

Is Empiric ^{131}I Therapy Justified for Patients with Positive Thyroglobulin and Negative ^{131}I Whole-Body Scanning Results?*

Chao Ma, MD¹; Jiawei Xie, BA²; and Anren Kuang, MD¹

¹Department of Nuclear Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; and

²Department of Stomatology, Linyi People's Hospital, Linyi, Shandong Province, China

The long-term monitoring of patients with differentiated thyroid carcinoma (DTC) is essential throughout the patient's life after total or nearly total thyroidectomy followed by ^{131}I remnant ablation and thyroid hormone suppression of thyroid-stimulating hormone (TSH). Sensitive surveillance for DTC recurrences and metastases includes radioiodine diagnostic whole-body scanning (DWBS) and measurement of serum thyroglobulin (Tg) levels after endogenous or exogenous TSH stimulation. Serum Tg levels during thyroid hormone withdrawal usually are correlated well with the results of DWBS. In general, Tg levels undetectable by DWBS suggest complete remission, whereas detectable or elevated Tg concentrations are suggestive of the presence of ^{131}I uptake in local or distant metastases. However, DTC patients with a positive Tg test and negative ^{131}I DWBS results (Tg⁺ DWBS⁻) have been observed in follow-up studies. The management of these cases begets controversy. **Methods:** We electronically searched Medline (1966–2004.3), Embase (1984–2003), the Cochrane Library (2004, 2nd edition), CNKI (1994–2004), and CBM-DISC (1978–2004). We also manually searched the *Chinese Journal of Isotopes*, *Radiologia pratica*, and the *Chinese Journal of Endocrinology and Metabolism*. **Results:** Ten serial observations and 3 nonrandomized controlled trials were found. The available data showed that of 314 patients who were treated empirically with ^{131}I , 194 (62%) of 314 displayed pathologic uptake in the thyroid bed, lung, bone, mediastinum, and lymph nodes. In studies with Tg-on and Tg-off data, 171 (63%) of 271 patients achieved a decrease in Tg. **Conclusion:** On the basis of data from recent studies, ^{131}I therapy should be individualized according to clinical characteristics. More significantly, a decrease in Tg levels was achieved in 63% of DTC patients with Tg⁺ DWBS⁻, suggesting that ^{131}I therapy does have a therapeutic effect when the Tg level is considered an index of tumor burden. The 62% positive posttherapy whole-body scanning results also indicated that a therapeutic dose of ^{131}I could reveal approximately one half of previously undiagnosed lesions in some patients. Therefore, ^{131}I

therapy may be justified in patients with Tg levels of $>10\text{ }\mu\text{g/L}$ and DWBS⁻ and who are at high risk of any recurrence.

Key Words: differentiated thyroid carcinoma; thyroglobulin; ^{131}I ; whole-body scan

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The predominant method for the treatment of differentiated thyroid carcinoma (DTC) is total or nearly total thyroidectomy followed by ^{131}I remnant ablation and thyroid hormone suppression of thyroid-stimulating hormone (TSH) (1,2). The prognosis of DTC generally is considered favorable, with overall survival rates of 80%–95% at 10 y for middle-aged adults (3). Local recurrences and distant metastases are seen frequently, particularly during the initial years of follow-up, but sometimes they occur many years later; overall survival rates decline to 40% when distant metastases are present (4,5). Therefore, the long-term monitoring of DTC recurrences and metastases is essential throughout the patient's life.

Generally, 2 markers of thyroglobulin (Tg) and ^{131}I whole-body scanning (WBS), when used at the same time, offer the best possibilities in the follow-up of patients with DTC (5,6). Serum Tg levels during thyroid hormone withdrawal (Tg-off) usually are correlated with the results of ^{131}I diagnostic WBS (DWBS) (7,8). Undetectable Tg levels with negative DWBS results (DWBS⁻) suggest complete remission, whereas detectable or elevated Tg concentrations are associated with the presence of ^{131}I uptake in local or distant metastases. However, discordant results of Tg measurements and ^{131}I WBS have been reported (9–18). A positive Tg test (Tg⁺) and DWBS⁻ were found in most of these cases (9–15). Deciding whether to treat such patients is the question that must be addressed. The objective of this article is to review currently available documents relevant to DTC patients with Tg⁺ DWBS⁻ metastases to establish the efficacy of ^{131}I treatment.

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For correspondence or reprints contact: Anren Kuang, MD, Department of Nuclear Medicine, West China Hospital, Sichuan University, Chengdu, Sichuan Province, 610041 China.

E-mail: machaopony@hotmail.com

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MATERIALS AND METHODS

We electronically searched Medline (1966–2004.3), Embase (1984–2003), the Cochrane Library (2004, 2nd edition), CNKI (1994–2004), and CBM-DISC (1978–2004). We also manually searched the following journals: the *Chinese Journal of Isotopes*, *Radiologia Pratica*, and the *Chinese Journal of Endocrinology and Metabolism*. As a result, a total of 14 documents searched were relevant to ^{131}I treatment for Tg^+ WBS^- metastases. Ten serial observations and 3 nonrandomized controlled trials were found. No randomized controlled trials were found. One of the 3 nonrandomized controlled trials was a historical controlled trial (10); the other 2 were concurrent controlled trials (14,19).

RESULTS

Summary of Data from Studies of Empiric High-Dose ^{131}I Treatment in Patients with Tg^+ WBS^- Metastases

A summary of data from studies of empiric high-dose ^{131}I treatment in patients with Tg^+ WBS^- metastases is listed in Table 1. Of 310 patients who were treated empirically with ^{131}I , 179 (57.74%) displayed pathologic uptake in the thyroid bed, lungs, bone, mediastinum, and lymph node. In studies in which data were available for serum Tg levels during thyroid hormone suppression therapy (Tg-on) or Tg-off, 171 of 271 patients (63%) showed decreases in Tg levels.

Management of DTC Patients with Tg^+ DWBS^-

Preference for Empiric ^{131}I Therapy. Some authors (11–15,19–23) are in favor of empiric ^{131}I therapy on the basis of improvements in various parameters of disease activity. First, the Tg level measured after ^{131}I thyroid remnant ablation is a well-known marker of tumor course. An elevated Tg level correlates well with persistent disease (10). Because the production of Tg and the incorporation of ^{131}I represent distinct differentiated functions of follicular cells, DTC metastases can be suggested by the presence of detectable serum Tg in the absence of ^{131}I uptake. Serum Tg measurement is more sensitive than DWBS for the detection of recurrences and metastases (24–27), even in patients with DWBS^- (13,14,18). A significant reduction in the Tg level can be obtained after ^{131}I therapy. In patients with Tg^+ DWBS^- , an elevation in the Tg level may be the first evidence (28–30) or the only method by which metastatic or recurrent disease is detected (6). Pacini et al. (10) compared the changes in serum Tg levels between treated and untreated patients with DTC; they noted a reduction in Tg levels and a disappearance of lung uptake with repeated therapy, and they recommended treating all patients with Tg^+ DWBS^- once with 3,700 MBq of ^{131}I and continuing therapy until posttherapy WBS (PTWBS) results become negative (PTWBS^-). Pineda et al. (13) noted that in a significant proportion of patients (50%), the therapeutic effectiveness of ^{131}I treatment is indicated by a conversion to WBS^- , a statistically significant decrease in the mean Tg level, and a reduction in the serum Tg level to 5 ng/mL or less. These studies suggested that empiric ^{131}I therapy may be useful for diffuse lung uptake, especially in young and

middle-aged patients with negative chest radiographs and DWBS^- .

Second, a therapeutic dose of ^{131}I increases the sensitivity of WBS and allows the detection of neoplastic foci not seen with a diagnostic dose of ^{131}I (10,12,22,23,29), achieving both diagnostic and therapeutic goals. On the basis of a frequent occurrence of PTWBS demonstrating neoplastic foci of ^{131}I uptake combined with a subsequent reduction in the serum Tg level, patients with Tg^+ DWBS^- after thyroidectomy and ablative treatment should receive empiric ^{131}I therapy with 3,700–11,100 MBq. Schlumberger et al. (6) first advocated empiric high-dose ^{131}I therapy for patients with Tg^+ DWBS^- . They showed the complete remission of lung metastases demonstrated by PTWBS in 20 of 23 patients with DTC when chest radiographs were normal. Koh et al. (14) found partial remission in 9 of 28 patients (32.1%) and progressive disease in 3 of 28 patients (10.7%) in the treated group. No partial remission or progressive disease was observed in 17 of 32 patients (53.1%) in the untreated group ($P < 0.001$). They concluded that the administration of a therapeutic dose of ^{131}I has a therapeutic effect, at least for palliation in the short term, when the serum Tg level is considered an index of tumor burden, and that it can reveal previously undiagnosed lesions in some DTC patients with Tg^+ DWBS^- . Mazzaferri and Kloos (15) reported on 10 patients with DWBS^- and with serum Tg levels of >15 ng/mL (TSH levels of >30 mIU/L). Eight of these patients had evidence of distant metastases on PTWBS. These investigators reported that 3 patients had subsequent PTWBS^- within 2–4 y and a reduction in serum Tg levels to 5 ng/mL.

Third, the poor prognosis of patients with metastatic DTC will be improved if it is detected and treated with ^{131}I early rather than late (31). More importantly, ^{131}I therapy is effective mostly in patients with small foci of recurrent disease. As shown by Kabasakal (32), a therapeutic effect was achieved in patients with Tg^+ WBS^- micrometastases. Among patients with micrometastases, 5 of 7 (71%) demonstrated a decrease in serum Tg levels. Among patients with macrometastases, 3 of 9 (33%) demonstrated a decrease in serum Tg levels, and 3 (33%) died as a result of metastatic thyroid cancer. Although there is no conclusive evidence that high-dose ^{131}I therapy changes patient outcome, it can reduce recurrences and improve survival in DTC by detecting micrometastases not shown by DWBS as early as possible and allowing them to be treated before they are evident on radiographic studies (6). Fatourechi and Hay (33) concluded that treatment with high doses of ^{131}I in DTC patients with Tg^+ DWBS^- allowed the detection of abnormal uptake on PTWBS, a finding particularly relevant to micrometastases (34).

Fourth, it is clear that patients with macronodular pulmonary metastases seen on chest radiographs but not detected by ^{131}I WBS have the worst prognosis, and large doses of ^{131}I have little therapeutic effect. However, it was reported that metastatic DTC with radiographic evidence but

TABLE 1
Summary of Data from Studies of Empiric High-Dose ^{131}I Treatment in Patients with Tg^+ WBS $^-$ Metastases

Reference	Histology (no. of patients)	No. of patients studied	No. of patients with Tg^+ DWBS $^-$ metastases and treated empirically	Duration of follow-up	Diagnostic dose (MBq)	Therapeutic dose (MBq)	No. (%) of PTWBS $^+$ patients	Results and outcome
22		17	17	In 12 patients, up to 2 y	185	2,775	16 (94.1)	At last follow-up, serum Tg (Tg-off?) was decreased in 7 patients and increased in 1 patient
13		17	17	6 mo–5 y	55.5–185	5,550–11,100	16 (94.1)	Decreased Tg-off in 13 of 16 patients after first empiric treatment and in 5 patients receiving third empiric dose; Tg-off never became undetectable
10	P	70	42	6.7 ± 3.8 y (mean \pm SD)	185	3,330–5,550	30 (71): C (3), N (18), L + N (9)	Undetectable or decreased Tg-off in 19 of 30 and 2 of 12 patients with PTWBS $^+$ and PTWBS $^-$, respectively; undetectable, decreased, and unchanged or increased Tg-off in 19, 6, and 3 untreated patients, respectively
15		10	10	2–4 y	166.5	3,700–7,400	8 (80)	PTWBS $^-$ and Tg-off of <5 ng/mL in 3 patients
11		22	16	1 y	No data	7,400	11 (69)	Decreased Tg-off in 9 patients with PTWBS $^+$ and in 3 patients with PTWBS $^-$; Tg-off never became undetectable
36	P (18), F (5), H (1)	24	24	6–33 mo	111	7,400	6 (25): L (1), C (1), M + C (1), thyroid bed (2), tracheostomy site (1)	Tg-on measured after ^{131}I treatment was decreased in 5 patients and increased in 18 patients; 5 patients died—4 of them had PTWBS $^-$ and 1 had partial PTWBS $^-$ (no uptake in bone metastases)
21	P (32), F (14), H (10)	56	56	4.5 ± 2.9 y (mean \pm SD)	No data	5,550	28 (50)	Complete remission was achieved ultimately in 18 of 28 patients with PTWBS $^+$ and 10 of 28 with PTWBS $^-$; no change in Tg-on measured before ^{131}I treatment and Tg-on measured after ^{131}I treatment in both groups
51	P (20), F (1)	21	11	1.5–34 mo	7.3 ± 1.8 (mean \pm SD)	119 ± 42 (mean \pm SD)	7 (63.6): N (4), M (2), L (1)	No data
52		61	11	Not given	No data	No data	8 (73)	No follow-up data in PTWBS $^+$ patients; 1 of 3 patients with PTWBS $^-$ had progressive disease within 5 mo
53		39	39	Up to 15 mo	No data	No data	22 (60)	Tg-on measured after ^{131}I treatment was decreased in PTWBS $^+$ group ($P = 0.035$) and increased in PTWBS $^-$ group ($P = 0.006$); follow-up by radiologic response showed better result ($P = 0.049$) in PTWBS $^+$ group; no data about clinical outcome
14	P	60	28	23.8 ± 19.6 mo (mean \pm SD)	148	5,550	12 (42.9): L (2), C (8), C + M (2)	Decreased Tg-off in 16 patients with PTWBS $^+$; percentage decreases in both Tg-on and Tg-off in treated group were significantly higher than those in untreated group ($P < 0.001$)
32	P (18), F (3), H (4), tall cell (2)	27	27	6.3 ± 5.8 y (mean \pm SD)	185	5,550–11,100	19 of 24 (79)	Serum Tg levels were decreased in 8 of 16 patients (50%); among patients with micrometastases, 5 of 7 (71%) demonstrated decreased serum Tg levels; among patients with macrometastases, 3 of 9 (33%) demonstrated decreased Tg levels, and 3 (33%) died as a result of metastatic thyroid cancer
19	P (15), F (11)	26	16	3.7 ± 1.2 y (mean \pm SD)	185	3,330–5,550	11 (68.75): C (4), L (6), B (1)	Decreased Tg-off in 14 patients in treated group; increased or unchanged Tg-off in 9 patients in untreated group; Tg-off measured after ^{131}I treatment was significantly lower than Tg-off measured before ^{131}I treatment in both groups ($P < 0.05$)
Total no. (%)			337				194 of 314 (62) 171 of 271 (63)	

P = papillary thyroid carcinoma; F = follicular thyroid carcinoma; H = HCC; C = cervical uptake; N = lymph node uptake; L = lung uptake; M = mediastinum uptake; B = bone uptake.

DWBS⁻ was successfully treated with high doses of ¹³¹I after the administration of recombinant human TSH (35). Controlled clinical studies are warranted to evaluate the safety and efficacy of recombinant human TSH in the ¹³¹I therapy of metastatic DTC.

Objection to Empiric ¹³¹I Therapy. Various authors (36–41) have discouraged routine ¹³¹I therapy in DTC patients with Tg⁺ DWBS⁻ on the basis of the following observations.

First, the therapeutic efficacy of ¹³¹I depends on the capacity of a tumor to trap and retain iodide (15). One half to two thirds of metastases trap ¹³¹I, but even after meticulous preparation and administration of large amounts of ¹³¹I, some metastases may not concentrate or retain enough ¹³¹I to achieve a therapeutic benefit (39,40). This situation is more common after age 40 and with Hürthle cell cancer (HCC) (40).

Second, there is little evidence, if any, that either partial reductions in serum Tg levels or elimination of radioiodine uptake, visible only on PTWBS, is associated with improved patient outcome (42). Only a few patients were reported to have achieved a reduction in Tg levels and an elimination of ¹³¹I uptake visible on PTWBS in extracervical sites. Long survival was observed in some patients because of the slow growth of DTC metastases, even for those not treated with ¹³¹I (43). ¹³¹I therapy in DTC patients without obvious recurrent or metastatic disease may not necessarily enhance overall survival. Moreover, when micrometastases are manifested only by elevations in serum Tg levels and when one is considering treating them with radioiodine, ¹³¹I may not be an optimal isotope. With small lesions (<0.05 mm in diameter), ¹²⁵I therapy, with lower energy emissions, may be more suitable (44).

Third, large Tg⁺ DWBS⁻ DTC metastases are unlikely to trap ¹³¹I even with higher doses of ¹³¹I. It was reported that aggressive DWBS⁻ macrometastases did not show significant uptake after therapeutic doses of ¹³¹I (34,36,45). Fatourehchi et al. (36) observed that only a few Tg⁺ DWBS⁻ follicular DTC patients showed meaningful uptake after high doses of ¹³¹I. Therefore, widespread use of empiric ¹³¹I therapy for patients with a large tumor burden should not be encouraged (25).

It is recommended that any recurrent lesion in the neck or mediastinum or isolated intraabdominal, intracranial, or bone metastasis should be considered for possible surgical excision (23). At present, the standard therapy for nonresectable scan-negative neck, bone, and occasionally cerebral lesions is external radiation therapy. The efficacy of chemotherapy with dacarbazine in combination with 5-fluorouracil, streptozocin, cyclophosphamide, or vincristine to date is not encouraging (33).

Fourth, risks for DTC-related morbidity or mortality have not been well described, particularly for patients without evidence of tumor mass by other imaging modalities (46). In addition, high-dose ¹³¹I therapy is not without risk. An increased prevalence of cancers of the bladder, salivary

gland, colon (47), and female breast has been reported. Oligospermia and transient ovarian failure also occur, but subsequent infertility is rare, except after very high doses (48,49). It is likely that high-dose ¹³¹I for the treatment of women with DTC has resulted in earlier menopause (50). Additionally, over time, a spontaneous reduction in serum Tg levels in untreated patients has been reported; this result may implicate less severe diseases as the source of serum Tg (residual thyroid tissue rather than metastases) and long-term effects of thyroid hormone suppression therapy on the possible atrophy and death of Tg-producing tissue (47). High doses of ¹³¹I have obvious therapeutic effects in patients with DTC metastases, but in view of the frequent normalization of Tg levels in untreated patients, ¹³¹I therapy does not seem to be well grounded.

Fifth, the cost of empiric ¹³¹I therapy with regard to the morbidity of hypothyroidism and its negative impact on productivity as well as the cost in health care dollars related to hospitalization and associated expensive technological procedures should not be ignored. ¹³¹I therapy may induce anaplastic changes associated with the p53 mutation and lead to the progression of DTC disease (36).

DISCUSSION

Until now, no randomized controlled trials or controlled prospective studies were evaluated. There has been no double-blind allocation of groups. Most of the studies have been self-control trials without a control group (9,11,13,15–18,21,22,36,51). Therefore, the reliability of results from these studies is limited. One of the 3 nonrandomized controlled trials was a historical controlled trial. The other 2 were concurrent controlled trials. There still exist many problems in currently available documents. Koh et al. (14) and Tian et al. (19) administered therapeutic doses of ¹³¹I according to patients' preferences. The sample sizes were not large, and the follow-up periods were not long enough (9,11,13,15–18,21,22,36,51) or were not reported (52). As shown in Table 1, the numbers of patients treated empirically with ¹³¹I varied from 17 to 42, and there was no mention of the calculation of sample size. The diagnostic and therapeutic doses of ¹³¹I were different among the clinical centers or were not reported in some studies (11,21,53). No study mentioned that ¹³¹I therapy was evaluated empirically. Baselines were mentioned but were not very similar among the trials. Tian et al. (19) did not compare the baselines of tumor burden and tumor differentiation status. In 1 study (11), the mean baseline serum Tg levels and follow-up periods were significantly different between treated and untreated groups. Pacini et al. (10) failed to compare the changes in Tg levels between treated and untreated subjects when serum Tg levels spontaneously dropped in untreated subjects. Koh et al. (14) did not compare long-term changes in serum Tg levels between the 2 groups because neck dissection surgery was performed for 14 patients (50%) treated with ¹³¹I.

Subjects with different differentiation of DTC and tumor staging in these studies were also observed. Most of the subjects in the study by Fatourehchi et al. (36) had aggressive high-risk cancer with a large tumor load. Twenty patients had clinical and radiologic evidence for persistent or metastatic disease. It is no surprise then that patients in that study achieved little benefit from ^{131}I treatment. As shown by Kabasakal (32), there were differences in outcome in patients with Tg^+ WBS^- macrometastases and patients with Tg^+ WBS^- micrometastases; the results seemed to be beneficial for patients with Tg^+ WBS^- micrometastases. Papillary cell cancer, follicular cell cancer, and HCC of the thyroid gland are commonly collectively referred to as DTC. Some studies included only papillary carcinoma, others included both papillary carcinoma and follicular carcinoma, and still others included HCC (21,36). HCC, a rare neoplasm, comprises 2%–10% of all DTCs. It is of follicular cell origin and is classified as a variant of follicular carcinoma of the thyroid. However, HCC is a relatively aggressive tumor with a prognosis worse than that of papillary carcinoma of the thyroid (54–56). In addition, HCCs usually produce Tg but typically do not take up ^{131}I . Therefore, ^{131}I treatment seems to be unsuitable for patients with HCC (57), and ^{131}I therapy may be of little benefit for HCC patients with Tg^+ WBS^- .

It is well known that thyroid hormone suppression therapy, unlike ^{131}I therapy, is mandatory for patients with Tg^+ DWBS^- . However, few studies mentioned it, and no studies statistically adjusted for the cointervention.

For the time being, there is no consensus as to the precise level of serum Tg that should be used to trigger treatment when a tumor cannot be identified by DWBS. Multiple studies have endeavored to define a cutoff value suggesting recurrence or metastasis. Some studies have regarded detectable serum Tg levels as positive (11,12). Pineda et al. (13) used a Tg level of 8 ng/mL in patients who were not receiving thyroid hormone treatment and who had undergone thyroid ablation. Pachucki and Burmeister (51) defined both Tg-on and Tg-off of >4.5 pmol/L as representing persistent thyroglobulinemia. There were insufficient data on DTC patients to assess their Tg response to ^{131}I or to evaluate the population as a whole because Tg-on and Tg-off were not determined in some patients (51). Schlumberger et al. (6) reported that if serum Tg-on was above 10 ng/mL and if serum Tg-off was above 40 ng/mL, 80% of patients would have detectable foci of ^{131}I uptake in the neck or at distant sites after the administration of therapeutic doses of ^{131}I . Colacchio et al. (58) reported that when a cutoff value of 15 $\mu\text{g/L}$ was used, both the Tg level and scanning were necessary for minimizing the number of patients with undiagnosed metastases. Conversely, Ozata et al. (7) found no Tg level that identified all patients as being free of disease, and detectable disease occurred at levels as low as 3 $\mu\text{g/L}$. Koh et al. (14) limited elevated Tg levels to a Tg-off of >10 $\mu\text{g/L}$ or a Tg-on of >2.0 $\mu\text{g/L}$ to select patients who were likely to have recurrent or metastatic

tumor cells. Recently, Toubeau et al. (59) reported that Tg levels in DTC patients after ^{131}I thyroid remnant ablation had a significant predictive value among many prognostic factors. Patients with Tg levels of >10 $\mu\text{g/L}$ after ^{131}I thyroid remnant ablation had a significantly increased risk of disease progression (odds ratio, 22.6; 95% confidence interval, 8.2–62.5; $P < 0.001$).

It is accepted by many investigators that a cutoff value of 10 $\mu\text{g/L}$ has a high predictive value for recurrence (4,6,7). Despite their efforts, the determination of a Tg level concordant with recurrence or metastasis and the degree of elevation of the Tg level that is associated with increased mortality if left untreated remain ambiguous (23). The lower the Tg cutoff value chosen, the higher the sensitivity and the lower the specificity of the test results. In addition, it has been questioned whether DTC with a lower Tg level is of clinical importance (60). Simultaneously, the biologic behavior of the tumor and the presence or absence of specific negative prognostic factors that have an impact on the pretest probability that a patient will have persistent, recurrent, or metastatic disease (7) should be taken into consideration, regardless of the Tg level used. Despite these arguments, the Tg cutoff value for empiric ^{131}I therapy, albeit arbitrary, is about 10 ng/mL without thyroxine therapy in many centers, including our institutions (12,14,19,23,34,50).

To justify ^{131}I therapy, the serum Tg level alone is not an optimal criterion for therapeutic effectiveness. The criteria should include long-term survival rate, change in mass size with imaging studies, and radiation-induced side effects of ^{131}I therapy. Most studies have compared only changes in Tg levels as an index of therapeutic effectiveness. In addition, the cutoff values for Tg were chosen in different ways in many studies on the effects of ^{131}I therapy. Do the decrease in Tg and undetectable Tg have the same clinical benefits for DTC patients with Tg^+ DWBS^- after ^{131}I therapy? If not, then Tg levels should be stratified according to individual Tg levels, such as undetectable or detectable Tg levels, which can be stratified according to the percent decrease in Tg levels.

To date, there is no strong evidence for or against the administration of high doses of ^{131}I in DTC patients with Tg^+ WBS^- . Randomized or prospective controlled trials of high quality are needed urgently to define the efficacy and acceptability of ^{131}I therapy for Tg^+ WBS^- metastases. However, randomized controlled trials are considered nearly impossible because of the anticipated formidable sample sizes required for a disease with an overall excellent prognosis, such as DTC. In the clinical setting, it is necessary to perform noninvasive techniques to localize recurrent or metastatic lesions in DTC patients with Tg^+ DWBS^- to enable the recommendation of surgery or external radiotherapy of the lesions when appropriate. Noniodine imaging agents, such as ^{201}Tl -chloride, $^{99\text{m}}\text{Tc}$ -sestamibi, $^{99\text{m}}\text{Tc}$ -tetrofosmin, ^{111}In -octreotide, ^{18}F -FDG, and ^{123}I , are primarily useful in the setting of Tg^+ DWBS^- (61–64). The major

advantage of noniodine isotopes is that without the withdrawal of levothyroxine therapy, patients can avoid the symptoms of long-lasting hypothyroidism. In addition, some of the agents used, such as ^{99m}Tc and ^{201}Tl , have physical imaging characteristics superior to those of ^{131}I .

On the basis of an evaluation of patients who were treated with therapeutic doses of ^{131}I but who had PTWBS⁻ and who showed no improvement in serum Tg levels, empiric ^{131}I therapy of pulmonary metastases found only on post-therapy scans usually reduces the tumor burden, but complete eradication of metastases nonetheless may be difficult to achieve (12). ^{131}I therapy should be individualized according to clinical characteristics. Considering the 63% decrease in Tg levels and the 62% positive PTWBS results (PTWBS⁺) for 310 patients with Tg⁺ WBS⁻ and who were treated with high doses of ^{131}I , ^{131}I therapy may be justified in patients with Tg levels of $>10\text{ }\mu\text{g/L}$ and DWBS⁻ and who are at high risk of any recurrence. Certain risk factors should be kept in mind in the decision-making process. Risk factors include extreme age (<15 or >45 y), histologic subtype (tall cell, columnar cell, or diffuse sclerosing papillary variants; widely invasive or poorly differentiated subtypes; and HCC), and extent of tumor (large tumor mass, extension beyond the thyroid capsule, and lymph node metastases) (15).

CONCLUSION

Because of the low incidence, prolonged clinical course, and anticipated formidable sample sizes required for DTC, which has an overall excellent prognosis, a randomized trial or a prospective trial on this issue will be difficult to design and conduct.

Therefore, clinicians need to rely on knowledge gained by retrospective analyses of the experience of tertiary referral centers dedicated to the management of DTC. Currently available data revealed that a decrease in Tg levels was achieved in 63% of DTC patients with Tg⁺ DWBS⁻, suggesting that ^{131}I therapy does have a therapeutic effect when the Tg level is considered an index of tumor burden. The 62% PTWBS⁺ also indicated that a therapeutic dose of ^{131}I could reveal approximately one half of previously undiagnosed lesions in some patients. Therefore, ^{131}I therapy may be justified in patients with Tg levels of $>10\text{ }\mu\text{g/L}$ and DWBS⁻ and who are at high risk of any recurrence.

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