Review article

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rhTSH-aided low-activity versus high-activity regimens of radioiodine in residual ablation for differentiated thyroid cancer: a meta-analysis

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The effects of low-activity versus high-activity radioiodine regimens in thyroid remnant ablation for patients with differentiated thyroid carcinoma (DTC) under recombinant human thyrotropin (rhTSH) stimulation have been widely quoted but there has been no systematic review of the evidence. We undertook a systematic review of randomized controlled trials to assess the effects of low-activity radioiodine in thyroid remnant ablation in patients with DTC under rhTSH stimulation compared with high-activity radioiodine. Studies were obtained from computerized searches of MEDLINE, EMBASE, and the Cochrane Library (all until September 2012). Randomized controlled trials were included. Altogether, 637 patients with DTC who participated in three trials for residual ablation were included. Overall, studies had a low risk of bias. We found no statistically significant differences between low-activity (1.11/1.85 GBq) and high-activity (3.7 GBq) radioiodine treatment aided by rhTSH in terms of successful ablation rates on the basis of diagnostic scans [odds ratio (OR) 0.85, 95% confidence interval (CI) 0.49–1.47, *P*=0.56], thyroglobulin levels (OR 0.66, 95% CI 0.38–1.15, *P*=0.14), and health-related quality of life (mean difference 0.07, 95% CI −0.96 to 1.09, *P*=0.9). In addition, the subgroup analysis of 1.11 versus 3.7 GBq (OR 0.83, 95% CI 0.46–1.49, *P*=0.53) and 1.85 versus 3.7 GBq (OR 1, 95% CI 0.23–4.35, *P*=1) also showed no significant differences. The lower activity of 1.11 GBq showed significant benefit in terms of reduction in adverse events including neck pain, radiation gastritis, and salivary dysfunction during and after ablation (OR 0.63, 95% CI 0.42–0.93, *P*=0.02). Limited data from three randomized controlled trials suggested that an rhTSH-aided low radioiodine activity level of as low as 1.115 GBq may be sufficient for thyroid remnant ablation when compared with 3.7 GBq, with fewer common adverse effects in patients with metastasis-free DTC. Further evidence is needed to confirm the effects of low-activity radioiodine for thyroid remnant ablation. Radioiodine treatment of 1.11 GBq showed significant benefit in terms of reduction in adverse events including neck pain, radiation gastritis, and salivary dysfunction during and after ablation (OR 0.63, 95% CI 0.42–0.93, *P*=0.02). rhTSH-aided low radioiodine activity levels of 1.11 and 1.85 GBq are sufficient for thyroid remnant ablation as compared with 3.7 GBq, with fewer common adverse effects in patients with metastasis-free DTC. A well-designed study that compares low-activity with high-activity radioiodine ablation is needed to fully understand the long-term adverse effects and relapse or metastases. *Nucl Med Commun* 34:1150–1156 © 2013 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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Introduction

Thyroid cancer is the most frequently occurring type of endocrine cancer, and its incidence has been increasing worldwide in recent decades. The principal standard treatment modality for these patients includes total or near-total thyroidectomy, followed by iodine-131 (^{131}I) therapy and lifelong thyroid hormone suppressive therapy. ^{131}I treatment with an activity level sufficient to remove residual thyroid tissue after thyroidectomy is called 'remnant ablation'. Eradication of normal-thyroid remnants can result in an undetectable level of serum thyroglobulin (Tg), which can facilitate biochemical follow-up. Traditionally, thyroid hormone withdrawal (THW) for 4–6 weeks has been used to attain the increase in serum thyroid-stimulating hormone concentrations that is believed to optimize the trapping and retention of radioiodine for diagnostic procedures, such as thyroid remnant ablation for patients with differentiated thyroid carcinoma (DTC). Exogenous stimulation with recombinant human thyrotropin (rhTSH) is approved for Tg testing or for diagnostic radioiodine scintigraphy in patients on thyroid hormone suppressive therapy in the USA and Europe. This offers an alternative to THW by avoiding the morbidity of hypothyroidism. We previously reported that rhTSH is as effective as THW in radioiodine thyroid remnant ablation with significant benefits on health-related quality of life (QOL) and adverse effects [1]. It is still uncertain whether both low activity

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(1.11 and 1.85 GBq) and high activity (3.7 GBq) of ^{131}I are equally effective for remnant ablation under rhTSH stimulation. Therefore, we evaluated the effects of low-activity versus high-activity regimens of radioiodine in thyroid remnant ablation for patients with DTC under rhTSH stimulation.

Methods

Criteria for considering studies for this review

Patients with DTC participating in randomized controlled clinical trials in any language were included after total or near-total thyroidectomy followed by rhTSH-aided radioiodine treatment for residual DTC.

We considered the ablation rate of postsurgical thyroid residues, health-related QOL, and death from any cause as primary outcomes; adverse effects, secondary malignancy, costs, relapse, and metastases of DTC iodine were considered as secondary outcomes. The follow-up had to be at least 6 months after radioiodine ablation.

Search strategy for identification of studies

We identified studies regardless of language or publication status by searching *The Cochrane Library* (issue 3, 2012), MEDLINE (until September 2012), and EMBASE (until 2012). We contacted authors of published trials, where appropriate, for further information. The search terms used were thyroid neoplasm/differentiated thyroid cancer, recombinant human thyrotropin, radioiodine, and/or randomized controlled trials.

Selection of studies

We included all published and unpublished randomized controlled trials (RCTs) that involved patients of any age who were receiving ^{131}I for thyroid remnant ablation and in which DTC stage had been adequately defined (TNM). All potentially relevant articles were investigated as full text. Inter-rater agreement for study selection was measured using the κ statistic [2]. We prespecified a minimum, mean, or median follow-up of 6 months from the time of ^{131}I treatment for prespecified outcomes. We also prespecified the following ablation rates for comparison purposes: 1.11 and 1.85 versus 3.7 GBq; 1.11 versus 3.7 GBq; and 1.85 versus 3.7 GBq. Additional outcome measures were health-related QOL and adverse effects.

Quality assessment

Quality assessment of RCTs included allocation concealment, whether intention-to-treat analysis had been carried out, comparability of groups at baseline, and blinding of outcome assessors.

Data abstraction

Two reviewers independently abstracted data and assessed the methodological quality of the studies. Any differences were resolved by discussion between reviewers.

Data synthesis and statistical analysis

We used Review Manager (RevMan), version 5.2. from the Cochrane collaboration for data analysis. Where appropriate, the results of comparable groups of trials were combined for odds ratios (ORs) using random-effect models in view of study heterogeneity. Results were presented with 95% confidence intervals (CIs). Heterogeneity was identified by visual inspection of the forest plots by using a standard χ^2-test and a significance level of $\alpha = 0.1$, in view of the low power of such tests. Heterogeneity was specifically examined with I^2, where I^2 values of 50% or higher indicate a substantial level of heterogeneity [3]. When heterogeneity was found, we attempted to determine potential reasons for it by examining individual study and subgroup characteristics.

Results

Results of the search

The electronic searches revealed 135 studies. Of these references, we excluded 116 citations. After reading the titles and abstracts, 19 potential controlled clinical trials were retrieved for further assessment. Three randomized controlled clinical trials [4–6] were included. Trial durations were from December 2001 to July 2010 in two trials [5–6]; the duration was not mentioned in one trial [4]. Four RCTs comparing rhTSH-aided versus THW-aided radioiodine remnant ablation [7–10], eight historical case–control studies [11–18], and four non-randomized prospective controlled clinical trials [19–22] on rhTSH -aided ^{131}I thyroid remnant ablation were excluded.

The characteristics and quality of the included studies

Altogether, 637 DTC patients participated in three trials. The characteristics and quality of the included studies are listed in Table 1. The risk of bias in the included trials was considered low. Summary data on age, sex, tumor pathology, and staging were reported for all participants. No significant differences were found between comparison groups. All included patients had undergone a total or near-total thyroidectomy before residual ablation. The diagnostic activity of radioiodine for assessment of ablation was between 140 and 185 MBq in all the included studies. The QOL was assessed using the Billewicz scale and Short Form-36 (SF-36) scores [5,6]. Inclusion and exclusion criteria were specified in all the included trials. Apart from L-T_4 replacement, comedications and comorbidities were not mentioned in all included trials.

Effects of recombinant human thyrotropin-aided low and high activity of iodine-131 thyroid remnant ablation

Ablation rate

Two RCTs compared ablation rates between 1.11 and 3.7 GBq, and one trial compared ablation rates between 1.85 and 3.7 GBq. The lower versus higher activity of ^{131}I aided by rhTSH showed no significant difference in successful ablation rate on the basis of either diagnostic

Table 1 Quality and characteristics of included studies for residual ablation

References	Country	Study center	Number of randomized	Female/ total	Inclusion criteria	Criteria for outcome assessment (ablation)	Number of lost to follow-up	AC	Blinding
Pilli *et al.* [4]	Italy	1	I1/C1/ total: 36/ 36/72	I1/C1/ total: 29/36, 31/36	Patients who were more than 18 years old with newly diagnosed T1–3 N0–1M0 DTC	No visible uptake on rhTSH-aided ^{131}I scans stimulated by rhTSH 6–8 months after ablation	None	Y	Y
Mallick *et al.* [5]	UK	29	I/C/total: 219/ 219/438	I/C/total: 169/ 219, 157/ 219	Patients who were 16 to 80 years with T1–3Nx-1 M0	$<$0.1% uptake of thyroid bed on 48 h ^{131}I scan and Tg $<$ 2.0 ng/ml 6–9 months after ablation	I/C/total: 9/8/17	Y	Y
Schlumberger *et al.* [6]	France	24	I/C/total: 374/ 378/752	I/C/total: 298/ 374, 292/ 378	Patients who were $\geq$ 18 years with pT1–2N0–1M0 DTC	Empty thyroid bed by ultrasonography and/or rhTSH-stimulated Tg $<$ 1 ng/ml, negative ^{131}I scans 8±2 months after ablation	I/C/total: 8/7/15	Y	Y

AC, allocation concealment; C, control; C1, 3.7 GBq radioiodine; DTC, differentiated thyroid cancer; ^{131}I, iodine-131; I, intervention; I1, 1.85 GBq radioiodine; p, pathology; rhTSH, recombinant human thyroid-stimulating hormone; Tg, thyroglobulin; Y, yes.

scans (OR 0.85, 95% CI 0.49–1.47, $P = 0.56$) or Tg levels (OR 0.66, 95% CI 0.38–1.15, $P = 0.14$) (Figs 1 and 2, respectively). In addition, the subgroup analysis of 1.11 versus 3.7 GBq (OR 0.83, 95% CI 0.46–1.49, $P = 0.53$) and 1.85 versus 3.7 GBq (OR 1, 95% CI 0.23–4.35, $P = 1$) also showed no significant differences (Figs 3 and 4, respectively).

Health-related quality of life

Two included trials compared different ^{131}I activity levels in terms of health-related QOL. The lower versus higher activity of ^{131}I aided by rhTSH showed no significant difference in QOL (Fig. 5) (mean difference 0.07, 95% CI −0.96 to 1.09, $P = 0.9$).

Adverse effects

An activity of 1.11 versus 3.7 GBq of radioiodine treatment aided by rhTSH showed significant benefit in terms of reduction in adverse events including neck pain, radiation gastritis, and salivary dysfunction during and after ablation (OR 0.63, 95% CI 0.42–0.93, $P = 0.02$) (Fig. 6).

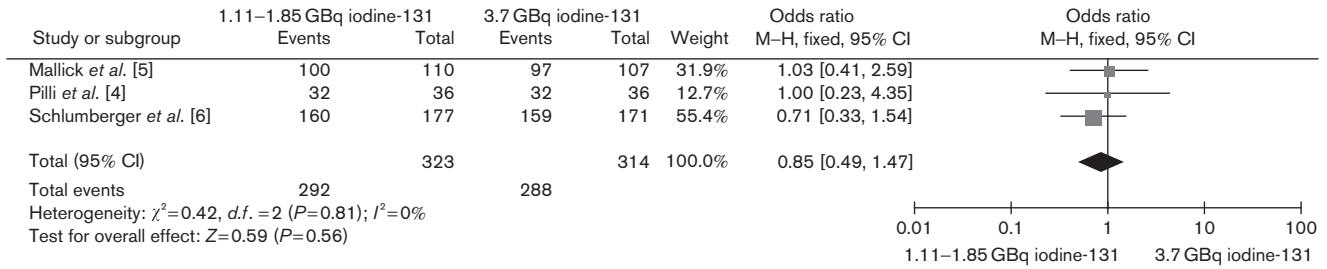
Discussion

Radioiodine ablation after total thyroidectomy is indicated generally for DTC patients to ablate normal thyroid tissue, eliminate any suspected but unproven metastases, and treat known persistent disease. We previously reported that rhTSH is as effective as THW in radioiodine thyroid remnant ablation with significant benefits on health-related QOL and adverse effects [1]. Unfortunately, there is uncertainty with regard to the activity of ^{131}I required for thyroid remnant ablation.

Decreased uptake of ^{131}I at 24 h after the administration of rhTSH was observed in two trials [3,18]. Therefore, rhTSH does not appear potent enough to induce ^{131}I uptake for therapeutic purpose when a small activity of ^{131}I is administered. Possible explanations for the reduced ^{131}I uptake may be the following: interference due to administration of T4, a low activity of 1.85 MBq [19] and 18.5 MBq of ^{131}I [7] 24 h after a single injection of rhTSH, accelerated iodine clearance [19], or faster renal clearance of iodine observed in euthyroid patients compared with patients treated for hypothyroidism [8]. However, no significant differences were found in thyroid uptake and in the effective half-life of ^{131}I in the remnant thyroid, which supported the idea that the pretherapy ^{131}I uptake does not correlate with the rate of successful ablation [7]. Similarly, one study indicates that rhTSH-aided 1.11 GBq radioiodine is not sufficient for a satisfactory thyroid ablation rate [19]. In 2004, the European Agency licensed rhTSH for use in thyroid remnant ablation with 3.7 GBq ^{131}I (European Medicines Agency, 2005). Therefore, we included three RCTs [4–6] to evaluate the effects of low-activity versus high-activity regimens of radioiodine in thyroid remnant ablation for patients with DTC under rhTSH stimulation.

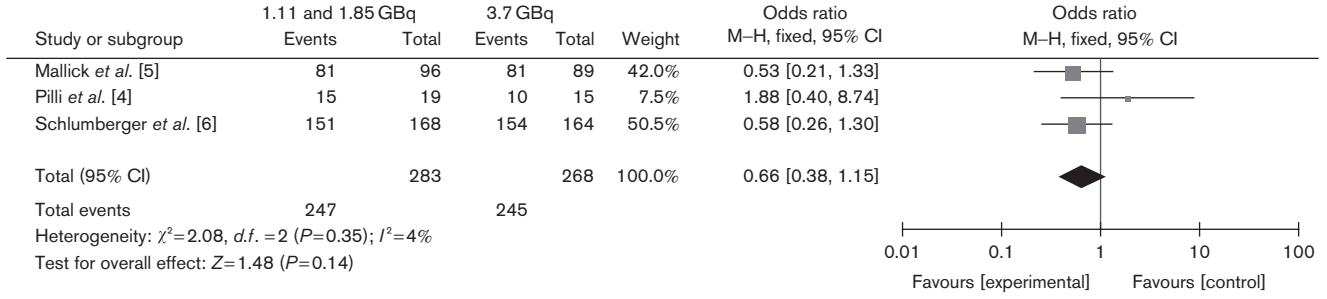
The quantity of evidence from three included trials is acceptable for rhTSH-aided radioiodine treatment. No significant heterogeneity was found between the trials. No serious adverse events were observed in the included trials; no data on costs and secondary malignancies were reported. All included patients in the three trials were at low risk for relapse. The first randomized trial reported that increasing the initial activity of ^{131}I from 1.11 GBq to more than 1.85 GBq resulted in a plateau of the dose–response curve when radiation-absorbed dose was calculated under THW. On the basis of dosimetry results, one should aim to deliver about 30 000 cGy to the thyroid remnant, as higher doses do not appear to yield a higher ablation rate [23]. In agreement with the original study [23], our result suggested that low activity (1.11 and 1.85 GBq) is as effective as high activity (3.7 GBq) in radioiodine ablation, with significant benefits in terms of reduction in adverse effects. There were no significant differences in health-related QOL scores on the Short Form-36 between patients receiving low-activity ^{131}I and

Fig. 1



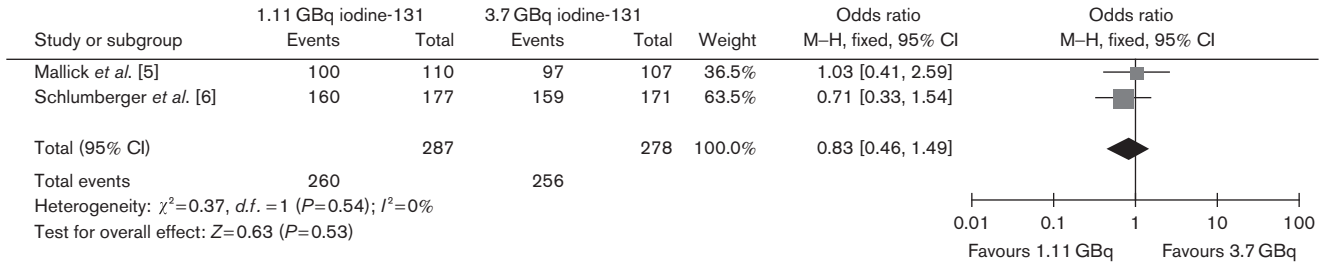
Effect of 1.11/1.85 versus 3.7 GBq iodine-131 under rhTSH stimulation on thyroid remnant ablation rate according to diagnostic scans. CI, confidence interval; rhTSH, recombinant human thyrotropin.

Fig. 2



Effect of 1.11/1.85 versus 3.7 GBq iodine-131 under rhTSH stimulation on thyroid remnant ablation rate according to thyroglobulin levels. CI, confidence interval; rhTSH, recombinant human thyrotropin.

Fig. 3

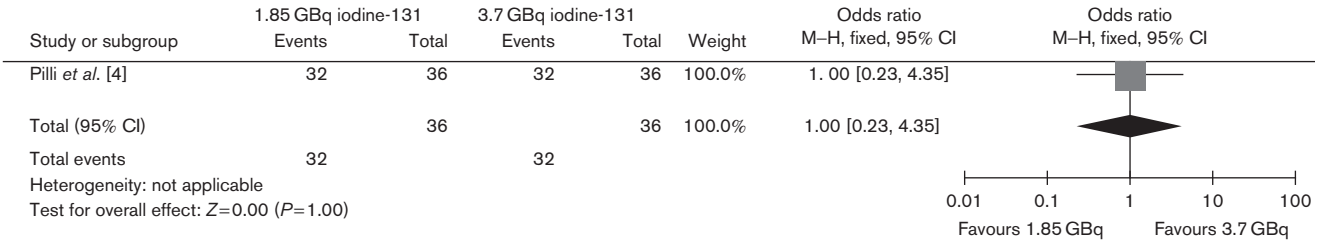


Effect of 1.11 versus 3.7 GBq iodine-131 under rhTSH stimulation on thyroid remnant ablation rate. CI, confidence interval; rhTSH, recombinant human thyrotropin.

those receiving high-activity ^{131}I on the day of ablation and 3 months after ablation. Therefore, low-activity (1.11 GBq) radioiodine was recommended for thyroid remnant ablation in patients with low risk for relapse.

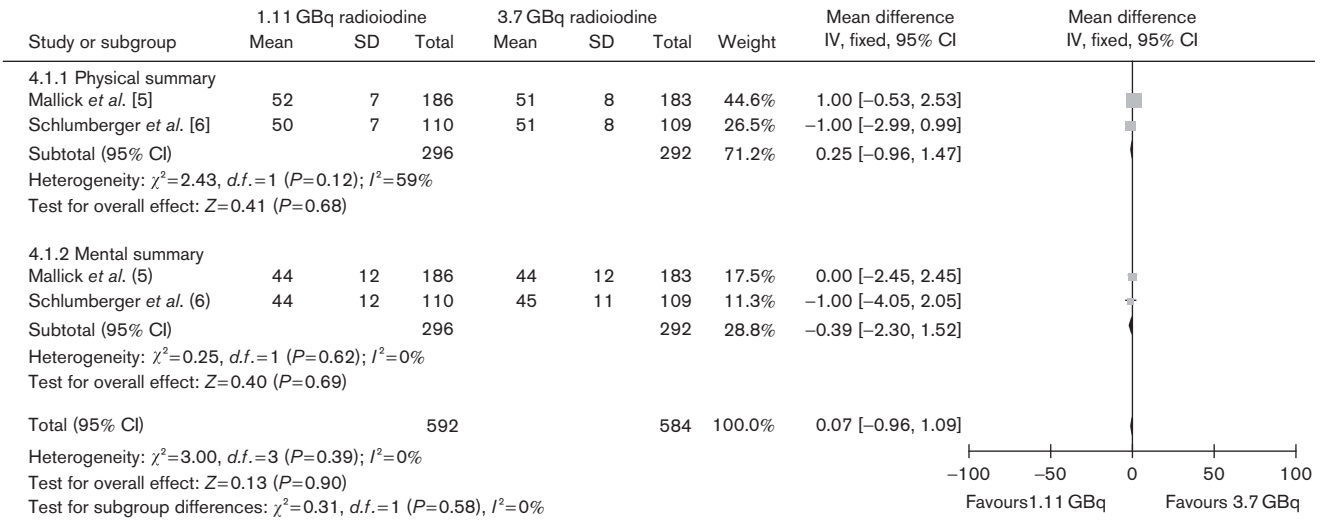
Because there is currently no accepted standard of diagnostic criteria for successful thyroid remnant ablation, the definition of successful ablation is different between the studies. Many studies used a visual inspection of the follow-up scan, others used a cutoff level associated with a quantitative measurement of neck uptake, and some studies used Tg measurements in addition to the scan result. To reduce the impact of this difference on the results, we performed a subgroup analysis on trials that evaluated the successful ablation rate on the basis of stimulated Tg levels. The results (OR = 0.66,

Fig. 4



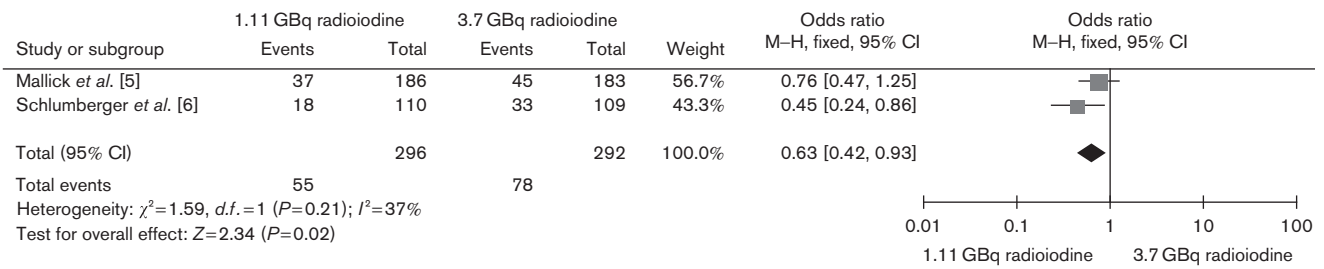
Effect of 1.85 versus 3.7 GBq iodine-131 thyroid remnant ablation on adverse effects. CI, confidence interval.

Fig. 5



Effect of 1.11 versus 3.7 GBq iodine-131 under rhTSH stimulation on health-related quality of life. CI, confidence interval; rhTSH, recombinant human thyrotropin.

Fig. 6



Effect of 1.11 versus 3.7 GBq iodine-131 thyroid remnant ablation on adverse effects. CI, confidence interval.

95% CI 0.38–1.15, $P = 0.14$) indicated that both 1.11 and 1.85 GBq are as effective as 3.7 MBq activity in achieving a successful ablation rate.

In our analysis, the assessment time of successful remnant ablation was between 6 and 12 months. We did not address future recurrences because no randomized trials on long-term adverse effects were found between low-activity and high-activity radioiodine ablation. Long-term follow-up is required to examine the recurrence rate and the risk for second primary cancer. A recent study with at least 10 years of follow-up reported that the long-term outcomes are similar in DTC patients treated with 1.1 GBq of ^{131}I and prepared either with rhTSH or

L-thyroxine (LT4) withdrawal [24]. The irradiation of ^{131}I to patients is an important factor for secondary malignancy. The absolute risk for radioiodine-induced second primary cancer had not been well established, but the risk for any second primary cancer after initial diagnosis of thyroid cancer was increased ~30% over that of the general population, and the risk appeared to increase with increasing cumulative administered activity [25,26]. A meta-analysis also indicated that the risk for second primary malignancies in thyroid cancer survivors treated with radioiodine is slightly higher compared with that of thyroid cancer survivors not treated with radioiodine [27]. Therefore, we again recommend low activity of radioiodine for residual ablation in patients with low risk for relapse. With respect to patients with high risk for relapse and metastases, the activity of radioiodine for residual ablation should be individualized. Future studies should pay more attention to secondary malignancy, relapse, and metastases of DTC on administration of low-activity compared with high-activity radioiodine ablation.

Conclusion

Limited data from three randomized controlled clinical trials suggest that rhTSH-aided low activity (1.11 and 1.85 GBq) radioiodine may be sufficient for thyroid remnant ablation as compared with 3.7 GBq, with fewer common adverse effects in patients with metastasis-free DTC. Further evidence is needed to confirm the effects of low-activity radioiodine for thyroid remnant ablation. A well-designed study comparing low-activity with high-activity radioiodine ablation is needed in order to fully understand the long-term adverse effects and relapse or metastases.

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Conflicts of interest

There are no conflicts of interest.

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