Comparison of the Distribution of Diagnostic and Thyroablative I-131 in the Evaluation of Differentiated Thyroid Cancers

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In 206 patients with differentiated thyroid cancer, the distributions of iodine-131 were compared after diagnostic (200-500 μCi) and thyroblative (~100 mCi) doses. In the diagnostic scans, only normal thyroid tissue could be seen, whereas in one-fourth of the patients the therapeutic scans showed tumor tissue as well, usually in lymph-node metastases. In 16% of patients, the therapeutic scan was the only way to demonstrate the presence of tumor tissue, since no further uptake was achievable. In patients in whom all tumor was believed to have been removed by surgery alone, a "preventive" I-131 ablation was used, and in 16 of these 97 patients tumor was revealed in the therapeutic scan. In ten more, tumor was found in subsequent followup scans, its functioning having been induced by destruction of postsurgical remnants of normal thyroid. Some possible explanations for the differences in scans are proposed, and the importance of therapeutic scans for correct staging of thyroid cancer is stressed.

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Whereas in most patients with differentiated thyroid cancer, scanning techniques are used to detect the distribution of diagnostic amounts of radioiodide, little if any attention is given to the distribution of therapeutic amounts. We have systematically checked the distribution of both diagnostic and therapeutic amounts of iodine-131 in thyroid-cancer patients for the past 12 years. We present here the results of our study in patients given thyroablative amounts (~100 mCi) of I-131.

PATIENTS AND METHODS

In 206 patients (148 females and 58 males) suffering from differentiated thyroid cancer, previous thyroid surgery failed to remove all thyroid tissue. These patients had been operated upon at other hospitals (usually without correct pre-operative diagnosis) and were sent to our institute for further treatment. Various surgical procedures were performed, such as subtotal or total lobectomy, subtotal thyroid resection, or attempted but unsuccessful total thyroidectomy. Lymph-node metastases had usually been removed when present, but their removal was not always complete. Whenever possible we attempted to achieve complete thyroid ablation by additional surgery; in such patients, however, incomplete thyroid surgery was followed by radioiodine thyroid ablation. Patients were classified into the following groups according to the staging of disease based on clinical and surgical findings and laboratory examinations performed before radioiodide treatment.

The pathological findings are summarized in Table 1.

Patients without suspected metastases (Group A).

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TABLE 1. PATHOLOGIC FINDINGS IN 206 PATIENTS UNDERGOING RADIOIODIDE THYROID ABLATION FOR DIFFERENTIATED THYROID CANCER

Histology	Age under 40 yr	Age 40 yr or over	Total
Follicular pure	30	60	90
Papillofollicular	29	26	55
Papillary pure	28	33	61
Total	87	119	206

TABLE 2. COMPARISON OF DIAGNOSTIC, THERAPEUTIC, AND FOLLOWUP SCANS IN PATIENTS UNDERGOING "PREVENTIVE" THYROID ABLATION

Type of scan	Diagnostic	Therapeutic	Followup
Uptake found in thyroid bed only	97	79	0
Tumor tissue:			
primary tumor	—	2	7 (1)*
lymph-node metastasis	—	15	2 (1)
distant metastasis	—	1	1 (0)
all tumors	0	18	10 (2)
No uptake	—	—	87

* In parentheses is the number of patients showing uptake in the same tumorous lesion in therapeutic and followup scans.

Iodine-131 ablation was performed in 97 patients where the tumor was believed to have been completely removed by previous surgery. There was no clinical evidence of residual tumor—hence the so-called "preventive thyroid ablation."

Patients with known or strongly suspected neoplastic tissue left after surgery, showing no uptake of I-131 in tumor on diagnostic scans (109 patients, Group B). Nineteen patients had unresectable tumor at surgery (see paragraph I, below). In 54 patients regional lymph nodes were infiltrated (see II, below); in some of them, lymph nodes were removed before thyroid surgery, and in others they were found and excised during the operation. In some of them it was possible, but by no means certain, that all the involved metastases were removed. Finally, in some patients lymph-node enlargement was found only after the patient was referred to us following thyroid surgery. In these patients, metastatic infiltration of the enlarged lymph nodes was strongly suspected but no definite proof was given at the time. In 36 patients, distant metastases usually pulmonary and/or skeletal were encountered at the time of radioiodide thyroid ablation (see III, below).

All 206 patients were treated as inpatients. As a part of the thyroid-function examination, plasma PBI and thyroxine were measured and, in the majority of cases, plasma TSH level was established. The results of the TSH plasma measurements in the course of thyroid-cancer treatment are to be published elsewhere. Patients prepared for thyroid ablation were almost invariably eumetabolic and had not been treated with thyroid hormones. The interval between thyroid surgery and diagnostic radioiodide administration was usually 4-6 wk. Diagnostic scans were performed on a rectilinear scanner 24 hr after administration of 200-500 μCi of I-131. Such scans showed only normal residues of thyroid tissue. All remnants in the thyroid bed were believed to represent noncancerous thyroid tissue, unless proved otherwise.

Radioiodine ablation was performed no later than 3 wk following diagnostic scans, usually within 10-14 days. Iodine-131 was administered in amounts of 80-120 mCi. The absorbed thyroid irradiation was calculated to be at least 80,000 rads. Therapeutic scans were made between the first and fifth days following treatment, depending on the amount of I-131 retained. Distribution of the diagnostic amounts of I-131 was compared with therapeutic scans obtained with the 200-2000 μCi radioiodine

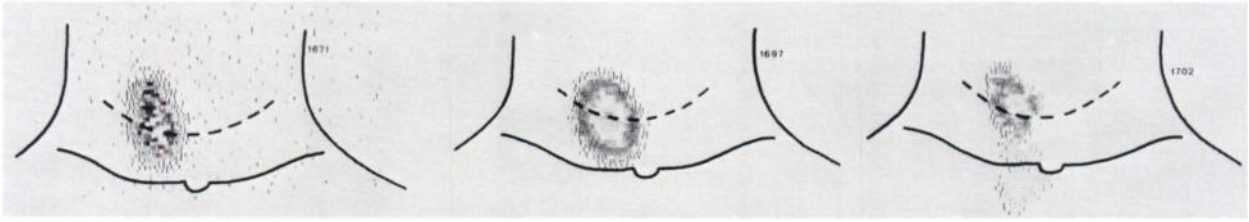

FIG. 1. A 30-year-old woman with follicular thyroid cancer; left lobectomy was performed. (Left) Diagnostic scan: uptake in right lobe only. (Center) Scan 72 hr after therapeutic I-131 (120 mCi); essentially identical with diagnostic scan. (Right) Therapeutic scan performed 4 days later (7th day after treatment) showing uptake below right lobe. No further uptake observed in followup scans.

retained in neck structures. Patients were re-examined 6-8 wk after thyroablative treatment, and further I-131 uptakes and scans were performed—the so-called followup scans. Further radioiodide treatment was given whenever uptake was found in tumor tissues (both inside and outside the thyroid bed), followed sometimes by surgical removal of tumor lesions. The followup system we used has been reported elsewhere (*5*) and is very similar to that recently published by Krishnamurthy and Blahd (*2*).

Patients with total thyroidectomy were not included, since no I-131 ablation was performed in them. Either no uptake was detected or function in the cancer tissues was induced by the absence of normal thyroid tissue.

RESULTS

Preventive thyroid ablation. In 18 of 97 patients with "clean" diagnostic scans, tumor tissue was revealed by the therapeutic scan. In 16 of these, there was no uptake in the followup scans 6 wk later. In only two patients did the uptake seen in the therapeutic scan turn up again at the followup examination, thus indicating further radioiodide treatment. In another eight patients, tumor tissue not visualized in the course of I-131 thyroid ablation turned up unexpectedly in the followup scans (Table 2, Fig. 1). Whereas tumor tissue found by therapeutic scans was located predominantly in the regional lymph nodes, followup scans detected mainly remnants of primary tumor believed to have been completely removed by surgery. Thus, in 26 patients the "preventive" thyroid ablation revealed unsuspected cancer.

I. Out of the 19 patients with known remaining primary tumor, only one showed tumor uptake in both the therapeutic and followup scans. In eight additional patients, uptake in primary tumor was induced by thyroid ablation without any change in the therapeutic scans (Table 3).

II. In 17 patients out of 54 with lymph-node metastases, uptake in lymph nodes was found on therapeutic scans but not on the followup scans. In a further 12 patients, the function of metastatic tissue in lymph nodes was induced by the total thyroid ablation. In seven patients without uptake in the lymph nodes on all three types of scans, it could reasonably be believed that all lymphatic metastases had been removed by radical surgery. In the remaining 18 patients, we failed to induce any uptake in palpable metastatic lesions (Table 4, Figs. 2 and 3).

III. In 18 out of 36 patients in this group, uptake was detected at least on one occasion—in 15 by therapeutic scan, with persistent uptake in the followup scans in ten. In an additional three patients, uptake was detected only in the followup scans (See Table 5, Fig. 4).

TABLE 3. COMPARISON OF DIAGNOSTIC, THERAPEUTIC, AND FOLLOWUP SCANS IN PATIENTS WITH KNOWN UNRESECTABLE PRIMARY THYROID CANCERS

Type of scan	Diagnostic	Therapeutic	Followup
Uptake found in thyroid tissue only	19	18	0
Primary tumor	0	1	9 (1)*
No uptake			10

* See footnote to Table 2.

TABLE 4. COMPARISON OF DIAGNOSTIC, THERAPEUTIC, AND FOLLOWUP SCANS IN PATIENTS WITH KNOWN LYMPH-NODE INVOLVEMENT

Type of scan	Diagnostic	Therapeutic	Followup
Uptake found in thyroid tissue only	54	37	0
lymph node metastases	0	17	17 (5)*
No uptake	—	—	37†

* See footnote to Table 2.

† In seven patients, lymphatic metastases were believed to be completely removed by radical surgery.

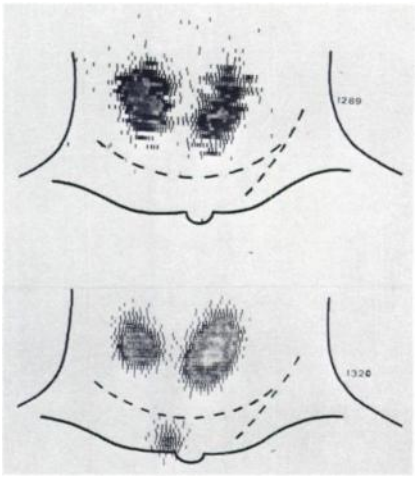

FIG. 2. A 25-year-old woman with papillary thyroid cancer; lymph node metastases were resected with conservative thyroid resection. No other metastases were palpable. (Top) Diagnostic scan showing remnants of both thyroid lobes. (Bottom) Therapeutic scan 5 days after 90 mCi of I-131; note right-sided lymph-node metastasis.

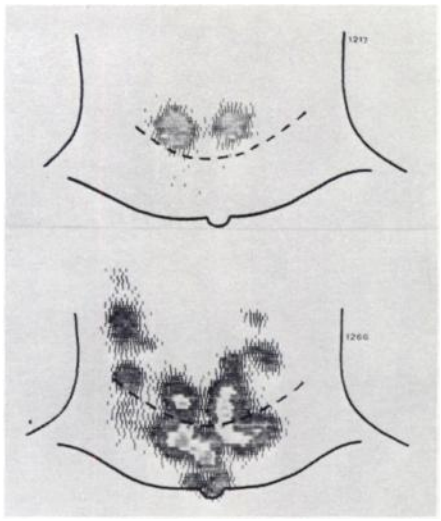

FIG. 3. A 23-year-old man with papillary thyroid cancer. Partial thyroid resection in presence of multiple bilateral lymph-node metastases. (Top) Diagnostic scan shows uptake in both upper poles of thyroid; traces in the region of resected lower pole on right side. (Bottom) Therapeutic scan performed 72 hr after 120 mCi of I-131. While uptake in normal thyroid tissue is still present, more radioiodine is accumulated in lymph-node metastases, and possibly in remnant of primary tumor. Followup scan showed spurious uptake only in metastases.

DISCUSSION

Treatment of differentiated thyroid cancers with radioiodide aims at achieving I-131 uptake in tumor tissue and is based on the repeatedly confirmed fact that total or almost total destruction of normal thyroid tissue is necessary to induce uptake in the tumor (*9,10*). In only a quarter of the patients with bone metastases is uptake in metastases encountered before any thyroid surgery (to be published). Repeated studies have showed that an interval of 6-10 wk is usually needed after surgical and/or radioiodide thyroid ablation before adequate uptake in tumor tissue can be seen (*8*). Uptake could be achieved only in some patients, however, depending on the tumor type, age, sex, location of metastases, and other factors. It is usually believed that uptake will eventually be achieved in 30-50% of patients (*8*). This figure is based on the study of followup scans, and in the present group of patients with known or suspected tumors (Group B), uptake was found in followup scans in 39 patients (35.8%). In therapeutic scans, uptake was seen in 33 patients (30.3%) and, which is of prime importance, in 17 patients the tumor tissue was visualized in therapeutic scans only (15.6%). In some patients, tumor tissue may be destroyed in the course of thyroid ablation and no uptake will be seen at followup.

In patients where no remaining tumor had been suspected, the tumor was believed to be limited to a thyroid nodule removed at surgery. In this group 97 patients were treated, and in ten of them uptake in tumor was found at followup. In a further 16, tumor tissue was detectable in therapeutic scans only. The same general rule as in Group B may be seen in these patients: low detectability of primary cancers in therapeutic scans compared with the followup scans, and high incidence of uptake in lymph nodes seen in therapeutic scans only.

It is important that in 26.8% of patients originally believed to have cancers limited to thyroid nodules, and to be cured by surgery alone, metastatic spread or primary remnants could be proved in the course of the first 2-3 mo after thyroid surgery. This is in accord and with the high recurrence rate found in our group of children after conservative surgery (*5*)

TABLE 5. COMPARISON OF DIAGNOSTIC, THERAPEUTIC, AND FOLLOWUP SCANS IN PATIENTS WITH KNOWN DISTANT METASTASES

Type of scan	Diagnostic	Therapeutic	Followup
Uptake found in thyroid tissue only	36	21	0
distant metastases	0	15	13 (10)*
No uptake	—	—	23

* See footnote to Table 2.

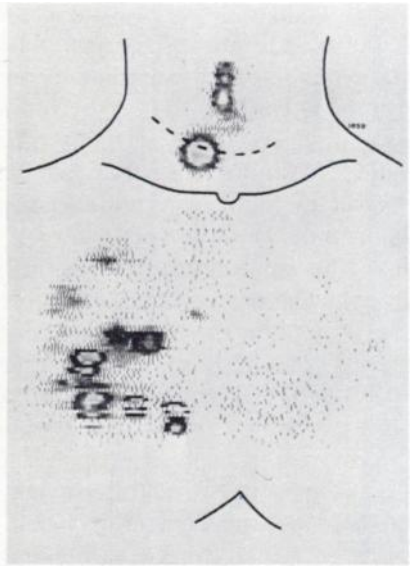

FIG. 4. A 49-year-old woman with follicular thyroid cancer. Following radical thyroid resection, remnants of right thyroid lobe and pyramidal lobe were seen on diagnostic scan (not shown). Therapeutic scan 24 hr following 120 mCi I-131 is identical in neck region; multiple lung metastases were not detectable on diagnostic scan.

contrasting with low recurrence rates encountered in patients in the U.S. (*1,11*). Radical treatment, even in patients with seemingly complete removal of thyroid cancers, seems to be imperative not only in Europe, but also in the U.S. (*2,4*).

Upon evaluation of the results of the whole group of 206 patients, therapeutic scanning was the only way to detect the presence of functionally active tumor tissue in 33 patients (16%). On the other hand, absence of any extrathyroidal uptake in 71 patients of Group A credibly confirmed the preventive character of thyroid ablation. In 8.7% of patients, uptake seen on therapeutic scans persisted (and usually increased) at the followup examination 6-8 wk later.

Scanning after therapeutic doses of radioiodide was introduced by Pfannenstiel and Hoffman in 1967 (*7*) to achieve better delineation of metastases from thyroid cancers with uptake in tumor tissue already induced, and in 1968 by our group (*6*) with the hope of deriving prognostic information on the probability of eventual function of metastases by study of the distribution of thyroablative iodine. It was originally believed that discovery of additional metastatic lesions after 100 mCi of I-131 is caused by larger amounts of radionuclide retained in the as yet undetected metastases with low functional activity (*7*). This explanation was confirmed by our studies in patients with uptake induced in metastases following surgery and/or I-131 thyroablation.

For our findings in the course of thyroid ablation, several possible mechanisms should be considered.

1. In a minority of patients, a true *de novo* induction of uptake in tumorous lesions takes place. This may be similar to the occasionally observed uptake in tumor tissue soon after thyroid surgery (*8*, and personal observations). Usually this induction is encountered on the followup scans only after a latent interval of induced hypothyroidism. The exact mechanism of the induction is not yet known but is believed to be connected with the plasma thyrotropin enhancement usually encountered at followup (*8*). Accepting the TSH mechanism, one would expect to see a TSH surge early after a thyroablative dose of I-131, yet this has not been reported. On the contrary, in most patients liberation of thyroid hormones from destroyed thyroid cells leads to a rise of plasma PBI and thyroxine.

Whatever the exact mechanism may be, it plays a role in some patients, where early therapeutic uptake is found in a distant metastasis that was missed by diagnostic I-131.

2. In the majority of patients, expecially in those with tumor tissue in the neck region, it may be speculated that uptake had been present at the time of diagnostic scanning but that it remained below

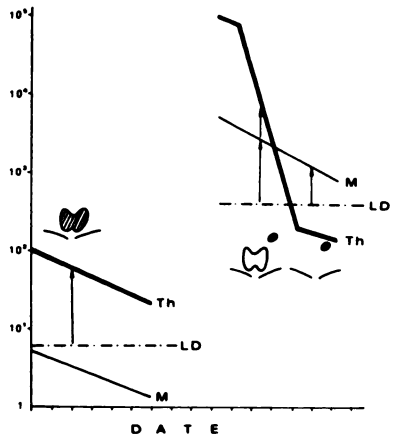

FIG. 5. Possible explanation of differences between diagnostic and therapeutic scans. Diagnostic scan is shown at left, where uptake in thyroid (Th) is 15 times that in adjacent metastases (M). Therapeutic scans (at right) are performed while thyroid is being destroyed: uptake in the metastatic lesion is now detectable. Extreme possibility is also shown when thyroid is destroyed and uptake is seen only in metastasis. LD = Scan's limit of detection.

the threshold of detection. The limit of detection by scan in these patients (see Fig. 5) depends not only on the usual difference between radionuclide concentration in tumor tissue and in blood but also other background. In a lymphatic metastasis close to the normal thyroid tissue, scanner adjustment makes the detection of the minute adjacent concentrations impossible. The possible hundredfold difference in uptake does not depend on background, and scanning later than 24 hr following diagnostic amounts cannot be expected to visualize these lesions. Only after the normal thyroid retention is rapidly injured by radiation, with little concomitant compromise of the metastatic tissue, can the latter be visualized (Fig. 5). This mechanism seems to explain most, if not all, cases of detection of metastases in regional lymph nodes.

In patients with low uptake, the blood level of I-131 is relatively high during the first few days after administration. The detection of metastatic lesions showing weak uptake is then difficult in highly vascularized tissues and in the lungs. When the blood levels of I-131 decrease, such lesions may be detected.

3. In theory, regional lymph nodes might become visible by retention in lymphatics of radioactive thyroglobulin liberated by thyroid destruction. This mechanism is only speculated, but suggestive scans have been obtained by radionuclide thyrolymphography in hyperthyroidism (*3*). In our hands, the scanning of thyrosuppressive amounts of I-131 in hyperthyroid patients has failed to show a similar pattern (unpublished observations).

Whatever may be the exact mechanism of the "early" uptake in tumor tissues found on therapeutic scans, this examination seems to be important for the correct staging of the disease. Moreover, frequent detection of unsuspected tumor is a further argument for systematic use of I-131 in the treatment of differentiated thyroid cancer as performed at our institute (*5,6*), and as recently confirmed in the United States (*2,4*).

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