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# Graves' orbitopathy development in thyroid cancer patients: a 16-year nationwide cohort study in South Korea

Minjeong Kim[1,4], Jooyoung Lee[2,4], Yu Been Hwang[2], Jinmo Kang[2], Hwa Young Ahn[3]✉ and Jeong Kyu Lee[1]✉



**BACKGROUND/OBJECTIVES:** We aimed to investigate the prevalence, risk factors, and prognosis of Graves' orbitopathy (GO) in patients with thyroid cancer without a history of hyperthyroidism.

**SUBJECTS/METHODS:** This retrospective cohort study analysed a sample from the Korean National Health Insurance Service database, which included 1,137,861 subjects from 2002 through 2019. Patients diagnosed with thyroid cancer, without a history of hyperthyroidism, were identified according to the Korean Standard Classification of Disease codes. The study compared the type of surgery, dose of radioactive iodine (RAI), and daily average thyroid hormone dose between patients who developed GO after being diagnosed with thyroid cancer and those who did not develop GO. We analysed the course of GO and the type of treatment.

**RESULTS:** A total of 8499 cancer patients without a history of hyperthyroidism were identified, among whom 7836 underwent thyroidectomy. Of those who underwent thyroidectomy, 12 developed GO postoperatively. Among the 663 patients who did not undergo thyroidectomy, none developed GO. The prevalence of GO among thyroid cancer patients was 0.14%. The GO group received a significantly higher total RAI dose than the non-GO group ($p = 0.036$). There were no significant differences in sex, age, type of surgery, rate of RAI treatment, or average thyroid hormone dose between the two groups. One of the 12 patients who developed GO required intravenous steroids.

**CONCLUSIONS:** Although GO rarely develops in thyroid cancer patients without coexisting hyperthyroidism, the total RAI dose may increase its risk. Further research would help clarify GO's association with thyroid cancer.

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## INTRODUCTION

Graves' orbitopathy (GO), also called thyroid-associated orbitopathy or thyroid eye disease, is a rare condition that deteriorates patients' quality of life and burdens public health [1]. It is characterised by lid retraction, periocular swelling, exophthalmos, and strabismus, frequently accompanying hyperthyroidism [2]. The subsequent autoimmune reaction from thyroid-stimulating hormone (TSH) receptor antibodies (TSH-R-Ab) and insulin-like growth factor-1 (IGF-1) receptor antibodies (IGF-1R-Ab) impacts orbital fibroblasts, leading to the development of this condition [2].

Thyroid cancer is diagnosed in 13-28% of Graves' disease (GD) patients postoperatively [3–5], and one report suggests that radioactive iodine (RAI) treatment may aggravate coexisting GO [6]. However, few studies have explored the occurrence of GO after thyroidectomy in individuals without GD. There are limited reports of euthyroid GO's association with thyroid cancer [7–9], and its pathogenesis remains unclear. Despite this, previous studies have noted both improvement and exacerbation of GO symptoms during thyroid cancer treatments, including surgery and RAI therapy [9, 10].

In this study, we collected GO case reports associated with thyroid cancer and analysed a large database from the Korean National Sample Cohort. We identified GO in twelve patients with thyroid cancer without a history of hyperthyroidism, categorised thyroid cancer patients into two groups according to GO diagnoses, and compared potential factors affecting GO development.

## METHODS

This population-based retrospective study focused on the National Health Insurance Service-National Sample Cohort (NHIS-NSC) in South Korea (2002-2019). The study's protocol followed the Declaration of Helsinki tenets and was approved by Chung-Ang University Hospital Institutional Review Board (IRB number: 2208-006-19430).

### Data source

The stratified random sampling of the selected 1,137,861 subjects by sex, age, region, and insurance premium levels in 2006 represented approximately 2% of the Korean population under public health insurance, including medical care recipients. The database provided demographic data, inpatient and outpatient diagnoses, prescriptions, and health examination data from 2002 to 2019. This sample was not available for public use as it contains personal information but could be accessed with a given license if intended for public health research.

### Case definition

We used official codes defined in the recent Korean Standard Classification of Diseases (KCD) for data analysis. Patients with more than one C73

[1]Department of Ophthalmology, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Republic of Korea. [2]Department of Applied Statistics, Chung-Ang University, Seoul, Republic of Korea. [3]Department of Internal Medicine, Chung-Ang University Hospital, Chung-Ang University College of Medicine, Seoul, Republic of Korea. [4]These authors contributed equally: Minjeong Kim, Jooyoung Lee. ✉email: ahy0809@gmail.com; lk1246@gmail.com

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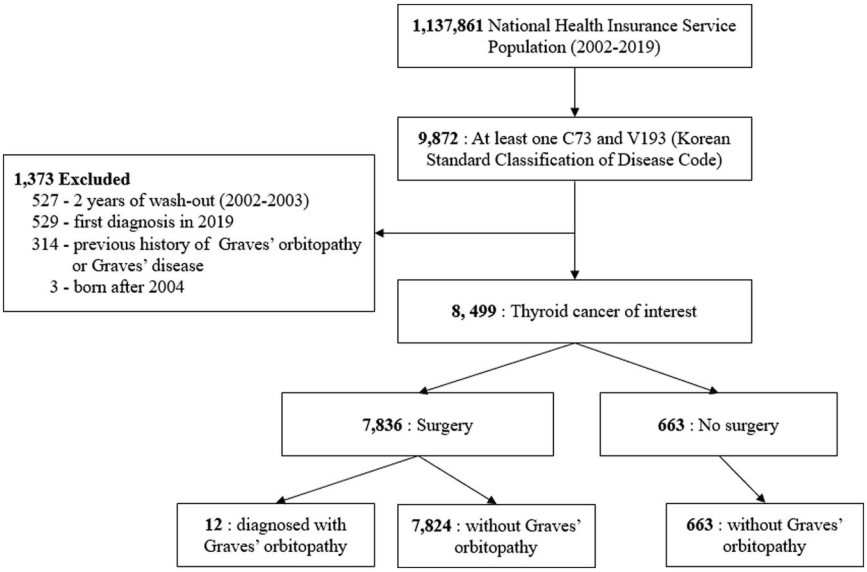


**Fig. 1** Flow chart of included patients.

(malignant thyroid gland neoplasm) and one V193 code (a cancer-specific insurance deductible) code were considered thyroid cancer subjects. We identified newly diagnosed thyroid cancer patients between 2004 and 2018 with a 2-year wash-out period (2002-2003). Patients first diagnosed with thyroid cancer after 2019, born after 2004, or with previous hyperthyroidism or GO history were excluded. Subjects diagnosed with KCD codes E05 (hyperthyroidism), E06 (thyroiditis), or E07 (other thyroid disorders) and prescribed antithyroid drugs (propylthiouracil, methimazole, carbimazole) at least twice were deemed hyperthyroidism patients. Subjects with at least two physician claims and an H062 KCD code (indicating dysthyroid exophthalmos) were considered GO patients. GO patients diagnosed after their thyroid cancer diagnosis were identified. Eligible patients were tracked from the date of their thyroidectomy until the occurrence of GO, death, loss to follow-up, or 31 December 2019.

### Case evaluation

Active GO phase criteria entailed at least six intravenous steroid administrations within 90 days following the initial dose after GO diagnosis. A lobectomy was identified by a single P4551 or P4553 surgical code. Alternatively, total thyroidectomy was defined as one P4552, P4554, or P4561 surgical code or more than one P4551 and P4553. Each case's post-thyroidectomy RAI therapy (Sodium iodide I-131) and thyroid hormone (levothyroxine sodium) duration and dose were investigated using drug codes available to the public from the NHIS. Intravenous or oral steroid prescriptions, immunosuppressants (azathioprine, cyclosporine, mycophenolate, cyclophosphamide, methotrexate), and orbit radiotherapy were also monitored. For accurate treatment assessment, we considered the primary (first-listed) diagnosis upon prescription and not the clinical record of irrelevance. Other than those listed above, secondary immunosuppressants are not covered by the national insurance in Korea and were not included in the national data.

### Statistical analysis

Patient characteristics were summarised as median (interquartile range, IQR) for continuous variables and percentage for categorical variables. Fisher's exact test was used for categorical variable comparisons; the Mann–Whitney test compared continuous variables. We used SAS software ver. 9.4 (SAS Institute, Cary, NC, USA) and R ver. 3.3 3 (R Foundation for Statistical Computing) for all analyses, and $p < 0.05$ was considered statistically significant.

## RESULTS

This study identified 8499 thyroid cancer patients without hyperthyroidism or GO. Of these, 7836 patients had undergone thyroidectomy, and 12 had developed GO postoperatively. In contrast, none of the 663 patients who did not undergo thyroidectomy developed GO (Fig. 1). The prevalence of GO among thyroid cancer patients was 0.14%.

We compared the type of surgery, the percentage and dose of RAI treatment, and the daily average thyroid hormone dose between the patients who developed GO after being diagnosed with thyroid cancer and those who did not develop GO (Table 1). All twelve GO patients and 81.3% of the non-GO patients were women. Furthermore, 83.3% of GO patients and 78.6% of non-GO patients underwent total thyroidectomy, and 41.7% of GO and 49.2% of non-GO patients received RAI treatment. There was no significant difference in sex, age of onset, type of surgery, rate of RAI treatment, or average thyroid hormone dose between the two groups. However, the GO group received a significantly higher average total RAI doses than the non-GO group ($p = 0.036$), ranging from 100 to 263 mCi. The average follow-up duration was shorter in the GO group, as the occurrence of GO was an endpoint of the follow-up

Table 2 summarises the 12 GO patients' clinical characteristics. One case had a previous history of Hashimoto's thyroiditis. GO was diagnosed within 57–5473 days following a thyroid cancer diagnosis. In addition, 4 of the 5 GO cases were diagnosed within 1 year after RAI therapy, and the total RAI dose was 168.5 (139.8–203.8) mCi, significantly higher than the 104 (40–160) mCi in non-GO patients. All patients received thyroid hormone supplementation post-thyroidectomy, with an 85 (70–120) μg average daily thyroid hormone dose before the development of GO. In particular, one patient had an active GO phase (Table 2, case 5) 18 months after the cancer diagnosis (surgery was conducted simultaneously), receiving intravenous steroids (methylprednisolone 0.5 g) nine times within 5 days. This was the only case for whom both intravenous and oral steroids were prescribed. No other case required steroids, immunosuppressants or orbital radiation.

## DISCUSSION

Notably, few papers have examined GO prevalence. Among them, a European Group on GO (EUGOGO) report estimated 90–305 GO cases in Europe within a population of 100,000, similar to the rate in Asia (100–300 out of 100,000) [11–13]. Approximately 86% of GO patients indicated a correlation with hyperthyroidism, 7.9% exhibited normal thyroid function, and 10% were related to

**Table 1.** Comparing patients with and without Graves' orbitopathy (GO) among thyroid cancer patients who received surgical intervention.

| | GO group ($N = 12$) | Non-GO group ($N = 7824$) | *P*-value |
|---|---|---|---|
| *Sex (%)* | | | 0.14 |
| Male | 0 (0) | 1469 (18.7) | |
| Female | 12 (100) | 6355 (81.3) | |
| Age at thyroid cancer diagnosis (median (IQR)) | 48 (42.8–49.6) | 48.80 (40.29–56.72) | 0.539 |
| Age at thyroidectomy (median (IQR)) | 48 (42.8–49.7) | 48.92 (40.41–56.85) | 0.536 |
| Surgery type (%) | | | 1 |
| Total | 10 (83.3) | 6148 (78.6) | |
| Partial | 2 (16.7) | 1676 (21.4) | |
| Radioactive iodine (RAI) (%) | 5 (41.7) | 3849 (49.2) | 0.775 |
| Total RAI dose (median (IQR)) (mCi) | 184 (153–200) | 104 (40–160) | **0.036** |
| Daily average thyroid hormone dose (median (IQR)) (μg) | 85 (70–120) | 100 (70–140) | 0.324 |
| Follow-up duration after surgery (median (IQR)) (days) | 458 (298.3–914) | 2763 (1768.5–3763.0) | **<0.001** |

Bold values indicate statistical significance $p < 0.05$.
*IQR* interquartile range.

**Table 2.** Characteristics of 12 patients diagnosed with Graves' orbitopathy (GO).

| **Patient No.** | **1** | **2** | **3** | **4** | **5** | **6** | **7** | **8** | **9** | **10** | **11** | **12** |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Sex | Female | Female | Female | Female | Female | Female | Female | Female | Female | Female | Female | Female |
| Age[a] | 49 | 47 | 62 | 32 | 39 | 55 | 50 | 34 | 48 | 47 | 48 | 43 |
| Previous GD/ Hashimoto's | −/+ | −/− | −/− | −/− | −/− | −/− | −/− | −/− | −/− | −/− | −/− | −/− |
| Cancer Dx (year) | 2010 | 2009 | 2011 | 2008 | 2014 | 2012 | 2004 | 2011 | 2009 | 2012 | 2011 | 2013 |
| Thyroidectomy (year) | 2010 | 2009 | 2012 | 2008 | 2014 | 2012 | 2004 | 2011 | 2009 | 2012 | 2011 | 2013 |
| Surgery type | Total | Total | Total | Total | Partial | Total | Total | Partial | Total | Total | Total | Total |
| Days between cancer and GO Dx | 444 | 2527 | 354 | 262 | 506 | 57 | 5473 | 1059 | 462 | 459 | 960 | 247 |
| RAI before GO | Yes | No | No | Yes | No | No | Yes | No | Yes | No | No | Yes |
| Days between RAI and GO Dx | 318 | | | 108 | | | 5189 | | 334 | | | 133 |
| Total RAI dose before GO (mCi) | 184 | | | 153 | | | 200 | | 263 | | | 100 |
| Daily thyroid hormone dose average before GO (μg) | 70 | 70 | 140 | 150 | 80 | 120 | 80 | 100 | 40 | 120 | 60 | 90 |
| Active GO (year) | | | | | 2015 | | | | | | | |

[a]Upon cancer diagnosis.
*GD* Graves' disease, *Dx* diagnosis, *RAI* radioactive iodine.
Active GO: at least six intravenous steroid administrations within 90 days after the initial dose.

hypothyroidism [14]. However, GO development regarding thyroid cancer patients without hyperthyroidism has yet to be explored: ten case reports are described in Table 3. This study detected only twelve GO cases in thyroid cancer patients without hyperthyroidism within a cohort population of over one million. Every case was female, corroborating previous conclusions that the disease is primarily female-dominant [15]. On average, patients diagnosed with thyroid cancer in their late forties received a thyroidectomy within a year.

Among the cancer patients who did not undergo a thyroidectomy, none were diagnosed with GO. Further studies are needed to ascertain whether the absence of GO among these patients was associated with the lack of surgery itself or with the low severity of their cancers (precluding the need for surgery). However, some studies could help explain this phenomenon as they showed that serum thyroglobulin (Tg) levels and thyroid autoimmunity were related to GO [16, 17]. In addition, thyroid cancer intensity is associated with thyroid antibodies [18, 19], and preoperative serum Tg levels correlate with nodule size and metastatic burden [20–22]. Consequently, patients with low-risk thyroid cancer who do not undergo surgery are likely to have low serum Tg or thyroid antibodies, potentially offering protection against GO.

Five out of twelve GO patients received RAI treatment in our study. RAI thyroid remnant ablation is an established method for preventing thyroid cancer recurrence after thyroidectomy in high-risk patients. It enables early detection and reduces the risk of cancer recurrence by destroying residual thyroid tissue. In our study, RAI doses significantly differed between GO and non-GO patients. Other research has indicated a link between the severity of GO following RAI treatment in thyroid cancer patients with

**Table 3.** New-onset Graves' orbitopathy reports in thyroid cancer patients without previous hyperthyroidism history.

| Patient no. | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 |
|---|---|---|---|---|---|---|---|---|---|---|
| Age | 67 | 30 | 58 | 53 | 51 | 49 | 47 | 55 | 58 | 44 |
| Sex | Female | Female | Female | Female | Female | Female | Female | Female | Female | Female |
| Cancer type | Metastatic follicular | Papillary | Papillary | Papillary | Papillary | Papillary | Papillary | Papillary | Papillary | Papillary |
| Thyroid cancer treatment | TT levothyroxine RAI (100 mCi) | PT thyroxine RAI (59.5 mCi) | TT levothyroxine RAI | TT levothyroxine RAI (100 mCi) | TT levothyroxine RAI (30 mCi) | TT levothyroxine RAI (30 mCi) | TT levothyroxine RAI (30 mCi) | TT levothyroxine RAI (30 mCi) | TT levothyroxine | TT levothyroxine |
| GO onset | 1-year post-RAI | 34 years post-RAI | 4 years post-RAI | 4 years post-RAI | 27 months post-surgery | 4 months post-surgery | 4 months post-surgery | 3 months post-surgery | 75 months post-surgery | 48 months post-surgery |
| At GO Dx | | | | | | | | | | |
| TFT | NL | T4 174 nmol/l (58–140) TSH 0.9 mU/l (0.3–4.0) | NL | T4 2.68 ng/dl (0.8–1.9) TSH < 0.05 μu/ml | T4 1.9 ng/dl TSH < 0.025 mIU/L[a] | T4 2.53 ng/dl TSH 0.14 mIU/L[a] | T4 2.03 ng/dl TSH 0.12 mIU/L[a] | T4 1.65 ng/dl TSH 0.4 mIU/L[a] | T4 1.76 ng/dl TSH < 0.025 mIU/L[a] | T4 1.67 ng/dl TSH < 0.025 mIU/L[a] |
| TSH-R-Ab | ↑ | NL | ↑ | ↑ | ↑ | NC | ↑ | ↑ | NL | ↑ |
| Tg | ↑ | ↑ | NL | NL | NL | NL | NL | NL | NL | ↑ |
| Tg antibody | ↑ | NL | NL | NL | NC | NC | NC | NC | NC | NC |
| Study | Murayama et al. [9] | Rogers et al. [32] | Antonelli et al. [33] | Giovansili et al. [24] | Jang et al. [10] | Jang et al. [10] | Jang et al. [10] | Jang et al. [10] | Jang et al. [10] | Jang et al. [10] |

[a]Normal range: TSH 0.4–3 mIU/L, free T4 0.7–1.48 ng/dL.
*TT* total thyroidectomy, *PT* partial thyroidectomy, *RAI* radioactive iodine, *NL* normal, *NC* not checked, *TSH* thyroid stimulating hormone, *TSH-R-Ab* TSH receptor antibody, *Tg* thyroglobulin.

hyperthyroidism and the dosage of RAI [6]. Also, de novo GO occurrences have been reported in thyroid cancer cases post-RAI, without a history of hyperthyroidism [10, 23, 24].

Following RAI treatment, orbital tissue seems to contain thyroid-originated Tg, which suggests that substantial amounts of soluble thyroid antigen (especially Tg) released from damaged thyroid tissue, could trigger an autoimmune response in GO patients [25–28]. Additionally, considering that most de novo GO is associated with the expression of TSH-R-Ab, autoimmunity stimulated by RAI-induced thyroid tissue inflammation followed by increased self-antigen presentation could contribute to GO development. Moreover, thyroid cancer is common in Hashimoto's thyroiditis patients [29]; thus, it is possible that thyroid cancer patients with underlying Hashimoto's thyroiditis might develop GO from autoimmune activity after receiving RAI treatment. Unfortunately, this hypothesis could not be verified in our current study.

In hyperthyroidism, TSH-R-Ab on thyroid follicles excessively induces thyroid hormones, demonstrating that the autoimmune reaction against orbital soft tissue and sympathetic stimulation from thyroid hormones prompt GO symptoms [7, 30, 31]. Our results did not confirm differences in daily thyroid hormone supplement doses between GO and non-GO patients. However, further study with a larger cohort is needed to evaluate this relationship.

There were limitations within this study, such as relying on big data from the national insurance system rather than on individual patient charts from clinics; thus, specific details, including autoantibody status, biopsy cancer results, and GO morphology and severity, were not available. The TSH-R-Ab titre might have exceeded the normal range upon GO onset, considering its tendency to develop alongside hyperthyroidism with TSH-R-Ab, which was not detectable in our study. Secondly, we could not determine significant differences in thyroid hormone dosage, and our study encompassed a relatively small number of GO patients. Further study with a sizable measure of cases would help clarify the relationship between the average thyroid hormone dosage and GO. Nevertheless, this was the first national data investigation to ascertain GO prevalence among thyroid cancer patients with euthyroid/hypothyroid status. Additional research regarding GO pathogenesis in similar cases would enhance clinicians' understanding of GO.

In conclusion, GO emergence in thyroid cancer patients without hyperthyroidism is a rare condition. Nonetheless, this study identified a potential correlation between thyroidectomy, postoperative RAI, thyroid hormone supplements, and GO pathogenesis. Future studies incorporating antibody status and clinical course would further elucidate details regarding the GO pathogenesis among patients with thyroid cancer.

## SUMMARY

What was known before

- Graves' orbitopathy rarely occurs in thyroid cancer patients without hyperthyroidism.

What this study adds

- The total dose of radioactive iodine was significantly higher in patients who developed Graves' orbitopathy after the diagnosis of thyroid cancer.

## DATA AVAILABILITY

Datasets used and analysed during the current study are available from the corresponding author upon reasonable request.

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## AUTHOR CONTRIBUTIONS

MK was responsible for writing the article. JL was responsible for designing the protocol and analysing the data. YBH contributed to data extraction and data analysis. JK contributed to data extraction. HYA was responsible for designing the protocol and interpreting the results. JKL was responsible for designing the protocol, interpreting results, and revising the article.

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## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

**Correspondence** and requests for materials should be addressed to Hwa Young Ahn or Jeong Kyu Lee.