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Therapy-related Secondary Malignancy After Treatment of Childhood Malignancy: Cases from a Single Center

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Background: Therapeutic outcomes for childhood malignancy have dramatically improved. However, secondary malignancies are a major concern, as they greatly affect the quality of life of survivors. This retrospective study evaluated the cumulative incidence, clinical features, and outcomes of secondary malignancies at Nippon Medical School Hospital.

Methods: We examined data from 275 cases of primary childhood malignancy diagnosed between 1980 and 2014. Information regarding treatment of the primary malignancy, including irradiation dose, site, and cumulative dose of anticancer drugs, was assessed. We also collected data on secondary malignancy, including patient sex, age at diagnosis, malignancy site, time from primary to secondary malignancy, and outcomes.

Results: Secondary malignancies developed in 11 patients and included acute myeloid leukemia (AML) (4), meningioma (4), Ewing sarcoma (1), germ cell tumor (1), and malignant parotid gland tumor (1). The primary malignancies included acute lymphoblastic leukemia (ALL) (9), non-Hodgkin lymphoma (1) and brain tumor (1). In 7 of the 9 ALL patients, chemoradiotherapy was the primary treatment. The meningiomas and 1 solid tumor developed within the radiation field. All AMLs and meningiomas developed within 5 years and after 20 years, respectively, of the primary diagnosis. The 10- and 20-year cumulative incidence rates for secondary malignancy in our hospital were 1.9% and 5.8%, respectively.

Conclusions: Our results revealed that the type of secondary malignancy depends on the interval after the end of treatment for primary malignancy. Meningioma, notably, develops many years after completion of primary malignancy treatment. Early detection during long-term follow-up is therefore essential. (J Nippon Med Sch 2019; 86: 207–214)

Key words: secondary malignancies, childhood cancer survivors, long-term follow-up, cumulative incidence, meningioma

Introduction

In recent years, treatment outcomes for childhood malignancies have improved dramatically. Today, more than 80% of children diagnosed with malignancies are expected to be long-term survivors[1]. However, secondary malignancies are directly linked to outcomes and often have a dramatic impact on the quality of life of cancer survivors. Exposure to radiation increases the risk of brain tumors, including meningiomas. In the United States and Europe, secondary malignancies developed in about 2% and 5% of survivors, respectively, within the first 20 years after a primary malignancy diagnosis[2–4]. Although pediatric chemo- and radiotherapy regimens have evolved to reduce toxicity while maximizing efficacy, the risk of secondary malignancies remains, and several reports recommend continuous and stringent follow-up[5,6].

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https://doi.org/10.1272/jnms.JNMS.2018_86-401
Journal Website (https://www.nms.ac.jp/sh/jnms/)

In Japan, a retrospective cohort study of 2,918 children who received a diagnosis of acute lymphoblastic leukemia (ALL), the most common pediatric malignancy, evaluated the incidence of secondary malignancies and associated factors such as treatment protocols, cranial irradiation (CRT), and other characteristics of primary ALL. The cumulative incidence of all secondary malignancies was 1.0% at 10 years and 2.4% at 20 years[7]. Furthermore, Ishida et al. reported that, among 5,387 patients from 15 centers in Japan who survived primary pediatric malignancies, 128 (2.4%) developed secondary malignancies. The cumulative incidence was 1.1% at 10 years and 2.6% at 20 years after a primary malignancy diagnosis[8]. These reports are the first from an Asian country to describe the epidemiology of secondary malignancies after ALL and other childhood malignancies. Hospital-based registration data from multiple centers have limitations, namely, that the number of patients with secondary malignancies might have been underestimated because of inadequate follow-up.

This retrospective study evaluated the cumulative incidence, clinical features, and outcomes of secondary malignancies at our hospital. The patient information collected at registration in our hospital was more detailed than that in previous reports. Additionally, to our knowledge, this is one of only a few reports on secondary childhood malignancies at a single center.

Materials and Methods

Patients

Data from 328 children with newly diagnosed primary malignancies (251 hematological malignancies and 77 solid tumors) treated at Nippon Medical School Hospital between January 1, 1980 and December 31, 2014 were considered for analysis. The study subjects were selected from these children by using the following inclusion criteria: (a) age <16 years at the time of primary malignancy diagnosis, (b) follow-up for >1 year, and (c) availability of outcome information. Follow-up for this study ended on December 31, 2015.

Collection of Follow-up Data

We obtained detailed information on treatment of primary malignancies, including irradiation dose and site and cumulative dose of anticancer drugs. Data on the secondary malignancy diagnosis were also collected, including sex, age at primary malignancy and secondary malignancy diagnoses, malignancy site, interval to secondary malignancy, and outcomes. Furthermore, our unit routinely performs brain magnetic resonance imaging (MRI) once every 2 or 3 years for all survivors who had received CRT.

The present definition of secondary malignancy was based on the description used in a nationwide epidemiological survey conducted in Japan[8]: "a histopathologically distinct tumor that occurs after diagnosis of a primary malignant tumor and for which it is possible to rule out metastasis or recurrence of the primary tumor. Moreover, in the case of secondary brain tumor, a benign tumor is regarded as secondary malignancy and is subject to registration".

Statistical Analysis

The cumulative incidence of secondary malignancies was calculated by using competing risk methods, with death regarded as a competing event[9]. BellCurve for Excel software was used for the analysis.

Results

Clinical Characteristics of Primary Malignancies

Primary malignancies were newly diagnosed and treated in 328 children (251 hematological malignancies and 77 solid tumors) in our hospital during the course of the study. We excluded 53 because of lack of follow-up data or a duration of follow-up less than 1 year. These included patients with missing information who had died from the primary malignancy. Ultimately, data from 275 patients were analyzed (**Table 1, 2**). The most common cause of death was progressive primary malignancy and relapse. The median follow-up period was 7 years, mean follow-up was 10 years, and maximum follow-up was 33 years. The duration of follow-up from primary malignancy diagnosis was <5 years for 99 patients, 5-10 years for 58 patients, 10-15 years for 41 patients, 15-20 years for 26 patients, and ≥20 years in 51 patients. Ten cases of secondary malignancy after a primary hematological malignancy (9 cases of ALL and 1 case of non-Hodgkin lymphoma [NHL]) were included in several Tokyo Children Cancer Study Group (TCCSG) studies (L81-10, L84-11, L89-12, L92-13, L92-14, L99-15, and T8801; **Table 3**). Details of the treatment regimens and main therapeutic outcomes have been published previously[10–13]. Prophylactic CRT was part of the treatment protocol for all patients in the L84-11 trial but was limited to the high-risk group in the more recent L99-15/L04-1502 trials, in which only 8.6% of patients received such treatment.

Incidence and Clinical Characteristics of Secondary Malignancies

The cumulative incidence rates of secondary malignancies among primary cancer survivors in our hospital

Table 1 Hematological malignancies

	Total	Survivors	Nonsurvivors
ALL	134	102	32
AML/MDS	34	18	16
CML	7	5	2
TAM	5	5	0
NHL	18	13	5
HL	1	1	0
LCH	8	8	0
CAEBV	3	2	1
Undiagnosed	1	0	1
Total	211	154	57

ALL: Acute lymphoblastic leukemia, AML: Acute myeloid leukemia, MDS: Myelodysplastic syndrome, CML: Chronic myeloid leukemia, TAM: Transient abnormal myelopoiesis, NHL: Non-Hodgkin lymphoma, HL: Hodgkin lymphoma, LCH: Langerhans cell histiocytosis, CAEBV: Chronic active EB viral infection

Table 2 Solid Tumors

	Total	Survivors	Nonsurvivors
Neuroblastoma	19	14	5
Nephroblastoma	7	7	0
Retinoblastoma	2	2	0
Germ cell tumor	10	10	0
Ewing sarcoma	5	3	2
Brain tumor	3	3	0
Rhabdomyosarcoma	1	0	1
Osteosarcoma	2	1	1
Melanoma	1	0	1
Medullary thyroid cancer	2	1	1
Nasopharyngeal cancer	2	2	0
Leiomyosarcoma	2	1	1
Adrenocortical carcinoma	1	1	0
Liposarcoma	1	0	1
Colon cancer	1	0	1
Desmoplastic tumor	1	0	1
Epithelioid hemangioendothelioma	1	1	0
Undiagnosed	3	3	0
Total	64	49	15

were 1.9% (95% confidence interval [CI] 0.3%-3.7%) at 10 years and 5.8% (95% CI 1.5%-10.2%) at 20 years from the time of primary malignancy diagnosis (**Fig. 1**). The clinical characteristics of the patients with secondary malignancies are summarized in **Table 3**. Until December 31, 2015, 11 secondary malignancies were diagnosed (4.0%): 4 cases of acute myeloid leukemia (AML), 4 of meningioma, and 1 each of germ cell tumor, malignant parotid gland tumor, and Ewing sarcoma (EWS). These 11 patients included 6 males and 5 females. All cases of AML developed within 5 years after the primary malignancy diagnosis, and 3 of the 4 patients died from disease progression during the study period.

The results of a chimeric fusion gene screening or a chromosome analysis (G-banding) test revealed that all AML cases were leukemia with translocation of chromosome 11q23. Translocation of t(9;11) (p22;q23) was found in 3 patients, all of whom died. Translocation of t(11;22) (q23;q13) was found in the remaining 1 patient, who has survived. These patients were all younger than 10 years. In contrast, all cases of meningioma were diagnosed more than 20 years after the primary malignancy diagnosis, and all patients had received CRT for their primary malignancy. Most cases were diagnosed by MRI and history of irradiation, but without biopsy. All 7 solid secondary malignancies were diagnosed more than 10 years after the primary malignancy diagnosis. Ten of the 11 secondary malignancies developed after primary hemato-

Table 3 Clinical characterristics of patients with secondary malignancies

No	Sex	Age at the diagnosis of primary cancer (year)	Primary cancer	treatment protocol	Etoposide (g/m^2)	Cyclophosphamide (g/m^2)	Doxorubicin (DXR) (mg/m^2)	Daunorubicin (DNR) (mg/m^2)	Pirarubicin (THP) (mg/m^2)	Irradiation (RT) (Gy)	site of RT	Relaps	Stem cell transplantation	Secondary cancer (SC)	Age at diagnosis of SC	Site of SC	Incubation time to SC (years)	outcome (age)
1	F	1	BCP-ALL	TCCSG L81-10 (HR) Arm A	0	10.5	0	300	0	24	Brain	N	N	Meningioma	30	Brain	29	Alive (34)
2	M	3	BCP-ALL	TCCSG L84-11 (SR) S1	0	0	0	0	0	18	Brain	N	N	Meningioma	31	Brain	28	Alive (33)
3	M	3	BCP-ALL	TCCSG L84-118 (SR) S1	0	0	0	0	0	18	Brain	N	N	Meningioma	28	Brain	25	Alive (32)
1	M	1	NHL (T-LBL)	TCCSG T8801	5.6	0	0	0	0	18	Brain	N	N	AML	6	Bone marrow	5	Alive (32)
5	M	2	BCP-ALL	TCCSG L84-11 (HR) H1	0	6.8	0	180	0	24	Brain	N	N	Meningioma	22	Brain	20	Alive (33)
6	F	4	BCP-ALL	TCCSG L84-11 (SR) S2	0	0	0	0	0	18	Brain	N	N	Paroid gland tumor	24	Lt parotid	20	Alive (33)
7	M	1	BCP-ALL	TCCSG L84-11 (HR) H2	0.825	1	240	60	0	28	Brain	Y	N	AML	6	Bone marrow	5	Dead (7)
8	F	3	T-ALL	TCCSG L95-14 (HEX)	0	4	200	100	220	18	Brain	N	N	Germ cell tumor	18	Uterus	15	Alive (21)
9	F	4	BCP-ALL	TCCSG L99-15 (HR)	0	4	100	100	220	-		N	N	AML	6	Bone marrow	2	Dead (8)
10	F	5	BCP-ALL	TCCSG L99-15 (HR)	0	4	100	100	120	-		N	N	AML	7	Bone marrow	2	Dead (10)
11	M	9	Brain tumor (germ cell tumor)		0	0	0	0	0	50+24	Brain+ spinal	N	N	Ewing sarcoma	22 (relaps 28)	duodenum	13	Alive (30)

BCP-ALL: B cell precursor Acute lymphoblastic leukemia, NHL: Non-Hodgkin lymphoma, T-ALL: T cell Acute lymphoblastic leukemia, T-LBL: Precursor T-cell lymphoblastic lymphoma, AML: Acute myeloid leukemia

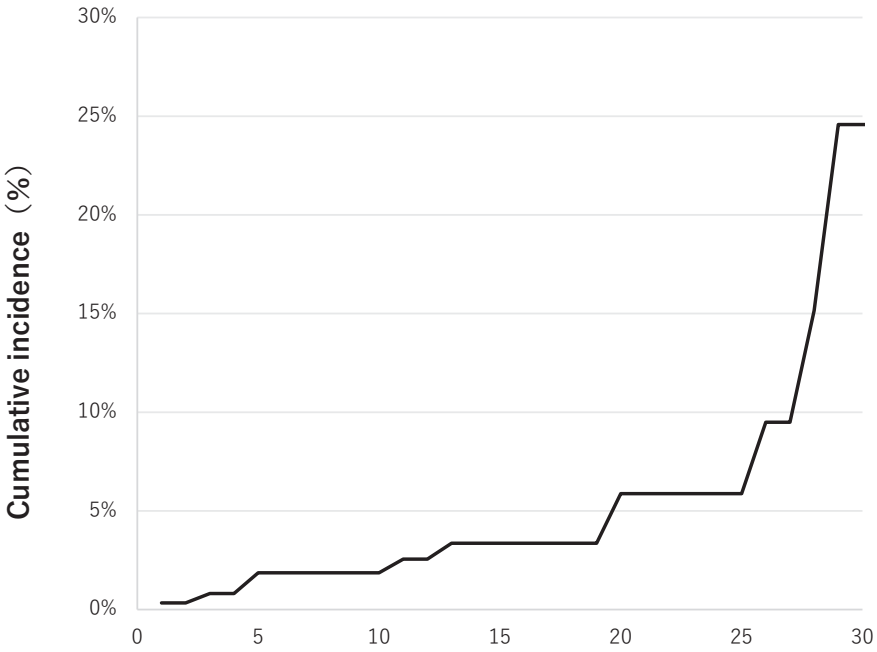

Fig. 1 Cumulative incidence of secondary malignancy in our hospital.

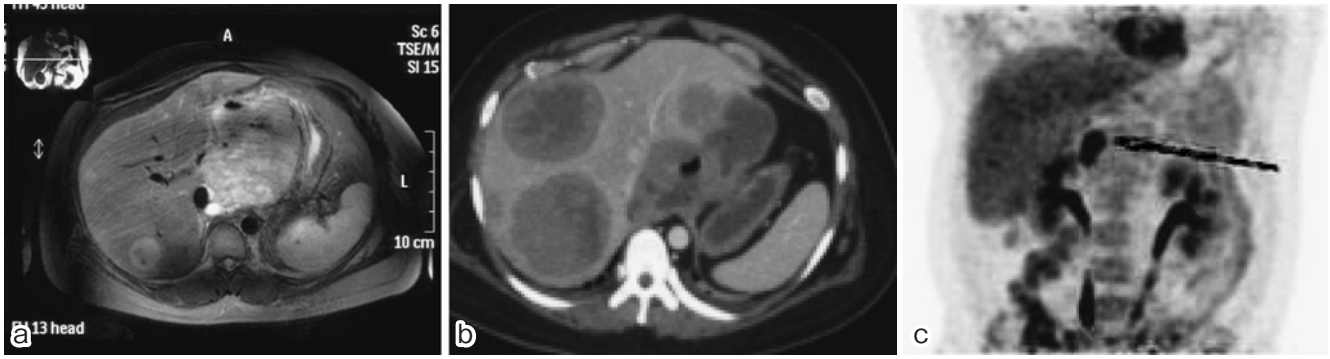

Fig. 2 Images of Ewing sarcoma (EWS). (a) Magnetic resonance image (T1WI) of secondary EWS shows a lesion (11 × 10 cm) with heterogeneous enhancement at a duodenal site. (b) Computed tomography identifies 5 to 6 lesions in the liver. (c) FDG-PET shows a duodenal tumor 5 years after treatment of EWS (arrow).

logical malignancies (ALL and NHL), 8 patients had received CRT and chemotherapy, and 2 had received chemotherapy only. Although all patients with meningioma received CRT (total dose, >18 Gy), 2 of the 3 patients with solid tumors had not received direct irradiation for secondary malignancies at rare sites (the duodenum in the case of EWS and uterus in the case of germ cell tumor). In the surviving patients, those with meningioma were followed-up or underwent surgical treatment, whereas those with AML received chemotherapy. Surgical treatment and chemotherapy were provided for other solid tumors. These patients were all able to perform activities of daily living, except for 1 patient with meningioma who lost their eyesight after surgery.

Here, we describe a case of duodenal EWS (Case 11) diagnosed 13 years after treatment for a primary pineal germ cell tumor and 5 years after treatment for EWS. The patient was diagnosed with a pineal germ cell tumor at age 9 years. He received 2 courses of cisplatin, vinblastine, and bleomycin, whole-brain radiotherapy (34 Gy), whole-spinal-cord radiotherapy (24 Gy), and pineal gland radiotherapy (16 Gy). Thirteen years later, at age 22, computed tomography performed for fever and upper abdominal pain revealed an intraperitoneal tumor (**Fig. 2a**) and multiple hepatic tumors (**Fig. 2b**). A biopsy of the tumors led to a diagnosis of liver metastasis of EWS. Surgical treatment was contraindicated because of the high risk involved. The patient instead received chemotherapy (ifosfamide, cyclophosphamide, etoposide, and doxorubicin) and proton therapy for the primary tu-

mor (40 Gy/20 fractions) and liver metastases (39.6 Gy/6 fractions), after which the primary tumor shrank. However, at age 28 (5 years after conclusion of treatment), upper abdominal pain recurred, and an endoscopic examination and a fluorodeoxyglucose positron emission tomography (FDG-PET) scan revealed a duodenal lesion (**Fig. 2c**). The biopsy results revealed recurrence of EWS. Duodenal EWS is quite rare, and the tumor site was not directly irradiated. After receiving chemotherapy and undergoing pancreaticoduodenectomy to excise the tumor completely, the patient is currently alive and free of disease.

Discussion

This study evaluated long-term clinical outcomes of 275 childhood cancer survivors treated at our institution. Almost 75% of the cases involved hematological malignancies. However, this number might be higher than that in other hospitals because our hospital has no pediatric surgeons, who are important in resection and treatment of solid tumors.

In this study, all cases of secondary AML developed within 5 years after the primary malignancy diagnosis, and 3 of the 4 patients died during the course of the study. The present median interval from treatment of primary malignancy to diagnosis of secondary malignancy, as well as the poor outcomes for secondary hematological malignancies, are consistent with previous findings[3,14]. Alkylating agents and topoisomerase inhibitors increase the risk of AML and myelodysplastic syndrome (MDS) in a dose- and schedule-dependent manner[15]. While the most common cytogenetic abnormalities in MDS/AML associated with alkylating agents are loss or deletion of chromosomes 5 and 7, those in topoisomerase inhibitor-associated leukemia include the mixed lineage leukemia locus (MLL) breakpoint at 11q23[16]. All AML patients in our study had MLL rearrangements, suggesting topoisomerase inhibitor involvement. Three of these patients did not have loss or deletion of chromosome 5 or 7, and chromosomal analysis (G-banding) data were missing for the remaining patient.

Outcomes for secondary hematological malignancies are poor; thus, identifying the factors associated with onset and progression is essential. On the basis of the Childhood Cancer Survival Study (CCSS), Robinson et al. reported that the 20-year cumulative risk of secondary malignancies among childhood cancer survivors followed for more than 5 years was about 3.2% and varies in relation to diagnostic subgroup: Hodgkin lymphoma (7.6%), soft tissue sarcoma (4.0%), bone sarcoma (3.3%), leukemia (2.2%), central nervous system malignancy (2.1%), neuroblastoma (1.9%), NHL (1.9%), or kidney tumor (1.6%). This incidence rate is approximately 10-fold that of the general population[17]. In the present study, 11 patients had secondary malignancies, and outcomes were generally favorable. After excluding cases involving treatment-related AML/MDS, 7 patients survived. However, this group included 4 patients with meningioma, which does not have a poor prognosis. Studies of secondary malignancies in Japan have reported that, among secondary tumors, the prognoses for meningioma, thyroid cancer, and adult cancers are better than the poor prognoses for hematologic malignancies[8].

Ishida et al. reported that the cumulative incidence of secondary malignancies was 1.1% at 10 years and 2.6% at 20 years after treatment of a primary malignancy[8]. The frequency and type of secondary malignancies varied in relation to initial diagnosis, treatment administered, and genetic predisposition. Therefore, during follow-up of survivors of pediatric malignancies, the properties and cumulative doses of chemotherapeutic drugs administered, total dose of irradiation received, and the area of treatment must be carefully noted. The interval from treatment of primary tumor to diagnosis of secondary malignancy differed in relation to the type of malignancy and was shortest for hematological malignancies (median 3.5 years), followed by meningiomas (median 26.5 years) and other solid carcinomas (median 13 years in this study), which is consistent with previous findings[8].

The cumulative incidence of secondary malignancies at our hospital in the past 20 years was 5.8%, which is higher than in previous reports[8,17]. This could be due to the longer outpatient follow-up at our hospital. Although a major limitation of our study is the very small sample size, our center has attempted to extend the follow-up of pediatric malignancy survivors, to collect more-detailed information on their long-term health status. An additional limitation of our study was that we did not perform a detailed analysis comparing primary tumor treatments for patients who did and did not develop secondary malignancies.

Radiotherapy is a major cause of secondary malignancy. Ishida et al. found that patients receiving CRT had a 6-fold higher risk of secondary malignancies, as compared with those not receiving CRT[7]. Meningioma is the most common secondary central nervous system (CNS) neoplasm and is strongly associated with radiation, as well as intrathecal methotrexate dose[18,19]. Even low-dose

radiation increases the risk of developing meningioma. In our study, meningioma was diagnosed more than 20 years after completion of treatment for primary malignancy, which was ALL in all cases. All patients received CRT (possibly >18 Gy), suggesting that secondary malignancies may be a long-term effect of radiation exposure. Patients who received brain RT for treatment of a primary malignancy were examined by brain MRI once every 2 to 3 years in our hospital[20]. We have continued clinical follow-up of these patients to promptly recognize often subtle neurological symptoms and avoid delayed diagnosis of large lesions.

In a study of 15 facilities in Japan, Ishida et al. reported that only 4 of 128 patients with a secondary malignancy were diagnosed with EWS[8]. Applebaum et al. reported that only 12.1% of patients with secondary EWS received radiation to the site of the tumor during treatment of primary malignancy. Five-year overall survival was worse for patients with secondary EWS than for those with primary EWS (34.3% vs. 52.2%; P=0.002)[21]. One patient in our study developed secondary EWS in the duodenum, which had metastasized to the liver and formed multiple hepatic tumors. The intestine is a rare site for EWS, and the site of secondary malignancy was not directly irradiated. Instead, the patient received spinal radiation. Low-dose irradiation of the gastrointestinal tract may have triggered onset of secondary EWS.

Another patient in our study (Case 8) was diagnosed with a secondary uterine germ cell tumor 15 years after being treated for ALL. Although radiotherapy for ALL included CRT (18 Gy), the uterus was not irradiated, and radiotherapy is therefore unlikely to be the cause of this secondary malignancy. Uterine germ cell tumor is rare, considering the age of the patient (18 years), and is therefore likely to be related to the chemotherapy administered for the primary ALL. It appeared to be an effect of the drugs administered (cyclophosphamide [4.6 g/m^2] and anthracycline [doxorubicin-equivalent dose, 275 mg/m^2]). Moreover, no study has reported uterine germ cell tumor after treatment of ALL. Further examination of such cases is important for clarifying the cause of such tumors.

Use of RT has decreased recently, especially in CNS prophylactic therapy for ALL patients, which is likely to reduce the incidence of secondary brain tumors in the future. However, close attention should be paid to therapy-related solid tumors such as those seen in our study. Efforts to identify the mechanisms underlying these secondary malignancies should continue, to improve the chance of a long and healthy life.

Conclusions

Onset of secondary hematological malignancies plateaus at 15 years post-treatment, while the incidence of secondary solid tumors was reported to increase exponentially after 10 years. In our hospital, the cumulative incidence of secondary malignancies is likely to increase during the next 10-20 years. The present results indicate that the type of second malignancy depends on the interval since the end of treatment for primary malignancy. Therefore, long-term follow-up is necessary for early detection of secondary malignancies.

Conflict of Interest: The authors declare that they have no conflicts of interest.

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(Received, September 4, 2018)
(Accepted, February 12, 2019)
(J-STAGE Advance Publication, April 26, 2019)