Association Between Immune-Related Hypothyroidism and Survival Outcomes in Patients with Head and Neck Cancer Treated with Nivolumab

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Research Article

Keywords: immune-related hypothyroidism, nivolumab, head and neck cancer, efficacy, adverse events

Posted Date: June 17th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-602071/v1

Abstract

Background

Immune-related hypothyroidism (irHT) triggered by nivolumab is known to affect drug efficacy in patients with non-small cell lung cancer (NSCLC). However, it is unclear whether there is an association between the drug efficacy and nivolumab-induced irHT in recurrent and/or metastatic head and neck cancer (R/M HNC). Hence, we retrospectively investigated the relationship between irHT and treatment outcomes in R/M HNC patients treated with nivolumab.

Methods

Patients with R/M HNC who received nivolumab monotherapy between April 2017 and June 2019 were selected. Those receiving levothyroxine treatment and with thyroid-stimulating hormone (TSH) levels > 10 μIU/mL before nivolumab administration were excluded. irHT was defined as one measurement of free T4 (FT4) < 0.8 ng/dL and/or TSH > 10 μIU/mL or as two successive abnormal levels of FT4 and/or TSH after nivolumab administration. To assess therapeutic efficacy, nivolumab-treated patients were divided into two groups: with or without irHT [irHT (+) and irHT (−) groups, respectively].

Results

Of the 31 nivolumab-treated patients, 14 developed irHT. The median time to onset was 76 days (17–274 days). The median overall survival was 704 days (95% confidence interval [CI], 223–not reached) in the irHT (+) group and 244 days (95% CI, 170–342) in the irHT (−) group (hazard ratio (HR) = 0.33, p = 0.0259). The median progression-free survival was 197 days (95% CI, 103–not reached) in the irHT (+) group and 105 days (95% CI, 52–151) in the irHT (−) group (HR = 0.32, p = 0.0115). The disease control rate was significantly higher in the irHT (+) group than in the irHT (−) group (78.6% vs. 35.3%; p = 0.0292). Although there was no difference in the incidence of grade 3 serious immune-related adverse events (irAEs) between the two groups, the incidence of multiple irAE events in each patient (50.0% vs. 5.9%; p = 0.0109) was significantly higher in the irHT (+) group than that in the irHT (−) group.

Conclusions

Our results suggest that the development of irHT, similarly to NSCLC, is associated with improved survival outcomes in R/M HNC patients treated with nivolumab.

Background

Combination chemotherapy with cisplatin, 5-fluorouracil, and cetuximab has been recommended for patients with recurrent and/or metastatic head and neck cancer (R/M HNC) [1]. Patients with R/M HNC

exhibiting disease progression within 6 months of initiation of platinum combination chemotherapy have poor prognoses, and researchers have only recently identified agents that can improve the survival rates [2] [3]. Nivolumab is an anti-programmed cell death-1 (PD-1) antibody that has been established as a more effective agent than standard chemotherapy for treating patients with platinum-refractory R/M HNC [4–6]. PD-1 ligands, PD-L1 and PD-L2, expressed on cancer-cell surfaces bind to PD-1 receptors on cytotoxic T-cells to inhibit their activation. The anti-tumor effect of nivolumab results from selectively binding to PD-1 receptors, thus blocking the inhibitory interaction of cancer cells with cytotoxic T-cells, leading to activation of the latter.

Despite the clinical benefits of nivolumab treatment, activation of host immunity by the drug causes overreactions from normal cells or immune-related adverse events (irAEs). These irAEs affect organs such as the skin, gastrointestinal tract, liver, and endocrine system [7]. The occurrence of irAEs may reflect both side effects and anti-tumor responses because of the anti-PD-1 treatment. A previous study in patients with non-small cell lung cancer (NSCLC) suggested that anti-PD-1-triggered irAE is often associated with the prolonged survival [8]. Interestingly, thyroid dysfunction is associated with prolonged overall survival (OS) in NSCLC patients treated with anti-PD-1 agents [9] [10].

Hypothyroidism is one of the most common irAEs, with up to 10% incidence in nivolumab-treated patients [11] [12]. However, limited information is available on the relationship between immune-related hypothyroidism (irHT) and therapeutic efficacy in patients with R/M HNC treated with nivolumab. Therefore, this study aimed to analyze the impact of irHT onset on therapeutic efficacy in patients with R/M HNC treated with nivolumab.

Methods

Study design, setting, and patient population

We retrospectively assessed nivolumab efficacy and toxicity in patients with R/M HNC from April 2017 to June 2019 at Kyushu University Hospital. The present study was approved by the Ethics Committee of the Kyushu University Hospital (Approval No. 2020 – 155) and was conducted in accordance with the principles of the Helsinki Declaration. The subjects comprised patients who received either 3 mg/kg or 240 mg of nivolumab per person every 2 weeks. Nivolumab was administered until disease progression or unacceptable toxicity was confirmed. Clinical data were extracted from electronic medical records: age, sex, Eastern Cooperative Oncology Group performance status, number of previous chemotherapies, most common metastatic sites, lines of chemotherapy after nivolumab treatment, and course of nivolumab treatment.

Assessment of thyroid function and definition of irHT

Thyroid stimulating hormone (TSH) and free-T4 (FT4) levels were measured at the first administration of nivolumab and every 4 or 6 weeks thereafter. irHT was defined as one measurement of FT4 < 0.8 ng/dL and/or TSH > 10 μIU/mL or as two successive measurements of FT4 < 1.0 ng/dL and/or TSH > 4.2

μIU/mL post-nivolumab administration (FT4 reference range: 1.0–1.8 ng/dL, TSH reference range: 0.27–4.2 μIU/mL). Subjects were categorized into two groups based on the presence (irHT (+)) or absence (irHT (−)) of nivolumab-induced irHT.

Evaluation of irHT and therapeutic effects

The clinical severity of irAEs, including irHT, was graded using the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The best overall response rate was determined in accordance with Response Evaluation Criteria in Solid Tumors version 1.1. The time for treatment assessment was determined by each physician. OS was defined as the time from the start of nivolumab treatment to the patient's death. Progression-free survival (PFS) was defined as the time from the start of nivolumab treatment to disease progression or death. The disease control rate (DCR) was defined as complete or partial response or stable disease, based on the evaluation of clinical response by computed tomography. The primary endpoint of this study was the determination of the relationship between irHT onset and OS in patients with R/M HNC. As secondary endpoints, we assessed the relationships between irHT onset and PFS or DCR and between irHT onset and other irAEs.

Statistical analysis

Categorical variables were analyzed using Chi-square or Fisher's exact test, whereas continuous variables were analyzed using the Mann-Whitney *U*-test. The Kaplan-Meier method with log-rank tests was used to assess OS and PFS. The follow-up period was at least 6 months from the start of nivolumab treatment. Data collection of patients without disease progression or unacceptable toxicity was completed at the end of June 2019. Data were analyzed using JMP 14.0.0 (SAS Institute Inc., Cary, NC, USA) and GraphPad PRISM version 8 (GraphPad Software, San Diego, CA, USA); $p < 0.05$ was considered to indicate a statistically significant difference between two groups.

Results

Patient characteristics

The study included 62 patients with R/M HNC who received nivolumab. We excluded 19 patients with pre-existing hypothyroidism, 17 on concomitant treatment with levothyroxine, and 2 with TSH ≥ 10 μIU/mL before nivolumab administration. We also excluded 6 patients whose treatments were discontinued within 28 days due to death, disease progression, or appearance of intolerable irAEs. Another 6 patients were excluded because they were transferred to other hospitals. Thus, the final analysis involved 31 patients (Fig. 1), 14 of whom (45%) showed some form of irHT. The number of nivolumab treatment courses in patients with irHT (median = 14 courses, range 4 − 39) was significantly higher than that in patients without irHT (median = 7 courses, range 4 − 25). Baseline TSH levels in irHT(+) and irHT(−) groups were 4.71 μIU/mL (range, 1.13–9.18 μIU/mL) and 1.82 μIU/mL (range, 0.85–4.02 μIU/mL), respectively. The baseline TSH level in the irHT(+) group was significantly higher than that in the irHT(−) group ($p < 0.001$). Baseline FT4 levels in irHT(+) and irHT(−) groups were 1.10 ng/dL (range, 0.90–1.64

ng/dL) and 1.25 ng/dL (range, 1.01–1.68 ng/dL), respectively. The baseline FT4 level in the irHT(+) group was significantly lower than that in the irHT(−) group ($p = 0.0252$). The two groups did not differ in age, sex, performance status, number of previous chemotherapies, most common metastatic sites, or post-nivolumab lines of chemotherapy (Table 1).

Table 1
Patient characteristics and immune-related hypothyroidism (irHT)

Characteristics	**irHT (+) (n = 14)**		**irHT (−) (n = 17)**		***p*-value**
Age (years), median (range)	65	(41–81)	66	(42–79)	0.8620
Sex					0.4564
Male	11		11		
Female	3		6		
Performance status					1.0000
0, 1	13		16		
≥ 2	1		1		
Lines of chemotherapy					0.2895
2nd	6		11		
≥ 3rd	8		6		
Course of nivolumab treatment, median (range)	14	(4–39)	7	(4–25)	0.0071
Metastatic sites					0.1611
Bones	1		2		
Lung	2		9		
Liver	2		0		
Lines of chemotherapy after nivolumab					0.1448
0	9		5		
1	4		10		
2	1		2		
TSH level at baseline (μIU/mL), median (range)	4.71	(1.13–9.18)	1.82	(0.85–4.02)	< 0.001
FT4 level at baseline (ng/dL), median (range)	1.10	(0.90–1.64)	1.25	(1.01–1.68)	0.0255

TSH, thyroid-stimulating hormone; *FT4*, free T4

Time to irHT onset

In the irHT (+) group, the median duration from the start of nivolumab treatment to irHT onset was 76 days (range 17–274 days) (Fig. 2). The incidence of irHT severity was 50.0% (n = 7) at grade 1 and 50.0% (n = 7) at grade 2. Seven patients at grade 2 began treatment with levothyroxine that continued throughout the observation period. irHT was found to occur in 5 patients with two successive measurements of FT4 < 1.0 ng/dL, 4 patients with two successive measurements of TSH > 4.2 μIU/mL, 3 patients with TSH > 10 μIU/mL, and 2 patients with two successive measurements of TSH > 4.2 μIU/mL and FT4 < 1.0 ng/dL, respectively.

Association between irHT and nivolumab treatment outcomes

The median OS in the irHT (±) group (median = 704 days, 95% confidence interval [CI] = 223–not reached) was significantly longer than that in the irHT (−) group (median = 244 days, 95% CI = 170–342), with a hazard ratio (HR) of 0.33 (95% CI = 0.12–0.90; $p = 0.0259$) (Fig. 3A). The median PFS in the irHT (+) group (median = 197 days, 95% CI = 103–not reached) was significantly longer than that in the irHT (−) group (median = 105 days, 95% CI = 52–151), with an HR of 0.32 (95% CI = 0.14–0.74; $p = 0.0115$) (Fig. 3B). The DCR was significantly higher in the irHT (+) group than in the irHT (−) group (78.6% vs. 35.3%; $p = 0.0292$) (Fig. 3C).

Comparison of irAEs between the irHT (+) and irHT (−) groups

After nivolumab administration, the incidence of irAEs in the irHT (±) and irHT (−) groups was 100.0% and 17.6%, respectively (Table 2). Particularly, 1 patient (7.1%) in the irHT (±) group experienced severe grade 3 irAEs. There were no significant differences in the incidence of other irAEs between the irHT (±) and irHT (−) groups. Seven patients (50.0%) in the irHT (+) group and 1 patient (5.9%) in the irHT (−) group experienced multiple irAEs, with the incidence of multiple irAEs being significantly higher in the irHT (±) group than in the irHT (−) group ($p = 0.0109$).

Table 2
Profile of immune-related adverse events (irAE) in the immune-related hypothyroidism (irHT) (+) and irHT (−) groups

Category	irHT (+) (n = 14) (%)		irHT (−) (n = 17) (%)		*p*-value
Number of patients with irAE					
Any grade	14	(100.0)	3	(17.6)	< 0.001
Grade ≥ 3	1	(7.1)	0	(0.0)	0.4516
Hypothyroidism					
Any grade	14	(100.0)	0	(0.0)	< 0.001
Grade ≥ 3	0	(0.0)	0	(0.0)	1.0000
Interstitial pneumonia					
Any grade	2	(14.3)	0	(0.0)	0.1957
Grade ≥ 3	0	(0.0)	0	(0.0)	1.0000
Hepatic enzymes increased					
Any grade	2	(14.3)	1	(5.9)	0.5764
Grade ≥ 3	1	(7.1)	0	(0.0)	0.4516
Fatigue					
Any grade	2	(14.3)	1	(5.9)	0.5764
Grade ≥ 3	0	(0.0)	0	(0.0)	1.0000
Creatinine increased					
Any grade	1	(7.1)	1	(5.9)	1.0000
Grade ≥ 3	0	(0.0)	0	(0.0)	1.0000
Anorexia					
Any grade	1	(7.1)	1	(5.9)	1.0000
Grade ≥ 3	0	(0.0)	0	(0.0)	1.0000
Rash					
Any grade	1	(7.1)	0	(0.0)	0.4516
Grade ≥ 3	0	(0.0)	0	(0.0)	1.0000
Infusion-related reaction					

Category	irHT (+) (n = 14) (%)		irHT (–) (n = 17) (%)		*p*-value
Any grade	1	(7.1)	0	(0.0)	0.4516
Grade ≥ 3	0	(0.0)	0	(0.0)	1.0000
Hypopituitarism					
Any grade	1	(7.1)	0	(0.0)	0.4516
Grade ≥ 3	0	(0.0)	0	(0.0)	1.0000
Diarrhea/Enteritis					
Any grade	0	(0.0)	1	(5.9)	1.0000
Grade ≥ 3	0	(0.0)	0	(0.0)	1.0000
Number of irAE events in each patient					0.0109
< 2	7	(50.0)	16	(94.1)	
≥ 2	7	(50.0)	1	(5.9)	

Discussion

In this study, OS and PFS for nivolumab treatment were significantly prolonged in the irHT (+) group of patients with R/M HNC. The DCR was significantly higher in the irHT (±) group than in the irHT (−) group. These results suggest that irHT by nivolumab treatment is involved in clinical benefit in patients with R/M HNC.

The occurrence of irAEs is more frequent in organs such as the skin, gastrointestinal tract, liver, and endocrine system [7]. Endocrine dysfunction includes thyroid dysfunction, hypopituitarism, hypoadrenocorticism, hypoparathyroidism, and type 1 diabetes [13]. Furthermore, thyroid dysfunction is classified into two types, hyperthyroidism and hypothyroidism. In particular, hypothyroidism is a common irAE caused by nivolumab treatment, and the incidence of nivolumab-induced irHT is 10% in melanoma [14], 15% in NSCLC [15], and 7.6% in R/M HNC [4]. Interestingly, 45% (14/31) of patients with R/M HNC in this study experienced irHT with nivolumab treatment. Although irAEs are typically evaluated using CTCAE, we evaluated irHT in this study based on our hospital's criteria. Symptoms of thyroid dysfunction are often absent or vague. Therefore, routine surveillance of thyroid function at each visit is necessary to identify these disorders. In fact, if hormone levels are low, hormone-replacement therapy is recommended (if TSH < 0.5 times the lower limit of normal, > 2 times the upper limit of normal, or consistently out of range in 2 subsequent measurements) [16–20]. As the evaluation method using CTCAE does not use quantified objective data such as TSH, FT4, and FT3 levels, such an assessment of thyroid dysfunction may be an underestimation. For these reasons, the evaluation of thyroid dysfunction based on our hospital's criteria was considered to be more clinical in practice. Several studies have similarly assessed

irHT based on their criteria, not on CTCAE, and reported the association between the onset of irHT and the clinical effect of nivolumab treatment [21]. Therefore, the high incidence of irHT in this study was attributed to the differences in evaluation methods.

It is difficult to predict the onset of irAE. However, Weber et al. [22] reported that the median time to onset of nivolumab-induced endocrine dysfunction was 73 days in melanoma. Nivolumab-induced hypothyroidism is considered to occur after a transient and asymptomatic period of hyperthyroidism [9]. Moreover, the median onset of hypothyroidism was 98 days in NSCLC [9]. Our results are supported by these results because the median onset of irHT was 76 days in this study. Seven patients (50.0%) classified as grade 2 in the irHT (+) group required treatment with levothyroxine during the observation period. In general, irHT has been reported as an irreversible adverse event [23]. These results suggest that it is important to constantly monitor the TSH and FT4 levels during the treatment period, especially in the first 3 months of treatment with nivolumab.

The relationship between the onset of irAEs and the clinical benefits of nivolumab is evaluated based on the anti-tumor effects of nivolumab on T cells to regulate and reactivate the immune response to tumor cells. However, irAEs are attributed to excessive autoimmune effects associated with the activation of normal cells. Several studies have reported an association of the onset of irAEs with clinical benefits in the treatment with immune checkpoint inhibitors (ICIs) [8] [24–26]. Freedman et al. [24] reported that cutaneous irAEs increased the prolongation of OS in melanoma. Moreover, Ricciuti et al. [25] reported that gastrointestinal tract and endocrine irAEs increased clinical benefits such as prolongation of the OS in NSCLC. In this study, clinical outcomes, such as OS and PFS, were significantly prolonged in the nivolumab-induced irHT (+) group. We also found that the DCR was significantly higher in the irHT (+) group than in the irHT (–) group. This result suggests that suppression of tumor growth might contribute to the prolongation of OS and PFS in the irHT (+) group.

In general, except for the onset of severe irAEs, such as interstitial pneumonia, renal dysfunction, and myasthenia gravis, ICI treatment can be continued with careful management of irAEs. The incidence of multiple irAEs was significantly higher in the irHT (+) group than in the irHT (–) group. DCR was also significantly higher in the irHT (+) group than in the irHT (–) group. Weber et al. [22] supported our results by reporting that patients with advanced melanoma who achieved an objective response to treatment with nivolumab experienced multiple irAEs. In this study, the number of nivolumab courses was significantly higher in the irHT (+) group than in the irHT (–) group. We speculated that the higher incidence of multiple irAEs in the irHT (+) group was related to more courses of nivolumab treatment and longer survival. However, since the frequency of serious irAEs did not differ between the irHT (+) and irHT (–) groups, appropriate treatment of irAEs by careful management may facilitate the continuation of nivolumab treatment in patients with R/M HNC.

Our study had several limitations. First, we excluded patients with hyperthyroidism or thyroiditis. Therefore, we could not examine the relationship between irHT onset and clinical outcomes in these patients. Second, this analysis has lead-time bias. We showed that patients in the irHT (+) group after

nivolumab treatment experienced better survival than those in the irHT (–) group. Although long-term survivors may have longer exposure to nivolumab and a higher risk of irHT onset, an extreme delay in the onset of irAEs is generally only observed in patients who respond to treatment [27]. Third, this was a single-center, retrospective study with a small number of patients with R/M HNC. Further studies with more patients and longer follow-up periods are needed to validate the findings.

Conclusions

This is the first study to clarify the relationship between irHT onset and the clinical benefits of OS prolongation in patients with R/M HNC. Our results suggest that the appropriate treatment of irHT could contribute to improved quality of life of R/M HNC patients receiving nivolumab treatment.

Abbreviations

irHT, immune-related hypothyroidism

R/M HNC, recurrent and/or metastatic head and neck cancer

TSH, thyroid stimulating hormone

FT4, free thyroxine

PD-1, programmed cell death-1

irAEs, immune-related adverse events

NSCLC, non-small cell lung cancer

OS, overall survival

PFS, progression free survival

DCR, disease control rate

Declarations

Ethics approval and consent to participate

The present study was conducted in accordance with the Declaration of Helsinki and its amendments. The protocol was approved by the Institutional Review Board of the Ethics Committee of Kyushu University Graduate School and the Faculty of Medicine (Approval No. 2020-155). Owing to the retrospective nature of this study, the need of informed consent was waived by the Institutional Review Board of the Ethics Committee of Kyushu University Graduate School and the Faculty of Medicine. The patients participating in this study were provided information by posting on the hospital website and opt-

out consent (http://www.pharm.med.kyushu-u.ac.jp/about/research), which was also approved by the Institutional Review Board of the Ethics Committee of Kyushu University Graduate School and the Faculty of Medicine.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding authors on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

The present study was funded in part by a Grant-in-Aid for Scientific Research (KAKENHI) from the Japanese Society for the Promotion of Science (JSPS, grant number JP16K08404 and JP17K08447).

Authors' contributions

All authors contributed to the study conception and design. Data collection was performed by K.H., M.Ikeda., M.Ikebe., A.K., N.O., R.M., M.M., and R.Y. Data analysis was performed by K.H. and H.W. The study was supervised by T.T., S.I., K.N., K.S., S.T., T.Y., N.E., T.N., and I.I. K.H. K.S., and H.W. wrote the first draft of the manuscript and all authors commented on subsequent versions of the manuscript. All authors have read and approved the final manuscript.

Acknowledgments

Not applicable.

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Figures

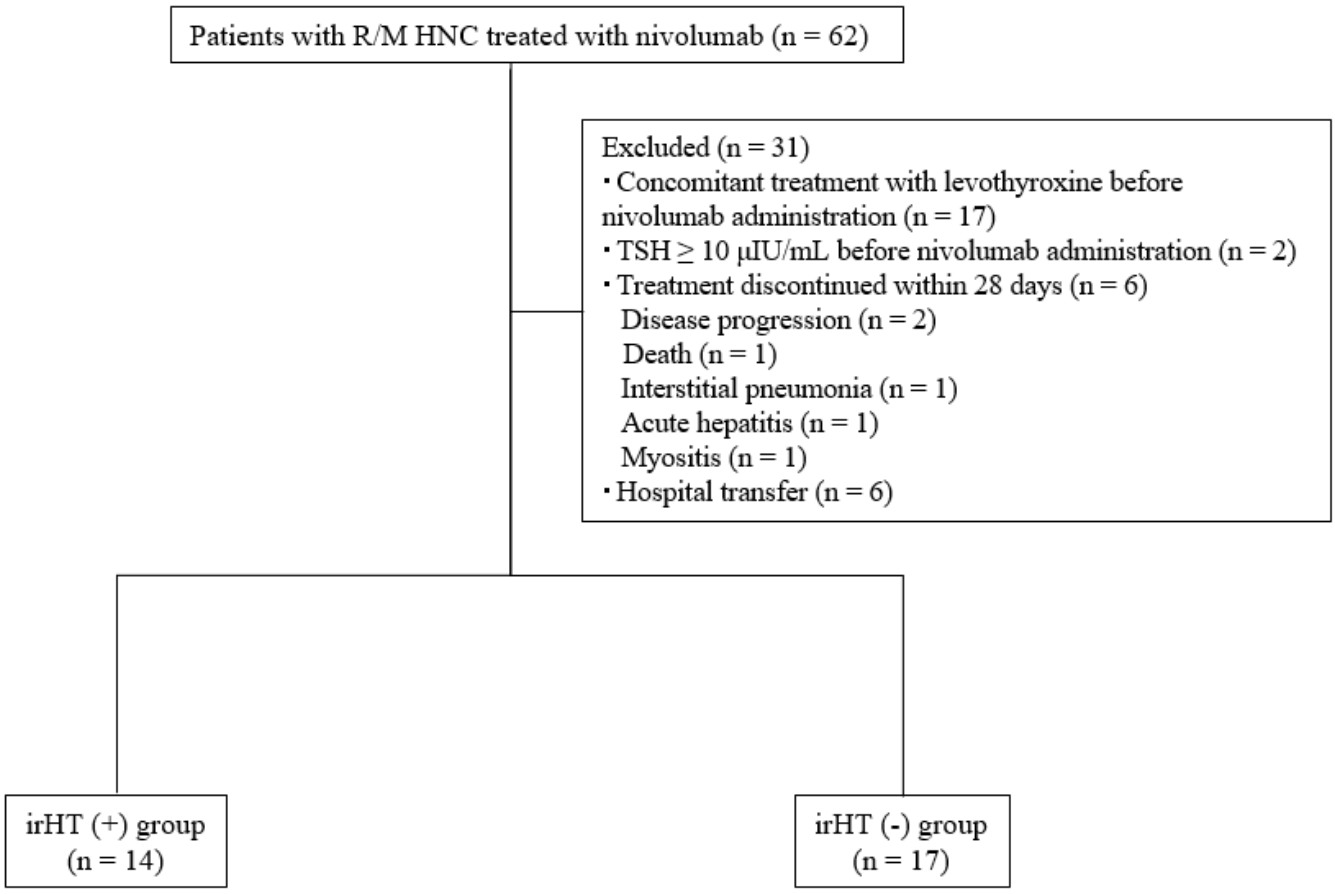

Figure 1

Patient enrollment flowchart in this study. R/M HNC, recurrent and/or metastatic head and neck cancer; TSH, thyroid stimulating hormone; irHT, immune-related hypothyroidism.

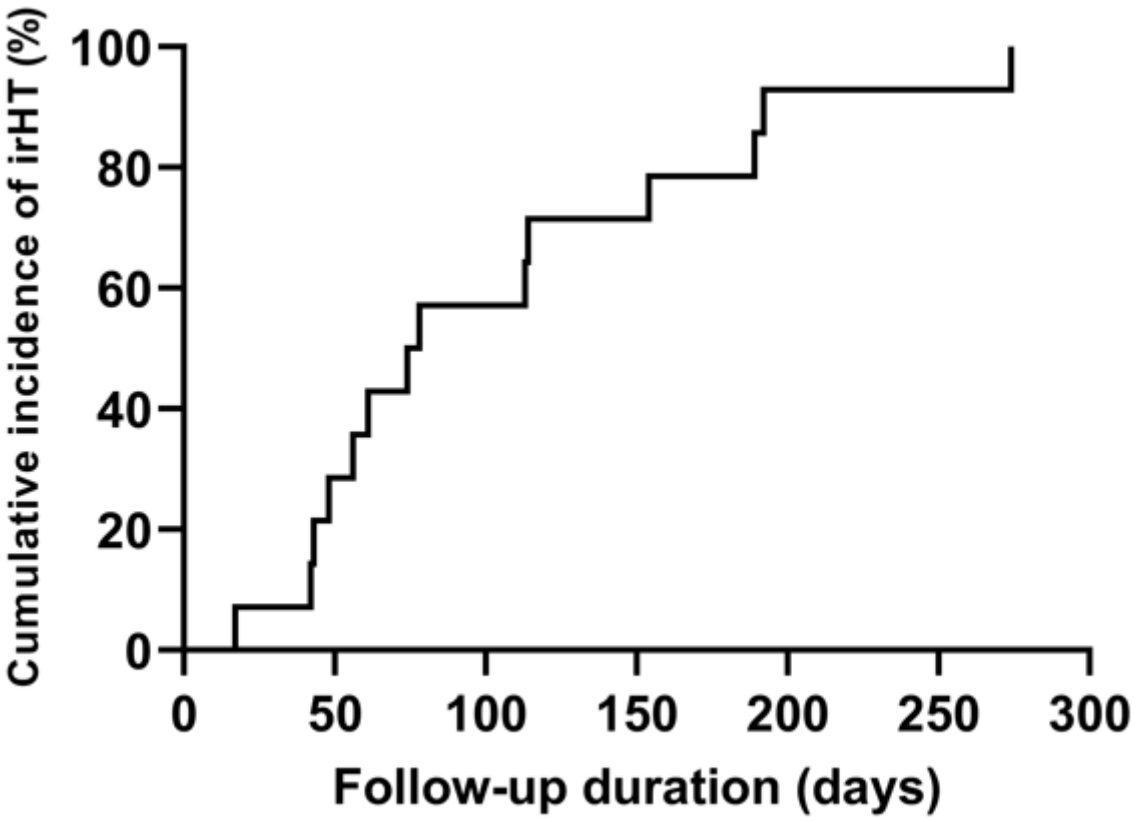

Figure 2

Time to onset of immune-related hypothyroidism in 14 patients. irHT, immune-related hypothyroidism.

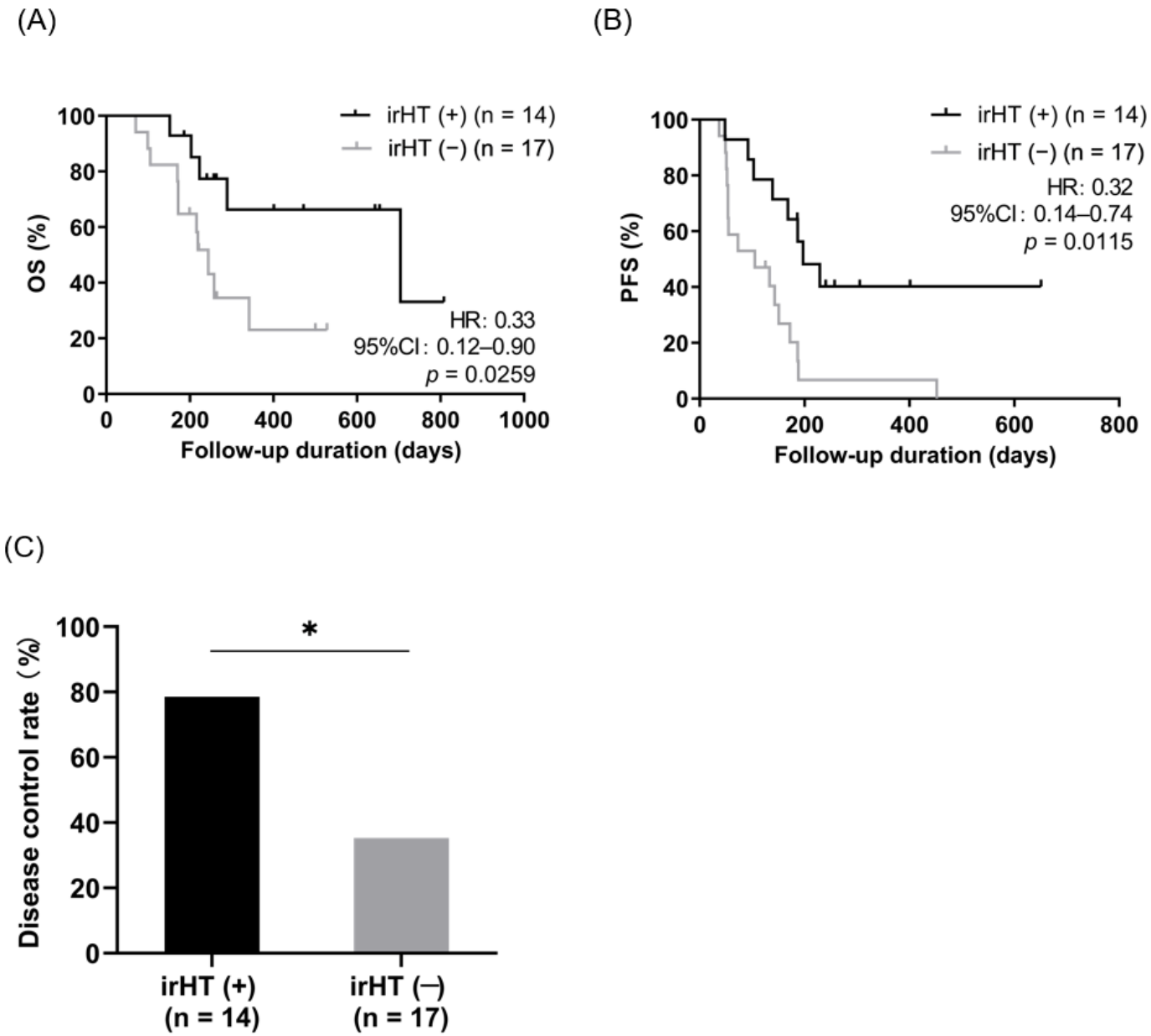

Figure 3

Association between immune-related hypothyroidism (irHT) onset and clinical outcome. Kaplan-Meier curves for (A) overall survival (OS) and (B) progression-free survival (PFS) in the irHT (+) and irHT (−) groups; p-values were determined using the log-rank test. HR, hazard ratio; CI, confidence interval. (C) Comparison of disease control rate between patients in the irHT (+) and irHT (−) groups; * $p < 0.05$.