CLINICAL STUDY

Diagnostic ^{131}I whole body scanning after thyroidectomy and ablation for differentiated thyroid cancer

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Abstract

Objective: To assess the value of the diagnostic whole body ^{131}I scan after thyroidectomy and ^{131}I ablation.

Design: Retrospective analysis of all patients with differentiated thyroid cancer treated in one centre between 1990 and 2000.

Results: A total of 153 consecutive patients who underwent diagnostic scanning following ablative therapy were identified. This diagnostic scan was positive in 20 patients (13%) and faintly positive in 16 patients (11%). The majority (117 patients) had negative scans. Of the 20 patients with positive scans, four received no further treatment, nine showed no abnormal uptake following a second ablative ^{131}I dose and seven had uptake in the thyroid bed (six) or in neck nodes (one) after repeat ablation.

Outcome: In the group with positive scans, the four patients who received no further treatment and the nine with a negative second ablation scan remained disease free during follow-up. No patient with a positive diagnostic scan received additional ^{131}I therapy which would not otherwise have been given based on the clinical findings, serum thyroglobulin (Tg) values or the presence of anti-Tg antibodies. Ten of the patients with negative scans developed recurrent disease which was always detected clinically or by a rising serum Tg value.

Conclusions: Diagnostic whole body ^{131}I scans add little extra information and in our experience do not influence patient management. They should be reserved for patients in whom serum Tg levels are unreliable because of the presence of antibodies or when there is clinical suspicion of tumour.

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Introduction

The management of differentiated thyroid carcinoma will usually require total or near-total thyroidectomy followed by ^{131}I ablation of any remnant thyroid tissue (1–3). A diagnostic ^{131}I whole body scan and serum thyroglobulin (Tg) measurements follow, either in the hypothyroid state or after recombinant thyroid-stimulating hormone (rhTSH) administration, to exclude residual disease in the neck or distant metastases (4–6).

The value of ^{131}I diagnostic imaging after thyroid ablation has recently been questioned by Cailleux *et al.* (7) who suggested that measurement of serum Tg after thyroxine withdrawal was a sufficiently sensitive marker of residual or metastatic disease by itself and that a diagnostic whole body scan yielded no additional information of clinical use. Similar conclusions were reached by Pacini *et al.* (8) in a study of patients with undetectable serum Tg after thyroid ablation.

In order to assess the potential value of the ^{131}I diagnostic scan after thyroid ablation, we have retrospectively examined the records of all patients with differentiated thyroid cancer treated in our unit over a 10-year period.

Patients and methods

The Royal Marsden Hospital serves as a tertiary referral unit for patients with thyroid disease and maintains a tumour registry of all thyroid cancer patients based on a confirmed histopathological report of thyroid malignancy. All information at presentation and during follow-up is entered, with patients followed until death; the cause of death is recorded.

Between 1990 and 2000, 153 consecutive patients with differentiated thyroid cancer were treated in our Unit according to departmental protocol; all patients underwent total thyroidectomy (defined as removal of

both thyroid lobes, the isthmus and pyramidal lobe) followed by iodine ablation (1.1–3 GBq ^{131}I). Residual normal thyroid tissue in the thyroid bed, with or without abnormal extra-thyroid radioiodine uptake, was detected in all cases on the ablation scan.

Four to six months later, a diagnostic ^{131}I scan (185 MBq) was performed after adequate thyroxine withdrawal (TSH > 30 U/l) according to our protocol and based on national guidelines (9). Blood was sampled for serum Tg at the time of the diagnostic scan (off thyroxine) and 1 month after the scan whilst taking thyroxine. Serum Tg was assayed by an immunoradiometric assay (Cis Bio-international, Saclay, France) with a detection limit of 0.5 µg/l. Tg measurements at the time of ablation and those taken at the time of the diagnostic scan were performed after adequate thyroxine withdrawal (TSH > 30 U/l).

Anterior and posterior whole body scans were obtained 48–72 h following oral administration of 185 MBq ^{131}I , following cessation of thyroxine for 3 weeks or tri-iodothyronine for 10 days. Patients were on a low iodine diet during the time that replacement hormone was stopped. Scans were obtained with a dual-headed gamma camera in whole-body scanning mode using a high energy collimator with a 20% energy window centred around 364 kiloelectron volts (keV).

The diagnostic whole body scan was assessed by two experienced nuclear medicine physicians (G H and C H) and classified as either *negative*, *faintly positive* or *definitely positive*. Scans categorised as *faintly positive* showed a ghost-like remnant of probably normal thyroid tissue, uptake was confined to the thyroid bed and was only just above background activity levels. *Definitely positive* scans showed uptake either by normal remnant thyroid tissue or by tumour in the thyroid bed or neck nodes.

A second ablative dose of radioiodine was administered to patients showing significant uptake on diagnostic scanning despite previous ablative therapy in accordance with national guidelines (9). The rationale for this further therapy was to ensure complete ablation of thyroid remnant tissue and eliminate any remnant disease.

Results

A total of 153 consecutive patients undergoing initial ^{131}I diagnostic whole body scan 4–6 months following total thyroidectomy and ablative ^{131}I were identified. Patients were treated between 1990 and 2000 with a median follow-up of 7 years (range 3–13 years). There were 125 females and 28 males of median age 43 years (range 15–78) with papillary (121), follicular (25) or Hurthle cell (seven).

Table 1 summarises the clinical stage and histological type of carcinoma in relation to appearances on

Table 1 Clinical stage and histological type in patients with positive, faintly positive and negative diagnostic whole body scans.

	Positive	Faintly positive	Negative
Patient nos	20	16	117
Male: female	5: 15	7: 9	16: 101
Age (mean years)	41	43	45
T stage			
T1	4	4	21
T2	8	11	67
T3	3	1	15
T4	5	0	9
TX	0	0	5
Nodal stage			
N0	16	13	94
N1	4	3	18
NX	0	0	5
Histology			
Papillary	17	12	92
Follicular	1	3	21
Hurthle	2	1	4

Staging by UICC (10).

the diagnostic whole body scan. Twenty patients had a *positive* scan, the scan was classified as *faintly positive* in 16 patients and in 117 the scan was *negative*.

Positive ^{131}I diagnostic whole body scan

In 20 patients (13%), the diagnostic scan was classified as positive with significant uptake in the thyroid bed or in local lymph nodes. Sixteen of these received a further dose of 5.5 GBq ^{131}I to ensure complete ablation of any remnant disease according to our protocol (based on national guidelines). The serum Tg values for these 16 patients is shown in Table 2.

The remaining four remained disease free after no further treatment, and uptake in the neck was considered to represent normal thyroid remnant. Mean serum Tg for these four patients was 1 µg/l (range 1–4.9) and in all patients fell to <1 µg/l 1 month after diagnostic scanning.

In nine of the 16, the scan became negative after repeat ablation ^{131}I ; all had normal serum Tg levels (<1 µg/l) 1 month after scanning (Table 2).

In the other seven patients, following the second ablative dose of radioiodine, scanning showed uptake in the thyroid bed in six and in neck nodes in one. Serum Tg was elevated at the time of the diagnostic scan in six of these seven patients and, because of this elevation, they would have received ^{131}I therapy irrespective of the scan appearance. The seventh patient had a normal serum Tg but anti-Tg antibodies were present at a titre of 1 in 160; according to protocol she would have required a diagnostic scan and would have proceeded to ^{131}I therapy. At follow-up all seven patients are alive, with no clinical or biochemical evidence of disease.

Table 2 Mean (range) serum Tg ($\mu\text{g/l}$) at the time of diagnostic scanning and 1 month later in patients with positive and faintly positive diagnostic scans following ablation.

	Patient nos	Tg at scan	Tg 1 month later
Positive scans remaining positive after second treatment	7	8 (1–1826)	13 (1–222)
Positive scans becoming negative after second treatment	9	8 (1–22)	<1
Faintly positive scans (no second treatment given)	15	3.7 (1–29)	<1
Faintly positive scan becoming negative after second treatment	1	24	5.5

Faintly positive scan

Faint uptake within the thyroid bed was documented in 16 (11%) of patients. Serum Tg in 15 of these patients was $<1 \mu\text{g/l}$ and these patients received no further treatment. In one patient the serum Tg was elevated at $24 \mu\text{g/l}$ at the time of the diagnostic scan and he received 5.5 GBq radioiodine therapy to eliminate any residual remnant disease. Following treatment, his scan became negative and 1 month after the scan Tg had fallen to $5.5 \mu\text{g/l}$. All 16 patients remain free of disease at follow-up.

Negative scan

Diagnostic whole body scanning was negative in 117 (76%) patients. In one patient, (patient 1; Table 3) serum Tg was elevated at $521 \mu\text{g/l}$ at the time of the scan and metastatic lung disease was visible on chest X-ray. He responded poorly to treatment and died of disease. No further radioiodine therapy was given to the remaining 116 patients in the year following the diagnostic scan. However, ten patients (9% of those with

negative diagnostic scans) developed evidence of recurrent thyroid carcinoma after 1–8 years. Clinical details and serum Tg results are shown in Table 3. Relapse was identified by rising serum Tg with or without a palpable neck mass (six patients) or by clinical findings (neck recurrence) with normal serum Tg. In two cases, the serum Tg was not recorded at the time of relapse.

Each patient was reviewed in a multidisciplinary setting and underwent surgery, further radioiodine or external beam radiotherapy as appropriate. At last follow-up, six of these ten patients remain well with no evidence of disease and four are alive with disease.

Discussion

The diagnostic whole body scan serves as an adjunct to clinical evaluation and serum Tg testing following thyroidectomy and ablative ^{131}I therapy. A positive diagnostic scan may demonstrate persistent disease following ablation (11) and confirms iodine avidity.

In this study, we found that the presence of a positive or faintly positive scan added little extra information

Table 3 Clinical details and serum Tg ($\mu\text{g/l}$) at the time of diagnostic scans and 1 month later in patients with negative diagnostic scans who subsequently relapsed.

Patient	Age (years)	Sex	Stage (histology grade)	Tg at scan (off T4)	1 month Tg (on T4)	Recurrence	Status
1	61	F	T1N0 Pap 1	521	NA	Lung at 8 years. Tg 627. Therapy scan – ve	AWD
2	70	M	T3N0 Pap 2	55	< 1	Submandibular at 6 years excised	NED
3	73	F	T3N0 Fol 1	2.8	1.6	Loco regional at 1 year. Tg 360. Diagnostic scan – ve	AWD
4	74	F	T4N0 Pap 2	< 1	< 1	Loco-regional at 2.5 years. Tg < 1. Surgery and external beam RT	NED
5	31	F	T2N1 Pap 1	< 1	< 1	Loco-regional at 6 years. Tg < 1. Further radioiodine	NED
6	48	F	T2N0 Pap 1	26	3	Loco-regional at 8 years. Surgery and radioiodine	NED
7	62	F	T4N1 Pap 1	19	3	Loco-regional at 1 year. Tg 105. Further radioiodine	AWD
8	43	F	T4N1 Pap 1	99	13	Loco-regional at 4 years. Tg 322. Further radioiodine	NED
9	45	F	T1N0 Pap 1	< 1	< 1	Loco-regional at 3 years. Rising serum Tg. Further radioiodine	NED
10	65	F	T2N0 Pap 1	22	18	Loco-regional at 2 years. Rising Tg. Further radioiodine	AWD

T4, thyroxine; M, male; F, female; Stage, staging by UICC (1997) TNM; Tg at scan, serum Tg at time of diagnostic scan; 1 month Tg, serum Tg 1 month after scan; Fol, follicular; Pap, papillary thyroid carcinoma; RT, radiotherapy; NED, no evidence of disease; AWD, alive with disease; NA, result not available; Loco-regional, recurrence in thyroid bed or local lymph nodes.

and would not have influenced patient management. The diagnostic whole body scan was considered definitely positive in 20 patients (13% of all patients) and faintly positive in an additional 16 patients (11% of all patients). Yet in none of these patients with a positive scan was a therapy dose given that would not otherwise have been administered on the basis of clinical findings, elevated serum Tg values or the presence of anti-Tg antibodies.

It seems likely that the uptake seen on the diagnostic scans in the four patients who received no further treatment and who remained disease free up to 10–13 years was in normal remnant thyroid tissue. A similar explanation applies to the positive scans in nine patients where the second ablation scans were negative. Scans following ablative ^{131}I have a greater sensitivity to detect residual disease than the diagnostic scan, since sensitivity relates to the dose of ^{131}I given (12–13). Furthermore, serum Tg values were undetectable in all nine, implying that these patients did not have persistent disease.

It is possible that the diagnostic ^{131}I dose may have resulted in a stunning effect resulting in a negative post-treatment scan in these nine patients. The dose of 185 MBq ^{131}I used in diagnostic imaging has been shown to reduce the subsequent uptake of ^{131}I sufficiently to affect the outcome of the therapy dose (14). Use of ^{123}I with a smaller radiation dose to the thyroid might prevent stunning without loss of diagnostic accuracy (14). However, a stunning effect from the diagnostic dose seems an unlikely explanation in our patients as a sub-optimal absorbed therapy dose would have been expected to have resulted in relapse in at least some of these patients but they all had low or undetectable serum Tg levels.

Other investigators have previously reported little value from diagnostic imaging after total thyroidectomy and ablative iodine therapy (8, 15). In these studies, undetectable serum Tg levels ($\text{Tg} < 1 \mu\text{g/l}$) whilst hypothyroid or after rhTSH stimulation were highly predictive of disease-free status and a diagnostic scan in these circumstances did not change clinical management. There was no evidence that faint uptake in the thyroid bed predicted persistent or recurrent disease.

At the time of relapse, we noted undetectable serum Tg on thyroxine therapy in two of ten patients. In a previous study, Mazzaferri & Kloos (15) reported low sensitivity of unstimulated Tg levels in the detection of persistent or recurrent disease: as many as 10% of patients with persistent tumour had low unstimulated serum Tg values.

However a serum Tg value $> 2 \mu\text{g/l}$ after rhTSH stimulation had a negative predictive value of 100% and a very low false positive rate. It is possible, therefore, that TSH-stimulated Tg values would have been elevated at the time of relapse in all our patients.

We found the TNM status of the tumour was frequently not predictive of persistent or recurrent disease

in keeping with a recent study (15). We observed disease relapse as frequently in patients with relatively low TNM status (T2N1 or less) as in those with higher initial tumour burdens. Relapse was detected by clinical findings in the neck or by a rising serum Tg level.

Our findings suggest that diagnostic whole body imaging using ^{131}I adds no information of value to further management. Patients with a definitely positive scan could have been predicted by clinical findings or serum Tg values; a faintly positive scan was of no clinical significance. Of those with a negative scan, recurrence was detected clinically or by serum Tg. Our results are based on a median follow-up of 7 years which is comparable with similar studies (7, 8) although we urge caution in interpreting results in patients with a follow-up of less than 5 years.

Surveillance with clinical examination supplemented by measurements of stimulated serum Tg (off thyroxine or after rhTSH) provides the best means of following patients treated for differentiated thyroid carcinoma and will be highly predictive of complete remission.

Tg measurement is unreliable in the presence of anti-Tg antibodies (16, 17) and for these patients diagnostic scanning retains a valuable role.

Current British guidelines do not include neck ultrasonography in the routine follow-up of patients treated for differentiated thyroid cancer. Other groups have found this to be useful (18). Ultrasound examination has the potential to detect lymph node disease when serum Tg is low or undetectable and may therefore be valuable in deciding on the need for further therapy.

We conclude that diagnostic whole body scans need not be performed routinely following total thyroidectomy and radioiodine ablation but should be reserved for those patients in whom serum Tg values are unreliable (in the presence of antibodies) or if TSH-stimulated Tg measurements are not available.

In agreement with current consensus guidelines, use of diagnostic scanning is considered optional (9). Further studies are needed to confirm whether diagnostic scans with ^{123}I will prove to have superior clinical usefulness to conventional ^{131}I scanning (19).

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