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Treatment Selection Criteria for Patients with Drug-resistant Graves' Disease : Radioactive Iodine Therapy *vs.* Surgery

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Objective : To identify the characteristics of patients with drug-resistant Graves' disease (GD) suitable for radioactive iodine (RI) therapy and surgery.

Methods : We retrospectively analyzed 373 patients with GD treated at Shinshu University Hospital between April 2015 and September 2023. Remission was defined as the absence of treatment for at least six months after discontinuation of antithyroid drugs (ATDs), RI therapy, or surgery. Clinical characteristics, including thyroid hormone levels, free triiodothyronine (FT3)/free thyroxine (FT4) ratio, thyroid antibodies, and the prevalence of T3-predominant GD, were compared among patients who achieved remission with ATDs (Drug group), RI therapy (RI group), or surgery (Surgery group).

Results : Of the 373 patients, 141 achieved remission : 73 in the Drug group, 23 in the RI group, and 45 in the Surgery group. The FT3/FT4 ratio differed significantly among the groups and was highest in the Surgery group (median 5.90) compared with the Drug group (2.99) and RI group (3.18) ($p<0.001$). Anti-thyroid stimulating hormone receptor antibodies (TRAb) levels were also significantly higher in the Surgery group (39.56 IU/L) than in the Drug (5.92 IU/L) and RI (18.67 IU/L) groups ($p<0.001$). T3-predominant GD was more frequent in the Surgery group (71.4 %) than in the Drug (8.2 %) and RI (11.1 %) groups. No significant differences were observed between the Drug and RI groups.

Conclusion : Higher FT3/FT4 ratios and TRAb levels were associated with patients achieving remission through surgery. The FT3/FT4 ratio may serve as a practical indicator for selecting surgical treatment in GD management. *Shinshu Med J 74 : 261—270, 2026*

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Key words : Graves' disease, antithyroid drugs, radioactive iodine therapy, thyroidectomy, T3-predominant Graves' disease

I Introduction

Graves' disease (GD) arises from autoimmune dysfunction targeting the thyroid. Continuous stimulation of thyroid membrane thyroid stimulating hormone (TSH) receptors by anti-TSH receptor antibodies (TRAb) causes diffuse thyroid swelling and excessive secretion of triiodothyronine (T3) and thyroxine (T4), leading to thyrotoxicosis.

The primary treatments for GD include antithyroid drugs (ATDs), radioactive iodine (RI) therapy,

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and surgery. All the three interventions normalize thyroid hormone levels within approximately six weeks[1]. ATDs are the first-line treatment for most patients with GD in Japan[2] and Europe[3]. However, no definitive guidelines exist on when to discontinue ATDs. If remission is not achieved after 18 months, further remission is unlikely, and RI or surgery is generally recommended. However, if thyroid hormone levels can be controlled with low-dose ATDs, therapy may be continued depending on the patient's preference[4].

According to Japanese thyroid guidelines, the absolute indication for RI treatment[5] is when ATDs cannot be used due to serious side effects. Relative indications include when ATD or surgical treatment is not desired ; when remission is not achieved with ATDs and continued therapy is not desired ; when GD recurs after surgery ; when complete correction of hyperthyroidism is desired ; when reduction of goiter size is needed ; and when chronic diseases, such as heart disease, liver disease, or diabetes are present. However, no clear information exists on the suitability of surgical treatment, and selecting a curative option is often difficult. In addition, only a limited number of facilities can provide RI or surgical treatment, and because these are invasive, many patients with GD remain on long-term ATD therapy, without achieving remission. This prolonged use increases the risk of drug-related side effects and thyroid enlargement, which may further complicate subsequent RI or surgical intervention.

In our previous study[6], we retrospectively examined patients who underwent surgery for GD and found that drug-resistant disease was associated with long disease duration, high free-T3 (FT3)/free-T4 (FT4) ratio, elevated TRAb, high thyroid weight, and T3-predominant GD. However, the study did not include patients receiving RI treatment, leading to uncertainty about which patients with GD may achieve remission with each treatment.

In this study, we aimed to identify the characteristics of patients with GD suitable for each treatment, particularly focusing on indicators for selecting RI or surgery in drug-resistant cases, by comparing remission outcomes across all the treatment groups.

Ⅱ Materials and Methods

A Patients

This study investigated 373 patients with GD who were treated at Shinshu University Hospital between April 1, 2015, and September 30, 2023. This study was approved by the Ethical Committee of the Shinshu University Graduate School of Medicine (approval number : 6154), and opt-out disclosure was provided.

GD was diagnosed in accordance with the 2021 Thyroid Disease Diagnostic Guidelines of the Japan Thyroid Association[7]. This included the presence of clinical signs of thyrotoxicosis, such as tachycardia, weight loss, finger tremors, increased sweating, diffuse thyroid enlargement, exophthalmos, and specific eye symptoms. Moreover, the following four test findings were required : high levels of either FT4 or FT3, or both ; low TSH levels (≤0.1 μU/mL) ; positive TRAb or thyroid stimulating antibody (TSAb) levels ; and in typical cases, high levels of RI (or technetium) thyroid uptake and diffuse accumulation on scintigraphy. Because probable GD can be diagnosed without RI (or technetium) thyroid uptake or scintigraphy, probable GD cases were also included in this study. The selection of treatment for each patient was made through collaborative decision-making between the attending physician and the patient, taking into consideration the patient's wishes and fertility status. Remission was defined as the absence of a need for GD treatment 6 months after discontinuation of ATD administration, RI treatment, or surgical treatment.

B Anthropometric and biochemical parameters

The following patient information was obtained : age, sex, body mass index (BMI), disease duration, reason for surgery or RI treatment, thyroid hormone levels at maximum FT3 (FT3, FT4, TSH, and FT3 divided by FT4 [FT3/FT4 ratio]), TRAb, antithyroid globulin antibody (TgAb), and antithyroid peroxidase antibody (TPOAb) at initial consultation or the first available measurement. The reasons for undergoing surgery or RI treatment were extracted from the medical records. T3-predominant GD was defined as FT4 below the upper limit of normal, FT3 high, and FT3/

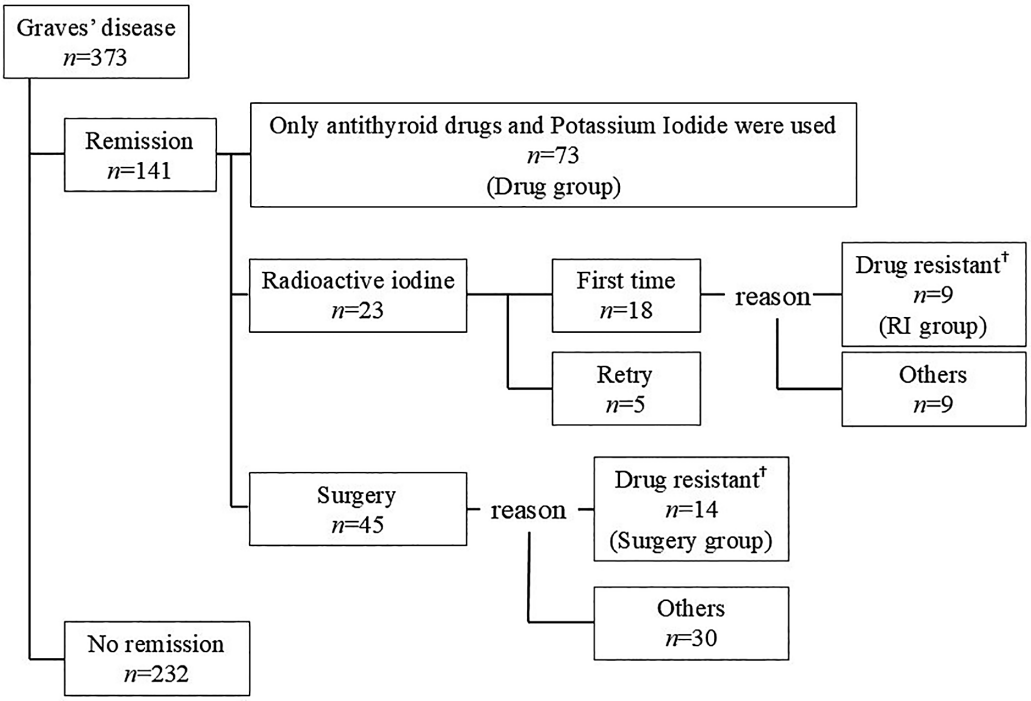

Fig. 1 Flowchart of the study participant selection. †Patients who did not achieve remission after 1.5 years of drug treatment and opted curative treatment were defined as drug-resistant.

FT4 ratio exceeding 3.3 for 3 months or more[8].

Serum levels of TSH, FT3, FT4, and TRAb were measured using a chemiluminescent immunoassay kit (Cobas pro e801 ; Roche Diagnostics, Tokyo, Japan), with reference ranges of 0.5000–5.000 μIU/mL for TSH, 2.30–4.00 pg/mL for FT3, and 0.90–1.70 ng/dL for FT4. The normal range for TRAb was <1.30 IU/L. Serum TgAb and TPOAb levels were measured using a chemiluminescent immunoassay kit (AIA-CL1200 ; TOSOH BIOSCIENCE, Tokyo, Japan), with normal ranges of <40.6 IU/mL for TgAb and <5.2 IU/mL for TPOAb. For analytical purposes, TSH values <0.005 μIU/mL were set to 0.005 μIU/mL, FT3 values >32.55 ng/dL were set to 32.55 ng/dL, and FT4 values >7.77 ng/dL were set to 7.77 ng/dL. In cases where the time of GD onset was unclear, the duration of GD was defined as the extractable period from the medical records.

C Statistical analysis

Data are expressed as median with interquartile ranges (IQR) (25–75th percentiles). Comparisons between the three groups were performed using the Kruskal–Wallis test for variables with skewed distributions that do not follow a normal distribution, and the chi-squared test for qualitative variables. Group differences were evaluated using the Mann–Whitney U-test for non-normally distributed variables with skewed distributions and the χ^2 test for qualitative variables. Correlations between two variables were assessed using simple correlation coefficients. All analyses were performed using StatFlex software, version 7. A p-value <0.05 was considered statistically significant.

Ⅲ Results

A Population

The selection process of study participants is shown in **Fig. 1**. A total of 373 patients with GD were included, of whom 141 achieved remission and 232 did not. Among those who achieved the remission, 73 patients received only ATDs or potassium iodide (Drug group), 23 underwent RI therapy, and 45 underwent surgical treatment. Of the 23 RI patients, 18 were first-time recipients and 5 received multiple RI treatments. Ten of the first-time RI patients chose RI therapy because of difficulties with drug treatment ; 9 of these

Table 1 Reasons for choosing treatment

Reasons	RI therapy (initial RI treatment cases only) Number (%)	Surgical treatment Number (%)
Side effects of drugs	8 (44.4 %)	19 (42.2 %)
Drug resistance†	9 (50.0 %)	14 (31.1 %)
Difficulty responding to drug therapy	1 (5.6 %)	1 (2.2 %)
Thyroid enlargement	0 (0 %)	5 (11.1 %)
Pregnancy preparation	0 (0 %)	4 (9.0 %)
Complication of thyroid tumor	0 (0 %)	2 (4.4 %)

Abbreviations : RI, radioactive iodine. †Patients who experienced difficulty with drug treatment and opted for radical treatment, and those whose disease duration was ≥ 1.5 years.

were drug-resistant and were classified into the RI group. All patients in the Surgery group underwent total thyroidectomy, including 15 with poor drug response, 14 drug-resistant (Surgery group) and 30 treated for other reasons.

The reasons for selecting RI or surgery are summarized in **Table 1**. For RI therapy, drug resistance (9 cases, 50.0 %) and adverse drug reactions (8 cases, 44.4 %) were the main reasons, while five patients repeated RI because remission was not achieved after the initial ATD treatment. In the Surgery group, the most common reasons were adverse drug reactions (19 cases, 42.2 %), followed by drug resistance (14 cases, 31.1 %).

B Characteristics of the Drug, RI, and Surgery group

The baseline demographics and characteristics of the Drug, RI, and Surgery groups are summarized in **Table 2**. The age and disease duration were assessed at the time of ATDs discontinuation for the Drug group, at the time of RI therapy for the RI group, and at the time of surgery for the Surgery group. The median age of the Drug, RI, and Surgery groups were 57 (IQR : 40–68) years, 41 (IQR : 37–67) years, and 52 (IQR : 27–57) years, respectively. The median disease duration was 9.0 (IQR : 3.0–14.0) years, 8.0 (IQR : 5.0–9.0) years, and 11.5 (IQR : 4.3–19.0) years, respectively. The proportion of female patients was 80.8 % ($n = 59$) in the Drug group, 88.9 % ($n = 8$) in the RI group, and 42.8 % ($n = 6$) in the Surgery group. Median BMI at the first hospital visit was 21.9 (IQR : 20.0–24.0) kg/m^2 in the Drug group, 20.7 (IQR : 20.1–22.2) kg/m^2 in the RI group, and 22.7 (IQR : 21.4–24.6) kg/m^2 in the Surgery group. The median thyroid function parameters at the time of maximum FT3 levels were as follows : FT3 levels of 14.56 (IQR : 7.60–20.89) pg/mL, 8.96 (IQR : 5.00–16.33) pg/mL, and 15.50 (IQR : 7.60–20.09) pg/mL ; FT4 levels of 4.53 (IQR : 2.67–7.70) ng/dL, 2.92 (IQR : 2.09–4.10) ng/dL, and 2.62 (IQR : 1.23–3.85) ng/dL ; and FT3/FT4 ratios of 2.99 (IQR : 2.51–3.64), 3.18 (IQR : 2.65–3.98), and 5.90 (IQR : 4.18–8.94) in the Drug , RI, and Surgery groups respectively. The median TRAb levels were 5.92 (IQR : 2.82–16.41) IU/L in the Drug group, 18.67 (IQR : 7.31–30.86) IU/L in the RI group, and 39.56 (IQR : 30.37–229.75) IU/L in the Surgery group. T3-predominant GD occurred in 6 patients (8.2 %) in the drug group, 1 patient (11.1 %) in the RI group, and 10 patients (71.4 %) in the Surgery group.

C Comparison of the Drug, RI, and Surgery group

Comparative analyses among the Drug, RI, and Surgery groups are summarized in **Table 2**. No significant differences were observed in disease duration. The proportion of female patients was significantly lower in the Surgery group than in both the Drug (42.8 % vs. 80.8 %, $p = 0.006$) and RI (42.8 % vs. 88.9 %, $p = 0.040$) groups.

Thyroid hormone levels at the time of maximum FT3 did not differ significantly among the three groups. However, FT4 levels differed significantly, being lower in the Surgery group than in the Drug group (2.62 vs. 4.53 ng/dL, $p = 0.005$). The FT3/FT4

Table 2 Baseline demographics and characteristics of patients in the Drug, RI, and Surgery groups

Patients' characteristics and parameter	Number of subjects concerned or median [IQR]						*p*-value			
	Drug group (D)		RI group (R)		Surgery group (S)		Three-group comparison (D vs. R vs. S)	D *vs.* R	D *vs.* S	R *vs.* S
n	73		9		14					
Female, *n*	59	(80.8 %)	8	(88.9 %)	6	(42.8 %)	0.006*	1.000	0.006**	0.040*
Age, y	57§	[40–68]	41§§	[37–67]	52§§§	[27–57]	0.067			
Disease duration†, y	9.0§	[3.0–14.0]	8.0§§	[5.0–9.0]	11.5§§§	[4.3–19.0]	0.753			
BMI at first visit to our hospital, kg/m^2	21.9	[20.0–24.0]	20.7	[20.1–22.2]	22.7	[21.4–24.6]	0.427			
Thyroid hormone levels at the maximum FT3 value										
TSH†, μIU/mL	0.005	[0.005–0.006]	0.005	[0.005–0.005]	0.005	[0.005–0.006]	0.972			
FT3†, pg/mL	14.56	[7.60–20.89]	8.96	[5.00–16.33]	15.50	[7.60–20.09]	0.268			
FT4†, ng/dL	4.53	[2.67–7.70]	2.92	[2.09–4.10]	2.62	[1.23–3.85]	0.003**	0.028*	0.005**	0.659
FT3/FT4	2.99	[2.51–3.64]	3.18	[2.65–3.98]	5.90	[4.18–8.94]	<0.001***	0.398	<0.001***	0.003**
Antibody status										
TRAb, IU/L	5.92	[2.82–16.41]	18.67	[7.31–30.86]	39.56	[30.37–229.75]	<0.001***	0.152	<0.001***	0.005**
TgAb, IU/mL	26.6	[10.0–250.8]	197.9	[104.0–1393.6]	47.7	[19.9–346.5]	0.659			
TPOAb, IU/mL	16.9	[2.1–168.9]	130.9	[71.0–1393.6]	389.7	[201.7–2862.6]	0.014*	0.410	0.004**	0.628
T3-predominant Graves' disease, *n*	6	(8.2 %)	1	(11.1 %)	10	(71.4 %)	<0.001***	0.571	<0.001***	0.009**

Drug group, patients who achieved remission with ATDs ; RI group, patients who underwent RI therapy due to drug resistance and achieved remission ; Surgery group, patients who underwent thyroidectomy due to drug resistance.

Abbreviations : ATDs, antithyroid drugs ; BMI, body mass index ; FT3, free-T3 ; FT4, free-T4 ; GD, Graves' disease ; IQR, interquartile range ; RI, radioactive iodine ; TgAb, anti-thyroglobulin antibody ; TPOAb, anti-thyroid peroxidase antibody ; TRAb, anti-thyroid stimulating hormone receptor antibody ; TSH, thyroid stimulating hormone. §Evaluation at the time of discontinuation of ATDs. §§Evaluation at the time of RI therapy. §§§Evaluation at the time of surgery. §§§§Evaluation at the time of discontinuation of ATDs or RI therapy. †For some patients, the time of onset is unknown, the disease duration is uncertain, and the range in which the prevalence of GD can be confirmed is described as the disease duration. †A TSH level less than 0.005 μIU/mL was regarded as 0.005 μIU/mL. A FT-3 level more than 32.55 ng/dL was regarded as 32.55 ng/dL. A FT-4 level more than 7.77 ng/dL was regarded as 7.77 ng/dL. *$p<0.05$, **$p<0.01$, ***$p<0.00$

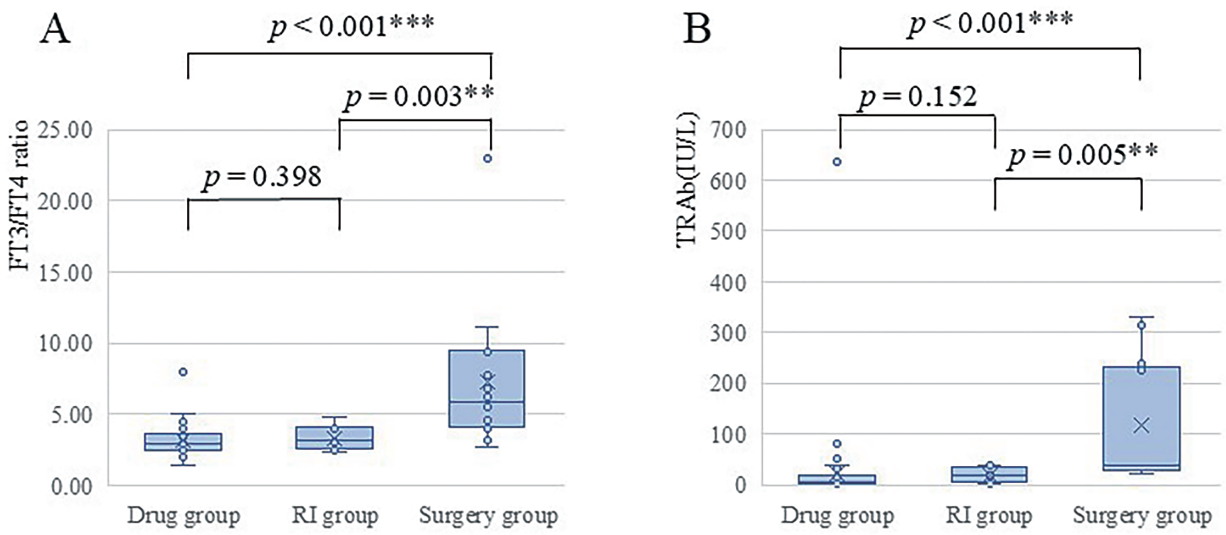

Fig. 2　Box plots of FT3/FT4 ratio and TRAb.

A : Among the Drug, RI, and Surgery groups. The FT3/FT4 ratio was significantly higher in the Surgery group than in the Drug (5.90 *vs.* 2.99, respectively ; $p<0.001$) or RI (5.90 *vs.* 3.18, respectively ; $p=0.003$) group.

B : Among the Drug, RI, and Surgery groups. The TRAb was significantly higher in the Surgery group than in the Drug (39.56 *vs.* 5.92, respectively ; $p<0.001$) or RI (39.56 *vs.* 18.67, respectively ; $p=0.005$) group. FT3, free-T3 ; FT4, free-T4 ; RI, radioactive iodine ; TRAb, anti-thyroid stimulating hormone receptor antibody. $^{*}p<0.05$, $^{**}p<0.01$, $^{***}p<0.001$.

ratio was also significantly different ($p<0.001$), with higher values in the Surgery group than in the Drug (5.90 vs. 2.99, $p<0.001$) and the RI (5.90 vs. 3.18, $p=0.003$) groups. Similarly, TRAb levels were significantly higher in the Surgery group than in the Drug (39.56 vs. 5.92, $p<0.001$) and the RI (39.56 vs. 18.67, $p=0.005$) groups. Box plots of FT3/FT4 ratios and TRAb levels are shown in **Fig. 2A and 2B**. The incidence of T3-predominant GD differed significantly among the three groups ($p<0.001$), with the Surgery group showing a significantly higher incidence compared to the Drug (71.4 % vs. 8.2 %, $p<0.001$) and RI (71.4 % vs. 11.1 %, $p=0.009$) groups.

Ⅳ　Discussion

This retrospective study of patients with GD who achieved remission revealed significant differences in the FT3/FT4 ratio and TRAb values between the drug-resistant patients who achieved remission with RI therapy and those who achieved remission through surgery.

Traditionally, remission with ATDs is often achieved within 1.5 years, and prolonged administration has not been regarded as improving remission rates[9)-11)]. Accordingly, we defined drug-resistant patients as those who experienced difficulty with drug treatment, opted for radical therapy, and had a disease duration ≥1.5 years. However, recent reports indicate that ATD treatment longer than 2 years is an independent predictor of long-term remission, with a cumulative remission rate of up to 57 %[12)]. Maintaining a minimum ATD dose for six months before discontinuation has also been associated with high remission[13)], suggesting that prolonged low-dose administration may facilitate dose reduction and sustain a minimal dose for an extended period, thereby enhancing remission[14)]. Although TRAb-negative patients with GD have a higher likelihood of remission and lower relapse rates[15)], approximately 30 % of TRAb-negative patients continue to relapse ; thus, treatment duration and other factors should be considered, as TRAb alone is an insufficient predictor.

Remission rates after RI therapy vary with the administered dose. Doses >500 MBq require hospitalization, whereas outpatient therapy typically uses lower doses based on estimated thyroid gland weight. Studies of fixed RI doses report remission rates of 66.6 % at 185 MBq and 84.6 % at 370 MBq[16)] ; however,

efficacy also depends on thyroid volume and iodine uptake. In our cohort, patients with GD received 370 MBq (n = 9, 90 %) or 481 MBq (n = 1, 10 %) at physician discretion.

Surgical options include total and subtotal thyroidectomy ; total thyroidectomy provides definitive disease control but carries a slightly higher risk of transient complications. Recurrence after subtotal thyroidectomy ranges from 0 % to 20 %, depending on residual thyroid volume and follow-up duration[17)-19)] Barczynski et al. reported a 9.5 % relapse rate over 5 years post-subtotal thyroidectomy[20)]. Although ophthalmopathy outcomes do not differ markedly between total and subtotal procedures, transient hypoparathyroidism is more frequent after total thyroidectomy, while rates of permanent hypoparathyroidism and recurrent laryngeal nerve palsy are comparable.

In this study, the Surgery group included a higher proportion of men than the other groups. Although GD is more common in women, some women may prefer surgery when planning pregnancy (to avoid post-RI pregnancy restrictions), which could reduce the number of women choosing surgery for drug resistance. Men may present with more severe thyroid eye disease[21)] and therefore, when selecting radical therapy, may be more likely to undergo surgery rather than RI.

In GD, increased expression and activity of deiodinase enzymes promote systemic symptoms by converting T4 to the more biologically active T3. Deiodinase types 1 (D1) and 2 (D2) generate T3, with D2 predominantly responsible for extrathyroidal conversion[22)]. The FT3/FT4 ratio reflects deiodinase activity, particularly 5′-deiodination of T4 to T3[23)]. In this study, significant differences in the FT3/FT4 ratio between the Surgery group and both the RI and Drug groups suggest enhanced T3 conversion, supporting the utility of this ratio as a treatment selection indicator. This finding is further reinforced by the high frequency of T3-predominant GD in the Surgery group. T3-predominant GD is characterized by increased thyroid deiodinase activity necessary for T4-to-T3 conversion[24)], with reports indicating enhanced expression of related genes[8)]. Compared with typical GD, patients with T3-predominant GD are less likely to achieve remission, more prone to relapse, and more likely to develop thyroid swelling during treatment, resulting in high thyroid weight[25)26)]. Thus, T3-predominant GD may serve as a valuable indicator for selecting surgical treatment.

Significant differences were also observed in TRAb levels between the groups. TRAb fluctuations have been shown to correlate with prognosis[27)]. Early decreases in TRAb during ATD therapy predict higher remission rates, whereas persistent increases or fluctuations indicate poor prognosis. However, this study only assessed TRAb values at the first visit, not their longitudinal changes. Moreover, because FT3 and FT4 were measured more frequently than TRAb, the limited number of patients in whom TRAb levels were measured at the peak of FT3 precluded analysis of trend patterns.

No significant differences were observed between the Drug and RI groups. RI therapy is generally tailored to thyroid weight and iodine uptake[28)] ; however, in our hospital, RI was administered on an outpatient basis without calculating individualized doses. Because thyroid weight is influenced by TRAb via the TSH receptor[29)], patients with higher TRAb may require higher RI doses. Larger glands also exhibit greater deiodinase activity, increasing T3 conversion and elevating the FT3/FT4 ratio[30)]. The significantly higher TRAb and FT3/FT4 ratios in the Surgery group suggest larger thyroid gland volumes and likely explain their failure to achieve remission with a single RI dose Conversely, prolonged disease duration before remission was noted in the Drug group. Since long-term ATD administration beyond two years is an independent predictor of sustained remission[31)], this group's higher remission rate was expected in this group. Patients who achieved remission with a single outpatient RI session likely had disease activity comparable to those who responded to long-term ATD therapy. Although disease duration did not differ significantly across groups, the RI group tended to have shorter disease duration than the Drug group, suggesting that RI therapy may have accelerated GD remission.

This study has several limitations. First, as a single-center study conducted at a tertiary care medical institution, most patients were referred, and initial treatment data were often lacking. Furthermore, referral bias may have led to the inclusion of more severe cases. Second, treatment selection was based on outpatient clinic criteria. Although the reasons for classification could be verified from medical records, judgments varied among specialists, and RI or surgical treatment was generally recommended for cases considered difficult to manage. Third, because this was a retrospective study, the number of patients treated with RI or surgery was small compared with those treated with antithyroid drugs, limiting the reliability of cutoff estimates. Nevertheless, by including only patients receiving oral medication or RI therapy, and by restricting analysis to those who underwent a single RI treatment, we were able to capture cases most likely to achieve remission with each therapy. Fourth, as ATDs are prioritized in Japan, the findings may not be directly comparable to studies from the United States, where RI is more commonly used as first-line therapy. Finally, given the retrospective design of this study, the observed elevations in the FT3/FT4 ratio and TRAb levels cannot be regarded as independent indications for surgery.

The present findings suggest that elevated FT3/FT4 ratios, higher TRAb levels, and T3-predominant GD are associated with the subsequent selection of thyroidectomy among patients who ultimately achieved remission. Although these parameters cannot be regarded as treatment-selection markers based on the current retrospective analysis alone, they may reflect disease characteristics that influence the suitability of definitive treatment strategies. Future prospective cohort studies enrolling newly diagnosed patients with Graves' disease are warranted to validate whether these factors can serve as predictive markers for treatment selection. Stratification according to baseline FT3/FT4 ratio, TRAb level, and T3 predominance may help determine whether specific patient subgroups are more likely to achieve remission with surgical therapy, RI therapy, or ATDs, thereby facilitating a more individualized therapeutic approach.

In conclusion, this retrospective study demonstrated significant differences in TRAb levels and FT3/FT4 ratios between patients with drug-resistant GD who achieved remission with surgery and those who achieved remission with RI treatment. These findings suggest that FT3/FT4 ratio, TRAb level, and T3 predominance may represent clinically relevant markers associated with treatment outcomes and warrant prospective validation as potential tools for treatment selection in GD.

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Data Availability: Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

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