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Follow-up of Patients with Differentiated Thyroid Carcinoma. Experience at Institut Gustave-Roussy, Villejuif

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Abstract—*The recent introduction of sTSH assays allows for a definite control of the inhibition of TSH secretion. Clinical examination and serum thyroid hormone measurements are necessary to obviate hyperthyroidism.*

Relapses may occur after decades of apparent complete remission. Follow-up should be pursued throughout the patient's lifetime. Two specific means allow the detection of relapses at a stage when X-rays are still normal: measurement of serum thyroglobulin and ^{131}I total body scan. Their combined use is recommended.

INTRODUCTION

THE follow-up of thyroid cancer patients has two main purposes: assessment of the inhibition of TSH secretion during T_4 treatment and detection of relapses.

Thyroxin (T_4) treatment is given post-operatively to all cancer patients. The recent introduction of sTSH measuremnt allows for a definite control of the inhibition of TSH secretion. A mean daily dose of 2.4 μg/kg/day decreases the sTSH level below 0.1 μU/ml. Clinical examination, free and total thyroid hormone measurements are necessary to obviate hyperthyroidism [1].

Many tools can be used for detecting cancer relapses: clinical evaluation, serum thyroglobulin (Tg) measurement, X-rays and ^{131}I total body scan. Long term results in patients with metastatic thyroid carcinoma have shown that the prognosis is strongly dependent upon the total tumor burden at the discovery of the metastases [2]. This should encourage the detection of metastases at a stage when X-rays are still normal.

Almost half the metastases are present at initial treatment. Relapses are discovered with a maximal frequency during the first years of follow-up, but may also occur after decades of apparent complete remission. Therefore follow-up should be intensive during the first 2–3 years but should also be pursued throughout the patient's lifetime. The use of Tg measurements with fewer ^{131}I scans should permit a reduction in cost, time loss and radiation exposure.

In the present paper, the main results of these tests in our series of patients are analyzed and the scheme used at IGR, Villejuif for the follow-up of thyroid cancer patients is described.

METHODS

Two specific methods are used for the detection of relapses: ^{131}I total body scan and Tg measurement.

Total body scan

Stimulation by TSH is of critical importance. Endogenous TSH stimulation is more effective than bTSH and the optimal length for the TSH stimulation of the radioiodine uptake appeared to be 2 weeks [3, 4]. Patients were taken off T_4 therapy for 3 weeks and then received T_3. Thereafter T_3 was withdrawn and TSH stimulation was performed according to one of two protocols. In patients without a thyroid remnant, T_3 was withdrawn for 14 days. In patients with thyroid remnants, 10 IU bTSH were injected i.m. daily for 3 days immediately after T_3 withdrawal. Allergic reactions may occur after injections of bTSH. These, however, were observed in less than 10% of the patients and were not severe.

The ^{131}I dose was 1–5 mCi [5]. Usually, the optimal scanning time is 72 h after the dose of radioiodine, when the background is lower and the physiological uptakes or secretions by organs such as salivary glands, stomach, colon, breast and bladder have diminished. A liver uptake is frequently observed in patients with thyroid remnants and is

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due to the concentration of labeled iodoproteins. Functional metastases close to normal sites of radioiodine concentration may be difficult to identify: oblique views, sequential views at 48, 72 and 96 h and overexposed scintigrams are useful to detect metastases with a low uptake.

Quantitative scintigraphies were performed using an Ohio Nuclear 84 FD scintiscanner, equipped with two opposed heads, a large crystal (1.25 cm in diameter and 5 cm thick) and a color TV monitor. Each metastasis was delineated on the TV image, and the integral of the counts within its area was calculated. Calibration of the equipment made it possible to assess metastatic uptakes with a precision of 20% of the measured value. This allows comparison between sequential examinations and assessment of radioiodine dosimetry. Uptake in the lungs as low as 1 μCi and in punctual sources as low as 0.1 μCi could be detected.

Serum Tg measurements

Tg has been shown to be the marker of differentiated thyroid carcinomas after the initial treatment [6]. Wide variations in results obtained from patients have been recorded and have been assumed to derive mainly from variation among assays used [7]. The assay has to be specific and sensitive, detecting serum concentrations as low as 1–2 ng/ml. Endogenous anti-Tg antibodies do interfere in most assays and when present, they do not allow for the determination of the actual Tg level. These antibodies are found in about 15% of patients with differentiated thyroid carcinoma and results obtained in this group should be excluded from clinical interpretation [7].

Tg was measured by RIA according to the Van Herle technique [8, 9]; the least detectable dose usually was 1.25 ng/ml; for a value of 17 ng/ml, intra-assay variation was 4.9% and inter-assay variation was 11.4%. The normal range of the RIA in control subjects was 13.9 ± 6.9 ng/ml.

RESULTS

Clinical evaluation

Neck recurrences are often discovered by cervical palpation. However prior external irradiation to the neck may hamper reliable clinical examination [10]. In suspicious cases, neck ultrasound and neck CAT scan may be helpful.

The usual locations of distant metastases are the lungs and the bones. Brain, liver and skin are rarely involved. Clinical symptoms of lung involvement such as thoracic pain or dyspnea, were present in only 21% of our patients with lung metastases, whereas clinical symptoms of bone involvement, such as pain, swelling or orthopedic complications were present in 84% of the patients with bone metastases. In most patients, symptoms were present with large metastases, i.e. macronodular lung metastases, pleural effusion or bone abnormalities on X-rays.

Radiological findings

In 141 patients with lung metastases, chest X-rays showed macronodules in 37% and micronodules, with a diameter inferior to 1 cm [11], in 33%. It is therefore often difficult to discover these micronodules on routine chest X-rays. In the other 30%, the chest X-ray was normal, and lung metastases were demonstrated by a ^{131}I total body scan. This is higher than in other studies [12–14] in which only 10% of the patients with lung metastases had normal chest X-ray and is probably due to the efforts made towards the detection of small metastases.

Lung tomograms in 26 patients with normal chest X-rays detected micronodules in only one patient. Lung computed tomography (CAT scan) was performed in 12 patients with normal tomograms and showed peripheral micronodules in five [15].

Metastatic thyroid carcinoma may involve any bony structure. In our series of patients, 29% had a single bone metastasis and 6% had no radiological abnormality. Bone metastases are often only osteolytic and therefore difficult to find on skeletal survey X-rays. ^{99m}Tc diphosphonate bone scans are more sensitive but may also be falsely negative. These two procedures are therefore not effective in the routine follow-up of these patients and should be performed only in those with suspicious or known metastatic disease [16].

Total body scan

Uptake of radioiodine was found in 2/3 of our patients with distant metastases [2]. It was more frequently observed in younger patients, in those with papillary or follicular well differentiated thyroid carcinoma and in those with small metatases.

In patients who are treated with 100 mCi ^{131}I, a post-therapeutic total body scan is mandatory 5 days later, as it permits the detection of unsuspected neoplastic uptake [17]. This revealed unsuspected lung uptake in one-third of our patients with lung metastases who had a normal chest X-ray [2].

Before Tg measurement was available, this procedure appeared to be effective even in patients with thyroid remnants [5]: in a sample of 30 patients in whom a neck recurrence or distant metastases were observed, 26 had thyroid remnants: in 25 the relapse was first discovered by a total body scan.

Furthermore, additional information was provided by the post-therapeutic total body scan in 11 patients.

Serum Tg measurements

Serum Tg is elevated in most patients with metastases [2, 6, 18]. Its level was not found to be related to the histological type of the differentiated thyroid carcinoma, to the age of the patient or to the amount of radioiodine uptake by the metastases [2]. It was elevated even in the absence of any detectable ^{131}I uptake in the metastases. However, Tg level was related to the volume of the metastases, being higher in patients with larger metastases [2]. Serum Tg can rise following endogenous TSH stimulation even in patients whose metastases do not pick-up radioiodine [9, 19].

The usefulness of Tg measurement depends upon the presence of thyroid remnants and the circumstances of measurement (i.e. on or off suppressive T_4 therapy).

In patients without thyroid remnant, serum Tg level should be undetectable and when Tg is detected, neoplastic tissue should be sought. Serum Tg levels were measured at the time of metastasis detection by other tools in 64 patients during T_4 treatment. It was above 10 ng/ml in 57, and undetectable in only one patient. This patient had only lung metastases detected by a total body scan performed with 1 mCi ^{131}I, the chest X-ray was normal. In these patients, TSH stimulation increases the sensitivity of Tg measurement: Tg level was above 10 ng/ml in the 88 patients with distant metastases in whom it was measured after thyroid hormone withdrawal and was above 40 ng/ml in 81 of them. False positive Tg measurements are more frequent: Tg was detected in 13% of the patients without any evidence of disease during T_4 treatment and in 49% of them after thyroid hormone withdrawal. However, Tg level was low, below 10 ng/ml in 98% during T_4 treatment and in 85% after thyroid hormone withdrawal. No prognostic value can so far be attributed to these detectable Tg levels in patients in whom no neoplastic foci could be demonstrated by other methods.

In patients with thyroid remnants, results are less satisfactory. The risk of relapse was low in patients whose Tg levels were below 10 ng/ml during T_4 treatment. Above 10 ng/ml, the higher the Tg level, the greater was the risk of relapse. In patients considered to be in complete remission, the Tg level during T_4 treatment was undetectable in 33%, detectable but below 10 ng/ml in 38%, and above 30 ng/ml in 3%. Among patients with thyroid remnants who relapsed, 93% had a Tg level above 10 ng/ml and 66% above 30 ng/ml during T_4 treatment. Measurement of the Tg level after TSH stimulation does not bring further information in these patients.

STRATEGY AND CONCLUSION

Ablation by radioiodine of thyroid remnants increases the detecting capacities of total body scan and of Tg measurement and should be performed in patients with high risk of relapse (i.e. age over 45 years, follicular moderately differentiated carcinoma) [20].

Since the routine use of Tg measurement, a strategy has been developed at IGR Villejuif for the follow-up of those patients who have no detectable anti-Tg autoantibodies (Figs. 1 and 2). During T_4 treatment Tg level is taken into account only when TSH level is below 0.1 μU/ml. When TSH is above 0.1 μU/ml, the daily dose of T4 is increased by 25 μg and T_4, TSH and Tg levels are remeasured in 3 months.

In all cases, a total body scan is performed each year for 2 or 3 years after the initial treatment. Thereafter, in patients with undetectable Tg levels, follow-up is resumed with clinical evaluation, T_4, TSH and Tg measurements, once a year, while on T_4 therapy. During T_4 treatment, false negative Tg measurements account for 0–10% of the patients and a low or undetectable level does not totally preclude a relapse [2, 18, 20–24]. Therefore a total body scan and a chest X-ray are performed every 5 years. However, most patients with low Tg levels who relapsed had a neck recurrence that could be frequently detected by clinical examination.

Patients with thyroid remnants, whose Tg levels are higher than 30 ng/ml during T_4 treatment, are given 100 mCi of radioiodine and a post-therapeutic total body scan is performed 5 days later. Patients with thyroid remnants whose Tg levels are detectable but low (< 10 ng/ml) are followed in a similar fashion to those with undetectable Tg levels.

In patients without thyroid remnant in whom serum Tg is detectable during T_4 treatment, a total body scan and chest X-ray are performed and Tg level is measured again after thyroid hormone withdrawal. TSH stimulation increases the sensitivity of Tg measurement and no false negatives have been so far described in this situation. Patients with a positive total body scan are treated with 100 mCi ^{131}I. The situation is more difficult in those patients with a negative total body scan. In patients with Tg levels below 10 ng/ml during T_4 treatment and after thyroid hormone withdrawal, T_4 treatment is resumed and another total body scan is performed 5 years later. In patients with Tg levels higher than 10 ng/ml either during T_4 treatment or after thyroid hormone withdrawal, additional attempts to localize thyroid tissue should be made (neck ultrasound, neck and thorax CAT scan). In these cases, 100 mCi ^{131}I are administered if Tg level increases above 40 ng/ml after thyroid hormone withdrawal. Since the production of Tg

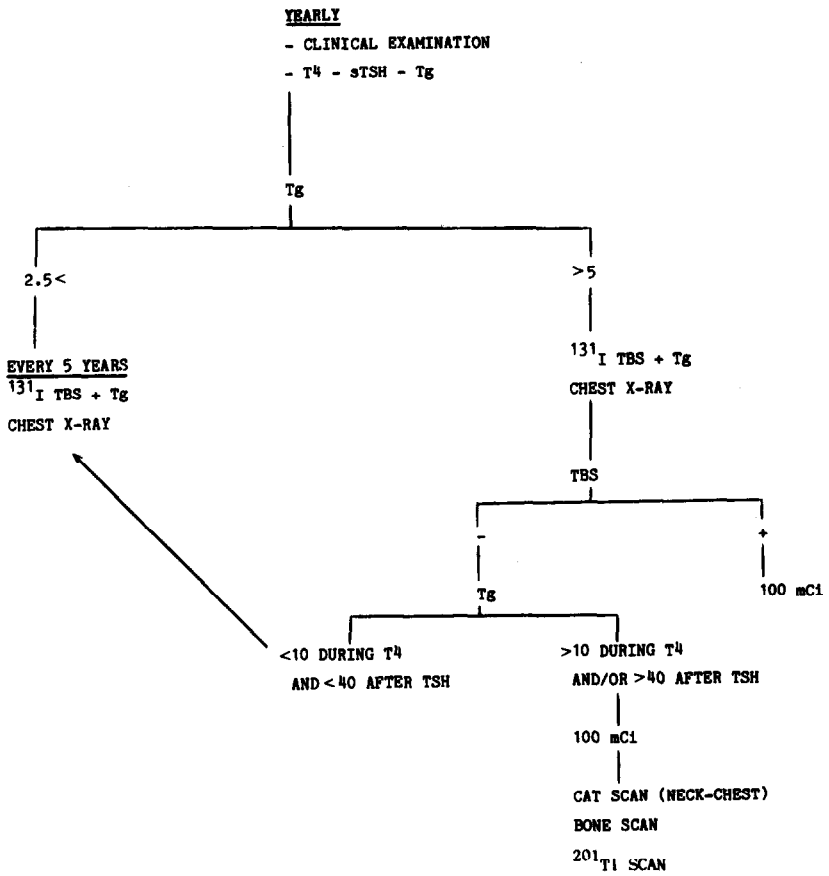

Fig. 1. Management of patients without thyroid remnants.

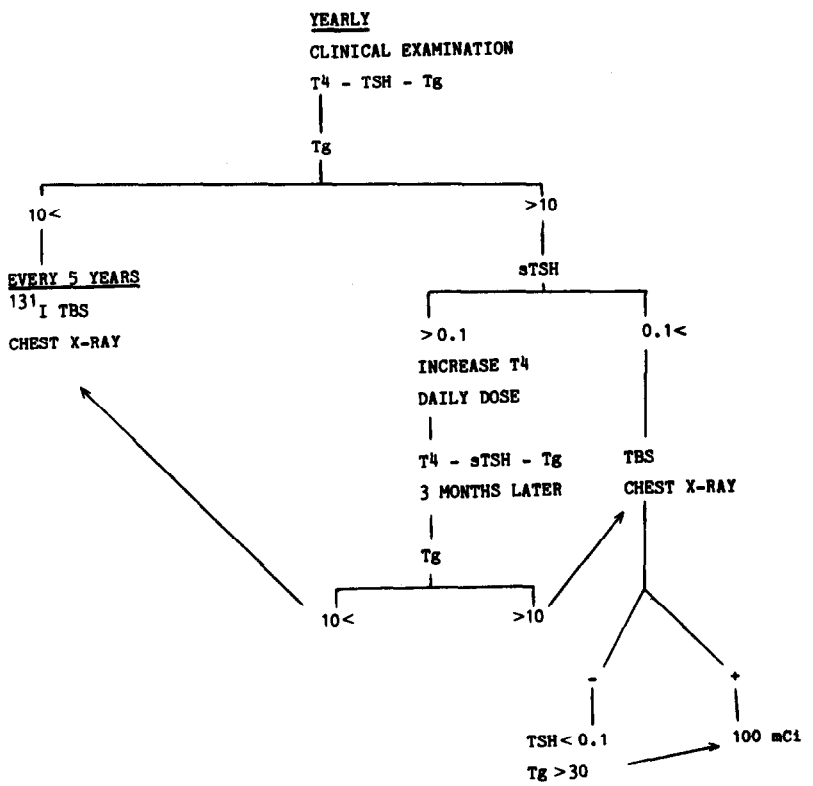

Fig. 2. Management of patients with thyroid remnants.

and the ^{131}I uptake can be differentially affected, patients who have high Tg levels but no apparent evidence of metastases are strictly followed and attempts to localize neoplastic tissue are performed again within 1 or 2 years. A recent study has stressed the interest of thallium-201 total body scan; it should be performed for the localization of the neoplastic tissue in these patients [25]. On the other hand, venous sampling catheterization did not reveal any concentration gradient in these patients either on or off T_4 suppressive treatment (unpublished data). ^{131}I labeled anti-Tg monoclonal antibody has been injected to nine patients with a neck recurrence: no specific concentration of the monoclonal anti Tg antibody could be found in tissue specimens obtained at surgery 3–5 days after injection.

Since the routine use of the Tg assay, the number ^{131}I of total body scans performed has been reduced. Furthermore total body scans are now more effective, as they are being performed with large ^{131}I doses. Before 1977, 13% of our patients with lung metastases had a normal chest X-ray. After the introduction of serum Tg as part of the follow-up, the proportion of patients with normal X-rays at the time of metatasis detection rose to 43%. Therefore, relapses are discovered earlier and this should improve the long term results of their treatment.

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