Infectious Agents and Cancer

RESEARCH

Open Access

# Immune checkpoint blockade PD-1 therapy for primary liver cancer: incidence and influencing factors of thyroid dysfunction

Huili Wu, Fang Xiong, Xuli Bao and Jun Lu*

## Abstract

**Objectives:** To investigate the incidence and influencing factors of thyroid dysfunction (TD) in patients with primary liver cancer (PLC) induced by PD-1 monoclonal antibodies.

**Methods:** Clinical data were collected from 195 PLC patients treated with PD-1. They were divided into TD group and normal thyroid function (NTF) group, and further divided into TD subgroups, the differences between groups and subgroups were analyzed.

**Results:** A total of 113 of 195 (57.9%) PLC patients developed TD. The positive rate of thyroid antibody (20.6% vs. 0%, $P=0.041$) and the median value of TSH (6.20 vs. 2.16 mU/L, $P=0.000$) in TD group were higher than those in NTF group. Ten patients (8.8%) had the CTCAE grade of TD above grade 3, of which 2 patients died of liver failure. There were 20 patients (17.7%) in hyperthyroidism group and 93 patients (82.3%) in hypothyroidism group. The decompensated cirrhosis in hyperthyroidism group was lower than that in hypothyroidism group (33.3% vs. 65.6%, $P=0.010$), and the proportion of patients who had previously received surgical treatment was higher than that in hypothyroidism group (35.0% vs. 9.7%, $P=0.003$); The proportion of clinical hyperthyroidism was higher than that of clinical hypothyroidism (70.0% vs. 31.2%, $P=0.001$), the proportion of decompensated liver cirrhosis in clinical hyperthyroidism group was lower than that in clinical hypothyroidism group (23.1% vs. 68.0%, $P=0.022$), and the proportion of previous or combined surgical resection was much higher than that in clinical hypothyroidism group (42.9% vs. 7.1%, $P=0.018$); The proportion of decompensated cirrhosis in primary TD group was lower than that in secondary TD group (36.5% vs. 83.3%, $P=0.002$), and the proportion of patients using antitumor targeted drugs was higher than that in secondary TD group (73.1% vs. 45.0%, $P=0.014$).

**Conclusion:** Patients with PLC had high incidence of TD after receiving PD-1 treatment, primary or subclinical hypothyroidism was the main manifestation type, which was related to the degree of disease and treatment.

**Keywords:** Primary liver cancer, Immune checkpoint inhibitors, Thyroid function, Immune related adverse reactions

## Introduction

Primary liver cancer (PLC) is a kind of malignant tumor originating from hepatocytes or intrahepatic bile duct epithelial cells. It is characterized by concealed onset, high degree of malignancy, rapid progress and difficult treatment. The incidence rate and mortality of PLC in China ranked first in the world, with a 5-year survival of only 12.1% [1]. At present, PD-1/PD-L1 antibody as checkpoint inhibitor combined with antitumor targeted drugs had become the first-line treatment of unresectable PLC. Previous clinical studies had shown that PD-1 was generally safe and well tolerated in the treatment of tumors. However, as a new generation of

*Correspondence: lujun98@ccmu.edu.cn

Department of Oncology, Beijing YouAn Hospital, Capital Medical University, 8 Xitoutiao, Youwai Street, Beijing 100069, China

immunotherapeutic drugs, PD-1 inhibitors reactivate the suppressed anti-tumor immune function of the body. Therefore, it is significantly different from traditional anti-tumor drugs, that is, the damage of PD-1 to the immune system is a unique adverse reaction. Endocrine organs, especially thyroid, are the most common target organs of immune-mediated adverse reactions. Previous studies had also observed that PD-1 had different degrees of thyroid dysfunction in the treatment of different tumors [2], but so far, there was few real-world studies on the occurrence of thyroid dysfunction in PLC patients after treatment, especially lack of detailed research on the manifestation types, clinical characteristics and influencing factors related to thyroid dysfunction. Therefore, this study retrospectively analyzed the clinical data of a large number of PLC patients treated with PD-1in our center, in order to provide more clinical experience for the prevention, diagnosis, treatment and management of TD adverse reactions after immunotherapy.

## Patients and methods

### Patients

We performed a retrospective study of the medical records of all 219 PLC patients who underwent PD-1(Camrelizumab or Sintilimab) therapy between January 2020 and September 2021. The diagnosis standard of PLC refers to the staging standard of BCLC strategy 2022 update [3]. Inclusion criteria: (1) PLC was diagnosed by clinical or histopathological examination; (2) received at least 2 cycles of standardized PD-1 treatment; (3) received analyzable clinical medical records or follow-up data. Exclusion criteria: (1) with thyroid disease history, operation history and examination determined before PD-1 treatment have TD, such as abnormal thyroid stimulating hormone (TSH), free thyroxine 4(FT4) or free thyroxine 3(FT3); (2) received thyroid regional radiotherapy; (3) taking drugs that affect thyroid function; (4) other immune checkpoint inhibitors were used before treatment; (5) incomplete information. After screening according to above criteria, a total of 24 cases were excluded, and the remaining 195 cases were included in the retrospective analysis (see Fig. 1).

### Data collection

The basic information, clinical data and prognosis of all patients included in the group were collected by querying the electronic medical record system or the attending physician, as well as telephone follow-up of patients and their families. The collection contents include: gender, age, body mass index(BMI), diabetes, hepatitis B /C virus infection, liver cirrhosis diagnosis, tumor classification and stage, history of tumor treatment and starting time, thyroid function and detection time before and after treatment, thyroid autoantibody detection, etc.

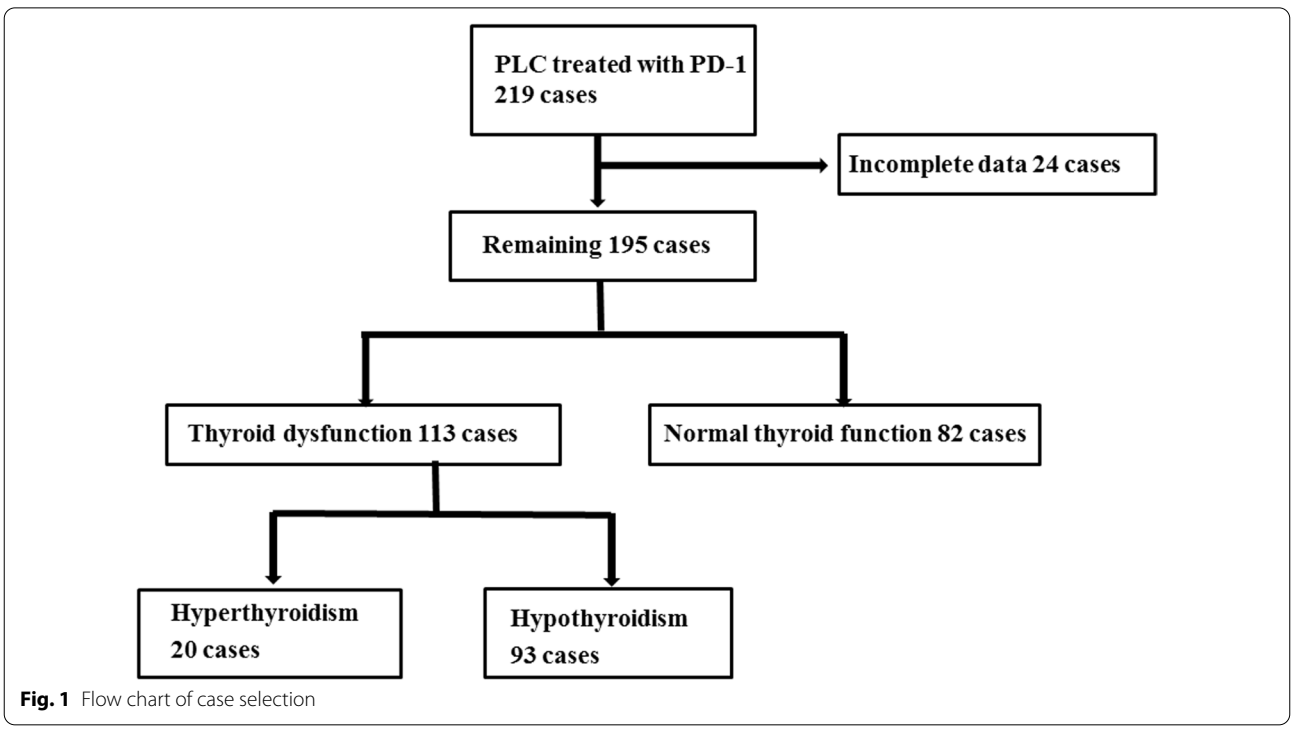


**Fig. 1** Flow chart of case selection

### Laboratory examination

TSH, FT3 and FT4 were detected by immunoluminescence method (Abbott architect i2000sr automatic immunoanalyzer), and thyroglobulin antibody (TG-Ab), thyroid peroxidase antibody (TPO-Ab) and thyrotropin receptor antibody (TSHR-Ab) were detected by automatic Electrochemiluminescence Method (Roche Cobase 801 chemiluminescence instrument). The normal value range was set as follows: TSH:0.35–4.94 mU/L, FT3:2.90–4.90 pmol/L, TT3:0.99–2.34 pmol/L, FT4:9.01–19.05 pmol/L, TT4:62.68–150.84 pmol/L.

### Evaluation of thyroid function

For the diagnostic criteria of immunotherapy related hyperthyroidism and hypothyroidism, referred to 2021 NCCN Guidelines Insights: Management of Immunotherapy-Related Toxicities [4] and 2016 American Thyroid Association Guidelines for Diagnosis and Management of Hyperthyroidism and Other Causes of Thyrotoxicosis [5]. They were divided into four groups according to symptoms: (1) subclinical hypothyroidism group: TSH increased, FT4/FT3 was normal, and there were no clinical symptoms; (2) clinical hypothyroidism: TSH increased > 10 mU/L, FT4/FT3 decreased, with clinical symptoms; (3) subclinical hyperthyroidism: TSH decreased, FT4/FT3 normal, no clinical symptoms; (4) clinical hyperthyroidism: TSH decreased and FT4/FT3 increased, with obvious clinical symptoms. According to the etiology: (1) primary TD: elevated TSH with decreased FT4/FT3, or decreased TSH with increased FT4/FT3; (2) secondary TD: TSH is normal and FT4/FT3 decreases or increases. Immune related adverse reactions (irAEs) referred to the standard of adverse event reporting terminology of American Cancer Center(CTCAE5.0) [6], which was divided into five levels according to the severity: Grade 1: Mild, asymptomatic or mild, only clinical or diagnostic findings, without treatment; Grade 2: moderate, requiring minor, local or non-invasive treatment, and age-related instrumental activities of daily living are limited; Grade 3: Serious or medically significant but not immediately life-threatening, resulting in hospitalization or prolonged hospitalization, disability, and limited self-care activities of daily living; Grade 4: life threatening, requiring emergency treatment; Grade 5: death related to adverse reactions.

### Treatment and follow-up

Patients needed at least one cycle of PD-1 treatment. Refer to the drug instructions for the dosage. The follow-up time was at least two cycles after receiving PD-1 treatment or 3 months after stopping PD-1 treatment.

### Statistical analysis

SPSS 16.0 and GraphPad Prism 5.02 were used for statistical analysis. The normal distribution of measurement data was expressed as mean ± standard deviation. T-test or Kruskal–Wallis ANOVA test was used for comparison among groups. Skewness distribution of measurement data was expressed as medians and ranges, Mann–Whitney U test was used for comparison among groups. The counting data were expressed by the number of cases and percentages, and the comparisons between groups were performed by $\chi^2$ test or Fisher's exact probability method. The difference was statistically significant ($P < 0.05$).

## Result

### Incidence and clinical characteristics of TD

After excluding 24 patients with incomplete data, 195 of 219 PLC patients were included in the analysis, including 154 males (79.0%) and 41 females (21.0%), with an average age of 58.1 ± 10.2 years. All patients had tested for normal thyroid function before treatment, including 182 patients with hepatocellular carcinoma, accounting for 93.3%, and the other 13 patients were intrahepatic cholangiocarcinoma and hepatic adenocarcinoma. There were 113 cases (57.9%) of TD and 82 cases (42.1%) of NTF after treatment (Fig. 1). There was no significant difference between TD group and NTF group in gender, age, BMI, diabetes, evaluation time, tumor classification and stage, combined virus infection, combined liver cirrhosis and previous treatment methods, but the positive rate of thyroid antibody in TD group was significantly higher than that in NTF group (20.6% vs. 0%, $P = 0.041$). There was no significant difference in thyroid function between the two groups before treatment, while the TSH level in TD group was higher than that in NTF group (6.20 vs. 2.16, $P = 0.000$), and there was significant statistical difference (Table 1). The treatment of patients with TD conforms to Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update [7].

### Classification and clinical characteristics of TD

According to the thyroid test results, 113 patients with TD were divided into hyperthyroidism group including 20 patients (17.7%) and hypothyroidism group including 93 patients (82.3%), and 93 patients with hypothyroidism (82.3%).In 195 treated patients, the total incidence of hyperthyroidism was 10.3% and hypothyroidism was 47.6%; According to the etiology, 113 patients with TD were divided into primary group including 93 patients (82.3%) and secondary group including 20 patients (17.7%); According to the symptoms, 113 patients with TD were divided into clinical group including

**Table 1** Comparison of clinical data between thyroid dysfunction group and normal thyroid function group

| | Thyroid dysfunction group (n = 113) | Normal thyroid function group (n = 82) | *P* | $t/x^2/Z$ |
|---|---|---|---|---|
| Gender (n, %) | | | 0.131 | 2.280 |
| Male | 85(75.2) | 69(84.1) | | |
| Female | 28(24.8) | 13(15.9) | | |
| Age(years,$x \pm s$) | 58.6 ± 10.7 | 57.3 ± 9.6 | 0.380 | 0.880 |
| BMI | 23.5 ± 3.3 | 22.8 ± 4.1 | 0.235 | 1.193 |
| Diabetes | | | 0.877 | 0.024 |
| Yes | 17(15.0) | 13(15.9) | | |
| No | 96(85.0) | 69(84.1) | | |
| Evaluation time [weeks,*M*(*Q1*,*Q3*)] | 10.0(3.0, 25.5) | 10.0(5.7, 21.0) | 0.503 | 0.669 |
| Hepatocellular carcinoma (n,%) | | | 0.786 | 0.074 |
| Yes | 105(92.9) | 77(93.9) | | |
| No | 8(7.1) | 5(6.1) | | |
| Staging of BCLC system(n,%) | | | 0.815 | 0.054 |
| B | 25(22.1) | 17(20.7) | | |
| C | 88(77.9) | 65(79.3) | | |
| HBV or HCV(n,%) | 101(85.8) | 69(79.3) | 0.280 | 1.165 |
| Cirrhosis (n,%) | 92(80.5) | 68(87.8) | 0.786 | 0.074 |
| Decompensation stage (n,%) | | | 0.371 | 0.799 |
| Yes | 50(44.2) | 39(47.6) | | |
| No | 42(55.8) | 43(52.4) | | |
| Previous or combined treatment (n,%) | | | | |
| Surgical resection | 16(14.2) | 16(19.5) | 0.319 | 0.993 |
| TAE or TACE | 85(75.2) | 52(63.4) | 0.094 | 2.810 |
| Tumor ablation | 55(48.7) | 42(51.2) | 0.725 | 0.123 |
| Targeted agent | 77(68.1) | 55(67.1) | 0.875 | 0.025 |
| Systemic chemotherapy | 6(5.3) | 4(4.9) | 1.000 | 0.000 |
| Radiotherapy | 14(12.4) | 5(6.1) | 0.144 | 2.139 |
| Name of PD-1 monoclonal antibody (n,%) | | | 0.591 | 0.289 |
| Sintilimab | 59(52.2) | 46(56.1) | | |
| Camrelizumab | 54(47.8) | 36(43.9) | | |
| Thyroid antibody (n,%) | | | **0.041** | – |
| Positive | 7(20.6) | 0(0.0) | | |
| Negative | 27(79.4) | 19(100.0) | | |
| Thyroid function before treatment of PD-1 | | | | |
| TSH[mU/L,*M*(*Q1*,*Q3*)] | 2.23(1.42, 3.88) | 2.05(1.33, 3.45) | 0.620 | 0.495 |
| FT4[pmol/L,*M*(*Q1*,*Q3*)] | 13.25(11.84, 15.00) | 12.59(11.37, 14.83) | 0.223 | 1.219 |
| FT3[pmol/L,*M*(*Q1*,*Q3*)] | 3.86(3.18, 4.42) | 3.80(3.27, 4.32) | 0.962 | 0.047 |
| Thyroid function after treatment of PD-1 | | | | |
| TSH[mU/L,*M*(*Q1*,*Q3*)] | 6.20(1.42, 10.17) | 2.16(1.52, 3.22) | **0.000** | 5.198 |
| FT4[pmol/L,*M*(*Q1*,*Q3*)] | 12.18(10.54, 14.33) | 12.32(11.60, 13.89) | 0.398 | 0.845 |
| FT3[pmol/L,*M*(*Q1*,*Q3*)] | 3.68(2.93, 4.40) | 3.80(2.96, 4.28) | 0.675 | 0.420 |

BCLC:Barcelona Clinic Liver Cancer; TAE: transarterial embolization;TACE: transar-terial chemoembolization; PD-1: programmed cell death protein 1; TSH: abnormal thyroid stimulating hormone; FT4: free thyroxine 4; FT3: free thyroxine 3

42 patients(37.2%) and subclinical group including 71 patients with subclinical group (62.8%); According to the severity of adverse reactions, patients were divided into grade 1–5 and 113 patients were in grade 1–3, of which grade 3 accounted for only 8.8%. In addition, in the hyperthyroidism group, clinical hyperthyroidism and subclinical hyperthyroidism accounted for 70% and 30.0% respectively, while in the hypothyroidism group,

clinical hypothyroidism accounted for 31.2% and subclinical hypothyroidism 68.8%, showing significant statistical difference ($P=0.001$) (Table 2).

#### Analysis of clinical characteristics of TD subgroup

The proportion of decompensated cirrhosis in hypothyroidism group was significantly higher than that in hyperthyroidism group (65.6% vs. 33.3%, $P=0.010$), while the proportion of previous surgery in hyperthyroidism group was higher than that in hypothyroidism group (35.0% vs. 9.7%, $P=0.003$); There was no difference between the two groups in combination with other treatments, such as intervention, ablation, targeted drugs, chemotherapy and radiotherapy, and there was no significant difference between the two groups in gender, age, BMI, diabetes, evaluation time, tumor classification and stage, combined virus infection and thyroid antibody expression (all $P>0.05$) (Table 3).

The proportion of patients with decompensated liver cirrhosis in primary TD group was significantly lower than that in secondary TD group (36.5% vs. 83.3%, $P=0.002$), and the proportion of patients treated with anti-cancer targeted drugs in primary TD group was higher than that in secondary thyroid dysfunction group (73.1% vs. 45.0%, $P=0.014$). In addition, the positive rate of thyroid antibody in primary TD group was 31.8%, while there was no positive thyroid antibody in secondary abnormal thyroid function group. The difference between the two groups was statistically significant ($P=0.036$) (Table 4).

There were no significant abnormalities between subclinical TD group and clinical TD group in terms of gender, age, diabetes, evaluation time, tumor classification and stage, combined virus infection, combined liver cirrhosis, previous treatment, immunosuppressant types and thyroid antibody expression (all $P>0.05$) except BMI($P=0.032$) (Table 5). However, the proportion of decompensated cirrhosis in the clinical hyperthyroidism group was significantly lower than that in the clinical hypothyroidism group (23.1% vs. 68.0%, $P=0.022$), but the previous or combined surgical resection in the clinical hyperthyroidism group was much higher than that in the clinical hypothyroidism group (42.9% vs. 7.1%, $P=0.018$) (Table 6).

Grade 3 adverse events occurred in 10 patients with TD. The clinical manifestations, characteristics and prognosis were shown in Tables 7 and 8. Among the 10 patients, there were 7 males and 3 females, aged between 43 and 84 years; Nine patients had HBV infection and cirrhosis, of which 3 patients were decompensated cirrhosis; Eight patients with liver cancer stage were stage C, two patients were stage B, nine patients had other treatment schemes, and two patients had thyroid antibody positive. The earliest time for patients to find TD was 1 week after treatment, and the latest was 36 weeks; There were 3 cases of hyperthyroidism, the main symptoms were palpitation, emaciation, fatigue and irritability, and 7 cases of hypothyroidism, the main symptoms were loss of appetite, fatigue, edema and fatigue; Among the 10 patients, only one patient recovered thyroid function after treatment and did not interrupt PD-1 treatment, 4 patients interrupted PD-1 treatment but recovered thyroid function after treatment, 1 patient partially recovered thyroid function, 2 patients did not fully recover thyroid function and died during the period, and the direct cause of death was liver failure.

**Table 2** Clinical classification of thyroid dysfunction related to PD-1 monoclonal antibody therapy in primary liver cancer

| | n | Hyperthyroidism (n = 20) | Hypothyroidism (n = 93) | *P* | $t/x^2/Z$ |
|---|---|---|---|---|---|
| Classification by causes (n,%) | | | | | |
| Primary thyroid dysfunction | 93 | 19(95.0) | 74(79.6) | 0.188 | 1.735 |
| Secondary thyroid dysfunction | 20 | 1(5.0) | 19(20.4) | | |
| Classification by symptom (n,%) | | | | | |
| Clinical thyroid dysfunction | 42 | 14(70.0) | 28(31.2) | **0.001** | 11.217 |
| Subclinical thyroid dysfunction | 71 | 6(30.0) | 65(68.8) | | |
| Classification by adverse reaction severity (n,%) | | | | 0.328 | 2.230 |
| Grade 1 | 61 | 8(40.0) | 53(57.0) | | |
| Grade 2 | 42 | 9(45.0) | 33(35.5) | | |
| Grade 3 | 10 | 3(15.0) | 7(7.5) | | |
| Grade 4 | 0 | 0(0.0) | 0(0.0) | | |
| Grade 5 | 0 | 0(0.0) | 0(0.0) | | |

**Table 3** Clinical characteristics of thyroid dysfunction related to PD-1 monoclonal antibody therapy in primary liver cancer

| | Hyperthyroidism (n = 20) | Hypothyroidism (n = 93) | *P* | $t/x^2/Z$ |
|---|---|---|---|---|
| Gender (n, %) | | | 0.460 | 1.057 |
| Male | 17(85.0) | 69(74.2) | | |
| Female | 3(15.0) | 24(25.8) | | |
| Age(years,$x \pm s$) | 56.5 ± 8.1 | 58.9 ± 11.1 | 0.353 | 0.933 |
| BMI | 23.7 ± 2.9 | 23.3 ± 3.6 | 0.729 | 0.348 |
| Diabetes | | | 1.000 | 0.000 |
| Yes | 3(15.0) | 15(16.1) | | |
| No | 17(85.0) | 78(83.9) | | |
| Evaluation time [weeks,*M*(*Q1*,*Q3*)] | 14.0(9.0, 29.5) | 11.0(3.0, 25.5) | 0.117 | 1.566 |
| Hepatocellular carcinoma (n,%) | | | 0.347 | - |
| Yes | 20(100.0) | 85(91.4) | | |
| No | 0(0.0) | 8(8.6) | | |
| Staging of BCLC system(n,%) | | | 1.000 | 0.000 |
| B | 4(15.0) | 21(19.4) | | |
| C | 16(85.5) | 72(80.6) | | |
| HBV or HCV(n,%) | 19(77.4) | 83(85.0) | 0.710 | 0.138 |
| Cirrhosis (n,%) | 18(80.5) | 65(87.8) | 0.384 | 0.759 |
| Decompensation stage (n,%) | 6(33.3) | 61(65.6) | **0.010** | 6.559 |
| Yes | 12(66.7) | 32(34.4) | | |
| No | | | | |
| Previous or combined treatment (n,%) | 7(35.0) | 9(9.7) | **0.003** | 8.684 |
| Surgical resection | 16(80.0) | 69(74.2) | 0.585 | 0.298 |
| TAE or TACE | 11(55.0) | 44(47.3) | 0.533 | 1.389 |
| Tumor ablation | 13(85.0) | 64(68.8) | 0.740 | 0.110 |
| Targeted agent | 0(0.0) | 6(6.5) | 0.588 | - |
| Systemic chemotherapy | 1(5.0) | 13(14.0) | 0.464 | 0.535 |
| Radiotherapy | 0(0.0) | 13(14.0) | 0.120 | - |
| Name of PD-1 monoclonal antibody (n,%) | | | 0.827 | 0.048 |
| Sintilimab | 10(50.0) | 49(52.7) | | |
| Camrelizumab | 10(50.0) | 44(47.3) | | |
| Thyroid antibody (n,%) | | | 1.000 | 0.000 |
| Positive | 2(22.2) | 5(20.0) | | |
| Negative | 7(77.9) | 20(80.0) | | |

BCLC:Barcelona Clinic Liver Cancer; TAE: transarterial embolization;TACE: transar-terial chemoembolization; PD-1: programmed cell death protein 1; TSH: abnormal thyroid stimulating hormone; FT4: free thyroxine 4; FT3: free thyroxine 3

## Discussion

With the widespread use of immunosuppressant in patients with PLC, we should not only pay attention to the curative effect, but also attach importance to the adverse reactions. TD is one of the common immune related adverse reactions caused by immunosuppressants. In this retrospective study, we found that more than half of PLC patients had TD after treatment of PD1, most of them showed hypothyroidism, mainly primary, subclinical and severity grade 1–2. The degree of liver cirrhosis and treatment methods may have an impact on TD. The vast majority of TD patients have a good prognosis.

At present, the reports of TD caused by immunosuppressant PD-1 monoclonal antibody treatment mostly come from clinical trials, rather than real-world studies, especially less studies of PD-1 monoclonal antibody treatment of PLC. As a real-world retrospective study, through the analysis of the clinical data of PLC patients after PD-1 treatment, we found that the incidence of thyroid adverse reactions can be as high as 57.9%, higher than 3.4–47.7% [2, 8], reported in previous Meta analysis

**Table 4** clinical characteristics of thyroid dysfunction related to PD-1 monoclonal antibody therapy in primary liver cancer

| | Primary thyroid dysfunction (n = 93) | Secondary thyroid dysfunction (n = 20) | *P* | $t/x^2/Z$ |
|---|---|---|---|---|
| Gender (n, %) | | | 0.264 | 1.247 |
| Male | 68(73.1) | 17(85.0) | | |
| Female | 25(26.9) | 3(15.0) | | |
| Age(years,$x \pm s$) | 58.0 ± 10.7 | 61.6 ± 9.9 | 0.174 | 1.368 |
| BMI | 22.1 ± 2.7 | 23.6 ± 3.5 | 0.132 | 1.520 |
| Diabetes | | | 1.000 | 0.000 |
| Yes | 15(16.1) | 3(15.0) | | |
| No | 78(83.9) | 17(85.0) | | |
| Evaluation time [weeks,*M*(*Q1*,*Q3*)] | 12.0(3.0, 27.8) | 10.0(3.3, 17.8) | 0.412 | 0.821 |
| Hepatocellular carcinoma (n,%) | | | 0.936 | 0.007 |
| Yes | 87(93.5) | 18(90.0) | | |
| No | 6(6.5) | 2(10.0) | | |
| Staging of BCLC system(n,%) | | | 0.350 | 0.875 |
| B | 19(20.4) | 6(30.0) | | |
| C | 74(76.0) | 14(70.0) | | |
| HBV or HCV(n,%) | 83(77.4) | 19(85.0) | 0.710 | 0.138 |
| Cirrhosis (n,%) | 74(80.5) | 18(87.8) | 0.441 | 0.595 |
| Decompensation stage (n,%) | 27(36.5) | 15(83.3) | **0.002** | 9.166 |
| Yes | 41(63.5) | 3(16.7) | | |
| No | | | | |
| Previous or combined treatment (n,%) | 15(16.1) | 1(5.0) | 0.346 | 0.887 |
| Surgical resection | 69(74.2) | 16(80.0) | 0.795 | 0.086 |
| TAE or TACE | 43(46.2) | 12(60.0) | 0.264 | 1.248 |
| Tumor ablation | 68(73.1) | 9(45.0) | **0.014** | 5.995 |
| Targeted agent | 5(5.4) | 1(5.0) | 1.000 | 0.000 |
| Systemic chemotherapy | 12(12.9) | 2(10.0) | 1.000 | 0.000 |
| Radiotherapy | 12(12.9) | 1(5.0) | 0.536 | 0.383 |
| Name of PD-1 monoclonal antibody (n,%) | | | 0.319 | 0.992 |
| Sintilimab | 50(53.8) | 9(45.0) | | |
| Camrelizumab | 43(46.2) | 11(55.0) | | |
| Thyroid antibody (n,%) | | | **0.036** | - |
| Positive | 7(31.8) | 0(0.0) | | |
| Negative | 15(68.2) | 12(100.0) | | |

BCLC:Barcelona Clinic Liver Cancer; TAE: transarterial embolization;TACE: transar-terial chemoembolization; PD-1: programmed cell death protein 1; TSH: abnormal thyroid stimulating hormone; FT4: free thyroxine 4; FT3: free thyroxine 3

of drug clinical trials, 42.37% reported by Wei Fenfen [9] and 29.0% reported by Yang Zizhong [10]. There were two main reasons for this difference. On the one hand, previous studies mostly involved lung cancer, melanoma, gastrointestinal tumors, breast cancer, hematological system tumors, etc., while PLC patients were rarely included in the above studies. PLC patients often had hepatitis B (C) virus infection and liver cirrhosis, accompanied by worse thyroid function. In our study, 80% of PLC patients were in Barcelona phase C and complicated with hepatitis B (C) virus infection and cirrhosis. On the other hand, less than 20% of PLC patients in our study have previously undergone surgical resection, and more than half of them have received TAE/TACE, tumor ablation and targeted drug therapy, which will promote the production of TD [11, 12]. In addition, the selection of therapeutic drugs may also affect the incidence of TD. There had few reports on the use of cindilimab and carrelizumab in previous studies, although there was no significant difference between the two antibodies in the incidence, type and severity of TD. At present, the pathogenesis of TD in PLC patients caused by PD-1 treatment is not clear, which may be related to patients' basic thyroid diseases, basic level of thyroid stimulating hormone

**Table 5** Clinical characteristics of thyroid dysfunction associated with PD-1 monoclonal antibody therapy in primary liver cancer

| | Clinical thyroid dysfunction (n = 71) | Subclinical thyroid dysfunction (n = 42) | *P* | $t/x^2/Z$ |
|---|---|---|---|---|
| Gender (n, %) | | | 0.854 | 0.034 |
| Male | 53(73.1) | 32(85.0) | | |
| Female | 18(26.9) | 10(15.0) | | |
| Age(years,$x \pm s$) | 57.6 ± 11.0 | 60.1 ± 9.6 | 0.219 | 1.235 |
| BMI | 24.5 ± 3.7 | 22.8 ± 3.1 | 0.032 | 2.18 |
| Diabetes | | | 0.144 | 2.132 |
| Yes | 8(11.3) | 9(21.4) | | |
| No | 63(88.7) | 33(78.6) | | |
| Evaluation time [weeks,*M*(*Q1*,*Q3*)] | 10.0(3.0, 25.5) | 10.0(5.7, 21.0) | 0.503 | 0.669 |
| Hepatocellular carcinoma (n,%) | | | 0.719 | 0.546 |
| Yes | 65(92.9) | 40(91.5) | | |
| No | 6(7.1) | 2(6.1) | | |
| Staging of BCLC system(n,%) | | | 0.4480 | 0.499 |
| B | 17(24.3) | 8(19.0) | | |
| C | 53(75.7) | 35(81.0) | | |
| HBV or HCV(n,%) | 63(88.7) | 38(90.5) | 1.000 | 0.000 |
| Cirrhosis (n,%) | 54(80.5) | 38(87.8) | 0.098 | 2.736 |
| Decompensation stage (n,%) | 30(55.6) | 20(52.6) | 0.782 | 0.077 |
| Yes | 24(44.4) | 18(47.4) | | |
| No | | | | |
| Previous or combined treatment (n,%) | 7(9.9) | 9(21.4) | 0.088 | 2.906 |
| Surgical resection | 51(71.8) | 34(81.0) | 0.278 | 1.178 |
| TAE or TACE | 33(46.5) | 22(52.4) | 0.544 | 0.368 |
| Tumor ablation | 49(69.0) | 28(66.7) | 0.796 | 0.067 |
| Targeted agent | 4(5.6) | 2(4.8) | 1.000 | 0.000 |
| Systemic chemotherapy | 10(14.1) | 4(9.5) | 0.678 | 0.173 |
| Radiotherapy | 9(12.7) | 4(9.5) | 0.840 | 0.041 |
| Name of PD-1 monoclonal antibody (n,%) | | | 0.254 | 1.303 |
| Sintilimab | 40(56.3) | 19(45.2) | | |
| Camrelizumab | 31(44.4) | 23(54.8) | | |
| Thyroid antibody (n,%) | | | 0.306 | 1.050 |
| Positive | 2(11.1) | 5(31.3) | | |
| Negative | 16(88.9) | 11(68.8) | | |

BCLC:Barcelona Clinic Liver Cancer; TAE: transarterial embolization;TACE: transar-terial chemoembolization; PD-1: programmed cell death protein 1; TSH: abnormal thyroid stimulating hormone; FT4: free thyroxine 4; FT3: free thyroxine 3

and thyroid antibody, changes in the number and function of immune cells, tumor microenvironment, homology of antigen expressed between tumor and thyroid tissue, BMI, etc. [13, 14]. It is speculated that it may be the direct effect of drugs on thyroid function or the result secondary to thyroiditis. We also found that the BMI index of patients with clinical TD was higher than that of patients with subclinical TD, which was consistent with the previous findings of Pollack et al.[15]. The mechanism may be that the Th1/Th2 imbalance and proinflammatory state caused by high levels of adipokines (leptin, adiponectin, resistin, visfatin) and cytokines (eg, tumor necrosis factor-α, interleukin-6 and interleukin-1β) in patients with high BMI.

We found that the incidence of hypothyroidism and hyperthyroidism were 47.7% and 10.3% respectively in PLC patients treated with PD-1, hypothyroidism was 4.6 times higher than hyperthyroidism. Previous meta-analysis had reported that the incidence of hypothyroidism after PD-1 treatment was 10–16.4%, and the incidence of hyperthyroidism was 9–10.4%. There was little difference between the two, but our study showed that the

**Table 6** Clinical characteristics of thyroid dysfunction associated with PD-1 monoclonal antibody therapy in primary liver cancer

| | Clinical hyperthyroidism (n = 14) | Clinical hypothyroidism (n = 28) | *P* | $t/x^2/Z$ |
|---|---|---|---|---|
| Gender (n, %) | | | 0.522 | 0.410 |
| Male | 12(85.7) | 20(71.4) | | |
| Female | 2(14.3) | 8(28.6) | | |
| Age(years,$x \pm s$) | 61.5 ± 9.9 | 57.1 ± 8.7 | 0.167 | 1.408 |
| BMI | 24.9 ± 2.6 | 24.3 ± 3.9 | 0.698 | 0.394 |
| Diabetes | | | 1.000 | 0.000 |
| Yes | 3(21.4) | 5(17.9) | | |
| No | 11(78.6) | 23(82.1) | | |
| Evaluation time [weeks,*M*(*Q1*,*Q3*)] | 11.5(3.0, 30.0) | 11.0(3.0, 23.3) | 0.742 | 0.348 |
| Hepatocellular carcinoma (n,%) | | | 0.545 | - |
| Yes | 14(100.0) | 26(92.9) | | |
| No | 0(0.0) | 2(7.1) | | |
| Staging of BCLC system(n,%) | | | 1.000 | 0.000 |
| B | 3(15.0) | 5(19.4) | | |
| C | 13(85.5) | 23(80.6) | | |
| HBV or HCV(n,%) | 14(77.4) | 24(85.0) | 0.283 | - |
| Cirrhosis (n,%) | 13(80.5) | 25(87.8) | 1.000 | 0.000 |
| Decompensation stage (n,%) | 3(23.1) | 17(68.0) | **0.022** | 5.238 |
| Yes | 10(76.9) | 8(32.0) | | |
| No | | | | |
| Previous or combined treatment (n,%) | 6(42.9) | 2(7.1) | **0.018** | 5.527 |
| Surgical resection | 12(85.7) | 22(78.6) | 0.578 | 0.309 |
| TAE or TACE | 8(57.1) | 14(50.0) | 0.662 | 0.191 |
| Tumor ablation | 9(64.3) | 19(67.9) | 0.817 | 0.05 |
| Targeted agent | 0(0.0) | 2(7.1) | 0.545 | - |
| Systemic chemotherapy | 1(7.1) | 3(10.7) | 1.000 | 0.000 |
| Radiotherapy | 0(0.0) | 4(14.3) | 0.283 | - |
| Name of PD-1 monoclonal antibody (n,%) | | | 0.273 | 1.201 |
| Sintilimab | 8(57.1) | 11(39.3) | | |
| Camrelizumab | 6(42.9) | 17(60.7) | | |
| Thyroid antibody (n,%) | | | 1.000 | 0.000 |
| Positive | 2(40.0) | 3(27.3) | | |
| Negative | 3(60.0) | 8(72.7) | | |

BCLC:Barcelona Clinic Liver Cancer; TAE: transarterial embolization;TACE: transar-terial chemoembolization; PD-1: programmed cell death protein 1; TSH: abnormal thyroid stimulating hormone; FT4: free thyroxine 4; FT3: free thyroxine 3

incidence of hypothyroidism was much higher than that of hyperthyroidism. Previous meta-analysis [16] reported that the incidence of hypothyroidism after PD-1 treatment was 10–16.4%, and the incidence of hyperthyroidism was 9–10.4%. There was little difference between the two, but our study showed that the incidence of hypothyroidism was much higher than that of hyperthyroidism. The incidence of hypothyroidism in these patients is high, but not serious. Less than 1/3 of them have clinical symptoms, and only 7.5% of them have adverse reactions above grade 3. On the contrary, the incidence of hyperthyroidism in these patients is low, but more than 2/3 of them have clinical symptoms, and 15.0% of them have adverse reactions above grade 3. Among the 10 patients with severity above grade 3, there were 3 patients with hyperthyroidism and 7 patients with hypothyroidism. Except that 2 patients with hyperthyroidism did not fully recover and 2 patients with hypothyroidism died of liver failure, the remaining 1 patient with hyperthyroidism and 5 patients with hypothyroidism fully recovered after treatment. Therefore, as long as TD can be found in time and treated actively, most patients with TD have a good prognosis. The high incidence of subclinical TD suggests that we need to closely monitor thyroid function in the

**Table 7** The clinical characteristics of patients with thyroid dysfunction caused by PD-1 monoclonal antibody therapy classified as grade 3 by CTCAE

| Case | Sex | Age | Name of PD-1 | Hepatitis virus | Cirrhosis | Decompensation stage | Staging of BCLC system | Previous or combined treatment | Thyroid antibody |
|---|---|---|---|---|---|---|---|---|---|
| 1 | M | 67 | S* | HBV | Yes | Yes | C | TACE, Targeted agent | No detect |
| 2 | F | 70 | C** | No | No | – | C | None | Negative |
| 3 | M | 43 | C | HBV | Yes | Yes | C | TACE | Negative |
| 4 | F | 49 | C | HBV | No | – | C | TACE, Tumor ablation, Systemic chemotherapy | No detect |
| 5 | M | 62 | C | HBV | Yes | No | C | Surgical resection, TACE, Tumor ablation, Targeted agent, Radiotherapy | TPO, TG positive |
| 6 | F | 58 | C | HBV | Yes | No | C | TACE, Tumor ablationTargeted agent, Radiotherapy | No |
| 7 | M | 58 | C | HBV | Yes | No | C | TACE, Tumor ablation, Targeted agent | No |
| 8 | M | 67 | C | HBV | Yes | No | B | TACE, Tumor ablation, Targeted agent | No |
| 9 | M | 47 | C | HBV | Yes | No | B | Surgical resection, TACE, Tumor ablation | No |
| 10 | M | 84 | C | HBV | Yes | Yes | C | Targeted agent | TPO, TG positive |

*Sintilimab; **Camrelizumab; TACE: transar-terial chemoembolization; PD-1: programmed cell death protein 1; TPO: thyroid peroxide-se antibody; TG: thyroglobulin antibody;

**Table 8** The symptoms and prognosis of patients with thyroid dysfunction caused by PD-1 monoclonal antibody therapy classified as grade 3 by CTCAE

| Case | Discovery time(week) | classification | First symptoms | Medication | PD-1 interrupt | Recovery of thyroid function | Tumor evaluation | Prognosis |
|---|---|---|---|---|---|---|---|---|
| 1 | 8 | Primary hyperthyroidism | Palpitation | Methimazole, propranolol | Yes | Full recovery | shrinkage | Persistence |
| 2 | 12 | Secondary hyperthyroidism | Loss of appetite, fatigue | Levothyroxine | Yes | Not recovered | progression | Death |
| 3 | 1 | Secondary hyperthyroidism | Loss of appetite, fatigue, edema | Levothyroxine | Yes | Not recovered | progression | Death |
| 4 | 26 | Primary hyperthyroidism | fatigue | Levothyroxine | No | Full recovery | progression | Persistence |
| 5 | 28 | Primary hyperthyroidism | Emaciation, fatigue | Methimazole | Yes | Partial recovery | Stability | Persistence |
| 6 | 36 | Primary hyperthyroidism | Loss of appetite, fatigue | Levothyroxine | Yes | Full recovery | Stability | Persistence |
| 7 | 24 | Primary hyperthyroidism | Edema | Levothyroxine | Yes | Full recovery | progression | Persistence |
| 8 | 12 | Primary hyperthyroidism | Edema, fatigue | Levothyroxine | Yes | Full recovery | Stability | Persistence |
| 9 | 3 | Primary hyperthyroidism | Fatigue, fidgety | unclear | Yes | Partial recovery | progression | Persistence |
| 10 | 35 | Secondary hyperthyroidism | Edema, fatigue | non-administration | Yes | unclear | progression | Persistence |

process of PD-1 treatment of PLC. When patients have common clinical symptoms of TD, such as fatigue, palpitation, loss of appetite, weight loss, edema and irritability, we need to be vigilant and give diagnosis and treatment in time to reduce the possibility of interrupting PD-1 treatment.

We also found some interesting differences. For example, the proportion of decompensated liver

cirrhosis was higher in the hypothyroidism group, especially in the clinical hypothyroidism group and the primary TD group, and the proportion of patients with previous surgery was higher in the hyperthyroidism group, especially in the clinical hyperthyroidism group, and the proportion of patients with previous or combined use of targeted drugs was the highest in the primary TD group. Previous studies have found that the liver is an organ that has an important impact on thyroid hormone metabolism in addition to the thyroid [17, 18]. The transformation and inactivation of thyroid hormones require the participation of the liver, including metabolic processes such as deiodination, deamination and combined bile secretion, and the synthesis of thyroid hormone binding protein is also completed in the liver. If the damage of hepatocytes leads to the decline of liver function, the production of thyroid hormone and binding protein will be significantly affected, resulting in the decrease of thyroid hormone and even thyroid atrophy and degradation, especially in decompensated liver cirrhosis. Therefore, it is easier to develop hypothyroidism in patients with decompensated liver cirrhosis who use immunosuppressant such as PD-1 to produce TD. The reason why the proportion of patients with hyperthyroidism treated by surgical resection increased significantly may be related to the high probability of surgical resection caused by the early detection of PLC. Due to the high recurrence rate of liver cancer after operation, the total diagnosis and treatment time of these patients is longer because of the subsequent recurrence and treatment. Therefore, trauma and stress caused by surgical treatment itself, immune function damage, and the ability to receive more iodine containing contrast agents in the process of long-term diagnosis and treatment may be part of the inducement for hyperthyroidism after PD-1 treatment [19]. PD-1 combined with molecular targeted drugs was commonly used in the treatment of liver cancer. The targeted drugs were tyrosine kinase inhibitors (TKIs), including sorafenib, renvatinib, bevacizumab and regofinib. Previous studies had shown that the probability of TD after TKIs treatment was high. Koizumi et al. [20] found that there were 7 (14.0%), 26 (52.0%) and 5 (10.0%) patients with subclinical hypothyroidism, dominant hypothyroidism and thyrotoxicosis in 50 patients with advanced liver cancer treated with renvatinib. At present, it was considered that the mechanism of TD caused by TKIs drugs may be related to the effect of drugs on tyrosine kinase in thyroid vascular function. For example, TKIs inhibits blood vessels, leading to ischemic thyroiditis, causing transient thyrotoxicosis, or hypothyroidism due to the decrease of thyroid blood supply and the gradual destruction of thyroid gland [21, 22]. In addition, TKI could also affect the synthesis of thyroid hormone by inhibiting the transport of iodothyronine [23] and produce immunostimulatory properties by inhibiting the expression of CTLA4 and PD1 on CD4 + T and CD8 + T cells [24]. Therefore, PD-1 inhibitors combined with targeted drugs were more prone to primary TD in the treatment of liver cancer.

## Conclusion

To sum up, by analyzing the changes of thyroid function in PLC patients treated with PD-1 inhibitors in the real world, our study found that the incidence of TD was higher than that in previous clinical trials, but the degree of adverse reactions was mild. Patients with grade 3 adverse reactions could recover after treatment, and most of them did not need to interrupt PD-1 treatment. The clinical types of TD are mainly primary, subclinical and hypothyroidism. Some combined treatment schemes also have a certain impact on TD. In addition, since female were more likely to have thyroid diseases than male, the low proportion of female in this study may affect the research results. Therefore, it is necessary to detect the thyroid function of PLC patients using PD-1 inhibitor regularly and intervene in time to ensure the smooth progress of treatment.

#### Acknowledgements

Not applicable.

#### Author contributions

Huili Wu conceived and designed the study and wrote the paper.. Fang Xiong and Xuli Bao collected the samples and performed the clinical part of the study. Huili Wu and Jun Lu participated in manuscript editing. Notably, all authors approved the definitive version of the manuscript.

#### Funding

This research was supported by: 1, Peak talent plan of Beijing Medical Management Center (DFL20021502). 2, Project of Beijing Municipal Commission of science and technology (Z211100002521029). 3, Capital health development scientific research project (2018-1-2181). 4, Original exploration program of NSFC guidance (82150110). 5, 2021 youth project of Beijing You'an Hospital Affiliated to Capital Medical University (YNKTQN2021008).

#### Availability of data and materials

All data generated or analysed during this study are included in this article. The other raw datasets used and/or analysed in this study will be made available upon reasonable request to the corresponding author.

### Declarations

#### Ethics approval and consent to participate

The study protocol and ethical issue were approved by Ethics Committee of Beijing You'an Hospital Affiliated to Capital Medical University (LL-2021-184-K). All participants were informed of the objectives of this study and signed a written consent form prior to their participation.

#### Consent for publication

Not applicable.

**Competing interests**
All authors declare they have no competing financial or intellectual interests.

Received: 9 July 2022 Accepted: 7 December 2022
Published online: 29 December 2022

**References**

1. Zeng H, Chen W, Zheng R, Zhang S, Ji J-S, Zou X, et al. Changing cancer survival in China during 2003–15: a pooled analysis of 17 population-based cancer registries. Lancet Glob Health. 2018;6:e555–67. https://doi.org/10.1016/s2214-109x(18)30127-x.
2. Barroso-Sousa R, Barry WT, Garrido-Castro AC, Hodi FS, Min L, Krop IE, et al. Incidence of endocrine dysfunction following the use of different immune checkpoint inhibitor regimens: a systematic review and meta-analysis. JAMA Oncol. 2018;4:173–82. https://doi.org/10.1001/jamaoncol.2017.3064.
3. Bruix J, Sherman M, Llovet JM, Beaugrand M, Lencioni R, Burroughs AK, et al. Clinical management of hepatocellular carcinoma. Conclusions of the Barcelona-2000 EASL conference. European Association for the Study of the Liver. J Hepatol. 2001;35:421–30. https://doi.org/10.1016/s0168-8278(01)00130-1.
4. Thompson JA, Schneider BJ, Brahmer J, Andrews S, Armand P, Bhatia S, et al. NCCN guidelines insights: management of immunotherapy-related toxicities, version 1.2020. J Natl Compr Canc Netw. 2020;18:230–41. https://doi.org/10.6004/jnccn.2020.0012.
5. Ross DS, Burch HB, Cooper DS, Greenlee MC, Laurberg P, Maia AL, et al. 2016 American thyroid association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016;26:1343–421. https://doi.org/10.1089/thy.2016.0229.
6. Freites-Martinez A, Santana N, Arias-Santiago S, Viera A. Using the common terminology criteria for adverse events (CTCAE—version 50) to evaluate the severity of adverse events of anticancer therapies. Actas Dermosifiliogr Engl Ed. 2021;112:90–2. https://doi.org/10.1016/j.ad.2019.05.009.
7. Schneider BJ, Naidoo J. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. J Clin Oncol. 2021;39:4073–126. https://doi.org/10.1200/jco.21.01440.
8. Antonia SJ, Borghaei H, Ramalingam SS, Horn L, De Castro CJ, Pluzanski A, et al. Four-year survival with nivolumab in patients with previously treated advanced non-small-cell lung cancer: a pooled analysis. Lancet Oncol. 2019;20:1395–408. https://doi.org/10.1016/s1470-2045(19)30407-3.
9. Wei F-F, Xiang L, Song G, Chen Z-D. Study on the occurrence and related factors of thyroid dysfunction caused by PD-1 monoclonal antibody. Chin Clin Oncol. 2020;25:930–4. https://doi.org/10.3969/j.issn.1009-0460.2020.10.013.
10. Yang Z-Z, Zhang G-Q, Qin B-Y, Zhang J, Sun Q, Li B-Q, et al. Clinical characters and influence factors of immune checkpoint inhibitor related thyroiditis. Med J Chin PLA. 2021;46:989–96. https://doi.org/10.11855/j.issn.0577-7402.2021.10.0610.
11. Arnaud-Coffin P, Maillet D, Gan HK, Stelmes JJ, You B, Dalle S, et al. A systematic review of adverse events in randomized trials assessing immune checkpoint inhibitors. Int J Cancer. 2019;145:639–48. https://doi.org/10.1002/ijc.32132.
12. Lee H, Hodi FS, Giobbie-Hurder A, Ott PA, Buchbinder EI, Haq R, et al. Characterization of thyroid disorders in patients receiving immune checkpoint inhibition therapy. Cancer Immunol Res. 2017;5:1133–40. https://doi.org/10.1158/2326-6066.cir-17-0208.
13. Agrawal L, Bacal A, Jain S, Singh V, Emanuele N, Emanuele M, et al. Immune checkpoint inhibitors and endocrine side effects, a narrative review. Postgrad Med. 2020;132:206–14. https://doi.org/10.1080/00325481.2019.1709344.
14. Delivanis DA, Gustafson MP, Bornschlegl S, Merten MM, Kottschade L, Withers S, et al. Pembrolizumab-induced thyroiditis: comprehensive clinical review and insights into underlying involved mechanisms. J Clin Endocrinol Metab. 2017;102:2770–80. https://doi.org/10.1210/jc.2017-00448.
15. Pollack R, Ashash A, Cahn A, Rottenberg Y, Stern H, Dresner-Pollak R. Immune checkpoint inhibitor-induced thyroid dysfunction is associated with higher body mass index. J Clin Endocrinol Metab. 2020. https://doi.org/10.1210/clinem/dgaa458.
16. de Filette J, Andreescu CE, Cools F, Bravenboer B, Velkeniers B. A systematic review and meta-analysis of endocrine-related adverse events associated with immune checkpoint inhibitors. Horm Metab Res. 2019;51:145–56. https://doi.org/10.1055/a-0843-3366.
17. Piantanida E, Ippolito S, Gallo D, Masiello E, Premoli P, Cusini C, et al. The interplay between thyroid and liver: implications for clinical practice. J Endocrinol Invest. 2020;43:885–99. https://doi.org/10.1007/s40618-020-01208-6.
18. Malespin M, Nassri A. Endocrine diseases and the liver: an update. Clin Liver Dis. 2019;23:233–46. https://doi.org/10.1016/j.cld.2018.12.006.
19. Kahaly GJ, Bartalena L, Hegedüs L, Leenhardt L, Poppe K, Pearce SH. 2018 European thyroid association guideline for the management of graves' hyperthyroidism. Eur Thyroid J. 2018;7:167–86. https://doi.org/10.1159/000490384.
20. Koizumi Y, Hirooka M, Hiraoka A, Ochi H, Tanaka T, Yukimoto A, et al. Lenvatinib-induced thyroid abnormalities in unresectable hepatocellular carcinoma. Endocr J. 2019;66:787–92. https://doi.org/10.1507/endocrj.EJ19-0140.
21. Rogiers A, Wolter P, Op de Beeck K, Thijs M, Decallonne B, Schöffski P. Shrinkage of thyroid volume in sunitinib-treated patients with renal-cell carcinoma: a potential marker of irreversible thyroid dysfunction? Thyroid. 2010;20:317–22. https://doi.org/10.1089/thy.2009.0125.
22. Illouz F, Braun D, Briet C, Schweizer U, Rodien P. Endocrine side-effects of anti-cancer drugs: thyroid effects of tyrosine kinase inhibitors. Eur J Endocrinol. 2014;171:R91-99. https://doi.org/10.1530/eje-14-0198.
23. Braun D, Kim TD, le Coutre P, Köhrle J, Hershman JM, Schweizer U. Tyrosine kinase inhibitors noncompetitively inhibit MCT8-mediated iodothyronine transport. J Clin Endocrinol Metab. 2012;97:E100-105. https://doi.org/10.1210/jc.2011-1837.
24. Jannin A, Penel N, Ladsous M, Vantyghem MC, Do CC. Tyrosine kinase inhibitors and immune checkpoint inhibitors-induced thyroid disorders. Crit Rev Oncol Hematol. 2019;141:23–35. https://doi.org/10.1016/j.critrevonc.2019.05.015.

## Publisher's Note