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Lack of Impact of Radioiodine Therapy in Tg-Positive, Diagnostic Whole-Body Scan-Negative Patients with Follicular Cell-Derived Thyroid Cancer

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Several reports have suggested a benefit from radioactive iodine (RAI) therapy in Tg-positive, whole-body scan-negative patients with follicular cell-derived thyroid cancer, who were said to have high rates of visualization of uptake in metastases after therapeutic doses of RAI. We sought to evaluate the rate of visualization of RAI uptake in these patients and determine the effect of such therapy on tumor progression and Tg levels. We studied 24 consecutive patients who had been treated with high-dose RAI, four of whom had no evidence of metastasis or persistent cancer. Our results showed that four patients had some uptake in posttherapy scans: in the neck, lung, and mediastinal metastases in one patient, in the thyroid remnant in two, and in a possible neck microrecurrence in one. In 13 patients with macrometastases—tumors 1 cm or greater—tumors progressed and serum Tg increased; five have died of thyroid cancer. The disease remained stable in the seven patients with micrometastases. We concluded that in high-risk patients with follicular cell-derived thyroid cancer with high Tg levels and negative diagnostic whole-body scans, only a small number showed meaningful uptake after high doses of RAI. Therefore, widespread use of empiric RAI therapy for such patients who have a large tumor burden should not be encouraged. (*J Clin Endocrinol Metab* 87: 1521–1526, 2002)

THYROGLOBULIN IS produced only by thyroid follicular cells and is not detectable in the serum of athyrotic persons. Both normal thyroid cells and most follicular cell-derived thyroid cancer (FCDTC) cells typically produce Tg (1). Thus, serum Tg represents a sensitive method for detection of FCDTC metastases, particularly after thyroid ablation (2–4). Radioiodine (RAI) diagnostic scans performed after withdrawal of thyroxine treatment are performed periodically to detect possible metastases in FCDTC patients who have had RAI ablation of their thyroid remnants (5, 6). The result of total-body RAI scanning depends on the ability of FCDTC cells to take up radioiodine when the serum TSH level is high (6). This can be achieved by either withdrawal of thyroxine (6) or administration of recombinant human TSH (rhTSH) (7, 8). If a diagnostic whole-body scan (WBS) is negative and TSH-stimulated or nonstimulated Tg is elevated, causes of false-negative scans, such as inadequate TSH elevation and iodine contamination, must be excluded (9). A true Tg-positive, diagnostic scan-negative FCDTC may result from disturbance of the iodine-concentrating mechanism (10). There is a possibility that micrometastases too small to be visualized by diagnostic doses of ^{131}I can be seen with higher therapeutic doses (11–13).

Three reports (14–16) suggested a benefit from empiric RAI therapy for scan-negative, Tg-positive FCDTC patients. On the basis of these studies, ^{131}I therapy of Tg-positive, scan-negative FCDTC patients has been recommended (15–17). This practice is controversial (18–21). To evaluate the rate of abnormal RAI uptake in posttherapy scans in patients with negative diagnostic WBS and high-serum Tg levels, we studied all such patients treated with RAI at the Mayo Clinic from September 1997 through July 2000. We also evaluated the impact of RAI therapy on tumor progression and posttherapy serum Tg levels.

Abbreviations: CT, Computed tomography; FCDTC, follicular cell-derived thyroid cancer; RAI, radioiodine; rhTSH, recombinant human TSH; WBS, whole-body scan.

Subjects and Methods

During the 35-month period September 1997 through July 2000, we studied all patients with FCDTC who had elevated serum Tg levels and a negative ^{131}I diagnostic WBS and were treated with RAI. The study was done with the approval of the Institutional Review Board. Patients without research authorization were not included. Patient records were reviewed for demographic data, surgical and pathologic findings, status of the FCDTC at the time of the initial surgery, extent of metastasis at the time of radioisotope scanning, subsequent operations, clinical findings, ultrasound and computed tomography (CT) results, and serum Tg and TSH levels. All patients had previously undergone definitive bilateral thyroid resection and RAI ablation therapy. In addition, four patients had more than one RAI therapy before the study WBS. In four patients, two posttherapy scans were available. Previous negative diagnostic WBS despite elevated serum Tg had been documented in 12 patients. The interval between the previous ablative or therapeutic RAI and the study WBS was more than 6 months in all patients. Treatment with T_4 had been stopped for 6 wk, and the patients were scanned 2 wk after having discontinued a 4-wk course of liothyronine.

At the time of the diagnostic WBS, the mean serum TSH level was 81.7 mIU/liter, median 77.2, and all patients had a serum TSH level above 30 mIU/liter. Serum TSH was above 50 mIU/liter in 21 patients. Patients were carefully questioned about exposure to exogenous iodine before scanning, and questionable patients with recent iodine exposure were not scanned. All patients were advised to avoid pharmacologic iodine during the period of preparation for diagnostic scan, but no detailed low-iodine diet was prescribed. In one patient, to exclude iodine absorption from a local disinfectant, serum iodine was measured and was normal. In diagnostic scans, normal uptake in salivary glands and the

gastrointestinal tract was in favor of lack of excess iodine intake. Thus, we are confident that iodine contamination was not the cause of negative diagnostic WBSs. Pretreatment scans were performed 48 h after the oral administration of ^{131}I. The patients had a diagnostic WBS with ^{131}I, with a median tracer dose of 3.0 mCi. The diagnostic WBS showed no evidence of thyroid tissue. The median therapeutic ^{131}I dose was 200 mCi, but doses ranged from 199 to 300 mCi, with a mean of 207.2. A whole-body Siemens body scan γ camera with high-energy collimator and energy setting of 364 keV and a 15% window was used. The posttherapy scans were most often done just before the patient was discharged after ^{131}I therapy (when the measured dose rate was <7 millirem/hr at 1 meter) or within 5 d of treatment, as dictated by the patient's travel arrangements. The patients changed clothing just before the scanning to avoid artifacts of contamination. A ^{131}I standard (20 μCi ^{131}I for diagnostic WBS and 100 μCi for posttherapy scanning) was placed in the neck phantom and positioned in the field of view and imaged with the patient. All images were acquired over 20 min (10 cm/min scan speed) in a 1024 × 256-word mode matrix. The diagnostic WBS and the posttherapy scan were reviewed by nuclear medicine specialists. Anatomic areas of definite or possible abnormal ^{131}I uptake in the posttherapy scans were identified. Serum Tg was measured in a chemiluminescent immunometric assay developed by Quest Diagnostics, Inc. (Nichols Institute, San Juan Capistrano, CA). Serum TSH was measured with a third-generation double antibody assay.

Twenty-four patients qualified for the study. The median serum Tg level during T_4 therapy was 51.1 ng/ml (range, 2.1–3185). Five patients had follicular, 18 papillary, and 1 Hürthle cell cancer. We included the Hürthle cell patient because of a very high level of TSH-stimulated Tg (4500 ng/ml, with a serum TSH of 104 mIU/liter). The mean age for papillary and follicular cancer patients was 54 and 68 yr, respectively. The female-to-male ratio for all patients was 1.5. At initial operation, 11 patients had incomplete excision, 20 had neck node metastases, 14 had local extension, and 4 had distant metastases. Tests for Tg antibodies were negative in all patients. This is not surprising because positive anti-Tg antibodies, because of interference with the assay, result in falsely low or undetectable values, and by definition these patients might have been excluded from the study. Micrometastasis was defined as negative chest x-ray and radiologic or ultrasonographic evidence of tumors less than 1 cm in diameter either on CT of the chest or on neck ultrasound (n = 7). Patients with tumors larger than 1 cm were arbitrarily defined as having macrometastasis (n = 13). After withdrawal of T_4 therapy, the median Tg was 491.5 ng/ml (range 22.0–12,400). Posttherapy scans were available for all and follow-up Tg studies (6–33 months) for 21 patients. One patient was lost to follow-up, and two patients did not have studies because they died of thyroid cancer after 12 and 15 months.

Statistical methods

Tg levels before and after ^{131}I therapy were compared by using the sign test for all patients, those with known metastases, those with macrometastases, and those with micrometastases. Only patients who had both pretherapy and posttherapy Tg levels on T_4 suppression were entered into computation of the effect of RAI therapy on serum Tg. When more than one posttherapy Tg was available, the lowest value was used. The baseline levels of Tg for patients with macrometastases *vs.* patients with micrometastases were compared with the Wilcoxon rank sum test. All comparisons of Tg levels were made with the patients receiving T_4 therapy ("on T_4") and after withdrawal of T_4 (when applicable), and all statistical tests were performed at an α rate of 0.05.

Results

Pretherapy Tg status

At the time of WBS, four patients had no anatomic or radiologic evidence of persistent disease. In these patients serum Tg on T_4 therapy ranged from 2.1 to 37 ng/ml (mean 15.8; median 7.8); after T_4 withdrawal, the range was 22 to 77 ng/ml (mean 43; median 36). Clinical or radiologic evidence of persistent thyroid cancer was present in 20 patients. In this group, serum Tg with the patient on T_4 ranged from 3.7 to 3,185 ng/ml (mean 326; median 47). After T_4 withdrawal, Tg ranged from 64 to 12,400 ng/ml (mean 1,960; median 586). Metastases at the time of therapy were located in the neck in 15 patients, lung in 16, bone in 6, mediastinum in 2, brain in 2, liver in 2, kidney in 1, and skin in 1. Chest x-ray was positive in 10 patients and chest CT in 16. With imaging studies, seven patients were considered to have micrometastasis, and 13 were considered to have macrometastasis (Table 1). For the micrometastasis group, serum Tg on T_4 ranged from 3.7 to 69.1 ng/ml (mean 46.7; median 23), and after withdrawal of T_4, it ranged from 89 to 2,810 ng/ml (mean 917; median 466). For the macrometastasis group, serum Tg on T_4 ranged from 8 to 3,185 ng/ml (mean 490; median 62.1), and after withdrawal of T_4, it ranged from 33.4 to 12,400 ng/ml (mean 2,518; median 946). Serum Tg levels, however, were higher in the macrometastasis group than in the micrometastasis group, although the difference did not achieve statistical significance ($P = 0.14$ on T_4 and $P = 0.43$ after withdrawal of T_4).

Posttherapy WBS (Table 2)

No abnormal radioiodine uptake was noted in 18 patients. In only one patient, who had lung, neck, mediastinal, and bone macrometastases, faint uptake was noted in the neck, lung, and mediastinum, but the bone metastases did not show uptake. In a patient who had a 0.5-cm micrometastasis on magnetic resonance imaging of the neck, uptake was noted in the same area. In two patients, only faint uptake in a thyroid remnant was noted. One of these two had lung and rib metastases without RAI uptake; the other had lung and brain metastases with no uptake. In one patient who had neck disease, no uptake in the neck metastases was noted, but faint lung uptake was described despite negative CT of the chest. One patient with a large mass in the larynx had very

TABLE 1. Clinical and radiological evidence of persistent or metastatic disease in 24 patients with FCDTC[a]

Neck metastases	15
Lung metastases	16
Bone metastases	6
Brain metastases	2
Other metastases (kidney, liver, skin)	3
Positive neck ultrasound	15
Positive chest x-ray	10
Positive chest CT	16
No known metastases	4
Micrometastases	7
Macrometastases	13

[a] All had elevated serum Tg levels and negative diagnostic whole-body ^{131}I scans at the time of radioiodine therapy.

TABLE 2. Results of postradioiodine therapy scans in 24 patients with FCDTC who had elevated Tg levels and negative diagnostic whole-body ^{131}I scans

Areas of ^{131}I uptake	No. of patients
No abnormal uptake	18
Thyroid remnant	2
Lung, neck, and mediastinum	1
Possible neck micrometastases	1
Uptake at tracheostomy site	1
Faint lung uptake (negative chest CT)	1

faint uptake around a tracheostomy site, which likely was related to the tracheostomy site rather than to the tumor. No RAI accumulated in the lung metastases in these three patients. In summary, only one patient showed uptake in macrometastases and another had uptake in a possible site of neck micrometastasis. None of the four patients without anatomic evidence of malignancy had positive posttherapy scans.

Outcome after RAI therapy

Follow-up diagnostic WBS. After 6–12 months, six patients were withdrawn from T_4 therapy for diagnostic WBS, and one other had an rhTSH-stimulated diagnostic WBS. All the follow-up scans were negative, and no subsequent RAI therapy was given. Five of these patients had a significant increase, and one had a mild reduction of serum Tg, compared with the baseline TSH-stimulated study. In one, measurement of Tg was not available. Although there was a trend toward increasing Tg (Table 3), this was not statistically significant ($P = 0.99$).

Follow-up serum Tg under T_4 suppression

There was a statistically significant increase in post-RAI follow-up Tg under T_4-suppressive therapy, compared with baseline values under T_4 therapy, $P = 0.03$ (Table 3 and Fig. 1). Subgroup analysis also showed increasing serum Tg in follow-up evaluation in the macrometastatic and micrometastatic groups (Table 4).

Outcome of subgroup without radiologic and clinical evidence of persistent disease

In the group (n = 4) with no anatomic evidence of disease at the time of therapy, two patients had recurrent disease in the neck and underwent excision. In one patient, follow-up Tg was not available. In the other patient, who had resection of a neck recurrence, after 1 yr, rhTSH-stimulated Tg was 20 ng/ml, compared with a pre-RAI therapy value of 29.9. WBS was again negative in this patient, and she did not receive RAI therapy. In the other two patients, Tg was reduced from 2.1 to 0.7 ng/ml in one and from 7.8 to 5.5 in the other. There was no imaging or clinical evidence of persistent disease in these two patients. All four patients were free of disease as defined by imaging studies at last follow-up.

TABLE 3. Post-RAI therapy Tg levels under T_4-suppressive therapy compared with pretherapy levels

Status	Tg on T_4 ($n = 18$), mean/median, ng/ml[a]	Tg off T_4 ($n = 6$), mean/median, ng/ml[b]
Before RAI therapy	162/35.5	2721/1035
Follow-up after RAI therapy	696/104	4250/1067

[a] Baseline and follow-up Tg levels with T_4 suppression in 18 patients with FCDTC who had negative diagnostic ^{131}I scans, for whom Tg values on T_4 suppression before and after RAI therapy were available. The difference is statistically significant, $P = 0.03$.

[b] Baseline and TSH-stimulated Tg levels in six patients who had follow-up diagnostic whole-body scans. There is a trend of increasing Tg levels that is not statistically significant, $P = 0.99$.

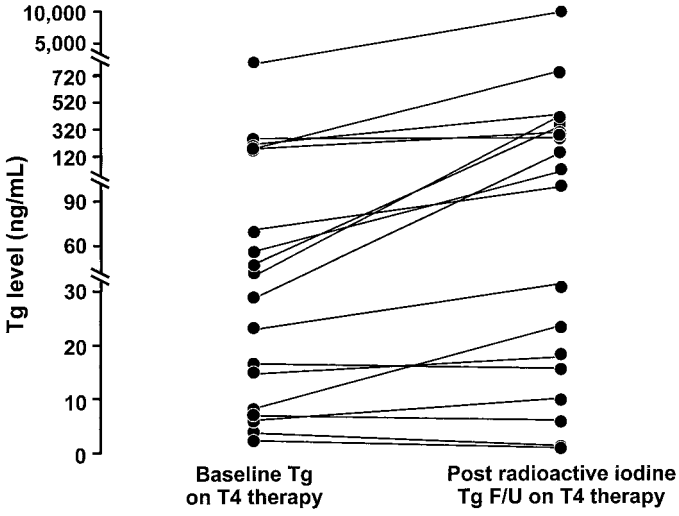

FIG. 1. Individual changes in serum Tg during T_4 therapy (mean and median serum TSH level 0.05 mIU/liter) before empiric radioiodine therapy and at follow-up (F/U) after radioiodine therapy in 18 patients with follicular cell-derived thyroid cancer. The minimum interval between baseline and posttherapy was 6 months. If more than one posttherapy Tg value was available, the lowest value was selected.

Outcome of subgroup with micrometastasis

The group of seven patients with micrometastasis remained stable within the follow-up period, and conventional imaging did not show any change in the size of the micrometastases. No surgical excision was performed. The median T_4-suppressed Tg increased from 23.0 to 32.0 ng/ml (Table 4). An increase in serum Tg was noted in all except two patients. In one of these, who had evidence of lung micrometastases, Tg on T_4 suppression was reduced from 3.7 to 0.6 ng/ml after 2 yr of follow-up, and Tg after T_4 withdrawal was reduced from 89.4 to 37.7 ng/ml, with negative WBS. No further RAI therapy was given to this patient. In the other patient, who had repeat withdrawal WBS, Tg increased after therapy from a pretherapy level of 69.1 ng/ml to 99 ng/ml; however, TSH-stimulated serum Tg was reduced from a pretherapy level of 517 ng/ml to 345 ng/ml. This patient was the one who had neck uptake in possible micrometastases in the posttherapy scan and in whom follow-up diagnostic WBS became negative.

Outcome of subgroup with macrometastasis

In this group, median serum Tg on T_4 increased from 51.2 to 265 ng/ml ($P = 0.004$). Patients in this group had progression of their disease. In two patients who died of thyroid cancer after 12 and 15 months of RAI therapy, no Tg levels were available. In a third patient, follow-up was not available. In all of the remaining 10 patients, serum Tg increased despite palliative surgical excision of tumor in four patients and external radiotherapy in one. The only patient in this group who had positive posttherapy scans in lung, mediastinum, and neck metastases, but not in bone metastases, had a subsequent negative diagnostic WBS and a significant increase in Tg from 12,400 to 20,850 ng/ml; the patient died after 1 yr from complications of the thyroid cancer. Three

TABLE 4. Pre- and post-RAI therapy Tg levels in 18 of 24 Tg-positive, whole-body scan-negative patients who had both pretherapy and follow-up Tg levels available[a]

Patient group	Number of Tg pairs	Median (IQR) Tg on T_4 therapy, ng/ml		
		Pretherapy	Posttherapy	P^b
All patients	18	39.0 (8.0–160)	99.0 (15.3–289)	0.03
With metastases	17	41.5 (15.5–160)	110 (23–289)	0.004
With macrometastases	10	51.2 (28.7–193)	265 (110–399)	0.004
With micrometastases	7	23.0 (14.7–69.1)	32.0 (15.3–99.0)	0.45

IQR, Interquartile range (25–75 percentile).
[a] If more than one follow-up Tg level was available, the lowest value on T_4 therapy was entered into the computation.
[b] $P \leq 0.05$ is statistically significant.

other patients also had follow-up negative withdrawal WBS. Serum TSH-stimulated Tg increased in one of these patients from 1,765 to 2,400 ng/ml, in another from 1,553 to 1,790 ng/ml, and in the third from 62 to 95 ng/ml. No repeat RAI therapy was given to any of these patients. To date, of these 13 patients, two are clinically symptomatic with persistent neck tumor, five have good quality of life, and five have died from complications of thyroid cancer; the status of one patient is unknown.

Discussion

A negative diagnostic WBS in the presence of known residual or metastatic FCDTC is not uncommon (16). A false-negative WBS can be owing to technical factors, such as excessive iodine pool, poor instrumentation, and inadequate serum TSH elevation. We are confident that our patients do not represent false-negative WBSs. There was adequate TSH elevation, and the majority (12 cases) had at least one previous negative diagnostic WBS despite elevated Tg. With a careful history, we can exclude iodine contamination in our practice. In 30 different groups of patients undergoing diagnostic scans with similar iodine precautions (unpublished data), median 24-h urinary iodine was 275 μg/24 h (2.1 μmol), with a range of 50–703 μg (0.39–5.5 μmol). A true-negative WBS can be owing to metastases too small to be visualized or to metastases with loss of ability to trap iodine, possibly related to an acquired mutation in the sodium/iodide symporter gene (22, 23).

It has been suggested that some of these tumors can be imaged with higher doses of RAI. Diagnostic doses as high as 10 mCi have been suggested. Because these doses may cause a stunning effect, which reduces the effectiveness of subsequent RAI therapy (24), this practice is not recommended. It is to be noted that a recent report questions the significance of ^{131}I-induced stunning (25). If metastatic lesions are not resectable and the RAI diagnostic scan is negative but serum Tg is elevated, some authors recommend empiric therapy with 100–200 mCi ^{131}I, followed by a posttherapy scan. If the posttherapy scan shows RAI uptake, therapy is repeated until the scan becomes negative (19, 26). This practice is controversial (18–21).

Reports of significant uptake after therapeutic doses in known macrometastases are scarce. One case of successful uptake after the administration of recombinant TSH in a patient with lung and bone metastases (27) has been reported. However, in two cases of FCDTC with known metastases reported by Lubin *et al.* (28), no uptake was noted in the known metastases after empiric therapy. This trend may also indicate that a lack of ^{131}I trapping is a sign of metabolic dedifferentiation of an otherwise histologically differentiated thyroid tumor (28–30). Also controversial and a subject of debate is the issue of RAI therapy in patients who have no radiologic evidence of thyroid cancer but have elevated serum Tg levels despite thyroid ablation (18–21).

Results of two European and one American series (14–16) are widely cited in favor of empiric therapy. These authors proposed that ^{131}I uptake may be too small to be visualized on diagnostic scans, either because the ability of the neoplastic tissue to concentrate iodine is low or the mass of the metastasis is too small and a larger dose makes visualization of uptake possible (17). There is no conclusive evidence that this approach changes patient outcome. However, data have been presented to suggest that various parameters of disease activity may improve. Evidence of a therapeutic effect of RAI has been reported in three series (15, 31, 32). Negative subsequent follow-up posttherapy scans in 80% and a Tg level below 5 ng/ml in 60%, along with normalization of chest CT scans in some patients, have been reported (16). In a recent review article, Mazzaferri and Kloos (33) reported on 10 Tg-positive, diagnostic WBS-negative patients with serum Tg levels more than 15 ng/ml (TSH more than 30 mIU/liter). Eight of these patients had evidence of distant metastases on posttherapy scans. They reported that three patients had subsequent negative posttherapy scans within 2–4 yr, with reduction of serum Tg to 5 ng/ml (33). The most recent report by Pacini *et al.* (32) compares the results of 28 untreated patients encountered before 1984 with those of 42 treated patients seen after that date. The authors found positive posttherapy WBS in 71%. They noted reduction in Tg and disappearance of lung uptake with repeated therapy and recommend treating all Tg-positive, WBS-negative cases once with 100 mCi of ^{131}I and continuing therapy until posttherapy WBS becomes negative. The patients and methodology in that study are not comparable with those of our study. In the Pacini group's study, patients with radiologic evidence of metastases were excluded, and a rectilinear scanner, which is less sensitive, was used for WBS. It is also difficult to explain why, in the untreated group, there was significant reduction of Tg similar to that in the treated group in the follow-up period. We agree with some authors who discourage routine RAI therapy in Tg-positive, scan-negative patients with thyroid cancer (18, 20, 21).

In the present study of 24 patients treated with RAI who had detectable Tg and negative diagnostic WBS, only two

patients had evidence of uptake in the metastases in post-therapy scans. Our study shows that in high-risk FCDTC patients with known metastasis who have undergone RAI ablation of the thyroid remnant, if a subsequent diagnostic WBS is negative despite elevated serum Tg, there is very little likelihood that therapeutic RAI will result in meaningful accumulation of ^{131}I in persistent disease. Of note, the single patient with aggressive tumors who had posttherapy uptake in the tumor did not benefit from therapy.

Our patient population differed from that of previously reported series. Almost all the previously reported cases had no evidence of detectable disease in conventional radiologic studies, or they had micrometastases. Most of our patients had aggressive high-risk cancer with large tumor loads. None of this group benefited from empiric RAI therapy. In the micrometastasis group, serum Tg levels increased in the follow-up period in all except one patient; thus, benefits are unlikely. Our study does not answer questions related to the group who had no imaging evidence of malignancy and mildly elevated serum Tg levels. We did not see any benefit in these four patients; however, we cannot draw conclusions for this small subgroup.

The risk of disease-related mortality or morbidity of such scan-negative, Tg-positive patients has not been well defined (18, 30) when there is no evidence of recurrence by high-resolution neck ultrasound or spiral CT scanning of the chest. The question remains whether there is any harm in RAI therapy. In clinically stable young patients without other evidence of detectable disease, the risks of deleterious effects of empiric RAI therapy, such as sialadenitis, bone marrow suppression, early menopause (34), and even carcinogenesis, should be considered.

A recent report (29) suggests that anaplastic changes associated with the p53 mutation in differentiated thyroid cancer may occur after insufficient RAI therapy. In this study, all 13 patients in whom RAI did not accumulate in the tumor died within 10 yr (29). It is of interest that 5 of 13 patients in our study who had macrometastases also died within a relatively short period, and all had progression of their disease.

We believe that the available information and our present report do not support benefits of empiric RAI therapy of diagnostic RAI scan-negative, Tg-positive FCDTC patients who have a large tumor burden. For FCDTC patients without evidence of disease on conventional imaging, the numbers in our study are too small to allow a definitive conclusion. For this subgroup, long-term randomized trials are needed to see whether such therapy is beneficial or harmful. For the management of FCDTC patients who do not have RAI accumulation and have unresectable tumors, innovations in therapy such as redifferentiation therapy, chemotherapy, and perhaps gene therapy are urgently needed.

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