RESEARCH

Dynamic follow-up of the effects of programmed death 1 inhibitor treatment on thyroid function and sonographic features in patients with hepatocellular carcinoma

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Abstract

Objective: Programmed cell death protein-1 (PD-1) inhibitors are widely used for the treatment of hepatocellular carcinoma (HCC). Thyroid dysfunction is common in patients treated with this therapy, although the dynamic changes in thyroid function and sonographic features remain unclear.
Methods: We analyzed 38 patients with HCC who received anti-PD-1 therapy at our hospital. Demographic, clinical, laboratory, and ultrasound data were extracted from electronic medical records. The grading of thyroid nodules was based on the American College of Radiology Thyroid Imaging Reporting and Data System classification. Statistical analyses were performed using GraphPad Prism 5.0.
Results: Fifteen patients (40%) had hypothyroidism, among which six had hypothyroidism at baseline, three had overt hypothyroidism, and six had subclinical hypothyroidism after anti-PD1 therapy. The proportion of patients with euthyroid function and thyroid antibody positivity was significantly lower than that of patients with thyroid dysfunction (10% vs 39%, $P < 0.05$). Nine patients (24%) had irregular echo patterns on sonographic imaging, six of whom had irregular echo patterns present during the treatment, but only one had them persist until the end of treatment. At baseline, the classification of most thyroid nodules was grade 3, with a significant increase in grade 4A and 4B classifications during treatment, though most nodules remained grade 3 at the end of treatment. There were no significant differences in survival rates between the euthyroid and thyroid dysfunction groups.
Conclusion: Anti-PD-1 therapy-induced thyroid dysfunction was accompanied by changes in thyroid function, antibodies, and ultrasonography. Therefore, in patients receiving anti-PD-1 therapy, close, dynamic monitoring of thyroid function, antibodies, and ultrasonographic characteristics is necessary.

Key Words
- PD-1
- immunotherapy
- thyroid dysfunction
- ultrasonography

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Introduction

Programmed cell death protein-1 (PD-1) blockade therapies are widely used for the treatment of hepatocellular carcinoma (HCC) (1). In addition to their antitumor effects, anti-PD-1 antibodies have been reported to cause immune-related adverse events (irAEs) (2). Among endocrine irAEs, thyroid dysfunction occurs most frequently in patients treated with anti-PD-1 therapy (3, 4). The mechanism by which anti-PD-1 treatment causes abnormal thyroid function is not yet fully understood. Some studies suggested that the presence of anti-thyroid antibodies at baseline was predictive of anti-PD-1 antibody-induced thyroid dysfunction (5, 6, 7). However, another study found that even in patients who are negative for anti-thyroid antibodies at baseline, the incidence of thyroid dysfunction after PD-1 antibody treatment is high and cannot be ignored (8).

Thyroid ultrasonography is widely used to evaluate autoimmune thyroiditis (hypoechogenicity or inhomogeneous echo) and thyroid nodules (9). It has been reported that internal echogenicity is lower and irregular after the development of thyroid dysfunction induced by PD-1 antibody therapy (10). Another study found that hypoechogenicity on thyroid sonography was associated with the development of thyroid dysfunction induced by PD-1 antibody treatment (11). However, the effect of PD-1 antibody treatment on the size and classification of thyroid nodules has not yet been reported.

Therefore, the aim of the present study was to determine the effects of PD-1 antibody treatment on thyroid function and sonographic features in patients with HCC.

Research design and methods

Patients

Thirty-eight patients with HCC treated with anti-PD-1 (sintilimab) antibody at our institute between January 2019 and January 2020 were identified through an electronic medical record database review and included in the present study. Patients with incomplete baseline data and follow-up less than 6 weeks were excluded. The study was approved by the Human Research Ethics Committee of our hospital. During the telephone follow-up, consent was obtained from each patient or relatives after fully explaining the purpose and nature of all data used.

Laboratory test

The serum levels of free triiodothyronine (FT3), free thyroxine (FT4), ultrasensitive thyroid-stimulating hormone (uTSH), and thyroid antithyroglobulin autoantibody (TgAb) were detected with an immunochemical-automated analyzer (Beckman Coulter UniCelDxI 800; Beckman Coulter, Inc., Brea, CA, USA).

Thyroid ultrasonography

Thyroid sonography was performed on an HD7 ultrasound system (Philips) by experienced technicians who were blinded to the purposes of this study. The ultrasonographic analysis was reviewed by radiologists (with more than 10 years of experience in thyroid imaging diagnosis) without any previous knowledge of the treatment. The diagnosis of thyroid nodules was made according to the American College of Radiology Thyroid Imaging Reporting and Data System (ACR TI-RADS) guidelines (2017) (12).

Definition of thyroid dysfunction

The diagnosis of thyrotoxicosis was defined as a TSH value <0.56 μIU/mL with (overt thyrotoxicosis) or without (subclinical thyrotoxicosis) elevated FT3 or FT4 levels. The presence of hypothyroidism was defined as a TSH value >5.91 μIU/mL with (overt hypothyroidism) or without (subclinical hypothyroidism) decreased FT3 or FT4 levels.

Statistical analysis

Statistical analyses were performed using GraphPad Prism 5.0. Continuous variables with nonnormal distributions are expressed as medians (interquartile range) and were compared via nonparametric testing (Mann–Whitney U test). Categorical variables are described as percentages (%) and were compared with the chi-square test or Fisher's test. The log-rank (Mantel–Cox) test was used to compare the survival curves. All statistical analyses were two-sided, and $P < 0.05$ was considered statistically significant.

Results

The clinical characteristics of patients with HCC who received anti-PD-1 therapy are summarized in Table 1, and the patient enrollment diagram is shown in Fig. 1. After excluding patients with no available data on thyroid function or ultrasound images and patients treated for less than 6 weeks (2 cycles), 38 patients (median age 47 years, 35 men and 3 women) were included in the analysis in this study. Eleven patients (29%) had a drinking history, and 9 patients (24%) had a smoking history. At baseline, 20

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Table 1 Clinical characteristics of 38 patients with HCC who received immunotherapy.

Characteristic	Patients with HCC
Age (years)	47 (34.5–55.5)
Sex	
Male, n (%)	35 (92.1)
Female, n (%)	3 (7.9)
Drinking	
Yes	11 (28.9)
No	27 (71.1)
Smoking	
Yes	9 (23.7)
No	29 (76.3)
Baseline AFP	
>200 ng/mL	20 (52.6)
<200 ng/mL	18 (47.4)
Duration of immunotherapy (weeks)	25.5 (11.25–51.75)

AFP, alpha-fetoprotein; HCC, hepatocellular carcinoma.

patients (53%) had a high level of alpha-fetoprotein (AFP) >200 ng/mL. The median duration of anti-PD-1 therapy was 25.5 weeks (interquartile range: 11.25–51.75 weeks).

Twenty patients (53%) did not develop thyroid dysfunction, and their FT3, FT4, and uTSH levels remained in the normal range. Eighteen patients (47%) had thyroid dysfunction, among which three (8%) had transient thyrotoxicosis (increased FT3 and FT4 and a large decrease in uTSH outside the normal range that returned to normal within 9 weeks after initiation of anti-PD-1). Fifteen patients (40%) had hypothyroidism, among which six had hypothyroidism at baseline, three patients had overt hypothyroidism, and six patients had subclinical hypothyroidism after anti-PD1 therapy. Individual changes in FT3, FT4, and uTSH are shown in Fig. 2A, B and C.

Nine patients (24%) were positive for anti-thyroglobulin antibody (TG-Ab), two of whom were positive at baseline and seven of whom became positive during anti-PD-1 treatment (a transient increase in TG-Ab occurred at approximately 9 weeks). Individual changes in TG-Ab are shown in Fig. 2D. The proportion of patients with normal thyroid function and anti-thyroglobulin positivity was significantly lower than that of patients with thyroid dysfunction (10% vs 38.9%, $P < 0.05$, shown in Fig. 3A). The proportion of AFP >200 ng/mL in patients with thyroid dysfunction was significantly higher than that of patients with normal thyroid function (73% vs 35%, $P < 0.05$, shown in Fig. 3B).

Nine patients (24%) had heterogeneous echogenicity (irregular echo pattern) on sonography: two presented this at baseline, and it persisted until the end of treatment; six presented this during the treatment, but only one had heterogeneous echogenicity that persisted until the end of treatment (Fig. 4A). The individual change in the maximum diameter of thyroid nodules over the treatment period is shown in Fig. 4B. At baseline, three patients had grade 2 thyroid nodules, nine patients had grade 3 nodules, and one patient had grade 4A nodules according to the ACR TI-RADS classification (2017). During treatment, two patients had grade 2 nodules, five had grade 3 nodules, six had grade 4A nodules, and two had grade 4B nodules. At the end of treatment, 3 patients had grade 2 nodules, 10 patients had grade 3 nodules, 2 patients had grade 4A nodules, and 1 patient had grade 4B nodules, as shown in Fig. 4C.

For analysis of the overall survival rate, data on patients who were alive at the last follow-up contact

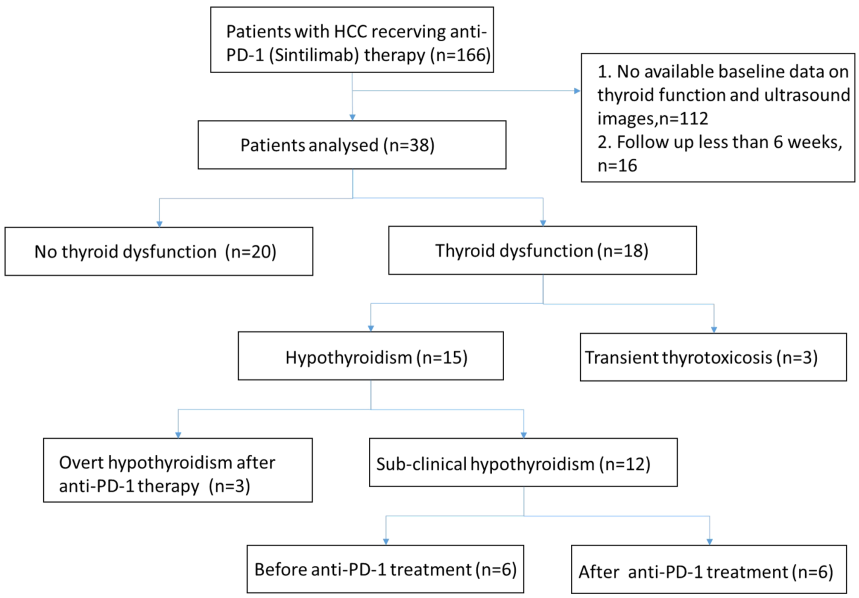

Figure 1
Patient enrollment diagram: patients with HCC treated with anti-PD-1 therapy. Patients with detailed data on thyroid function and antibodies and ultrasound images were enrolled for analysis. HCC, hepatocellular carcinoma; PD-1, programmed cell death protein-1.

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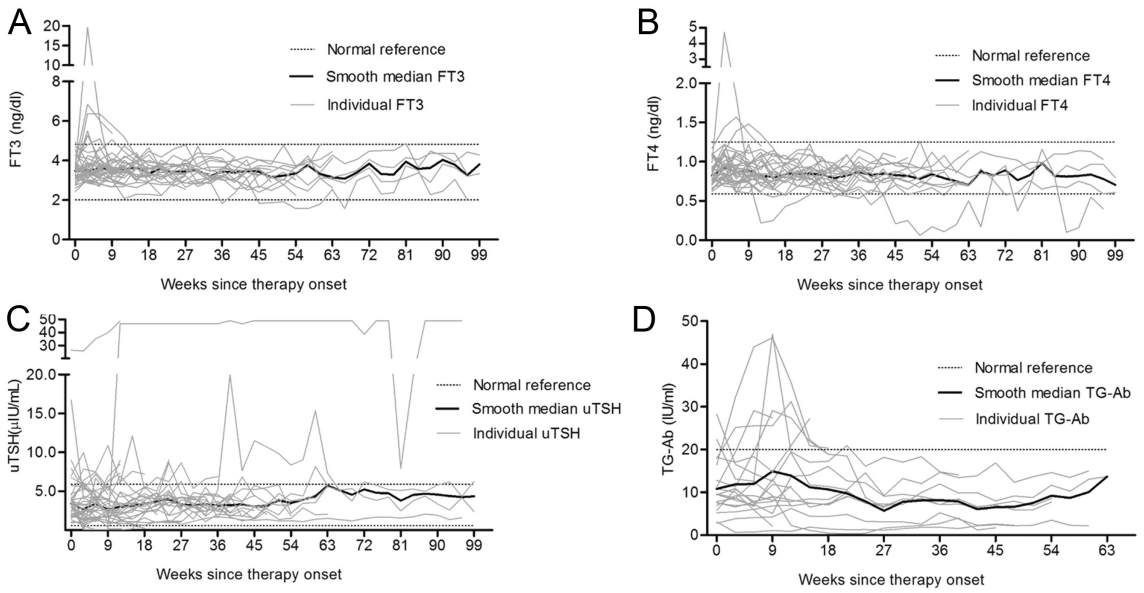

Figure 2
Dynamic changes in thyroid function and TG-Ab in patients with HCC receiving anti-PD-1 therapy. (A) Change in FT3 over time. (B) Change in FT4 over time. (C) Change in uTSH over time. (D). Change in TG-Ab over time. FT3, free triiodothyronine; FT4, free tetraiodothyronine; PD-1, programmed cell death protein-1; TG-Ab, thyroglobulin antibody; uTSH, ultrasensitive thyroid stimulation hormone.

were removed. The overall survival rate of patients with normal thyroid function was 60%, that of patients with thyroid dysfunction was 54%, and the hazard ratio was 0.85 (95% CI, 0.28–2.65, $P=0.57$). There were no significant differences in survival rates between the two groups (Fig. 5).

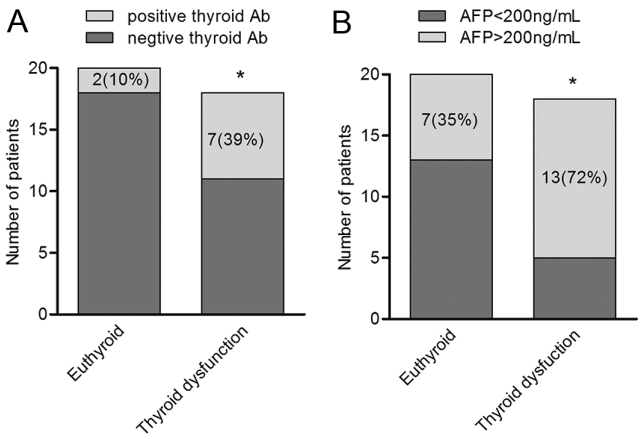

Figure 3
Thyroid antibody positivity and high AFP levels in the euthyroid and thyroid dysfunction groups. (A) Proportion of individuals positive for thyroid antibodies in euthyroid and thyroid dysfunction patients. (B) Proportion of individuals with AFP levels >200 ng/mL in the euthyroid and thyroid dysfunction groups. A patient was considered to be positive for antibodies if anti-thyroglobulin antibodies were present at any point during the treatment. *P < 0.05 two-tailed Fisher's exact test.- AFP, alpha-fetoprotein.

Discussion

This is a study on thyroid function and sonographic features in patients with HCC treated with anti-PD-1 therapy. In this study, most of the patients were men, approximately one in four patients had a history of drinking or smoking, and approximately half of the patients had high levels of AFP before the start of immunotherapy. Eighteen patients had thyroid dysfunction, six of whom had pre-existing subclinical hypothyroidism requiring no thyroid replacement therapy. Twelve patients (32%) with HCC treated with sintilimab developed thyroid dysfunction. The incidence of thyroid dysfunction in this cohort is higher than that in reports from larger anti-PD-1 clinical trials, where rates range from 5% to 30% (13, 14, 15). The reason for the high incidence of thyroid dysfunction in this study may be explained by the frequency of thyroid function monitoring in this study being relatively high (assessment of thyroid function every 3 weeks) regardless of whether the patients had clinical symptoms of thyroid dysfunction. Such a high monitoring frequency can greatly reduce the rate of underdiagnosis of transient thyroid dysfunction.

In this study, three patients developed a transient and asymptomatic period of thyrotoxicosis, and six patients developed hypothyroidism after anti-PD-1 therapy. Most of the cases developed thyroid dysfunction early in the course of anti-PD-1 therapy, with a relative onset

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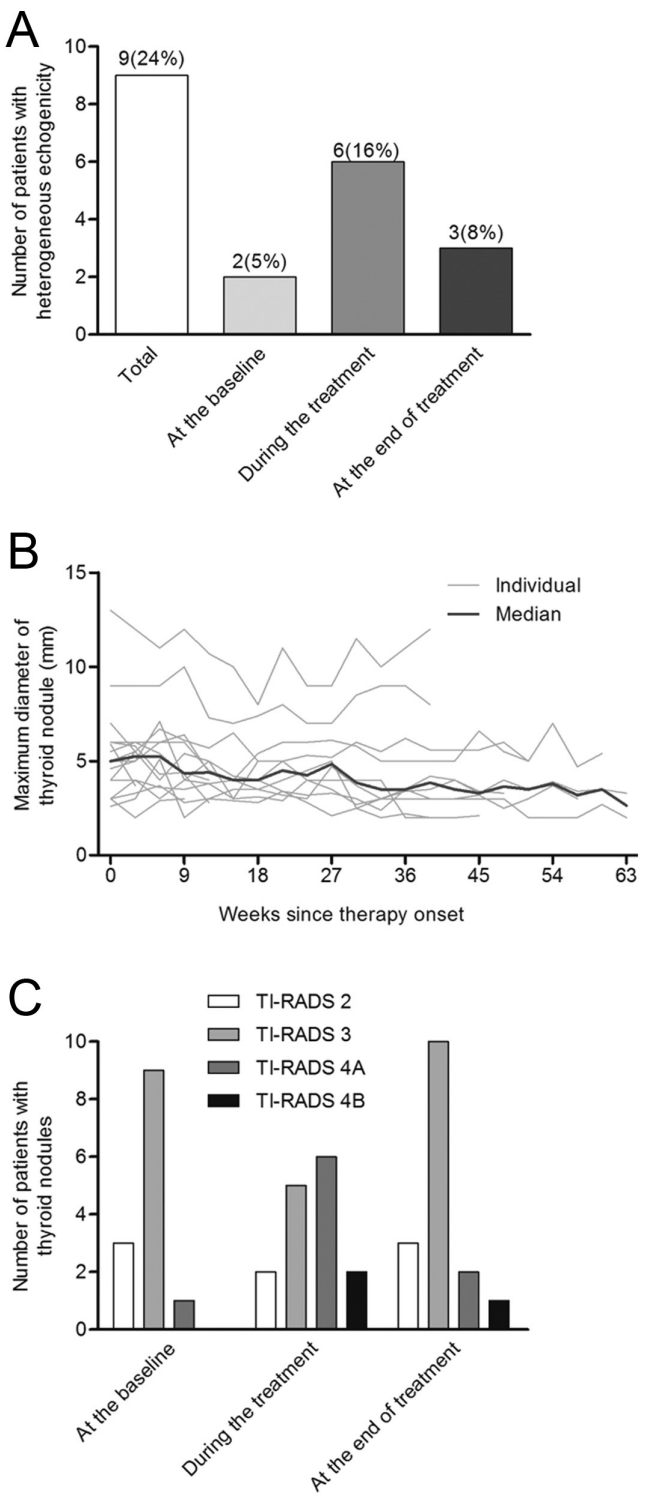

Figure 4
Dynamic change in thyroid ultrasound images in patients with HCC after anti-PD-1 therapy. (A) Number of patients with heterogeneous echogenicity. (B) Change in maximum diameter of thyroid nodules over time. (C) Number of patients with different TI-RADS categories of thyroid nodules at baseline, during treatment, and at the end of anti-PD-1 treatment. HCC, hepatocellular carcinoma; PD-1, programmed cell death protein-1; TI-RADS, Thyroid Imaging Reporting and Data System.

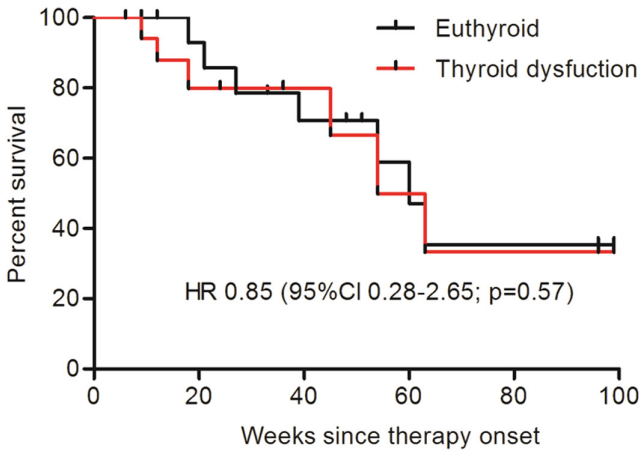

Figure 5
Comparison of the survival rate of patients with euthyroid (black line) and thyroid dysfunction (red line). The log-rank (Mantel–Cox) test was used to compare the survival curves. The mean survival rate of patients with normal thyroid function was 60%, that of patients with thyroid dysfunction was 54%, and the hazard ratio was 0.85 (95% CI, 0.28–2.65, P = 0.57).

time of approximately 9 weeks after the beginning of immunotherapy. Consistent with the transient increase in thyroid hormone, thyroid antibody levels also had a transient rise during immunotherapy. The proportion of individuals positive for thyroid antibodies in the thyroid dysfunction group was significantly higher than that in the euthyroid group. All of these results indicated that thyroid dysfunction induced by anti-PD-1 might be associated with increased thyroid antibody levels induced by thyroiditis and the destruction of thyroid follicles (16, 17).

Of note, we found that six patients with HCC (16%) presented subclinical hypothyroidism at baseline. The proportion of individuals with AFP >200 ng/mL in the patients with thyroid dysfunction was significantly higher than that in the patients with normal thyroid function, which indicated that patients with thyroid dysfunction might have a poor prognosis with respect to HCC. Studies have reported a hypothyroidism prevalence of 10–20% in patients with chronic hepatitis C or liver cirrhosis (18). Another study reported that 20% of patients with advanced HCC who had not received prior systemic therapy were identified as having hypothyroidism. They found that hypothyroidism was associated with poor prognosis in patients with HCC (19). Some studies speculated that hypothyroidism might be a possible additional risk factor for HCC (20, 21). Although the mechanisms whereby hypothyroidism can favor the occurrence of HCC development are unclear, a complex relationship exists between the thyroid and liver. The liver plays an important physiological role in thyroid hormone activation and inactivation, transport, and metabolism.

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Conversely, thyroid hormones affect the activities of hepatocytes and hepatic metabolism (22). The mechanism underlying the association between hypothyroidism and poor prognosis for advanced HCC could be multifactorial and needs further study. The finding that elevated AFP concentration is more common in subjects with thyroid dysfunction may be explained by the stimulation of immune response by the tumor. This is of interest in the context of the recently proposed theory of autoimmune surveillance of hypersecreting mutants (ASHM) (23). The ASHM mechanism can remove mutants of HCC but at the cost of autoimmune thyroid dysfunction.

Ultrasonography has been proven to be the most efficient method for diagnosing thyroid diseases (24). Several studies have reported that hypoechogenicity or an irregular echo pattern is associated with hypothyroidism (25). A recent cohort study (n = 209) reported that an irregular echo pattern in the thyroid is a risk factor for destructive thyroiditis and/or hypothyroidism in patients positive for anti-thyroid antibodies before the start of anti-PD-1 treatment. They showed that the incidence of hypothyroidism was much higher in patients with an irregular echo pattern on thyroid ultrasonography than in those with a regular pattern. They suggested that performing thyroid ultrasonography in patients positive for anti-thyroid antibodies was useful for identifying those at higher risk of thyroid dysfunction induced by anti-PD-1 antibodies (7). In our study, only two patients had irregular echo patterns on thyroid ultrasonography at baseline. Four patients developed a new irregular echo pattern during the course of anti-PD-1 treatment, three of whom showed the pattern transiently, and one had an irregular echogenic thyroid until the end of treatment. The size of thyroid nodules fluctuated slightly during anti-PD-1 treatment, but the overall change was small. However, the TI-RADS grading of thyroid nodules changed notably. At baseline, the classification of thyroid nodules was dominated by category 3, with a significant increase in categories 4A and 4B during treatment, and at the end of follow-up, most nodules were still categorized as category 3. The increased classification of thyroid nodules during PD-1 therapy may be related to the unclear margins and irregular shape of nodules caused by inflammation. As one study said, thyroiditis, regardless of type, may produce transitory ultrasound changes that confound the accurate classification of thyroid nodules (26).

A recent study (n = 74) found that hypothyroidism was associated with prognosis in patients with HCC treated with anti-PD-1 therapy, and the prognosis was more favorable in patients with hypothyroidism than in those without hypothyroidism. Hypothyroidism was independently associated with patient prognosis (27). However, in our study, we found that the overall survival rates of patients with normal and abnormal thyroid function were 60% and 54%, respectively. The survival rate was not significantly different between the two groups, which might be due to the small sample size of our study. The main limitation of this study is that the number of patients included is relatively small, and the event rate is accordingly low, thereby limiting the power and reliability of the statistical analysis. It is difficult to draw a statistically significant conclusion if a subgroup analysis is performed. A larger study sample is needed for subgroup analysis in the future.

Conclusion

In summary, considering the high risk of thyroid dysfunction among patients with advanced HCC and that anti-PD-1 therapy for advanced HCC can cause thyroid dysfunction, routine examination of thyroid function before initiating immunotherapy should be considered in patients with advanced HCC. Anti-PD-1 therapy-induced thyroid dysfunction was accompanied by changes in thyroid antibodies, echo patterns, and nodule classification on thyroid ultrasonography. Therefore, for HCC patients receiving anti-PD-1 therapy, close, dynamic monitoring of thyroid function, thyroid autoantibodies, and thyroid ultrasonographic characteristics is necessary.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Ethics approval
The study was approved by the Human Research Ethics Committee of the First Affiliated Hospital of Chongqing Medical University.

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