Low- or High-Dose Radioiodine Remnant Ablation for Differentiated Thyroid Carcinoma: A Meta-Analysis

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Context: There is uncertainty over the dose of ^{131}I required for thyroid remnant ablation. Most previous studies have been inadequately powered to establish the best fixed dose of ^{131}I for effective ablation.

Objective: The aim of the study was to assess the effects of low- vs high-dose regimens of radioiodine in thyroid remnant ablation for patients with differentiated thyroid carcinoma.

Data Sources: Sources included the Cochrane Library, MEDLINE, EMBASE, and SCOPUS (all until September 2012).

Study Selection: Randomized controlled trials that assess the efficacy of low- or high-dose of radioiodine ablation of thyroid remnants were collected.

Data Extraction: Two authors performed the data extraction independently.

Data Synthesis: Nine randomized controlled trials involving 2569 patients were included. The 1100-MBq vs the 3700-MBq radioiodine showed no statistically significant difference in successful thyroid remnant ablation (risk ratio [RR], 0.91 [0.79 to 1.04]; $P = .15$), both the 1100 vs the 1850 MBq (RR, 0.95 [0.83 to 1.10]; $P = .52$) and the 1850 vs the 3700 MBq (RR, 1.00 [0.85 to 1.17]; $P = .98$) also showed no significant differences (95% confidence intervals were calculated for each estimate). Also, no significant differences existed in quality-of-life scores on the SF-36 between different ^{131}I-dose groups both on the day of ablation (RR, 0.15 [−0.65 to 0.96], $P = .71$; $I^2 = 29\%$, $P = .24$) and 3 months after ablation (RR, −1.1 [−2.37 to 0.17], $P = .09$; $I^2 = 22\%$, $P = .26$). A low dose of 1100 MBq radioiodine showed significant benefits in reducing adverse effects (total RR, 0.65 [0.55 to 0.77], $P < .1$; $I^2 = 31\%$, $P = .14$) and shorter hospital isolation (RR, 0.4 [0.32 to 0.50]; $P < .05$).

Conclusions: The low dose of 1100 MBq radioiodine activity is sufficient for thyroid remnant ablation as compared to 3700 MBq radioiodine activity with similar quality of life, less common adverse effects, and a shorter hospital stay. **(*J Clin Endocrinol Metab* 98: 1353–1360, 2013)**

Thyroid cancer is the most frequently occurring endocrine cancer, and its incidence has been increasing worldwide during recent decades (1). Most cases are differentiated thyroid carcinoma (DTC), which is associated with a 10-year cancer-specific mortality rate of less than 10% (2). The principal standard treatment for these patients includes total or near-total thyroidectomy, followed by radioiodine-131(^{131}I) therapy and lifelong thyroid hormone suppressive therapy (3).

^{131}I treatment with a dose sufficient to remove residual thyroid tissue left after thyroidectomy is called "remnant ablation." Eradication of normal-thyroid remnants can achieve an undetectable serum thyroglobulin level to facilitate biochemical follow-up. Additionally, some studies indicate that remnant ablation is associated with reduced risk of development of recurrence and metastases and long-term mortality (4, 5). Therefore, complete or successful remnant ablation is an important goal at the early

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Abbreviations: DTC, differentiated thyroid carcinoma; ^{131}I, radioiodine-131; RCT, randomized controlled trial; rhTSH, recombinant human TSH; RR, risk ratio; THW, thyroid hormone withdrawal; WBS, whole-body scan.

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stage of treating DTC patients. However, there is uncertainty over the dose of ^{131}I required for effective ablation. Most clinicians prescribed an empiric fixed dose of ^{131}I for thyroid remnant ablation. The amount of ^{131}I fixed dose regimen varies from low doses such as 800 to 1110 MBq (20–30 mCi) to high doses of 2960 to 3700 MBq (80–100 mCi) or even 5550 MBq (150 mCi). Generally, a high-dose ablation regimen has been recognized as giving higher successful ablation rates of approximately 80 to 87% (6). However, this high level of successful ablation has to be weighted against its disadvantages, including patient isolation, cost, higher adverse events, and increased risk of second primary malignancies (7–10).

Most previously published studies were small-scale observational studies. The number of randomized controlled trials (RCTs) was limited, and most of them included a limited number of patients. There is a need to systematically review the relevant RCTs in order to guide thyroid remnant ablation for patients with DTC. Consequently, in this study we included all the relevant published randomized studies and assessed the successful remnant ablation, quality of life, adverse effects, and hospital isolation of low- and high-dose ^{131}I ablation.

Patients and Methods

Study selection

Studies were eligible for inclusion if they were RCTs of adult patients (at least 16 years of age) who: 1) had well-differentiated thyroid cancer (defined as papillary, follicular, or follicular variant of papillary); 2) had undergone total or near-total thyroidectomy as an initial treatment; 3) had ^{131}I ablation for the first time within 3 months after surgery; and 4) had assessment of the successful remnant ablation at 6 to 12 months after ^{131}I ablation. Cases with locoregional or distant metastases were excluded, as were pregnant women. When studies of overlapping groups of patients were identified, only the report with the largest number of patients was included, unless additional reports provided nonoverlapping information.

Data sources and searches

We collected the eligible trials by searching the Cochrane Library, MEDLINE, EMBASE, and SCOPUS up to September 2012. The Cochrane Highly Sensitive Search Strategy for identifying RCTs in MEDLINE (Ovid format) was used. The MEDLINE search strategy was also adapted in other databases.

All references to relevant articles were scanned, and all additional studies of potential interest were retrieved for further analysis. Two reviewers (W.C. and C.M.) independently analyzed the list of references and selected the studies.

Data extraction

After obtaining studies that fulfill selection criteria, 2 authors (W.C. and C.M.) independently extracted the relevant data using standard data extraction forms from all included studies. Any differences in data extraction were resolved by consensus, with participation of a third reviewer analyzing the data of the original articles. We sought any relevant missing information on the trial from the original author(s) of the article, if required. We used the name of the first author and the year of publication of the article for identification.

Statistical analysis and synthesis

All meta-analyses were performed using Review Manager 5.1 (RevMan 5.1, The Nordic Cochrane Centre, The Cochrane Collaboration, Copenhagen, Denmark). Dichotomous data were compared using a risk ratio (RR), and 95% confidence intervals were calculated for each estimate. We identified heterogeneity by visual inspection of the forest plots and by using a standard χ^2 test with a significance level of 0.1, in view of the low power of this test. We specifically examined heterogeneity employing the I^2 statistic, which quantifies inconsistency across studies to assess the impact of heterogeneity on the meta-analysis (11), where an I^2 statistic of 75% or more indicates a considerable level of inconsistency (12). When we found heterogeneity, we attempted to determine potential reasons for it by examining individual study and subgroup characteristics.

Results

We screened 405 trials and identified 9 RCTs that compared low and high doses of ^{131}I for thyroid remnant ablation in DTC. Of the 9 included trials, 2 trials reported the health-related quality of life of patients (20, 21). Three trials studied the adverse effect of ^{131}I ablation, and 2 trials compared the hospital isolation of patients (17, 20, 21). A diagram representing the flow of identification and inclusion of trials is shown in Supplemental Figure 1 (published on The Endocrine Society Journal's Online web site at http://jcem.endojournals.org). Methodological details potentially related to bias are separately described in Supplemental Table 1. Table 1 shows selected characteristics of the 9 randomized trials and the methods of TSH stimulation. The successful ablation rate and quality of life were defined as primary outcomes. The adverse effects and the days of hospital isolation were secondary outcomes.

Primary outcomes

Successful remnant ablation

There were 6 randomized trials in which the 1100- and 3700-MBq ^{131}I activities were compared. The heterogeneity was found between different studies ($I^2 = 83\%$; $P < .1$), and the random effect model was used. The 1100-MBq activity vs the 3700-MBq activity showed no statistically significant difference in successful thyroid remnant ablation (RR, 0.91 [0.79 to 1.04]; $P = .15$) (Figure 1). When successful ablation of the thyroid residue was defined as negative whole-body scan (WBS) alone, the rate of successful ablation of 3700-MBq activity was a little higher

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Table 1. Selected Characteristics of the 9 Randomized Trials and the Methods of TSH Stimulation

First Author, Year (Ref.)	Country	Patients Enrolled (n)	TNM	Pathology (P/F)	Type of Surgery	Dose (MBq)	Follow-up Time (mo)	Definition of Successful Ablation	Method of TSH Stimulation[a]
Bal, 1996 (13)	India	149	TxNxMo	87/62	NTT and STT	1100 vs 1850	6–12	No uptake on neck and WBS scan	Withdrawal
Bal, 2004 (14)	India	509	TxNxMo	410/99	NTT and STT/HT	1100 vs 1850	6	No uptake on WBS and Tg ≤10 ng/ml	Withdrawal
Zaman, 2006 (15)	Pakistan	40	TxNxMo	23/17	TT and NTT	1850 vs 3700	6	No uptake on WBS and Tg <2.0 ng/ml	Not mentioned
Pilli, 2007 (16)	Italy	72	T1-3NxMo	66/6	NTT	1850 vs 3700	6–8	No uptake on WBS and Tg <1.0 ng/ml	rhTSH
Mäenpää, 2008 (17)	Finland	160	TxNxMo	146/11[b]	TT and NTT	1100 vs 3700	4–8	No uptake on WBS and Tg ≤1.0 ng/ml	Withdrawal and rhTSH
Fallahi, 2012 (18)	Iran	341	TxNxMo	326/15	TT and NTT	1100 vs 3700	12	No uptake on WBS and Tg <2.0 ng/ml with anti-Tg-off <100 IU/ml	Withdrawal
Caglar, 2012 (19)	Turkey	108	T1-2NxMo	101/4[b]	TT	800 vs 3700	6–12	Neck uptake <0.2%, Tg <2.0 ng/ml and neck ultrasound (-)	Withdrawal
Mallick, 2012 (20)	United Kingdom	438	T1-3NxMo	NC	TT and NTT	1100 vs 3700	6–9	Neck uptake <0.1% and Tg ≤2.0 ng/ml	Withdrawal and rhTSH
Schlumberger, 2012 (21)	France	752	T1-2NxMo	693/59	TT	1100 vs 3700	6–10	Neck ultrasound (-) and Tg ≤1.0 ng/ml[c]	Withdrawal and rhTSH

Abbreviations: P/F, papillary/follicular; TT, total thyroidectomy, NTT, near total thyroidectomy; STT, subtotal thyroidectomy; HT, hemithyroidectomy; NC, not clear; Tg, thyroglobulin.

[a] Withdrawl, withdrawn from L-T_4 for at least 4 wk; rhTSH, administered rhTSH on 2 consecutive days before ablation.

[b] Three patients with both papillary and follicular.

[c] In cases of detectable antithyroglobulin antibody, if the control ^{131}I total-body scan was normal, ablation was also considered complete.

than 1100-MBq activity (RR, 0.93 [0.87 to 0.98], $P = .01$; $I^2 = 43\%$, $P = .16$) (Figure 2).

There were 3 randomized trials in which the 1850- and 3700-MBq ^{131}I activities were compared. The 1850-MBq activity vs the 3700-MBq activity showed no statistically significant difference in successful thyroid remnant ablation (RR, 1.00 [0.85 to 1.17], $P = .98$; $I^2 = 7\%$, $P = .34$) (Figure 1). When successful ablation of the thyroid residue was defined as negative WBS alone, there was also no significant difference between the 1850-MBq activity and the 3700-MBq activity (RR, 0.97 [0.84 to 1.13], $P = .71$; $I^2 = 0\%$, $P = .39$) (Figure 2).

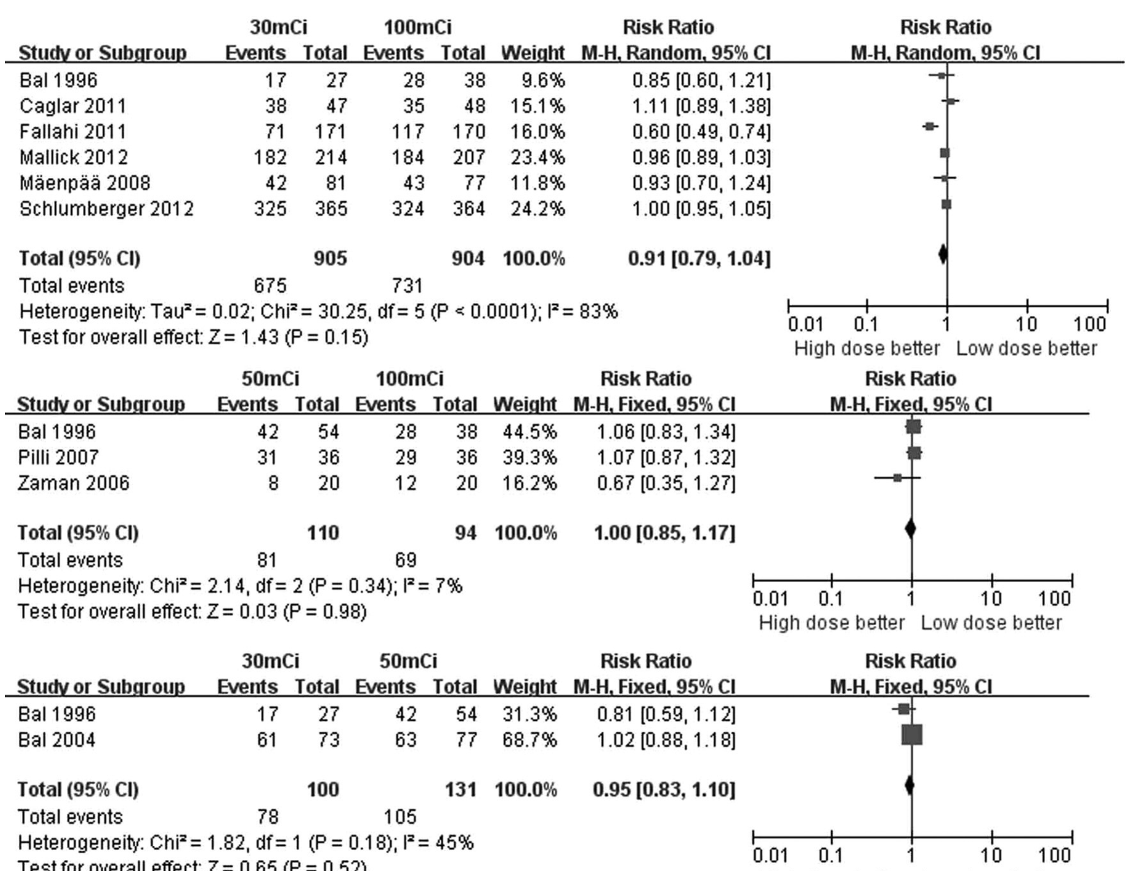

Figure 1. Comparison of the successful remnant ablation between different ^{131}I activities.

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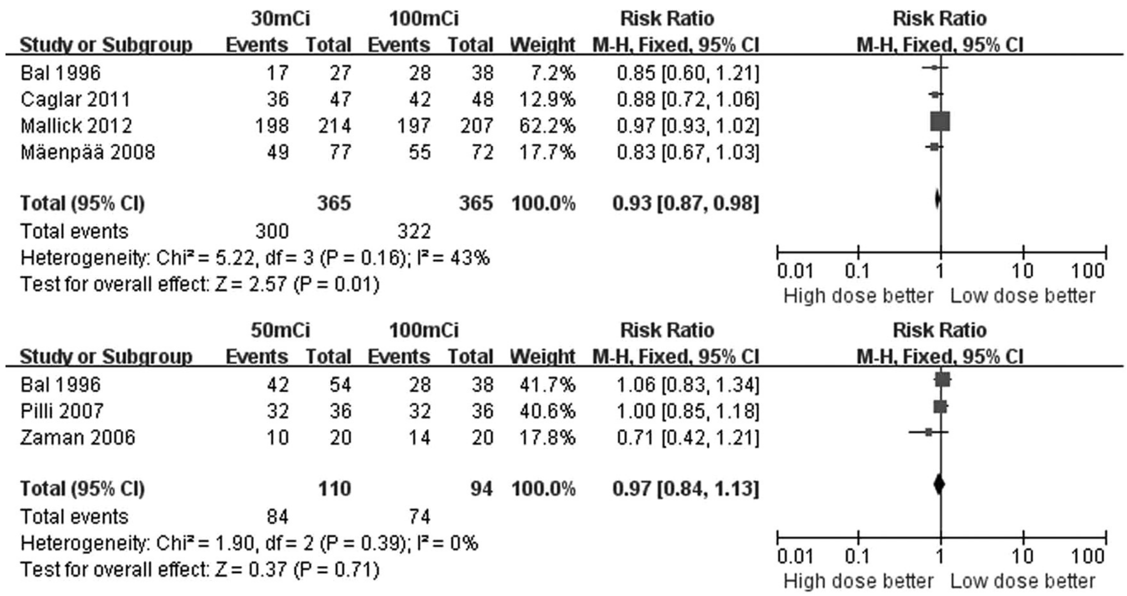

Figure 2. Comparison of the successful remnant ablation between different ^{131}I activities while the definition of successful ablation was based on WBS only.

There were 2 randomized trials in which the 1100- and 1850-MBq radioiodine activities were compared. The 1100- vs 1850-MBq activity showed no statistically significant difference in successful thyroid remnant ablation (RR, 0.95 [0.83 to 1.10], $P = .52$; $I^2 = 45\%$, $P = .18$) (Figure 1).

Quality of life

Two included trials compared the health-related quality of life between different ^{131}I activity groups. The Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) was used to evaluate patients' quality of life (scores range from 0–100, with higher scores indicating better health status) (22). On the day of ablation, available data showed no significant difference in scores on the SF-36 between patients receiving low-dose ^{131}I and those receiving high-dose ^{131}I (RR, 0.15 [−0.65 to 0.96], $P = .71$; $I^2 = 29\%$, $P = .24$) (Figure 3A). Three months after ablation, 1 study showed no difference between the 2 groups (RR, −1.1 [−2.37 to 0.17], $P = .09$; $I^2 = 22\%$, $P = .26$) (Figure 3B), whereas the other did not give scores on SF-36 for the comparison of 2 different ^{131}I activities.

Secondary outcomes

Days of hospital isolation

Patients receiving low-dose ^{131}I spent less time in hospital isolation than those receiving high-dose ^{131}I (RR, 0.4 [0.32 to 0.50]; $P < .05$), without significant heterogeneity between studies ($I^2 = 0\%$; $P = .43$) (Figure 4).

Adverse effects

Of the 9 RCTs included, 3 trials addressed adverse effects of radioiodine. Adverse events were recorded during the first week and 3 months after treatment. In the trial of Mäenpää et al, 11 patients were reported with severe nausea (4 patients in the 1100-MBq group, and 7 patients in the 3700-MBq group) (17). In the trial of Mallick et al (20), 6 patients were reported with serious adverse events, whereas in the trial of Schlumberger et al (21), 5 serious adverse events occurred; however, none of these events were thought to be related to treatment. In this meta-analysis, the data showed that patients who received a lower ^{131}I activity had fewer adverse events during the first week (total RR, 0.65 [0.55 to 0.77], $P < .1$; $I^2 = 31\%$; $P = .14$) (Supplemental Figure 2A). Among the reported adverse events, however, dry mouth, taste abnormalities, and lacrimal dysfunction were shown not to be dose-dependent. Three months after ablation, no significant differences were seen for the comparison of 2 ^{131}I activities (total RR, 0.72 [0.35 to 1.47], $P = .36$; $I^2 = 28\%$, $P = .23$) (Supplemental Figure 2B). None of the 9 included trials reported the long-term follow-up adverse effects.

Discussion

Radioiodine remnant ablation is increasingly being used to eliminate the postsurgical thyroid remnant (23). Ablation of the small amount of residual normal thyroid tissue may facilitate the early detection of recurrence and reduce the rates of disease recurrence and cause-specific mortality as well. However, some studies argued that remnant ablation should not be required for all DTC patients (23, 24). They suggested that radioiodine ablation may show no benefit in patients with the lowest risk for mortality. In our study, patients in 4 of the included RCTs had low to in-

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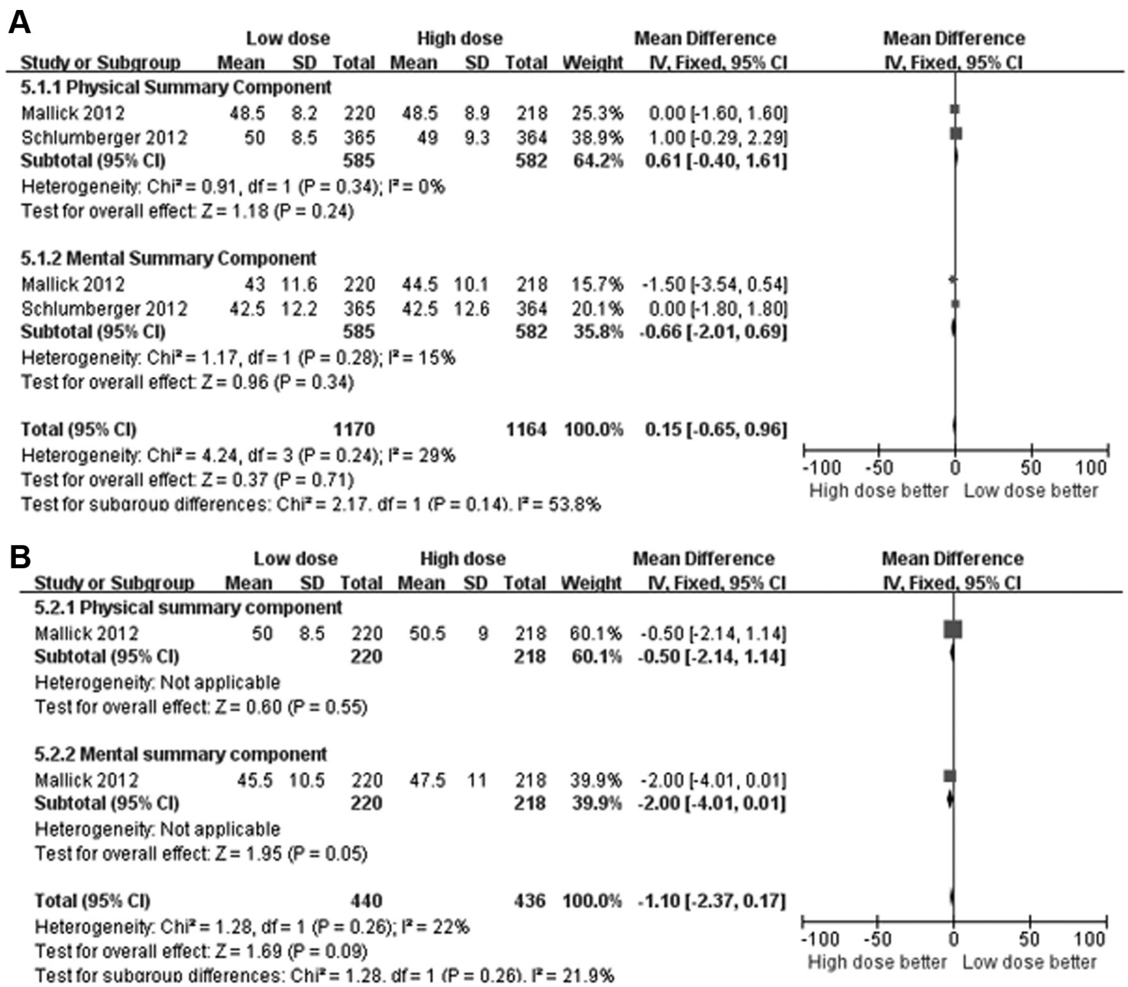

Figure 3. Comparison of the health-related quality-of-life scores on the SF-36 between patients receiving different ^{131}I activities. A, Comparison on the day of ablation; B, comparison 3 months after the ablation.

termediate risk of relapse ($T_{1-3}N_xM_0$). Although the other trials did not mention the patients' TNM, they stressed that the patients were all without high-risk features. We agree with the American Thyroid Association (ATA) that remnant ablation is not necessary in patients with microcarcinomas (unifocal or multifocal tumors <1.0 cm) without other high-risk features (25). For patients with tumors >1.0 cm, or with residual or metastatic disease or other high-risk features, the radioiodine ablation is recommended (25). Radioiodine ablation after total thyroidectomy is indicated generally for 3 reasons: 1) remnant ablation to ablate normal thyroid tissue; 2) adjuvant therapy to eliminate any suspected but unproven metastases; and 3) ^{131}I therapy to treat known persistent disease (25).

Unfortunately, there is uncertainty over the dose of ^{131}I required for thyroid remnant ablation. For patients with low-risk features, the recommendation from the ATA is that "the minimum activity (1100 MBq-3700 MBq) necessary to achieve successful remnant ablation should be utilized" (25). The European consensus report indicates that for patients with tumors larger than 1 cm who had less than total thyroidectomy or unfavorable histology and no lymph node dissection, the recommendation is "high or low activity (3700 MBq or 1100 MBq)" (26). In this study,

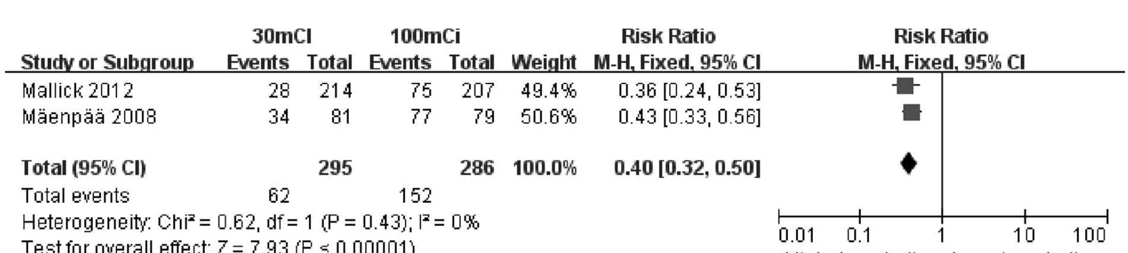

Figure 4. Comparison of hospital isolation between different ^{131}I activities.

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we included 9 RCTs that were similar in relation to patients' characteristics (Table 1). Different dosages of ^{131}I, such as 1100-, 1850-, and 3700-MBq activities, were used in the included trials, and we performed meta-analysis on every 2 different dosages. The heterogeneity was found ($I^2 = 84\%$) in the pooled analysis of 1100- vs 3700-Mbq activity. We tried to investigate the reasons of heterogeneity, but no clinical heterogeneity or methodological heterogeneity was found; a random effect model was then used for meta-analysis (27). The comparison of low- vs high-dose ^{131}I in thyroid remnant ablation was not statistically significant in the present meta-analysis. Therefore, the low-dose ^{131}I activity (1100 MBq) is sufficient for remnant ablation in DTC patients with low and intermediate risk of relapse. For patients with regional or distant metastases, however, we agree with the higher activity (≥3700 MBq) recommended in the ATA and the European consensus report as well (25, 26).

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 thyroglobulin measurements in addition to the scan result. To reduce the impact of this difference on the results, we then performed the subgroup analysis on trials that evaluated the success ablation rate by WBS alone, and the results indicated that the 1100-MBq activity has a 7% lower successful ablation rate (RR, 0.93 [0.87, 0.98]; $P = .16$) than 3700-MBq activity. In our opinion, although the high-dose group had a 7% higher successful ablation rate, this advantage may not be obvious when factors such as adverse effects and hospital isolation are taken into consideration. In addition, because ^{131}I WBS generally had low sensitivity after radioiodine ablation (28), now few studies used WBS alone as the standard of diagnostic criteria for successful thyroid remnant ablation.

As stated above, there were no significant differences in health-related quality-of-life scores on the SF-36 between patients receiving low-dose ^{131}I and those receiving high-dose ^{131}I on the day of ablation and 3 months after ablation. In addition, both trials also assessed the effects of TSH alfa (recombinant human TSH [rhTSH]) and thyroid hormone withdrawal (THW) with ^{131}I treatment for DTC, and the results showed improved quality of life in patients prepared with rhTSH, in comparison to those undergoing THW (20, 21). In our previous work, we had compared the effects of THW- and rhTSH-aided radioiodine treatment for normal residual or metastatic DTC, and the results revealed that the rhTSH preparation was not different from THW, with a better quality of life and cost-effectiveness (29). The use of rhTSH has been reported with a better quality of life, a shorter hospitalization length, and the partial compensation of its acquisition cost (30–32). The significantly lower radiation effects of rhTSH than THW have also been confirmed by 2 other studies (33, 34). The review of Chen et al (35) has revealed that rhTSH provided us an option of safe, convenient, and better-quality patient care, and rhTSH has now been approved for remnant ablation in Europe, the United States, and many other countries around the world (36).

The ablation radioiodine for DTC patients was generally well tolerated, and the frequency of adverse effects decreased with time. It was recognized that a higher dose of ^{131}I would lead to increased adverse effects and longer hospital isolation. In the present meta-analysis, patients who received a higher activity had more adverse events. In addition, sialadenitis, dry eyes, and other adverse events also were noted with higher doses of ^{131}I (17, 20). Permanent gonadal damage had been observed, with cumulative activities exceeding 18.5–22.2 GBq (37). Dry mouth, however, had not been reported to be dose-dependent (38, 39), which was consistent with our analysis. Two of the included randomized trials also compared the days of hospital isolation. Patients receiving low-dose ^{131}I spent less time in hospital isolation than those receiving high-dose activity, with 21.0% (62 of 295) vs 53.1% (152 of 286) requiring 3 days of hospital isolation or more (17, 20).

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 the low- and high-dose radioiodine ablation. Long-term follow-up should be required to examine recurrence rate and the risk of second primary cancer. A prospective study of 715 patients had reported that the recurrence rate was low in patients receiving low-dose ^{131}I (40). The absolute risk for radioiodine-induced second primary cancer had not been well established. One study including 30 278 patients from 17 population-based registries has found a greater risk of second primary cancer for both patients who received ^{131}I therapy and those who did not, such as for cancers of the breast, kidney, or prostate, suggesting that other factors such as shared genetic susceptibility or surveillance bias may be responsible for this observation (41). However, an increased risk for leukemia and stomach cancer has been demonstrated in patients who received ^{131}I therapy (41). In addition, Rubino et al (42) found that the risk of solid tumors and leukemia appeared to increase with increasing cumulative administered activity.

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In conclusion, the 1100-MBq radioiodine activity is sufficient for thyroid remnant ablation in comparison with 3700-MBq radioiodine activity, with similar quality of life, fewer common adverse effects, and a shorter stay in a radiation protection unit. Combined with our previous study of the effects of rhTSH-aided ^{131}I treatment, therefore, low-dose ^{131}I plus rhTSH should be recommended for patients with metastasis-free DTC. A well-designed study on long-term adverse effects and relapse or metastases is needed between the low- and high-dose radioiodine ablation.

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