1995–2006) *vs.* 4.3% (2007–2016) at 60 months (P=0.022); (B) age at transplant; (C) sex; (D) proteasome inhibitors (PI) not immunomodulatory drugs (IMiDs) *vs.* other than PI not IMiDs; (E) IMiDs not PI *vs.* other than IMiDs not PI; (F) radiation, development of SPM: 2.1% (radiation [–]) *vs.* 13.8% (radiation [+]) at 60 months (P<0.001).

Table 3. Risk factors of second primary malignancy and predictor of overall survival.

Independent variables	SPM				Overall survival			
	HR (95% CI) for SPM from univariate analysis	*P* for univariate analysis	HR (95% CI) for SPM from multivariate analysis	*P* for multivariate analysis	HR (95% CI) for OS from univariate analysis	*P* for univariate analysis	HR (95% CI) for OS from multivariate analysis	*P* for multivariate analysis
Age in years, ≤65 *vs.* 65<	1.591 (0.564-4.488)	0.380	NA	NA	1.160 (0.833-1.614)	0.381	1.247 (0.891-1.745)	0.198
Sex, female *vs.* male	1.097 (0.600-2.006)	0.760	NA	NA	1.122 (0.954-1.319)	0.164	1.144 (0.973-1.345)	0.105
Treatments of PI and IMiDs								
PI (-) and IMiDs (-)	1	NA	1	NA	1	NA	1	NA
PI (+) and IMiDs (-)	1.352 (0.594-3.081)	0.470	1.183(0.495-2.828)	0.710	0.543 (0.411-0.716)	<0.0001	0.479(0.360-0.638)	<0.000001
PI (-) and IMiDs(+)	2.694 (1.108 - 6.550)	0.029	2.738 (1.142-6.568)	0.024	0.713 (0.502-1.012)	0.059	0.660 (0.462-0.941)	0.022
PI (+) and IMiDs (+)	1.096 (0.483-2.486)	0.830	0.840 (0.368-1.917)	0.680	0.785 (0.628-0.981)	0.034	0.681 (0.537-0.863)	0.001
Local radiation therapy	3.657 (1.542-8.672)	0.003	4.151 (1.687-10.210)	0.002	1.413(0.989-2.019)	0.057	1.462 (1.017-2.100)	0.040
Single *vs.* tandem ASCT	0.849 (0.431-1.671)	0.630	NA	NA	0.904 (0.760-1.076)	0.258	0.788 (0.656-0.947)	0.011

OS: overall survival; PI: proteasome inhibitors; IMiDs: immunomoduratory drugs; (+): administered; (-): not administered; HR: hazard ratio; CI: confidence interval; ASCT: autologous stem cell transplantation; NA: not applicable.

demonstrated that the incidence rate of SPM increases among patients with MM who receive lenalidomide.[1,20-22] Recently, using the Myeloma XI trial data, Jones *et al.* reported that TE patients receiving lenalidomide maintenance had an SPM incidence rate of 12.2% at 7 years, compared with 5.8% in those being observed (P=0.003). They also demonstrated that the SPM incidence rate was higher in patients treated with lenalidomide at both induction and maintenance compared with single exposure or no exposure,[23] suggesting a dose-dependent risk of lenalidomide on SPM. Hematological SPM was almost all confined to lenalidomide-treated patients using the Myeloma XI data.[23] Regarding patients with hematological SPM (n=12) in our cohort, only four of the 12 (33%) patients had received IMiDs before SPM diagnosis.

Regarding the types of SPM, we mainly observed MDS in hematological SPM and lung, stomach, and breast cancers in solid cancer SPM. In contrast, Jones *et al.* demon-

strated that hematological malignancies (MDS or acute myeloid leukemia [AML]) and non-melanoma skin cancer (BCC or squamous cell carcinoma) were mostly confined to patients receiving lenalidomide maintenance.[23] The incidence rates of solid tumors were similar between the lenalidomide maintenance and observation groups. The types of solid tumors were prostate (incidence rate, 2%) and breast (incidence rate, 1%) cancers, but not gastric cancer. Engelhardt *et al.* also did not observe any gastric cancer in SPM cases.[5] Although the trend in hematological SPM type (MDS/AML) in our cohort is almost the same as that reported in Western countries, the types of solid

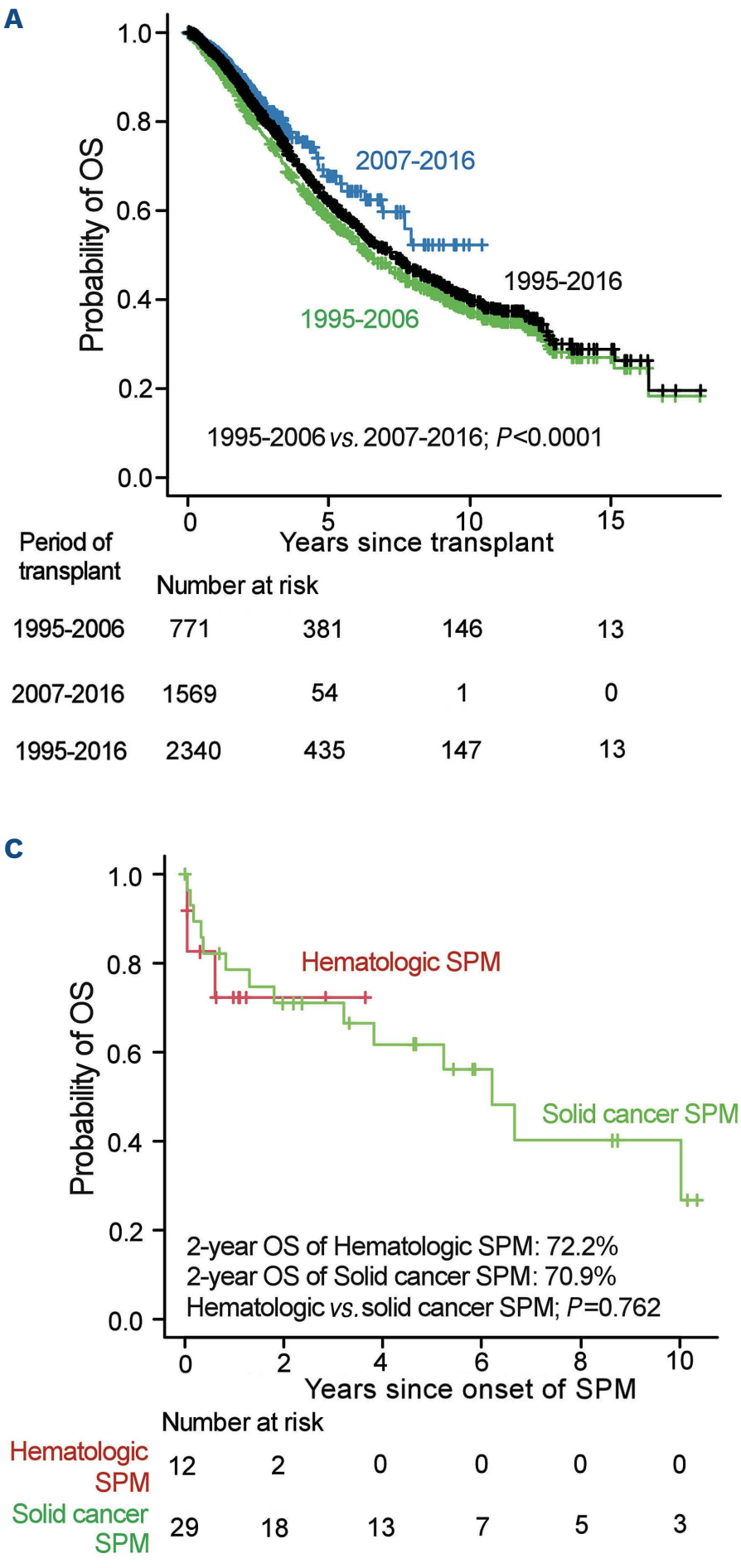


Figure 2. Influence of second primary malignancies on overall survival rates. (A) Comparison of overall survival (OS) rates between pre-novel (1995–2006) and novel (2007–2016) agent eras. (B) OS rates according to second primary malignancy (SPM) occurrence after autologous stem cell transplantation. (C) OS rates of patients with SPM post-SPM occurrence. (D) OS rates of Japanese patients with primary cancer who were matched to patients with SPM in this cohort by age, sex, and cancer type.

cancer SPM seem to differ from those in Western countries, suggesting a reflection of ethnic and environmental background. For example, stomach cancer is not as common in Western countries as in Asian countries, possibly owing to the infection rate of *Helicobacter pylori* in the stomach, and skin cancer is relatively rarer in Japan than in Western countries. Tzeng *et al*. also reported a high incidence rate of stomach cancer and low incidence rate of skin cancer among Taiwanese patients with MM.[10]

Compared with reports from Western countries,[5,6,24-29] there are only a few reports on SPM in Asian countries.[10-12] Ailawadhi *et al*. reported that the risk of developing SPM among patients varied depending on the patient's ethnic background.[7] Owing to the genetic and environmental differences between Asians and Westerners, SPM may be different. Reports from Western countries showed that the incidence rate of SPM at 60 months was between 4% and 11%,[5,25,27-29] which is higher than that in our study (0.8% [95% CI: 0.4-1.2] and 2.5% [95% CI: 1.7-3.6%] at 24 and 60 months), particularly for hematological cancers (0.8% at 60 months). Conversely, the reports from Taiwan demonstrated that the incidence rate of SPM was 1.8 % (0.9% solid cancers and 0.9% hematological cancers) at 23 months[10] and 1.8% (1.5% solid cancers and 0.3% hematological cancers) at 24 months;[12] similarly, reports from Japan showed that the incidence rate of SPM was 4.7% (3.7% solid cancers and 1.0% hematological cancers)[30] and 5.6% (4.0% solid cancers and 1.7% hematological cancers) at 60 months.[11] According to these data, the incidence rate of SPM might be less among Asian patients with MM. Yamasaki *et al*. analyzed the risk factors for SPM among Japanese patients with MM. Multivariate analysis identified a history of high-dose cyclophosphamide use for peripheral blood stem cell harvest in TE patients with MM and aged >65 years at diagnosis or a history of adriamycin, lenalidomide, or thalidomide use in transplant-ineligible patients with MM as independent risk factors for SPM (P<0.001), and lenalidomide did not facilitate SPM development in TE patients with MM, all of whom received oral or high-dose melphalan.[11] Of the 211 TE patients analyzed, only 18 received lenalidomide. Given the small number of cases, it would be challenging to evaluate the impact of lenalidomide on SPM. Interestingly, Liu *et al*. reported that contemporary treatment regimens using novel agents (mainly bortezomib) were associated with a lower risk of SPM than chemotherapy alone. However, in their cohort, thalidomide-containing regimens were used, lenalidomide was not used, and its effect on SPM was not revealed. Therefore, our study is the first to demonstrate that the use of IMiDs is a risk factor for SPM in TE Asian patients with MM.

The prognosis of patients with MM after SPM diagnosis has also been reported. Cooper *et al*. reported the survival rate of 2,837 patients with MM diagnosed with SPM using ASCO CancerlinQ™ analysis.[31] They showed that patients with secondary AML had the worst prognosis, followed by those with lung cancer. In our data, we could not analyze the prognosis of patients with SPM based on the type of secondary cancer because of the small incidence rates. However, there was no evident difference in OS rates between patients with non-SPM and SPM when SPM were divided into hematological and solid SPM (Figure 2B). Our results are consistent with those of a previous study.[8]

There have been few reports that describe the prognostic comparisons of patients with SPM post-ASCT and the general population. Barth *et al*. examined the OS and cause-specific survival and cumulative incidence function of cancer-related death among patients with MM with SPM of the breast, prostate, lung, colon/rectum, or bladder or melanoma using the population-based Surveillance, Epidemiology, and End Results Registry (2004-2015). For all studied cancers, except those of the lung, overall mortality was significantly higher among patients with MM than among controls (HR=1.84-2.81). However, the cumulative incidence function of cancer-related death did not differ (sub-HR=0.84-0.99).[9] Tzeng *et al*. analyzed patients with MM in Taiwan using data from population-based insurance claims and demonstrated that the overall incidence rate of secondary malignancy was lower in the MM cohort than in the comparison cohort (93.6 *vs*. 104.5 per 10,000 person-years, incidence rate ratio=0.90; 95% CI: 0.78-1.04). However, the incidence rate of hematological malignancies was 11-fold greater in patients with MM (47.2 *vs*. 4.09 per 10,000 person-years) with an adjusted HR of 13.0 (95% CI: 7.79-21.6) compared with the comparison cohort. The relative risk of secondary malignancy was also high for myeloid leukemia (21.2 *vs*. 1.36 per 10,000 person-years).[10] In our study, the OS rate in patients with SPM post-ASCT was compatible with that of primary cancers in the general Japanese population.

This study had some limitations. First, we could not confirm the duration of induction and post-ASCT therapy, including the doses of medications and radiation. Second, we could not completely exclude the existence of a primary malignancy that led to SPM because there were no strict entry criteria to exclude primary malignancy at the entry of the patient. Third, the median follow-up period of 24 months after ASCT was relatively short for monitoring SPM. Not all occurrences of SPM were possibly captured within this timeframe in the registration because of a long latency before the development of SPM. Therefore, we must follow up for a longer period and estimate the risk of SPM. Fourth, we could not compare the patients who received ASCT with high-dose melphalan and those who were not exposed to high-dose melphalan. Recently, Richardson *et al*. reported that 5-year cumulative incidences of SPM were 10.4% in the triplet therapy (lenalidomide, bortezomib, and dexamethasone [RVD])-alone group and 10.7% in the transplantation group, and the incidence was similar in the two groups. Hematologic SPM

occurred in 2.5% in the RVD-alone group and 3.6% in the transplantation group, with AML or MDS reported in none of the patients in the RVD-alone group, as compared with 2.7% in the ASCT group (P=0.002).[27] Finally, we could not obtain information on treatments for SPM to analyze their prognosis after SPM occurred.

In conclusion, although the risk of SPM increased among patients who received IMiDs (P=0.024) and used radiation (P=0.002), the mortality rate of SPM was lower than that of other causes (primarily MM). Considering the increase in the number of long-term survivors of MM, the occurrence of SPM should be monitored cautiously.

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Contributions

HT designed the research study, performed research, collected, analyzed, interpreted data, and wrote the manuscript. SM, TT, SF, IH and KS designed the research study, performed research, and collected data. TM analyzed the survival of solid and hematological cancers in the general population in Japan. KK, NT, MM, AH, ND, NU, MS, YM, S. Kurahashi, KN, YH, S. Kako, SI, TI, YK and YA performed research and collected data.

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Data-sharing statement

Qualified researchers can request access to data and related study documents, including statistical analysis plan and dataset specifications.

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