Therapeutic implications of thymic uptake of radioiodine in thyroid carcinoma

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Abstract. The management of 38 consecutive patients with differentiated thyroid carcinoma in the period 1991–1996, who each received at least one therapy dose of iodine-131, was reviewed, looking in particular at those in whom anterior mediastinal uptake was demonstrated on scans taken 3 and 7 days post-therapy. Such activity was noted in ten patients. On the basis of clinical follow-up, thyroglobulin measurement and radiological and other scintigraphic imaging, in nine of the ten patients the anterior mediastinal activity was attributed to physiological thymic uptake. Of those nine, all were under 50 years of age; seven were considered disease free, one had residual disease in the neck and one had distant metastases. Physiological uptake by the thymus was more prominent on the 7-day scans and in patients with low tumour volumes. For appropriate patient management it is essential to recognise that physiological uptake of ^{131}I by the thymus in patients under 50 years of age is a potential cause of false-positive therapy scans.

Key words: Anterior mediastinum – Thymus – Radioiodine – Therapy scans

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Introduction

Differentiated thyroid cancer is an uncommon tumour, but has a good prognosis when treated adequately. The mainstay of treatment is surgical removal of the primary malignancy and debulking of large accessible secondaries. Radioiodine treatment is often used as an adjunct to surgery since this has been associated with increased survival. There remains debate, however, over the selection of patients for radioiodine therapy. Although therapy is safe, there have been reports that there is a small risk of second malignancies [1, 2], especially where the cumulative dose has exceeded 1 Ci (37000 MBq) [3]. Treatment is usually well tolerated but can be associated with nausea or vomiting, radiation thyroiditis or sialadenitis [4, 5]. Admission to hospital and isolation for a period of time for radiation protection purposes is often required. With this background it is clear that the indications for radioiodine therapy should be clearly defined and clinically justifiable.

A controversy in the management of patients with thyroid cancer relates to the optimum protocol for monitoring patients to identify recurrent disease. Thyroglobulin measurements are highly sensitive but are subject to individual assay variation, and some differentiated tumours which concentrate iodine do not secrete thyroglobulin [6]. Differences exist between thallium (^{201}Tl), ^{99}Tc-sestamibi, ^{18}F-fluorodeoxyglucose (FDG) and iodine tracer scans [7, 8] in the detection of disease. It is accepted that low dose iodine tracer scans can be negative when therapy scans are positive [9]. Further concern arises as to whether tracer scans may result in stunning of malignant disease, with resultant reduced uptake of radioiodine used in therapy [10]. Perhaps, therefore, the only true assessment of the ability of a tumour to take up radioiodine is whether the post-therapy scan is positive. If post-therapy scans are considered to be the investigation of choice to determine further treatment, it is likely that some patients will receive radioiodine who no longer have tumour present. This likelihood may be further increased in patients who have false-positive iodine scans.

False-positive uptake has been found in a number of situations following radioiodine administration [4]. Amongst the causes of false-positive uptake there have been several case reports of mediastinal activity following therapy doses of radioiodine in young people, which on biopsy turned out to be uptake in normal thymus [11–15]. Where uptake of radioiodine occurs in the thymus, misinterpretation could lead to inappropriate therapy, the incidence of which might be reduced if patterns of physiological uptake in the thymus can be characterised.

We have reviewed patients treated with radioiodine with post-therapy scans to assess the frequency and na-

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ture of thymic uptake, with specific reference to the timing of post-therapy scans and the pattern of mediastinal uptake seen.

Materials and methods

A retrospective analysis of patients treated with radioiodine for thyroid cancer between 1991 and 1996 was performed. All patients had undergone surgical removal of the tumour which was carried out at several referral centres with the surgical resection varying from partial to total thyroidectomy.

After surgical resection patients had a thallium scan and thyroglobulin measurement prior to treatment with an ablative activity of radioiodine in the range 2220–2775 MBq. Patients were retreated until all thyroid tissue was ablated or the uptake on therapy scans was so low that further therapy was considered unjustified. All patients were monitored with regular thyroglobulin measurements taken whilst on thyroid hormone replacement and with suppressed thyroid-stimulating hormone (TSH) levels. Other imaging tests were performed to exclude residual disease and included scanning with ^{201}Tl, magnetic resonance imaging (MRI), computed tomography (CT) or FDG positron emission tomography (PET).

All patients scheduled to receive radioiodine had thyroid hormone replacement stopped prior to therapy. Patients taking thyroxine were converted to tri-iodothyronine for 6 weeks, which was then stopped 10 days prior to radioiodine therapy and restarted after the last post-therapy scan. Iodine-131 with activities in the range 2220–7400 MBq was administered under in-patient supervision and scintigraphic images obtained 3 and 7 days post therapy. Iodine images were acquired using a Starport (IGE Medical Systems) single-headed gamma camera with a high-energy collimator. Three days post therapy, two sets of images were taken, the first being anterior and posterior whole-body views with acquisition times of 10–15 min per metre, the second, a single anterior view of the neck and thorax (acquisition time of 5–10 min). Seven days post therapy, further anterior and posterior views of the head and neck were taken with other views when clinically indicated.

During the in-patient stay, all patients were reviewed daily and when they attended for the day 7 scan. Further clinical review was undertaken 8–12 weeks post therapy, at which time TSH and thyroglobulin (Tg) were measured. Regular clinical follow-up ranged from 2- to 6-month intervals and the Tg and TSH levels were rechecked. Where there was concern of disease progression, additional imaging such as CT, ^{201}Tl, MRI or FDG PET imaging (or, if appropiate, surgical re-exploration) was carried out and the requirement for further therapy reassessed. When CT was performed this was usually done without contrast and with 10-mm slices. In some cases where CT was performed immediately after radioiodine therapy, contrast was given, but further radioiodine therapy was never administered until at least 3 months after contrast in these cases.

The scintigraphic images obtained were reviewed retrospectively by two nuclear medicine physicians looking initially for mediastinal uptake on either the day 3 or day 7 scans and then for any differences in appearance between this pair of scans. The management of those patients in whom mediastinal activity was present was then reviewed in detail.

The clinical findings, biochemistry and additional nuclear and radiographic imaging were reviewed by a nuclear medicine physician and radiologist not directly responsible for the patient's care. All CT scans were reviewed without knowledge of the patient's identity or clinical details. The likelihood of residual or recurrent disease being present was assessed at the time of review and the probable nature of the mediastinal activity commented upon. The impact of mediastinal uptake on management was also considered.

Table 1. Clinical characteristics, post-therapy scan findings and follow-up data of study patients with mediastinal uptake

Pt. no.	Age (yrs)	Sex	Tumour type	CT appearance of thymus	Persistent uptake outside the mediastinum	Mediastinal uptake pattern	Thyroglobulin (μg/l)	ΣT	F/up (mo)	Disease status
1	20	F	Mixed	N	No	Diffuse	<1	2	6	DF
2	29	M	Papillary	N	No	Diffuse	Raised initially <1 after therapy	7	75	DF
3	32	F	Mixed	Ns	No	Diffuse	28 prior to surgery, 10 after resection of normal thyroid	2	19	?DF
4	33	F	Hürthle	Ns	No	Diffuse	<1	1	7	DF
5	36	F	Mixed	N	No	Diffuse	Raised initially <1 after therapy	3	31	DF
6	42	M	Hürthle	N	No	Dumbbell	<1	2	12	DF
7	45	M	Mixed	N	No	Dumbbell	<1	3	27	DF
8	26	F	Mixed	N	Neck	Diffuse	<1	3	18	LD
9	27	F	Papillary	Abnormal initially, N with therapy	Lung	Diffuse	Raised	13	69	MD
10	85	F	Papillary	Abnormal	Lung	Focal	Raised	10	75	MD

N, Normal; Ns, no scan; ΣT, number of treatments given; F/up, follow up; DF, disease free; LD, local disease; MD, metastatic disease

Results

Thirty-eight consecutive adult patients (13 male, 25 female) were reviewed, of whom ten (the study group) were found to have radioiodine uptake within the mediastinum, following a therapeutic dose of ^{131}I (2220–7400 MBq). Among these ten, the number of therapy doses individual patients had received ranged from 1 to 13 (mean 5), with nine of the study group having received more than one ablative dose of radioiodine.

The study group comprised three males and seven females with an age range of 20–85 years (mean 37.5; median 32.5); nine of these patients were under the age of 45 years. They were followed-up for a mean period of 34 months (range 6–75, median 23). At the time the review was undertaken, seven were considered to be disease free, one had residual disease in the neck and two had metastatic disease (Table 1).

The remaining 28 patients (10 males and 18 females), were aged 22–86 years (mean 59; median 62) with seven under the age of 45 years. They were followed-up for a mean period of 38 months (range 1–71, median 33). Of this group, 16 were considered to be disease free, six had local disease and six had metastatic disease. The number of therapies given to individual patients in this group ranged from 1 to 8 (mean 3).

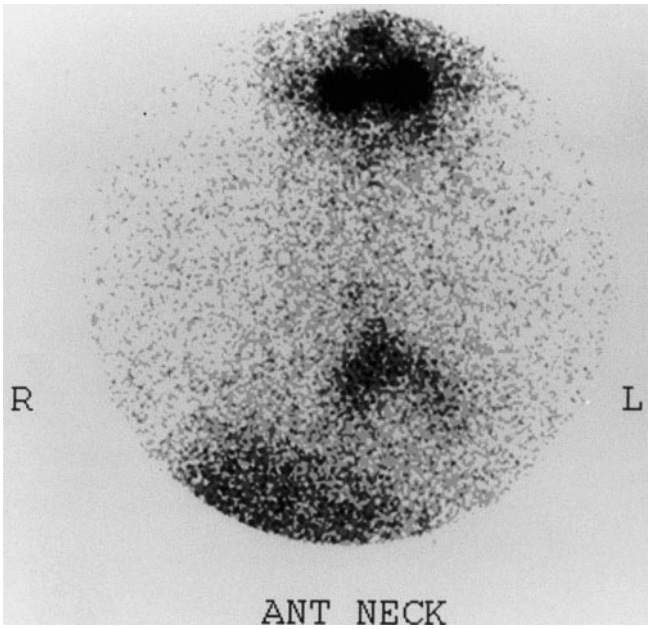

Fig. 2. Patient 7. Striking uptake of radioiodine is seen in the anterior mediastinum on the 7-day post-therapy scan in this 45-year-old man which appears "dumbbell" shaped. The patient was given therapy after this scan was performed, probably unnecessarily as this appearance was later deemed to represent physiological uptake in normal thymus

Scan findings in the ten patients with mediastinal uptake

Three-day (early) and 7-day (late) post-therapy scans were reviewed for each patient to assess mediastinal activity. Patient 1 had uptake on both early and late scans. Patients 2–8 demonstrated persistent mediastinal activity only on the late scans; patient 9 showed mediastinal activity on both the early and late scans in the first nine post-therapy scans, subsequently mediastinal activity was seen only on late scanning. Patient 10 showed no mediastinal activity on the final two post-therapy scans (Table 1).

The activity was characterised as focal in one case (Fig. 1A, patient 10), as "dumbbell" shaped in two cases (Fig. 2, patients 6 and 7) and as diffuse in the remaining seven cases (Fig. 3). The uptake in the mediastinum ap-

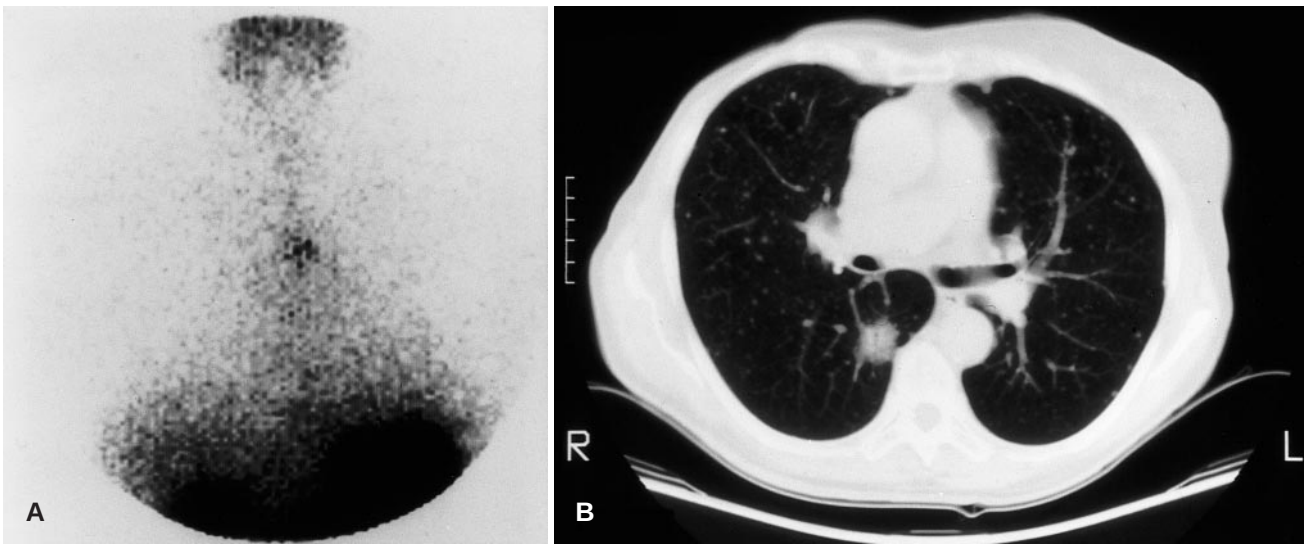

Fig. 1A, B. Patient 10. Focal increased uptake of radioiodine is seen on the 7-day post-therapy scan acquired of the anterior neck and chest in this 85-year-old patient (**A**). No accumulation of iodine is seen within the multiple pulmonary metastases visible on the CT scan (**B**)

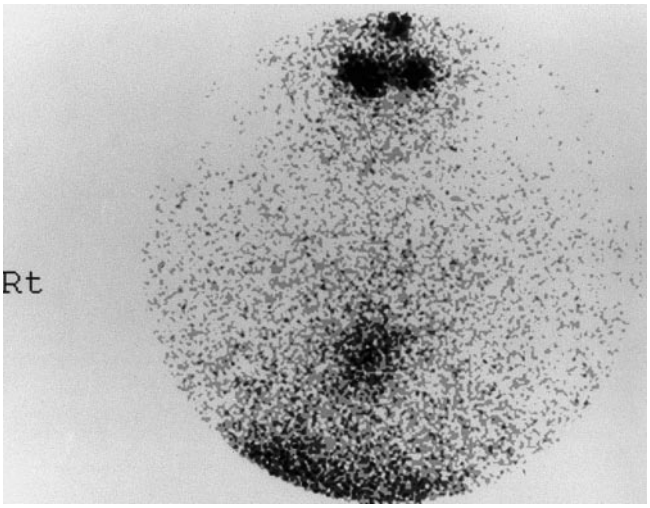

Fig. 3. Patient 2. Diffuse uptake of radioiodine in the anterior mediastinum was the most commonly observed pattern of physiological thymic uptake

peared to increase with repeated therapy as the amount of thyroid tissue or tumour concentrating radioiodine diminished (Fig. 4, patients 1–3 and 5–9).

Radioiodine uptake in the rest of the body was also recorded. In patient 1, a thyroid remnant was identified in the initial scan. In patient 3 uptake in the neck was seen which was subsequently resected and proved to be normal thyroid tissue. In patient 8, there was persistent abnormal accumulation indicative of residual tumour in the neck. Patients 9 and 10 had pulmonary metastases with poor radioiodine accumulation.

Of the nine patients who received more than one dose, five (patients 2, 3, 5, 9, 10) were retreated because of abnormal Tg and increased uptake on the post-therapy radioiodine scans. Three patients were retreated on the basis of aggressive histology and persistent thyroid bed activity (1, 6, 8) but had normal Tg levels. Patient 7 was retreated because of unexpected mediastinal accumulation of radioiodine on the late images, deemed by the reviewers to represent normal thymic uptake. As a result of review, the mediastinal uptake was considered physiological in nine of the ten study cases.

Patients 1, 2, 4, 5, 6 and 7 were regarded as disease-free at the time of the review. This conclusion was based on clinical examination and undetectable Tg levels combined with negative post-therapy scans (except for mediastinal uptake). In addition, CT showed normal thymus in patient 2. CT and MRI in patient 5 showed normal small thymus and normal mediastinum respectively. CT in patient 6 showed a normal mediastinum. CT in patient 7 showed a normal thymus with physiological uptake of FDG only on the PET scan.

Patient 3 had an elevated thyroglobulin level despite total thyroidectomy, rising to 28 μg/l during the course of treatment with focal uptake in the right side of the neck on post-therapy scanning. At repeat surgery, normal thyroid tissue was excised. Subsequent post-therapy scanning showed no uptake except persistent faint diffuse mediastinal uptake. Thyroglobulin level fell to 10 μg/l 3 months after operation. Continued follow-up will be required to determine whether this patient is now disease free.

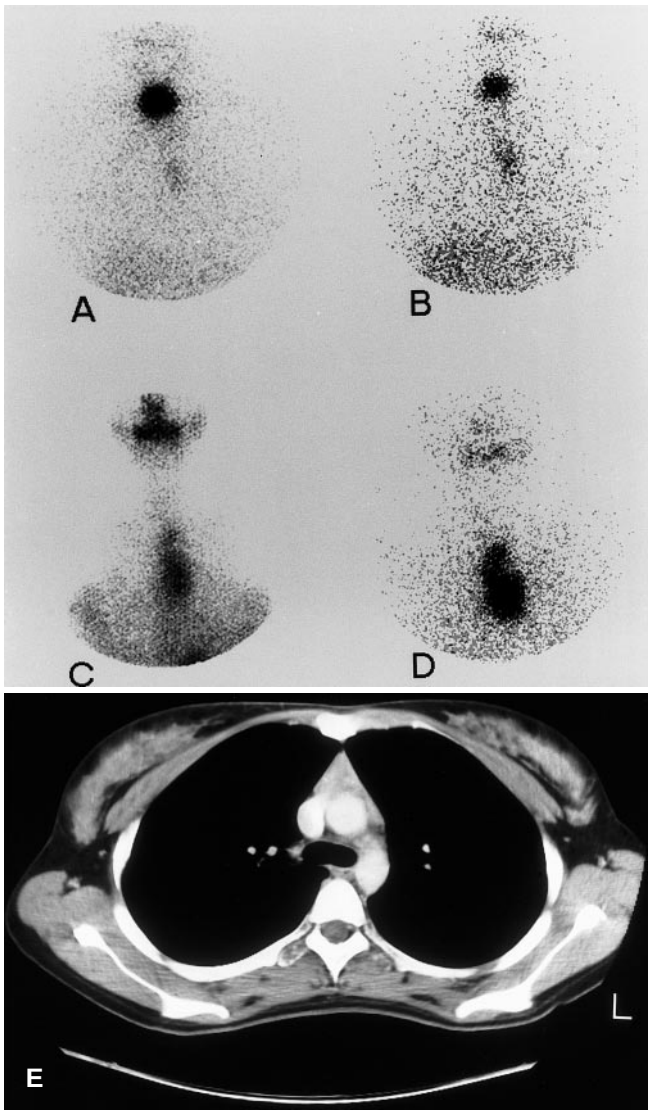

Fig. 4A–E. Patient 1. Low-grade uptake of iodine is seen after the first radioiodine treatment in the thymus gland of the youngest patient in the study group. Uptake is also seen in the thyroid remnant. (**A**) Thymic uptake intensifies at 7 days compared with the earlier scan (**B**). On the second therapy, where there is less thyroid remnant to concentrate radioiodine, the uptake in the thymus gland is increased at 3 days (**C**) and at 7 days (**D**) compared with previous scans. CT scanning of the chest after the second therapy dose revealed a normal thymus gland (**E**)

Patient 8 had evidence of residual disease in the neck with persistent uptake on post-therapy scans despite three administrations of radioiodine. Her Tg was never elevated. CT scan, however, demonstrated a normal thymus at the site of low-grade uptake in the anterior mediastinum on late therapy scanning.

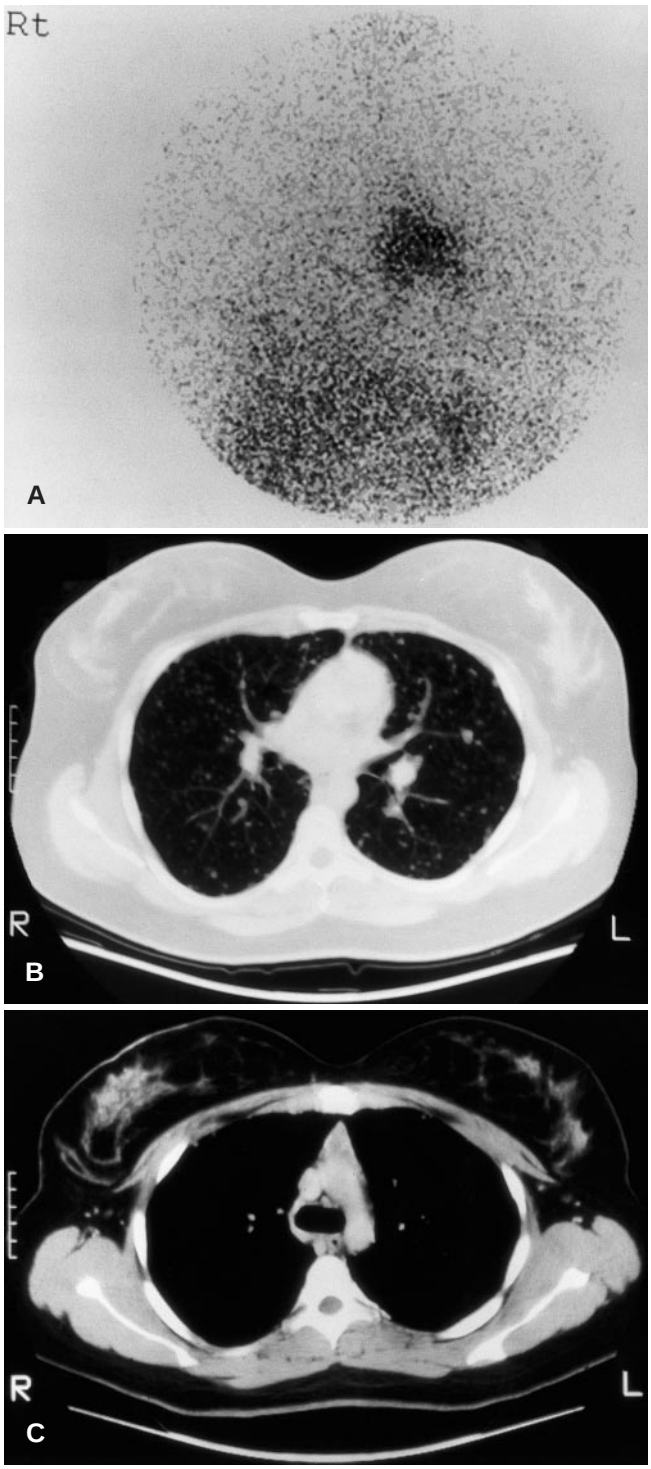

Fig. 5A–C. Patient 9. Diffuse uptake of radioiodine is seen in the thymus of this 27-year-old patient on the post-therapy scan following her 10th treatment (**A**). No uptake of radioiodine is seen within the multiple pulmonary metastases seen on CT (**B**). Her thymus gland had a normal appearance on CT (**C**)

Patients 9 and 10 had extensive metastatic pulmonary disease demonstrated by CT with rising Tg levels. The mediastinal uptake was deemed to be physiological in patient 9 at the completion of the study (Fig. 5) and pathological in patient 10 (Fig. 1). The mediastinal uptake in patient 9 was initially seen on early and late therapy images and corresponded to a bulky mass in the region of the thymus, which was regarded as tumour. Initially high iodine retention in the lungs diminished as the disease progressed. Despite reduction of iodine uptake at the sites of known metastases in the lung fields, low-grade activity continued to be present but only on the late post-therapy images in the anterior mediastinum. The mediastinal activity appeared to intensify as the ability of the tumour in the lungs to take up radioiodine decreased. Repeat CT demonstrated pulmonary metastases but a normal appearance to the thymus in contrast to earlier scans.

Patient 10 was the oldest patient in the study group at 85 years. The mediastinal uptake seen on post-therapy scanning was focal in nature and diminished as the avidity of the tumour for radioiodine decreased. In combination with evidence of disease progression on CT and rising thyroglobulin measurements, the mediastinal activity seen during the course of treatment was considered pathological.

Scan findings in the 28 patients with no mediastinal uptake

None of this group had evidence of mediastinal uptake on either the early or the late scans. Sixteen were considered to be disease free (based on negative scans and negative Tg results), six had local disease (evidenced by elevated Tg and uptake in the thyroid bed on post-therapy scans and/or thallium scans) and six had metastatic disease (pulmonary and bone iodine uptake).

Discussion

Radioiodine therapy has been an established part of the treatment of thyroid cancer for more than 40 years. The primary treatment of malignant thyroid disease is surgical resection, the extent of which remains a matter of some controversy [16, 17]. In reality, often the thyroid specialist is presented with patients from a variety of surgeons with treatments that range from lobectomy to subtotal or total thyroidectomies and thus ablative therapy or therapy for metastatic disease is necessary.

The decision to treat a patient is based on a variety of factors, but will typically involve the nature and size of the primary tumour, evidence of local or distant spread, and the age of the patient. Perhaps more controversial is the decision when to retreat. The presence of an elevated Tg level indicates the presence of functioning thyroid tissue and should indicate therapy with iodine if there is no specific contraindication. The role of tracer scans is a subject of controversy concerning both the optimal activity for diagnostic information and the induction of stunning [7, 10]. Whatever activity is administered, there is no doubt that post-therapy scans can depict a larger

volume of disease than is found using tracer studies. The protocol employed in our practice is to use the previous post-therapy scan to demonstrate disease and as an indication for further therapy, until the therapy scan becomes negative or until uptake is so poor that further therapy is not justified. Whilst other parameters, particularly Tg measurements, play an important part in monitoring patients, the therapy scan is a pivotal investigation in our institution.

The variable uptake that can occur in normal thymus is a potential limitation to using the post-therapy scan in this way. Practitioners must be wary of such uptake which may be misinterpreted as presence of disease and led to an inappropriate administration of radioiodine in one patient in our series. Ramanna et al. [18] described uptake of iodine in the mediastinum in 10 out of 85 patients with both tracer and post-therapy scans which was attributed to ectopic, non-malignant thyroid tissue. A number of other case reports have demonstrated this phenomenon. We have described the pattern of physiological mediastinal activity as either "diffuse" or "dumbbell". The relevance of these patterns is uncertain but although not formally commented upon, they have been illustrated in case reports with associated biopsy evidence of thymic uptake [11–15]. Imaging in these studies was performed within 4 days of iodine administration and the patients were under 28 years of age, with the exception of a single patient of 43 years who had faint mediastinal uptake [15]. We observed that physiological thymic uptake was seldom apparent (with one exception; patient 1, the youngest) on the scan performed at 3–4 days but was clearly seen on the 7-day scan. This is likely to reflect a combination of clearance of blood pool activity and the comparative relative inefficiency with which the thymus traps iodine. Thymic hyperplasia has been demonstrated after chemotherapy [19], but there is no documented evidence of this after ^{131}I therapy.

Michigishi et al. [14] suggest that patients with mediastinal uptake can be separated into benign and malignant causes on the basis of the following criteria: (a) uptake that becomes more prominent with repeated treatment, (b) requirement of higher than usual iodine doses to visualise the area, (c) a young age, (d) a large thymus on CT and (e) a low serum Tg level. The results of Ramanna et al. [18] demonstrate that occasionally uptake in the mediastinum can be seen even with tracer scans. Our study confirms that with high activities and late scans physiological uptake in the thymus is commonly seen in young patients. With repeated therapy there was a tendency for the thymic uptake to become more prominent as the volume of normal thyroid and/or tumour concentrating radioiodine decreased. A low Tg is helpful in supporting a benign aetiology for mediastinal uptake, but corroboration with CT, MRI, ^{201}Tl or FDG PET is required in cases of uncertainty before proceeding to further radioiodine administration.

Our results also suggest that "young" may need to be defined as less than 50 years since physiological uptake was seen in a 45-year-old. Vermiglio et al. [11] have demonstrated that iodine is concentrated within follicle-like structures, formed with the involution of the Hassall's bodies of the thymus. D'Anna et al. [20] describe the involution phase of the thymus as comprising a number of active processes, one such being the re-organization, in terms of structure and function, of the epithelial framework. Although maximal activity occurs in younger people, there is variability between individuals as to the age at which this occurs. Amongst our study population, of those patients under 50 years, half had thymic uptake and half had no thymic uptake. With reference to disease state and number of therapies, these two groups were well matched.

Conclusion

Thyroid carcinoma is usually treatable and therapy is planned in the majority of patients with "cure" as the aim. However, it is important to acknowledge that therapy can have associated small risks, both at the time of administration and in the longer term. For this reason the administration of unnecessary therapy doses of radioiodine should be avoided. This study, combined with other case reports, illustrates the need to be aware of physiological uptake in the thymus as a cause for false-positive post-therapy scans, which are not uncommonly seen in patients under 50.

References

1. Edmonds CJ, Smith T. The long-term hazards of the treatment of thyroid cancer with radioiodine. *Br J Radiol* 1986; 59: 45–51.
2. De Vathaire F, Schlumberger M, Delisle MJ et al. Leukaemias and cancers following iodine-131 administration for thyroid cancer. *Br J Cancer* 1997; 75: 734.
3. Pochin EE. Long-term hazards of radioiodine treatment of thyroid carcinoma. In: Hedinger C, ed. *UICC monograph series, vol 12. Thyroid cancer.* Berlin Heidelberg New York: Springer; 1969: 293–304.
4. O'Doherty MJ, Nunan TO, Croft DN. Radionuclides and therapy of thyroid cancer. *Nucl Med Commun* 1993; 14: 736–755.
5. Allweiss P, Braunstein GD, Katz A et al. Sialadenitis following I-131 therapy of thyroid carcinoma: a concise communication. *J Nucl Med* 1984; 25: 755–758.
6. Sherman SI, Tielens ET, Sostre S et al. Clinical utility of post treatment radioiodine scans in the management of patients with thyroid carcinoma. *J Clin Endocrinol Metab* 1994; 78: 629–634.
7. Reynolds JC, Robbins J. The changing role of radioiodine in the management of differentiated thyroid cancer. *Semin Nucl Med* 1997; 2: 152–164.
8. Fridrich L, Messa C, Landoni C et al. Whole-body scintigraphy with ^{99}Tc^{m}-MIBI, ^{18}F-FDG and ^{131}I in patients with metastatic thyroid carcinoma. *Nucl Med Commun* 1997; 18: 3–9.
9. Nemec J, Rohling S, Zamrazil V et al. Comparison of the distribution of diagnostic and thyro-ablative I-131 in the evaluation of differentiated thyroid carcinoma. *J Nucl Med* 1979; 20: 92–97.

10. Coakley AJ. Thyroid stunning. *Eur J Nucl Med* 1998; 25: 203–204.
11. Vermiglio F, Baudin E, Travagali JP et al. Iodine concentration by the thymus in thyroid carcinoma. *J Nucl Med* 1996; 11: 1830–1831.
12. Bestagno M, Pagliaini R, Maira G, Pizzocaro C. Mediastinal uptake of 131-I in patients with thyroid cancer: may it be referred to the normal thymus [letter]? *Eur J Nucl Med* 1993; 20: 648.
13. Veronikis IE, Limkin P, Braverman LE. Thymic uptake of iodine-131 in the anterior mediastinum. *J Nucl Med* 1996; 37: 991–992.
14. Michigishi T, Mizukami Y, Shuke N et al. Visualization of the thymus with therapeutic doses of radioiodine in patients with thyroid cancer. *Eur J Nucl Med* 1993; 20: 75–79.
15. Jackson GL, Flickinger FW, Graham WP et al. Thymus accumulation of radioactive iodine. *Penn Med* 1979; 11: 37–38.
16. Baldet L, Manderscheid JC, Gluioer D et al. The management of differentiated thyroid cancer in Europe in 1988. Results of an international survey. *Acta Endocrinol* 1989; 120: 57–62.
17. Mazzafferri EL. Papillary thyroid carcinoma: factors influencing prognosis and current treatment. *Semin Oncol* 1987; 14: 315–332.
18. Ramanna L, Waxman AD, Brachmnaan MB et al. Correlation of Tg measurements and radioiodine scans in the follow-up of patients with differentiated thyroid cancer. *Cancer* 1985; 55: 1525–1529.
19. Carosino L, Dibenedetto A, Feffer S. Thymic hyperplasia following successful chemotherapy. *Cancer* 1985; 56: 1526–1528.
20. D'Anna F, Rossi F, Arbicio R. Hassall's corpuscle: a regressive formation. *Bas Appl Histochem* 1981; 25: 1969–1981.