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Clinical features of immune-related thyroid dysfunction and its association with outcomes in patients with advanced malignancies treated by PD-1 blockade

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Abstract. Programmed cell death protein-1 (PD-1) blockade therapy has improved outcomes in the treatment of advanced cancers. The therapy is well-tolerated, although it occasionally causes immune-related adverse events (irAEs). Thyroid dysfunction is one of the most common irAEs seen. Our aim was to clarify the clinical characteristics of thyroid dysfunction induced by PD-1 blockade and its association with the therapeutic effect of the treatment in advanced cancers. A total of 174 patients who received nivolumab or pembrolizumab for metastatic or unresectable advanced cancers were included in this retrospective study. The patients were divided into two groups: The thyroid dysfunction group and the euthyroid group. In the present study, the clinical characteristics, the association with anti-thyroid antibodies, as well as the progression-free survival (PFS) and overall survival (OS) were estimated. An adjusted Cox proportional hazard regression model was used to evaluate prognostic factors for OS and PFS. This study showed that 25 out of 150 patients (16.7%) developed immune-related thyroid dysfunction. Hypothyroidism occurred in the early stage of the clinical course (median: 12 weeks); subsequently, 9 of the 25 patients underwent a transient period of hyperthyroidism, all with mild symptoms. The presence of positive anti-thyroid antibodies at baseline was significantly higher in the thyroid dysfunction group (13/22) than in the euthyroid group (18/100, P=0.0002). Moreover, PFS (median: 66 vs. 27 weeks, hazard ratio (HR): 0.50, 95% CI: 0.26-0.89, P=0.02) and OS (median 156 vs. 59 weeks, HR: 0.34, 95% CI: 0.13-0.75, P=0.01) were significantly longer in the thyroid dysfunction group than in the euthyroid group. Multivariable analysis also revealed that thyroid dysfunction was an independent prognostic factor for OS (HR: 0.42, 95% CI: 0.16-0.97, P=0.04). These findings may enable the early recognition and appropriate management of thyroid dysfunction, and help in maximizing the therapeutic effect of PD-1 blockade.

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Abbreviations: ICI, immune checkpoint inhibitors; PD-1, programmed cell death protein 1; NSCLC, non-small cell lung cancer; MM, malignant melanoma; irAEs, immune-related adverse events; CTLA-4, cytotoxic T-lymphocyte associated protein 4; TSH, thyroid-stimulating hormone; FT4, free thyroxine; FT3, free triiodothyronine; TgAbs, anti-thyroglobulin antibodies; TPOAbs, anti-thyroid peroxidase antibodies; PFS, progression-free survival; OS, overall survival; HR, hazard ratio; CI, confidence interval; PS, performance status

Key words: PD-1, thyroid dysfunction, hypothyroidism, hyperthyroidism, irAEs, nivolumab, pembrolizumab

Introduction

Immune checkpoint inhibitors (ICIs), specifically those targeting the programmed cell death protein-1 (PD-1) pathway, have improved outcomes in the treatment of several advanced cancers such as non-small cell lung cancer (NSCLC), malignant melanoma (MM), renal cell carcinoma, urothelial cancer, head and neck cancer, gastric cancer, and Hodgkin's lymphoma (1-6). PD-1 is highly expressed on activated T and B cells and PD-1 ligands have been identified as programmed

death-ligand 1 (PD-L1) and PD-L2. PD-L1 and PD-L2 have been shown to down-regulate T cell activation upon binding to PD-1. The PD-1 blockade suppresses its negative signal and potentiates T cell responses, thereby activates tumor immunity (7). Based on this mechanism, PD-1 blockade therapy, which includes nivolumab and pembrolizumab, has evoked persistent antitumor responses and long term remissions in a subset of patients with a broad spectrum of cancers. Generally, this treatment is better tolerated than conventional chemotherapy. However, it occasionally causes inflammatory side effects, which are called immune-related adverse events (irAEs), likely owing to the enhanced autoimmunity (8,9). Various regions, such as the skin, lungs, liver, intestinal tract, thyroid, and other endocrine glands have been reported to be affected by this treatment. The mechanisms that result in irAEs are still under research. Some potential mechanisms include increasing T cell activity against antigens that are present in tumors and healthy tissue, increasing levels of preexisting autoantibodies, an increase in the level of inflammatory cytokines, and enhanced complement-mediated inflammation due to direct binding of an antibody against cytotoxic T-lymphocyte antigen 4 (CTLA-4) with CTLA-4 expressed on normal tissue (10).

In addition, the development of irAEs has been found to be associated with durable responses and better prognoses in MM and NSCLC (11-14). However, contradictory reports exist, and no consensus has been reached yet.

Thyroid dysfunction is one of the most frequent irAEs induced by PD-1 blockade. In one study, it was observed in 8.6% of patients with MM who were treated with nivolumab (15), and in another, it was reported in 21% of patients with NSCLC in a phase 1 clinical trial for pembrolizumab (16). Some studies indicated that thyroid disorders are likely to occur in patients with preexisting antithyroid antibodies with the implication that PD-1 blockade modulates humoral immunity, enhancing these antibodies (16,17).

The aim of the present study was to clarify the clinical characteristics of thyroid dysfunction mediated by PD-1 blockade, and its association with the therapeutic effect of the treatment in advanced cancers.

Patients and methods

Patients. We performed a retrospective review of electronic medical records of all 174 patients who received nivolumab or pembrolizumab for metastatic or unresectable advanced cancers from September 2014 to July 2018 at Kyoto Prefecture University of Medicine. Among these patients, 24 were excluded for the following reasons: 21 patients were administered a PD-1 blockade once, 1 patient required immune-modulating agents for the initiation of PD-1 blockade therapy, thyroid function estimation data was unavailable for 1, and 1 had cancer of an unknown primary origin. None of the patients had a history of pretreatment with other ICIs such as ipilimumab, which is an anti-cytotoxic T-lymphocyte associated protein 4 (CTLA-4) antibody. The treatment was administered until disease progression or unacceptable toxicity was noted.

Assessments. All enrolled patients received PD-1 blockade intravenously, according to a schedule of 3 mg/kg every 2 weeks for nivolumab, and 2 mg/kg every 3 weeks for pembrolizumab. Screening with thyroid function tests, including those for serum thyroid-stimulating hormone (TSH), free thyroxine (FT4), and free triiodothyronine (FT3), were conducted at baseline and during treatment. Additionally, a majority of the patients were tested for the presence of anti-thyroglobulin antibodies (TgAbs) and anti-thyroid peroxidase antibodies (TPOAbs) within one month before the induction of PD-1 blockade. Serum levels of FT3, FT4, TSH, TgAbs and TPOAbs were measured using electro chemiluminescence immunoassays. The normal ranges of FT3, FT4, TSH, TgAbs and TPOAbs were 2.30 to 4.00 pg/ml, 0.90 to 1.70 ng/dl, 0.500 to 5.000 μIU/ml, <28 and <16 IU/ml, respectively.

Based on the development of thyroid dysfunction, we divided the patients into two groups: The thyroid dysfunction group (patients with at least two consecutive abnormal TSH level measurements) and the euthyroid group (patients with normal TSH levels or with fewer than two abnormal TSH level measurements). Patients with hypothyroidism at baseline (hypothyroidism which was graded one or more according to CTCAE 4.0 criteria) were categorized into the thyroid dysfunction group, wherein the initiation of levothyroxine or a dose increase was required, and the others to the euthyroid group. Overt hypothyroidism was defined by elevated serum TSH and low FT4 levels, and subclinical hypothyroidism was defined by elevated TSH with normal FT4 levels. The severity of thyroid dysfunctions was graded according to CTCAE 4.0 criteria. The patients' characteristics such as gender, age, performance status (PS), type of tumor, prior therapy lines, and development of other irAEs were also retrieved from medical records. PS was based on the Eastern Cooperative Oncology Group (ECOG) scale (18). The detailed description of the scaling system is shown in Table S1. Prior therapy lines were defined by the number of chemotherapy regimens used before PD-1 treatment.

Furthermore, progression-free survival (PFS) and overall survival (OS) were also evaluated in the study. PFS was defined as the time from the start of treatment to the date of documented disease progression or death due to any cause, whereas OS was defined as the time from the start of treatment to death due to any cause. Those without progression or death were censored at the time of the last imaging assessment before the data-lock on July 31, 2018. The evaluation of clinical responses was based on the Response Evaluation Criteria in Solid Tumors (RECIST) and laboratory findings.

Statistical analysis. Mann-Whitney U tests were used to compare continuous variables between the thyroid dysfunction and euthyroid groups. The associations between the development of thyroid dysfunction, anti-thyroid antibodies, other (non-thyroid) irAEs, and clinical features in response to PD-1 blockade were examined using the Chi-square test (or Fisher's exact test). Kaplan-Meier cumulative-event curves and the log-rank test were used to compare OS and PFS between the two groups. Furthermore, Cox proportional hazard regression models were used to estimate hazard ratios (HRs) with 95% confidence intervals (CIs) for OS and PFS according to thyroid dysfunction, age, gender, PS, and line of treatment. All statistical tests were two sided and $P<0.05$ was

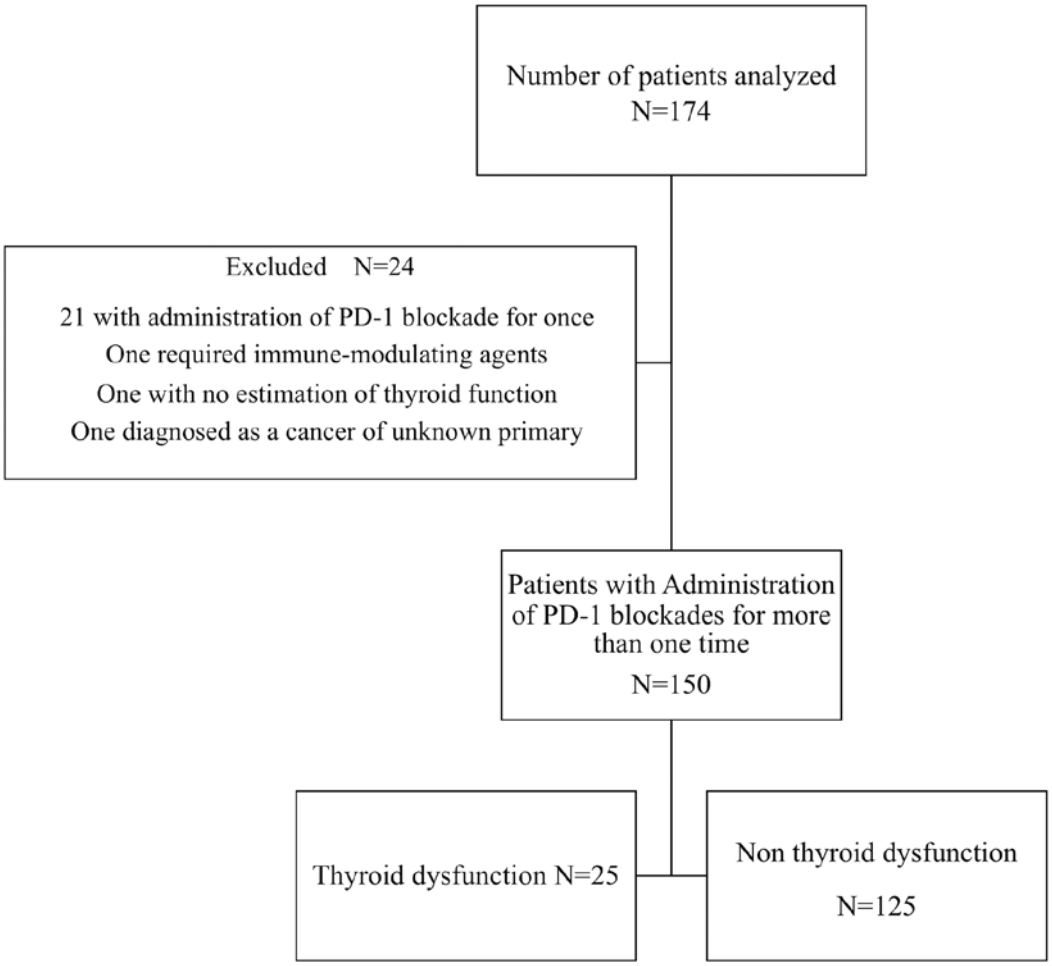

Figure 1. Schematic depicting the subjects treated with PD-1 blockade who were examined in this study. Patients were classified into two groups according to the development of thyroid dysfunction. PD-1, programmed cell death protein 1.

considered to indicate a statistically significant difference. All statistical analyses were performed using JMP® 13 (SAS Institute Inc., Cary, NC, USA).

Results

Baseline characteristics. The group of 150 patients in this study was composed of 59 patients with non-small cell lung carcinoma (NSCLC), 26 with malignant melanoma (MM), 24 with renal cell carcinoma, 19 with head and neck cancer, 16 with gastric cancer, 5 with urothelial cancer, and 1 with Hodgkin's lymphoma. Of these, 117 received nivolumab and 33 received pembrolizumab. At the time of analysis, the median follow-up duration was 29 weeks (range 4-203 weeks). The median number of administrations for PD-1 blockade was 8 (range 2-68). The baseline clinical characteristics of the patients in the thyroid dysfunction and euthyroid groups are shown in Table I. There were no significant differences in age, gender, performance status (PS), tumor type, prior therapy lines, thyroid dysfunction at baseline, and type of PD-1 blockade administered between the two groups. On the other hand, among the 122 patients whose TPOAbs and/or TgAbs were examined, 13 of 22 (59%) in the thyroid dysfunction group tested positive for TPOAbs and/or TgAbs at baseline, whereas in the euthyroid group, only 18 of 100 patients did; this difference was statistically significant. Moreover, two patients initially tested negative for thyroid antibodies, but eventually showed the presence of TPOAbs at the onset of hypothyroidism.

Clinical features of thyroid dysfunction induced by PD-1 blockade. Thyroid dysfunction was observed in 25 of 150 patients (16.7%) (Fig. 1), which is a similar ratio to that reported previously (19). Twenty-one out of 115 patients developed thyroid dysfunction newly and 4 out of 35 patients showed worsening hypothyroidism. Subsequently, among the 21 patients who newly developed thyroid dysfunction, 9 patients underwent an initial period of transient hyperthyroidism. They were all asymptomatic and did not require any medication. Among these 9 patients, 5 developed continuous hypothyroidism, whereas the status normalized in the rest. The median time to onset of hyperthyroidism was 10 weeks (range 4-15 weeks), which is rather long as compared with previous reports (16,20). Furthermore, hypothyroidism occurred in 17 patients, with a median time to onset of 17.8 weeks (range 5-56), which is similar to that reported previously (16,20). In the 4 patients who had worsening hypothyroidism, no patient underwent transient hyperthyroidism, and the median time to onset of worsening hypothyroidism was 9.5 weeks (range 5-12). The results also showed that the severity of hypothyroidism was

Table I. Baseline characteristics.

Characteristics	Thyroid dysfunction, n=25	Non- thyroid dysfunction, n=125	P-value
Age (median)	72 (56-83)	69 (38-87)	0.08
Sex, male/female	16/9	85/40	0.70
PS			0.14
0	17	68	
1	8	41	
≥2	0	16	
Tumor type			0.19
NSCLC	11	48	
MM	6	20	
RCC	4	20	
Head and neck	2	17	
Gastric	1	15	
Urothelial cancer	0	5	
HL	1	0	
Thyroid dysfunction at baseline	4 (16%)	31 (24.8%)	0.34
Prior therapy lines ≤1/≥2	12/13	64/61	0.77
Nivolumab/Pembrolizumab	21/4	96/29	0.43
Preexisting anti-thyroid Abs	13 (59%)[a]	18 (18%)[b]	0.0002

[a]Total of 22 patients (3 patients were not examined); [b]Total of 100 patients (25 patients were not examined). Abs, antibodies; PS, performance status; NSCLC, non-small cell lung carcinoma; MM, malignant melanoma; RCC, renal cell carcinoma; HL, Hodgkin's lymphoma.

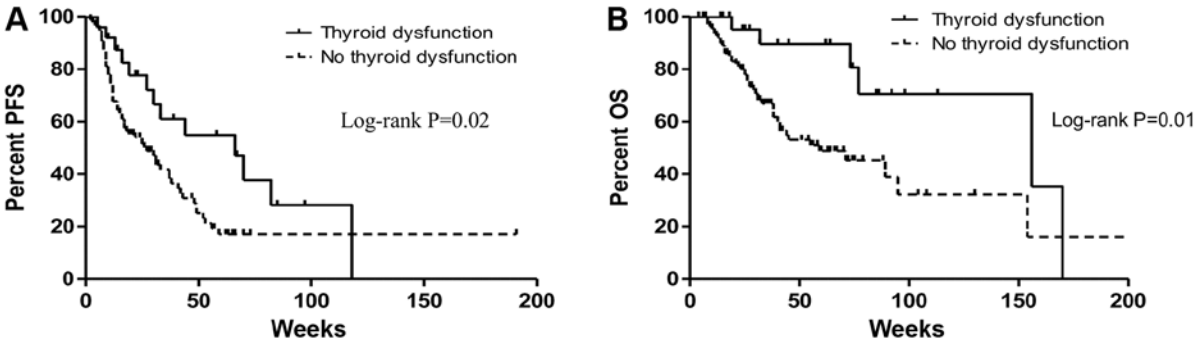

Figure 2. Association between immune-related thyroid dysfunction and clinical outcomes. Kaplan-Meier curves for (A) PFS and (B) OS in the thyroid dysfunction and euthyroid groups. PFS, progression-free survival; OS, overall survival.

mild and controllable; initially, we noted grade 1 in 5 (24%), and grade 2 (that is, demanding levothyroxine replacement) in 16 (76%) of 21 patients. Overt and subclinical hypothyroidism were noted in 12 and 9 patients, respectively. No patient was required to discontinue or delay PD-1 blockade administration due to thyroid dysfunction. Moreover, none of the patients were diagnosed with secondary hypothyroidism caused by hypopituitarism. Furthermore, there was no difference in the development of irAEs, with the exception of thyroid dysfunction, between these two groups (data not shown).

Association between the development of thyroid dysfunction and the efficacy of treatment. OS and PFS were estimated among the 150 patients. The PFS of the thyroid dysfunction group was significantly longer than that of the euthyroid group (median: 66 vs. 27 weeks, HR: 0.50, 95% CI: 0.26-0.89, P=0.02; Fig. 2A). A statistically significant improvement in OS was also noted in patients with thyroid dysfunction, when compared to those who had none (median: 156 vs. 59 weeks, HR: 0.34, 95% CI: 0.13-0.75, P=0.01; Fig. 2B). Furthermore, the effects of the development of thyroid dysfunction on PFS and OS were examined based on a hazard ratio using time-dependent Cox regression analyses (Table II). In the multivariate analysis, statistically significant improvement in OS was found to be associated with PS (P<0.0001, HR: 0.12, 95% CI: 0.06-0.23) and the development of thyroid dysfunction (P=0.04, HR: 0.42, 95% CI: 0.16-0.97). Moreover, the association between the development of thyroid dysfunction and the improvement in PFS was numerically but not statistically significant (P=0.058, HR: 0.56, 95% CI: 0.29-1.02); PS was the only independent predictive factor (P=0.038, HR: 0.41, 95% CI: 0.20-0.95). Moreover, age, gender, and therapy

Table II. Cox proportional hazard regression analysis of PFS and OS, according to thyroid dysfunction and other factors.

A, Univariate

	OS		PFS	
Factor	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age (≤69)	1.36 (0.79-2.38)	0.27	1.43 (0.91-2.26)	0.12
Sex (Male)	1.12 (0.65-2.01)	0.68	1.32 (0.83-2.18)	0.24
Prior therapy lines (≤1)	1.20 (0.69-2.11)	0.52	1.27 (0.80-2.02)	0.31
PS (≤1)	0.10 (0.05-0.20)	<0.0001	0.38 (0.19-0.88)	0.026
Thyroid Dysfunction	0.34 (0.13-0.75)	0.006	0.50 (0.26-0.89)	0.016

B, Multivariate

	OS		PFS	
Factor	Hazard Ratio (95% CI)	P-value	Hazard Ratio (95% CI)	P-value
Age (≤69)	-	-	1.38 (0.87-2.20)	0.168
Sex (Male)	-	-	-	-
Prior therapy lines (≤1)	-	-	-	-
PS (≤1)	0.12 (0.06-0.23)	<0.0001	0.41 (0.20-0.95)	0.038
Thyroid Dysfunction	0.42 (0.16-0.97)	0.04	0.56 (0.29-1.02)	0.058

PFS, progression-free survival; OS, overall survival; PS, performance status.

were not associated with PFS nor OS. Interestingly, when we focused on patients with NSCLC and MM individually, the correlation between thyroid dysfunction and improvement in PFS and OS almost reached statistical significance (P=0.058, P=0.076 respectively) in patients with NSCLC, whereas no significance effects were noted in patients with MM (P=0.261, P=0.512 respectively; Fig. 3A-D).

Discussion

In the present study, we described the clinical features of thyroid dysfunction in patients with metastatic and/or unresectable malignancies treated with PD-1 blockade. Some previous related studies on NSCLC and MM patients have been conducted (16,19); however, to our knowledge, ours is the first study to evaluate these specific irAEs in multiple advanced cancers. Data showed that 16.7% of the patients treated with nivolumab or pembrolizumab developed thyroid dysfunction. Nevertheless, the incidence of thyroid dysfunction was not related to the type of tumor nor the type of PD-1 blockade, but was strongly correlated with the presence of anti-thyroid antibodies. Evidently, most cases had occurred in a fixed and relatively early time period, with a similar clinical course. Many of these patients ultimately developed hypothyroidism, and in some cases, a preceding transient period of hyperthyroidism was observed. However, the severity of dysthyroidism was low and no discontinuation of PD-1 blockade was required. Furthermore, the development of thyroid dysfunction showed a statistically significant effect on the improvement of PFS and OS, and it was also an independent prognostic factor for OS after adjustment for other factors. When we focused on NSCLC and MM individually, there was a correlation between the development of thyroid dysfunction and the improvement in PFS and OS in patients with NSCLC; however, no relationship was noted in MM, suggesting that this trend may vary based on the type of tumor.

There was a uniform pattern of immune-related thyroid dysfunction among the patients, namely, a transient period of hyperthyroidism, followed by hypothyroidism and then destructive thyroiditis. The onset of hyperthyroidism in this study was seen in the later stage; this contrasts with the results of the previous studies, which reported a median of 3-5 weeks (16,20). Thus, perhaps, the estimation of thyroid function was unjustified and was dependent on the attending doctor, leading to a lag in detection. In addition, no symptomatic hyperthyroidism was observed, which also might contribute to the delay. In the present study, hypothyroidism persisted and no patient experienced spontaneous recovery. Clearly, a larger number of patients and a longer period of observation are needed to validate this trend.

The mechanism of thyroid dysfunction is consistent with the onset of acute inflammation and destruction of thyroid glands. As is indicated in several studies (16,17), anti-thyroid antibodies are highly correlated to thyroid dysfunction. This suggests that immune responses to thyroglobulin or thyroid peroxidase may be responsible for thyroiditis, although the precise immunological pathogenesis remains unclear.

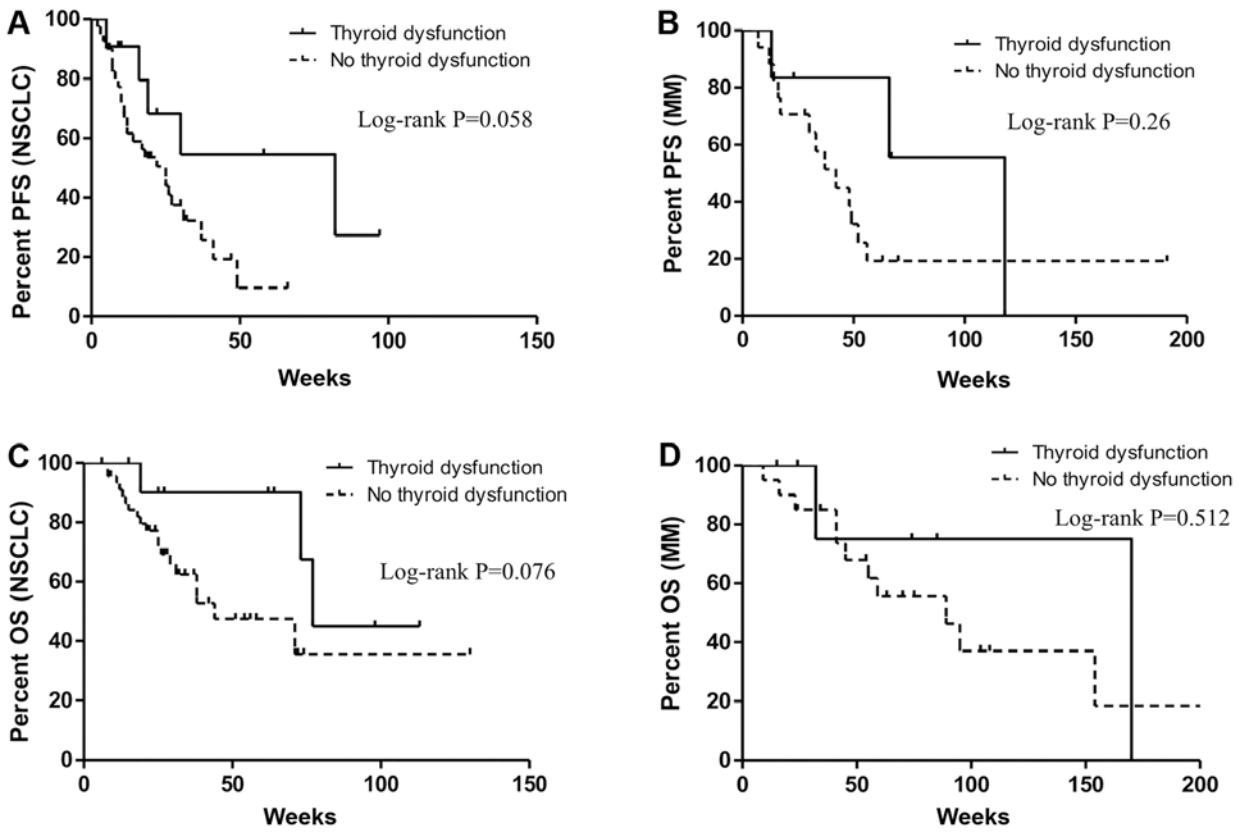

Figure 3. Association between immune-related thyroid dysfunction and clinical outcomes in non-small cell lung cancer and malignant melanoma. Kaplan-Meier curves for PFS in patients with or without thyroid dysfunction in addition to (A) NSCLC or (B) MM. Kaplan-Meier curves for OS in patients with or without thyroid dysfunction in addition to (C) NSCLC or (D) MM. PFS, progression-free survival; OS, overall survival; NSCLC, non-small cell lung cancer; MM, malignant melanoma.

The management of thyroid dysfunction induced by PD-1 blockade needs more investigation and is still controversial. Levothyroxine replacements are recommended in patients with overt hypothyroidism, whereas subclinical hypothyroidism can be followed up biologically without treatment; however, principles for medication administration have not yet been determined. Additionally, guidelines based on other clinical scenarios for subclinical hypothyroidism suggest that patients with symptoms or TSH levels ≧10 mlU/l should receive levothyroxine replacement (21,22). In our study, every patient with overt hypothyroidism, and 3 out of 10 patients with subclinical hypothyroidism, received levothyroxine replacement. Furthermore, no patient was required to discontinue the use of PD-1 blockade due to the clinical influence of thyroid disorders.

Hyperthyroidism induced by antitumor immunotherapy is self-limited and frequently asymptomatic. Hence, observation rather than additional diagnostic testing or anti-thyroid drug administration is recommended (23). For patients with symptomatic hyperthyroidism, beta-blockers can be considered along with a frequent assessment of thyroid function.

It is worthy to note that there is a close association between the development of thyroid dysfunction and an improvement in survival in patients with advanced cancers. The correlations between all irAEs and clinical outcomes in NSCLC have been described (14,24), and a report of meta-analysis has shown that cutaneous irAEs have a significant association with increased survival in malignant melanoma (13). Some reports have recently demonstrated that the presence of thyroid dysfunction is related to the improvement of survival in NSCLC, but not in other malignancies (16,25,26). Our study also showed this trend, suggesting that the correlation may vary by tumor type. However, differences in clinical conditions and immunological backgrounds, depending on the tumor type, may influence the results. This implies that further investigation with larger patient sample sizes and longer observation periods is needed for arriving at a strong conclusion.

This study has some limitations. First, this was a single center retrospective study; therefore, the nature of analysis and the limited comprehensive evaluations of thyroid function and tumor response may be insufficient for precise diagnosis. Moreover, the patient sample size for each advanced cancer was relatively small. Second, we did not perform a landmark analysis, which is more appropriate for estimating the association between adverse events and treatment efficacy. However, we noted that this association was not simply related to the fact that patients with longer treatment periods were at a greater risk of developing adverse events, as thyroid dysfunction was observed early in the clinical course.

In conclusion, thyroid dysfunction induced by PD-1 blockade occurs frequently in the early period, but with mild symptoms. An examination of anti-thyroid antibodies can facilitate the prediction of thyroid dysfunction. Therefore, a close estimation of thyroid function is recommended before and during PD-1 treatment for relevant patient care and optimizing the application of antitumor immunotherapy.

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Availability of data and materials

The datasets used or analyzed during the present study are available from the corresponding author on reasonable request.

Author's contributions

TS, TI, YI and KT were responsible for the design of the study, and the collection, analysis and interpretation of the data. TS, TI, YI and KT critically revised the manuscript for important intellectual content. JU, YC, SK, JA, TN, AA, TsK, HT, ToK, HK, FH, MI, SH, OU and TT were responsible for the acquisition and clinical interpretation of the data. All authors contributed to the writing of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Medical Ethics Review Committee of the Kyoto Prefectural University of Medicine (approval no. ERB-C-867-1). Given the retrospective nature of this work, informed consent was waived for the individual participants included in the study in accordance with the standards of the Kyoto Prefectural University of Medicine Institutional Medical Ethics Review Committee.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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