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Effects of Low-Dose and High-Dose Postoperative Radioiodine Therapy on the Clinical Outcome in Patients with Small Differentiated Thyroid Cancer Having Microscopic Extrathyroidal Extension

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Background: It is unclear whether differentiated thyroid cancer (DTC) patients classified as intermediate risk based on the presence of microscopic extrathyroidal extension (ETE) should be treated with low or high doses of radioiodine (RAI) after surgery. We evaluated success rates and long-term clinical outcomes of patients with DTC of small tumor size, microscopic ETE, and no cervical lymph node (LN) metastasis treated either with a low (1.1 GBq) or high RAI dose (5.5 GBq).
Methods: This is a retrospective analysis of a historical cohort from 2000 to 2010 in a tertiary referral hospital. A total of 176 patients with small (≤2 cm) DTC, microscopic ETE, and no cervical LN metastasis were included. Ninety-six patients were treated with 1.1 GBq (LO group) and 80 patients with 5.5 GBq (HI group). Successful RAI therapy was defined as (i) negative stimulated thyroglobulin (Tg) in the absence of Tg antibodies, and (ii) absence of remnant thyroid tissue and of abnormal cervical LNs on ultrasonography. Clinical recurrence was defined as the reappearance of disease after ablation, which was confirmed by cytologically or pathologically proven malignant tissue or of distant metastatic lesions.
Results: There was no significant difference in the rate of successful RAI therapy between the LO and HI groups ($p = 0.75$). In a subgroup analysis based on tumor size, success rates were not different between the LO group (34/35, 97%) and the HI group (50/56, 89%) in patients with a tumor size of 1–2 cm ($p = 0.24$). In patients with smaller tumor size (≤1 cm), there was no significant difference in success rates between the LO (59/61, 97%) and HI groups (22/24, 92%; $p = 0.30$). No patient had clinical recurrences in either group during the median 7.2 years of follow-up.
Conclusions: Low-dose RAI therapy is sufficient to treat DTC patients classified as intermediate risk just by the presence of microscopic ETE.

Introduction

Postoperative radioiodine (RAI) therapy has been used for patients with differentiated thyroid cancer (DTC) to remove residual normal thyroid tissue after thyroidectomy (remnant ablation), or to treat potential metastatic disease (adjuvant therapy). Successful RAI therapy enhances the usefulness of serum thyroglobulin (Tg) as a biochemical marker and may improve clinical outcomes (1). Low-risk patients are given a low dose of ^{131}I to achieve remnant ablation for the purpose of facilitating follow-up. In patients with significant risk of potential micrometastasis, a high dose of ^{131}I is routinely administered for tumoricidal effect as an adjuvant therapy, not just for remnant ablation. However, the optimal dose of RAI therapy remains controversial. A recent meta-analysis that included nine randomized controlled trials suggested that a low dose (1.1 GBq) of RAI is sufficient for successful remnant ablation when compared to a high dose (3.7 GBq) (2). Patients treated with a low dose of RAI had a similar quality of life, less common adverse effects, and a shorter hospital stay when compared with those treated with a high dose of RAI (2). In a study by Mazzaferri *et al.*, low-dose RAI is as effective as high-dose RAI in controlling tumor recurrence and improving overall survival (1).

The recent American Thyroid Association (ATA) guidelines recommended no RAI therapy for very low-risk patients

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(tumor size ≤1 cm, intrathyroidal) (3). They advocate postoperative RAI therapy for selected patients with TNM stage I disease, if they have multifocal disease, cervical lymph node (LN) metastasis, more aggressive histologies, vascular invasion, and/or extrathyroidal extension (ETE) (3). ETE is one of the important risk factors for local recurrence of DTC. It covers a wide range of tumor extent from minimal, microscopic invasion into perithyroidal fat or sternothyroid tissue to extensive invasion into adjacent organs. Previous studies suggested that microscopic ETE did not affect the clinical outcomes of DTC patients (4,5). However, it is unclear whether patients classified in the intermediate risk group based only on the presence of microscopic ETE should be treated with low- or high-dose RAI in order to have clinical benefits in terms of recurrence-free survival or cancer-specific survival.

This study aimed at evaluating the success rates and long-term clinical outcomes of patients with small tumor size of DTC, microscopic ETE, and no cervical LN metastasis undergoing postoperative RAI therapy with either a low (1.1 GBq) or a high (5.5 GBq) dose of ^{131}I.

Materials and Methods

Study population

This is a retrospective analysis of a historical cohort including patients who underwent total thyroidectomy and postoperative RAI therapy for DTC at the Asan Medical Center (Seoul, South Korea) between 2000 and 2010. Inclusion criteria were as follows: DTC, including classical papillary thyroid carcinoma (PTC), follicular variant PTC, and follicular thyroid carcinoma (FTC); patients who underwent total thyroidectomy with central neck dissection (CND) followed by immediate RAI therapy; small primary tumor size (maximal diameter ≤2 cm); and presence of microscopic ETE, pathologic N0 according to the TNM staging. Microscopic ETE was defined as presence of microscopic minimal extension of cancer to sternothyroid or perithyroidal tissues. Pathologic N0 was defined as absence of metastatic cervical LNs among four or more removed central LNs on pathological examination. Histopathological or cytopathological diagnosis and microscopic ETE was reconfirmed by one experienced pathologist (D.E.S.).

A total of 176 patients were classified into two groups according to the dose of RAI therapy. Ninety-six patients received 1.1 GBq of RAI (LO group), and 80 patients received 5.5 GBq (HI group). Our review protocol was approved by the institutional review board.

Postoperative RAI therapy and follow-up strategy

Patients received ablative doses of ^{131}I after thyroxine withdrawal five to six weeks after initial surgery. A post-ablation whole body scan (WBS) was obtained five to seven days after the administration of ^{131}I. If there were abnormal findings on the WBS image, additional single photon emission computed tomography (SPECT) was performed. Thyroxine suppression therapy was initiated just after the RAI therapy. A medical history and physical examinations, including neck palpation, were done in all patients at each visit. A diagnostic WBS, a serum stimulated thyroglobulin (sTg) level, and anti-thyroglobulin antibodies (TgAb) were usually obtained 12 months after the RAI therapy. The level of sTg was determined after thyroxine withdrawal with an elevated thyrotropin (TSH) level >30 mU/L. Neck ultrasonography (US) was done simultaneously with sTg measurement. If there were abnormal findings on neck US, US-guided fine needle aspiration cytology (FNAC) was performed. During subsequent follow-up exams, a physical examination and titration of thyroid hormone level were regularly performed every three to six months. Neck US was performed annually or biannually. Measurement of sTg and TgAb levels was carried out every one or two years on the basis of clinical suspicion. When the sTg was >2 ng/mL or if there was clinical suspicion of recurrence, one or more imaging methods, such as neck US, neck/chest CT, or F-18-fluorodeoxyglucose positron emission tomography, were performed for localization.

Successful postoperative RAI therapy was defined as (i) sTg level <1 ng/mL and negative TgAb <60 U/mL, and (ii) absence of remnant thyroid tissue and of thyroid bed nodules or cervical LNs with any suspicious finding on neck US, regardless of the results of the WBS (uptake in the thyroid bed). Clinical recurrence was defined as the reappearance of disease after ablation, which was confirmed by cytologically or pathologically proven malignant locoregional tissue or of distant metastatic lesions. Biochemical recurrence was defined as detectable basal and/or sTg, or positive TgAb, but no evidence of disease by imaging such as US.

Measurement of Tg, TgAb, and TSH

Serum Tg levels were measured by immunoradiometric assay (ELSA-hTG kit; Schering-CIS Bio-International, Gif-sur-Yvette, France) with a functional sensitivity of 1 ng/mL. We were unable to standardize serum Tg against the CRM-457 protocol, but instead developed our own Tg-reference interval according to the laboratory medicine practice guidelines suggested by the National Academy of Clinical Biochemistry (available at www.nacb.org/Impg/main.stm). Our generated Tg-reference interval was approximately 1.0–27.4 μg/L (mean 5.2 μg/L). Serum TgAb levels were determined by radioligand assay (HENNING test anti-Tg kit; BRAHMS Diagnostica, Berlin, Germany), and TgAb values >100 U/mL were considered positive. The functional sensitivity (20% interassay variation coefficient) was approximately 31 U/mL, whereas the analytical sensitivity from the optimal curve was 20 U/mL. Intraassay and interassay coefficients of variation were 3.1% and 4.5% respectively. Serum TSH was measured by radioimmunometric assay (SPAC-S TSH kit; Daiichi, Tokyo, Japan), with a reference range of 0.5–5.0 mU/L, an intraassay coefficient of variation of 2.1%, and an interassay coefficient of variation of 2.5%.

Statistical analysis

Categorical variables are presented as numbers and percentages and continuous variables are expressed as means (± standard deviations) or medians (interquartile range). Comparisons of continuous variables were done by Student's *t*-test. Comparisons between each group according to categorical variables were done using Fisher's exact test (two-sided). R (v2.13; R Foundation for Statistical Computing, Vienna, Austria; www.R-project.org) was used for statistical analysis. The association between ablation success and low/

high RAI activity was presented as an odds ratio (OR) with a confidence interval (CI) calculated by binominal logistic regression. All *p*-values were two-sided, with $p < 0.05$ considered statistically significant.

Results

Baseline clinicopathological characteristics

Baseline characteristics of study subjects are summarized in Table 1. The mean age was 50 years old, and 96% of patients were women. The majority of patients had PTC (including classic and follicular variants); one patient had FTC. The mean tumor size was 1.1 cm, and 48% of patients had a tumor size ≤1 cm. According to the TNM staging (Tumor, Lymph Node, Metastasis—a classification system of the International Union Against Cancer and the American Joint Committee on Cancer, revised in 2002), 45 patients had stage I and 131 had stage III disease. Percentages of patients with multifocality, bilaterality, and lymphovascular invasion were 36.4%, 26.1% and 9.7%, respectively. The mean number of removed cervical LNs by surgery was 10.5.

A total of 96 patients were treated with 1.1 GBq (LO group), and 80 patients were treated with 5.5 GBq ^{131}I (HI group). There was no significant difference in the age, sex, and pathological subtypes. The tumor size was larger in the HI group (1.3 ± 0.4 cm) compared with the LO group (1.0 ± 0.4 cm, $p < 0.001$). The frequency of tumor size ≤1 cm was about 64% in the LO group and 30% in the HI group. There was no significant difference in multifocality, bilaterality, lymphovascular invasion, or the number of removed cervical LNs, and Tg values at ablation between the two groups.

Successful postoperative RAI therapy according to the dose of RAI

Clinical findings after low-dose and high-dose RAI therapy according to the tumor size are shown in Table 2. RAI therapy was successful in 97% (93 out of 96) in the LO group and 90% (72 out of 80) in the HI group. There was no significant difference between the two groups ($p = 0.75$). After adjusting for tumor size, age, and sex, there was no association with successful therapy and the RAI dose (OR 0.31 [CI 0.06–1.27], $p = 0.124$).

We additionally analyzed success rates of adjuvant RAI therapy in subgroups divided according to tumor size because there was a significant difference in tumor size between the LO and HI group. In patients with relatively larger tumor size (1–2 cm), 35 patients were included in the LO group and 56 in the HI group. About 97% of patients in the LO group had negative sTg and TgAb values, and there were no abnormal findings on neck US. In the HI group, 91% of patients had negative sTg and TgAb values. In one of these patients, a suspicious LN was found on neck US, but there was no abnormal findings on US-guided FNAC. Two patients with detectable TgAbs had Hashimoto's thyroiditis in the surgical specimen. There was no significant difference in the success rates of RAI therapy between the HI group (89%) and LO group (97%) in this subgroup of patients ($p = 0.24$).

In subgroup analysis of patients with smaller tumor size (≤1 cm), 61 patients were included in the LO group and 24 in the HI group. About 97% of patients in the LO group had negative sTg and TgAb levels, and there were no abnormal pathological findings on neck US and diagnostic WBS. In the HI group, 91% of patients had negative sTg and TgAb values, and all of them had successful RAI as determined by the absence of any abnormal findings on follow-up neck US. There was no significant difference in the success rates of RAI therapy between the two groups in this subgroup analysis ($p = 0.30$).

Long-term outcomes of enrolled patients

All of the enrolled patients were followed up at the Asan Medical Center for a median of 7.2 years (range 3.3–9.4).

Table 1. Baseline Clinicopathological Characteristics of Study Subjects

Initial characteristics	*Total* (n = *176*)	*LO group* (n = *96*)	*HI group* (n = *80*)	p-*Value*
Age (years)	50.1 ± 9.0	51.3 ± 8.4	48.7 ± 9.6	0.92
Sex				0.46
Men	7 (4.0%)	5 (5.2%)	2 (2.5%)	
Women	169 (96.0%)	91 (94.8%)	78 (97.5%)	
Pathology				0.21
PTC	173 (98.3%)	95 (99.0%)	78 (97.5%)	
FV-PTC	2 (1.1%)	0 (0%)	2 (2.5%)	
FTC	1 (0.6%)	1 (1.0%)	0 (0%)	
Tumor size (cm)	1.1 ± 0.5	1.0 ± 0.4	1.3 ± 0.4	<0.001
≤1	85 (48.3%)	61 (63.5%)	24 (30.0%)	
>1–2	91 (51.7%)	35 (36.5%)	56 (70.0%)	
AJCC TNM stage (2002)				0.12
Stage I	45 (25.6%)	20 (20.8%)	25 (31.2%)	
Stage III	131 (74.4%)	76 (79.2%)	55 (68.8%)	
Multifocality	64 (36.4%)	35 (36.5%)	29 (36.2%)	0.99
Bilaterality	46 (26.1%)	24 (25.0%)	22 (27.5%)	0.73
Lymphovascular invasion	2 (9.7%)	1 (1.0%)	1 (1.3%)	0.99
No. of removed LNs	10.5 ± 7.1	10.3 ± 7.6	10.7 ± 6.7	0.80
Serum Tg level at ablation	1.0 ± 2.4	0.7 ± 1.5	1.4 ± 3.2	0.09

PTC, papillary thyroid carcinoma; FV-PTC, follicular variant PTC; FTC, follicular thyroid carcinoma; LNs, lymph nodes; Tg, thyroglobulin.

Table 2. Clinical Findings After Low-Dose and High-Dose Radioactive Iodine Therapy According to Tumor Size

	Tumor size: 1–2 cm			*Tumor size: ≤1 cm*		
	LO group (n=*35*)	*HI group* (n=*56*)	p-*Value*	*LO group* (n=*61*)	*HI group* (n=*24*)	p-*Value*
TgAb positive	0 (0%)	2 (3.6%)		2 (3.3%)	0 (0%)	
TgAb negative	35 (100%)	54 (96.4%)		59 (96.7%)	24 (100%)	
sTg <1 ng/mL	34 (97.1%)	51 (91.0%)		59 (96.7%)	22 (91.7%)	
sTg ≥1 ng/mL	1 (2.9%)	3 (5.4%)		0 (0%)	2 (8.3%)	
Neck ultrasonography						
Normal	35 (100%)	55 (98.2%)		61 (100%)	24 (100%)	
Suspicious	0 (0%)	1 (1.8%)		0 (0%)	0 (0%)	
Cytology: normal	0	1				
Diagnostic whole body scan						
No uptake	32 (91.4%)	54 (96.4%)		54 (88.5%)	24 (100%)	
Thyroid bed uptake	3 (8.6%)	2 (3.6%)		7 (11.5%)	0 (0%)	
Pathological uptake	0 (0%)	0 (0%)		0 (0%)	0 (0%)	
Successful ablation	34/35 (97%)	50/56 (89%)	0.243	59/61 (97%)	22/24 (92%)	0.304

TgAb, serum antithyroglobulin antibody; sTg, serum-stimulated thyroglobulin.

Among the 176 patients, 100 patients were followed up for more than five years. No patients received second RAI therapy in either group. None of the patients had a clinical recurrence during the follow-up. Among the patients without successful ablation (three patients in the LO group, and eight patients in the HI group), one patient in the LO group (patient 1 in Table 3) and two patients in the HI group (patients 4 and 5 in Table 3) had a biochemical recurrence. The serum TgAbs of patient 1 and patient 5 were still detectable but decreasing (216 U/mL to 90 U/mL in patient 1, and 106 U/mL to 76 U/mL in patient 5). Patient 4 had a positive but low sTg value (1.7 ng/mL) at last follow-up. Clinical information of these 11 patients without successful ablation is summarized in Table 3. Among the patients with successful ablation (93 patients in the LO group, and 72 patients in the HI group), no patient had clinical or biochemical evidence of a recurrence.

Discussion

In this study, we demonstrate that successful ablation rates and long-term clinical outcomes after postoperative RAI therapy were similar between low and high doses of RAI in DTC patients with small tumor size, microscopic ETE, and no cervical LN metastasis. The intermediate risk category of DTC includes a relatively wide variety of patients with microscopic or vascular invasion, cervical LN metastasis, and aggressive histology. In this study, we only included intermediate risk patients with microscopic ETE because we wanted to focus on the clinical meaning of microscopic ETE. The criteria for successful RAI therapy included the level of serum sTg, TgAb, and results of neck US. We did not include the result of diagnostic WBS, and no patients had pathological uptake on WBS in our study. Recent studies reported that the results of a diagnostic WBS one year after postoperative RAI therapy does not necessarily correlate with the level of sTg (6), and an undetectable level of sTg in the early postoperative period was found to be of better predictive value for complete remission than the results of WBS (7). There was no significant difference in disease-free survival between patients with and without persistent neck uptake on diagnostic WBS one year after thyroidectomy (8). The ATA guidelines also suggest that a diagnostic WBS one year after thyroidectomy is usually not necessary for low-risk patients (3).

Table 3. Long-Term Outcomes of 11 Patients Without Successful Ablation

			1 year after RAI			*Last follow-up*			
No.	*Age/sex*	*RAI dose (GBq)*	*sTg*	*TgAb*	*US*	*sTg*	*TgAb*	*Clinical recurrence*	*Biochemical recurrence*
1	50/F	1.1	<1	pos	neg	<1	pos	(–)	(+)
2	69/F	1.1	<1	pos	neg	<1	neg	(–)	(–)
3	52/F	1.1	1.8	neg	neg	<1	neg	(–)	(–)
4	28/F	5.5	1.3	neg	neg	1.7	neg	(–)	(+)
5	39/F	5.5	<1	pos	neg	<1	pos	(–)	(+)
6	42/F	5.5	<1	pos	neg	<1	neg	(–)	(–)
7	52/F	5.5	1.3	neg	neg	<1	neg	(–)	(–)
8	55/F	5.5	1.3	neg	neg	<1	neg	(–)	(–)
9	47/F	5.5	2.3	neg	neg	<1	neg	(–)	(–)
10	52/F	5.5	1.6	neg	neg	<1	neg	(–)	(–)
11	44/F	5.5	<1	neg	pos	<1	neg	(–)	(–)

Negative TgAb, TgAb <60 U/mL; US, ultrasonography.

Adjuvant RAI therapy is frequently used for patients with DTC, but the optimal dose remains controversial. Patients undergoing high-dose RAI tend to have more adverse effects such as damage to the salivary glands, impaired gonadal function, and secondary neoplasm (9). Therefore, many experts advocate the utilization of low-dose RAI in low-risk DTC patients because survival benefits of adjuvant RAI therapy is uncertain in this group. Recent studies demonstrated that low-dose RAI is sufficient for remnant ablation therapy for low-risk DTC patients (10,11). Schlumberger *et al*. compared the success rate of 1.1 GBq and 3.7 GBq in DTC patients with pT1 anyN M0 and T2 N0 M0 disease (10). A similar study also suggested that the rate of successful ablation was similar between 0.8 GBq and 3.7 GBq in patients with pT1–T2 anyN M0 disease (11). However, these two studies did not include patients with small tumors but pT3 disease based on microscopic ETE. Few studies evaluated the difference in RAI dose in DTC patients with pT3 tumors (12,13). One study reported comparable success rates in DTC patients with T3 anyN M0 disease treated with 1.85 GBq and 3.7 GBq (12). However, the results of neck US were not considered as a definition of successful therapy in that study. In a study by Mallick *et al*., 1.1 GBq of RAI had a similar effectiveness and with fewer adverse events compared to 3.7 GBq in patients with T3 N0–N1 or Nx M0 disease (13). We wondered about the role of the lymph node stage for the risk stratification in patients with pT3. The presence of LN metastasis is an important prognostic factor for DTC patients (14,15) and could be a critical factor for choosing the RAI dose. Therefore, we only included patients without cervical LN metastasis to evaluate the effect of RAI therapy in patients with microscopic ETE. The studies mentioned above were limited to evaluate the efficacy of RAI in terms of remnant ablation, not the long-term clinical outcomes. In our study, none of the patients had a clinical recurrence during a median seven years of follow up. Three patients had a biochemical recurrence without clinical recurrence, and none of these patients had a successful initial ablation. However, biochemical recurrence in these patients was clinically insignificant, either with decreasing TgAb levels or a sTg value that was <2 ng/mL. This suggests that patients with small DTCs with microscopic ETE and no cervical LN metastasis do not require treatment with high-dose RAI and that they have an excellent prognosis. A recent study conducted focusing on patient in the intermediate risk category who underwent postsurgical low- or high-dose RAI therapy found similar clinical outcomes (16).

The fundamental question is whether RAI therapy is indeed necessary for DTC patients with microscopic ETE. In a study on the comparison of the pT1/pT2 and upstaged pT3 cohort due to microscopic ETE, there was no difference in the 10-year disease-specific survival and recurrence-free survival, and administration of postoperative RAI in the pT3 cohort did not impact survival or recurrence (5). These findings support that this selected group of patients had similar outcomes to low-risk patients and that RAI therapy is not necessary.

Serum Tg levels at ablation (Table 1) were very low in both groups. Of the 176 patients, 121 patients (71 in the LO group and 50 in the HI group) had an undetectable sTg at ablation in the absence of TgAb. This raises the question of whether there is any indication and benefit of RAI in these patients. Nascimento *et al*. suggested that RAI therapy could be avoided in patients without LN metastasis and aggressive histological DTC variants if the postoperative sTg level is undetectable and the US does not show evidence of residual disease (17). Randomized studies are needed to evaluate the clinical benefit of RAI therapy in these patients.

The present study had several limitations. First, there is a possibility of selection bias, and the relative statistical power is low due to the retrospective nature of this study. Therefore, we applied strict inclusion criteria to enroll a homogenous group of patients. Second, we only enrolled patients with a tumor size <2 cm and microscopic ETE. Hence, we did not include other patients who would fall into the pT3 category such as size >2–4 cm with microscopic ETE or size >4 cm. Third, we could not compare patients with small DTC and microscopic ETE that were treated with RAI to untreated patients in order to assess whether RAI is of any benefit. Fourth, we used 5.5 GBq as a high dose of RAI therapy in our study population because patients with microscopic or gross ETE were considered to be in the high-risk group until the early 2000s at our institution. Fifth, it is not easy to make conclusions about the long-term outcomes given the relatively small sample size. Despite these limitations, this is one of the largest studies addressing the efficacy and long-term clinical outcomes of RAI therapy in patients with microscopic ETE.

In conclusion, low-dose (1.1 GBq) RAI therapy is sufficient in DTC patients with small tumor size (≤2 cm), microscopic ETE, and no cervical LN metastasis.

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Author Disclosure Statement

The authors have nothing to disclose.

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