Empiric High-Dose 131-Iodine Therapy Lacks Efficacy for Treated Papillary Thyroid Cancer Patients with Detectable Serum Thyroglobulin, but Negative Cervical Sonography and ^{18}F-Fluorodeoxyglucose Positron Emission Tomography Scan

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Context: Some patients with elevated serum thyroglobulin (Tg) but a negative diagnostic whole body scan (WBS) after initial therapy for differentiated thyroid carcinoma may benefit from empirical radioactive iodine (RAI) therapy. However, previous studies enrolled patients with negative diagnostic WBS, regardless of neck ultrasonography (USG) and/or ^{18}F-fluorodeoxyglucose positron emission tomography (FDG-PET), which have become the preferred diagnostic procedures in such patients.

Objective: The aim of this study was to evaluate the usefulness of empirical RAI therapy in patients with elevated stimulated Tg level and negative USG/FDG-PET findings after initial therapy for papillary thyroid carcinoma (PTC).

Design: This comparative study enrolled 39 patients with elevated stimulated Tg, negative diagnostic WBS, and negative USG/FDG-PET 1 yr after initial treatment. Empirical RAI therapy was performed in 14 patients (treatment group), whereas 25 patients were followed up without therapy (control group).

Results: There was no significant between-group difference in basal clinicopathological parameters. None of the 14 patients in the treatment group showed iodine uptake on posttreatment WBS. Five of 14 patients (36%) in the treatment group and eight of 25 (32%) in the control group had recurrence during the median 37 months of follow-up ($P = 0.99$). Changes in serum stimulated Tg concentrations did not differ between the two groups.

Conclusion: Empirical RAI therapy and posttreatment WBS were not useful diagnostically or therapeutically in patients with positive serum stimulated Tg if such patients had negative USG and negative FDG-PET findings after initial treatment of PTC. (***J Clin Endocrinol Metab* 95: 1169–1173, 2010)**

Empirical radioactive iodine (RAI) therapy and posttreatment whole body scan (WBS) have been considered useful diagnostic tools in patients with elevated serum thyroglobulin (Tg) and a negative diagnostic WBS after bilateral thyroidectomy and remnant ablation for differentiated thyroid carcinoma (DTC) (1–6). Diagnostic WBS is no longer routinely recommended for follow-up of low-risk patients with DTC. Rather, neck ultrasonography

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Abbreviations: DFS, Disease-free survival; DTC, differentiated thyroid carcinoma; FDG, ^{18}F-fluorodeoxyglucose; LN, lymph node; PET, positron emission tomography; PTC, papillary thyroid carcinoma; RAI, radioactive iodine; Tg, thyroglobulin; TgAb, Tg antibody; USG, ultrasonography; WBS, whole body scan.

(USG) has now become the preferred diagnostic procedure in patients with elevated serum Tg because most recurrences are in the neck area (7, 8). If neck USG is negative, chest computerized tomography or ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET) is recommended (9).

Thyroid cancer tissues that do not take up iodine tend to have high glucose metabolic rates and elevated FDG uptake on PET imaging (10), whereas tumors that take up iodine do not show avidity for FDG (11). Thus, patients with positive Tg and positive FDG-PET are not likely to benefit from empirical RAI therapy. Rather, only patients with negative FDG-PET should be candidates for trials of therapeutic RAI. Previous studies, however, have included patients with positive Tg and negative diagnostic WBS (1, 12, 13), in the absence of diagnosis with neck USG and/or FDG-PET, in RAI therapy procedures.

We therefore investigated the usefulness of empirical high-dose RAI therapy in patients with positive Tg, negative neck USG, and negative FDG-PET after initial treatment for papillary thyroid carcinoma (PTC).

Patients and Methods

Patients

Between 2000 and 2003, 803 consecutive patients with PTC were treated with bilateral thyroidectomy followed by remnant ablation, according to a protocol established by the Endocrinology Division of the Asan Medical Center (Seoul, Korea). Of these, 729 patients underwent diagnostic WBSs and tests for serum stimulated Tg (Tg1) and Tg antibody (TgAb) levels 1 yr after initial therapy. Patients were excluded if they had poorly differentiated PTC, preoperative evidence of distant metastasis, RAI uptake outside the thyroid bed on initial posttreatment WBS, positive first diagnostic WBS, or TgAb concentration of at least 100 U/ml. Neck USG and FDG-PET were performed to localize residual or recurrent disease in 74 patients with elevated Tg1 concentrations ($\geq$10 μg/liter).

After excluding patients with positive USG and FDG-PET findings, 39 patients with elevated Tg1 ($\geq$10 μg/liter), negative diagnostic WBS, and negative neck USG/FDG-PET 1 yr after initial treatment were included in the present study. Full information on potential benefits and side effects of empirical RAI therapy was given to all patients, and patients voluntarily selected the treatment. Fourteen patients were treated (treatment group), and 25 patients were not treated (control group). Written informed consent was obtained from each patient, and our local Ethics Committee approved the protocol.

Remnant ablation and follow-up with diagnostic WBS

Patients underwent ablative I-131 (5.55 GBq) treatment and posttreatment WBS 5 to 6 wk after surgery, as previously described (14). Suppressive treatment with T_4 was initiated after ablation and was titrated every 3 months. Diagnostic WBS was performed 12 months after remnant ablation (14).

Neck USG and FDG-PET

USG examination of the entire neck was performed by experienced radiologists (J.H.L. and J.H.B.), as previously described (15, 16). Lesions considered to represent recurrences or of indeterminate nature were further investigated by USG-guided fine needle aspiration biopsy. FDG-PET scans were performed as previously described (17) and were visually interpreted by an experienced nuclear physician (J.-S.R.). Any focal abnormal increase in uptake other than from a physiological or benign inflammatory cause was considered to be a positive result.

Assessment of efficacy of empirical RAI therapy

After 4 wk of T_4 withdrawal, 5.55 GBq of I-131 was administrated to patients in the treatment group who had a serum TSH level of at least 30 mU/liter. Posttreatment WBS was performed 7 d later, evaluated semiquantitatively by an experienced nuclear physician (J.-S.R.), and classified as none, faint, or increased.

Therapeutic efficacy was assessed by duration of disease-free survival (DFS) during follow-up and change in stimulated Tg concentration after 1 yr. Each patient underwent a regular physical examination every 3 months. Concentration of serum stimulated Tg (Tg2) and TgAb during T_4 withdrawal were measured 1 yr after empirical RAI in the treatment group and 1 yr after the first diagnostic WBS in the control group, as previously described (14, 18). All patients underwent neck USG every 6–12 months to localize recurrences, with additional diagnostic modalities such as FDG-PET or chest computerized tomography performed every 12 months in patients at clinical suspicion for distant metastasis, for example with persistently elevated Tg. "Recurrence" was defined as the reappearance of disease after complete ablation of thyroid remnants and was confirmed cytologically or histopathologically.

Statistics

Data are expressed as means ± SD values or medians with ranges. Associations between variables were analyzed using contingency tables and Fisher's exact test. The Mann-Whitney *U* test was employed to compare continuous variables. The Kaplan-Meier method with the log-rank test was used to compare DFS between the two groups. All *P* values were two-sided; $P < 0.05$ was considered statistically significant. All data were analyzed using SPSS version 14.0 (SPSS Inc., Chicago, IL).

Results

Baseline characteristics

As shown in Table 1, there were no significant differences in age, gender, tumor size, frequency of extrathyroidal invasion, multifocality, or cervical lymph node (LN) metastasis between the empirical RAI and the control groups. The pathology was conventional PTC in all patients.

Results of posttreatment WBS in the treatment group

Of the 14 patients in the empirical RAI group, none showed any pathological uptake in posttreatment WBS, although seven showed faint diffuse liver uptake.

TABLE 1. Baseline clinicopathological characteristics of study subjects with positive stimulated Tg and negative neck USG and FDG-PET after initial therapy for PTC

	Total	Empirical RAI group	Control group	*P* value
n	39	14	25	
Age (yr)	47 (10–69)	47 (23–63)	47 (10–69)	0.81
Gender (males/females)	7/32	1/13	6/19	0.37
Tumor size (cm)	2.5 (0.4–7)	3.2 (0.4–7)	2.5 (0.8–6)	0.58
Extrathyroidal invasion	30 (77)	9 (64)	21 (84)	0.24
Multifocal tumor	15 (39)	8 (57)	7 (28)	0.10
Lymphovascular invasion	5 (13)	1 (7)	4 (16)	0.64
Cervical LN metastasis				0.81
Level VI only	21 (54)	7 (50)	14 (56)	
Beyond level VI	12 (31)	4 (29)	8 (32)	
Distant metastasis	0	0	0	N/A
AJCC/UICC TNM staging				0.52
I/II	17 (44)	5 (36)	12 (48)	
III/IV	22 (56)	9 (64)	13 (52)	

Data are expressed as median (range) or number (percent). AJCC/UICC TNM, American Joint Committee on Cancer/International Union against Cancer Tumor-Node-Metastases classification; N/A, not available.

Disease recurrence

Median follow-up duration in the 39 patients was 37 months (3–104 months). Thirteen of the 39 (33%) patients experienced recurrence—five of 14 (36%) patients in the treatment group and eight of 25 (32%) in control group. All recurrences were in the cervical LN, which was confirmed by neck USG and guided aspiration. There was no significant difference in DFS between the two groups ($P = 0.99$) (Fig. 1A).

Changes in serum stimulated Tg concentrations

Follow-up Tg2 concentrations were available for 12 of 14 (86%) patients in the treatment group and 19 of 25 (76%) in the control group. More patients in the treatment group had a decreased serum stimulated Tg concentration (92 *vs.* 53%, $P = 0.05$; Fig. 1, B and C), but, decreases of greater than 50% were observed in only five of 12 (42%) patients in the treatment group and five of 19 (26%) in control group ($P = 0.30$).

Recurrent disease and change in serum stimulated Tg

Of the 31 patients for whom follow-up Tg2 values were available, 10 showed increases and 21 showed decreases. Of these patients, seven (70%) and five (24%), respectively, had recurrences (Fig. 1, B and C), with no significant association between increased serum stimulated Tg and recurrent disease ($P = 0.08$). Recurrence was confirmed in three patients with decreased serum stimulated Tg in the treatment group and two such patients in the control group.

Adverse effects of empirical RAI therapy

Four of 12 patients experienced mild symptoms of dry mouth, but there were no serious adverse events in the treatment group. There were no significant abnormalities in blood cell counts or liver enzyme or electrolytes levels, and no patient experienced a secondary malignancy during follow-up.

Discussion

We evaluated the usefulness of empirical RAI therapy in PTC patients with a positive serum Tg, negative diagnostic WBS, negative neck USG, and negative FDG-PET after initial total thyroidectomy and ablation therapy. Posttreatment WBS showed no abnormal uptake in the treatment group, and the between-group difference in recurrence rate was not significant. Although serum stimulated Tg concentrations decreased in most patients in the treatment group, the proportions of patients showing significant changes in stimulated Tg concentration were comparable in the two groups.

Traditionally, serum Tg and WBS have been the mainstay of follow-up in DTC patients. An undetectable Tg concentration, together with negative diagnostic WBS, suggests complete remission, whereas elevated serum Tg has been associated with recurrent disease. About 10–15% of patients have shown a combination of elevated Tg with negative diagnostic WBS, and empirical RAI therapy could localize regional recurrence or metastasis in 43–94% of patients (1–6, 12). To date, however, no prospective controlled study has evaluated the efficacy of empirical RAI therapy (19). Neck USG and FDG-PET are now the preferred diagnostic tools for patients with positive Tg, and additional surgical intervention, if feasible, is preferred for regional recurrence (9). Performance of neck USG or FDG-PET before empirical RAI in previous studies may alter the treatment strategy in many patients with

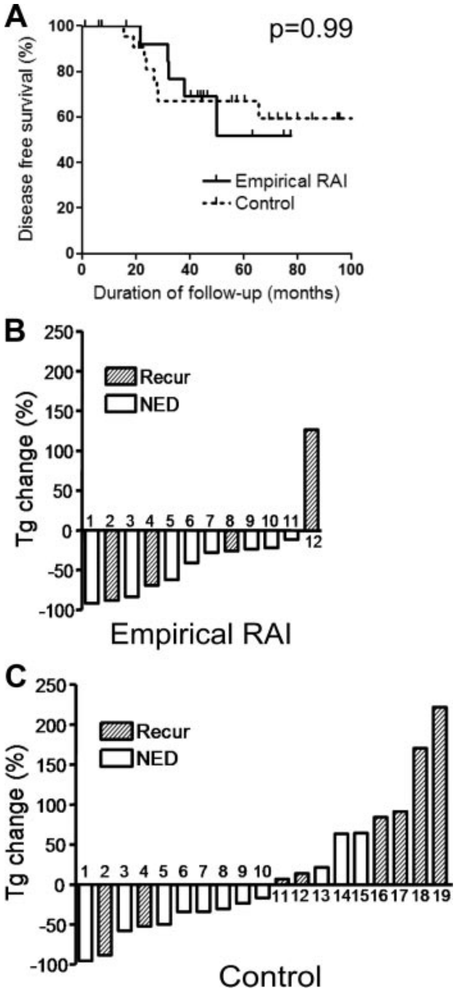

FIG. 1. DFS of the empirical RAI treatment and control groups (A), and changes in serum stimulated Tg levels of the empirical RAI treatment group (B) and the control group (C). Follow-up stimulated Tg (Tg2) levels were available for 12 of 14 (86%) patients in the empirical RAI treatment group (B) and 19 of 25 (76%) patients in the control group (C). The 95% confidence intervals of recurrence rates were 13–65% in the empirical RAI group and 15–54% in the control group. NED, No evidence of disease.

localized recurrence. In our cohort, 35 of 74 patients with elevated Tg had localized recurrence, as shown by neck USG and/or FDG-PET, and these patients were excluded from this study.

Neck USG is useful for evaluating the thyroid bed and cervical LNs because the neck is the most common and treatable site of recurrence. We found that posttreatment WBS after empirical RAI did not show any abnormal uptake, whereas follow-up neck USG localized recurrences in four of 14 patients who underwent reoperation. This finding suggested that, in patients with positive Tg and negative USG/FDG-PET, T_4 suppression and more intensive follow-up with neck USG should be the management of choice. Because of potential side effects and discomfort, empirical RAI therapy should be performed only in carefully selected patients for whom definite clinical evidence is available.

Serum stimulated Tg concentration had a highly negative predictive but a lower positive predictive value because Tg concentration may decrease slowly in some patients. Previous retrospective studies have noted that about 70% of patients with positive Tg and negative diagnostic WBS remained disease-free during 8 yr of follow-up (20). In the cited study, serum stimulated Tg concentration decreased spontaneously in 53% of patients in the control group, with 80% of these remaining disease-free. Although there was no significant association between changes in serum stimulated Tg concentration and recurrence, patients with increasing Tg tended to show more recurrences, suggesting that Tg change after 1 yr may provide prognostic information.

The present study had several limitations. Because of the small-sized and nonrandomized design, this controlled study had limited statistical power, and we cannot exclude selection bias. Larger studies, focusing on the effectiveness of empirical RAI in subsets of patients, may provide more definitive evidence. This, however, is the first comparative study to evaluate the effectiveness of empirical RAI treatment in patients with positive Tg and negative neck USG/FDG-PET. In addition, FDG-PET was performed in the absence of TSH stimulation, which may have reduced the sensitivity of disease localization. Finally, we included only patients with conventional PTC; thus, our results may not be applicable to patients with other variants of PTC or follicular carcinomas.

In conclusion, we found that empirical RAI therapy was of no benefit in patients with elevated serum stimulated Tg and negative diagnostic WBS, if such patients were also negative by USG and FDG-PET imaging after initial treatment of PTC. Empirical RAI therapy should not be routinely recommended for such patients.

Acknowledgments

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