

Received: 2015.11.03
Accepted: 2015.12.28
Published: 2016.07.13

I-131 for Remnant Ablation in Differentiated Thyroid Cancer After Thyroidectomy: A Meta-Analysis of Randomized Controlled Evidence

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

BCE 1 **Yan Shengguang**
CDE 2 **Choi Ji-Eun**
A 3 **He Lijuan**

1 International Education Center, North China University of Science and Technology, Tangshan, Hebei, P.R. China
2 Department of Education, Jeonju University, Jeonju-si, South Korea
3 Department of Hepatobiliary Surgery, Kailuan General Hospital, Tangshan, Hebei, P.R. China

Corresponding Author: He Lijuan, e-mail: helijuanhb@163.com
Source of support: Departmental sources

Background: The aim of this study was to compare the success rate of various levels of I-131 activity for use in remnant ablation in low-risk differentiated thyroid cancer.





Material/Methods: We identified eligible studies in 5 electronic databases up to December 2014 and the reference lists of original studies and review articles were hand searched for additional articles on this topic. Summary relative risks with their 95% confidence intervals were calculated with a random-effects model. Heterogeneity was assessed using I^2 statistics.

Results: Fourteen randomized clinical trials met the eligibility criteria. The data suggest that the pooled successful ablation rate is 5% lower (95% CI, 1–9% lower) when using 30 mCi compared with 100 mCi (test for heterogeneity, $p=0.468$, $I^2=0.0\%$). In stratified analysis, ablation success rates using 30 mCi are similar to 100 mCi in Asia (SRRs=0.91; 95%CI=0.72–1.14). However, the results favor 100 mCi in Europe (SRRs=0.95; 95%CI=0.91–0.99). Ablation success rates using 30 mCi are similar to 100 mCi in patients who underwent TT/NTT (total thyroidectomy/near total thyroidectomy) (SRRs=0.96; 95%CI=0.92–1.00) and TT/STT (SRRs=0.98; 95%CI=0.73–1.31). However, the result favor 100 mCi in patients who underwent ST/HT (subtotal thyroidectomy/ hemithyroidectomy) (SRRs=0.80; 95%CI=0.65–0.99). There was no publication bias in the present meta-analysis.

Conclusions: High radioiodine activity is better than low activity in terms of successful ablation rate in low-risk differentiated thyroid cancer, but the advantage of high activity seems to only exist in patients who underwent hemithyroidectomy/subtotal thyroidectomy, but not lymph node involvement, preparation before ablation, and definition of successful ablation.

MeSH Keywords: **Meta-Analysis • Parathyroid Neoplasms • Thyroglobulin**

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/896535>

 3291  3  6  52



Background

Thyroid cancer is currently the fifth most common malignancy diagnosed in women, with the incidence increasing every year, and it occurs 2 to 3 times more frequently in women than in men [1]. Most cases are differentiated (including papillary and follicular) thyroid cancer, which has a high 10-year survival rate (90% to 95%) [2]. Radioiodine ablation of residual thyroid tissue after total or near-total thyroidectomy is accepted by many practitioners for 2 reasons: first, to eradicate any occult carcinoma focus in order to decrease the risk of recurrence; second, to facilitate long-term surveillance of improvement in sensitivity of an I-131 whole body scan (WBS) and specificity for thyroglobulin measurements [3]. A systematic review conducted by Sawka also showed that radioactive iodine ablation may be beneficial in decreasing recurrence of well-differentiated thyroid cancer [4].

However, the optimal I-131 activity required to achieve remnant ablation remains controversial. Recent randomized trials [5–7] show that low-activity (30 mCi) radioiodine was as effective as high-activity (100mCi or more) radioiodine for low-risk thyroid cancer. Furthermore, there are several advantages to patient and healthcare provider in using a lower activity radioiodine, including less time in isolation, a shorter hospital stay, and lower financial cost. High-activity radioiodine may induce lacrimal and salivary gland disturbances, as well as transient gonadal dysfunction, especially in male patients. Although risk of radioiodine-induced cancers has not been well established, pooled data show a 30% increased risk of a second primary cancer after thyroid cancer [8], and an increased risk of solid tumors and leukemias was found with increasing cumulative activity of I-131 administered [9]. Thus, the lower the activity administered, the lower the risk.

The recommendations on ablation activity from the guidelines [10–12] are not entirely consistent with each other. A meta-analysis conducted by Doi in 2000 [13] concluded that high-activity was more efficient than low-activity for remnant ablation, and reported a pooled reduction of failure in the high-activity group of about 27% (95% confidence interval, 13% to 39%). However, this effect was seen only in the observational studies, with a 31% pooled reduction (95% CI, 16 to 43%) that was not statistically significant in randomized trials. Another meta-analysis conducted by Hackshaw in 2006 [14] drew a more cautious conclusion that there is currently insufficient evidence to reliably determine whether ablation success rates using 30 mCi are similar to those using 100 mCi. The pooled ablation success rate in observational studies was 10% lower using 30 mCi compared with 100 mCi (95% CI, 3 to 17%). However, the meta-analysis of 6 randomized trials produced equivocal results.

Both of the 2 above meta-analysis had several limitations. First, the conclusions were mostly based on observational studies,

which are likely to be affected by inherent biases. Second, there were several important methodological differences between the studies included, for example, definitions of “low” and “high” activity, extent of surgery (total or subtotal), definitions of successful ablation, and preparation for I-131 ablation. These methodological differences could greatly affect the interpretation of outcomes.

Therefore, we conduct this meta-analysis based on high-quality evidence in order to draw a more reliable conclusion about the appropriate level of activity to use in radioiodine ablation. We will further investigate whether the conclusion is robust and stable between different subgroups.

Material and Methods

Study identification and selection

Five electronic databases (Medline, EMBASE, PubMed, the Cochrane Central Register of Controlled Trials, and Web of Science) were searched to identify titles and abstracts of all possible randomized trials on the topic of interest up to December 2014. Reference lists of original studies and review articles on this topic were hand-searched to find other potentially eligible studies. We searched the eligible studies with the following text words and/or Medical Subject Heading (MeSH) terms: “thyroid”, “cancer” or “carcinoma” or “neoplasm”, and “ablation”. No language restrictions were imposed. Three reviewers independently screened the databases. Full texts that met the study eligibility criteria (Table 1) were retrieved for detailed evaluation, and eligible studies were included. Disagreements were solved by joint reevaluation of the manuscript.

Data extraction

Three authors independently evaluated all of the studies retrieved according to the prespecified selection criteria. The following information from each study was extracted using a standardized data collection form: first author's last name, year of publication, country, extent of surgery, whether lymph node metastatic patients were included, whether a preablation scan was performed (isotope and the activity), preparation for I-131 ablation, the definition of successful ablation, and the proportion of patients who achieved successful ablation in each group. Study authors were contacted in the case of missing data. Disagreements were resolved through discussion.

Quality assessment

The risk of bias was assessed following Cochrane recommendations, considering random sequence generation, allocation concealment, blinding of participants and personnel, blinding

Table 1. Study eligibility criteria for inclusion in the review*.

Types of participants	Age of 18 years or older, not pregnant or breastfeeding
	Received total or subtotal thyroidectomy
	Histological confirmation of differentiated thyroid cancer (papillary, follicular, or mixed)
	Pathological tumor-node-metastasis (TNM) classification, pT1 to T3 with the possibility of lymph node involvement but no distant metastasis
Types of interventions	Low-activity radioiodine, defined as 20–30 mCi
	Moderate-activity radioiodine, defined as 50–60 mCi
	High-activity radioiodine, defined as 75–100 mCi
	Excluded studies that cannot be clearly divided into the above groups
Definition of successful ablation	Met at least 1 of the following criteria
	#1 Undetectable Tg level
	#2 No uptake in WBS
Types of studies	All randomized trials. Trials may be blinded or not blinded.

Tg – thyroglobulin; WBS – whole body scan. * A study must meet eligibility for all 4 components for inclusion in the study.

of outcome assessment, incomplete outcome data, and selective reporting. Each category was assessed as low, unclear, or high risk of bias and summarized in a table with a plus sign, question mark, or minus sign, respectively.

Statistical analysis

Relative risk estimates with their corresponding 95% CIs were combined and weighted to produce pooled RRs using a fixed/random-effects model. To investigate the sources of heterogeneity across these studies, we carried out heterogeneity tests, sensitivity analysis, and subgroup analysis. In heterogeneity tests, we used the Cochran *Q* and *I*² statistics [15], which were used to test the differences obtained between studies due to chance. For the *Q* statistic, a *p*-value of less than 0.10 was considered representative of statistically significant heterogeneity. The *I*² statistic is the proportion of total variation contributed by between-study variation. It has been suggested that *I*² values of 25%, 50%, and 75% are assigned to low, moderate, and high heterogeneity, respectively [16]. We conducted sensitivity analysis to estimate the influence of each individual study on the summary results. We evaluated the role of several potential sources of heterogeneity and investigated whether the conclusion was robust and stable between different subgroups by subgroup analyses according to country, extent of surgery, whether lymph node metastatic patients were included, preablation scan, preparation for I-131 ablation (low-iodine diet recommended and TSH stimulation), definition of successful ablation, and sample size.

Funnel plots and the Egger's test were performed to test evidence of publication bias. Meta-analyses were carried out using STATA12.0 (Stata Corp, College Station, TX, USA). A two-tailed *p*-value less than 0.05 was considered to be significant.

Results

Study identification and selection

Using the outlined search strategy, a total of 1042 citations were obtained for review of title and abstract; 1003 were excluded for irrelevance and 3 for being duplicates. Full text of the remaining 36 studies was retrieved for review. Hand-searching the references of previous studies and systematic reviews identified 3 relevant studies. Identification and selection of eligible studies are summarized in Figure 1. Among the 31 full-text articles, 17 studies were excluded. Two studies had less than 10 cases [17,18], 4 studies had unclearly defined the I-131 activity [19–22], and 11 studies were observational studies [23–33]. References of the 14 remaining studies were hand searched and no other eligible studies were found. Thus, 14 randomized trials [5–7,34–44] were identified and included in the meta-analysis. Although a language restriction was not placed on the search, all included studies were reported in English. The 2 reviewers had perfect agreement in selecting the 14 studies using the stated eligibility criteria.

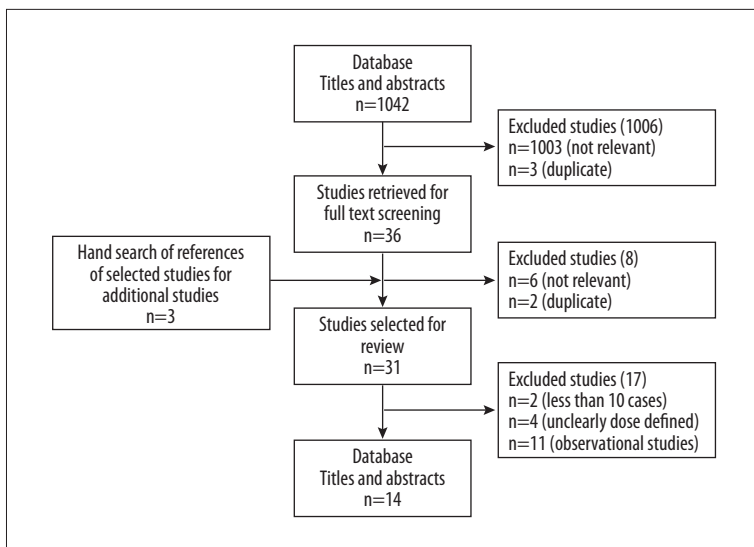


Figure 1. Flow chart of selection of studies included in the meta-analysis.

Characteristics of included studies

Selected studies (14 randomized trials) were published between 1987 and 2013. Sample size for the included studies ranged from 20 to 650 patients. The successful ablation rate ranged from 39.2% to 91.2% in low-activity groups, 40.0% to 86.7% in moderate-activity groups, and 55.8% to 93.4% in high-activity groups. Details of study characteristics are provided in Table 2.

Bias

Most of the included studies had a low risk of bias (Figure 2). More than half of the studies did not clearly describe the method of random sequence generation (57.1%), and blinding of the participants and personnel (78.6%). Five studies did not provide a detailed description of allocation concealment. Most of the studies had a low risk of detection bias, attrition bias, and reporting bias. The methodological quality of all included studies was assessed by the 3 reviewers using the ‘risk of bias’ assessment tool provided by The Cochrane Collaboration.

Data synthesis and review

30 mCi vs. 100 mCi

A test for heterogeneity of the 10 studies using a low activity of approximately 30 mCi compared with a high activity of approximately 100 mCi was statistically significant (SRRs=0.90; 95%CI=0.82–0.99; $p<0.001$, $I^2=71.5%$), indicating that effects differed across studies. We carefully reevaluate characteristics and quality of each study. We found that all studies clearly met the stated eligibility criteria. In a sensitivity analysis, the overall homogeneity and effect size were calculated by removing 1 study at a time. We found that study conducted by Fallahi published in 2012 [37] appeared to be an outlier, and omitting the

study greatly influenced the summary relative risk from 0.90 (0.82–0.99) to 0.96 (0.93–1.00) (Figure 3). A funnel plot also showed that the study was clearly outside the 95% CI lines (Figure 4). According to protocol in Cochrane reviews, its influence on a meta-analysis might be assessed by excluding it.

We subsequently conducted a meta-analysis of all 9 randomized trials [5,6,7,35,36,38–41] that compared the outcome of successful ablation rate in 30 mCi vs. 100 mCi using a fixed-effects model. The summary risk ratio of having a successful ablation was 0.95 (95%CI, 0.91–0.99), indicating that the pooled ablation success rate was 5% lower using 30 mCi compared with 100 mCi (95% CI, 1% to 9%) with low heterogeneity among studies (test for heterogeneity, $p_{\text{heterogeneity}}=0.468$, $I^2=0.0%$) (Figure 5).

We subsequently conducted subgroup analysis according to country, extent of surgery, whether lymph node metastatic patients were included, preablation scan, preparation for I-131 ablation (low-iodine diet recommended and TSH stimulation), definition of successful ablation, and sample size (Table 3). In stratified analysis by country, ablation success rates using 30 mCi are similar to 100 mCi in Asia (SRRs=0.91; 95%CI=0.72–1.14). However, the result favor 100 mCi in Europe (SRRs=0.95; 95%CI=0.91–0.99).

In stratified analysis by extent of surgery, ablation success rates using 30 mCi were similar to 100 mCi in patients who underwent TT/NTT (SRRs=0.96; 95%CI=0.92–1.00) and TT/STT (SRRs=0.98; 95%CI=0.73–1.31). However, the results favor 100 mCi in patients who underwent ST/HT (SRRs=0.80; 95%CI=0.65–0.99).

In stratified analysis by whether lymph node metastatic patients were included in studies, no significant difference was

Table 2. Characteristics and results from 14 randomized clinical trials.

Author year	Country	Extent of surgery	LN metastasis	Preablation scan (activity)	Prepared for I-131 ablation		Definition of successful ablation	Low activity		High activity	
					Low-iodine diet	TSH stimulation		mCi	Success rate (n)	mCi	Success rate (n)
Giovanella 2013	Switzerland	STT/HT	N	5.0 mCi/ ^{99m} Tc	Y, 2 weeks	N	Tg ≤2 ng/ml No uptake on WBS	30	53.5% (36/67)	100	69.5% (48/69)
Fallahi 2012	Iran	TT/NTT	N	2.5–3.0 mCi/ ¹³¹ I	Y, 2 weeks	Withdrawal	Tg ≤2 ng/ml No uptake on WBS	30	39.2% (67/171)	100	64.1% (109/170)
Caglar 2012	Turkey	TT	N	0.2 mCi/ ¹³¹ I	Y,4 weeks	Withdrawal	Tg ≤2 ng/ml No uptake on WBS Neck USG (-)	21.6	80.9% (38/47)	100	72.9% (35/48)
Schlumberger 2012	France	TT	Y	NA	NA	Withdrawal and rhTSH	Tg ≤1 ng/ml Neck USG (-)	30	91.2% (301/330)	100	93.4% (299/320)
Mallick 2012	UK	TT/NTT	Y	2.16 mCi/ ^{99m} Tc	Y,3 weeks	Withdrawal and rhTSH	Tg ≤2 ng/ml neck uptake <0.1%	30	85.0% (182/214)	100	88.9% (184/207)
Kukulska 2010	Poland	TT	Y	NA	NA	Withdrawal	Tg ≤10 ng/ml No uptake in neck	30 60	78.0% (67/86) 86.7% (111/128)	100	88.4% (84/95)
Maenpaa 2008	Finland	TT/NTT	Y	0.2 mCi/ ¹³¹ I	Y	Withdrawal	Tg ≤1ng/ml No uptake on WBS	30	51.9% (42/81)	100	55.8% (43/77)
Pilli 2007	Italy	NTT	Y	0.1 mCi/ ¹³¹ I	NA	rhTSH	Tg ≤1ng/ml No uptake on WBS	50	86.1% (31/36)	100	80.6% (29/36)
Zaman 2006	Pakistan	TT/NTT	N	2.0 mCi/ ¹³¹ I	NA	NA	Tg ≤2 ng/ml No uptake on WBS	50	40.0% (8/20)	100	60.0% (12/20)
Sirisalipoch 2006	Thailand	At least STT	NA	1.0 mCi/ ¹³¹ I	Y	Withdrawal	Tg ≤10 ng/ml neck uptake <0.2%	50	65.1% (41/63)	100	86.7% (65/75)
Bal 2004	India	TT/NTT STT/HT	N	2.0–3.0 mCi/ ¹³¹ I	N	Withdrawal	Tg ≤10 ng/ml No uptake on WBS	30	83.6% (61/73)	50	81.8% (63/77)
Bal 1996	India	NTT STT/ HT	N	5.0 mCi/ ¹³¹ I	NA	Withdrawal	Tg ≤10 ng/ml No uptake on WBS	30 50	63.0% (17/27) 77.8% (42/54)	90	73.7% (28/38)
Johansen 1991	Saudi Arabia	TT/STT	Y	N	N	rhTSH	No uptake on WBS	29	80.8% (21/26)	100	82.4% (14/17)
Creutzig 1987	Germany	NTT	N	NA	NA	NA	Neck uptake <0.5%	30	50.0% (5/10)	100	60.0% (6/10)

1 mCi = 37 MBq; TT – total thyroidectomy; NTT – near total thyroidectomy; STT – subtotal thyroidectomy; HT – hemithyroidectomy; LN – lymph node; WBS – whole body scan; Y – yes; N – no; NA – data not applicable; rhTSH – recombinant human thyrotropin; Tg – thyroglobulin. Withdrawal withdrawn from L-T4, rhTSH administered rhTSH on 2 consecutive days before ablation.

* Tg levels obtained at the central site.

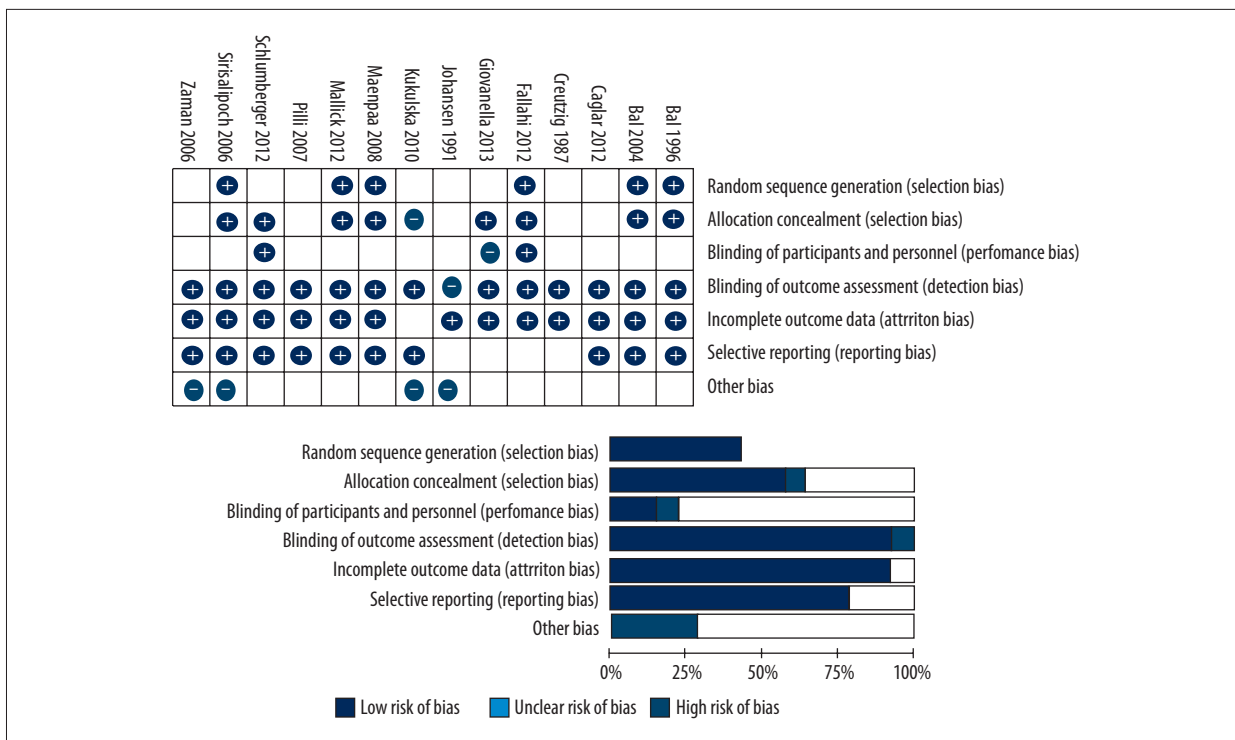


Figure 2. Risk of bias assessment. – indicates a high risk of bias, + indicates a low risk of bias, ? indicates an unclear risk of bias.

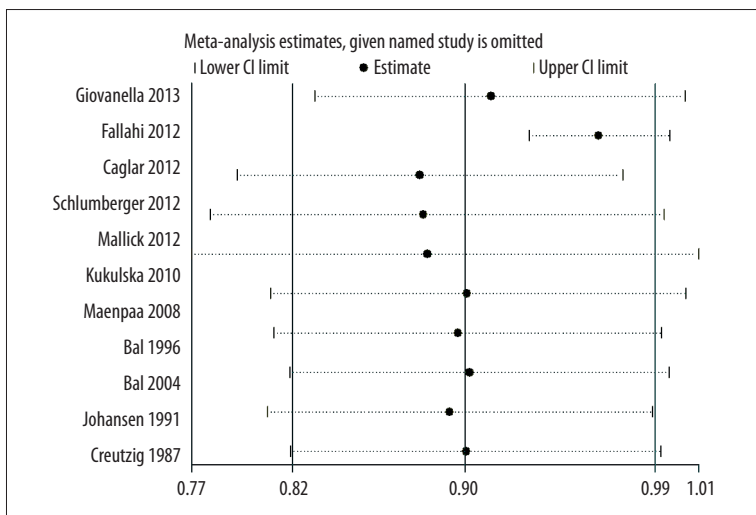


Figure 3. Sensitivity analysis. We found that the study conducted by Fallahi 2012 appeared to be an outlier, and omitting the study greatly influenced the summary relative risk, changing it from 0.90 (0.82–0.99) to 0.96 (0.93–1.00).

found in studies that included lymph-node metastatic patients (SRRs=0.96; 95%CI=0.92–1.00), and the same was found in the group that included patients without lymph node metastatic (SRRs=0.90; 95%CI=0.77–1.05).

The SRRs were not statistically significant in activity of preablation scan <2.0 mCi group (SRRs=1.01; 95%CI=0.84–1.21), and the same was found in the ≥2.0 mCi group (SRRs=0.85; 95%CI=0.60–1.21). However, the results favor 100 mCi in preablation scan using the technetium-99m group (SRRs=0.92; 95%CI=0.85–0.99).

When we stratified the studies according to preparation for I-131 ablation (low-iodine diet recommended and TSH stimulation), the SRRs were not statistically significant whether or not a low-iodine diet was recommended (recommended SRRs=0.94; 95%CI=0.87–1.02 vs. not recommended SRRs=0.98; 95%CI=0.73–1.31). The same result was found in various levels of TSH stimulation (T4 withdrawal: SRRs=0.93; 95%CI=0.84–1.04 vs. rhTSH administered: SRRs=0.98; 95%CI=0.73–1.31 vs. both: SRRs=0.97; 95%CI=0.93–1.01) (Table 3).

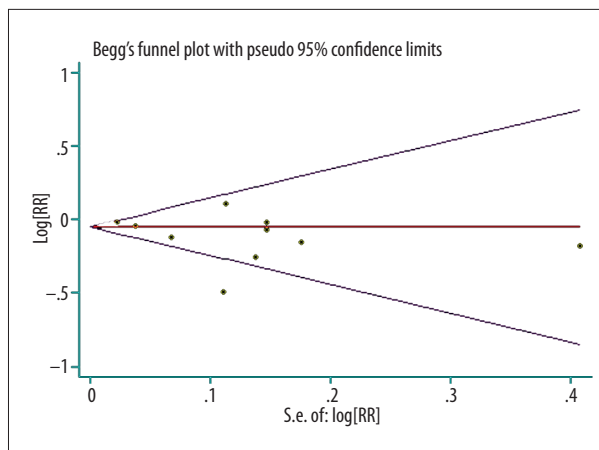


Figure 4. Funnel plot of studies evaluating the outcome of successful ablation rate in low-activity vs. high-activity group.

In stratified analysis by definitions of successful ablation, the SRRs were not statistically significant in different definitions of successful ablation (Tg <2 ng/mL and WBS: SRRs=0.96; 95%CI=0.92–1.00 vs. Tg <10 ng/mL and WBS: SRRs=0.88; 95%CI=0.77–1.00 vs. only WBS: SRRs=0.94; 95%CI=0.70–1.26) (Table 3).

When we stratified the studies according to sample size, the SRRs were not significantly different in the small sample size

(n<80) group (SRRs=0.90; 95%CI=0.72–1.13). However, the results favor the 100 mCi large sample size (n≥80) group (SRRs=0.95; 95%CI=0.91–0.99).

30 mCi vs. 50 mCi and 50 mCi vs. 100 mCi

Figure 6 shows the risk ratio of having a successful ablation of 30 mCi vs. 50 mCi and 50 mCi vs. 100 mCi activity of radioiodine. No significant difference was found when using a low activity of approximately 30 mCi compared with a moderate activity of approximately 50 mCi in a random-effects model (SRRs=0.93; 95%CI=0.84–1.02; $p_{\text{heterogeneity}}=0.275$, $I^2=22.6\%$) (Figure 6A), similar to when using a moderate activity of approximately 50 mCi compared with a high activity of approximately 100 mCi in a random-effects model (SRRs=0.94; 95%CI=0.81–1.09; $p_{\text{heterogeneity}}=0.052$, $I^2=57.5\%$) (Figure 6B). Results were robust and stable in sensitivity analysis.

Publication bias

The shape of the funnel plots for studies comparing the I-131 activity 30 mCi vs. 100 mCi seemed symmetrical, indicating no publication bias. Because there were fewer than 10 included studies comparing the I-131 activity at 30 mCi vs. 50 mCi and 50 mCi vs. 100 mCi, we did not plot studies onto a funnel plot.

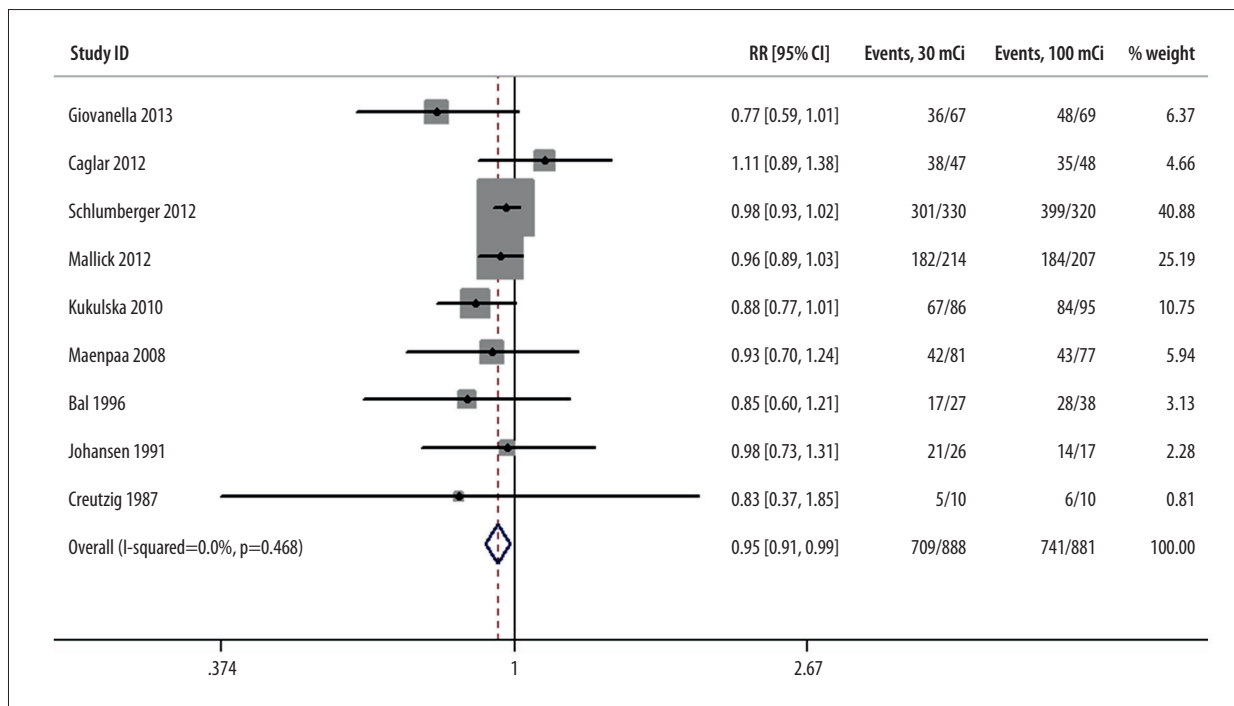


Figure 5. Forest plots comparing the outcome of 9 randomized trials using a fixed-effects model in terms of successful ablation rate in low-activity vs. high-activity groups.

Table 3. Subgroup analysis*.

Subgroup	References	Relative risk (95%CI)	Tests for heterogeneity	
			P	I ² (%)
Country				
Euro	[5-7,36,38,40,41]	0.95 (0.91, 0.99)	0.318	14.7
Asia	[35,39]	0.91 (0.72, 1.14)	0.531	0.0
Extent of surgery				
TT/NTT	[5-7,36,40,41]	0.96 (0.92, 1.00)	0.569	0.0
STT/HT	[35,38]	0.80 (0.65, 0.99)	0.652	0.0
With LN metastatic patients included				
Y	[5,6,39-41]	0.96 (0.92, 1.00)	0.665	0.0
N	[7,35,36,38]	0.90 (0.77, 1.05)	0.189	37.3
Preablation scan				
Tc-99m	[6,38]	0.92 (0.85, 0.99)	0.101	62.8
I-131 <2.0 mCi	[7,41]	1.01 (0.84, 1.21)	0.312	2.2
I-131 ≥2.0 mCi	[35]	0.85 (0.60, 1.21)	NA	NA
Low-iodine diet				
Y	[6,7,38,41]	0.94 (0.87, 1.02)	0.229	30.6
N	[39]	0.98 (0.73, 1.31)	NA	NA
TSH stimulation				
Thyroid hormone withdrawal	[7,35,40,41]	0.93 (0.84, 1.04)	0.350	8.6
rhTSH administered	[39]	0.98 (0.73, 1.31)	NA	NA
Both	[5,6]	0.97 (0.93, 1.01)	0.637	0.0
Definition of successful ablation				
Tg <2 ng/mL & WBS	[5-7,38,41]	0.96 (0.92, 1.00)	0.311	16.3
Tg <10 ng/mL & WBS	[35,40]	0.88 (0.77, 1.00)	0.867	0.0
Only WBS	[36,39]	0.94 (0.70, 1.26)	0.685	0.0
Sample size				
large (n≥80)	[5-7,38,40,41]	0.95 (0.91, 0.99)	0.233	26.9
Small (n<80)	[35,36,39]	0.90 (0.72, 1.13)	0.791	0.0

1 mCi = 37 MBq; TT – total thyroidectomy; NTT – near total thyroidectomy; STT – subtotal thyroidectomy; HT – hemithyroidectomy; LN – lymph node; WBS – whole-body scan; Y – yes; N – no; NA – data not applicable; rhTSH – recombinant human thyrotropin; Tg – thyroglobulin. Withdrawal withdrawn from L-T4, rhTSH administered rhTSH on 2 consecutive days before ablation.

* The result was calculated in fixed-effect model.

Discussion

Radioiodine ablation is a safe and effective method for the treatment of patients with differentiated thyroid cancer after total or near total thyroidectomy. However, the benefits

of radioiodine remnant ablation in decreasing recurrence and thyroid cancer-related mortality were inconsistent among centers. An early study on the long-term outcome of thyroid remnant ablation was conducted by Mazzaferri [45] and another study conducted at Mayo Clinic [46] showed that if papillary

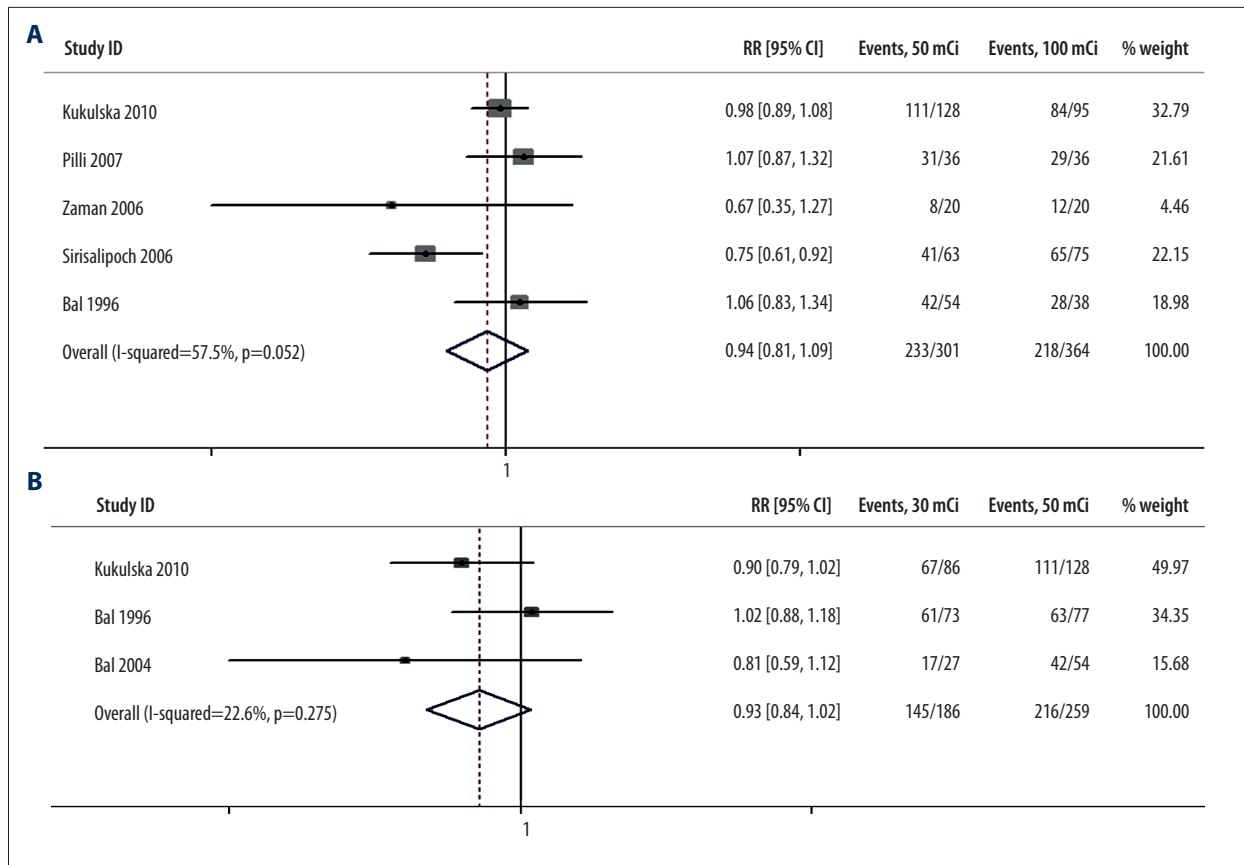


Figure 6. (A) Forest plots comparing the outcome of successful ablation rate in moderate-activity vs. high-activity groups. (B) Forest plots comparing the outcome of successful ablation rate in low-activity vs. moderate-activity groups.

thyroid carcinoma patients were managed by near-total thyroidectomy and conservative nodal excision, further increasing use of radioiodine remnant ablation had not apparently improved the already excellent outcome. A systematic review conducted by Sawka concluded that radioiodine remnant ablation may be beneficial in decreasing recurrence of well-differentiated thyroid cancer, while the incremental benefit of remnant ablation in low-risk patients who underwent near-total thyroidectomy was unclear. In conclusion, radioiodine remnant ablation is recommended in high-risk patients postoperatively by most physicians, but whether to ablate in low-risk patients remains controversial. In most guidelines, low-risk is usually defined as youth with well-differentiated thyroid cancer confined to the thyroid gland, and without evidence of lymph node or distant metastasis. However, there is still insufficient evidence to draw a firm conclusion, such as the cutpoint of certain tumour size will represent a high risk factor. Therefore, radioiodine should be used with great care to minimize harm.

There is no consensus regarding the ideal radioiodine activity to ablate the remnant thyroid in patients with low-risk thyroid cancer after total thyroidectomy. Moreover, no randomized trials have evaluated the efficiency of various levels of

radioiodine activity in long-term outcome (recurrence and thyroid cancer-related mortality). We confine the present meta-analysis to the 9 high-quality randomized trials using a low activity of approximately 30 mCi compared with a high activity of approximately 100 mCi. We found a significant difference between these 2 groups, showing that high-activity radioiodine was more effective than low-activity in terms of successful ablation rate. The advantage of high-activity in terms of successful ablation rate seems only existed in Europe studies and in patients who underwent hemithyroidectomy/subtotal thyroidectomy. However, no significant difference was found when using 30 mCi vs. 50mCi and 50 mCi vs. 100mCi.

These results will serve as important evidence when physicians are making decisions about the appropriate level of radioiodine activity for use in remnant ablation.

Previous systematic reviews have compared the use of recombinant human thyrotropin (rhTSH) and thyroid hormone withdrawal for I-131 ablation [47], so we did not compare these 2 preparations in the present review. Previous reviews showed that stimulation by rhTSH was equivalent to thyroid hormone withdrawal in achieving ablation while avoiding detrimental

symptoms of hypothyroidism and significantly lowering the whole-body radiation activity. Hypothyroidism was apparent by patient reports of fatigue, constipation, and sensitivity to cold, while rhTSH maintain a better quality of life. Interestingly, rhTSH might not be costly, because rhTSH-prepared patients lost less time from work and required fewer encounters with health care providers [47].

Previous review showed that I-131 administered for preablation imaging can cause stunning, a decrease in uptake of radioiodine subsequently given for ablation. Use of a 2-mCi or less tracer has not been shown to cause stunning, but the risk increases progressively with larger amounts [48]. The issue of stunning was first raised by Park in 1994 [49]. More convincing evidence of stunning was published by Muratet, reporting a 72% success rate in patients who received a 1-mCi tracer before ablation, but only a 50% success rate in those who received a 3-mCi tracer [50]. However, no convincing evidence shows in which group (high or low radioiodine activity) larger amounts tracer will produce a stronger effect. In the present systematic reviews, the activity of preablation scan seemed not to cause significant stunning in low- or high-activity groups, which might lead to a result that favored the opposite activity in successful ablation rate.

The definition of successful ablation varied across the studies. Some centers defined successful ablation as no uptake on whole-body and neck scan, while others used plus serum thyroglobulin level. Visualization of faint thyroid bed uptake might not increase the risk of recurrence or relate to poor prognosis [51], but serum thyroglobulin is a highly specific and sensitive tumor marker for differentiated thyroid cancer after total thyroidectomy. Thyroglobulin level and radioiodine scans are independent indicators of residual or metastatic thyroid cancer [52]. Results of the present systematic review show that the definition of successful ablation greatly influences the interpretation of the outcome. Visualization of faint uptake might be observed on the follow-up scan in the low-activity group, while leading to the result that favored high-activity in successful ablation rate. We plan to assess the success rate using the thyroglobulin level and radioiodine scans together in further studies.

Our meta-analysis has limitations that affect interpretation of the results. First, although all included studies in this meta-analysis were randomized trials, most of them did not describe the methods of random sequence generation and blinding of the participants and personnel, which make our analysis more susceptible to selection and performance biases. Second,

only the Estamibl study and the HiLo study published in 2012, with an impressive number of included patients and a superior design, can really fulfill the criteria for controlled prospective randomized trials.

There was insignificant heterogeneity observed across studies due to the inclusion criteria, so we conducted the meta-analysis using a fixed-effects model. As in any meta-analysis, the possibility of publication bias is of concern. However, the results obtained from the funnel plot analysis did not provide evidence of such a bias.

Our meta-analysis has several strengths: (1) Studies were included after a comprehensive and systematic search of the literature by using an extensive search strategy. Several studies published recently were included; (2) All included studies were randomized trials, which were the best way to compare different ablation activity; (3) We clearly defined the “low”, “moderate”, and “high” activity, defined the timing of follow-up scan simply as 6–12 months post-ablation, and stratified the analysis according to the definition of successful ablation. These 3 important methodological differences dramatically reduced the reliability and credibility of the previous reviews.

We mentioned above that whether to ablate and the appropriate activity level for remnant ablation in low-risk differentiated thyroid cancer after total thyroidectomy remains controversial. Most previous studies have paid much attention to the successful ablation rate. Future studies, especially randomized trials, should focus on the long-term outcome of various levels of radioiodine activity.

Conclusions

The present study shows that high radioiodine activity is better than low activity in terms of successful ablation rate in low-risk differentiated thyroid cancer, but the advantage of high activity seems only to exist in patients who underwent hemithyroidectomy/subtotal thyroidectomy, and did not exist for lymph node involvement, preparation before ablation, and definition of successful ablation. There was no significant difference between using low activity compared with moderate activity, or moderate activity compared with high activity.

Conflict of interest

There is no potential conflict of interest among the authors.

References:

1. Siegel R, Ward E, Brawley O, Jemal A: Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. *Cancer J Clin*, 2011; 61: 212–36
2. Sawka AM, Thephamongkhon K, Brouwers M et al: Clinical review 170: A systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. *J Clin Endocrinol Metab*, 2004; 89: 3668–76
3. Pagano L, Klain M, Pulcrano M et al: Follow-up of differentiated thyroid carcinoma. *Minerva Endocrinol*, 2004; 29: 161–74
4. Sawka AM, Thephamongkhon K, Brouwers M et al: Clinical review 170: A systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. *J Clin Endocrinol Metab*, 2004; 89: 3668–76
5. Schlumberger M, Catargi B, Borget I et al: Strategies of radioiodine ablation in patients with low-risk thyroid cancer. *N Engl J Med*, 2012; 366: 1663–73
6. Mallick U, Harmer C, Yap B et al: Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. *N Engl J Med*, 2012; 366: 1674–85
7. Caglar M, Bozkurt FM, Akca CK et al: Comparison of 800 and 3700 MBq iodine-131 for the postoperative ablation of thyroid remnant in patients with low-risk differentiated thyroid cancer. *Nucl Med Commun*, 2012; 33: 268–74
8. Sandeep TC, Strachan MW, Reynolds RM et al: Second primary cancers in thyroid cancer patients: a multinational record linkage study. *J Clin Endocrinol Metab*, 2006; 91: 1819–25
9. Rubino C, de Vathaire F, Dottorini ME et al: Second primary malignancies in thyroid cancer patients. *Br J Cancer*, 2003; 89: 1638–44
10. Watkinson JC: The British Thyroid Association guidelines for the management of thyroid cancer in adults. *Nucl Med Commun*, 2004; 25: 897–900
11. Pacini F, Schlumberger M, Harmer C et al: Post-surgical use of radioiodine (131I) in patients with papillary and follicular thyroid cancer and the issue of remnant ablation: a consensus report. *Eur J Endocrinol*, 2005; 153: 651–59
12. Cooper DS, Doherty GM, Haugen BR et al: Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. *Thyroid*, 2009; 19(11): 1167–214
13. Doi SA, Woodhouse NJ, Thalib L, Onitilo A: Ablation of the thyroid remnant and I-131 dose in differentiated thyroid cancer: A meta-analysis revisited. *Clin Med Res*, 2007; 5: 87–90
14. Hackshaw A, Harmer C, Mallick U et al: 131I activity for remnant ablation in patients with differentiated thyroid cancer: A systematic review. *J Clin Endocrinol Metab*, 2007; 92: 28–38
15. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. *Stat Med*, 2002; 21: 1539–58
16. Higgins JP, Thompson SG, Deeks JJ, Altman DG: Measuring inconsistency in meta-analyses *BMJ*, 2003; 327: 557–60
17. Hodgson DC, Brierley JD, Tsang RW, Panzarella T: Prescribing 131Iodine based on neck uptake produces effective thyroid ablation and reduced hospital stay. *Radiother Oncol*, 1998; 47: 325–30
18. Ramacciotti C, Pretorius HT, Line BR et al: Ablation of nonmalignant thyroid remnants with low doses of radioactive iodine: Concise communication *J Nucl Med*, 1982; 23: 483–89
19. Maxon HR, Englaro EE, Thomas SR et al: Radioiodine-131 therapy for well-differentiated thyroid cancer – a quantitative radiation dosimetric approach: Outcome and validation in 85 patients. *J Nucl Med*, 1992; 33: 1132–36
20. Logue JP, Tsang RW, Brierley JD, Simpson WJ: Radioiodine ablation of residual tissue in thyroid cancer: Relationship between administered activity, neck uptake and outcome. *Br J Radiol*, 1994; 67: 1127–31
21. Liu RT, Huang MJ, Huang HS et al: [Comparison of 30mCi and higher doses of iodine-131 for postoperative thyroid remnant ablation]. *Taiwan Yi Xue Hui Za Zhi*, 1987; 86: 524–28
22. Lin JD, Kao PF, Chao TC: The effects of radioactive iodine in thyroid remnant ablation and treatment of well differentiated thyroid carcinoma. *Br J Radiol*, 1998; 71: 307–13
23. Cherk MH, Kalff V, Yap KS et al: Incidence of radiation thyroiditis and thyroid remnant ablation success rates following 1110 MBq (30 mCi) and 3700 MBq (100 mCi) post-surgical 131I ablation therapy for differentiated thyroid carcinoma. *Clin Endocrinol*, 2008; 69: 957–62
24. Degroot LJ, Reilly M: Comparison of 30- and 50-mCi doses of iodine-131 for thyroid ablation. *Ann Intern Med*, 1982; 96: 51–53
25. Doi SA, Woodhouse NJ: Ablation of the thyroid remnant and 131I dose in differentiated thyroid cancer. *Clin Endocrinol*, 2000; 52: 765–73
26. Fish SA, Basu S, Alavi A, Mandel SJ: Comparison of efficacy of 2220 MBq versus 3700 MBq I-131 for ablation of thyroid remnant in patients with differentiated thyroid cancer. *Q J Nucl Med Mol Imaging*, 2010; 54: 560–63
27. Kim EY, Kim TY, Kim WG et al: Effects of different doses of radioactive iodine for remnant ablation on successful ablation and on long-term recurrences in patients with differentiated thyroid carcinoma. *Nucl Med Commun*, 2011; 32: 954–59
28. Kusacic KS, Samardzic T, Tesic V et al: Thyroid remnant ablation in patients with papillary cancer: A comparison of low, moderate, and high activities of radioiodine. *Nucl Med Commun*, 2009; 30: 263–69
29. Lin JD, Chao TC, Huang MJ et al: Use of radioactive iodine for thyroid remnant ablation in well-differentiated thyroid carcinoma to replace thyroid reoperation. *Am J Clin Oncol*, 1998; 21: 77–81
30. McCowen KD, Adler RA, Ghaed N et al: Low dose radioiodide thyroid ablation in postsurgical patients with thyroid cancer. *Am J Med*, 1976; 61: 52–58
31. Ramanna L, Waxman AD, Brachman MB et al: Evaluation of low-dose radioiodine ablation therapy in postsurgical thyroid cancer patients. *Clin Nucl Med*, 1985; 10: 791–95
32. Rosario PW, Reis JS, Barroso AL et al: Efficacy of low and high 131I doses for thyroid remnant ablation in patients with differentiated thyroid carcinoma based on post-operative cervical uptake. *Nucl Med Commun*, 2004; 25: 1077–81
33. Verkooijen RB, Stokkel MP, Smit JW, Pauwels EK: Radioiodine-131 in differentiated thyroid cancer: A retrospective analysis of an uptake-related ablation strategy. *Eur J Nucl Med Mol Imaging*, 2004; 31: 499–506
34. Bal CS, Kumar A, Pant GS: Radioiodine dose for remnant ablation in differentiated thyroid carcinoma: A randomized clinical trial in 509 patients. *J Clin Endocrinol Metab*, 2004; 89: 1666–73
35. Bal C, Padhy AK, Jana S et al: Prospective randomized clinical trial to evaluate the optimal dose of 131 I for remnant ablation in patients with differentiated thyroid carcinoma. *Cancer*, 1996; 77: 2574–80
36. Creutzig H: High or low dose radioiodine ablation of thyroid remnants? *Eur J Nucl Med*, 1987; 12: 500–2
37. Fallahi B, Beiki D, Takavar A et al: Low versus high radioiodine dose in post-operative ablation of residual thyroid tissue in patients with differentiated thyroid carcinoma: A large randomized clinical trial. *Nucl Med Commun*, 2012; 33: 275–82
38. Giovannella L, Piccardo A, Paone G et al: Thyroid lobe ablation with iodine-(1)(3)(1) in patients with differentiated thyroid carcinoma: A randomized comparison between 1.1 and 3.7 GBq activities. *Nucl Med Commun*, 2013; 34: 767–70
39. Johansen K, Woodhouse NJ, Odugbesan O: Comparison of 1073 MBq and 3700 MBq iodine-131 in postoperative ablation of residual thyroid tissue in patients with differentiated thyroid cancer. *J Nucl Med*, 1991; 32: 252–54
40. Kukulka A, Krajewska J, Gawkowska-Suwinska M et al: Radioiodine thyroid remnant ablation in patients with differentiated thyroid carcinoma (DTC): prospective comparison of long-term outcomes of treatment with 30, 60 and 100 mCi. *Thyroid Res*, 2010; 3: 9
41. Maenpaa HO, Heikkonen J, Vaalavirta L et al: Low vs. high radioiodine activity to ablate the thyroid after thyroidectomy for cancer: A randomized study. *PLoS One*, 2008; 3: e1885
42. Pilli T, Brianzoni E, Capocetti F et al: A comparison of 1850 (50 mCi) and 3700 MBq (100 mCi) 131-iodine administered doses for recombinant thyrotropin-stimulated postoperative thyroid remnant ablation in differentiated thyroid cancer. *J Clin Endocrinol Metab*, 2007; 92: 3542–46
43. Sirisalipoch S, Buachum V, Pasawang P et al: Prospective randomised trial for evaluation of efficacy of low vs. high dose I-131 for post operative remnant ablation in differentiated thyroid cancer. *Chula Med J*, 2006; 10: 695–706
44. Zaman M, Toor R, Kamal S et al: A randomized clinical trial comparing 50mCi and 100mCi of iodine-131 for ablation of differentiated thyroid cancers. *J Pak Med Assoc*, 2006; 56: 353–56

45. Mazzaferri EL: Thyroid remnant ¹³¹I ablation for papillary and follicular thyroid carcinoma. *Thyroid*, 1997; 7: 265–71
46. Hay ID, Thompson GB, Grant CS et al: Papillary thyroid carcinoma managed at the Mayo Clinic during six decades (1940–1999): Temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. *World J Surg*, 2002; 26: 879–85
47. Yoo J, Cosby R, Driedger A: Preparation with recombinant humanized thyroid-stimulating hormone before radioiodine ablation after thyroidectomy: A systematic review. *Curr Oncol*, 2009; 16: 23–31
48. Hurley JR: Management of thyroid cancer: radioiodine ablation, “stunning,” and treatment of thyroglobulin-positive, (¹³¹I) scan-negative patients. *Endocr Pract*, 2000; 6: 401–6
49. Park HM, Perkins OW, Edmondson JW et al: Influence of diagnostic radioiodines on the uptake of ablative dose of iodine-131. *Thyroid*, 1994; 4: 49–54
50. Muratet JP, Daver A, Minier JF, Larra F: Influence of scanning doses of iodine-131 on subsequent first ablative treatment outcome in patients operated on for differentiated thyroid carcinoma. *J Nucl Med*, 1998; 39: 1546–50
51. Kim K, Kim SJ, Kim IJ et al: Clinical significance of diffuse hepatic visualization and thyroid bed uptake on post-ablative iodine-131 whole body scan in differentiated thyroid cancer. *Onkologie*, 2012; 35: 82–86
52. Harish K: Thyroglobulin: current status in differentiated thyroid carcinoma (review). *Endocr Regul*, 2006; 40: 53–67