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# History of Radiation to the Neck Increases the Risk of Denovo Thyroid Dysfunction after Receiving Immune Checkpoint Inhibitors

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**Abstract:** Thyroid dysfunction is a common endocrine side effect of immune checkpoint inhibitors (ICI). We designed a retrospective study, including patients who received ICI for any cancer at our institution. Thyroid-stimulating hormone (TSH), free T4 levels, and time to development of thyroid dysfunction were measured, and medication used to treat thyroid dysfunction were identified. We reviewed the charts of 104 patients with complete records obtained from our tumor registry. A total of 91 patients were included in the analysis, after excluding 13 patients with a pre-existing thyroid disorder. Twenty-eight (30.77%) patients developed thyroid dysfunction after starting ICI. Race (*p*-0.048), age (*p*-0.014), history of radiation therapy (RT) to the neck (*p*-0.004), history of RT to the chest (*p*-0.012), and history of venous thrombosis (*p*-0.004) were significantly associated with thyroid dysfunction on univariate analysis. For multivariate analysis, the history of RT to the neck, adjusted for age, race, and sex, was significantly associated with thyroid dysfunction (adjusted OR-9.64, 95%CI: 1.88, 49.36, *p*-0.007). In patients receiving ICI for any type of cancer, the previous history of RT to the neck was significantly associated with the development of thyroid dysfunction after starting ICI.

**Keywords:** immunotherapy; checkpoint inhibitor; anti-PD-1 inhibitor; anti-CTLA4 inhibitor; radiation therapy; thyroid dysfunction

## 1. Introduction

Immune checkpoint inhibitors (ICI) have introduced a new paradigm in cancer treatment, especially when we consider the durable responses it can achieve in patients with metastatic disease. ICI principally blocks cytotoxic T-lymphocyte protein 4 (CTLA-4), programmed cell death-1 (PD-1), or programmed cell death receptor ligand-1 (PDL-1) [1]. Both CTLA-4 and PD-1/PDL-1 play a central role in preventing autoimmunity by downregulating the T-cell responses against self-antigens, a process called peripheral tolerance [1]. The concept of cancer immunotherapy is based on the notion that cancer cells develop mechanisms to evade immune systems, and CTLA-4 and/or PD-1/PDL-1 play a critical part in the process [1]. Hence, blocking these receptors with ICI therapy can result in a clinical response that has been demonstrated in multiple tumor types. However, the use of ICI therapy can also block these receptors on any ''normal'' body organ, and lead to a unique set of adverse events known as immune-related adverse events (irAE) [1].

Although irAE can occur in any organ of the body, the most common irAE are noted in the gastrointestinal, lung, skin, and endocrine systems [2–5]. In comparison with other systems, the endocrine-related irAE is often irreversible [4]. Hypophysitis (with attendant hypopituitarism) and

thyroid dysfunction are the most common endocrine irAE associated with the use of ICI therapy [4,6,7]. Rarely autoimmune diabetes and primary adrenal insufficiency have also been reported in patients receiving ICI therapy [3,5,8]. In clinical trials, the overall prevalence of thyroid dysfunction is reported between 3.8% and 16.1%, depending on what agent was used and whether monotherapy or dual checkpoint inhibitor therapy was used [8,9]. Despite thyroid dysfunction being a common irAE, little is known in terms of factors that can identify patients who are at higher risk. Measuring the anti-thyroglobulin and antithyroid peroxidase antibodies in the blood has met with conflicting results [7,10–13]. In this retrospective study, we evaluate the clinical factors associated with the development of thyroid dysfunction in patients receiving ICI.

## 2. Materials and Methods

This is a single-institution retrospective study, conducted at John H. Stroger, Jr. Hospital of Cook County, that obtained data of patients who were treated with either anti-PD-1 (nivolumab, pembrolizumab), anti-PDL-1 (atezolizumab), or anti-CTLA4 (ipilimumab), for any tumor type from April 2015 to June 2018. The study protocol was reviewed and approved by our institutional review board. After excluding patients with incomplete medical records, we reviewed the clinical records of a total of 104 patients from the tumor registry at our institution. The clinical course of these patients was monitored, and pertinent lab findings were recorded. As per our institutional policy, we recorded TSH and free T4 values prior to the start of ICI (as a baseline) and with each cycle.

### *2.1. Definitions*

The National Comprehensive Cancer Network Guidelines (Version 1.2020, Management of Immunotherapy-Related Toxicities) defines thyroid dysfunction secondary to ICI use as abnormal TSH and/or abnormal free T4. Similar definitions have been used by other authors, where they have used the reference of their own lab as upper and lower limits for TSH and free T4 [4,7,11]. For the purpose of this study, we defined thyroid dysfunction in a patient receiving ICI therapy, when abnormal levels of TSH and/or free T4 were recorded. For the purpose of this study, patients with two consecutively abnormal levels of TSH and/or free T4 (recorded at the time of administering therapy) were included in the final analysis.

### *2.2. Statistical Analysis*

Descriptive statistics were presented as mean ± standard deviation (SD) for quantitative variables and percentages for qualitative variables. Pearson chi-square and "independent sample t-test" were used to compare different variables among patients who developed thyroid dysfunction and patients who did not develop thyroid dysfunction. Logistic and linear regression were used as multivariate analysis. SPSS software version 22 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis, and a $p$-value $< 0.05$ was considered statistically significant.

## 3. Results

Charts of 104 patients treated with ICI were reviewed for this study by two independent reviewers. Thirteen patients had a history of thyroid dysfunction (either functional or euthyroid goiter) before starting treatment with ICI and were excluded from the final analysis. Hence, a total of 91 patients were included in the final analysis of the study. All patients received either anti-PD-1 (nivolumab, pembrolizumab), anti-PDL-1 (atezolizumab), and/or anti-CTLA-4 (ipilimumab) therapy. Tables 1 and 2 summarizes the different demographic and clinical features of the study participants. Fifty-nine (65%) patients were male, and 32 (35%) were female. A total of 20 patients receiving nivolumab, 5 patients receiving pembrolizumab, 5 patients receiving dual checkpoint inhibitors, and 1 patient each receiving atezolizumab, ipilimumab, and dual checkpoint inhibitors, developed thyroid dysfunction.

**Table 1.** Clinical features of 104 patients whose charts were reviewed (HNSCC: head and neck squamous cell carcinoma; GE: gastroesophageal junction adenocarcinoma; CTLA-4: Cytotoxic T-lymphocyte associated protein 4; PD-1: programmed cell death protein-1; PDL-1: programmed death ligand-1; COPD: chronic obstructive pulmonary disease; SBRT: Stereotactic body radiaition therapy; ICI: immune-checkpoint inhibitor).

| Type of Cancer | Frequency (%) |
|---|---|
| HNSCC | 22 (14.4%) |
| Lung adenocarcinoma | 38 (24.8%) |
| Lung squamous cell carcinoma | 6 (3.9%) |
| Lung small cell carcinoma | 9 (5.9%) |
| melanoma | 9 (5.9%) |
| Renal cell carcinoma | 13 (8.5%) |
| GE adenocarcinoma | 1 (0.7%) |
| Bladder cancer | 3 (2%) |
| Merkel Cell | 1 (0.7%) |
| Kaposi sarcoma | 1 (0.7%) |
| Breast cancer | 1 (0.7%) |
| **Type of ICI** | |
| Nivolumab | 74 (71.1%) |
| Pembrolizumab | 22 (21.2%) |
| Atezolizumab | 1 (1%) |
| Ipilimumab | 2 (1.9%) |
| CTLA-4 + PD-1/PDL-1 inhibitor | 5 (4.8%) |
| **Race** | |
| African American | 47 (45.2%) |
| White | 24 (23.1%) |
| Hispanic | 26 (25%) |
| Asian | 5 (4.8%) |
| Others | 2 (1.9%) |
| **Stage at the Time of Starting ICI Therapy** | |
| I | 0 (0%) |
| II | 1 (1%) |
| III | 8 (7.7%) |
| IV | 95 (92.3%) |
| **Treatments Received Prior to Receiving ICI** | |
| Chemotherapy | 32 (30.8%) |
| Chemotherapy and radiation therapy | 42 (40.4%) |
| Surgery | 8 (7.7%) |
| Targeted therapy | 2 (1.9%) |
| Surgery and targeted therapy | 9 (8.7%) |
| Surgery and chemotherapy and radiation therapy | 5 (4.8%) |
| Surgery and chemotherapy | 2 (1.9%) |
| Surgery and radiation therapy | 1 (1%) |
| None | 3 (2.9%) |

**Table 1.** Clinical features of 104 patients whose charts were reviewed (HNSCC: head and neck squamous cell carcinoma; GE: gastroesophageal junction adenocarcinoma; CTLA-4: Cytotoxic T-lymphocyte associated protein 4; PD-1: programmed cell death protein-1; PDL-1: programmed death ligand-1; COPD: chronic obstructive pulmonary disease; SBRT: Stereotactic body radiaition therapy; ICI: immune-checkpoint inhibitor).

| **History of Radiation Therapy before ICI Started** | |
|---|---|
| Head and neck (excluding brain) | 18 (17.3%) |
| Brain (whole brain RT, no SBRT) | 13 (12.5%) |
| Chest | 32 (30.8%) |
| Osseous structures | 8 (7.7%) |
| Any other part of the body excluding above | 18 (17.3%) |
| **Clinical Data** | **Median** |
| Age at diagnosis (years) | 58.5 (21–85) |
| Total number of cycles with ICI | 8 (2–70) |
| Survival from date of diagnosis (months) | 31 (6–109) |
| Time lag between diagnosis and starting ICI (weeks) | 73.3 (3.14–412.28) |
| Time on ICI (weeks) | 16 (2–143) |

**Table 2.** The clinical data pertaining to thyroid dysfunction in patients receiving ICI therapy (ICI: immune checkpoint inhibitor; TSH: thyroid stimulating hormone).

| **Number of Cycles/Time Lag to Developing Thyroid Dysfunction** | **Median (Min–Max)** |
|---|---|
| Number of cycles after which thyroid dysfunction started | 2 (1–16) |
| Number of weeks on ICI therapy prior to developing thyroid dysfunction | 8.5 (2–34) |
| ICI used as which line of treatment | 2 (1–4) |
| Stage at starting ICI | 4 (3–4) |
| Total number of cycles received before ICI was discontinued | 9.5 (3–53) |
| Baseline TSH (mU/L) | 2.39 (0.013–5.06) |
| Baseline free T4 (ng/dL) | 0.825 (0.68–1.39) |
| Survival after stopping ICI (weeks) | 7.6 (0–77) |

Among the 91 patients included in the final analysis, 28 patients (31%) developed thyroid dysfunction after starting ICI. Thirteen patients developed hypothyroidism (high TSH, low or normal free T4), twelve patients developed hyperthyroidism followed by hypothyroidism, and three patients developed hyperthyroidism (low TSH and high or normal free T4). There was no significant difference between the two groups with respect to the type of ICI used, type of cancer, gender, hypertension, diabetes, and receiving different modalities of treatment for cancer (i.e., chemotherapy, chemoradiation therapy, and surgery). However, patients of Hispanic origin and younger patients had a higher incidence of thyroid dysfunction secondary to ICI therapy (Table 3). None of the patients who

developed thyroid dysfunction due to ICI therapy ever exhibited signs or symptoms of thyroid dysfunction or developed thyroid-related emergencies.

**Table 3.** Significant results from univariate analysis (VTE: venous thrombo-embolism; RT: Radiation therapy; ICI: Immune checkpoint inhibitor; OR: Odds Ratio).

| Categorical Demographic/Clinical Feature | Frequency—n (%) | *p*-Value |
|---|---|---|
| Race | | 0.048 |
| African American | 06 (21%) | |
| Hispanic | 12 (43%)—OR-5.34 (CI: 1.64,17.42) | |
| Caucasian | 08 (29%) | |
| Asian | 02 (7%) | |
| History of RT to neck before ICI | 8 (29%)—OR—5.9 (CI: 1.61,21.72) | 0.007 |
| History of RT to chest before ICI | 4 (14.5%)—OR—4.22 (CI:1.31,13.61) | 0.015 |
| History of VTE | 8 (29%)—OR—5.9 (CI: 1.61,21,72) | 0.007 |
| **Continuous Demographic/Clinical Feature** | | ***p*-Value** |
| Age at diagnosis, years | Median—58 years, $\chi^2$—6.11 (CI: −0.11, −0.02) | 0.009 |

Table 3 summarizes the significant associations of different clinical and demographic factors with the development of thyroid dysfunction. Multivariate logistic regression showed that the history of radiation therapy (RT) to the neck was the only significant predictor of developing thyroid dysfunction after adjustment for age at diagnosis, race, and gender (adjusted OR 9.64, 95% CI 1.88–49.36, *p*-0.007). The history of RT to the chest was not a significant predictor of developing thyroid dysfunction after adjustment for age at diagnosis, race, and gender (adjusted OR 0.33, 95% CI 0.091–12.44).

## 4. Discussion

Thyroid dysfunction is the most common adverse effect of ICI use amongst all endocrine irAE [14,15]. Despite this, the clinical factors to predict de novo thyroid dysfunction in patients receiving ICI remain unclear. Ours is the first study to report that the history of receiving RT to the head and neck region is a significant predictor of developing 'de novo' thyroid dysfunction in patients who are treated with ICI and have a normal value of TSH and free T4 before starting therapy. In our study, 28 patients (26.9%) treated with ICI developed thyroid dysfunction. The cumulative incidence of thyroid dysfunction is similar to recent studies that report 14–21% of thyroid dysfunction with the use of anti-PD-1 ICI [9,13,16]. Eight patients (44.45%) who had received RT to the neck developed thyroid dysfunction after starting treatment with ICI. Out of these eight patients, six patients developed thyroid dysfunction within 1–3 cycles of starting ICI therapy. It must be noted here that we excluded the patients who were diagnosed with functional thyroid dysfunction before starting the ICI treatment. Our study did not identify any significant association between age, gender, race, or type of cancer, and the development of thyroid dysfunction, which is congruent with the existing literature [8,9]. Kobayashi et al., in their prospective study, reported that the presence of anti-thyroglobulin antibodies and antithyroid peroxidase antibodies before starting nivolumab had been associated with a higher incidence of developing thyroid-related irAE [10]. However, other authors have reported no statistically significant relationship between the presence of these antibodies before the development of thyroid-related irAE [7,13]. In our practice, we do not routinely check for these antibodies. None of the patients in our study developed thyroid emergencies or required interruption or termination of treatment. The majority of patients with thyroid dysfunction became

hypothyroid (89%, 25/28 patients), amongst whom twelve patients developed thyroiditis like the picture (hyperthyroidism followed by hypothyroidism). A similar pattern of thyroid irAE has been reported by other authors [4,7,11,13]. Although we excluded patients with functional thyroid dysfunction, we did observe a worsening of TSH and free T4 after starting treatment with ICI.

The mechanism of thyroid dysfunction caused by ICI remains anecdotal. CTLA-4 is a central regulator of the immune system that prevents autoreactive T-cells from getting activated in the naïve stages. On the other hand, PD-1/PDL-1 has a more ''peripheral" action: it downregulates activated T-cells to prevent autoimmunity [1,4,7,13,17]. It is also known that polymorphisms and mutations in CTLA-4 or PD-1/PDL-1 lead to a wide array of autoimmune conditions, including autoimmune thyroiditis [1,4,13]. It is widely believed that the use of ICI can lead to a block of T-cell regulatory pathways and activates autoreactive T-cells; however, the theory yet remains to be proven conclusively [4,13]. The combination of radiotherapy with ICI is currently a topic of investigation for multiple trials. It is postulated that the tumoricidal effects of RT lead to exposure of tumor antigens that can lead to clonal expansion of activation of T-cells [18,19]. In addition to this, RT also increases the pro-inflammatory cytokines (CD91, MHC-1, Interferon-1) that can further activate T-cells in the periphery [18,19]. In theory, this effect could also explain the inflammatory responses seen in the thyroid gland. Although no patients received RT and ICI concomitantly in our group, we postulate that the subtle changes in the thyroid gland brought about by RT to the neck were worsened by the introduction of ICI, leading to precipitation of frank thyroid dysfunction. Our proposition is further strengthened by our observation in patients with functional thyroid dysfunction before starting ICI, in whom we noticed a worsening of TSH and free T4 after starting treatment with ICI. Harding et al. have reported an increase in pre-existing antithyroid antibodies after treatment with ipilimumab [20]. Likewise, Snozl et al. have also observed (in unpublished data) a marked increase in antithyroid antibodies that could, in theory, explain the worsening of thyroid dysfunction after starting ICI therapy [4]. We recently conducted a database analysis, where we report that patients with head and neck cancer (HNC), who were treated with ICI, developed thyroid dysfunction at a higher rate than other cancers where ICI was used [21]. We think that this disparity is primarily because RT to the head and neck region is a principal treatment modality for patients with HNC. In our study as well, six out of eight patients who received RT to the neck belonged to the HNC group.

The strength of our study lies in the diversity of tumor types included in the analysis and the fact that we excluded all patients who had any form of thyroid dysfunction (functional or anatomical). We included all kinds of ICI that were approved by USFDA at the time of this study period. These factors help in the generalization of the results and mimicry of real-world scenarios. Our study has certain limitations. First, the retrospective nature of the study introduces selection bias; however, to minimize this, we strictly adhered to the study protocol. The second limitation of this study is including very few patients receiving the combination of anti-CTLA-4 and anti-PD-1, which skews the data pertaining to the incidence of thyroid dysfunction with dual ICI. We have acknowledged this in the results section.

## 5. Conclusions

Our study explores the clinical factors associated with the development of thyroid dysfunction in patients receiving ICI therapy for any tumor type. After adjusting for age, race, and gender, we find that RT to the neck region is significantly associated with the development of hypothyroidism after initiating ICI therapy. Given study design causality cannot be inferred. Future prospective studies are needed to validate this finding.

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