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Comparison of the efficacy of low-dose and high-dose radioactive iodine ablation in differentiated thyroid carcinoma patients post-total thyroidectomy: A systematic review and meta-analysis study

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Abstract: The aim of this study is to perform a meta-analysis to compare the efficacy of low-dose and high-dose radioactive iodine ablation in patients with differentiated thyroid carcinoma post-total thyroidectomy. A systematic review was conducted following the meta-analysis study using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines from English databases, including PubMed, Elsevier, and Sage journals. In total, 1,258 records were found, and 7 eligible articles met the inclusion criteria of the study, involving 2,164 patients. The risk of bias for this study was assessed using the Effective Public Health Practice Project (EPHPP), and all articles received a strong global rating. Low-dose radioactive iodine ablation was significantly better than high-dose radioactive iodine in differentiated thyroid carcinoma post-total thyroidectomy (Odds ratio (OR) 1.28 [95% confidence interval (CI): 1.05-1.56]; $p = 0.01$, $I^2 = 24\%$). Low-dose radioactive iodine ablation has better efficacy than high-dose radioactive iodine ablation in patients with differentiated thyroid carcinoma post-total thyroidectomy, especially in patients with low and intermediate risk stratification according to the 2015 American Thyroid Association (ATA) guideline.

Keywords: *Differentiated thyroid carcinoma, Efficacy, Meta-analysis, Radioactive iodine ablation.*

1. Introduction

Thyroid carcinoma is a malignancy of the endocrine gland with the highest incidence. The incidence of thyroid carcinoma has increased rapidly in the last 30 years. The most common type of thyroid carcinoma was Differentiated Thyroid Carcinoma (DTC). DTC is consisted of papillary and follicular thyroid carcinoma. Patient with DTC can be conducted total thyroidectomy and followed by radioactive iodine ablation. DTC has recurrency rate 30% [1]. DTC patient post total thyroidectomy should be followed by examination of thyroglobulin level, thyroid ultrasonography, and whole-body scan to detect recurrency. The indicated patient can be given radioactive iodine ablation to prevent the recurrency.

Radioactive iodine (RAI) ablation has several dosages within 925 MBq (25 mCi) to 7400 MBq (200 mCi) [2]. Several studies stated that there was no significant difference in the efficacy of low dose or high dose RAI for the treatment of thyroid carcinoma [3]. However, other studies show that high doses RAI have a higher rate of therapeutic success [4].

In our hospital in Surabaya, low dose radioactive iodine ablation had been maintained. The high dose radioactive iodine ablation (150 mCi or more) had some disadvantage such as higher cost, higher exposure to environment, extend length of stay, and more side effects and complications. Considering cost, exposure, and side effects, our study was about to perform meta-analysis to compare the efficacy of low dose and high dose of radioactive iodine ablation by performed meta-analysis.

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2. Material and Methods

The methods used in this study were based on the guidelines in the Cochrane handbook for systematic reviews of interventions [5], and performed meta-analysis based on Preferred Reporting Items for Systematic Reviews and Meta Analysis (PRISMA) statement [6].

This study protocol was registered in PROSPERO, recorded with protocol ID CRD42024621855.

2.1. Setting

In this study, cohort, cross-sectional, and randomized control trial were included. Inclusion criteria were including article from databases until December 2023. The research comparing low dose and high dose of radioactive iodine ablation on patient with thyroid carcinoma post total thyroidectomy with low and intermediate risk stratification based on ATA Guidelines 2015 [7]. Exclusion criteria were including non-English study, no full text article, case series, case report, literature review.

2.1.1. Primary Outcomes

Efficacy of low dose and high dose radioactive iodine ablation in patients with differentiated thyroid carcinoma post total thyroidectomy.

2.1.2. Secondary Outcomes

Staging, type of surgery, dosage of radioiodine, follow-up time, successful rate definition based on the thyroglobulin level, thyroid ultrasound, whole-body scan, recurrency of malignancy.

2.2. Search Strategy

A literature search was performed in electronic database of the PubMed, Elsevier, and Sage Journal until December 2023. A systematic review was performed by applying this following search strategies from search engine with keywords:

2.2.1. *Carcinoma thyroid* and *differentiated* AND *Radioactive Iodine Ablation Therapy* and *dose*

The result study titles and abstracts were screened for relevance, followed by evaluation of the remaining publication.

2.3. Selection of Studies

All articles found were identified, screened and removed duplicate by two authors (MRD and S) independently within the selection criteria. Title and abstract article were screened, full texts were evaluated, and articles not eligible were excluded. Author AW controls the discrepancies as necessary.

2.4. Data Extraction

Our authors (MRD and S) extracted data independently based on inclusion criteria. Articles published not in English were excluded. Our third author (AW) resolved any discrepancy or conflicts during data extraction as necessary.

2.5. Risk of Bias Evaluation of Included Studies

Risk of bias of this study was performed by using EPHPP (*Effective Public Health Practice Project*) tool. Three investigators (MRD, S, and AW) independently assessed the risk of bias.

2.6. Assessment of Heterogeneity

Statistical heterogeneity was assessed through the I^2 statistics, using Review Manager Version 5.4.

2.7. Publication Bias

The funnel plot was used to check for the publication bias.

2.8. Statistical Analysis

As all the data were continuous, a standardized mean difference with 95% CI was used. As significant clinical heterogeneity was evident, the fixed effects model was applied [5].

We conducted analysis to determine the efficacy of radioactive iodine ablation by collecting data of number of samples, study design, staging, type of surgery, dosage of radioiodine, follow-up time, successful rate definition based on the thyroglobulin level, thyroid ultrasound, whole-body scan. Two authors reviewed all eligible articles and extract the relevant data.

3. Results

3.1. Included Studies

From 1258 articles found, only 7 articles included in this study. The screening process according to PRISMA are shown in Figure 1. Our study identified seven articles, three articles in clinical trial studies and four articles in cohort studies, conducted from several countries such as Italy, Japan, Korea, Pakistan, and China. The articles included in our study were described in this following Table 1 [8-14]. The total number of samples that analyzed was 2,164 patients.

3.2. Risk of Bias for Included Studies

All articles included had strong global rating according to EPHPP. The results are shown in Table 2.

3.3. Efficacy Of Low Dose and High Dose Radioactive Iodine Ablation

The outcome for this meta-analysis were low dose radioactive iodine ablation 1.28 more effective than high dose radioactive iodine ablation (95% CI: 1.05-1.56; $I^2 = 24\%$; $p = 0.01$). p value < 0.005 shows that there is statistically significant relationship between the dosage of radioactive iodine ablation and the efficacy of radioactive iodine ablation therapy. Data are shown in Figure 2 and 3.

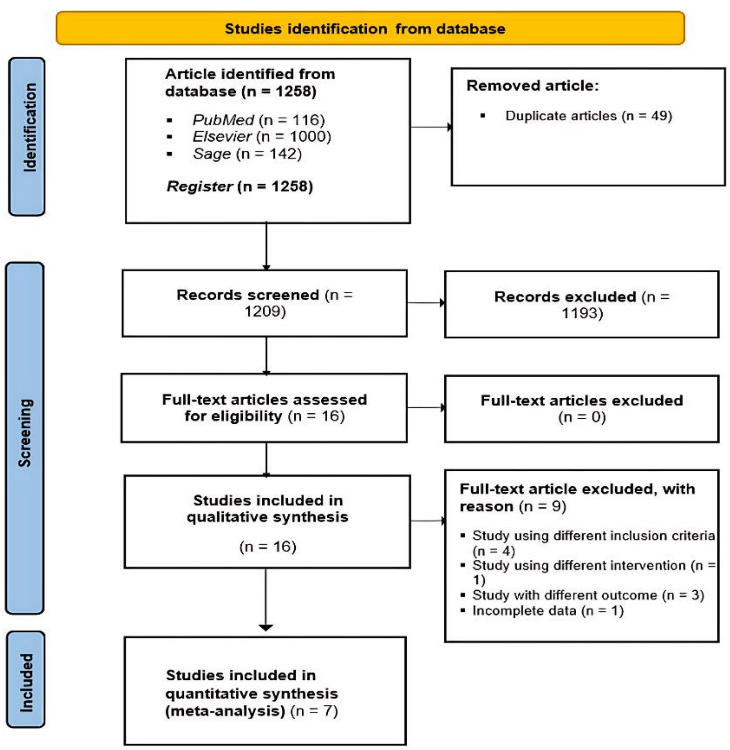

Figure 1.
Flow chart according to PRISMA guidelines.

Table 1.
Characteristics of included articles.

No	Author, year	Country	Number of patients	Study Design	Staging	Type of surgery	Radioiodine activity (Dosage)	Follow-up time	Successful rate definition	Efficacy
1	Castagna[8], 2013	Italy	225	Retrospective	ATA intermediate risk	Total /Near total thyroidectomy	30-80 mCi (n = 82) ≥100 mCi (n = 140)	6-18 months (median 9 months)	Tg < 1, USG negative	There is no significant different efficacy
2	Iizuka[9], 2019	Japan	119	Retrospective	ATA intermediate risk dan high risk	Total thyroidectomy	30 mCi (n = 68) 80-100 mCi (n = 51)	6-12 months	Tg < 2, WBS negatif	There is no significant different efficacy
3	Joung[10], 2014	Korea	570	Retrospective	T1-T3, N0-N1, M0	Total thyroidectomy	30 mCi (n = 261) 100 mCi (n = 206)	6-12 months	Tg < 2, WBS negatif	There is no significant different efficacy
4	Kim[11], 2011	Korea	1024	Retrospective	T1-4, N0-N1, M0	Total thyroidectomy	30 mCi (n = 181) 100 mCi (n =717)	12 months	Tg < 2, USG negatif, WBS negatif	There is no significant different disease-free survival
5	Yasmin[12], 2021	Pakistan	84	RCT	ATA low risk and intermediate risk	Total /Near total thyroidectomy	30 mCi (n = 42) 100 mCi (n = 42)	6 months, 12 month, 24 months	Tg < 2, USG negatif, WBS negatif	There is no significant different efficacy
6	Zaman[13], 2006	Pakistan	40	RCT	T1-4, N0-N1, M0	Total /Near total thyroidectomy	30 mCi (n = 20) 100 mCi (n = 20)	6 months	Tg < 2, WBS negatif	High dose has better efficacy
7	Zhang[14], 2015	China	102	RCT	T4, N0, M0	Total thyroidectomy	30 mCi (n = 51) 100 mCi (n = 51)	6 months	Tg < 1, USG negatif, WBS negatif	There is no significant different efficacy

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Table 2.
Risk of bias for included studies.

EPHPP	Selection bias	Study design	Confounders	Blinding	Data collection methods	Withdrawals and dropouts	Global rating
Castagna, 2013	1	2	1	1	1	1	Strong
Iizuka, 2019	1	2	1	1	1	1	Strong
Joung, 2014	1	2	1	1	1	1	Strong
Kim, 2011	1	2	1	1	1	1	Strong
Yasmin, 2021	1	1	1	1	1	1	Strong
Zhang, 2015	1	1	1	1	1	1	Strong
Zaman, 2006	1	1	1	1	1	1	Strong

Note: *1 = strong, 2 = moderate, 3 = weak.

3.4. Forest plot and Funnel Plot

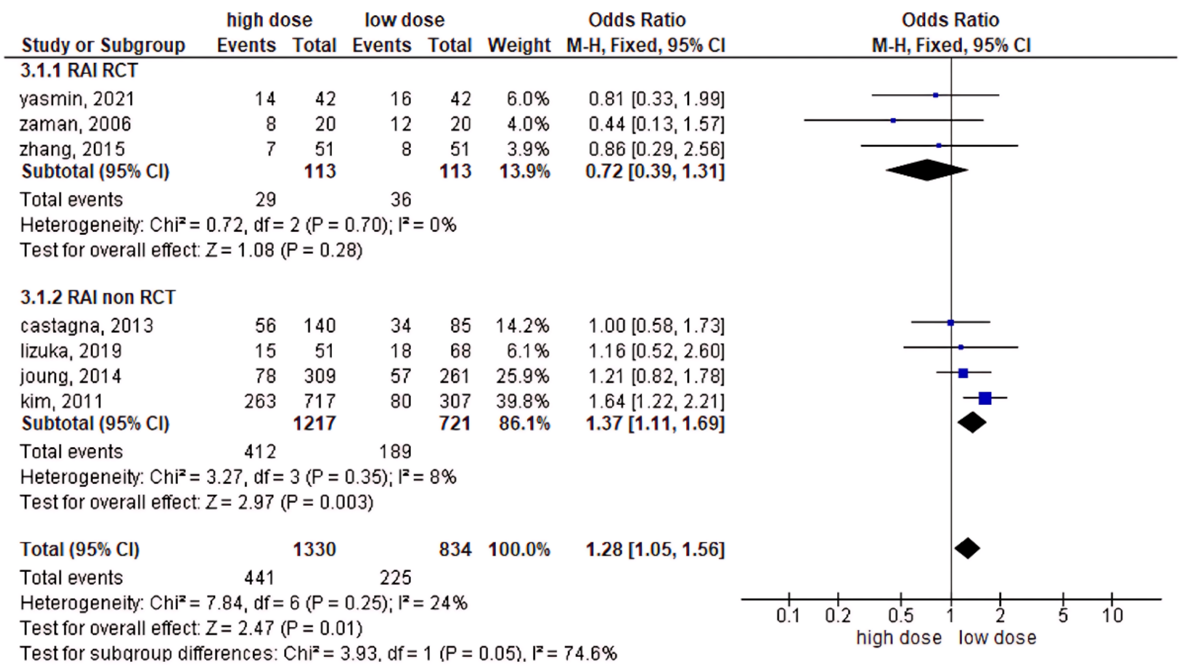

Figure 2.
Forest plot.

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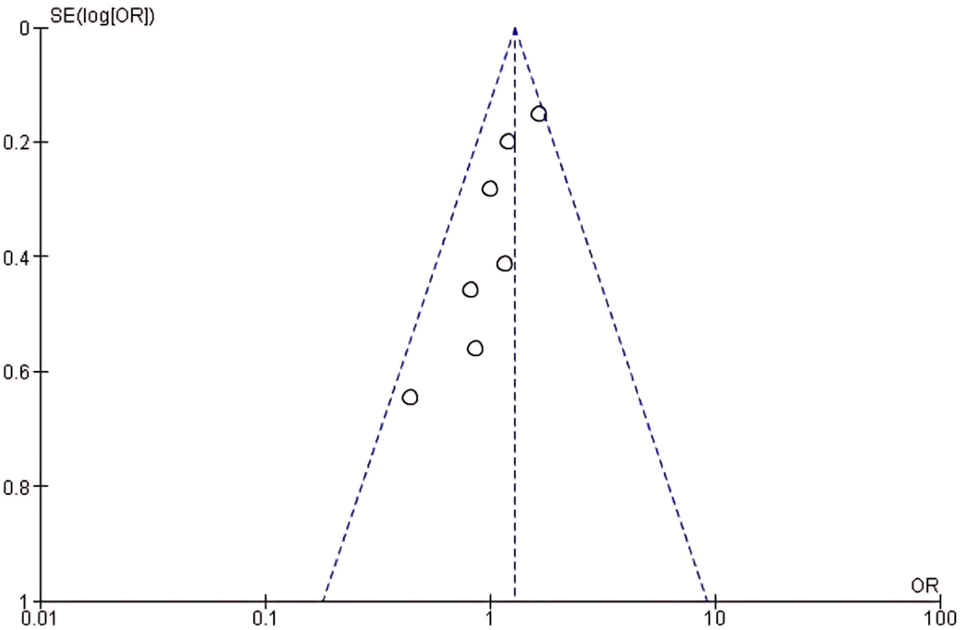

Figure 3.
Funnel plot.

4. Discussion

The administration of radioactive iodine (RAI) ablation in patients with differentiated thyroid carcinoma following total thyroidectomy aims to reduce recurrence rates and mortality. According to the American Thyroid Association (ATA) guidelines risk stratification, patients that stratified as high-risk require high-dose RAI [7]. However, for patients that stratified as low-risk and intermediate-risk, there are no established guidelines regarding the appropriate RAI dosage. Several studies suggested that low-dose dose radioactive iodine ablation has similar efficacy as high dose radioactive iodine ablation, while other studies indicated that the high dose radioactive iodine ablation is more effective than the low dose radioactive iodine ablation. Therefore, this study aims to compare and analyze the efficacy between low dose and high dose dose radioactive iodine ablation in patients with low risk and intermediate risk stratification.

Radioactive iodine ablation works on differentiated thyroid cells by uptake of I^{131} through the sodium/iodide symporter (NIS), causing a TSH molecular cascade at the TSH receptor which will trigger activity in the nucleus of differentiated thyroid carcinoma cells. I^{131} plays a role in inhibiting cell proliferation and increasing cell apoptosis, by down regulating the cell cycle effector gene BCl2 and up regulating the β-cell translocation gene which mediates activation of the JNK-nf kb pathway. With activation of this pathway, intracellular I^{131} will emit high energy β particles that can cause cell death [15, 16].

Based on known data, the cytotoxic effects of I^{131} are dose-dependent. The cytotoxic effects induced either apoptosis or necrotic cell death. High-dose I^{131} primarily results in a necrotic cell phenomenon, whereas low-dose I^{131} primarily induces apoptosis. With apoptosis predominating over necrosis, low-dose radioactive iodine therapy often leads to a slower onset of effects, allowing for a sustained reduction in thyroid cell volume within several months to year. This can explain why low-dose radioactive iodine ablation may offer comparable efficacy to high-dose radioactive iodine ablation in certain patients over the long-term. Administration of low dose and high dose radioactive iodine ablation has the same mechanism of action, so it can provide similar efficacy in patients with differentiated thyroid carcinoma [17].

The study that was conducted by Kim, et al. [11] have obtained the significant factors that associated with the recurrence rate of thyroid carcinoma such as male gender, size of tumor, multifocal tumor, invasion to lymphovascular, positive resection margin, extrathyroidal extension, and presence of cervical lymph node metastasis (p-values = 0.001, 0.008, 0.002, 0.002, and <0.001, respectively) Kim, et al. [11]. The similar findings were also obtained in study by Yasmin, et al. [12] they stated that tumor size was the significant factors that affected the success rate of radioactive iodine (RAI) ablation therapy. Smaller tumor size (1-3 cm), have tendency to show good ablation therapy result than larger size of tumor, multifocality, and also peri/extrathyroidal extension [12]. Patient selection prior to ablation plays a critical role in determining the efficacy of RAI therapy. Therefore, for patients with such characteristics, the consideration should be given to administer higher dose of RAI or implementing stricter monitoring for recurrency in patients.

The reason of similar efficacy of low-dose and high-dose radioactive iodine (RAI) ablation therapy can be explained by the sufficiency of low-dose RAI in destroying residual normal thyroid tissue, provided that thyroidectomy has been performed completely Kim, et al. [11]. Other study conducted by Zhang, et al. [14] obtained that there was same efficacy between low dose and high dose radioactive iodine (RAI) ablation in patient with macroscopic extrathyroidal extension (MAEE) if the values of pre-ablative-stimulated thyroglobulin (ps-Tg) < 5 ng/mL [14]. The ps-Tg value is an important prognostic factor in success rate thyroid carcinoma therapy. It measures the treatment of surgical or the completeness of thyroid resection. Completeness resection is one of significant factors to decrease the recurrence rate of thyroid carcinoma. The higher ps-Tg value regarded the higher recurrence rate of thyroid carcinoma[14]. Other study conducted by Iizuka, et al. [9] also stated that stimulated-Tg values > 5 ng/mL were associated with increased rate of low dose RAI ablation failure after surgical (post total thyroidectomy) thyroid hormone withdrawal (THW) [9].

According to the study conducted by Castagna, et al. [8] the results may be subject to bias due to differences in pre-ablation patient preparation. Patients receiving high-dose RAI were more frequently prepared with thyroid hormone withdrawal (THW), while those receiving low-dose RAI were more commonly prepared with recombinant TSH (rhTSH). Another potential source of bias was the longer follow-up duration for patients treated with high-dose RAI (median 6.9 years) compared to low-dose RAI (median 4.2 years) and for patients prepared with THW (median 8.4 years) compared to rhTSH (median 4.5 years). The study indicated that pre-ablation preparation using either rhTSH or THW did not significantly impact outcomes in patients treated with high-dose or low-dose RAI (for rhTSH, median follow-up 4.5 years; for THW, median follow-up 8.4 years, p < 0.0001). A non-inferiority analysis showed an absolute risk reduction of 0.092 (lower 95% CI bound = -0.014) between patients prepared with rhTSH or THW. The lower CI bound exceeded the pre-defined non-inferiority margin of -20%, supporting the non-inferiority of rhTSH preparation. Thus, it was concluded that for patients with intermediate-risk thyroid carcinoma, neither the RAI dose (low or high) nor the pre-ablation preparation method (THW or rhTSH) significantly affected patient outcomes [8]. Similar findings were reported by Joung, et al. [10] demonstrating that rhTSH is as effective as THW in pre-ablation preparation [10].

This study analyzed seven selected studies to be performed meta-analysis. The forest plot revealed a combined effect size positioned to the right side of value 1 (favoring low-dose), with an Odds Ratio 1.28 (95% CI: 1.05–1.56; I^2 = 24%; p = 0.01). The meta-analysis yielded a p-value of 0.01 (less than 0.05), indicating a significant association between low-dose and high-dose radioactive iodine ablation in terms of therapeutic efficacy.

In this study, the characteristics of the literature based on the type of research include 3 randomized controlled trials and 4 retrospective studies. All studies included in this meta-analysis have high methodological quality, in accordance with the procedures outlined in the research methods. Each study employed appropriate designs and methods to achieve the research objectives, with confounding factors addressed to minimize bias that could affect the results. For this reason, we believe that the findings obtained in this study are reliable. The geographic distribution of the research in the included journals

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shows that the studies were conducted in various countries, including China, Korea, Italy, Pakistan, and Japan. The majority of the research samples were from Asian countries, which share similar patient characteristics with the home country of the researchers. The seven reviewed articles demonstrated variation effect size, with the smallest sample size being 40 and the largest 1024. The total sample size included in the meta-analysis was 2164, which is sufficiently large for robust analysis. The heterogeneity test results indicated that the samples were homogeneous ($I^2 = 24$).

This strength of our study was particularly in its patient selection criteria. The inclusion criteria consisted of patients that classified as T0-T4, N0, without metastasis prior to receiving radioactive iodine ablation therapy, specifically those with low and intermediate risk stratification. The result of this research was similar with study by Mallick, et al. [18]. The study concluded that low dose RAI has the same efficacy with high dose RAI with TSH recombinant (*thyrotropin alfa*) or thyroid withdrawal. With low recurrence rates, low-dose radioactive iodine ablation offers the advantage of fewer side effects. Additionally, patients receiving low-dose radioactive iodine ablation can benefit from reduced costs due to shorter hospital stays, as they can transition to outpatient care shortly after the treatment. In contrast, patients receiving high-dose radioactive iodine ablation require isolation in a lead-lined room for three days. Based on our experience, our patients who need higher dose RAI must be referred to the other hospitals with isolation room facilities in other cities. This situation would affect to more costs to the patient and their families. According to this study, by the similar efficacy of low dose and high dose radioactive iodine ablation, the patients could be administered low dose radioactive iodine ablation in our hospital. If low-dose and high-dose therapies yield similar success rates and recurrence rates, then low-dose radioactive iodine ablation can reduce healthcare costs and can be implemented in hospitals without isolation rooms facilities, such as at Dr. Soetomo General Hospital in Surabaya.

5. Limitations

This study has several limitations, including the distribution of research across various countries with diverse ethnicities and patient characteristics. Additionally, the study includes both randomized controlled trials (RCTs) and cohort studies, which may introduce potential biases.

6. Conclusion

Low dose radioactive iodine ablation has 1.28 times better efficacy than high dose radioactive iodine ablation in patient with thyroid carcinoma post total thyroidectomy, especially in patient with low and intermediate risk stratification based on ATA guideline 2015.

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Author's Contribution Statement:

All authors contributed in concept, design, data screening, data analysis, interpretation, and statistical analysis.

Conflict of Interest:

The authors declare that there is no conflict of interest in this study.

Transparency:

The authors confirm that the manuscript is an honest, accurate, and transparent account of the study; that no vital features of the study have been omitted; and that any discrepancies from the study as planned have been explained. This study followed all ethical practices during writing.

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Abbreviation

ATA : American Thyroid Association
CI : Confidence Interval
DTC : Differentiated Thyroid Carcinoma
EPHPP: Effective Public Health Practice Project
mCi : Millicurie
NIS : Sodium/iodide symporter
OR : Odds Ratio
PRISMA : Preferred Reporting Items for Systematic Review and Meta-analyses
RAI : Radioactive Iodine
rhTSH : Recombinant TSH
Tg : Thyroglobulin
THW : Thyroid hormone withdrawal
TSH : Thyroid-stimulating Hormone
USG : Ultrasonography
WBS : Whole Body Scan

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