Changes in thyroid hormone levels indicate immunotherapy efficacy in gastric cancer

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Abstract. Immune-related thyroid dysfunction (irTD) has been associated with clinical outcomes in non-endocrine tumors. However, the association between irTD and therapeutic efficacy or prognosis in gastric cancer remains unclear. The present study retrospectively investigated the occurrence of irTD during immunotherapy for gastric cancer and analyzed its association with clinical efficacy and patient prognosis. A total of 106 patients with advanced gastric cancer, treated with either first-line or second-line programmed cell death protein 1 (PD-1) monoclonal antibody (MAB) in combination with chemotherapy between January 2019 and December 2022 at the Department of Oncology of Changzhou Tumor Hospital (Changzhou, China), were included. Thyroid hormone levels, including thyroid-stimulating hormone, free thyroxine, free triiodothyronine and thyroid peroxidase (TPO), were determined before and after treatment using the electroluminescence method. The changes in the levels of thyroid hormones based on various clinical characteristics were evaluated in relation to the treatment outcomes, including progression-free survival (PFS) and overall survival (OS), in response to PD-1 MAB therapy. No significant associations were detected between the thyroid hormone levels and different clinical characteristics. Among the patients receiving first-line treatment, 40.6% developed irTD and 49.3% experienced TPO abnormalities. Patients with irTD demonstrated a significantly longer median PFS time than those without irTD (312.0±47.6 vs. 222.0±14.7 days; P=0.040), although no significant difference was noted in the median OS time. Similarly, patients with TPO abnormalities exhibited a longer median PFS time when compared to those without abnormalities (312.0±52.5 vs. 222.0±13.6 days; P=0.006), yet no significant difference was noted in the median OS time. In the second-line treatment, the incidence of irTD was 45.9, and 59.5% of the patients showed TPO abnormalities. Although there were no statistically significant differences in the median PFS or OS times between patients without or with irTD or TPO abnormalities, a trend toward longer PFS and OS was recorded in patients with TPO abnormalities. In conclusion, the occurrence of irTD and TPO abnormalities is associated with better efficacy and prolonged survival in patients with gastric cancer undergoing immunotherapy. These thyroid-related changes may serve as valuable biomarkers for predicting the response to PD-1 MAB therapy in this patient population.

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Abbreviations: MAB, monoclonal antibody; TPO, thyroid peroxidase; PFS, progression-free survival; OS, overall survival; irTD, immune-related thyroid dysfunction; irAE, immune-related adverse event; ICI, immune checkpoint inhibitor; PD, progressive disease; SD, stable disease; PR, partial remission; CR, complete remission; NSCLC, non-small cell lung cancer

Key words: thyroid hormone, immunotherapy, gastric cancer, irAE, irTD

Introduction

According to the GLOBOCAN 2020 estimates, as compiled by the International Agency for Research on Cancer, ~19.3 million new cancer cases and nearly 10 million cancer-related deaths (excluding non-melanoma skin cancer) occurred globally in 2020. Gastric cancer ranked fifth in terms of incidence and fourth in terms of mortality worldwide (1). In China, according to the National Cancer Registry Report, gastric cancer ranked third in terms of both incidence and mortality among all malignant tumors in 2020. The incidence of gastric cancer was significantly higher in men than in women. In 2020, China recorded 480,000 new cases of gastric cancer and 370,000 associated deaths, with gastric cancer projected to remain the fourth-most common malignancy in the country by the year 2022. Although the incidence and mortality rates of gastric cancer have slightly declined since 2020, the disease continues to pose a significant threat to public health, with 358,700 new cases and 260,400 associated deaths reported in China in 2022 (2,3).

Owing to the high heterogeneity of gastric cancer, traditional treatment modalities, such as chemotherapy, surgery, radiotherapy, targeted drug therapy and traditional Chinese medicine therapy (4-6), can only achieve suboptimal clinical outcomes. In recent years, targeted drugs or other drugs combined with chemotherapy have become the focus of clinical

and basic research on gastric cancer, and some progress has been made in reversing chemotherapy resistance and increasing drug efficacy (7-10). However, immunotherapy, particularly with programmed cell death protein 1 (PD-1)/programmed death ligand 1 (PD-L1) monoclonal antibodies (MABs), has demonstrated significant advancements in the treatment of advanced gastric cancer, irrespective of HER2 expression level. PD-1 MABs combined with chemotherapy have now become the standard first-line therapy for advanced gastric cancer (11-16).

With the increasing use of PD-1 MABs, which play a critical role in improving immune tolerance, the incidence of immune-related adverse events (irAEs) has also risen. These adverse events can affect various organs, with the most commonly impacted ones being the skin, colon, liver, lungs and endocrine organs (17,18). Endocrine dysfunctions, including thyroid dysfunction, insulin-deficient diabetes, pituitaritis and primary adrenal insufficiency, are some of the most common complications associated with immune checkpoint inhibitors (ICIs) (19-21). Past studies on non-endocrine tumors, such as lung cancer and melanoma, have identified an association between immune-related thyroid dysfunction (irTD) and clinical outcomes, including increased efficacy and prognosis (22-26). However, the association between irTD and therapeutic efficacy or prognosis in gastric cancer remains unclear. Therefore, the present retrospective study was conducted to investigate the occurrence of irTD during immunotherapy for gastric cancer and to analyze its association with the resultant clinical efficacy and patient prognosis.

Patients and methods

Subjects. The present retrospective study was conducted on patients with advanced gastric cancer who received PD-1 MAB combined with chemotherapy in the Department of Oncology of Changzhou Tumor Hospital (Chongqing, China) between January 2019 and December 2022. The patients were divided into first-line (n=69) and second-line (n=37) treatment groups. All patients had complete medical and follow-up records irrespective of their HER-2 status. The following inclusion criteria were applied: i) Age >18 years; ii) gastric adenocarcinoma or gastroesophageal junction adenocarcinoma confirmed by pathology and clinical stage IV (according to the 8th edition of the American Joint Committee on Cancer Cancer Staging Manual) (27); iii) administration of at least 2 cycles of chemotherapy combined with PD-1 MAB treatment; iv) no history of thyroid hormone drug therapy before the treatment; and v) near doubling of the levels of thyroid hormones [thyroid-stimulating hormone (TSH), thyroid peroxidase (TPO), thyroxine (T4)/free T4 (FT4) and triiodothyronine (T3)/free T3 (FT3)] after the initiation of immunotherapy. The exclusion criteria included: i) A history of thyroid underlying disease; and ii) having received less than two courses of immunotherapy. The study protocol was approved by the Ethics Committee of the Changzhou Tumor Hospital [approval no. 2023 (SR) NO.003].

Research methods

Patient data. The baseline data from patient's medical records were collected for the following parameters: Age, sex, site of gastric cancer, site of metastasis, comprehensive treatment line number and combined chemotherapy scheme, and TSH, FT4, FT3 and TPO levels.

Outcome measures. For irTD, the time, management and outcome of the first occurrence of thyroid dysfunction were recorded. Subclinical hypothyroidism was classified as TSH >5 μIU/ml and a normal FT4/FT3 level (FT3: 3.1-6.8 pmol/l; FT4: 12-22 pmol/l). Subclinical hyperthyroidism was classified as TSH <0.4 μIU/ml and a normal FT4/FT3 level. Hypothyroidism was classified as TSH >5 μIU/ml and a lower than normal FT4/FT3 level, or TSH ≥10 μIU/ml, regardless of the FT4/FT3 level. Hyperthyroidism was classified as TSH <0.4 μIU/ml and an higher than normal FT4/FT3 level.

Clinical efficacy and research objectives. According to the evaluation criteria listed in RECIST1.1 guidelines (28), the efficacy was categorized into progressive disease (PD), stable disease (SD), partial remission (PR) and complete remission (CR). The sum of CR + PR proportion statistics was considered as the objective response rate (ORR), and the sum of CR + PR + SD proportion statistics was considered as the disease control rate (DCR). Progression-free survival (PFS) was defined as the time from initial chemotherapy combined with immunotherapy until PD or death from any cause. Overall survival (OS) after initial treatment was assessed by using the follow-up data.

Statistical grouping. Based on the occurrence of thyroid dysfunction after treatment, the patients were categorized into irTD and non-irTD groups, and then further divided into a TPO-change group and no-TPO-change group based on whether a TPO change occurred.

Statistical analysis. SPSS26.0 statistical software (IBM Corp.) was used for statistical analysis and processing. All measurement data conforming to a normal distribution are presented as the mean ± standard deviation, and an independent sample t-test was performed for comparison among two groups. When three groups were compared, one-way ANOVA was used for intergroup comparisons. The counting data are described as n (%), and the differences between the groups were analyzed by the χ^2 test or Fisher's exact probability method. Single-factor survival analysis was performed using the Kaplan-Meier method and survival curves were drawn. Meanwhile, PFS and OS between the groups were compared using a log-rank non-parametric test. P<0.05 was considered to indicate a statistically significant difference.

Results

General information

Changes in irTD and TPO levels in patients with first-line gastric cancer with different clinical characteristics. Among the 69 patients with advanced gastric cancer who received first-line treatment, 28 (40.6%) developed irTD. All cases of irTD were hypothyroidism, with clinical hypothyroidism being the most prevalent type (25 cases; 89.3%) and subclinical hypothyroidism occurring in 3 (10.7%) cases. TPO abnormalities were observed in 34 (49.3%) patients, and all patients with irTD exhibited TPO abnormalities. However, 6 patients with TPO abnormalities did not develop irTD. No significant associations were found between irTD or TPO abnormalities and clinical characteristics, such as age, sex, tumor location,

Table I. Occurrence of immune-related thyroid dysfunction in patients with gastric cancer with different clinical characteristics in first-line treatment.

Characteristic	Thyroid function normal group (n=41)	Thyroid function abnormal group (n=28)	Statistic	P-value
Mean age ± SD, years	66.66±10.77	67.68±9.89	-0.40	0.6910
Sex, n (%)				
Male	27 (65.85)	19 (67.86)	0.03	0.8624
Female	14 (34.15)	9 (32.14)		
Metastatic site, n (%)				
Liver	16 (39.02)	14 (50.00)	0.82	0.3665
Others	25 (60.98)	14 (50.00)		
Treatment, n (%)				
Oxaliplatin	24 (58.54)	13 (46.43)	1.53	0.4643
Nab-paclitaxel	8 (19.51)	9 (32.14)		
Other treatment	9 (21.95)	6 (21.43)		
Site of gastric cancer, n (%)				
GEJ	11 (26.83)	10 (35.71)	0.62	0.4309
Non-GEJ	30 (73.17)	18 (64.29)		

GEJ, gastroesophageal junction.

Table II. Occurrence of TPO change in gastric cancer patients with different clinical characteristics in first-line treatment.

Characteristic	TPO normal group (n=35)	TPO abnormal group (n=34)	Statistic	P-value
Mean age ± SD, years	67.26±10.50	66.88±10.37	0.15	0.8819
Sex, n (%)				
Male	22 (62.86)	24 (70.59)	0.46	0.4958
Female	13 (37.14)	10 (29.41)		
Metastatic site, n (%)				
Liver	13 (37.14)	17 (50.00)	1.16	0.2814
Others	22 (62.86)	17 (50.00)		
Treatment, n (%)				
Oxaliplatin	19 (54.29)	18 (52.94)	0.14	0.9333
Nab-paclitaxel	8 (22.86)	9 (26.47)		
Other treatment	8 (22.86)	7 (20.59)		
Site of gastric cancer, n (%)				
GEJ	9 (25.71)	12 (35.29)	0.75	0.3872
Non-GEJ	26 (74.29)	22 (64.71)		

GEJ, gastroesophageal junction; TPO, thyroid peroxidase.

metastatic organs or the main first-line treatment drugs, as detailed in Tables I and II.

Association between clinical characteristics and patient outcomes in first-line gastric cancer treatment. In patients receiving first-line treatment for gastric cancer, clinical characteristics, such as age, sex, tumor site, metastatic organs and the main first-line treatment drugs, showed no significant associations with the clinical outcomes. These results are presented in Table III.

Incidence of irTD and TPO abnormalities in patients receiving second-line treatment for gastric cancer. Among the 37 patients treated with second-line therapy for advanced gastric cancer, 17 (45.9%) developed irTD. All cases of irTD were associated with hypothyroidism, with clinical hypothyroidism being the most common form (16 cases, 94.1%), while 1 case of subclinical hypothyroidism was observed (5.9%). TPO abnormalities were present in 22 (59.5%) patients. All patients with irTD also exhibited TPO abnormalities, although

Table III. Associations between the best clinical efficacy in first-line treatment for gastric cancer patients and different clinical characteristics.

Characteristic	PD (n=13)	PR (n=29)	SD (n=27)	Statistic	P-value
Mean age ± SD, years	68.77±9.47	68.31±11.39	64.93±9.58	0.96	0.3882
Sex, n (%)					
Male	8 (61.54)	18 (62.07)	20 (74.07)	1.10	0.5780
Female	5 (38.46)	11 (37.93)	7 (25.93)		
Metastatic site, n (%)					
Liver	8 (61.54)	10 (34.48)	12 (44.44)	2.69	0.2605
Others	5 (38.46)	19 (65.52)	15 (55.56)		
Treatment, n (%)					
Oxaliplatin	5 (38.46)	14 (48.28)	18 (66.67)	4.54	0.3418
Nab-paclitaxel	3 (23.08)	9 (31.03)	5 (18.52)		
Other treatment	5 (38.46)	6 (20.69)	4 (14.81)		
Site of gastric cancer, n (%)					
GEJ	4 (30.77)	9 (31.03)	8 (29.63)	0.01	0.9931
Non-GEJ	9 (69.23)	20 (68.97)	19 (70.37)		
Thyroid function, n (%)					
Normal group	5 (38.46)	17 (58.62)	19 (70.37)	3.72	0.1558
Abnormal group	8 (61.54)	12 (41.38)	8 (29.63)		

GEJ, gastroesophageal junction; PD, progressive disease; PR, partial response; SD, stable disease.

5 patients had TPO abnormalities without irTD. The data are presented in Tables IV and V.

Association between clinical characteristics and treatment efficacy in patients with second-line gastric cancer. In second-line treatment for gastric cancer, no significant associations were observed between clinical characteristics, such as age, sex, tumor site, metastatic organs or the primary second-line treatment drugs, and clinical outcomes. These findings are summarized in Table VI.

Efficacy evaluation and survival analysis

Association between irTD and PFS/OS in patients with first-line gastric cancer. In patients with first-line gastric cancer, those with irTD had a median PFS time of 312.0±47.6 days compared to 222.0±14.7 days in patients without irTD. This difference was statistically significant (P=0.040), indicating that patients with irTD experienced longer PFS times. However, there was no statistically significant difference in the median OS time, which was 417.0±121.5 days for patients with irTD vs. 388.0±17.7 days for those without irTD (P=0.483). While a trend toward longer OS time was indicated in patients with irTD, the difference did not reach statistical significance (Fig. 1).

Association between TPO abnormalities and PFS/OS in patients with first-line gastric cancer. In patients with first-line gastric cancer with TPO abnormalities, the median PFS time was 312.0±52.5 days compared with 222.0±13.6 days in patients without TPO abnormalities. This difference was statistically significant (P=0.006), suggesting that patients with TPO abnormalities had significantly longer PFS times. However, the median OS time was 460.0±160.2 days for patients with TPO abnormalities vs. 388.0±20.2 days for those without, and this difference was not statistically significant (P=0.257). While patients with TPO abnormalities exhibited a trend toward longer OS time, the difference was not statistically significant (Fig. 2).

Association between irTD and PFS/OS in patients with second-line gastric cancer. In patients with second-line gastric cancer, those with irTD had a median PFS time of 182.0±8.2 days compared with 167.0±4.5 days in patients without irTD. There was no statistically significant difference between the two groups (P=0.429). Similarly, the median OS time was 385.0±98.1 days for patients with irTD vs. 299.0±80.5 days for those without, and although there was a trend toward longer OS time in patients with irTD, the difference was not statistically significant (P=0.066) (Fig. 3).

Association between TPO abnormalities and PFS/OS in patients with second-line gastric cancer. Among patients with second-line gastric cancer, those with TPO abnormalities had a median PFS time of 189.0±31.7 days when compared with 163.0±25.6 days in patients without TPO abnormalities. Although there was a trend toward longer PFS time in patients with TPO abnormalities, the difference was not statistically significant (P=0.112). The median OS time was 385.0±51.6 days for patients with TPO abnormalities vs. 232.0±51.5 days for those without. While patients with TPO abnormalities showed a trend toward longer OS, the difference was not statistically significant (P=0.089) (Fig. 4).

Discussion

Gastric cancer is one of the most prevalent malignant tumors globally, with its morbidity and mortality rates ranking among

Table IV. Occurrence of immune-related thyroid dysfunction in patients with gastric cancer with different clinical characteristics in second-line treatment.

Characteristic	Thyroid function normal group (n=22)	Thyroid function abnormal group (n=17)	Statistic	P-value
Mean age ± SD, years	65.75±9.86	62.18±9.55	1.11	0.2726
Sex, n (%)				
Male	14 (70.00)	15 (88.24)	-	0.2455
Female	6 (30.00)	2 (11.76)		
Metastatic site, n (%)				
Liver	10 (50.00)	8 (47.06)	-	>0.9999
Others	10 (50.00)	9 (52.94)		
Treatment, n (%)				
Oxaliplatin	0 (0.00)	3 (17.65)		0.0648
Nab-paclitaxel	4 (20.00)	6 (35.29)		
Irinotecan	6 (30.00)	1 (5.88)		
Other treatment	10 (50.00)	7 (41.18)		
Site of gastric cancer, n (%)				
GEJ	8 (40.00)	7 (41.18)	-	>0.9999
Non-GEJ	12 (60.00)	10 (58.82)		

GEJ, gastroesophageal junction.

Table V. Occurrence of TPO change in patients with gastric cancer with different clinical characteristics in second-line treatment.

Characteristic	TPO normal group (n=15)	TPO abnormal group (n=22)	Statistic	P-value
Mean age ± SD, years	64.60±8.43	63.77±10.74	0.25	0.8040
Sex, n (%)				
Male	9 (60.00)	20 (90.91)	-	0.0421
Female	6 (40.00)	2 (9.09)		
Metastatic site, n (%)				
Liver	7 (46.67)	11 (50.00)	-	>0.9999
Others	8 (53.33)	11 (50.00)		
Treatment, n (%)				
Oxaliplatin	0 (0.00)	3 (13.64)	-	0.5138
Nab-paclitaxel	4 (26.67)	6 (27.27)		
Irinotecan	4 (26.67)	3 (13.64)		
Other treatment	7 (46.67)	10 (45.45)		
Site of gastric cancer, n (%)				
GEJ	5 (33.33)	10 (45.45)	-	0.5144
Non-GEJ	10 (66.67)	12 (54.55)		

GEJ, gastroesophageal junction; TPO, thyroid peroxidase.

the highest for all malignancies both in China and worldwide (1-3). Before 2018, treatment options were primarily limited to chemotherapy drugs, with only a few targeted therapies, such as herceptin and ramucirumab, available for controlling the disease. However, due to the spatial and temporal heterogeneity of gastric cancer, patients often face short survival times and a poor prognosis. The development of immunotherapy in recent years has brought new hope, particularly for advanced gastric cancer. Immunotherapy combined with chemotherapy has demonstrated the potential to extend survival and improve clinical outcomes (11-16). However, irAEs frequently occur during the use of immunotherapy, commonly affecting the skin, colon, liver, lungs and endocrine organs (17). Endocrine complications, particularly thyroid dysfunction, are among the most prevalent irAEs associated with ICIs, alongside diabetes, pituitaritis and primary adrenal insufficiency (19,20). Notably,

Table VI. Association between the best clinical efficacy of patients with gastric cancer with different clinical characteristics in second-line treatment.

Characteristic	PD (n=8)	PR (n=14)	SD (n=15)	Statistic	P-value
Mean age ± SD, years	62.25±12.36	63.71±8.78	65.47±9.61	0.29	0.7499
Sex, n (%)					
Male	6 (75.00)	11 (78.57)	12 (80.00)	-	>0.9999
Female	2 (25.00)	3 (21.43)	3 (20.00)		
Metastatic site, n (%)					
Liver	4 (50.00)	8 (57.14)	6 (40.00)	-	0.6426
Others	4 (50.00)	6 (42.86)	9 (60.00)		
Treatment, n (%)					
Oxaliplatin	0 (0.00)	1 (7.14)	2 (13.33)	-	0.4722
Nab-paclitaxel	3 (37.50)	5 (35.71)	2 (13.33)		
Irinotecan	1 (12.50)	1 (7.14)	5 (33.33)		
Other treatment	4 (50.00)	7 (50.00)	6 (40.00)		
Site of gastric cancer, n (%)					
GEJ	1 (12.50)	7 (50.00)	7 (46.67)	-	0.2209
Non-GEJ	7 (62.50)	7 (50.00)	8 (53.33)		
Thyroid function, n (%)					
Normal group	4 (50.00)	6 (42.86)	10 (66.67)	-	0.4765
Abnormal group	4 (50.00)	8 (57.14)	5 (33.33)		

GEJ, gastroesophageal junction; PD, progressive disease; PR, partial response; SD, stable disease.

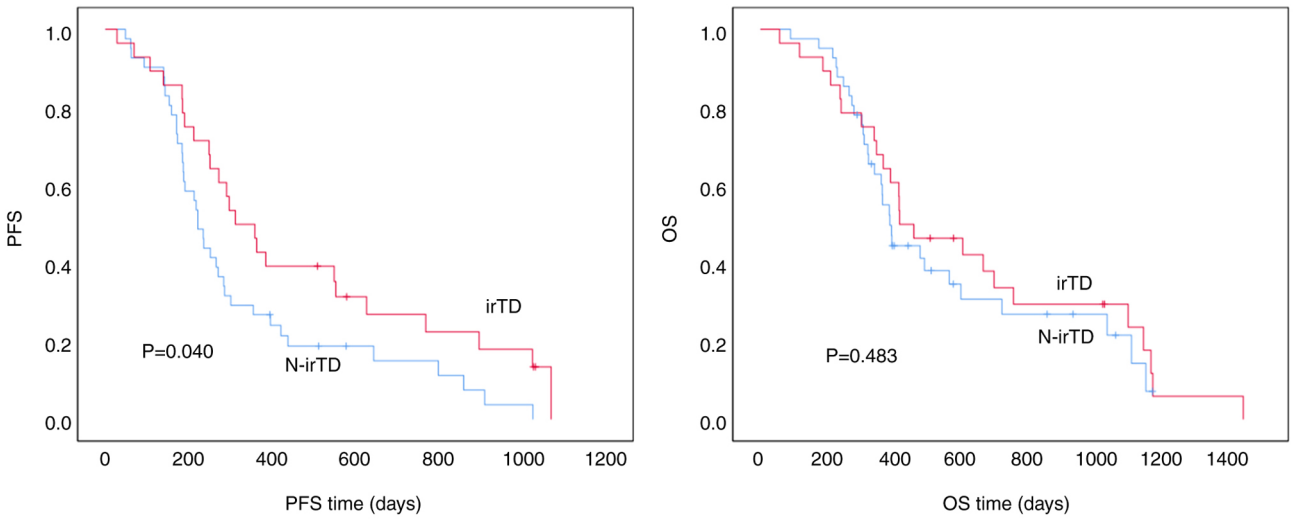

Figure 1. Association between irTD and PFS and OS of patients with gastric cancer in first-line treatment. PFS, prosgression-free survival; OS, overall survival; N-irTD, non- immune-related thyroid dysfunction.

PD-1/PD-L1 inhibitors have been found to frequently induce thyroid dysfunction (21,29).

Past studies on the incidence of irTD have yielded inconsistent findings. In a retrospective study conducted in South Korea, Yoon *et al* (29) reported that 50.5% (164/325) of the patients with cancer treated with PD-1/PD-L1 MABs experienced at least one type of thyroid dysfunction. Chilelli *et al* (30) studied 75 patients with non-small-cell lung cancer (NSCLC) and found that 25.3% of the participants developed irTD. Meanwhile, Ferreira *et al* (25) reported an irTD incidence of 18% during immunotherapy, while Li *et al* (31) found a 13.2% incidence of thyroid dysfunction, predominantly hypothyroidism, in patients with NSCLC. Zhou *et al* (32) also observed thyroid dysfunction in 11.2% (27/241) of patients with NSCLC following immunotherapy. Horesh *et al* (33) conducted a retrospective analysis of patients with NSCLC treated with PD-1 MABs and found that 34.6% (37/107) developed thyroid dysfunction. These studies highlight the relatively

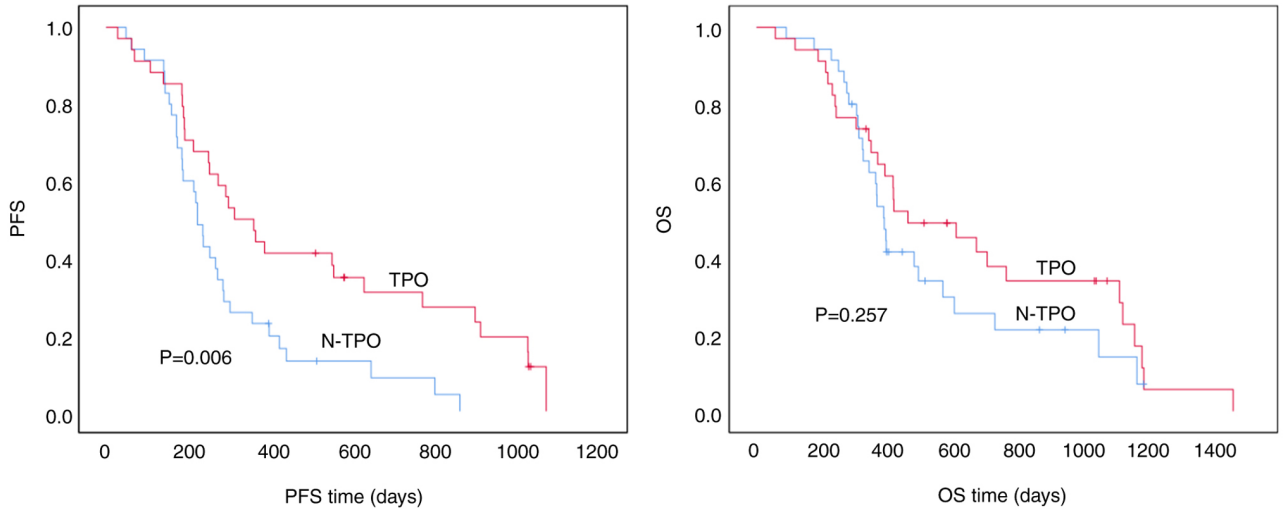

Figure 2. Association between TPO and PFS and OS of patients with gastric cancer in first-line treatment. PFS, progression-free survival; OS, overall survival; N-TPO, non-thyroid peroxidase.

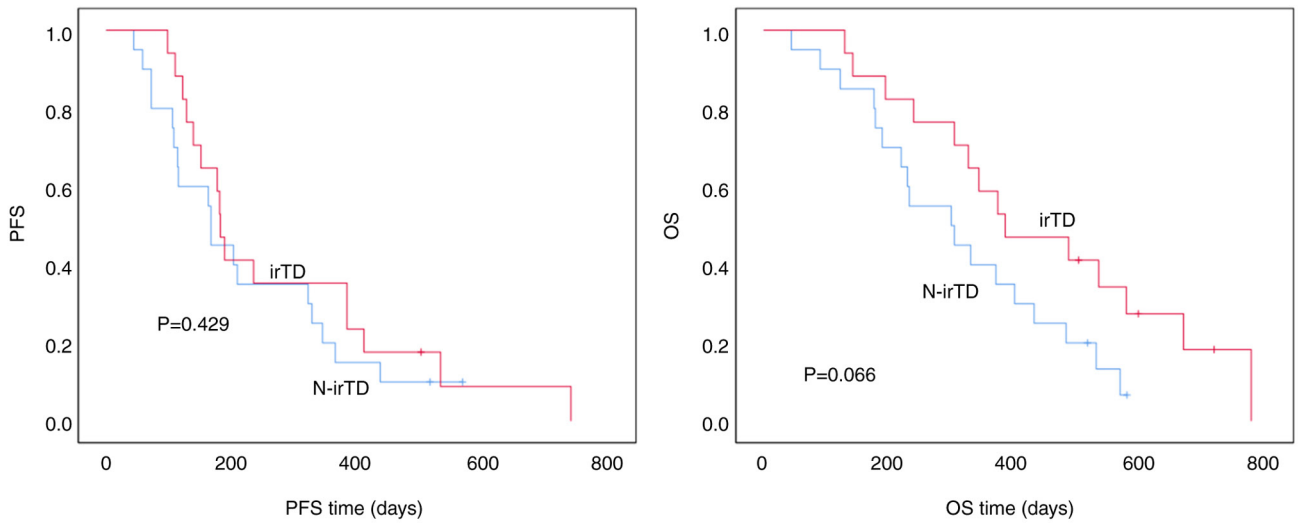

Figure 3. Association between irTD and PFS and OS of patients with gastric cancer in second-line treatment. PFS, progression-free survival; OS, overall survival; N-irTD, non- immune-related thyroid dysfunction; N-TPO, non-thyroid peroxidase.

common occurrence of thyroid dysfunction associated with immunotherapy, although the specific incidence rates vary across studies.

Similarly, patients with gastric cancer experience a high incidence of irTD following immunotherapy. According to several first-line clinical studies on gastric cancer (13-16), hypothyroidism is the most frequently observed irTD, with reported incidences of 11.0-13.6%, whereas hyperthyroidism is much less common, with an incidence of 4.0-6.1%. However, the true incidence in real-world settings remains unclear. In the present study, it was observed that the incidence of thyroid dysfunction in patients with gastric cancer was 40.6% (28/69) during first-line treatment and 45.9% (17/37) during second-line treatment, with hypothyroidism being the predominant presentation. These findings align with the incidence rates reported in the aforementioned previous literature, thereby further emphasizing the significance of irTD in patients with gastric cancer undergoing immunotherapy.

Regarding the timing of irTD induced by immunotherapy, Zhou *et al* (32) found that thyroid dysfunction typically occurs within 3-6 months after initiating ICI treatment, although, in some cases, it may occur even after the discontinuation of ICIs. Similarly, the study by Ferreira *et al* (25) reported a median time of irTD onset of 10.6 weeks (range, 6.1-31.1 weeks), with irTD most often arising after the fourth cycle of treatment. Horesh *et al* (33) observed a marked increase in irTD incidence following the administration of PD-1 or PD-L1 MABs, with the median time to thyroid dysfunction in patients with NSCLC being 45.0 days (interquartile range, 29.5-91.0 days). In the present study, the median time for thyroid dysfunction was 82 days (range, 21-302 days), which aligns with the previous literature.

The pathogenesis of thyroid dysfunction under ICIs remains unclear. However, it has been noted that PD-L1 and PD-L2 are expressed in normal thyroid tissues. As a result, blocking PD-1 in normal thyroid tissues may reduce immune tolerance

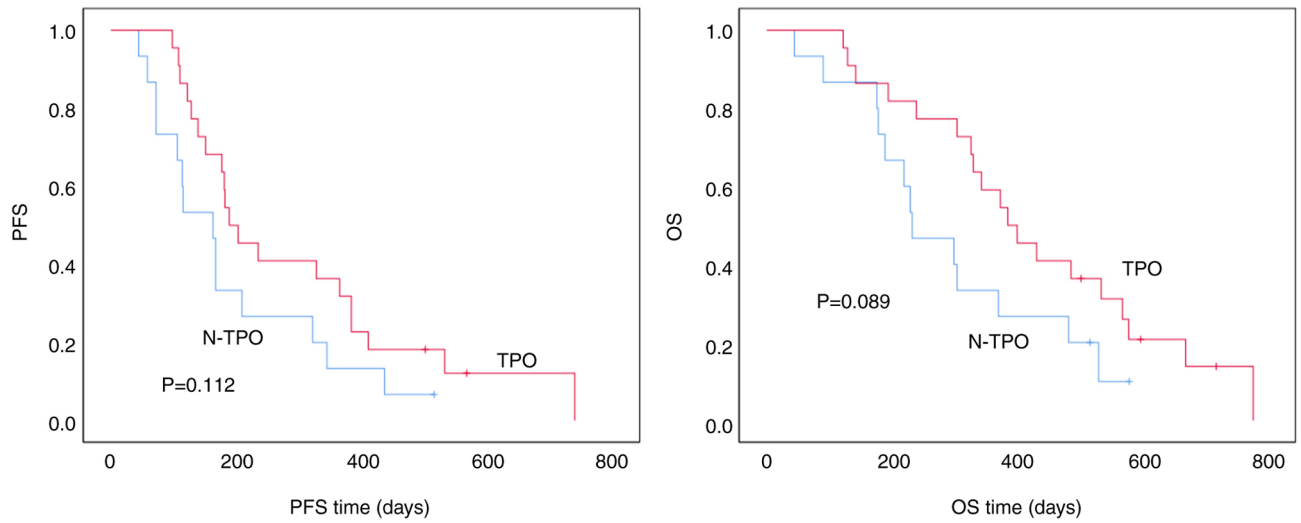

Figure 4. Association between TPO and PFS and OS of patients with gastric cancer in second-line treatment. PFS, progression-free survival; OS, overall survival; N-irTD, non- immune-related thyroid dysfunction; N-TPO, non-thyroid peroxidase.

and promote the development of thyroid inflammation (34). In addition, PD-1 is believed to regulate autoimmune balance and may trigger thyroid inflammation from latent autoimmune exposure or induce anti-thyroid antibody-mediated thyroid inflammation through PD-1-regulated humoral immunity (35). Thyroid antibodies are common autoantibodies found in the serum of patients with autoimmune thyroid diseases and may have predictive value for irAEs induced by immunosuppressive therapies. Yoon *et al* (29) reported a significant association between hypothyroidism and the presence of anti-TPO antibodies at the baseline in patients treated with PD-1/PD-L1 inhibitors. However, different studies have reported conflicting conclusions, and the matter remains controversial. Some studies have demonstrated that baseline thyroid antibodies are significantly associated with an increased risk of thyroid dysfunction, while others have found no such association (36-39). Currently, the prevailing view is that comprehensive measurement of autoimmune-related antibodies before ICI therapy has limited predictive value for irAEs. Nonetheless, TPO antibodies are considered a risk factor for the development of ICI-induced thyroid dysfunction and can be used to monitor thyroid function changes (40). Recent studies have suggested that the positive conversion of thyroid antibodies during PD-1/PD-L1 inhibitor treatment serves as a potential marker for thyroid irAEs (41). Furthermore, hypothyroidism is significantly associated with the presence of anti-thyroglobulin antibodies during treatment (29). In the present study, it was observed that 34 patients who had normal TPO levels before treatment experienced a positive conversion of TPO after treatment, with 28 of these patients developing thyroid dysfunction. This finding suggests that TPO conversion is a predictor of thyroid irAEs. In addition, when thyroid dysfunction improves, either through hormone replacement therapy or spontaneously, TPO conversion tends to resolve more slowly than changes in the FT3, FT4 and TSH levels.

Thyroid irAEs can manifest as hypothyroidism, hyperthyroidism or fluctuations in thyroid function. Most cases of thyrotoxicosis associated with PD-1/PD-L1 inhibitors are mild and typically present as painless thyroiditis. Only a few instances of PD-1/PD-L1 inhibitor-induced autoimmune hyperthyroidism, such as Graves' disease, have been documented (42,43). Following treatment, some patients may experience a restoration of normal thyroid function, while others require lifelong thyroid hormone replacement therapy due to severe thyroid failure (44,45). In the present study, only one case of hyperthyroidism was identified among the thyroid dysfunction cases in irAEs, with the remaining 27 cases classified as hypothyroidism or subclinical hypothyroidism. Thyroid hormone replacement therapy was initiated when T3/T4 levels fell below normal, and this therapy was continued for 6 months following the conclusion of immunotherapy. Meanwhile, hormone replacement therapy did not reduce the patient's quality of life and the clinical symptoms worsened during the treatment process. irAE-induced thyroid failure is often irreversible, necessitating long-term thyroid hormone replacement therapy. Notably, none of the present patients had to discontinue immunotherapy due to hypothyroidism. Additionally, 14 cases of thyroid dysfunction accompanied by hypopituitarism were found. Immunotherapy was continued under active treatment with thyroid hormone and glucocorticoid supplementation; however, subsequent immunotherapy was frequently suspended or delayed due to the patient's abnormal pituitary function.

Thyroid irAEs induced by PD-1/PD-L1 inhibitors are associated with prolonged OS and PFS times (46-49). Hussaini *et al* (50) retrospectively studied patients with major malignancies, including melanoma, and lung, kidney, and head and neck tumors, and found that patients experiencing irAEs had higher ORRs and longer PFS/OS times compared with those without irAEs. This finding suggests that irAEs have predictive implications for the efficacy of ICIs, with thyroid dysfunction being the most prevalent irAE supported by objective evidence. In a retrospective study of 75 patients with NSCLC, immunological thyroid dysfunction occurred in 25.3% of patients treated with ICIs. The ORR and DCR for patients with irTD were 42.1 vs. 7.1% and 78.9 vs. 32.1%, respectively, when compared with those for patients without irTD. The median PFS time was 15.7 months for patients

with irTD vs. 3.6 months for patients without irTD, while the median OS time was 18.6 vs. 5.1 months, indicating a significant improvement in ORR and DCR, alongside a reduced risk of PD and mortality (30).

Similarly, a retrospective study involving PD-1 MAB in advanced solid tumors revealed that the thyroid dysfunction group achieved longer median PFS (66 vs. 27 weeks) and median OS (156 vs. 59 weeks) times compared with the non-thyroid dysfunction group. Subsequent multivariate analysis identified thyroid dysfunction as an independent prognostic factor for OS, associated with a 58% reduction in the risk of death, highlighting its significant survival benefit (51). In another retrospective study of metastatic renal cancer, ~67.4% of patients experienced irAEs, with thyroid dysfunction being the most common. The median PFS time for patients with thyroid dysfunction was notably longer following treatment initiation, and multifactorial analysis confirmed thyroid dysfunction as an independent prognostic factor. PFS time was significantly prolonged in patients with thyroid dysfunction (P=0.028). The median PFS time for the group with normal thyroid function was 121 days (interquartile range, 92-305 days), while the median PFS time for the group with thyroid dysfunction was not reached. Patients with irTD exhibited significant benefits in terms of PFS time (52). Yu *et al* (53) retrospectively analyzed 425 patients with advanced NSCLC treated with anti-PD-L1 monotherapy and divided them into the irAE group (n=127) and irAE group (n=298). The occurrence of overall irAEs was significantly associated with higher PFS (11.2 vs. 3.4 months; P<0.001) and OS (31.4 vs. 14.0 months; P<0.001) times. For organ-specific irAEs, patients with skin, thyroid and liver-related irAEs demonstrated significantly improved survival times when compared with the group without irAEs, while those with pneumonia-related irAEs did not (53). Similarly, in another retrospective study of 244 patients with NSCLC, 140 (57.4%) had irAEs. Patients with irAEs had higher ORRs (73.6 vs. 52.9%; P<0.001) and DCRs (97.9 vs. 79.8%; P<0.001), as well as longer median PFS (8.8 vs. 4.5 months; P<0.001) and OS (23.2 vs. 21.6 months; P<0.05) times. Among the different types of irAEs, thyroid dysfunction, rash and pneumonia were the most powerful indicators of PFS improvement (54). A few studies have investigated whether thyroid dysfunction in patients with gastric cancer treated with ICIs has a similar prognostic effect (13-16). Multivariable Cox regression analysis of organ-specific irAEs found in gastric cancer studies has shown favorable survival outcomes in patients with thyroid, adrenal and cutaneous irAEs when compared with patients without these irAEs (21). In the present study, 45 out of 106 patients developed irTD, yielding an incidence rate of 42.5%. Among these, 28 out of 69 patients with first-line gastric cancer and 17 out of 37 patients with second-line gastric cancer were analyzed based on the presence or absence of irAEs. Patients with first-line gastric cancer who experienced irAEs received more effective treatment than those without irAEs. The irAE group demonstrated a better PFS time (P=0.04), although there was no significant difference in the OS time between the two groups (P=0.483), which may be related to subsequent treatments.

In patients with gastric cancer receiving second-line therapy, while the PFS and OS times in the irAE group were higher than those in the non-irAE group in the present study, the two survival curves exhibited a divergent trend without a statistically significant difference, possibly due to the small sample size. Meanwhile, since PD-1 MABs were included in the medical insurance reimbursement scope in 2023, patients with advanced gastric cancer often use PD-1 MABs in the first-line treatment. The same type of PD-1 MABs are no longer used for the subsequent second-line treatment. Therefore, it is difficult to increase the sample size for the second-line treatment. Moreover, since TPO changes are closely associated with irTD, the present study found that 56 out of 106 patients had positive TPO conversion, indicating an incidence of 52.8%. Among these, 34 out of 69 patients with first-line gastric cancer and 22 out of 37 patients with second-line gastric cancer were analyzed based on TPO changes. In the first-line treatment group, patients with TPO changes displayed a better PFS time than those without TPO changes (P=0.006), although there was no significant difference in OS between the two groups (P=0.483). Similarly, in patients receiving second-line treatment for gastric cancer, the group with TPO changes exhibited higher PFS and OS times than the group without changes; however, this difference was not statistically significant.

The association between irAE and efficacy after the use of ICIs is unclear. The underlying mechanism may be as follows: i) irAE and antitumor mechanisms have some common pathways related to cytotoxic memory $CD4^+$ T cell markers, which are activated by PD-1 blockers (55). ii) irAEs caused by PD-(L)1 inhibitor activation of autoantigen-specific T cells may indirectly reflect the killing ability of tumor-specific T cells (56). ICIs reactivate depleted T cells that are cross-reactive to tumor and normal tissue antigens, thereby enhancing antitumor immunity and irAEs (57). ICIs can enable tissue-resident memory T cells in tumors to be reactivated and proliferated. Killing of tumor cells is achieved by the secretion of effector molecules such as interferon-γ (IFN-γ), and this event also has some off-target effects (58). iii) The relevant immune response induced by ICIs is non-specific, which makes the attack on tumor and non-tumor cells indistinguishable (59). iv) Inflammatory cytokines involved in the occurrence of irAEs affect the treatment rate in patients with cancer. For example, patients with melanoma with risk allelic mutations in the interleukin 7 gene may have both a higher incidence of irAEs and improved survival (60). Changes in another cytokine, IFN-γ, are associated with the occurrence and clinical outcome expectations of irAEs in patients with liver cancer/NSCLC (58,61-63).

Currently, the comprehensive treatment of gastric cancer has achieved substantial progress, yet the overall effectiveness remains at only 50-65% due to the considerable heterogeneity of the disease. Therefore, further screening for biomarkers related to the efficacy of PD-1 MABs is clinically significant for patient selection, assessing treatment response and predicting potential outcomes. Based on the present findings, changes in irTD and TPO may serve as additional predictors of the efficacy of immunotherapy, similar to combined positive score of PD-L1, microsatellite instability status and Epstein-Barr virus infection. Thyroid dysfunction occurring during chemotherapy combined with immunotherapy for gastric cancer is a relatively safe adverse reaction, allowing the continuation of immunotherapy under careful monitoring and active treatment. Moreover, thyroid irAEs are mainly

hypothyroidism, and, under the premise of hormone replacement therapy, this irAE has little impact on the patient's quality of life. However, due to the limitations of this retrospective study, including a small sample size and single-center design, further prospective studies are warranted to validate its clinical significance. At the same time, more basic research is needed to confirm the mechanism of the association between irTD and efficacy.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

MX and ZYB contributed to the conception and design of the study. LLQ analyzed data. QZ, JM, QXL and QL collected data and performed some data analysis. MX wrote and revised the manuscript. MX and ZYB confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

The study protocol was in accordance with the Declaration of Helsinki of the World Medical Association. The study was approved by the Ethical Committee of Changzhou Tumor Hospital [Changzhou, China; approval no. 2023 (SR) NO.003]. The requirement for informed consent was waived for this study, as the research was retrospective and conducted on anonymized data

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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