# Detection and Treatment of Lung Metastases of Differentiated Thyroid Carcinoma in Patients with Normal Chest X-Rays

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Lung metastases were demonstrated by total-body $^{131}I$ scans in 23 patients with differentiated thyroid carcinoma, at a time when chest x-ray was normal. This total-body $^{131}I$ scan was performed after the administration of 2 mCi (in 11 patients) or 100 mCi (in 12 patients). Overall uptake of $^{131}I$ in lungs was <1% of the administered dose in 11 patients. All patients were treated with radioiodine. No lung uptake was found in 20 patients at the last 100 mCi post-therapy scan. Among them, Tg level became undetectable during $T_4$ treatment in eight, lung CT scan showed the disappearance of the micronodules in seven, and lung biopsy did not show evidence of disease in two patients. No patient developed radiation lung fibrosis. In conclusion, favorable responses to radioiodine treatment were observed despite relatively low overall uptake, in relation to the small size of lung metastases. This provides high concentrations of radioiodine and therefore high radiation doses.

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In a previous report of our series of patients with differentiated thyroid carcinoma, the extent of disease at discovery of metastases appeared to be an important prognostic factor for both complete remission and survival (*1*). These findings parallel those reported by Samaan et al. (*2*). Thus, we have advocated a follow-up strategy, based on thyroglobulin (Tg) measurements and on total-body iodine-131 ($^{131}I$) scans, to detect distant metastases at a stage when chest x-rays are still normal (*1,3*). Furthermore, patients with elevated Tg levels, where total-body $^{131}I$ scan with 2 to 5 mCi did not show abnormal uptake accounted for 13% of our patients (*3*), and for 12.6% of the patients in the series of Pacini et al. (*4*) reported during the preparation of this manuscript. In these patients the administration of 100 mCi $^{131}I$ with a total-body scan 5 days later, has been proposed as a diagnostic and therapeutic tool (*1, 3,4*). In Pacini's series, this technique was applied to 17 of these patients, with the post-therapy scan demonstrating metastases in 13 (*4*).

However, the usefulness of this procedure remains controversial as only indirect evidence of its therapeutic benefits has been reported (*4*). Furthermore, due to the slow growth rate of neoplastic thyroid tissue, long survivals have been observed in some patients with distant metastases, even if they had not been treated with radioiodine (*1,5*).

The present study demonstrates the efficacy of treating lung metastases with radioiodine in 23 patients with normal conventional chest x-rays in whom lung metastases were documented by using the above follow-up strategy.

## PATIENTS AND METHODS

### Patients

Between 1981 and 1986, lung metastases were demonstrated by a total-body iodine-131 ($^{131}I$) scan in 23 patients with normal conventional chest x-rays who had no other distant metastasis detected. These 23 patients (19 females and four males, ranging in age from 13 to 62 yr) were selected for this study among the 1,500 patients with differentiated thyroid carcinoma followed at Institut Gustave-Roussy, Villejuif.

Postoperatively, these patients underwent the following protocol. A dose of 100 mCi $^{131}I$ was given for ablation of their thyroid tissue after incomplete surgery, and following complete resection only in those above 45 yr or with follicular moderately differentiated histologic type (*6,7*). Therefore, after complete surgery, patients younger than 45 yr and with

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papillary carcinoma did not receive an ablative dose of $^{131}I$. Thereafter, $T_4$ treatment was given to decrease serum TSH level below 0.1 $\mu$U/ml (*8*). A total-body $^{131}I$ scan was carried out each year, for the first 2 yr. Thereafter, in patients in complete remission with undetectable Tg levels, clinical examination, serum $T_4$, TSH, and Tg measurements were performed yearly while on $T_4$ treatment and a total-body $^{131}I$ scan was performed with 2 mCi $^{131}I$, every 5 yr. In patients without thyroid remnant where Tg level was detectable during $T_4$ treatment, a total-body $^{131}I$ scan was performed with 2 mCi. A dose of 100 mCi $^{131}I$ was given to patients with elevated Tg levels (>10 ng/ml during $T_4$ treatment, or >40 ng/ml after thyroid hormone withdrawal) even if no uptake was found with 2 mCi $^{131}I$. In patients with thyroid remnants, who had not previously received 100 mCi $^{131}I$, where Tg level was elevated during $T_4$ treatment (>30 ng/ml), a dose of 100 mCi $^{131}I$ was also given.

### Methods

Serum thyroglobulin (Tg) was measured by RIA (*9*). The normal range in control subjects was 2.5–28 ng/ml, with a limit of detectability 2.5 ng/ml. Anti-Tg auto-antibodies were sought using the tanned red cell agglutination technique (Wellcome).

Total body $^{131}I$ scan was performed using a Ohio Nuclear 84FD scintiscanner (Mentor, OH), equipped with two opposed heads, a memory bank and a color TV monitor. This equipment permitted the scanning of patients with thyroid remnants; its calibration made it possible to assess metastatic uptake with a precision of 20% of the measured value, with uptake in lungs as low as 1 $\mu$Ci being detected. To achieve TSH stimulation (*10*), $T_4$ therapy was discontinued, $T_3$ given for 3 wk, $T_3$ withdrawn for 2 wk before the scan was performed in patients without thyroid remnant and bovine TSH (10 IU × 3) given in those with thyroid remnants. Serum TSH was measured and a total-body scan was performed, either 72 hr after the administration of 2 mCi $^{131}I$ or 5 days after 100 mCi $^{131}I$.

Chest x-rays were performed by high kilovoltage and lung computed tomography (CT scan) performed with a CE. 10000 scanner (C.G.R., France). The slices were at centimeter intervals with a 1 cm collimation. Scanning time was 6.8 sec and the matrix was 512 × 512. No contrast medium was injected (*11*).

### Treatment

The standard $^{131}I$ treatment was 100 mCi. Five days after each treatment, a quantitative total-body scan was performed and $T_4$ treatment resumed. Iodine-131 treatment was given following thyroid hormone withdrawal every 4 to 6 mo until the post-therapy scan did not show any abnormal uptake (*1*).

## RESULTS

### Discovery of Lung Metastases

Lung metastases were discovered in 23 patients up to 288 mo after the initial treatment of the thyroid tumor (Table 1): 17 patients had thyroid remnants and six had previously received an ablative dose of radioiodine. Lung metastases were documented by total body $^{131}I$ scan performed with 2 mCi $^{131}I$ in 11 patients and only after administration of 100 mCi in 12 patients (Figs. 1 and 2). This 100 mCi $^{131}I$ dose was given postoperatively in four patients (Cases 4, 5, 12, and 13), for elevated Tg levels in four patients (Cases 1, 2, 3, and 16), and for neck relapse in four patients (Cases 6, 11, 14, and 15).

Tg level was below 10 ng/ml during $T_4$ treatment in three patients, including two with thyroid remnants. Tg level was below 40 ng/ml after thyroid hormone withdrawal in three patients with thyroid remnants.

Overall radioiodine uptake in lung metastases was low in most patients, being below 1% of the administered dose in 11. It was lower in metastases which were documented after 100 mCi $^{131}I$ than in those discovered after 2 mCi $^{131}I$ ($p < 10^{-4}$).

Lung CT scan was normal in 13 patients and showed peripheral micronodules in ten patients. Despite a pattern of diffuse uptake of radioiodine in the lungs, only 1 to 10 micronodules could be demonstrated.

### Treatment Results

All patients were treated with radioiodine (Table 1). No lung uptake was found in 20 of 23 patients at the last 100 mCi post-therapy scan. Among these 20 patients, the median total amount of radioiodine administered was 300 mCi where there was an initially abnormal CT scan and 100 mCi where there was a normal CT scan; this was not different between patients whose metastases were discovered either after 2 or 100 mCi $^{131}I$. Among these 20 patients without lung uptake after $^{131}I$ treatments, eight initially had an abnormal CT scan. After $^{131}I$ treatments, lung CT scan showed the disappearance of micronodules in seven patients and the persistence of one micronodule in one patient. Serum Tg level during $T_4$ treatment decreased to undetectable levels in eight patients and below 8 ng/ml in the others. Following thyroid hormone withdrawal, Tg level increased in 12 patients but remained far below its initial value. Nine of these patients have been followed for more than 2 yr after the last treatment and Tg levels have not increased with time. Furthermore, a dose of 100 mCi $^{131}I$ was given again after thyroid hormone withdrawal to three patients, 12 to 24 mo after the last treatment, and no uptake was found on the post-therapy scan. Two patients (Cases 8 and 11) had lung biopsies performed in a blind fashion after treatments, which did not show any evidence of disease. No patient developed radiation lung disease.

In the four patients still under treatment at the time of the study, a decrease in lung uptake of radioiodine and in Tg level has been observed.

**TABLE 1**
Characteristics of the 23 Patients with Lung Metastases of Differentiated Thyroid Cancer

| | Age (yr) | Sex | Histology* | 131I dose† at discovery (mCi) | Thyroid remnants | Interval‡ Treatment Discovery (Mo) | Uptake¶,** in lung metastases (%) | Tg/$T_4$¶ (ng/ml) | Tg/TSH¶ (ng/ml) | CT scan¶ (nodules) | Total dose $^{131}$I (mCi) | Follow-up after last treatment (Mo) |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 24 | F | Pap | 100 | + | 141 | 0.5–0 | 44–8 | 150–58 | 10–1 | 800 | 0 |
| 2 | 13 | F | Pap | 100 | – | 30 | 0.5–0 | 26–4 | 391–24 | 10–0 | 470 | 0 |
| 3 | 44 | F | Pap | 100 | – | 96 | 0.7–0 | 15–<2.5 | 51–22 | 3–0 | 300 | 6 |
| 4 | 38 | F | FMD | 100 | + | 8 | 0.1–0 | 11–6 | 15–8 | 3–0 | 100 | 41 |
| 5 | 44 | F | Pap | 100 | + | 0 | 0.5–0 | 34–5 | 21–6 | 4–0 | 100 | 44 |
| 6 | 31 | F | Pap | 100 | + | 144 | 1.0–0.5 | 20–16 | 218–33 | 5–1 | 600 | — |
| 7 | 30 | F | FMD | 2 | + | 6 | 1.2–0 | 6–<2.5 | 13–<2.5 | 2–0 | 100 | 25 |
| 8 | 16 | M | FMD | 2 | + | 2 | 1.3–0 | 52–5 | 550–37 | 10–0 | 380 | 34 |
| 9 | 62 | F | FMD | 2 | + | 0 | 2.0–0 | 35–6 | X–X | 1–0 | 300 | 19 |
| 10 | 31 | F | Pap | 2 | + | 228 | 8.3–0.4 | 81–5 | X–14 | 10 | 300 | — |
| 11 | 30 | F | Pap | 100 | + | 30 | 0.4–0 | X–8 | 110–X | 0–0 | 200 | 69 |
| 12 | 21 | F | Pap | 100 | + | 3 | 0.7–0 | 29–5 | 283–4 | 0 | 300 | 36 |
| 13 | 41 | M | FWD | 100 | + | 1 | 3.1–0 | X–<2.5 | 45–<2.5 | 0 | 200 | 12 |
| 14 | 48 | M | Pap | 100 | + | 180 | 0.7–0 | 8–<2.5 | X–8 | 0 | 100 | 13 |
| 15 | 18 | F | FMD | 100 | + | 156 | 0.5–0 | 19–<2.5 | X–6 | 0 | 100 | 6 |
| 16 | 52 | F | Pap | 100 | – | 288 | 0.2–0 | 12–5 | 13–X | 0 | 100 | 6 |
| 17 | 27 | F | FMD | 2 | + | 0 | 2.4–0 | 29–X | 130–37 | 0 | 100 | 7 |
| 18 | 23 | F | Pap | 2 | – | 12 | 2.0–0 | 77–Ab | 429–Ab | 0 | 200 | 43 |
| 19 | 24 | F | Pap | 2 | – | 24 | 1.3–0 | X–<2.5 | 65–12 | 0 | 200 | 20 |
| 20 | 28 | F | Pap | 2 | + | 6 | 0.8–0 | 34–4 | 210–20 | 0 | 100 | 30 |
| 21 | 21 | F | Pap | 2 | – | 14 | 1.5–0 | 7–<2.5 | 74–10 | 0–0 | 200 | 48 |
| 22 | 27 | F | FMD | 2 | + | 75 | 1.0–0.1 | 14–<2.5 | 184–9 | 0 | 300 | — |
| 23 | 23 | M | FMD | 2 | + | 1 | 8.8–0 | X–4 | 640–37 | 0 | 300 | 6 |

* Histology: Pap, papillary; FMD: follicular moderately differentiated, FWD: follicular well differentiated (7).

† $^{131}$I dose at discovery: dose of $^{131}$I given at the total-body scan which allowed the discovery of lung metastases.

‡ Interval treatment discovery: interval of time (in months) between initial treatment of the thyroid tumor and discovery of lung metastases.

¶ For each of these parameters, values before and after treatments are given; X: not determined; Ab: presence of detectable anti Tg antibodies in the serum. Tg/$T_4$: Tg measurement during T4 treatment. Tg/TSH: Tg measurement after thyroid hormone withdrawal.

** Uptake in lung metastases was expressed as the percentage of the administered dose of $^{131}$I.

## DISCUSSION

This management strategy allowed the discovery of lung metastases in 23 patients with differentiated thyroid carcinoma, at a stage when conventional chest x-rays were normal. Of interest, treatment response was similar in those whose metastases were discovered after either 2 or 100 mCi $^{131}$I.

At that time, 74% of these patients had thyroid remnants, demonstrating that although this decreases the detecting capacity of Tg measurement and total body $^{131}$I scan, performed with 2 or 100 mCi, it does not prevent the discovery of lung metastases. In 12 patients, lung metastases were documented only after the administration of 100 mCi $^{131}$I, related to low uptake and underlining the need for a total body scan after each administration of 100 mCi $^{131}$I (*1,3,4,12–15*), even in the presence of thyroid remnants.

In three patients, including two with thyroid remnants this strategy permitted the detection of lung metastases despite low Tg levels during $T_4$ treatment. Furthermore, false-negative measurements, although infrequent, do exist during $T_4$ treatment and this emphasizes the importance of combining serum Tg measurements and total-body $^{131}$I scan (*1,16–18*). On the other hand, the routine use of Tg measurement allows a decrease in the number of total-body $^{131}$I scans performed. These are currently more effective, because their indications are better defined.

In four patients, only the administration of 100 mCi $^{131}$I for elevated Tg levels allowed the discovery of lung metastases. In keeping with other studies (*1,3,4,16*), this confirms that elevated Tg levels in patients with no detectable uptake on the routine total body $^{131}$I scan warrant further investigation including the administration of 100 mCi $^{131}$I with a total-body scan 5 days later. A lower $^{131}$I dose (i.e., 10 or 30 mCi) may also be administered in these patients but this does not have the advantage of being both diagnostic and therapeutic. Furthermore, the irradiation delivered by these doses may lower the uptake of the subsequent administration and therefore interfere with the therapeutic use of $^{131}$I.

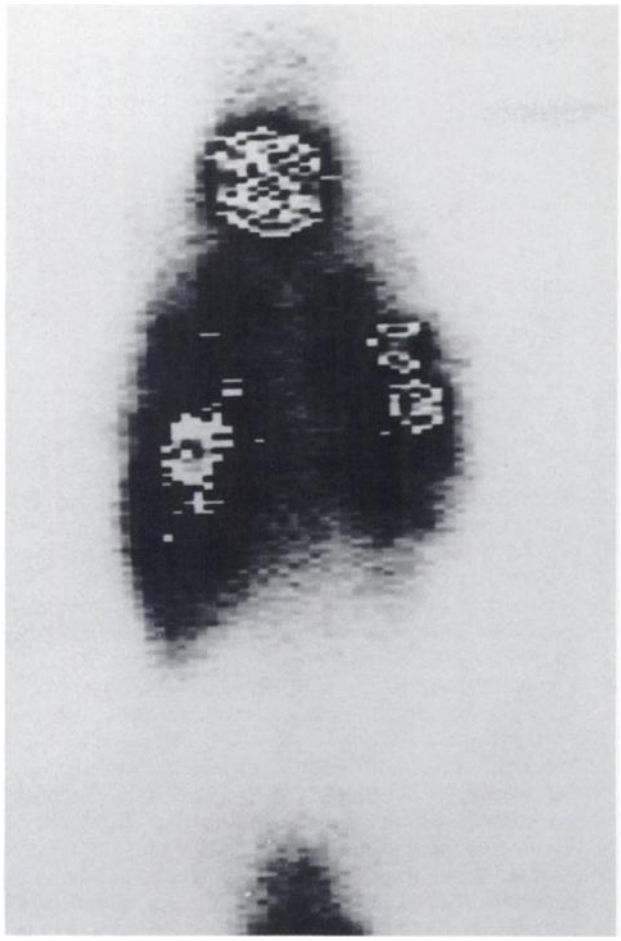

**FIGURE 1**
Post-therapy $^{131}I$ scan in Patient 10. At Day 5, uptake in the neck was 3.2 mCi (5.3% of the administered activity), 2.2 mCi (3.7%) in the right lung and 2.8 mCi (4.6%) in the left lung.

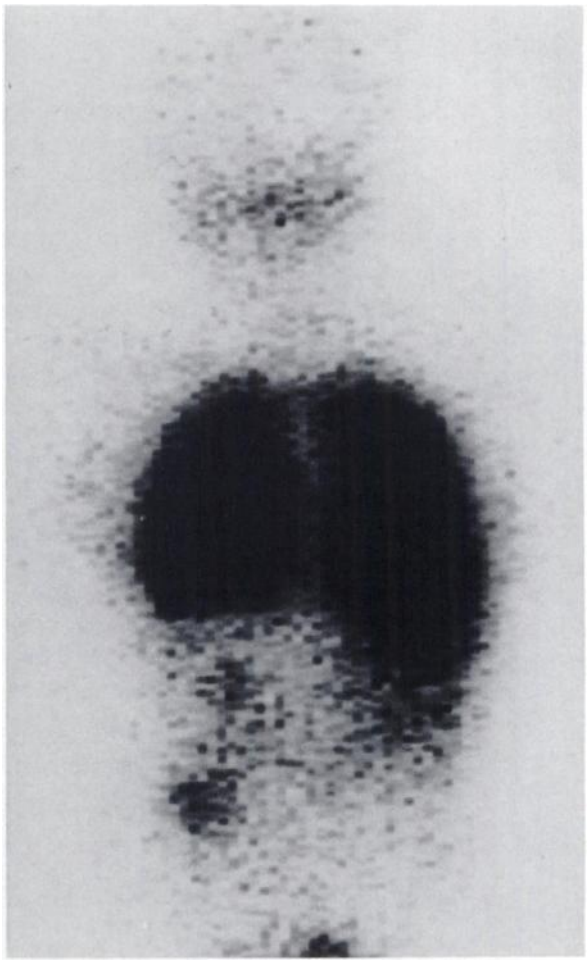

**FIGURE 2**
Post-therapy $^{131}I$ scan, performed 5 days after the administration of the second dose of 100 mCi, in Patient 10. It shows a diffuse uptake of $^{131}I$ in the lungs and the absence of uptake in the neck.

Evidence of regression of lung metastases was observed in all patients, and in 20 patients no radioiodine uptake was found after the last administration of 100 mCi $^{131}I$. Among these 20 patients, lung CT scans normalized in seven of the eight patients where this was initially abnormal, Tg levels during $T_4$ treatment decreased to low levels, and became undetectable in eight patients, and two patients had lung biopsies which did not show any neoplastic tissue. Indeed lung biopsies were performed in a blind fashion, but before any treatment metastases were diffuse in both lungs and if neoplastic tissue was still present, the yield would have been high. Hence, these 20 patients were considered to be in complete remission.

Of interest, these favorable results were obtained after the administration of a lower total amount of $^{131}I$, than in our overall series of metastatic patients (*1*), and even lower in those with an initially normal lung CT scan. This dose was not different between patients whose metastases were discovered after the administration of either 2 mCi or 100 mCi, suggesting that the treatment response is similar in all. This shows that early discovery of the metastases allows a reduction in the total amount of $^{131}I$ necessary for cure and hence a reduction in the total body exposure.

Despite relatively low uptake, favorable treatment results were obtained. These are mainly related to the small size of the metastases: a given amount of $^{131}I$ taken up in a small mass is more effective than a larger amount of radioiodine taken-up by a much larger tumor mass, resulting in a lower concentration. These dosimetric aspects have been discussed elsewhere (*19*). In this context, it should be recalled that conventional chest x-rays cannot always detect pulmonary nodules with a diameter smaller than 1 cm, whereas CT scan detects nodules of 3 mm in diameter. When a nodule is undetectable on CT scan, its diameter is therefore smaller than 2 mm (*11*). In fact, in our previous report (*1*), the only predictive parameter for the achievement of a complete remission was the size of the metastases.

In most patients considered to be in complete remis-

sion, Tg levels increased after thyroid hormone withdrawal, suggesting the persistence of neoplastic foci which either were unable to concentrate radioiodine or were too small to be detected by other means. In these patients, Tg levels remained stable over time and three patients were treated again with 100 mCi $^{131}I$, 12 to 24 mo after the last treatment, and no recurrence was observed. Nevertheless, as already stated (*6*), this follow-up is much too short to predict for a definitive cure. However in our previous report (*1*), no patient in complete remission after therapy for distant metastases had relapsed with a median follow-up of 9 yr.

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