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ORIGINAL ARTICLE – ENDOCRINE TUMORS

Distinct Clinical Manifestations of Thyroid Cancer After Hematopoietic Stem Cell Transplantation

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ABSTRACT

Background. The incidence of a secondary solid malignancy after hematopoietic cell transplantation (HCT) is increasing in long-term survivors.

Objective. The aim of this study was to compare the clinicopathological characteristics of HCT recipients with secondary thyroid cancer (STC), with those of non-HCT thyroid cancer patients.

Methods. We retrospectively investigated 5184 patients who received HCT between 1983 and 2016. Of these, 18 patients developed STC and underwent thyroidectomy due to differentiated thyroid cancer. We compared the clinicopathological characteristics of post-HCT thyroid cancer patients (post-HCT group) with those of a primary differentiated thyroid carcinoma cohort (cohort group) from Seoul St. Mary's Hospital.

Results. The mean ages at HCT and thyroidectomy after HCT were 22.0 and 31.8 years, respectively, and the median time interval between HCT and thyroidectomy was 5 years (range 1–16). Compared with the cohort group, the post-HCT group was younger at cancer onset and frequently had a palpable mass at initial diagnosis. The post-HCT group had more aggressive features, including larger tumor size, frequent extrathyroidal extension, lymphatic invasion, perineural invasion, and frequent lateral neck node metastasis and distant metastasis, relative to the cohort group; however, most patients (83.2%) in the post-HCT group were stage I or II. Additionally, *BRAF* V600E mutation was less frequent in the post-HCT group.

Conclusions. We found that STC after HCT showed younger presentation and more aggressive clinical presentation. Therefore, a policy of regular screening, including neck ultrasound examination, may promote early detection and treatment in HCT recipients.

Hematopoietic cell transplantation (HCT) has become an effective treatment for a variety of malignant and non-malignant diseases.[1–3] Higher post-HCT survival is attributed to improved histocompatibility matching, improved prophylaxis and treatment of graft-versus-host disease (GVHD), reduced toxicity of conditioning regimens, and improved management of post-transplant infections.[2,4] However, many studies show that long-term HCT survivors later experience significant effects, particularly secondary malignancy.[1,3–14] The incidence of secondary solid malignancies after HCT continues to rise and has not plateaued after a 20-year follow-up.[13] Secondary thyroid cancer (STC) is the leading solid malignancy that occurs after HCT. The risk factors for this malignancy include radiation during conditioning therapy, female sex, a transplantation age younger than 20 years,

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and the presence of chronic GVHD.[4,5,7–13,15] However, few studies are available regarding the prognosis of STC after HCT.

The aim of this study was to assess the clinicopathologic characteristics of patients with STC who received HCT and to compare their clinicopathological characteristics with those of primary differentiated thyroid carcinoma.

PATIENTS AND METHODS

We investigated 5880 patients who received HCT from 1983 to 2016 at Yeouido, and Seoul St. Mary's Hospital, The Catholic University of Korea, College of Medicine. Of these, 696 patients were excluded from the analysis because they were lost to follow-up. We observed that 1140 patients received HCT at < 19 years of age, of whom 482 patients received HCT at < 10 years of age. In the HCT cohort, 35 patients were diagnosed with differentiated thyroid cancer. Thirteen patients showed thyroid cancer before HCT. Of these, 12 patients underwent thyroidectomy prior to HCT and one patient underwent active surveillance. Four patients were diagnosed with thyroid cancer within 1 year after the first HCT, and 18 patients developed thyroid cancer more than 1 year after HCT. We compared the clinicopathological characteristics of these 18 patients with those of 723 patients in a primary differentiated thyroid carcinoma cohort at Seoul St. Mary's Hospital from August 2012 to July 2013.

The management of thyroid cancer was determined according to guidelines issued by the American Thyroid Association (ATA).[16,17] Total thyroidectomy was performed in patients with a history of head or neck radiotherapy, bilateral lesions, or thyroid capsular invasion during surgery. In our institution, prophylactic ipsilateral central compartment neck dissection was performed in all thyroid cancer patients. In patients with a clinically involved lymph node, therapeutic lymph node dissection was performed. Postoperatively, all patients took levothyroxine for thyroid-stimulating hormone suppression. Radioactive iodine therapy was administered 6–8 weeks after total thyroidectomy, based on risk factors according to the ATA guidelines.[16,17] Observation of serum thyroglobulin levels and neck ultrasonography were regularly performed during follow-up.

We retrospectively reviewed the medical records for patient demographics associated with HCT, characteristics, and management of thyroid cancer. B-Raf proto-oncogene serine/threonine kinase (*BRAF*) V600E mutation data were collected from available surgical specimens. We used Sanger sequencing to analyze *BRAF* V600E mutations.[18] The tumor, node, and metastasis (TNM) stage of thyroid cancer was classified according to the 7th edition of the American Joint Committee on Cancer and the International Union Against Cancer.[19]

The cumulative incidence of STC following HCT was estimated considering competing risks, including death and follow-up loss. All statistical analyses were conducted using R 3.1.1 (The R Foundation for Statistical Computing, Vienna, Austria) and SPSS 18 statistical software (SPSS Inc., Chicago, IL, USA). We considered p values < 0.05 to be statistically significant. The study protocol was approved by the Institutional Review Board of the Catholic Medical Center (KC15RISI0312, KC16SISE0381).

RESULTS

Clinical Characteristics of Bone Marrow Transplantation

The 5-, 10-, and 15-year cumulative incidence of STC after HCT was 0.2% (95% confidence interval [CI] 0.1–0.4), 0.4% (95% CI 0.2–0.7), and 0.6% (95% CI 0.3–1.0), respectively (Fig. 1). Patient demographics associated with HCT are described in Table 1. The median age at transplant was 22.0 years (range 3–54 years) and 9 patients (50%) received HCT in childhood or adolescence. In the 18 patients who developed thyroid cancer more than 1 year after HCT, the underlying primary disease was aplastic anemia (seven patients, 38.9%), acute lymphoblastic leukemia (four patients, 22.2%), acute myelogenous leukemia (three patients, 16.7%), diffuse large B cell lymphoma (one patient, 5.6%), myelodysplastic syndrome (one patient, 5.6%), Burkitt lymphoma (one patient, 5.6%), or multiple myeloma (one patient, 5.6%). The pretransplant conditioning was different for each disease. Briefly, 10 patients received total body irradiation (TBI) for conditioning, and TBI doses varied from 800 to 1320 cGy. One patient received an additional 1800 cGy of radiation therapy to the brain for central

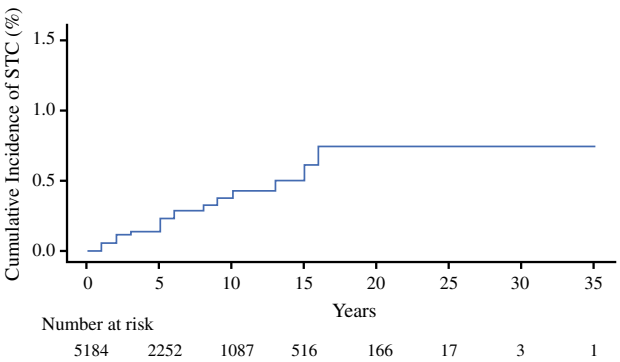

FIG. 1 Cumulative incidence of secondary thyroid cancer after hematopoietic cell transplantation. *STC* secondary thyroid cancer

TABLE 1 Clinical characteristics of hematopoietic cell transplantation patients

Nos.	Sex	Age at HCT (years)	Disease	Conditioning regimen/intensity			cGVHD	Age at thyroidectomy (years)	Interval (years)	Presentation	Main histology	Tumor size (cm)	TNM stage, AJCC 7th edition	*BRAF* mutation
				Radiation (TBI, cGy)	Chemotherapy	Intensity								
1	F	16	AML	850	ARA-C/MPL	MAC	–	21	5	Neck mass	Papillary	2	T3N1aM0, I	NA
2	M	36	DLBL	1200	RTX/ARA-C/MPL	MAC	–	37	1	Incidentaloma	Papillary	0.8	T3N1aM0, I	NA
3	F	17	AA	800	CY	RIC	–	22	5	Incidentaloma	Papillary	0.6	T1N1aM0, I	Yes
4	F	18	AA	–	CY/ALG	RIC	–	26	8	Neck mass	Papillary	1.8	T3N1aM0, I	NA
5	F	3	ALL	850[a]	VCR/ARA-C/IDA	MAC	–	16	13	Neck mass	Follicular Papillary	2.1	T2N0M0, I	No
6	F	17	ALL	1320	CY	MAC	Yes	27	10	Incidentaloma	Papillary	1.1	T3N0M0, I	Yes
7	F	30	AML	–	BU/THIO/MPL	MAC	–	46	16	Incidentaloma	Papillary	0.7	T3N0M0, III	No
8	F	22	MDS	1200	CY	MAC	–	31	9	Neck mass	Papillary	1.5	T1N1bM0, I	No
9	F	30	AA	800	CY	RIC	Yes	31	1	Neck mass	Papillary	1.5	T3N1aM0, I	No
10	F	24	AA	800	CY	RIC	–	27	3	Neck mass	Papillary	1.3	T1N1aM0, I	No
11	F	12	BL	–	BEAM	MAC	–	14	2	Incidentaloma	Follicular	0.9	T1NxM0, I	No
12	F	18	AML	1320	CY	MAC	–	24	6	Neck mass	Papillary	4.8	T4N1bM1, II	No
13	F	54	MM	–	MPL	MAC	–	59	5	Incidentaloma	Papillary	0.7	T3N1aM0, III	Yes
14	F	32	AA	–	CY/ATG	RIC	–	34	2	Incidentaloma	Papillary	1.5	T3N1aM0, I	Yes
15	F	44	ALL	–	FLU/MPL	RIC	Yes	50	6	Incidentaloma	Papillary	1.2	T3NxM0, unknown	Yes
16	M	42	AA	–	CY/ATG	RIC	–	43	1	Neck mass	Papillary	3.7	T3N1bM0, I	No
17	F	17	AA	–	FLU/CY/ATG	RIC	–	19	2	Incidentaloma	Papillary	1.2	T3N1bM0, I	No
18	M	11	ALL	1200	Cy	MAC	–	26	15	Incidentaloma	Papillary	1.7	T3N1bM0, I	No

HCT hematopoietic cell transplantation, *TBI* total body irradiation, *cGVHD* chronic graft-versus-host disease, *F* female, *M* male, *AML* acute myelogenous leukemia, *DLBL* diffuse large B-cell lymphoma, *AA* aplastic anemia, *ALL* acute lymphoblastic leukemia, *MDS* myelodysplastic syndrome, *MM* multiple myeloma, *ARA-C* cytarabine, *MPL* mephalan, *CY* cyclophosphamide, *ALG* antilymphocyte globulin, *VCR* vincristine, *IDA* idarubicin, *BU* busulfan, *THIO* thiotepa, *BEAM* BCNU/etoposide/cytarabine/melphalan, *FLU* fludarabine, *MAC* myeloablative conditioning, *RIC* reduced intensity conditioning, *BRAF* B-Raf proto-oncogene serine/threonine kinase, *RTX* rituximab, *BL* Burkitt lymphoma, *CNS* central nervous system, *ATG* antithymocyte globulin, *AJCC* American Joint Committee on Cancer, *NA* not applicable

[a]Additional CNS prophylaxis 1800 cGy

nervous system prophylaxis. Eleven patients received conditioning regimens that included cyclophosphamide, and three patients developed chronic GVHD.

Clinicopathologic Characteristics of Secondary Thyroid Cancer After Hematopoietic Cell Transplantation (HCT)

Mean age at thyroid cancer diagnosis after HCT was 31.8 years (range 14–59). Two patients underwent thyroidectomy during adolescence. The median time from HCT to thyroidectomy was 5 years (range 1–16). Eight patients (44.4%) had palpable neck masses at the initial presentation of thyroid cancer.

Sixteen patients (88.8%) had papillary thyroid carcinoma, one (0.6%) had follicular carcinoma, and one (0.6%) had both papillary and follicular carcinoma. The mean tumor size was 1.64 cm (range 0.6–4.8). Fourteen patients (77.8%) were classified as stage I, one was classified as stage II, and three were classified as stage III. We detected the *BRAF* V600E mutation in 5 of the 15 cases that we tested for the mutation.

Case 12 showed tracheal wall invasion and simultaneous lung metastasis at initial diagnosis. The patient received 200 mci of radioactive iodine therapy; however, multiple lung nodules were radioactive iodine non-avid. Tyrosine kinase inhibitor therapy was considered for the progressive lung metastasis. The patient also showed regional recurrence on the tracheal wall and operative bed 2 years after operation, and underwent partial tracheal wall resection and excision of metastatic lesions. Cases 4 and 9 had recurrence within 1 year of postoperative follow-up, underwent lateral neck node dissection, and received additional radioactive iodine therapy (data not shown).

Comparison of Thyroid Cancer After HCT Versus the Thyroid Cancer Cohort

We compared the clinicopathologic characteristics of a group of patients with STC after HCT (post-HCT) and a group with primary differentiated thyroid cancer (cohort group) (Table 2). The mean age of the post-HCT group was significantly younger than the cohort group (31.8 years vs. 45.5 years, $p < 0.001$). At initial presentation, a palpable mass was more common in the post-HCT group (38.8% vs. 2.4%, $p < 0.001$). We found that follicular thyroid carcinoma occurred more frequently in the post-HCT group.

In terms of the extent of surgery, 15 patients underwent total thyroidectomy and 5 patients underwent combined lateral neck node dissection, based on nodal metastasis at initial diagnosis in the post-HCT group. Therefore, total thyroidectomy and lateral neck node dissection were more frequently performed in the post-HCT group than the cohort group (83.4% vs. 64.3%, and 27.7% vs. 12.0%, respectively). Radioactive iodine therapy was more frequently used in the post-HCT group (42.0% vs. 72.2%, $p = 0.014$).

Mean tumor size was larger in the post-HCT group than the cohort group (1.64 cm vs. 0.92 cm, $p = 0.023$). Additionally, aggressive clinical features, including extrathyroidal extension, lymphatic invasion, and perineural invasion, were more frequent in the post-HCT group than the cohort group. However, the number of tumors, multiplicity, vascular invasion, and number of metastatic nodes were not significantly different between the two groups. Tumor, node, and metastasis staging was more advanced in the post-HCT group. However, 83.2% of the post-HCT group was classified as stage I and II because of the young ages of the patients, despite their aggressive clinical features. Additionally, the *BRAF* V600E mutation was less frequent in the post-HCT group than the cohort group (33.3% vs. 84.6%, $p < 0.001$).

We performed case–control matching to clarify the characteristics of STC after HCT. First, controls were selected by stratified, random sampling, with a ratio of six controls to one case, who were matched for tumor size (Electronic Supplementary Table 1). Second, we also performed case–control matching for age. Controls were selected by stratified, random sampling, with a ratio of five controls to one case, who were matched for age at the time of thyroid cancer diagnosis. Age was classified into 5-year intervals. Two cases (Cases 5 and 17) were excluded because there were no matched controls (Electronic Supplementary Table 2). After case–control matching for tumor size or age at the time of thyroid cancer diagnosis, STC after HCT showed more aggressive features, including frequent lymphatic invasion, perineural invasion, and advanced TNM stages, than a primary thyroid cancer cohort.

DISCUSSION

Our study provides the first description of the clinicopathological differences between a group of patients with STC after HCT and a primary thyroid cancer cohort. In the present study, STC after HCT had a younger age at onset and was frequently a clinical disease at initial diagnosis, even though the majority of HCT patients had regular medical checkups for their primary diseases. Furthermore, thyroid cancer after HCT was more aggressive, as evidenced by larger tumor size, frequent extrathyroidal extension, lymphatic invasion, and perineural invasion. We also observed that metastasis, including that of the lateral neck node and lung, was more frequent in the post-HCT

TABLE 2 Comparison of thyroid cancer after hematopoietic cell transplantation versus the thyroid cancer cohort

	Thyroid cancer cohort (N = 723)	Thyroid cancer after HCT (N = 18)	p value
Age, years	45.5 ± 12.1	31.8 ± 12.5	< 0.001
Sex ratio (M:F)	160:563 (1:3.52)	3:15 (1:5)	0.397
Presentation [n (%)]			< 0.001
Palpable mass	17 (2.4)	8 (44.4)	
Incidentaloma	706 (97.6)	11 (55.6)	
Type of cancer [n (%)]			0.002
Papillary	722 (99.9)	16 (88.8)	
Follicular	0 (0)	1 (5.6)	
Papillary + follicular	1 (0.1)	1 (5.6)	
Operation type [n (%)]			0.194
Less than TT	258 (35.7)	3 (16.6)	
TT	465 (64.3)	15 (83.4)	
Neck node dissection [n (%)]			0.001
No CCND	10 (1.4)	2 (11.1)	
CCND	626 (86.6)	11 (61.1)	
CCND + mRND	87 (12.0)	5 (27.7)	
Radioactive iodine therapy [n (%)]			0.014
No	419 (58.0)	5 (27.8)	
Yes	304 (42.0)	13 (72.2)	
Tumor size, cm	0.92 ± 0.71	1.64 ± 1.14	0.023
Extrathyroidal extension [n (%)]			0.041
No	418 (57.8)	5 (27.7)	
Yes	305 (42.2)	13 (72.3)	
Number of tumors	1.7 ± 1.7	1.9 ± 1.8	0.754
Multiplicity [n (%)]			0.447
Single	438 (60.6)	9 (50.0)	
Unilateral	113 (15.6)	2 (11.1)	
Bilateral	172 (23.8)	7 (38.9)	
Vascular invasion [n (%)]			0.314
No	707 (97.8)	17 (94.5)	
Yes	16 (2.2)	1 (5.5)	
Lymphatic invasion [n (%)]			0.031
No	505 (69.8)	7 (38.8)	
Yes	218 (30.2)	11 (61.2)	
Perineural invasion [n (%)]			0.014
No	716 (99.0)	16 (88.8)	
Yes	7 (1.0)	2 (11.2)	
Number of metastatic nodes	2.5 ± 4.5	5.7 ± 10.4	0.237
T stage [n (%)]			< 0.001
1	400 (55.3)	4 (22.2)	
2	13 (1.8)	1 (5.6)	
3	309 (42.7)	12 (66.7)	
4	1 (0.1)	1 (5.6)	
N stage [n (%)]			0.007
Unknown	10 (1.4)	2 (11.1)	
0	351 (48.5)	3 (16.6)	
1a	279 (38.6)	8 (44.4)	
1b	83 (11.5)	5 (27.7)	
Distant metastasis	1 (0.1)	1 (5.6)	0.048
Stage [n (%)]			0.032
I	479 (66.3)	14 (77.8)	
II	3 (0.4)	1 (5.5)	
III	203 (28.1)	2 (11.1)	
IV	30 (4.1)	0 (0)	
Unknown	8 (1.1)	1 (5.5)	
BRAF mutation[a] [n (%)]			< 0.001
No	111 (15.4)	10 (66.7)	
Yes	612 (84.6)	5 (33.3)	

HCT hematopoietic cell transplantation, *TT* total thyroidectomy, *CCND* central compartment neck dissection, *mRND* modified radical neck dissection, *BRAF* B-Raf proto-oncogene serine/threonine kinase, *M* male, *F* female

[a]*BRAF* mutation was analyzed in only 15 cases of thyroid cancer after HCT

group than in the primary thyroid cancer cohort. However, stage I and II were more frequent in the post-HCT group due to the young ages of the patients.

In terms of recurrences, 3 of the 18 STC patients experienced regional recurrences within 2 years, and 1 patient showed progressive lung metastasis, despite the use of radioactive iodine therapy. This study lacked survival data for patients with STC after HCT due to its relatively short follow-up period. Several studies show that survival rates for post-HCT patients with STC are similar to those in the general population.[9,14] The similarity in these survival rates may be partially explained by the younger ages of the post-HCT group compared with the cohort group. There is also a risk of underestimation due to mortality, which is a rare event in thyroid cancer. Additionally, previous studies had relatively short follow-up periods and small

populations.[9,13,14] Therefore, a future large cohort study with long-term follow-up is needed to assess the prognosis of STC after HTC.

Inamoto et al.[12] stated that the increased incidence of STC was sixfold higher in an HCT cohort than in the general population of a similar age and sex. In this study, we studied 18 patients who developed thyroid cancer, out of 5184 patients who received HCT. We found that the incidence of STC after HCT was 347 per 100,000 individuals. This incidence was much higher than the incidence of thyroid cancer in the general population, which was 64.1 per 100,000 individuals, according to data from the Korea Cancer Registry from 2008 to 2010.[20,21] Furthermore, the actual incidence of STC after HCT for our institution might have been underestimated because of a loss of follow-up for long-term HCT survivors.

Known risk factors associated with STC after HCT include young age at transplantation, a conditioning regimen that consists of TBI with combined chemotherapy, and chronic GVHD.[4,5,7–13,15] Cohen et al.[9] reported a significantly higher incidence of STC only in patients who received HCT at < 20 years of age. Socié et al.[7] reported that the risk of developing thyroid cancer increased in children after receiving an allogenic marrow transplantation, compared with an age- and sex-matched general child population. Additionally, ionized radiation exposure of the head and neck area, and a younger age at the time of TBI for pretransplantation conditioning, were especially associated with STC risk in HCT survivors.[7,10,17,22,23] The risk of secondary solid cancer increased 55-fold for patients who received HCT with conditioning TBI at < 10 years of age, sixfold for those aged 10–19 years, and fourfold for those aged 20–29 years.[10] In this study, we found that the incidence of STC was higher in patients who underwent HCT in childhood and adolescence than those who underwent HCT in adulthood (9/1140 vs. 9/4044). Ten patients (55.6%) received TBI as conditioning prior to HCT, six (60.0%) of whom received TBI at < 19 years of age. This suggests that receiving HCT during childhood and adolescence, particularly when combined with TBI pretransplant conditioning, results in a higher risk of STC; therefore, watchful monitoring of this cohort is recommended.

Cohen et al.[9] indicated that HCT recipients might have aggressive malignant changes in the thyroid gland. HCT recipients had a relatively short interval from the time of initial treatment to the development of STC, compared with patients who were exposed to other types of irradiation.[9,24] A higher incidence of follicular carcinoma in the post-HCT group was consistent with previous reports, whereas pediatric follicular thyroid cancer was rare in the general cohort.[9,25] Additionally, a lower frequency of *BRAF* V600E mutations in post-HCT patients suggests a different carcinogenic mechanism for STC in HCT recipients.[18]

The numbers of long-term post-HCT survivors have been increasing and one of the leading causes of late mortality is secondary malignancy.[13,14] Therefore, early detection of a secondary malignancy can reduce the morbidity and mortality that is associated with secondary cancer.[15] Regarding thyroid cancer treatment, Clement et al. reported that identification of thyroid cancer at an early stage was beneficial for both children and adults.[26] In this study, the major treatment approach for STC patients was total thyroidectomy combined with radioactive iodine ablation, due to its aggressive presentation. Early diagnosis might not only reduce the extent of surgery required but might also reduce the use of radioactive iodine, which would lower the risk of developing a third malignancy after radioactive iodine therapy for HCT recipients.[26–28] Furthermore, early identification could reduce recurrent disease and improve quality of life after treatment.[26]

Curtis et al.[5] reported that STC risk increases over time and is highest 5 or more years after HCT. The median interval between HCT and STC diagnosis is described by Cohen et al. and Danner-Koptik et al.[9,11] as 8.5 and 6.8 years, respectively. In this study, the median time from HCT to thyroidectomy was 5 years. According to guidelines for the general population, Inamoto et al.[12] recommend a yearly physical examination after HCT to screen for thyroid cancer. However, in the present study, 10 patients (55.6%) were asymptomatic. Similarly, Cohen et al.[8] reported that half of the patients with STC were asymptomatic Therefore, regular neck ultrasounds should be considered, especially in patients who received HCT at a young age.[8,9] Additionally, aggressive pursuit of fine needle aspiration on suspicious nodules should be considered in this group. An appropriate time to initiate screening for STC after HCT should be carefully established, with consideration for its potential clinical utility and cost effectiveness.

This study had several limitations. First, this was a retrospective design for a small number of patients in a single institution. Second, the present study could not show the long-term prognosis of STC after HCT. Therefore, a multicenter, prospective, large cohort study should be conducted in the future to establish an appropriate surveillance protocol of STC in HCT patients. Third, although we observed a relatively high incidence of non-irradiated patients with STC, we did not find a distinct relationship between STC and other risk factors, such as preconditioning chemotherapy and presence of chronic GVHD, due to incomplete medical records. Finally, our mutational analysis was limited in this study. To address this, a future study should investigate gene fusion with RET/PTC rearrangement, PAX8/PPARG and NTRK in patients with TBI conditioning or other genetic predispositions of HCT patients.

CONCLUSION

In this cohort study, we found that STC after HCT had different clinical manifestations than primary thyroid cancer, including younger presentation and more aggressive features. We recommend a policy of regular screening, including neck ultrasound examination, to promote early detection and earlier intervention of STC after receiving HCT, especially those who received HCT at a young age.

DISCLOSURES The authors declare that they have no conflict of interest.

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