Medical practice in thyroid disorders varies widely. You will find yourself disagreeing with some of the statements below. This overview does not claim to describe the best way of using imaging to the benefit of thyroid patients, but merely a sensible one.

Benign thyroid disease
Imaging the hyperthyroid patient
There are two common indications for performing a thyroid scan in a hyperthyroid patient:
• To establish the cause of hyperthyroidism – whether a patient has Graves’ disease or toxic nodule(s) is important for treatment and prognosis, as only Graves’ disease can show a lasting response to antithyroid drugs and only Graves’ disease comes with a risk of endocrine eye disease.
• To assess whether there is sufficient uptake for treatment with 131I (radioiodine treatment).

Graves’ disease is the most common cause of hyperthyroidism in regions with sufficient iodine supply (such as the UK). Exophthalmos is a characteristic sign, but is only proportional in a minority of patients. Serum antibodies against the UK). Exophthalmos is a characteristic sign, but is only present in a minority of patients. Serum antibodies against the TSH receptor are highly specific for Graves’ disease, but this test is not universally available. More commonly measured antibodies against thyroid peroxidase (TPO) are not diagnostically helpful, as they occur in patients with Graves’ disease and Hashimoto’s thyroiditis, as well as a substantial proportion of the normal population. For a good overview of treatment options, see the guidelines of the American Thyroid Association. Briefly, Graves’ hyperthyroidism can show a lasting response following a 6-18 month course of antithyroid drugs (carbimazole, propylthiouracil (PTU)) in 30-50% of patients, with a better response in younger patients and non-smokers. It can also be treated by radioiodine or surgery, either after unsuccessful antithyroid drug treatment or initially. A thyroid scan will show high, homogeneous uptake throughout the thyroid. Total thyroid uptake is typically higher than in toxic nodule(s). A very high uptake (≥10% of the administered 131I is practically exclusive to Graves’ disease) will make normal uptake in salivary glands and any background activity invisible, and may show up the thin pyramidal lobe (figure 1).

A toxic adenoma (either singular or in a multinodular toxic goitre, see figure 1) is outside the pituitary-thyroid regulatory mechanism (functional autonomy), it will continue to produce thyroid hormone even in the absence of thyroid stimulating hormone (TSH). Autonomous nodules do not show a lasting response to antithyroid drugs and require treatment with radioiodine or surgery. A thyroid scan will show preferred or exclusive uptake in the nodule(s), with uptake in normal thyroid tissue more or less blocked. Normal uptake in salivary glands and background activity often remain visible (figure 1).

Hashimoto’s thyroiditis may show no uptake (“blocked”) even in the early hyperthyroid phase when the diagnosis may be difficult to make, although this is not a consistent finding. In de Quervain’s thyroiditis uptake is usually blocked.

Image the euthyroid patient
Radioisotope scans in euthyroid patients are not commonly undertaken. In particular, a non-toxic goitre is not an indication for a scan, unless radioiodine treatment is considered to shrink it.

Evaluation of a thyroid nodule for malignancy. In this scenario, an ultrasound scan, (ultrasound-guided) fine-needle aspiration cytology (FNAC) and the presence of certain risk factors (eg prior neck irradiation) are used to judge the risk of a thyroid nodule being malignant. Not infrequently, these tests will be inconclusive prior to surgery, particularly in cases of follicular lesions that are only malignant if there is vascular invasion that cannot be shown on FNAC.

Thyroid scans may be helpful in this situation in two ways:
• The finding of a non-functioning (“cold”) nodule will indicate an approximately 20% likelihood of malignancy, but more importantly, 95% of normally functioning nodules are benign. Before diagnosing a cold nodule, correlation with ultrasound and TSH is essential – a thyroid cyst may give similar appearances, and a cold nodule in a hyperthyroid patient should not be labelled as such.
• Increased uptake of the perfusion tracer 99mTc-sestamibi (routinely used for myocardial perfusion and parathyroid imaging, see below) in a nodule increases the risk of malignancy to about 20%, with a negative predictive value of about 95%.

Suppression scintigraphy is a thyroid scan performed after the patient’s TSH has been intentionally suppressed by giving levothyroxine. Previously employed for identifying partially functionally autonomous thyroid tissue, it is now largely disused.

Tissue characterisation. Functioning thyroid tissue outside the thyroid bed (lingual thyroid, mediastinal goitre, struma ovarii) can be identified as such on a 123I scan. SPECT/CT may aid anatomical localisation.

Imaging the hypothyroid patient
Radioisotope scans in hypothyroid adult patients are not normally indicated, except to occasionally aid in the evaluation of a thyroid nodule as described above.

Congenital hypothyroidism. Thyroid scans in infants identified as hypothyroid during screening are useful to establish whether there is functioning thyroid tissue in or outside the thyroid bed (figure 1), with profound implications for future, but not usually immediate, management.

General notes
Choice of isotope. 99mTc-pertechnetate will often be the preferred choice over 123I, for reasons of cost, convenience (shorter injection-to-scan time) and lower radiation dose. 99mTc and 123I images can very rarely be discrepant, but the clinical consequences of this are poorly understood. 123I should not be used in benign disease due to its unfavourable dosimetry, except in dosimetric studies prior to radioiodine treatment (an uncommon approach in the UK where fixed radioiodine activities are used).

Thyroid function tests (TFTs), particularly TSH, are essential for correct image interpretation and should be performed with any thyroid imaging. Clinical examination and ultrasound of the neck are very useful adjuncts to thyroid scans which will add morphological information.
Thyroid mediation can have a profound effect on the appearances of the thyroid on the scan. Blanket recommendations are often applied, eg to stop levothyroxine (T4) for four weeks, thyroxine (T3) for 2-3 weeks, PTU for four weeks, but will be unhelpful for image interpretation in some patients. An individual decision, taking the clinical question, thyroid medication and TFTs into account, will result in a meaningful scan more often. Consider the following scenarios:

- A patient with a suspected toxic nodule who is euthyroid (TSH 1mU/l) on a small dose of carbimazole (10mg). Under those conditions, the scan would show a normal thyroid, so a potential toxic nodule will be missed. Carbimazole should have been stopped for three weeks and TFTs repeated to confirm hyperthyroidism before the scan is undertaken.

- A patient with very florid Graves’ disease (serum free T4 50nmol/l) despite maximum antithyroid treatment (PTU 400mg) is referred for radioiodine treatment. High dose PTU may block thyroid uptake, but stopping PTU will exacerbate the patients’ hyperthyroidism to potentially dangerous levels. In this scenario, a thyroid scan should be performed on PTU to see whether there is sufficient uptake for radioiodine treatment. If there is not, a dose reduction and repeat scan should be considered, or the drug could be stopped for just 2-3 days. The potential risk from a non-diagnostic thyroid scan (radiation exposure with no benefit) is much smaller than that from an unsuccessful radioiodine treatment performed blindly without confirming sufficient uptake beforehand.

Imaging related to radionuclide treatment for thyroid cancer

131I is an established treatment for differentiated (papillary, follicular) thyroid cancer that gives improved survival and easier follow-up for very little side effects. It is used to ablate remnant thyroid tissue after total thyroidectomy, or to treat local recurrences or distant metastases.

Prior to the first radioiodine treatment, imaging with 99mTc or 123I is occasionally undertaken to judge the size of the thyroid remnant and to reduce the administered activity of 131I in case of a large remnant to avoid radiation thyroiditis. Metastases may be detected at this time, but as most of the tracer will be taken up by the thyroid remnant, a negative scan will not exclude metastatic disease.

Immediately after any radioiodine treatment, the distribution of 131I is documented by means of a planar whole-body scan at discharge (commonly two days after administration). Mild laxatives during the inpatient stay, a drink of water and voiding just before the scan will reduce physiological uptake in bowel, oesophagus and bladder, respectively, but uptake in salivary glands and stomach will remain (figure 2A). The scan is primarily used to look for distant metastases. The size of the thyroid remnant is also apparent, but we found this to be a poor predictor of the likelihood of needing a second ablation. Anatomical landmarks are scarce, so unexpected findings may benefit from precise anatomical localisation by SPECT/CT. A second scan around seven days post-administration will show much better clearance of background activity and can occasionally be useful in detecting small metastases not apparent on the early scan (figure 2B).

For follow-up, a diagnostic scan is undertaken 4-6 months after any radioiodine treatment to check whether there has been the desired response or whether a further administration is necessary. Please refer to the section below for some of the technical points (rhTSH, choice of iodine isotope, false positives) that are worth considering.

To minimise the delay to a potential further treatment, we have found the following protocol useful at six months after any radioiodine treatment:

- Stop T4, start T3, low iodine diet
- PTU
- Repeat scan 18–24 hours later

Imaging suspected recurrence

Recurrence of a thyroid carcinoma after achieving complete remission by means of thyroidectomy and radioiodine is rare. It may become apparent clinically (eg a neck lump), in other imaging (eg a new pulmonary nodule), but most frequently is first noticed as an increase in serum thyroglobulin. This very useful tumour marker should ideally become immunoassays on serum thyroglobulin levels without evidence of disease progression. The speed of change over time is often more informative than the absolute thyroglobulin value.

An iodine whole-body scan is a sensitive first imaging test for most patients with suspected recurrent thyroid cancer because uptake at a site of disease offers a therapeutic option – radioiodine. Thyroglobulin should be measured at the time of the scan. The protocol outlined in the section above may be followed, but additional points to consider are:

- Choice of iodine isotope for imaging. 18F has been used traditionally, and allows a longer tumour uptake time due to its longer half-life. However, its high gamma energy means spatial resolution is poor. The presence of β-radiation leads to a high radiation burden (not a significant concern in patients who have previously been given a much higher activity during radioiodine treatment), but is also thought to cause stunning. This term refers to a potentially lower uptake in a cancer lesion during 131I treatment if 123I has been administered for a diagnostic scan previously. Stunning has been a very controversial subject for a long time, but it can be avoided by giving less 123I (probably ≤185 MBq) or administering the therapeutic dose soon after the diagnostic one (probably ≤7 days). 124I is used increasingly, with the benefit of superior spatial resolution and no stunning, but its shorter half-life limits tumour uptake to 24 or at most 48 hours. Diagnostic performance is, however, largely equivalent to 123I, so we exclusively use 123I for imaging now. 111In PET is attractive in terms of superior spatial resolution and absolute quantitation of tracer uptake for dosimetric studies, but it is not widely available.

- Recombinant human TSH (rhTSH) vs thyroxine withdrawal. Iodine uptake in thyroid cancer is much greater during hypothyroidism, hence a TSH <30mU/l is generally required before any imaging or treatment. This has traditionally been achieved by switching from long-acting T4 to short-acting T3 for a few weeks, and then withdrawing all thyroid hormone for 10 days. Most patients will experience some symptoms of hypothyroidism during this time, occasionally these can be debilitating, and very occasionally the associated tumour growth can become dangerous (eg cord compression from a bone metastasis). Two intramuscular injections of rhTSH on the days before iodine administration will lead to an elevated serum TSH without the need for thyroid hormone withdrawal, but the kinetics of radioiodine will be altered; this is not considered of major importance for diagnostic purposes. The efficacy of rhTSH in terms of diagnostic quality of the scan is probably largely comparable to thyroxine withdrawal, but there are a number of reports of a poorer diagnostic performance. High cost and poor availability are also significant drawbacks with regard to routine use. We are limiting the use of rhTSH to patients in whom thyroxine withdrawal would be potentially less safe.

- False-positive iodine uptake is most commonly associated
with radioactive saliva, sweat, urine or faeces. Salivary gland pathology may cause asymmetric iodine uptake. Breast uptake may be seen during lactation. Other non-specific causes of iodine uptake have been described in a wide variety of conditions, including normal thyroid uptake, inflammatory conditions (eg sinusitis, dental disease), fluid collections (eg haematomata, pleural effusion), other tumours (eg meningioma) and wigs.

• **Serial follow-up iodine scans** have been extensively used previously, but with more sensitive thyroglobulin assays and gamma cameras, the prognostic power of a negative TSH-stimulated serum thyroglobulin and negative iodine scan six months after radioactive iodine treatment is now very high, so this may no longer be justified in low-risk patients.

• **18F-Fluorodeoxyglucose (FDG).** Patients with suspected recurrent thyroid cancer but negative iodine scan (indicating dedifferentiation of the tumour) have a comparatively poor prognosis, as radioactive iodine is no longer a therapeutic option. However, it is worth trying to identify a discrete lesion which may be amenable to surgical or radiotherapy. Previously, a number of tracers, including 99mTc-sestamibi and 201Tl-chloride, have been used for this purpose, but now 18F-FDG is almost exclusively used, as the combined sensitivity of 123I and 18F-FDG is approaching 100% – well-differentiated tumours accumulate iodine, poorly or dedifferentiated ones take up FDG (“flip-flop pattern”). Because of this, some groups advocate routine FDG PET/CT to document complete response after successful radiiodine ablation, but the additional diagnostic gain in this large group of patients with generally well-differentiated tumours will be small. As for iodine, diagnostic yield of FDG is higher with a hyperthyroid patient and with serum thyroglobulin levels >10ng/ml. Thyroid uptake is a not uncommon incidental finding on an FDG PET scan – if diffuse, it is likely to be Graves’ disease or Hashimoto’s thyroiditis, but focal uptake carries an approximately 1:5 risk of thyroid malignancy.

• **Somatostatin receptor** subtypes 2 and 3 have been shown to be upregulated in papillary thyroid cancer and occasion use is made of β-labellled somatostatin receptor analogues for treating patients with iodine-negative metastasized thyroid cancer, with associated diagnostic imaging using the equivalent 68Ga-labelled agents.

**Primary hyperparathyroidism**

Radionuclide parathyroid imaging is the most sensitive test for localising parathyroid adenoma, although there is no radiopharmaceutical with exclusive uptake in parathyroid tissue and normal parathyroid glands are below the spatial resolution of a gamma camera. Strictly speaking, parathyroid scintigraphy should be used for localising a parathyroid adenoma prior to surgery in patients with known primary hyperparathyroidism. However, in practice it is often used in patients in whom the diagnosis of hyperparathyroidism is doubtful (normal parathyrome with low-normal serum calcium, low-normal parathyroid hormone), and in those with (likely) secondary hyperparathyroidism, but in those scenarios diagnostic yield will be lower.

**Imaging protocols**

There are two competing techniques, but they have a similar diagnostic performance.

- **Positive findings do not completely overlap between the two techniques.** Therefore, if one technique does not demonstrate a parathyroid adenoma, it is reasonable to try the other technique. In practice, we start with a 99mTc-sestamibi washout scan (because it allows SPECT/CT), and only perform a 201Tl subtraction scan if the washout scan does not show a parathyroid adenoma (but shows a normal thyroid). A number of hybrid imaging protocols that make use of both the subtraction and washout technique have been described, but our own experience with them is not good. Ultrasound provides valuable anatomical information and is worth performing with every parathyroid scan.

**Subtraction technique.** This method unmasks a parathyroid adenoma by performing a weighted subtraction of a thyroid image from a combined thyroid-parathyroid image (figure 3, top row). The former can be obtained with either 99mTc-pertechnetate or 123I, and 99mTc or 201Tl-sestamibi is used for the latter. Imaging should be performed dynamically (to be able to correct for patient movement) with the patients’ neck reclinied (to minimise collimator-to-neck distance). This technique is not suitable in patients with an abnormal thyroid scan as this will result in a false-positive finding (figure 3, bottom row).

**Washout technique.** This method relies on a faster washout of 99mTc-sestamibi from thyroid compared to parathyroid tissue. Therefore, a scan obtained a few minutes after injection will show a combined thyroid-parathyroid image, whereas at the time of the late scan (usually 1.5-2.5 hours pi), the tracer should have washed out from the thyroid and only a parathyroid adenoma will remain visible (figure 4). SPECT or SPECT/CT of the neck and mediastinum can be performed at this time for better sensitivity and anatomical localisation (figure 4). Radioguided surgery is also feasible. As 99mTc-sestamibi is a perfusion tracer, false-positive findings in benign and malignant thyroid nodules, lymphoma and inflammatory lymph node pathologies have been described.

**References**


FIGURE 1
Imaging benign thyroid disease. From left: toxic nodule (note normal uptake in salivary glands), multinodular toxic goitre (note normal mediastinal blood pool), Graves’ disease (note homogeneous uptake, very little background activity, pyramidal lobe), congenital hypothyroidism (small amount of functioning thyroid tissue in the thyroid bed).

FIGURE 2
Anterior whole-body scan two days (A) and seven days (B) after administration of 7400 MBq $^{131}$I. Bone metastases from thyroid cancer are more clearly depicted in the late scan when background activity has cleared. Normal uptake in salivary glands, stomach, bowel, bladder. Diffuse hepatic uptake in the late scan is a normal finding.
FIGURE 3
Parathyroid subtraction scans. Top row: Parathyroid adenoma below the lower pole of the left thyroid lobe. Bottom row: Cold area in the right lower lobe of the thyroid in the $^{99m}$Tc-pertechnetate scan, leading to a potentially false-positive finding in the subtraction scan. Left column: $^{201}$TI thyroid+parathyroid image. Centre column: $^{99m}$Tc thyroid image. Right column: weighted subtraction image.

FIGURE 4
Parathyroid washout scan. Planar early (left) and late (centre) images show nearly complete tracer washout from the thyroid, with a mediastinal parathyroid adenoma confirmed on SPECT/CT (right).