BMJ Best Practice

Toxic thyroid adenoma

Straight to the point of care

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Summary

A toxic thyroid adenoma is typically a single large thyroid nodule accompanied by clinical and biochemical hyperthyroidism.

Diagnosis confirmed by thyroid scan demonstrating a hot area and suppression of extranodular thyroid tissue.

Hyperthyroidism caused by toxic adenomas generally does not remit.

Definitive treatment, such as radioactive iodine therapy or surgery, is usually required.

Complications of untreated toxic adenomas may include sequelae of hyperthyroidism such as cardiac dysfunction or bone loss, or tracheal compression by large nodules.

Definition

A toxic adenoma is an autonomously functioning thyroid nodule which causes hyperthyroidism.[1] These nodules are almost always benign. Some autonomous nodules cause only subclinical hyperthyroidism, with suppressed thyroid-stimulating hormone (TSH) level and normal concentrations of free thyroid hormones.

THEORY

Epidemiology

In the US, toxic adenomas are most common in younger adults (age 20 to 40 years) and account for about 5% of cases of hyperthyroidism.[3] Thyrotoxicosis develops at a rate of about 4% per year in euthyroid patients with autonomous adenomas.[4] However, this rate depends on several factors, including the size of the adenoma, iodine intake, and age.[4] In iodine-deficient areas, toxic adenomas and toxic nodular goiters are more common causes of hyperthyroidism than is Graves disease.[5] [IGN: global scorecard of iodine nutrition in 2021] (https://www.ign.org/cm_data/IGN_Global_Scorecard_MAP_2021_SAC_-_7_May_2021.pdf)

Toxic thyroid adenomas in children are rare, and evidence about them is limited.[6]

Etiology

Single toxic adenomas are benign monoclonal tumors that grow and produce thyroid hormones independently of thyroid-stimulating hormone (TSH).[5] [7] [8] These arise after activating (gain of function) germline mutations in thyroid cells. The mutations most commonly affect the TSH receptor and less commonly the alpha subunit of stimulating G-protein.[5] [9] Genetic and environmental factors (e.g., iodine deficiency) and thyrocyte heterogeneity may influence which clones eventually become autonomous nodules.[10]

Worldwide, iodine deficiency is the best-studied epidemiologic risk factor for goiter.[11] In individuals with autonomous nodules, an iodine load (e.g., from iodinated radiographic contrast, amiodarone, or a change in diet) may also cause iodine-induced hyperthyroidism (the Jod-Basedow phenomenon).[12]

Pathophysiology

Growth and function of thyroid cells are normally stimulated by thyroid-stimulating hormone (TSH) via the TSH receptor.[5] TSH receptor activity is mediated through the alpha subunit of stimulating G-protein.[10] [13] In the case of thyroid cells the effector is cAMP. Increased cAMP levels cause growth and excess function of thyrocytes, leading eventually to hyperthyroidism.[8] [14] [15] Other mechanisms, such as alterations of G-protein signaling, may also be involved in the evolution of toxic thyroid adenomas.[16] Euthyroidism is gradually followed by subclinical hyperthyroidism and finally overt hyperthyroidism.[17]

Case history

Case history #1

A 30-year-old woman presents with several months of gradually increasing heat intolerance and nervousness. She has lost 2 to 3 kg. There is no history of head and neck irradiation. She grew up in a mountainous area of Greece and recently immigrated to the US. Her grandmother had a goiter. Physical exam reveals a mildly anxious woman with pulse 90 bpm and BP 140/60 mmHg. There is a 4-cm mobile right-sided thyroid nodule without lymphadenopathy or bruit. She has mild stare and lid lag without exophthalmos; warm moist skin; and a slight tremor. Reflexes are brisk. The remainder of the exam is normal.

Other presentations

Occasionally, patients present with compressive symptoms (hoarseness, dysphagia or dyspnea). Rarely, a patient presents with sudden thyroidal pain after hemorrhage into an autonomously functioning thyroid nodule, associated with transient thyrotoxicosis.[2]

Approach

Patients with toxic adenomas usually present with signs and symptoms of hyperthyroidism.

Clinical exam

In most cases nodules are larger than 3 cm before the development of overt thyrotoxicosis.[3] History may reveal that the patient has resided in an iodine-deficient region. There may be hyperphagia and weight loss, oligomenorrhea, sweating, heat intolerance, nervousness, palpitations, shortness of breath or hyperdefecation. Onset is often more insidious and symptoms less dramatic than for Graves disease.

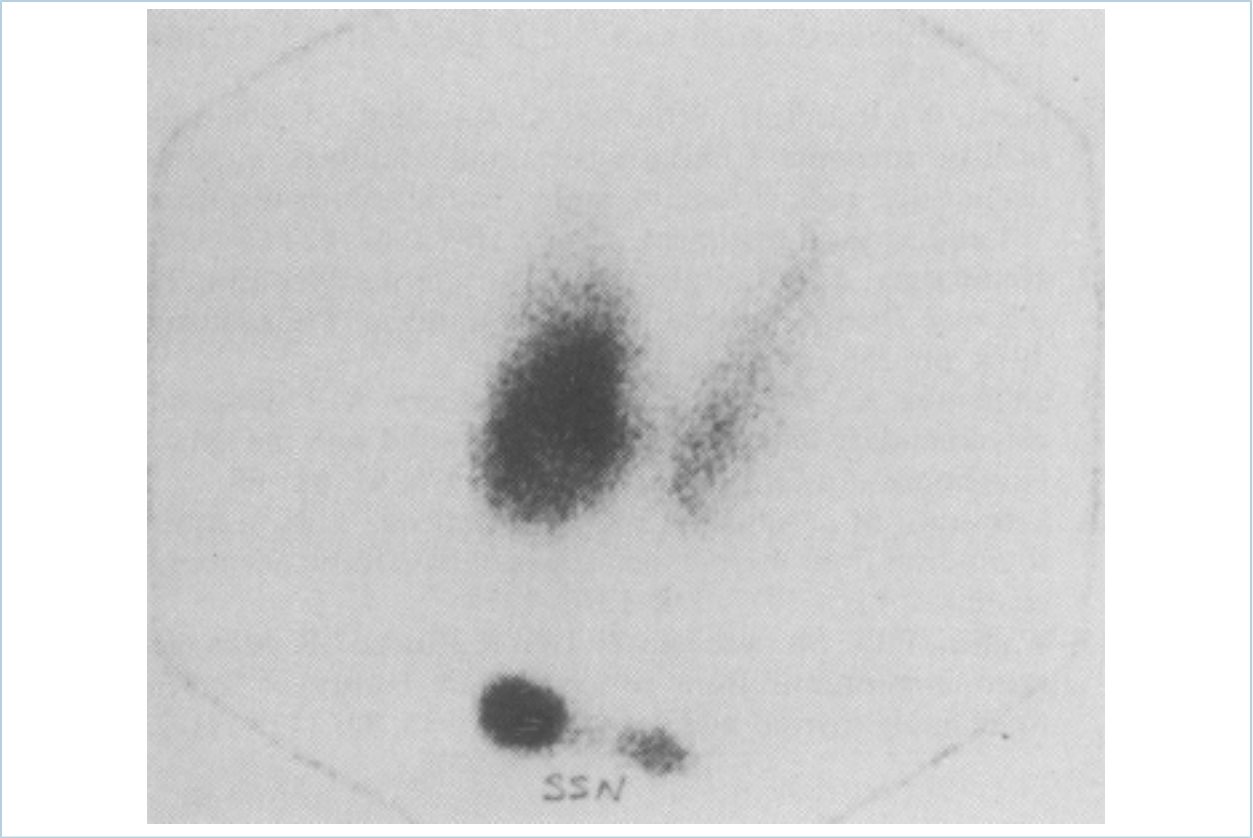
Physical exam may show tachycardia, stare, lid lag, warm moist skin, tremor or generalized/proximal muscle weakness. Stigmata of Graves disease (exophthalmos or pretibial myxedema) are absent.

Patients may have a choking sensation, dysphagia or hoarseness.[21] Usually these are not caused by apparent thyroid disease, and esophageal, cardiac, pulmonary or local pathology must be excluded.

Tests

The initial screening test is a thyroid-stimulating hormone (TSH) level.[1] [22] Do not order more tests until the results of the TSH test are available as a TSH value within the reference range excludes the majority of primary thyroid diseases.[23] If suppressed, thyroid hormone levels (triiodothyronine [T3]/thyroxine [T4]) should be measured. The preferred tests are free T4, and total T3 plus a measure of binding. Some patients may have normal levels of thyroid hormones (subclinical hyperthyroidism) or have elevation of T3 alone (T3 toxicosis).[1]

If biochemical hyperthyroidism is confirmed, a thyroid scan and uptake (thyroid scintigraphy) is the next step.[1][24][25] In toxic adenoma, this shows a hot (i.e., hyperfunctioning) nodule with suppression of surrounding thyroid tissue.[1]



Hyperfunctioning thyroid nodule suppressing contralateral gland on thyroid scan (SSN = suprasternal notch)

Arem R. Recurrent transient thyrotoxicosis in multinodular goitre. Postgrad Med J. 1990 Jan;66(771):54-6

Hot nodules are almost always benign.

If a hot nodule is not confirmed, other causes of hyperthyroidism such as Graves disease should be considered.

Thyroid ultrasound should be obtained in all patients with known or suspected thyroid nodules.[24] Do not routinely order thyroid ultrasound as part of the initial investigations for hyperthyroidism if there is no palpable abnormality of the thyroid gland.[1][26] Cold (i.e., nonfunctioning) or warm (i.e., isofunctioning) nodules >1 cm in diameter or with suspicious ultrasonographic characteristics (such as more-tall-than-wide shape, irregular margins, microcalcifications, increased vascularity, or marked hypoechogenicity) should be considered for further evaluation such as fine needle biopsy.[21] [24]

Routine laboratory tests (CBC and metabolic panel) are not helpful for diagnosis, but may show nonspecific anemia, leukocytosis, elevated aminotransferases, hypercalcemia or elevated alkaline phosphatase. Elevated alkaline phosphatase is generally of bony origin, due to increased bone turnover. Most patients with hyperthyroidism will have elevated transaminases prior to initiating treatment and levels typically improve with antithyroid drug therapy.[27] Baseline white blood cell count is useful prior to starting antithyroid drugs. Mild neutropenia should not be regarded as a contraindication to use of antithyroid drug therapy and hyperthyroidism typically normalizes the neutrophil count.[28]

Thyroid peroxidase antibodies may occasionally be helpful in distinguishing toxic adenoma from autoimmune forms of thyrotoxicosis. TSH receptor antibodies may be required to distinguish toxic adenoma from Graves disease, for example, when a clinical diagnosis cannot be made and nuclear scan is contraindicated.

An ECG may be required for suspected dysrhythmia. Occasionally a noncontrast computed tomography (CT) scan of the neck is indicated to evaluate a large goiter with compressive symptoms, or as part of a preoperative evaluation before thyroidectomy.

History and exam

Key diagnostic factors

palpable thyroid nodule (common)

- Characteristics of nodules are not diagnostic, but typically nodule is >3 cm if patient is hyperthyroid.[3]

younger age (common)

- Toxic thyroid adenomas are most common in younger adults (ages 20-40).

Other diagnostic factors

hyperphagia (common)

- A clinical feature of hyperthyroidism. Due to accelerated metabolism and higher basal metabolic rate requiring increased caloric intake.

weight loss (common)

- A clinical feature of hyperthyroidism. Due to accelerated metabolism and higher basal metabolic rate.

sweating/heat intolerance (common)

- A clinical feature of hyperthyroidism. Due to an increased metabolism leading to higher body temperature.

nervousness (common)

- Nervousness, irritability, and anxiety are common clinical features of hyperthyroidism.

palpitations (common)

- Palpitations may suggest a dysrhythmia such as atrial fibrillation. Dysrhythmias are more common in older patients.[29]

oligomenorrhea (common)

- Menstrual disturbances are common in thyroid dysfunction. Oligomenorrhea may be present in severe hyperthyroidism.[30]

hyperdefecation (common)

- A clinical feature of hyperthyroidism. Due to accelerated metabolism and higher basal metabolic rate.

dyspnea (common)

- Pulmonary or cardiac etiologies should be ruled out.[21]

stare or lid lag (common)

- Stigma of Graves disease (exophthalmos) is absent.

tachycardia (common)

- A common sign of hyperthyroidism.

tremor (common)

- Usually a fine resting tremor.

warm moist skin (common)

- A common sign of hyperthyroidism. Due to accelerated metabolism and higher basal metabolic rate.

muscle weakness (uncommon)

- May be generalized or proximal.

hoarseness (uncommon)

- Local causes should be ruled out.[21]

dysphagia (uncommon)

- Esophageal causes should be ruled out.[21]

choking (uncommon)

- Local causes should be ruled out.[21]

mood change (uncommon)

- Isolated depression or other mood change may be seen in apathetic hyperthyroidism, but is more common in older adults with toxic multinodular goiter.[29]

Risk factors

Strong

iodine deficiency

- Worldwide, iodine deficiency is the most common cause of nodular goiter.[5] [18]
- Iodine supplementation of foods has made nodular goiters and toxic nodules less common in many countries.[19]

Weak

young adult age

- Toxic adenomas are most common in ages 20 to 40 years.

head and neck irradiation

- The most common reason for head and neck irradiation is treatment for a malignancy such as lymphoma.
- Accidental exposure to radiation may also be a risk factor.

family history of thyroid nodules

- Development of nodular disease is influenced by environmental factors interacting with genetic background, sex, and age.[11]

female sex

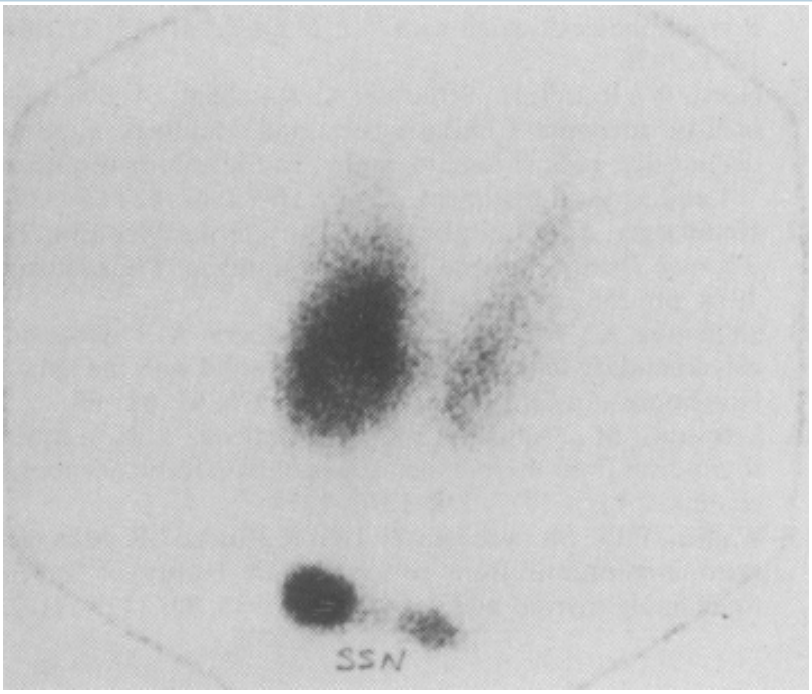
- Nodular thyroid disease is more common in women, although the underlying mechanisms are not well understood.[11]

Tests

1st test to order

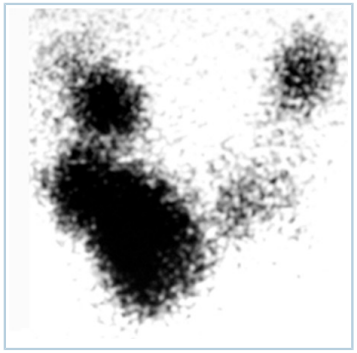
Test	Result
thyroid stimulating hormone (TSH) • Initial screening test. Also used for follow up. • If not suppressed, toxic adenoma is essentially ruled out.[1] Do not order more tests until the results of the TSH test are available as a TSH value within the reference range excludes the majority of primary thyroid diseases.[22] [23] If suppressed, thyroid hormone levels (triiodothyronine [T3]/thyroxine [T4]) should be measured. • In some cases of thyroid autonomy, TSH may be below the lower limits of normal for the assay but not completely suppressed.[1] • Confirms presence of thyroid dysfunction, but not its cause.	**suppressed**

Other tests to consider

Test	Result
free thyroxine (T4; or total T4 with a measure of binding) • Elevated free T4 (or total T4 plus a measure of binding) confirms hyperthyroidism. • Free T4 may be normal in subclinical hyperthyroidism or in triiodothyronine (T3) toxicosis. If free T4 is normal, elevated T3 should be sought. • Confirms presence of thyroid dysfunction, but not its cause.	**elevated**
total T3 with a measure of binding (or free T3) • Total T3 with a measure of binding is considered to be the more reliable assay. • Elevated free T3 (calculated or assay) confirms hyperthyroidism. • Free T4 may be normal or elevated. Isolated elevation of free T3 occurs in T3 toxicosis. • If free T3 is normal, with a suppressed TSH and normal free T4, subclinical hyperthyroidism should be suspected. • Confirms presence of thyroid dysfunction, but not its cause.	**elevated**
thyroid scan and uptake • Typical appearance of hot nodule with suppression of surrounding thyroid tissue confirms toxic adenoma.[1] [4]  *Hyperfunctioning thyroid nodule suppressing contralateral gland on thyroid scan (SSN = suprasternal notch)* *Arem R. Recurrent transient thyrotoxicosis in multinodular goitre. Postgrad Med J. 1990 Jan;66(771):54-6* • I-123 is the preferred isotope. Tc-99 scan is less commonly used in the US because there is a risk of false-positive images and uptake cannot be measured.[21]	**hot nodule**

Test	Result
thyroid ultrasound • Should be obtained in all patients with known or suspected thyroid nodules.[24] • Do not order thyroid ultrasound as part of the initial investigations for hyperthyroidism if there is no palpable abnormality of the thyroid gland.[1] [26] • Cold (i.e., nonfunctioning) or warm (i.e., isofunctioning) nodules >1 cm in diameter or with suspicious ultrasonographic characteristics (such as more-tall-than-wide shape, irregular margins, microcalcifications, increased vascularity, or marked hypoechogenicity) should be considered for further evaluation such as fine needle biopsy.[21] [24] • In rare cases of hemorrhage into a toxic nodule associated with atypical scan findings, may show fluid in the nodule.	**nodule(s)**
metabolic panel • Findings are nonspecific. • Elevated alkaline phosphatase is generally of bony origin, due to increased bone turnover. • Most patients with hyperthyroidism will have elevated transaminases prior to initiating treatment and levels typically improve with antithyroid drug therapy.[27]	**may show: hypercalcemia; elevated aminotransferases or alk phos**
CBC • Findings are nonspecific. Baseline with differential is advisable before antithyroid drug treatment. • Mild neutropenia should not be regarded as a contraindication to use of antithyroid drug therapy and hyperthyroidism typically normalizes the neutrophil count.[28]	**may show anemia, leukocytosis**
TSH receptor antibodies • May be needed to differentiate toxic adenoma from Graves disease when the diagnosis is unclear and nuclear scan contraindicated.	**negative**
thyroid peroxidase antibodies • Sensitive but not specific for Graves disease.	**negative**
ECG • Hyperthyroidism, overt or subclinical (i.e., reduced serum TSH concentration but free T4 levels within reference ranges) is associated with increased risk of atrial fibrillation.[31] • Older adults may present with apathetic hyperthyroidism, such as atrial fibrillation alone.	**may show dysrhythmia**
CT neck (noncontrast) • Occasionally indicated for signs or symptoms of neck compression, or as part of preoperative evaluation before thyroid surgery.	**may delineate large goiter**

Differentials

Condition	Differentiating signs / symptoms	Differentiating tests
Graves disease	• Exophthalmos or pretibial myxedema may be present. • Onset and symptoms often more dramatic than for toxic nodule.	• Thyroid scan shows diffuse uptake. • Thyroid-stimulating hormone (TSH) receptor antibodies are positive.
Toxic multinodular goiter	• Patients usually >40 to 50 years of age. • Apathetic hyperthyroidism more likely, with weight loss, mood change or atrial fibrillation alone.[29]	• Scan shows areas of both increased and decreased uptake, indicating nonfunctioning and functioning nodules.[1]  *Thyroid scan showing variegated uptake in toxic multinodular goiter* *Courtesy of Dr Elizabeth Pearce* Uptake often normal.
Thyrotoxic phase of painless lymphocytic thyroiditis	• Most often occurs postpartum.	• Absent or low uptake on I-123 scan. • Often there is evidence of thyroid autoimmunity (i.e., positive thyroid peroxidase antibodies), although this is not diagnostic.
Thyrotoxic phase of subacute granulomatous thyroiditis	• Associated with anterior neck pain and tenderness.	• Absent or low uptake on I-123 scan. • Erythrocyte sedimentation rate (ESR) elevated.
Iodine-induced hyperthyroidism	• History of an iodine load (from iodinated radiographic contrast, amiodarone, or a change in diet) in the setting of autonomous nodular thyroid disease (the Jod-Basedow phenomenon).[1]	• Low uptake on I-123 scan. • 24-hour urine iodine high.

Condition	Differentiating signs / symptoms	Differentiating tests
Marine-Lenhart syndrome (nodular Graves disease)	• Exophthalmos or pretibial myxedema may be present.	• Thyroid scan shows diffuse uptake with a cold rather than hot area in the region of the palpable nodule. The nodule appears hot on scan only following treatment for Graves disease.[32]
Functional follicular thyroid cancer	• Very rare. • There may be bulky metastatic disease or cervical lymphadenopathy.	• Total body scan shows uptake of radioactive iodine over metastases.
Thyroidal hemiagenesis plus Graves disease	• Very rare. • Exophthalmos or pretibial myxedema may be present.	• Ultrasound shows absence of the contralateral lobe.[33]

Screening

The US Preventive Services Task Force (USPSTF) has concluded that current evidence is insufficient to assess the balance of risks and benefits of screening for thyroid dysfunction in nonpregnant, asymptomatic adults.[34] The American Thyroid Association (ATA) does not recommend for or against routine screening due to insufficient evidence that it would lead to reduced morbidity or mortality.[24] However, serum thyroid-stimulating hormone (TSH) should be measured in all patients with known thyroid nodules and in those with signs or symptoms of thyrotoxicosis.

Approach

The hyperthyroidism of toxic adenomas generally does not remit, and therefore definitive treatment is usually required.

Patient values and preferences

These are an important part of any therapeutic decision-making about definitive treatments. Patients choosing I-131 therapy would most likely favor avoidance of issues surrounding surgery, such as anesthesia or hospitalization, and their possible complications. Those choosing surgery may prefer avoidance of radioactivity; desire very rapid control of hyperthyroidism; or have a lower concern about risks of surgery.[1] Individual issues such as cardiovascular risk also play a role in choice of therapy.

Symptomatic treatment

Beta-blockers are generally recommended for older adults with symptoms or younger people with heart rate >90 bpm.[1] In the absence of contraindication, beta-blockers may be used, if needed, for symptomatic relief while awaiting results of definitive treatment. Propranolol has been most commonly used and also blocks thyroxine (T4) to triiodothyronine (T3) conversion, a theoretical advantage.[37] A selective beta-blocker such as atenolol may be used in patients who cannot tolerate propranolol or who prefer once-daily dosing. An alternative is a calcium-channel blocker if beta-blockers are contraindicated.

Radioactive iodine

I-131 therapy is a preferred treatment for most nonpregnant, nonlactating patients. Dose is generally either fixed; calculated based on goiter size; or computed based on amount of radiation to be delivered.[21] In patients with mild symptoms, I-131 can be administered as a one-time dose, along with symptomatic beta-blocker therapy. Occasionally a second dose of radioactive iodine is required after full therapeutic effect has been achieved at 3 to 6 months post-therapy. In elderly patients or those who have severe symptoms or comorbidities such as cardiac disease, a course of antithyroid drugs (e.g. methimazole) may be used to normalize thyroid function prior to I-131 therapy.[38]

Radioactive iodine is a less-preferred option than surgery in patients with large masses causing compressive symptoms, but can be utilized when surgery is contraindicated or refused. Nodule shrinkage may occur post-treatment.[39] [40] [41]

I-131 therapy is contraindicated in pregnancy and during lactation.

Antithyroid drugs

Antithyroid drugs are the preferred treatment for pregnant or lactating women.[3] Methimazole is the preferred drug (except during the first trimester of pregnancy), due to a higher risk of hepatotoxicity with propylthiouracil. Because of possible congenital defects (e.g., aplasia cutis, choanal atresia) associated with methimazole, propylthiouracil has been preferred during the first trimester.[42] However, more recent data suggest there may also be a rare propylthiouracil-associated embryopathy with defects of the urinary system and face/neck.[43] Methimazole also has the advantage of less-frequent dosing.

Drugs should also be considered for nonpregnant patients who are not candidates for, or who refuse, radioactive iodine or surgery. Indefinite treatment is generally required, but definitive therapy is appropriate for women after delivery and lactation. Rare but serious complications include agranulocytosis, hepatitis and vasculitis. A course of antithyroid drugs may also be used before I-131

therapy to attain euthyroidism, particularly in patients with severe symptoms or in those who are older or have comorbidities such as heart disease. Antithyroid drugs are used to normalize thyroid function prior to surgery.

Pregnant women should be managed by a multidisciplinary team. Maternal and fetal hypothyroidism must be avoided to prevent damage to fetal neural development, risk of miscarriage, or preterm delivery.[35] Generally doses of antithyroid drugs are lower in pregnancy, and maternal levels of free thyroid hormones are kept high-normal to slightly elevated. Low-to-moderate doses of antithyroid drugs can be safely used during lactation.[35]

Surgery

Subtotal thyroidectomy is an option for people who decline or are resistant to radioactive iodine, or who prefer surgery. Rarely, it is required for pregnant women whose hyperthyroidism cannot be controlled with antithyroid drugs. Rarely, it is an option for patients who remain hyperthyroid after radioactive iodine therapy but decline a second dose. It can also be used as first-line treatment for people with very large nodules causing obstructive symptoms. An experienced, high-volume surgeon is recommended.[1] Complications such as hypoparathyroidism or recurrent laryngeal nerve damage are uncommon when the surgeon is experienced.

Subclinical hyperthyroidism

Treatment of subclinical hyperthyroidism (isolated suppression of thyroid-stimulating hormone (TSH) with normal levels of free thyroid hormones) should be individualized. Treatment is controversial because of a lack of prospective randomized controlled trials regarding benefits, despite an increased risk of complications such as bone loss or dysrhythmia from prolonged TSH suppression.[44] [45] Patients should undergo careful consideration of the possible risks and benefits of treatment, by an endocrinologist.

Treatment algorithm overview

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing (summary)		
nonpregnant nonlactating adults without mass effect		
	1st	radioactive iodine therapy (I-131)
	adjunct	pretreatment with antithyroid drugs
	2nd	subtotal thyroidectomy
	adjunct	pretreatment with antithyroid drugs
	3rd	antithyroid drugs alone
■ with moderate/severe symptoms and/or increased cardiovascular risk	plus	beta-blockers pending effects of definitive treatment
nonpregnant nonlactating adults with mass effect		
	1st	subtotal thyroidectomy
	adjunct	pretreatment with antithyroid drugs
	2nd	radioactive iodine therapy (I-131)
	adjunct	pretreatment with antithyroid drugs
■ with moderate/severe symptoms and/or increased cardiovascular risk	plus	beta-blockers pending effects of definitive treatment
pregnant or lactating		
	1st	antithyroid drugs
	2nd	subtotal thyroidectomy
■ with moderate/severe symptoms and/or increased cardiovascular risk	plus	beta-blockers pending effects of definitive treatment

Treatment algorithm

Please note that formulations/routes and doses may differ between drug names and brands, drug formularies, or locations. Treatment recommendations are specific to patient groups: see disclaimer

Ongoing

nonpregnant nonlactating adults without mass effect

1st **radioactive iodine therapy (I-131)**

» Patient values and preferences are an important part of any therapeutic decision-making about definitive treatment. For example, patients choosing I-131 therapy would most likely favor avoidance of issues surrounding surgery, such as anesthesia or hospitalization, and their possible complications.[1] I-131 is a preferred treatment for most nonpregnant and nonlactating patients.

» Dose is generally either fixed; calculated based on goiter size; or computed based on amount of radiation to be delivered.[21]

» Antithyroid drugs, if used adjunctively, are stopped 3 to 5 days before I-131 treatment and restarted 3 to 5 days afterward.

» I-131 may worsen thyrotoxicosis for several days due to thyroid hormone leakage.[46]

» Contraindicated in pregnant or lactating women. Pregnancy test in women of childbearing age is required prior to therapy.[21]

» Caution required in older adults, especially in those with cardiac disease.[21] Those patients require consideration of pretreatment with antithyroid drugs, and careful monitoring.

» Occasionally a second dose is needed 3 to 6 months after the first dose.

adjunct **pretreatment with antithyroid drugs**

Treatment recommended for SOME patients in selected patient group

Primary options

» methimazole: 5-60 mg/day orally given once daily or in 2-3 divided doses; doses rarely exceed 40 mg/day in practice

Secondary options

» propylthiouracil: 50-400 mg/day orally given in 3 divided doses

Ongoing

» May be useful for pretreatment of older adults, those with severe symptoms, or those with comorbidities such as heart disease.

» Can also be restarted, if needed, after I-131 therapy is given. Some controversy exists as to the necessity for pretreatment antithyroid drugs if symptoms are controlled with beta-blockade.[1]

» Methimazole is the preferred drug, due to a higher risk of hepatotoxicity with propylthiouracil. Methimazole also has the advantage of less-frequent dosing.

» Rare but serious complications include agranulocytosis (0.1% to 0.5% of patients) or liver toxicity.[47]

» Vasculitis can occur with propylthiouracil.[48]

2nd **subtotal thyroidectomy**

» The hyperthyroidism of toxic thyroid adenoma generally does not remit spontaneously, and therefore definitive treatment is usually required. Patient values and preferences are an important part of any therapeutic decision-making about definitive treatment. For example, those choosing surgery may prefer avoidance of radioactivity, desire very rapid control of hyperthyroidism, or have a lower concern about risks of surgery.[1]

» Surgery is an option for those resistant to, or who decline, radioactive iodine, or who prefer surgery. Reduction of thyroid function is immediate, although recurrent hyperthyroidism or subsequent hypothyroidism is possible.

» Complications include rare recurrent laryngeal nerve damage and hypoparathyroidism. An experienced, high-volume surgeon is recommended.[1]

adjunct **pretreatment with antithyroid drugs**

Treatment recommended for SOME patients in selected patient group

Primary options

» methimazole: 5-60 mg/day orally given once daily or in 2-3 divided doses; doses rarely exceed 40 mg/day in practice

Secondary options

» propylthiouracil: 50-400 mg/day orally given in 3 divided doses

Ongoing

» Given prior to surgery to normalize thyroid function, especially for older patients and for those with severe symptoms or comorbidities such as heart disease. Regular monitoring of thyroid function is required.

» Methimazole is the preferred drug, due to a higher risk of hepatotoxicity with propylthiouracil. Methimazole also has the advantage of less-frequent dosing.

» Rare but serious complications include agranulocytosis (0.1% to 0.5% of patients) or liver toxicity.[47]

» Vasculitis can occur with propylthiouracil.[48]

3rd **antithyroid drugs alone**

Primary options

» methimazole: 5-60 mg/day orally given once daily or in 2-3 divided doses; doses rarely exceed 40 mg/day in practice

Secondary options

» propylthiouracil: 50-400 mg/day orally given in 3 divided doses

» Not usually first-line therapy in nonpregnant patients, because remission of hyperthyroidism in patients with toxic adenoma is rare.[3]

» Methimazole is the preferred drug, due to a higher risk of hepatotoxicity with propylthiouracil. Methimazole also has the advantage of less-frequent dosing.

» Also used when required before surgery or I-131 therapy, especially for older patients, for those with severe symptoms or comorbidities such as heart disease, or when more definitive therapies are contraindicated or refused.

» Regular monitoring of thyroid function is required.

» Rare but serious complications include agranulocytosis (0.1% to 0.5% of patients) or liver toxicity.[47]

» Vasculitis can occur with propylthiouracil.[48]

with moderate/severe symptoms and/or increased cardiovascular risk **plus** **beta-blockers pending effects of definitive treatment**

Treatment recommended for ALL patients in selected patient group

Primary options

MANAGEMENT

Ongoing

» propranolol hydrochloride: 10-40 mg orally (immediate-release) four times daily

Secondary options

» atenolol: 25-50 mg orally once daily, increase if necessary to 100 mg/day

» Used for symptoms such as palpitations, anxiety, or tremor.[37] [46] Also used for patients at higher cardiovascular risk, although caution is needed in the presence of heart disease. Generally recommended for older adults with symptoms or younger people with heart rate >90 bpm.[1]

» Dose gradually increased until symptoms and pulse are controlled, then tapered when patient is euthyroid.

» Useful prior to surgery or I-131 therapy, or while waiting for antithyroid drugs to take effect.

» A selective beta-blocker (e.g., atenolol) can be used for patients who cannot tolerate propranolol.

» A calcium-channel blocker is an alternative if beta-blockers are contraindicated.

nonpregnant nonlactating adults with mass effect

1st **subtotal thyroidectomy**

» Option for patients with obstructive symptoms such as choking, hoarseness or dyspnea that are caused by very large nodules.[1]

» Reduction of thyroid function is immediate, although recurrent hyperthyroidism or subsequent hypothyroidism is possible.

» An experienced, high-volume surgeon is recommended.[1] Complications include rare recurrent laryngeal nerve damage and hypoparathyroidism. Hypocalcemia due to hypoparathyroidism may be transient or permanent.

adjunct **pretreatment with antithyroid drugs**

Treatment recommended for SOME patients in selected patient group

Primary options

» methimazole: 5-60 mg/day orally given once daily or in 2-3 divided doses; doses rarely exceed 40 mg/day in practice

Ongoing

Secondary options

» propylthiouracil: 50-400 mg/day orally given in 3 divided doses

» Thyroid function is normalized prior to surgery. Regular monitoring of thyroid function is required.

» Methimazole is the preferred drug, due to a higher risk of hepatotoxicity with propylthiouracil. Methimazole also has the advantage of less-frequent dosing.

» Rare but serious complications include agranulocytosis (0.1% to 0.5% of patients) or liver toxicity.[47]

» Vasculitis can occur with propylthiouracil.[48]

2nd **radioactive iodine therapy (I-131)**

» Radioactive iodine is a less-preferred option than surgery in patients with large masses causing compressive symptoms, but can be utilized when surgery is contraindicated or refused. Nodule shrinkage may occur post-treatment.[39] [40] [41]

» I-131 therapy is contraindicated in pregnancy and during lactation.

adjunct **pretreatment with antithyroid drugs**

Treatment recommended for SOME patients in selected patient group

Primary options

» methimazole: 5-60 mg/day orally given once daily or in 2-3 divided doses; doses rarely exceed 40 mg/day in practice

Secondary options

» propylthiouracil: 50-400 mg/day orally given in 3 divided doses

» Useful for pretreatment of older adults, those with severe symptoms, or those with comorbidities such as heart disease.

» Methimazole is the preferred drug, due to a higher risk of hepatotoxicity with propylthiouracil. Methimazole also has the advantage of less-frequent dosing.

» Rare but serious complications include agranulocytosis (0.1% to 0.5% of patients) or liver toxicity.[47]

Ongoing

» Vasculitis can occur with propylthiouracil.[48]

with moderate/severe symptoms and/or increased cardiovascular risk

plus

beta-blockers pending effects of definitive treatment

Treatment recommended for ALL patients in selected patient group

Primary options

» propranolol hydrochloride: 10-40 mg orally (immediate-release) four times daily

Secondary options

» atenolol: 25-50 mg orally once daily, increase if necessary to 100 mg/day

» Used for symptoms such as palpitations, anxiety, or tremor.[37] [46] Also used for patients at higher cardiovascular risk, although caution is needed in the presence of heart disease. Generally recommended for older adults with symptoms or younger people with heart rate >90 bpm.[1]

» Dose gradually increased until symptoms and pulse are controlled, then tapered when patient is euthyroid.

» Useful prior to surgery or I-131 therapy, or while waiting for antithyroid drugs to take effect.

» A selective beta-blocker (e.g., atenolol) can be used for patients who cannot tolerate propranolol.

» A calcium-channel blocker is an alternative if beta-blockers are contraindicated.

pregnant or lactating

1st

antithyroid drugs

Primary options

» propylthiouracil: 50-300 mg/day orally given in 3 divided doses; consult specialist for further guidance

OR

» methimazole: 5-30 mg orally once daily or given in 2-3 divided doses; consult specialist for further guidance

» Methimazole is the preferred drug except in the first trimester of pregnancy, due to a higher risk of hepatotoxicity with propylthiouracil. Because of possible congenital defects (e.g.,

Ongoing

aplasia cutis) associated with methimazole, propylthiouracil has been preferred during the first trimester.[42] However, more recent data suggest there may also be a rare propylthiouracil-associated embryopathy with defects of the urinary system and face/neck.[43] Methimazole also has the advantage of less-frequent dosing.

» Pregnant women should be managed by a multidisciplinary team. Maternal and fetal hypothyroidism must be avoided to prevent damage to fetal neural development, risk of miscarriage, or preterm delivery. Generally doses of antithyroid drugs are lower in pregnancy, and maternal levels of free thyroid hormones are kept high-normal to slightly elevated. Women wishing to breastfeed should have specialty care to discuss dosing of antithyroid drugs to minimize the infant's exposure.[49] Low-to-moderate doses (e.g., methimazole <20 mg/day) of antithyroid drugs can be safely used during lactation.[35]

» Subclinical hyperthyroidism (suppressed thyroid-stimulating hormone [TSH] with normal levels of free thyroid hormones) during pregnancy does not require drug treatment.

» Rare but serious complications include agranulocytosis (0.1% to 0.5% of patients), liver toxicity or vasculitis.[47] [48]

2nd **subtotal thyroidectomy**

» Rarely required. Possible reasons for subtotal thyroidectomy during pregnancy include serious adverse reaction to antithyroid drugs which precludes their use; nonadherence to or marked resistance to antithyroid drugs, leading to uncontrolled hyperthyroidism;[35] or severe compressive symptoms.

» When performed, if unavoidable, the second trimester is the preferred time for surgery.[35] An experienced, high-volume surgeon is recommended.

» Complications include rare recurrent laryngeal nerve palsy and hypoparathyroidism.

with moderate/severe symptoms and/or increased cardiovascular risk

plus **beta-blockers pending effects of definitive treatment**

Treatment recommended for ALL patients in selected patient group

Primary options

Ongoing

» propranolol hydrochloride: consult specialist for guidance on dose

OR

» labetalol: consult specialist for guidance on dose

» Used for symptoms such as palpitations, anxiety, or tremor.[46] Also used for patients at higher cardiovascular risk.

» Dose gradually increased until symptoms and pulse are controlled, then tapered when patient is euthyroid.

» Useful while waiting for antithyroid drugs to take effect, or in the rare instance of surgery.

» Labetalol is considered the safest beta-blocker in pregnancy. Propranolol may be used for the short-term control of hyperthyroid symptoms in pregnant women, but its use has been associated with fetal bradycardia and growth restriction.

Emerging

Percutaneous ethanol injection

This has been studied as a therapy for subclinically or overtly hyperfunctioning thyroid nodules.[50] Patients with smaller nodules (<15 mL) may respond more favorably than those with larger nodules. Decrease in nodule size may occur, but multiple injection sessions (2-16) were needed, and recurrence of thyrotoxicosis is common. Use of this technique has been confined to centers with expertise, and has not become widespread in the US, being most applicable to patients who are not candidates for standard therapies.[51]

Radiofrequency ablation

This has been examined as a therapy for subclinically or overtly hyperfunctioning thyroid nodules.[50] [52] It appears to be more effective than treatment with laser thermal ablation at decreasing nodule volumes. Regrowth of hyperfunctioning thyroid nodules has been reported if nodule margins are incompletely ablated. This treatment is currently only performed in selected centers.

Laser thermal ablation

This has been used successfully to normalize thyroid function in some patients with autonomous nodules, although multiple treatments may be required.[50] A meta-analysis has found laser ablation to be less effective than radiofrequency ablation at decreasing benign nodule volume.[53] This treatment is currently only performed in selected centers, and use is not widespread.

Primary prevention

Iodine supplementation of foods has made toxic nodules a relatively uncommon cause of hyperthyroidism in many countries,[19] but iodine deficiency remains a major public health problem worldwide.[18] [20] [IGN: global scorecard of iodine nutrition in 2021] (https://www.ign.org/cm_data/IGN_Global_Scorecard_MAP_2021_SAC_-_7_May_2021.pdf)

Secondary prevention

Iodinated contrast or high-dose iodine supplementation should be avoided in people who have autonomously functioning thyroid nodules.[1] Administration may result in the Jod-Basedow effect (iodine-induced hyperthyroidism), and may also preclude treatment with radioactive iodine for a period of time.

Patient discussions

Patients receiving radioactive iodine should frequently wash their hands following treatment, because iodine is eliminated in the urine, saliva and feces. They should also avoid close contact with other people, especially with children and pregnant women. These precautions should last for a few days, although evidence is lacking regarding duration.[55]

Patients taking antithyroid drugs should be advised to immediately report fever, rash, sore throat or any symptoms of infection.

Monitoring

Monitoring

Following treatment, thyroid function tests (TFTs) should be monitored along with clinical exam. There are no specific guidelines for the monitoring schedule. One approach after I-131 therapy is to monitor at 2 and 6 weeks; 3, 6, and 12 months; and then yearly.

Baseline CBC with differential for any patient taking antithyroid drugs is reasonable, but there are no specific guidelines, and no demonstrated benefit to routine follow-up CBC. Immediate patient reporting of any symptoms of infection is important because agranulocytosis may occur unpredictably. CBC with differential should be checked in any patient who develops fever, rash, or pharyngitis while taking antithyroid drugs.

FOLLOW UP

Complications

Complications	Timeframe	Likelihood
surgery-related recurrent laryngeal nerve damage	**short term**	**low**
Risk is low with an experienced surgeon.		
surgery-related hypoparathyroidism	**short term**	**low**
Risk is low with an experienced surgeon. Hypocalcemia may be transient or permanent.		
atrial fibrillation	**long term**	**medium**
Hyperthyroidism, overt or subclinical (i.e., reduced serum thyroid stimulating hormone [TSH] concentration but free thyroxine levels within reference ranges) is associated with increased risk of atrial fibrillation.[31] More common in older patients with toxic multinodular goiter than in people with single toxic nodules. People aged >60 years with untreated subclinical hyperthyroidism are about 3 times more likely to develop cardiac dysfunction, including atrial fibrillation, over 10 years than are euthyroid people.[44] The risk of systemic embolism is unknown.		
I-131-related hypothyroidism	**long term**	**medium**
Risk of hypothyroidism may not be related to the dose of radioactive iodine.[39] [40] [41] [60] Patients are more likely to become hypothyroid if they have underlying autoimmune thyroiditis or have initially incomplete suppression of extranodular tissue.[56] In a 20-year retrospective study, 60% of patients treated with I-131 for a toxic adenoma eventually became hypothyroid. Pretreatment with methimazole increased risk for hypothyroidism. However, the effects of methimazole seemed to depend on the baseline degree of suppression of extranodular thyroid parenchyma.[57]		
surgery-related hypothyroidism	**long term**	**medium**
In one meta-analysis, the overall risk of hypothyroidism after hemithyroidectomy was 22%.[61] Patients need lifelong annual monitoring for the development of hypothyroidism after surgery for toxic adenoma.		
neck compression	**long term**	**low**
Can occur with large nodules. Gastrointestinal, cardiac, local or pulmonary causes should be sought for symptoms such as choking, dysphagia or hoarseness.[21] Iodinated contrast computed tomography (CT) scans should be avoided in evaluation of goiters, because of risk of iodine-induced hyperthyroidism (Jod-Basedow effect).		

Complications	Timeframe	Likelihood
bone mineral loss	**long term**	**low**
Osteoporosis is a feature of untreated thyrotoxicosis.[58] Bone mineral density has been shown to improve in patients treated for hyperthyroidism.[58]		
thyroid storm	**long term**	**low**
Rare severe, life-threatening condition that can occur after an illness in patients with hyperthyroidism. Patients may present with weakness, severe tachycardia and fever.[59] Treatment includes beta-blockers, antithyroid drugs, supportive care, and corticosteroids; an endocrine specialist should be consulted.		
antithyroid drug-related agranulocytosis	**variable**	**low**
Rare, but may be idiosyncratic.		

Prognosis

Prognosis is generally good. Most patients have resolution of hyperthyroidism following treatment. About 45% to 75% of patients are euthyroid several years following I-131 therapy.[56] However, both surgery and radioactive iodine therapy[57] confer a moderate long-term risk of hypothyroidism.

Nodule size may eventually be reduced by about 45% to 70%.[39] [40] [41] Much of this reduction occurs during the first 3 months after therapy.[40]

Diagnostic guidelines

International

ACR appropriateness criteria. Thyroid disease. 2018 (https://www.acr.org/Clinical-Resources/Clinical-Tools-and-Reference/Appropriateness-Criteria) [25]

Published by: American College of Radiology **Last published:** 2018

2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum (http://www.thyroid.org/professionals/ata-professional-guidelines) [35]

Published by: American Thyroid Association **Last published:** 2017

2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis (http://www.thyroid.org/professionals/ata-professional-guidelines) [1]

Published by: American Thyroid Association **Last published:** 2016

2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer (http://www.thyroid.org/professionals/ata-professional-guidelines) [24]

Published by: American Thyroid Association **Last published:** 2015

Thyroid nodule algorithmic tool white paper (https://pro.aace.com/disease-state-resources/thyroid/guidelines) [36]

Published by: American Association of Clinical Endocrinology/American College of Endocrinology/Associazione Medici Endocrinologi **Last published:** 2021

Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules (https://pro.aace.com/disease-state-resources/thyroid/guidelines) [21]

Published by: American Association of Clinical Endocrinologists; Associazione Medici Endocrinologi; European Thyroid Association **Last published:** 2016

Treatment guidelines

International

Practice parameter for treatment of benign and malignant thyroid disease with I-131 sodium iodide (https://www.acr.org/-/media/ACR/Files/Practice-Parameters/I131SodiumIodide.pdf) [54]

Published by: American College of Radiology, American College of Nuclear Medicine, American Society for Radiation Oncology, Society of Nuclear Medicine and Molecular Imaging, Society for Pediatric Radiology

Last published: 2019

2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum (http://www.thyroid.org/professionals/ata-professional-guidelines) [35]

Published by: American Thyroid Association

Last published: 2017

2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis (http://www.thyroid.org/professionals/ata-professional-guidelines) [1]

Published by: American Thyroid Association

Last published: 2016

2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer (http://www.thyroid.org/professionals/ata-professional-guidelines) [24]

Published by: American Thyroid Association

Last published: 2015

Radiation safety in the treatment of patients with thyroid diseases by radioiodine 131I (http://www.thyroid.org/professionals/ata-professional-guidelines) [55]

Published by: American Thyroid Association

Last published: 2011

Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules (https://pro.aace.com/disease-state-resources/thyroid/guidelines) [21]

Published by: American Association of Clinical Endocrinologists; Associazione Medici Endocrinologi; European Thyroid Association

Last published: 2016

Online resources

1. IGN: global scorecard of iodine nutrition in 2021 (https://www.ign.org/cm_data/IGN_Global_Scorecard_MAP_2021_SAC_-_7_May_2021.pdf) *(external link)*

Key articles

- Ross DS, Burch HB, Cooper DS, et al. 2016 American Thyroid Association guidelines for diagnosis and management of hyperthyroidism and other causes of thyrotoxicosis. Thyroid. 2016 Oct;26(10):1343-421. Full text (http://online.liebertpub.com/doi/full/10.1089/thy.2016.0229) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27521067?tool=bestpractice.bmj.com)
- Gharib H, Papini E, Garber JR, et al. American Association of Clinical Endocrinologists, American College of Endocrinology, and Associazione Medici Endocrinologi medical guidelines for clinical practice for the diagnosis and management of thyroid nodules - 2016 update. Endocr Pract. 2016 May;22(5):622-39. Full text (http://journals.aace.com/doi/pdf/10.4158/EP161208.GL) Abstract (http://www.ncbi.nlm.nih.gov/pubmed/27167915?tool=bestpractice.bmj.com)
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Images

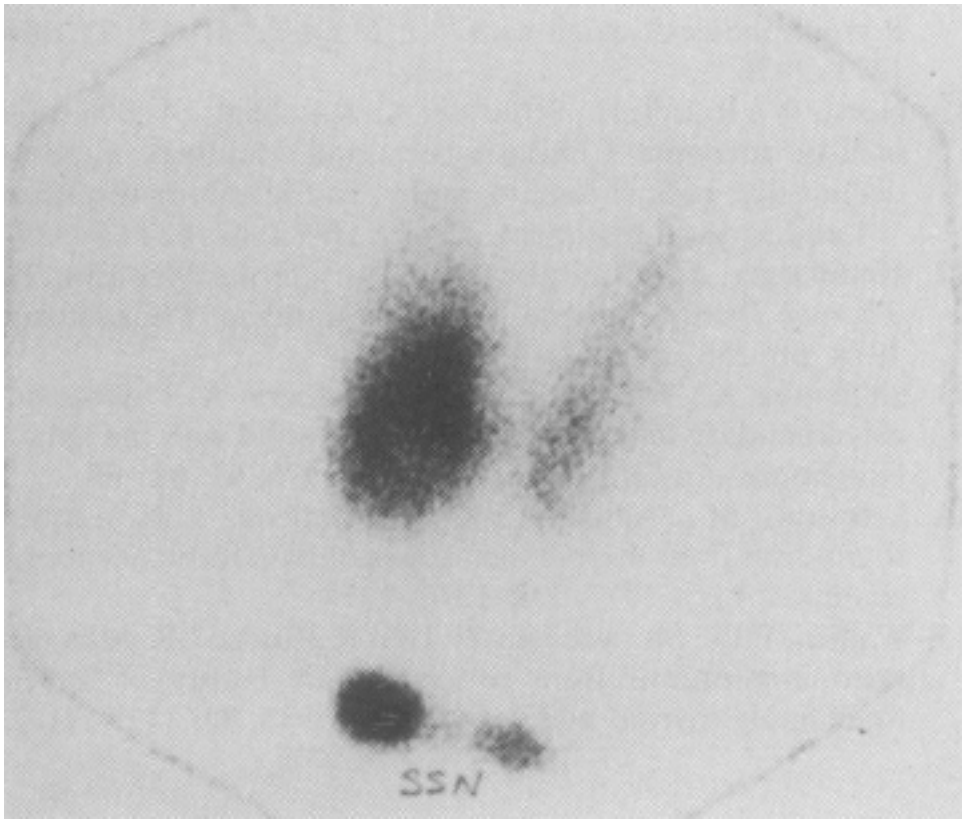

Figure 1: Hyperfunctioning thyroid nodule suppressing contralateral gland on thyroid scan (SSN = suprasternal notch)

Arem R. Recurrent transient thyrotoxicosis in multinodular goitre. Postgrad Med J. 1990 Jan;66(771):54-6

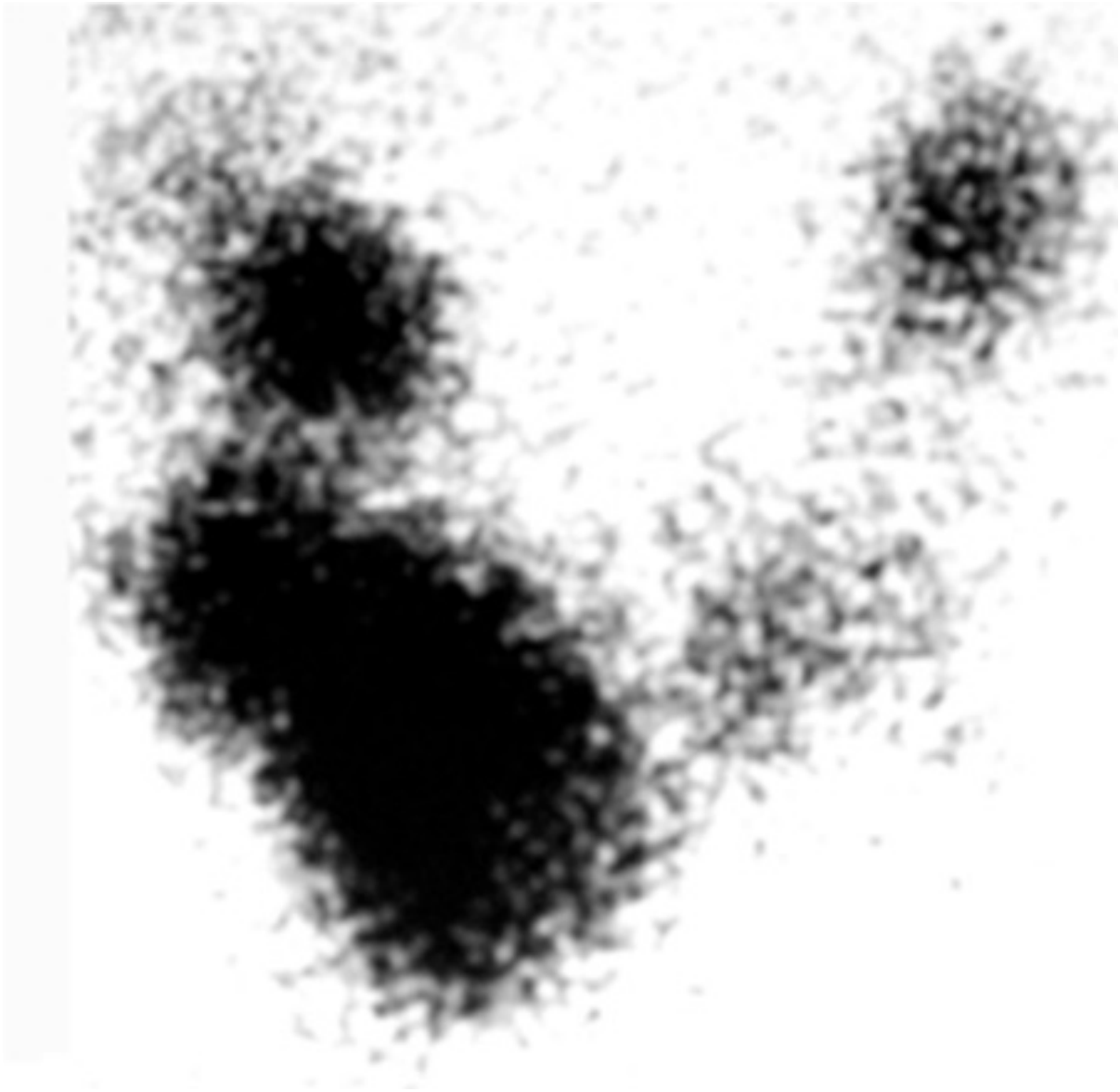

Figure 2: Thyroid scan showing variegated uptake in toxic multinodular goiter

Courtesy of Dr Elizabeth Pearce

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This approach is in line with the guidance of the International Bureau of Weights and Measures Service.

Figure 1 – BMJ Best Practice Numeral Style

5-digit numerals: 10,000

4-digit numerals: 1000

numerals < 1: 0.25

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