



2025 Korean Thyroid Association Management Guidelines for Radioactive Iodine Therapy in Patients with Hyperthyroidism

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Hyperthyroidism is a condition marked by excessive thyroid hormone production, most commonly due to Graves' disease. Treatment options include antithyroid drugs (ATD), radioactive iodine (RAI) therapy, and thyroidectomy. To develop standardized clinical recommendations for RAI therapy with a focus on safety, efficacy, and monitoring, the Korean Thyroid Association formed a task force to create evidence-based guidelines. Six key clinical questions were identified through expert consensus, and a systematic literature review from 2013 to 2022 was conducted. Clinical indications for RAI therapy were categorized into three groups: strongly recommended, may be considered, and not recommended. A fixed dose of 10 to 15 mCi is recommended. Although a strict low-iodine diet is unnecessary, iodine-rich foods should be avoided for at least 1 week before treatment. ATD should be stopped 3 to 7 days before RAI and may be resumed in select cases. Prophylactic glucocorticoids are recommended for patients with mildly active thyroid eye disease and may be considered for others at risk. Thyroid function should be monitored at 4–6 weeks post-treatment, every

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2–3 months until stabilized, and then every 6–12 months. These guidelines highlight recent advances and underscore the importance of individualized treatment based on clinical features, comorbidities, and patient preferences in Korea.

Keywords: Hyperthyroidism; Graves disease; Radioactive iodine; Practice guideline; Korean Thyroid Association

INTRODUCTION

Hyperthyroidism is a clinical condition characterized by the excessive production of thyroid hormones, resulting in thyrotoxicosis, with Graves' disease being the most common underlying cause [1-3]. In Korea, the age-standardized incidence of hyperthyroidism has increased from 42.23 per 100,000 persons in 2004 to 105.13 in 2018, with the highest incidence observed in women in their 50s and 60s [4]. Treatment modalities include antithyroid drug (ATD), radioactive iodine (RAI) therapy, and thyroidectomy [5-7]. ATD maintain euthyroidism by suppressing thyroid hormone production, while RAI therapy and thyroidectomy treat hyperthyroidism by ablating or removing thyroid tissue, thereby eliminating the source of hormone excess [5-7]. Each treatment option has distinct advantages and disadvantages, and the choice of therapy should be individualized based on clinical factors, such as patient age, goiter size, symptom severity, and treatment adherence, as well as non-clinical factors, including socioeconomic conditions, accessibility to RAI treatment facilities, patient preferences, and the national healthcare system. Treatment preferences for hyperthyroidism vary by country. In Korea, RAI therapy is used less frequently than in Europe and the United States [4]. According to the Korean Thyroid Association (KTA) Fact Sheet [8] and National Health Insurance Service data, 97.3% of Korean patients with hyperthyroidism receive ATDs as a first-line treatment. The proportion of patients receiving RAI therapy decreased from 5.46% in 2003 to 2.66% in 2018, whereas the rate of thyroidectomy increased slightly from 1.43% to 1.95% over the same period [4].

The KTA published a consensus statement on the diagnosis and management of hyperthyroidism in 2013 [9], followed by guidelines from the American Thyroid Association in 2016 [5], the European Thyroid Association in 2018 [6], and the National Institute for Health and Care Excellence in 2019 [7]. However, the direct application of international guidelines to Korean clinical settings is limited by practical constraints. Moreover, the 2013 KTA consensus requires revision to reflect current clinical realities in Korea and to provide more explicit criteria for appropriate treatment selection. In particular, the low utilization of RAI therapy in Korea underscores the need for updated guide-

lines detailing its indications, procedures, and follow-up protocols. In response to these needs, the present guideline provides evidence-based recommendations derived from a systematic review of literature or from an experts' consensus. Key points in each section are presented within a framework that includes specific recommendations and levels of evidence. This guideline has been published in the official journal of the KTA, the *International Journal of Thyroidology*, and is also available on the KTA website (www.thyroid.kr).

DEVELOPMENT PROCESS OF THE KTA CLINICAL PRACTICE GUIDELINE FOR RAI THERAPY IN PATIENTS WITH HYPERTHYROIDISM

Composition of the guideline development task force and process for recommendations

The KTA convened a multidisciplinary task force in 2022, comprising experts in internal medicine and nuclear medicine, to develop revised clinical practice guidelines for RAI therapy in patients with hyperthyroidism. A total of 10 meetings were held by the task force to formulate key clinical questions, assess the relevant evidence, and derive corresponding recommendations. A comprehensive literature review was performed using database such as PubMed and Embase, with 'hyperthyroidism' and 'Graves' disease' as the primary keywords, covering publications from 2013 to 2022. Additional studies published during the manuscript preparation were also included. The selected literature was reviewed, and relevant evidence was extracted to formulate the recommendations.

This guideline provides evidence-based recommendations for the use of RAI therapy in adult patients with suspected or confirmed hyperthyroidism, with a focus on autoimmune hyperthyroidism and the exclusion toxic nodular disease. It is intended to support clinical decision-making regarding RAI therapy for healthcare professionals managing patients with hyperthyroidism across various medical settings. Other treatment options, such as ATD therapy and surgery, are beyond the scope of this guideline and are not discussed in detail.

The draft guidelines were presented at the KTA Spring Scien-

Table 1. Korean Thyroid Association Recommendation Levels for Clinical Strategies, Diagnostic Testing, or Treatment in Patient Care

Grade	Level	Definition
1	Strongly recommend for/against	Sufficient and objective evidence exists that performing (or avoiding) the recommended action leads to significant health benefits or harms.
2	Conditionally recommend for/against	Evidence suggests important health benefits or harms, but the evidence is uncertain or indirect, making a uniform recommendation difficult.
3	Expert consensus recommendation	In the absence of strong clinical evidence, the recommendation is based on expert consensus and patient-specific considerations.
4	Inconclusive	Insufficient or conflicting evidence exists regarding significant health benefits or harms; no definitive recommendation for or against the action can be made.

tific Meeting in March 2024 to solicit feedback. They were subsequently revised based on comments from the KTA Board of Directors and advisory committees comprising representatives from five related academic societies: the Korean Endocrine Society, the Korean Society of Nuclear Medicine, the Korean Association of Endocrine Surgeons, the Korean Society of Head and Neck Surgery, and the Korean Society of Thyroid Radiology. Final approval was obtained through member feedback collected via the KTA website and formal endorsements from these same five societies.

Levels of recommendation and summary

Table 1 outlines the grading of recommendations, based on the framework previously used in the KTA guidelines to ensure consistency. Recommendations regarding the RAI therapy for patients with hyperthyroidism are summarized in Table 2.

Survey on the use of RAI therapy for hyperthyroidism

To better understand the current practice patterns regarding RAI therapy in Korea, the KTA task force conducted a survey of its members from January 24 to February 4, 2024. A total of 169 respondents completed a 15-item questionnaire. Among them, 77% (130/169) of respondents had experience administering RAI therapy, and only 16% (27/169) had selected it as the initial treatment for newly diagnosed hyperthyroidism.

The most frequently reported challenge in managing patients treated with RAI was concern about treatment-related complications, such as exacerbation of ophthalmopathy, sialadenitis, and the potential risk of secondary malignancies (113 respondents, 66.9%). Other commonly reported barriers included the considerable time required to explain RAI therapy to patients (108 respondents, 63.9%) and concerns about social stigma and other negative perceptions associated with RAI treatment (102 respondents, 60.4%). Of note, 89% (151/169) of respondents

indicated that explaining RAI therapy required more time than explaining ATD therapy. Differences in perception were observed according to the respondents' experience with RAI treatment. For instance, concern about post-treatment hypothyroidism was reported by 45.5% of those without prior experience, compared to 15.4% of those with experience. Similarly, concerns regarding adverse effects were more prevalent among respondents without experience (45.9% vs. 26.2%).

When asked about the management of patients maintained on low-dose ATD for more than 5 years without achieving remission, 71% (120/169) of respondents reported that they would not consider RAI therapy. Likewise, 51% (85/169) responded that they would not choose RAI therapy for patients with relapse after ATD treatment. These findings indicate that RAI therapy is not actively considered in Korea, even in situations where ATD treatment has failed—unlike the treatment patterns commonly observed in the United States and Europe. In response to these findings, the task force formulated six key clinical questions to guide the appropriate use of RAI therapy, which served as the basis for this updated guideline.

EFFICACY AND SAFETY OF RAI THERAPY IN HYPERTHYROIDISM

Successful treatment of hyperthyroidism is defined as the elimination of excessive thyroid hormone production, resulting in either euthyroidism or hypothyroidism. In patients receiving RAI therapy, remission is achieved in approximately 50%–90% of cases within 3–12 months. A Korean study reported remission rates of 62.8% at 1 year and 76.8% at 2 years following the initial RAI treatment [10]. In contrast, the 2-year remission rate after ATD therapy was 41%, suggesting that RAI therapy offers a higher likelihood of long-term remission [11]. As RAI therapy is intended to cure hyperthyroidism with a single administra-

Table 2. Summary of 2025 Korean Thyroid Association Guidelines Statements for Radioactive Iodine Therapy in Patients with Hyperthyroidism**Section 1. Indications for RAI therapy in patients with hyperthyroidism**

- 1.1. RAI therapy should be considered in the following clinical situation.
 - 1.1.1. When the patient prefers an initial treatment option with a high likelihood of cure. [Recommendation level 1]
 - 1.1.2. When serious adverse events occur during ATD therapy. [Recommendation level 1]
 - 1.1.3. In patients who experience recurrent hyperthyroidism after remission with ATD therapy and desire a definitive cure. [Recommendation level 1]
 - 1.1.4. When thyroid function remains poorly controlled despite appropriate ATD therapy. [Recommendation level 1]
- 1.2. RAI therapy may be considered in the following clinical situation.
 - 1.2.1. In patients with poor adherence to ATD therapy. [Recommendation level 2]
 - 1.2.2. In patients with comorbidities that may lead to clinical instability if hyperthyroidism worsens (e.g., uncontrolled arrhythmia or heart failure). [Recommendation level 2]
 - 1.2.3. In patients requiring prolonged high-dose ATD therapy to maintain euthyroidism (particularly in women planning pregnancy in the next 6 months or beyond). [Recommendation level 3]
- 1.3. RAI therapy is not recommended in the following clinical situation.
 - 1.3.1. Pregnant or breastfeeding women. [Recommendation level 1]
 - 1.3.2. Patients with active moderate-to-severe thyroid eye disease. [Recommendation level 1]
 - 1.3.3. Patients with coexisting thyroid cancer. [Recommendation level 1]

Section 2. Determination of the RAI dose in patients with hyperthyroidism

- 2.1. A fixed dose of RAI (10–15 mCi) sufficient to induce hypothyroidism is recommended when determining the appropriate RAI dose. [Recommendation level 2]

Section 3. Need for a low-iodine diet before RAI therapy in patients with hyperthyroidism

- 3.1. A low-iodine diet is not routinely recommended before RAI therapy for hyperthyroidism; but iodine-rich foods should be avoided for at least 1 week prior to treatment. [Recommendation level 3]

Section 4. Appropriate discontinuation period of ATD before and after RAI therapy

- 4.1. Discontinuation of ATD for 3 to 7 days before RAI therapy is recommended. [Recommendation level 1]
- 4.2. Resumption of ATD within 3–7 days after RAI therapy may be considered in patients who received ATD prior to treatment or are at high risk of clinical deterioration due to worsening hyperthyroidism. [Recommendation level 2]

Section 5. Use of glucocorticoid before RAI therapy to reduce the development or progression of TED

- 5.1. RAI therapy is not recommended in patients with active moderate-to-severe TED. [Recommendation level 1]
- 5.2. Prophylactic corticosteroid therapy is recommended when RAI therapy is administered to patients with active mild TED. [Recommendation level 1]
- 5.3. In patients with inactive moderate-to-severe TED, prophylactic corticosteroid therapy may be considered during RAI treatment when additional risk factors—such as high TSH receptor antibody levels or smoking—are present. [Recommendation level 2]
- 5.4. Prophylactic corticosteroid therapy is not recommended during RAI treatment in patients with inactive mild TED when additional risk factors—such as high TSH receptor antibody levels or smoking—are not present. [Recommendation level 1]

Section 6. Intervals for thyroid function test after RAI therapy

- 6.1. Thyroid function test, including TSH and free T4, may be considered within 4 to 6 weeks after RAI therapy. [Recommendation level 2]
- 6.2. Thyroid function can be monitored every 2 to 3 months for up to 6 months after RAI therapy or until TSH levels normalize. [Recommendation level 2]
- 6.3. Thyroid function test may be repeated every 6 to 12 months, once thyroid function has been confirmed to be stable and within the normal range on at least two consecutive assessments. [Recommendation level 2]
- 6.4. Thyroid function test is recommended when symptoms of hyperthyroidism or hypothyroidism are suspected. [Recommendation level 2]

RAI, radioactive iodine; ATD, antithyroid drug; TED, thyroid eye disease; TSH, thyroid stimulating hormone; T4, thyroxine.

tion, the dose used is often sufficient to induce hypothyroidism [5-7]. Consequently, many patients who achieve remission after RAI therapy require lifelong thyroid hormone replacement. The incidence of hypothyroidism within the first year after treatment

ranges from 24% to 87%, with higher rates observed a higher RAI doses [12,13]. Even among patients who initially maintain normal thyroid function, hypothyroidism subsequently develops at an annual rate of approximately 3% to 5% [14,15].

RAI therapy may lead to both short- and long-term adverse effects. The short-term complications include transient pain, swelling, and sialadenitis, while long-term risks involve permanent hypothyroidism and a potential increased in secondary malignancies. However, evidence regarding the risk of secondary malignancies remains inconclusive. Although some studies have reported an elevated risk [16,17], a recent meta-analysis involving 479,452 patients with hyperthyroidism found no significant difference in overall cancer incidence between those treated with RAI and those who were not (risk ratio, 1.02; 95% confidence interval [CI], 0.95 to 1.09) [18]. A Korean study comparing 10,737 patients treated with RAI therapy to 53,003 untreated patients also found no significant increase in overall cancer risk (hazard ratio [HR], 0.96; 95% CI, 0.83 to 1.10) [19]. Moreover, recent evidence suggests that RAI therapy may be associated with lower all-cause and cardiovascular mortality compared to ATD therapy [20,21]. Some studies have further reported a lower risk of cardiovascular event in patients undergoing thyroidectomy than in those treated with RAI therapy [22,23]. In addition, early remission of hyperthyroidism has been linked to reduced cardiovascular mortality [21], highlighting the clinical importance of the timely restoration of euthyroidism. Collectively, these findings support the efficacy and safety of RAI therapy as a valid therapeutic option for the management of hyperthyroidism.

Section 1. Indications for RAI therapy in patients with hyperthyroidism

1.1. RAI therapy should be considered in the following clinical situation

- 1.1.1. When the patient prefers an initial treatment option with a high likelihood of cure. [Recommendation level 1]
- 1.1.2. When serious adverse events occur during ATD therapy. [Recommendation level 1]
- 1.1.3. In patients who experience recurrent hyperthyroidism after remission with ATD therapy and desire a definitive cure. [Recommendation level 1]
- 1.1.4. When thyroid function remains poorly controlled despite appropriate ATD therapy. [Recommendation level 1]

Comparative studies of ATD, RAI therapy, and surgery in patients with Graves' disease have reported relapse rates of 34%–42%, 21%, and 3%–8%, respectively [24]. ATDs is generally associated with lower remission rates (approximately 50%) and higher relapse rates, while RAI therapy achieves initial success rate of 75% to 81% [25–27]. Therefore, for patients who priori-

tize definitive treatment, RAI therapy or thyroidectomy should be considered as a first-line option. Although thyroidectomy offers the highest cure rate, it is associated with potential risks such as surgical scarring, complications related to general anesthesia, hypocalcemia, and vocal cord palsy. Therefore, in patients with high surgical risk or limited access to experienced surgeons, RAI therapy may be the preferred option.

RAI therapy is also indicated for patients who experience serious complications related to ATD therapy, such as agranulocytosis, hepatotoxicity, or vasculitis; those who relapse after achieving remission with ATD; and those whose hyperthyroidism remains uncontrolled despite adequate ATD treatment [28,29]. Due to the risk of cross-reactivity among ATDs, switching to another ATD is generally not recommended in cases of severe adverse effects. Notably, patients who develop agranulocytosis and subsequently receive RAI therapy have shown high remission rates (88.8%) [30].

The standard duration of ATD therapy is typically 12 to 18 months. Patients whose thyroid function remains unstable after 12 to 18 months of adequate ATD therapy, or those who relapse following discontinuation, should be considered for definitive treatment with RAI or surgery [5,6]. A meta-analysis of 3,388 patients from 26 randomized controlled trials demonstrated that extending ATD therapy beyond 18 months did not significantly improve remission rates [31]. Prolonged or inadequately controlled hyperthyroidism is known to be associated with increased mortality [20,32]. In addition, the remission rate with ATD retreatment after relapse is approximately 23%, which is lower than that of initial treatment [33]. Korean study involving 247 patients with Graves' disease, the success rate of RAI therapy as a second-line treatment was reported to be approximately 62.8% [10]. Therefore, in patients whose thyroid function remains unstable despite sufficient use of ATD for the standard treatment duration, definite therapy such as RAI or surgery should be considered.

1.2. RAI therapy may be considered in the following clinical situation

- 1.2.1. In patients with poor adherence to ATD therapy. [Recommendation level 2]
- 1.2.2. In patients with comorbidities that may lead to clinical instability if hyperthyroidism worsens (e.g., uncontrolled arrhythmia or heart failure). [Recommendation level 2]
- 1.2.3. In patients requiring prolonged high-dose ATD therapy to maintain euthyroidism (particularly in women planning pregnancy in the next 6 months or beyond). [Recommendation level 3]

Although a 12- to 18-month course of ATD therapy is generally required to achieve remission in patients with Graves' disease [31], extended treatment durations are frequently needed in real clinical practice [34,35]. Therefore, in patients requiring long-term therapy who demonstrate poor adherence to ATD, RAI therapy may be considered as a definitive treatment option. Nevertheless, as RAI-induced hypothyroidism also necessitates lifelong thyroid hormone replacement, clinicians should carefully assess the patient's adherence to both ATDs and thyroid hormone therapy before selecting a treatment strategy.

Fluctuating or inadequately controlled thyroid hormone levels are associated with an increased risk of cardiovascular diseases, such as arrhythmia and heart failure [36,37]. In a retrospective cohort study of 4,189 patients with newly diagnosed Graves' disease, outcomes were compared across three groups: those treated with ATD, those who achieved remission after RAI therapy, and those in whom hyperthyroidism persisted after RAI therapy. Compared with the ATD group, the RAI remission group showed significantly lower risks of major cardiovascular events (HR, 0.59; 95% CI, 0.38 to 0.92) and all-cause mortality (HR, 0.50; 95% CI, 0.29 to 0.85). In contrast, patients in whom hyperthyroidism persisted after RAI therapy had an increased risk of major cardiovascular events (HR, 1.51; 95% CI, 1.01 to 2.28), while no statistically significant difference in mortality was observed (HR, 1.51; 95% CI, 0.96 to 2.37) [21]. Notably, patients with subnormal thyroid stimulating hormone (TSH) levels 1 year after diagnosis exhibited higher rates of major cardiovascular events and mortality. Therefore, RAI therapy may be considered in patients with underlying conditions—such as uncontrolled arrhythmia or heart failure—in whom worsening hyperthyroidism could lead to clinical instability.

RAI therapy may also be considered in patients requiring sustained high-dose ATD therapy (e.g., >15–20 mg/day of methimazole or >150–300 mg/day of propylthiouracil) to maintain euthyroidism. Recent studies have reported that the risk of serious adverse events, such as agranulocytosis and toxic hepatitis, increases with higher ATD dosages [38–40]. In particular, for women with hyperthyroidism who are planning to conceive in more than 6 months and required ongoing high-dose ATD therapy, RAI therapy may be a reasonable option. However, because TSH receptor antibody (TRAb) levels may be transiently increase following RAI therapy [41], it is advisable to delay pregnancy until thyroid function stabilized—typically for at least 6 months after RAI therapy. In male patients, considering the spermatogenesis cycle, deferring conception for 3 to 4 months after RAI therapy is also recommended [5,42].

In women treated for hyperthyroidism, pregnancy is recommended after thyroid function has been stable within the normal range for at least two consecutive measurements under a stable treatment regimen [43,44]. For those planning pregnancies within 6 months, surgical treatment may be considered as the first treatment option. As current evidence is insufficient to recommend a single optimal treatment approach for women with hyperthyroidism planning pregnancy, it is essential to carefully evaluate the benefits and potential risks of each option in the context of the patient's clinical status. Shared decision-making with the patient is crucial in determining the most appropriate treatment strategy.

1.3. RAI therapy is not recommended in the following clinical situation

- 1.3.1. Pregnant or breastfeeding women. [Recommendation level 1]
- 1.3.2. Patients with active moderate-to-severe thyroid eye disease. [Recommendation level 1]
- 1.3.3. Patients with coexisting thyroid cancer. [Recommendation level 1]

Radioactive isotope freely crosses the placenta and can accumulate in the fetal thyroid gland, posing a risk of fetal hypothyroidism and impaired neurodevelopment. Therefore, RAI therapy is strictly contraindicated during pregnancy [42]. In addition, RAI is excreted in breast milk, making it contraindicated in breastfeeding women as well [42]. To prevent radiation exposure, breastfeeding must be discontinued before treatment. Pregnancy must be excluded by testing within 48 hours before RAI administration.

RAI therapy is not recommended in patients with moderate-to-severe active thyroid eye disease (TED), as it may worsen ophthalmopathy [5,45–47]. In patients with hyperthyroidism and mild TED, prophylactic corticosteroid may be considered to reduce the risk of TED progression when RAI therapy is selected (see Part V for detailed guidance). In patients with coexisting thyroid cancer, RAI therapy is not recommended for treating hyperthyroidism.

Although the following are not absolute contraindications, they are associated with a higher risk of RAI treatment failure: (1) large goiter, and (2) high titers of TRAb. In addition, RAI therapy may increase the risk of adverse events in patients with severe thyrotoxicosis with markedly elevated thyroid hormone levels.

A retrospective study of 388 patients with Graves' disease who received RAI therapy identified that the presence of a large

goiter, defined as a visible cervical swelling consistent with thyroid enlargement on palpation [48], and elevated TRAb levels at the time of RAI administration were observed to be significant predictors of decreased treatment success [49]. Other studies have also reported that TRAb levels greater than 40 U/L at diagnosis or at the time of treatment are associated with lower rates of treatment success [50]. In such cases, surgical thyroidectomy may be a more appropriate treatment option than RAI therapy, particularly when rapid resolution of hyperthyroidism is required. Although a thyroid storm following RAI therapy is very rare [51,52], transient increases in the serum thyroid hormone levels may occur immediately after treatment [53,54]. Therefore, in patients with markedly elevated pretreatment thyroid hormone levels, ATD therapy should be used to achieve euthyroidism prior to RAI administration. In cases where ATD use is not feasible and rapid control of thyroid function is required, alternative approaches such as inorganic iodine [55], lithium [56,57], or therapeutic plasma exchange [58–60] have been suggested. Inorganic iodine should be used only for a short duration (7 to 10 days) due to the risk of the escape phenomenon, and should be discontinued at least 1 to 2 weeks before RAI therapy, as it can interfere with RAI uptake. In addition, the use of lithium is limited in clinical practice due to its potential toxicity, which necessitates regular serum level monitoring. Therefore, its application remains restricted in current Korean clinical settings. Detailed guidance on the use of ATD before and after RAI therapy is provided in part IV.

Section 2. Determination of the RAI dose in patients with hyperthyroidism

2.1. A fixed dose of RAI (10–15 mCi) sufficient to induce hypothyroidism is recommended when determining the appropriate RAI dose. [Recommendation level 2]

The goal of RAI therapy is to cure hyperthyroidism by administering a sufficient dose to induce hypothyroidism [5–7]. The determination of RAI dosage can follow either a fixed-dose approach—typically 10 to 15 mCi—or a calculated-dose approach, which considers individual factors such as thyroid gland size and RAI uptake. In a study of 88 patients with hyperthyroidism, participants were assigned to either a fixed-dose group (low dose: 6.3 mCi; high dose: 9.5 mCi) or a calculated-dose group (adjusted low doses and adjusted high doses). No significant differences in clinical outcomes were observed between the two groups during the median follow-up of 63 months [61]. Similarly, a meta-analysis comparing the rates of euthyroidism

or hypothyroidism found no difference between fixed-dose and calculated-dose approaches. In fact, the calculated-dose method was associated with a higher rate of persistent or recurrent hyperthyroidism [7], suggesting that it does not offer greater clinical benefit than the fixed-dose method. Another meta-analysis, however, reported that maintaining euthyroidism was more likely when the absorbed radiation dose was within the range of 120 to 180 Gy, and that the risk of hypothyroidism or recurrence increased when the dose was outside this range [62], indicating the potential utility of calculated dosing when euthyroidism is the treatment goal. Nevertheless, considering the limited feasibility of applying calculated-dose methods in current Korean clinical practice and the lack of domestic studies, this guideline recommends the use of a fixed-dose approach. Future evidence evaluating the clinical applicability and effectiveness of calculated dosing in Korean settings may help inform recommendations supporting individualized dosing strategies.

The success rates of RAI therapy vary according to the administered dose: 61% with 5.4 mCi [63], 69% with 8.2 mCi [64], 69%–74% with 10 mCi [15,26], 75%–81% with 15 mCi [13], and 86% with 15.7 mCi [13]. However, many of these studies were conducted in patients without prior use of ATD, and there remains insufficient evidence to determine the optimal dose for successful treatment. Therefore, this guideline recommends a minimum dose of 10 mCi and supports the use of a sufficient fixed dose of 10 to 15 mCi, considering factors such as prior ATD use [65]. In patients with large goiters, a dose higher than 15 mCi may be considered; however, close monitoring is required due to the potential risk of transient thyroiditis following treatment.

A significant reduction in thyroid volume, one of the advantages of RAI therapy, is typically observed beginning around 6 months after treatment, with an average decrease of more than 50% to 70%. In a multicenter prospective study, the median reduction in thyroid volume was 57% at 6 months and 71% at 12 months post-treatment [66]. Similarly, a recent ultrasound-based study reported a mean thyroid volume of 43.01 cm³ before treatment, which decreased to 11.58 cm³ at 6 months, corresponding to an average reduction of approximately 73% [67].

Section 3. Need for a low-iodine diet before RAI therapy in patients with hyperthyroidism

3.1. A low-iodine diet is not routinely recommended before RAI therapy for hyperthyroidism; but iodine-rich foods should be avoided for at least 1 week prior to treatment. [Recommendation level 3]

A low-iodine diet is generally not recommended for patients with hyperthyroidism undergoing RAI therapy. However, the intake of iodine-rich supplements, health products, and seaweed may interfere with treatment efficacy; therefore, discontinuation of such products at least 1 week prior to therapy should be considered [5].

Due to geographic and environmental factors, as well as traditional dietary habits, seaweed consumption (e.g., laver, kelp, and sea mustard) is common in Korea. According to the Korea National Health and Nutrition Examination Survey (2013–2017), the average daily iodine intake among Koreans was 416.5 µg/day (median, 129.0 µg/day), nearly three times the recommended daily intake of 150 µg/day for adults [68]. Therefore, RAI therapy administered following a typical Korean diet may result in reduced treatment efficacy.

In a single-arm study involving 21 patients with hyperthyroidism, a low-iodine diet was prescribed to limit daily iodine intake to below 400 µg/day starting 1 week prior to RAI therapy. As a result, urinary iodine excretion significantly decreased from a baseline of 511 to 41 µg/gCr. Moreover, patients with urinary iodine excretion levels below 100 µg/gCr showed a significant increase in RAI uptake [69]. However, there is insufficient evidence to conclude that strict low-iodine diets improve the efficacy of RAI therapy. In a small randomized study comparing the effects of a low-iodine diet with a regular diet, patients in the low-iodine group ($n=31$) showed a significant reduction in urinary iodine levels compared to the control group ($n=36$)—by 23% at 1 week and 42% at 2 weeks. However, there was no significant difference in the cure rate of hyperthyroidism between the two groups at 6 months after RAI therapy [70]. Therefore, given the lack of clear evidence that strict low-iodine diets enhance the efficacy of RAI therapy, routine prescription of a low-iodine diet prior to treatment is not recommended. However, excessive iodine intake may interfere with the efficacy of RAI therapy. Given the high average dietary iodine intake among Koreans, it is recommended to avoid iodine-rich foods—such as seaweed (e.g., laver, kelp, sea mustard) and high-dose iodine-containing supplements—for at least 1 week prior to treatment. In addition, when RAI therapy is being considered for patients who have recently used or are currently taking agents known to affect iodine uptake—such as iodine contrast media or amiodarone—the potential impact of these substances should be carefully evaluated. Inorganic iodine should be discontinued at least 1 to 2 weeks before RAI therapy.

Section 4. Appropriate discontinuation period of ATD before and after RAI therapy

- 4.1. Discontinuation of ATD for 3 to 7 days before RAI therapy is recommended. [Recommendation level 1]
- 4.2. Resumption of ATD within 3–7 days after RAI therapy may be considered in patients who received ATD prior to treatment or are at high risk of clinical deterioration due to worsening hyperthyroidism. [Recommendation level 2]

A meta-analysis of 14 randomized controlled trials involving a total of 1,306 patients found that the use of ATD up to the time of RAI therapy was associated with a reduced risk of post-treatment hypothyroidism (relative risk [RR], 0.68; 95% CI, 0.53 to 0.87; $P=0.006$), but an increased risk of treatment failure (RR, 1.28; 95% CI, 1.07 to 1.52; $P=0.006$) [52]. The ATD used in the included studies were propylthiouracil (50–300 mg/day), methimazole (5–30 mg/day), and carbimazole (20–30 mg/day). In the withdrawal groups, ATD were discontinued 3 to 7 days prior to RAI therapy. Compared to patients who did not receive ATDs before RAI therapy, those who did had a significantly higher risk of treatment failure (RR, 1.48; 95% CI, 1.09 to 2.00). Similarly, the post-treatment use of ATD was also associated with a significantly increased risk of treatment failure (RR, 1.32; 95% CI, 1.04 to 1.68) [52].

Several studies have reported that propylthiouracil may reduce the efficacy of RAI therapy due to its radioprotective effects [71,72]. Based on these findings, the European Association of Nuclear Medicine recently recommended discontinuing propylthiouracil for at least 2 weeks prior to RAI therapy [73]. However, based on the literature review, there is currently insufficient evidence to support extending the ATD withdrawal period beyond 1 week. Therefore, this guideline recommends discontinuing ATDs for 3 to 7 days before RAI therapy.

A transient increase in thyroid hormone levels may be observed following RAI therapy [51–54,74]. Although rare, thyroid storm can occur and is associated with an increased risk of severe cardiovascular and cerebrovascular events [51]. Therefore, in patients with severe hyperthyroidism, advanced age, or comorbidities that lead to clinical deterioration in the event of thyroid storm—such as atrial fibrillation, heart failure, pulmonary hypertension, renal failure, infection, trauma, poorly controlled diabetes, cerebrovascular disease, or pulmonary disease—thyroid function and underlying conditions should be adequately controlled with ATD before initiating RAI therapy.

A transient increase in serum thyroid hormone levels may occur after RAI therapy, even in patients pretreated with ATD or

those with normalized thyroid function prior to treatment. Therefore, thyroid hormone levels should be closely monitored following RAI therapy. In a randomized study of 42 patients, those who received ATD pretreatment showed post-RAI increases in free thyroxine (T4) and triiodothyronine (T3) by 52.4% and 61.8%, respectively, whereas the control group (no pretreatment) showed decreases of 32.4% and 32.9%, with only two of 21 patients (9.5%) showing hormone elevation [54]. Another randomized controlled trial reported that patients who did not receive ATD pretreatment exhibited a significant decline in thyroid hormone levels beginning on day 5 after RAI, with stabilization observed by day 30. In contrast, the ATD group showed a 70% increase in free T4 on day 7 (peaking at 107% on day 14), and an 85% increase in T3 on day 2, followed by a gradual decline between days 14 and 30 [75].

Based on these findings, ATD should be discontinued 3 to 7 days before RAI therapy, as continuing ATD up to the time of treatment has been associated with transient elevations in serum thyroid hormone levels. However, in elderly patients or those at high risk of complications from worsening thyrotoxicosis, resumption of ATD within 3 to 7 days after RAI therapy may be considered [51,54,75]. Following treatment, thyroid hormone levels should be monitored regularly to determine the need for continued ATD therapy.

Section 5. Use of glucocorticoid before RAI therapy to reduce the development or progression of thyroid eye disease

- 5.1. RAI therapy is not recommended in patients with active moderate-to-severe TED. [Recommendation level 1]
- 5.2. Prophylactic corticosteroid therapy is recommended when RAI therapy is administered to patients with active mild TED. [Recommendation level 1]
- 5.3. In patients with inactive moderate-to-severe TED, prophylactic corticosteroid therapy may be considered during RAI treatment when additional risk factors—such as high TSH receptor antibody levels or smoking—are present. [Recommendation level 2]
- 5.4. Prophylactic corticosteroid therapy is not recommended during RAI treatment in patients with inactive mild TED when additional risk factors—such as high TSH receptor antibody levels or smoking—are not present. [Recommendation level 1]

Approximately one-third of patients with Graves' disease exhibit signs and symptoms of TED, with about 5% experiencing moderate-to-severe forms [76]. Therefore, assessing the severity and activity of TED is essential for appropriate treatment deci-

sion-making in patients with hyperthyroidism [5]. In patients with moderate-to-severe TED or sight-threatening manifestations such as optic neuropathy or corneal ulceration, prompt treatment of hyperthyroidism is required. In these cases, ATD therapy or thyroidectomy is generally preferred over RAI treatment [5].

In patients with moderate-to-severe TED, rapid normalization of thyroid function with ATD therapy is effective in preventing progression of TED. Long-term use of ATD is also considered a safe and effective option for inducing remission of TED [34]. Thyroidectomy has also shown efficacy; in a study of 44 patients with active moderate-to-severe TED who underwent thyroidectomy, all patients demonstrated improvement in TED within 3 years postoperatively [77]. This finding suggests that thyroidectomy not only does not exacerbate TED, but may also contribute to symptomatic improvement in selected patients.

In contrast, RAI therapy has been associated with a 3.2- to 5.8-fold higher risk of worsening TED compared to ATD therapy [78,79]. A recent randomized controlled trial also reported a higher incidence of new-onset TED in the RAI group than in the ATD group (38.7% vs. 21.3%; RR, 1.8) [80].

In patients with mild and inactive TED, prophylactic low-dose oral glucocorticoids have been shown to be effective in preventing the development or progression of TED following RAI therapy [45,79,81-83]. A meta-analysis of 850 patients demonstrated that oral glucocorticoids significantly reduced the risk of worsening TED with a risk ratio of 0.14 (95% CI, 0.06 to 0.35; $P < 0.01$) [82]. Therefore, in patients with mild active TED undergoing RAI therapy, oral glucocorticoids may be safely administered for prophylaxis, unless contraindicated. Common adverse effects include worsening of diabetes, hypertension, osteoporosis, psychiatric symptoms, increased risk of infection, and reactivation of viral hepatitis [5]. However, standard prophylactic dosing with oral prednisone (initial dose of 0.1 to 0.4 mg/kg with gradual tapering) is generally considered safe [84]. A recent retrospective cohort study reported that short-term, low-dose oral prednisone (0.1 to 0.2 mg/kg, tapered over 6 weeks) was as effective as higher-dose regimens (0.3 to 0.5 mg/kg) [85]. Although low-dose intravenous regimens have also been proposed, their requirement for weekly hospital visits over 4-week period limits their practical feasibility [83].

In patients with inactive TED, the risk of disease progression or reactivation after RAI therapy is low [82]. In one study, none of the 72 patients with inactive TED experienced disease progression after receiving RAI therapy without steroid prophylaxis [86]. A recent study from Japan comparing 295 patients with

Table 3. Recommendations for RAI Therapy and Prophylactic Steroid Use Based on TED Severity, Activity, and Risk Factors

TED activity	Severity			
	Mild		Moderate-to-severe	
	No risk factors	With risk factors	No risk factors	With risk factors
Inactive	No steroid prophylaxis required	Consider steroid prophylaxis	No steroid prophylaxis required	Steroid prophylaxis recommended
Active	Consider steroid prophylaxis	Steroid prophylaxis recommended	RAI therapy not recommended	RAI therapy not recommended

Active TED: TED is considered active when the Clinical Activity Score (CAS) is ≥ 3 out of 7. The CAS includes the following signs: spontaneous retrobulbar pain, pain on attempted upward or downward gaze, redness of the eyelids, redness of the conjunctiva, swelling of the caruncle or plica, swelling of the eyelids, and conjunctival edema (chemosis) [88]. Mild TED: Defined as TED that has little impact on daily life and does not require immunosuppressive therapy. Typical features include lid retraction < 2 mm, mild exophthalmos, and intermittent or no diplopia that can be managed with lubricating eye drops [88]. Moderate-to-severe TED: Characterized by TED that does not threaten vision but significantly affects daily functioning and justifies the risk of immunosuppression (if active) or surgical treatment (if inactive). It usually presents with ≥ 2 of the following: lid retraction ≥ 2 mm, moderate-to-severe soft-tissue involvement, exophthalmos ≥ 3 mm above normal, or constant/inconstant diplopia [88]. Risk factors: smoking and high titers of thyrotropin receptor antibodies (TRAb).

RAI, radioactive iodine; TED, thyroid eye disease.

no TED or inactive TED found no significant difference in the risk of TED progression between those who received prophylactic steroids and those who did not. Among patients without risk factors, the progression rate was as low as 4.2% [87]. Furthermore, steroid prophylaxis conferred no additional benefit in patients without TED [5]. Therefore, prophylactic steroid therapy is not recommended for patients with inactive TED and no risk factors, or for those without TED. Recommendations for steroid use during RAI therapy, based on TED severity, activity, and the presence of risk factors, are summarized in Table 3 [88].

Section 6. Intervals for thyroid function test after RAI therapy

- 6.1. Thyroid function test, including TSH and free T4, may be considered within 4 to 6 weeks after RAI therapy. [Recommendation level 2]
- 6.2. Thyroid function can be monitored every 2 to 3 months for up to 6 months after RAI therapy or until TSH levels normalize. [Recommendation level 2]
- 6.3. Thyroid function test may be repeated every 6 to 12 months, once thyroid function has been confirmed to be stable and within the normal range on at least two consecutive assessments. [Recommendation level 2]
- 6.4. Thyroid function test is recommended when symptoms of hyperthyroidism or hypothyroidism are suspected. [Recommendation level 2]

An initial thyroid function test is recommended within 4 to 6 weeks after RAI therapy. During this period, serum TSH levels

may remain suppressed even in the presence of hypothyroidism due to delayed recovery of TSH secretion [89]. Therefore, both TSH and free T4 levels should be measured to ensure accurate assessment of thyroid function [90].

Changes in thyroid function typically emerge between 2 and 6 months following RAI therapy; however, hypothyroidism may develop as early as 4 weeks post-treatment. While uncommon, transient hypothyroidism may develop around 2 months post-treatment and persists for 1 to 4 months [89]. At 8 weeks post-treatment, approximately 40% of patients developed hypothyroidism, with the incidence increasing to over 80% by 16 weeks [91]. In another report, 80% to 90% of patients reached either euthyroidism or hypothyroidism within 6 months [92]. Additionally, a separate study reported that 50% to 90% of patients reached stable thyroid function between 3 and 12 months after RAI therapy [93]. Therefore, thyroid function tests can be monitored every 2–3 months for 6–12 months following RAI therapy, or until TSH levels normalize.

After the first year following RAI therapy, an additional 3% to 5% of patients may develop hypothyroidism annually [14]. In a prospective study, the cumulative incidence of hypothyroidism in patients with Graves' disease was 24% at 1 year, 59% at 10 years, and 82% at 25 years after RAI therapy—substantially higher than in patients with toxic multinodular goiter, whose corresponding rates were 4%, 15%, and 32%, respectively [12]. These findings indicate that hypothyroidism following RAI therapy is relatively common and tends to increase over time. Therefore, long-term and regular monitoring of thyroid function may be recommended to ensure timely detection and manage-

ment of hypothyroidism after RAI therapy. Even after thyroid function has stabilized, annual testing is recommended, with additional tests performed when thyroid dysfunction is clinically suspected.

CONCLUSIONS

This guideline is an updated version of the 2013 KTA consensus statement on the diagnosis and treatment of hyperthyroidism, specifically focusing on RAI therapy. Treatment options for hyperthyroidism include ATD, RAI therapy, and thyroidectomy. The choice of therapy should be made through shared decision-making, considering the patient's clinical condition, comorbidities, treatment efficacy, and potential side effects. This guideline provides detailed clinical recommendations regarding indications for RAI therapy—particularly in cases where it is preferred or contraindicated—pre- and post-treatment management, and the use of prophylactic steroids in patients with coexisting TED. Given the relatively low utilization of RAI therapy in Korea, further research is warranted to assess the long-term outcomes of prolonged ATD therapy and post-RAI thyroid function, including the incidence of hypothyroidism and the maintenance of euthyroidism. These studies will contribute to a more systematic evaluation of the efficacy and safety of RAI therapy and strengthen the evidence base for future treatment guidelines.

CONFLICTS OF INTEREST

Young Joo Park is an editor-in-chief and Eun Kyung Lee is an associate editor (chief) of the journal. But they were not involved in the peer reviewer selection, evaluation, or decision process of this article. No other potential conflicts of interest relevant to this article were reported.

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