# 1 Thyroid

## Hashimoto's thyroiditis (chronic autoimmune thyroiditis)

### Definition and epidemiology
Hashimoto's thyroiditis (HT), or chronic lymphocytic thyroiditis, is an autoimmune disease in which the thyroid gland is attacked by a variety of cell and antibody-mediated immune processes. The name "Hashimoto's thyroiditis" is derived from the 1912 original report by Hashimoto describing patients with both goiter and intense lymphocytic infiltration of the thyroid (Figs 1.1 & 1.2) as "struma lymphomatosa."

Hashimoto's thyroiditis is the most common cause of primary hypothyroidism in iodine-sufficient areas of the world; it is among the most common causes of nonendemic goiter. On average 1.0–1.5/1000 people suffer from this disease. It occurs far more often in women than in men (incidence of 10 : 1 to 20 : 1, respectively), and it is most prevalent between 45 and 65 years of age. Occurrence in children is also uncommon, especially in populations where iodine is not a dietary scarcity.

### Etiology and pathogenesis
Autoantibodies may be present against thyroid peroxidase, thyroglobulin, and thyroid-stimulating hormone (TSH) receptors, although a small percentage of patients may have none of these antibodies present. Antibody-dependent cell-mediated cytotoxicity is a substantial factor behind the apoptotic fallout of HT. Activation of cytotoxic T lymphocytes (CD8$^+$ T cells) in response to cell-mediated immune response affected by helper T lymphocytes (CD4$^+$ T cells) is central to thyrocyte destruction. Recruitment of macrophages is another effect of helper T-lymphocyte activation, with Th1-axis lymphocytes producing inflammatory cytokines within the thyroid tissue to further macrophage activation and migration into the thyroid gland for a direct effect. Infection, stress, sex steroids, pregnancy, iodine intake, and radiation exposure are known possible precipitating factors for HT. Fetal microchimerism within the maternal thyroid is also a possibility.

### Signs and symptoms
Hashimoto's thyroiditis very often results in hypothyroidism with bouts of hyperthyroidism. Symptoms of HT include weight gain, depression, mania, sensitivity to heat and cold, paresthesia, fatigue, panic attacks, bradycardia, tachycardia, high cholesterol, reactive hypoglycemia, constipation, migraine, muscle weakness, cramps, memory loss, infertility, hair loss, and myxedematous psychosis.

### Diagnosis

#### Laboratory findings
Laboratory tests for HT include:
• Antithyroid peroxidase antibodies (TPOAbs) and thyroglobulin antibodies (TgAbs)
• TSH, free thyroxine (FT$_4$)
• Total cholesterol, high density lipoprotein (HDL), and triglycerides

#### Imaging tests
Imaging tests for HT include:
• Neck ultrasound (Fig. 1.3)
• Computed tomography (CT) scan (rare)
• $^{99m}$TcO$_4$ thyroid scintigraphy (Fig. 1.4)

### Treatment
In patients with primary hypothyroidism, the main treatment is levothyroxine.
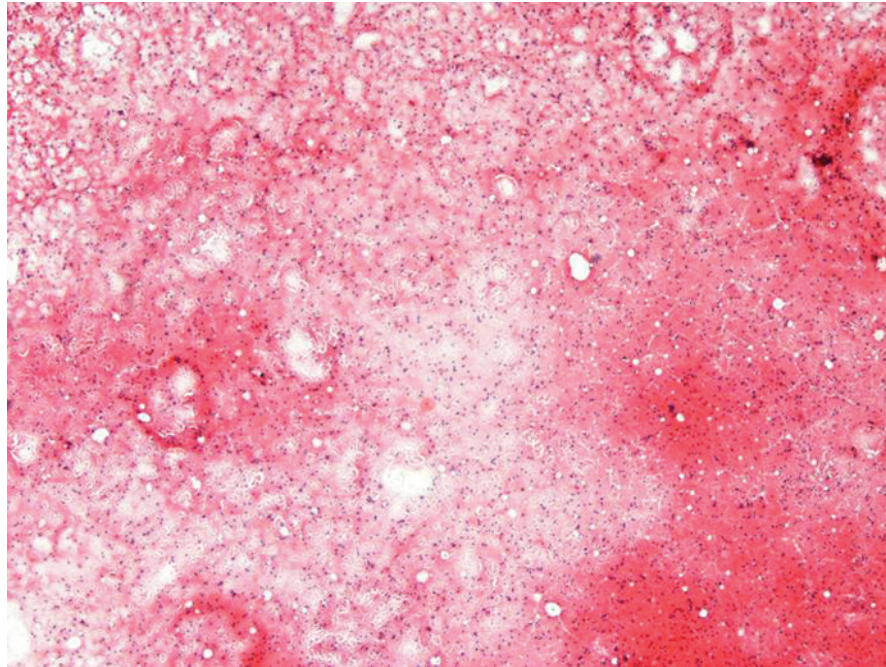
**Illustrations (Figs 1.1–1.4)**



**Figure 1.1** Cytology of thyroiditis. This figure shows rare and normal thyrocytes associated with numerous lymphocytes (Papanicolau, 10 × ).
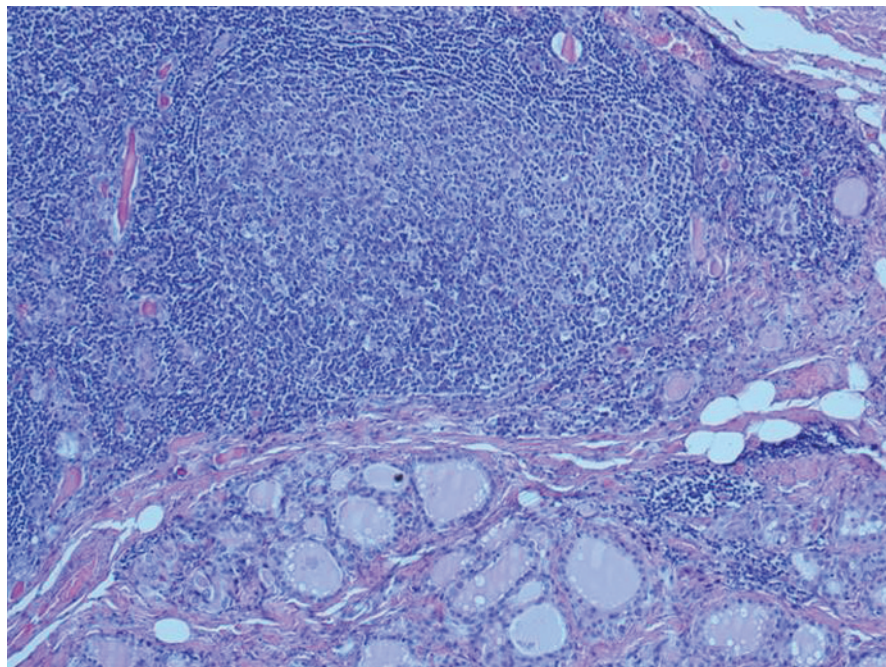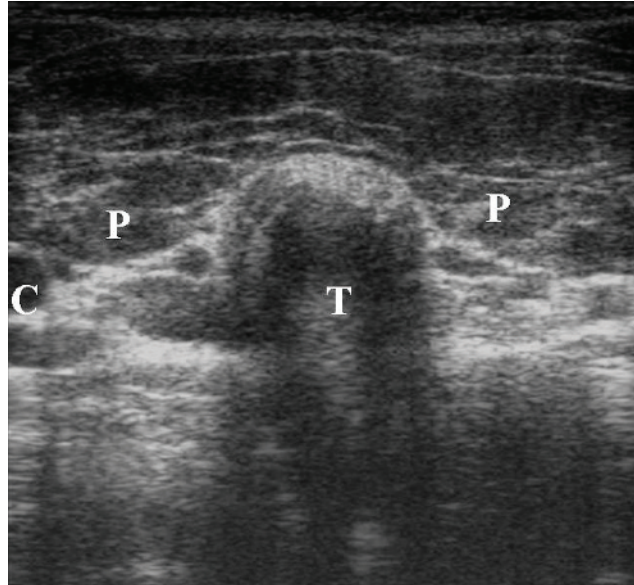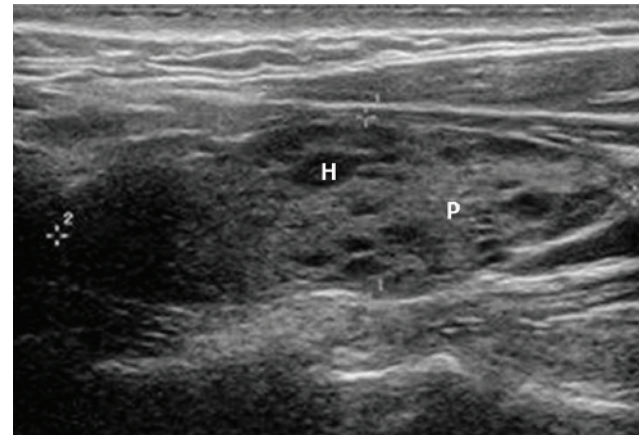


**Figure 1.2** Histology of thyroiditis. Hashimoto thyroiditis is characterized by Hürthle cells associated with follicular lymphoid structures (HE, 10 × ).

(a)



(b)

**Figure 1.3**  A 46-year-old woman with a recent episode of cervical tenderness and a familiar history of thyroid disease. The patient complained of fatigue and reported a weight gain of about 10 kg in the last 2 months. (a) Thyroid ultrasound – cross section. This ultrasound shows a thyroid with a slight increase in volume, globular shape, and homogeneous structure, and less echogenic than normal. (b) Thyroid ultrasound – longitudinal section. This ultrasound shows diffuse patchy hypoechoic lesions throughout the gland. This sonographic appearance is called a "leopard skin" pattern and is seen in lymphocytic infiltration of the thyroid in Hashimoto's thyroiditis. The hypoechoic lesions within the thyroid are areas of lymphocytic infiltration of the thyroid tissue. C, carotid artery; H, hypoechoic lesions; P, thyroid parenchyma; T, trachea.

**Figure 1.4**  The same patient as in Fig. 1.3: $^{99m}$TcO$_4$ thyroid scintigraphy with iodine uptake curve. Iodine uptake was 2% at 4 hours (a) and 2% at 24 hours (b). The scan showed no uptake in the thyroid bed. The free triiodothyronine (FT$_3$) and free thyroxine (FT$_4$) levels were low with elevated thyroid stimulating hormone (TSH) and antibodies against thyroperoxidase (TPOAb) values. The patient started levothyroxine treatment.



(a)



(b)
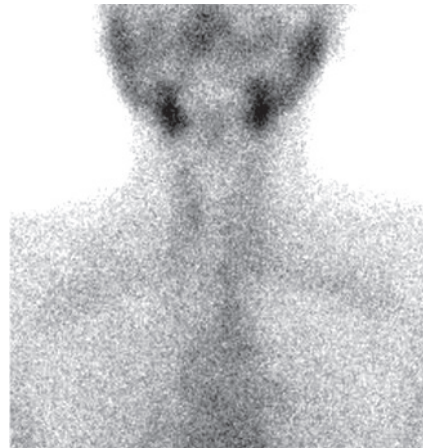
## Graves' disease (Basedow's disease)

### Definition and epidemiology

Graves' disease (GD) is an autoimmune disease representing the most common cause of hyperthyroidism (60–90% of all cases).

Graves' disease has a powerful hereditary component, affecting up to 2% of the female population, and is between five and ten times more common in females than in males (incidence of 5 : 1 to 10 : 1, respectively). It is also the most common cause of severe hyperthyroidism, which is accompanied by extended clinical signs and symptoms and laboratory abnormalities compared with milder forms of hyperthyroidism. About 30–50% of patients with GD will also suffer from Graves' ophthalmopathy, which is caused by inflammation of the eye muscles mediated by an inflammatory immune process.

### Etiology and pathogenesis

Graves' disease is an autoimmune disorder in which the body produces antibodies to the receptor for thyroid stimulating hormone (TSHrAb). (Antibodies to thyroglobulin and thyroperoxidase may also be produced.) TSHrAb bind to the thyroid stimulating hormone (TSH) receptors, which are located on cells producing thyroid hormone in the thyroid gland (follicular cells), and chronically stimulate them, resulting in an abnormally high production of triiodothyronine ($T_3$) and thyroxine ($T_4$). There are several factors that predispose to GD and Graves' ophthalmopathy; in particular, genetic susceptibility, infection, smoking, pregnancy, iodine, and iodine-containing drugs.

### Signs and symptoms

Signs and symptoms of GD all result from the direct and indirect effects of hyperthyroidism, with the main exceptions being Graves' ophthalmopathy, goiter, and pretibial myxedema.

### Diagnosis

#### Laboratory findings

Laboratory tests for GD include:
- Thyroid stimulating hormone (TSH), free triiodothyronine ($FT_3$), and free thyroxine ($FT_4$)
- TSHrAb
- Total cholesterol, high density lipoprotein (HDL), triglycerides

#### Imaging tests

Imaging tests for GD include:
- Thyroid ultrasound (Fig. 1.5)
- $^{99m}TcO_4$ thyroid scintigraphy (Fig. 1.6)
- Computed tomography (CT) neck scan
- Orbital nuclear magnetic resonance (NMR)

### Treatment

Treatment options for GD are:
- Beta blockers (rapid amelioration of symptoms)
- Thionamide
- Radioiodine ablation
- Surgery
- Glucocorticoid (for Graves' ophthalmopathy)
- Orbital irradiation (for Graves' ophthalmopathy)
- Orbital decompression surgery (for Graves' ophthalmopathy)
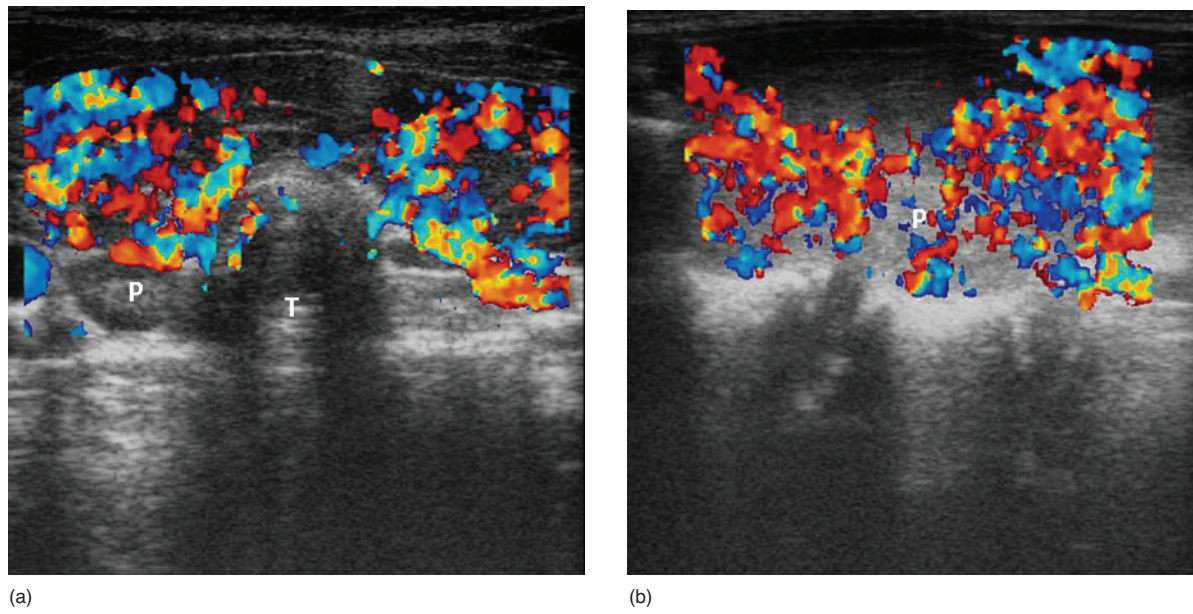
**Illustrations (Figs 1.5 & 1.6)**



(a)



(b)

**Figure 1.5**  A 32-year-old man presented with an unintentional 15 kg weight loss but with an otherwise normal physical examination. Laboratory studies revealed a suppressed thyroid stimulating hormone (TSH) concentration and an elevated thyroxine level, which are consistent with hyperthyroidism. Thyroid ultrasound – (a) cross section and (b) longitudinal section. These ultrasound/color Doppler images reveal markedly increased vascularity throughout the thyroid gland ("thyroid hell"). P, thyroid parenchyma; T, trachea.
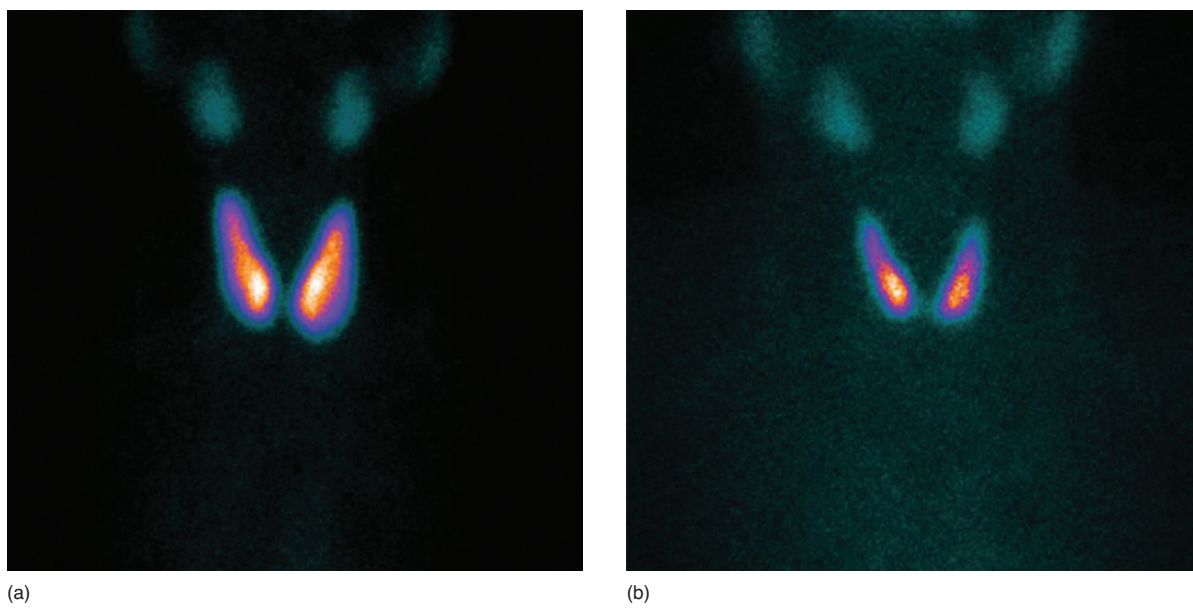


(a)



(b)

**Figure 1.6**  Thyroid scan of the same patient from Figure 1.5 with $^{99m}TcO_4$. The thyroid scan with $^{99m}TcO_4$ before (a) and after (b) treatment with methimazole. Intense and homogeneous uptake of the radiopharmaceutical in both lobes of thyroid gland is seen before therapy. The post-therapy scan was performed 6 months after therapy and shows a reduction of thyroid size and uptake.

## Subacute thyroiditis (de Quervain's thyroiditis)

### Definition and epidemiology

Subacute thyroiditis (ST) is a subacute granulomatous thyroiditis that belongs to a group of thyroiditis conditions known as resolving thyroiditis. Other names for this disorder are de Quervain's thyroiditis, subacute nonsuppurative thyroiditis, giant cell thyroiditis, and painful thyroiditis. It has an incidence of 12.1/100 000 per year with a higher incidence in females than in males (19.1 and 4.1/100 000 per year, respectively). It is most common in young adulthood (24/100 000 per year) and middle age (35/100 000 per year), and decreases with increased age.

### Etiology and pathogenesis

Subacute thyroiditis is presumed to be caused by a viral infection or a postviral inflammatory process. The majority of patients have a history of an upper respiratory infection prior to the onset of thyroiditis (typically 2–8 weeks beforehand). The disease was thought to have a seasonal incidence (higher in the summer), and clusters of cases have been reported in association with Coxsackievirus, mumps, measles, adenovirus, and other viral infections. Thyroid autoimmunity does not appear to play a primary role in the disorder, but it is strongly associated with HLA-B35 in many ethnic groups. A unifying hypothesis might be that the disorder results from a common subclinical viral infection that provides an antigen, either of viral origin or resulting from virus-induced host tissue damage, that uniquely binds to HLA-B35 molecules on macrophages. The resulting antigen-HLA-B35 complex activates cytotoxic T lymphocytes that then damage thyroid follicular cells, since the cells have partial structural similarity with the infection-related antigen. Unlike autoimmune thyroid disease, however, the immune reaction is not self-perpetuating, so the process is limited. The resulting thyroid inflammation damages thyroid follicles and activates proteolysis of the thyroglobulin stored within the follicles. The result is an unregulated release of large amounts of thyroxine ($T_4$) and triiodothyronine ($T_3$) into the circulation resulting in clinical and biochemical hyperthyroidism.

### Signs and symptoms

Subacute thyroiditis is a self-limiting thyroid condition associated with a triphasic clinical course of hyperthyroidism, hypothyroidism, and return to normal thyroid function. In particular, ST may be responsible for 15–20% of patients with thyrotoxicosis and 10% of patients presenting with hypothyroidism. Pain is the main symptom and it may be limited to the thyroid region or it may radiate to the upper neck, jaw, throat, upper chest, or ears. It can be exacerbated by coughing or turning the head. Fever, fatigue, malaise, anorexia, and myalgia are common.

### Diagnosis

#### Laboratory findings

Laboratory tests for ST include:
- Thyroid stimulating hormone (TSH), free triiodothyronine ($FT_3$), and free thyroxine ($FT_4$)
- Erythrocyte sedimentation rate (ESR)
- Polymerase chain reaction (PCR) for C-reactive protein
- Hemochrome

#### Imaging tests

A neck ultrasound is needed (Fig. 1.7).

### Treatment

Subacute thyroiditis is a self-limiting condition and so in most patients no specific therapy, such as antithyroid or thyroid hormone replacement therapy, is necessary. Treatment of patients with ST should be directed at providing relief for thyroid pain (e.g. prednisone) and tenderness, and ameliorating symptoms of hyperthyroidism (e.g. with a beta blocker such as propranolol).
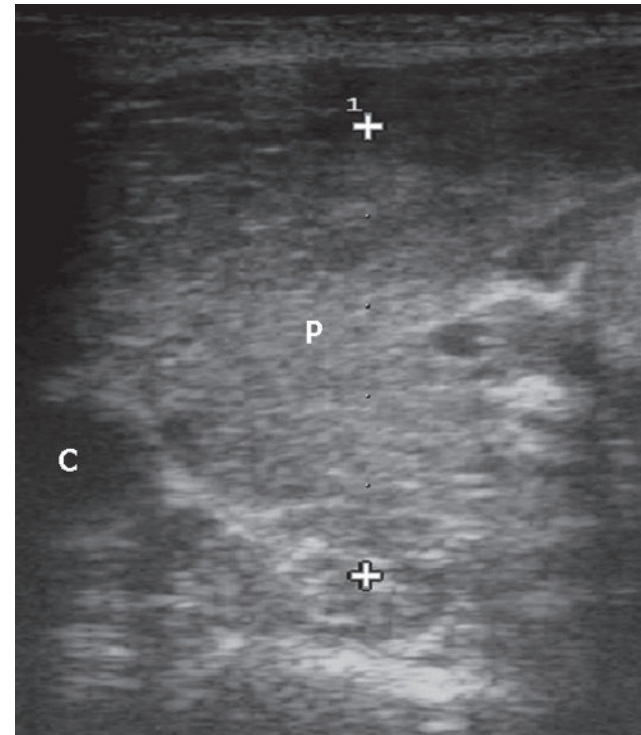
**Illustration (Fig. 1.7)**



(a)



(b)
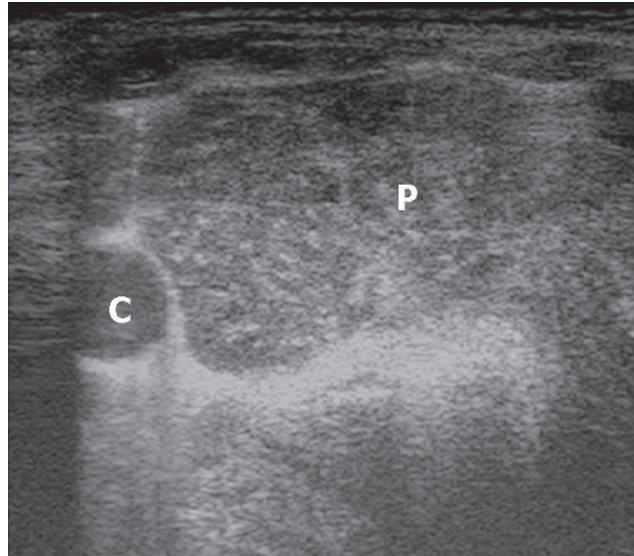
**Figure 1.7** A 47-year-old woman presents with pain and tenderness on her right side due to a chronic goiter. Her erythrocyte sedimentation rate was elevated and her thyroid laboratory tests suggested subclinical hypothyroidism. Two weeks previously, she had a fever and now her $^{99m}$Tc pertechnetate uptake is markedly decreased. (a) Thyroid ultrasound – cross section (before treatment). Focal hypoechogenicity in the painful area with decreased vascular flow by Doppler scan. C, carotid artery; P, thyroid parenchyma. The patient's clinical symptoms showed a dramatic response to glucocorticoid treatment. She became hypothyroid and began levothyroxine therapy. (b) Thyroid ultrasound – cross section (after treatment). The focal hypoechogenicity is reduced and the thyroid parenchyma has become more homogeneous. C, carotid artery; P, thyroid parenchyma.

## Benign thyroid nodules

### Definition and epidemiology

Thyroid nodules are the most common of thyroid diseases. They affect up to 5% of the general population and are more frequent in iodine deficient areas and in women (female to male ratio, 5 : 1). Thyroid nodules are mostly benign (adenoma, cysti, focal hyperplasia) and the incidence of malignant neoplasia is very low (4/100 000 per year).

Thyroid nodules are abnormal cell growths in the thyroid gland. The thyroid can be uninodular when a single nodule is present or multinodular when multiple nodules are present.

Thyroid nodules are mostly nonfunctioning but can be hyperfunctioning (toxic multinodular goiter, Plummer's disease) leading to symptoms of hyperthyroidism.

### Etiology and pathogenesis

The etiology of thyroid nodules is unknown. There are several factors that predispose to these nodules; in particular, genetic susceptibility, iodine deficiency, neck irradiation, and unknown environmental agents.

### Signs and symptoms

Usually thyroid nodules are asymptomatic and they are occasionally discovered during physical examination or an ultrasound neck scan.

Signs and symptoms of large nodules or multinodular goiter mainly result from thyroid increased volume and neck compression. The signs and symptoms include:
• Neck lump
• Neck pain, dyspnea, dysphagia, dysphonia
• Symptoms due to hyperthyroidism (in toxic multinodular goiter or Plummer's adenoma)

### Diagnosis

The gold standard for diagnosing thyroid nodules consists of both a neck ultrasound scan (evaluating nodules size and eventually suspicious features) and fine needle cytology (FNC) to diagnose malignant neoplasia.

### Laboratory and cytology tests

The laboratory and cytology tests for thyroid nodules include:
• Calcitonin (in nodules suspicious for medullary carcinoma)
• Thyroid stimulating hormone (TSH), free triiodothyronine ($FT_3$), free thyroxine ($FT_4$)
• Cytology (fine needle cytology)

### Imaging tests

Imaging tests for thyroid nodules include:
• Thyroid ultrasounds (Figs 1.8a, 1.9a & 1.10a): Relevant ultrasound scan features of thyroid nodules are: echostructure (solid, cystic, or mist nodules), echogenicity (ipo-, iso-, or anechogen nodules), vascular pattern, presence of microcalcifications (regular or irregular), and defined or undefined margins
• Computed tomography (CT) neck scan (Fig. 1.11)
• Neck X-ray
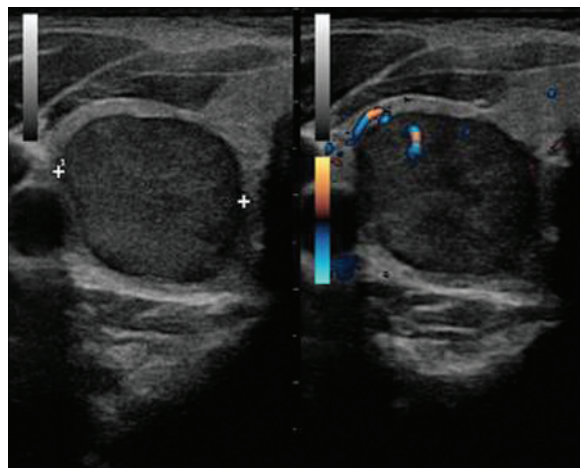• Scintigraphy thyroid scans (Figs 1.8b, 1.9b & 1.10b)
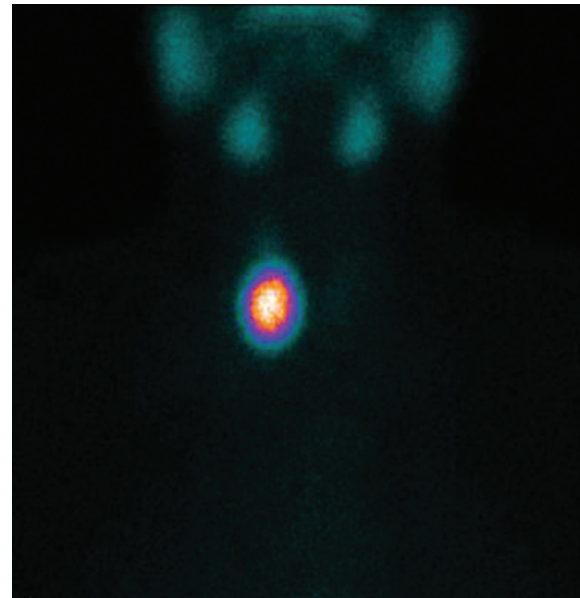
### Treatment

Treatment options for thyroid nodules are:
• Clinical and ultrasound scan follow-up
• Surgery (for compressive symptoms, tracheal or neck vessel compression or dislocation, mediastinal thyroid)
• Treatment of hyperthyroidism (toxic multinodular goiter, Plummer's adenoma)

## Illustrations (Figs 1.8–1.11)



(a)



(b)

**Figure 1.8** A case of thyroid toxic adenoma. A 56-year-old female patient with symptoms of hyperthyroidism. Hormonal blood levels showed increased free triiodothyronine (FT$_3$), free thyroxine (FT$_4$), and suppressed thyroid stimulating hormone (TSH). (a) Thyroid ultrasound showed a hypoechoic solid nodule of 14 × 15 mm with intra- and perinodular vascularization in the lower third of the right thyroid lobe. (b) The thyroid morpho-functional study was performed with 50 μCi of $^{131}$I orally and 3 mCi of $^{99m}$TcO$_4$ intravenously to evaluate thyroid uptake of iodine and scintigraphic distribution of Tc, respectively. Thyroid uptake was 17% at 6 hours, 29% at 24 hours, and 22% at 48 hours (data relevant for dosimetric calculations). The thyroid scan confirmed the clinical suspicion of Plummer's adenoma and showed complete functional inhibition of extranodular glandular tissue (inhibiting adenoma), which is the ideal condition for performing $^{131}$I therapy.
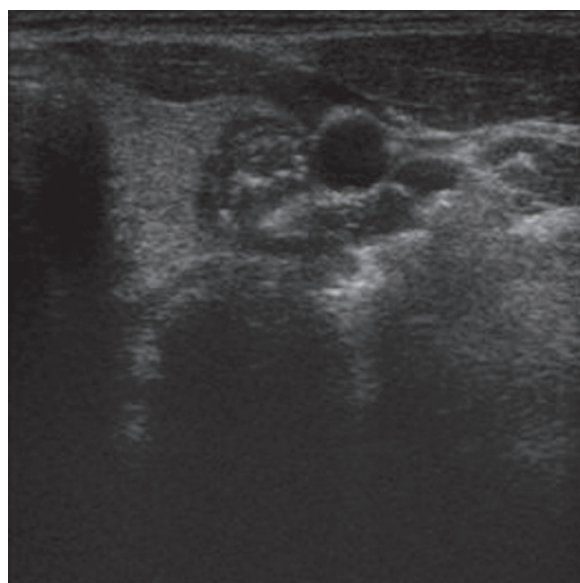


(a)
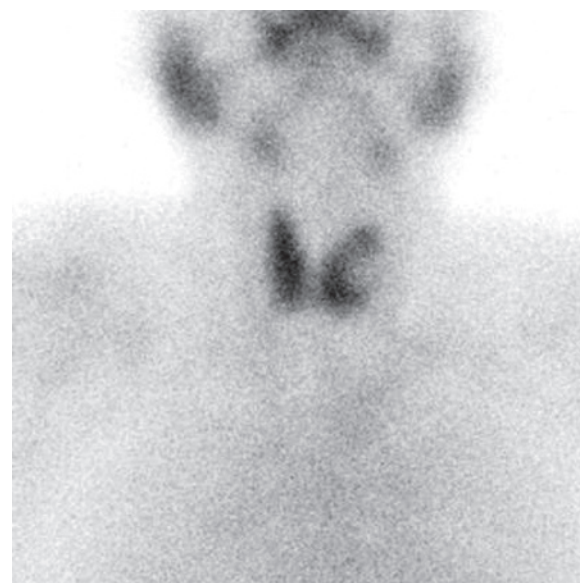


(b)

**Figure 1.9** A case of single thyroid nodule. A 25-year-old patient with incidental ultrasound finding of a thyroid nodule in the left lobe. (a) Thyroid ultrasound shows a solid hypoechoic nodule, with microcalcifications. (b) Thyroid scintigraphy shows the "cold" nodule with no detectable $^{99m}$TcO$_4$ uptake. The patient underwent fine needle cytology and the cytology was suspicious for papillary carcinoma.
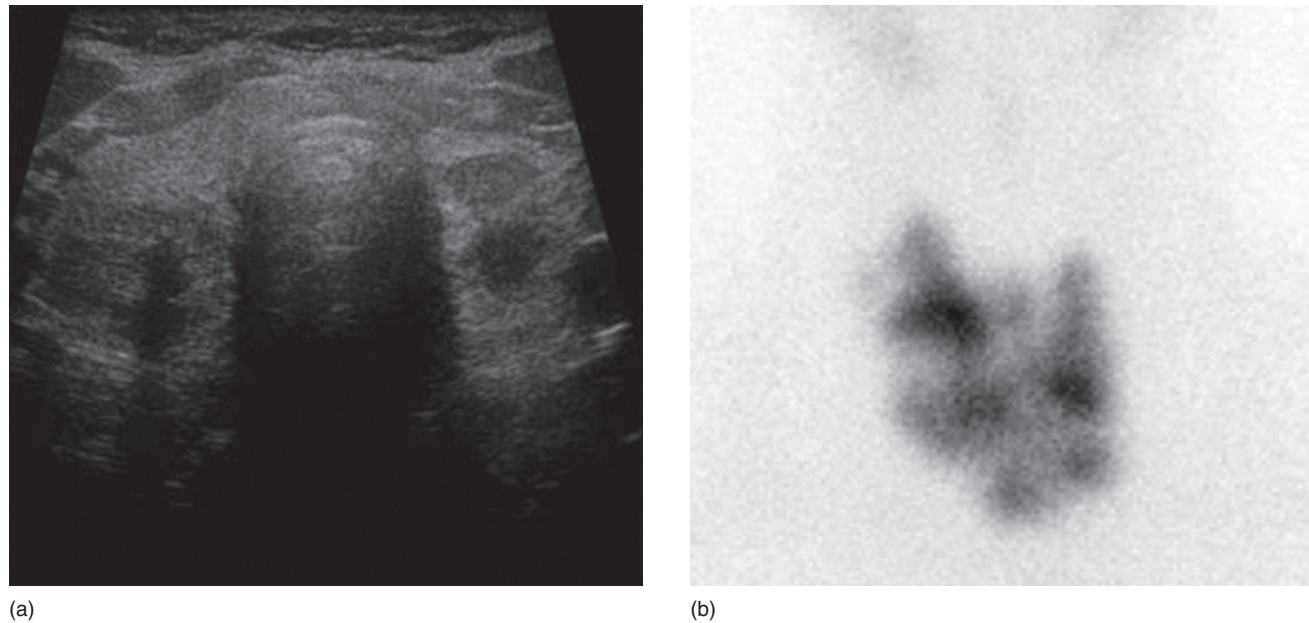
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(a)                                      (b)

**Figure 1.10** A case of multinodular toxic thyroid. A hyperthyroid 46-year-old woman with a palpable multinodular thyroid. (a) Ultrasound scan shows an enlarged thyroid with multiple nodules in both right and left lobe. The gland seems to extend in the mediastinum. (b) Thyroid scan with $^{99m}TcO_4$. The scan shows intense uptake in the glandular parenchima with multiple "cold" areas in correspondence to the major nodules seen at ultrasound. This finding is consistent with the diagnosis of a "multinodular toxic thyroid." The patient underwent surgery.



**Figure 1.11** A case of goiter. A 70-year-old man with a palpable multinodular goiter. The axial contrast-enhanced computed tomography (CT) image shows increased thyroid volume compressing the tracheal and esophageal lumen.

## Thyroid cancer

### Definition and epidemiology

Carcinoma of the thyroid is an uncommon cancer but it is the most common malignancy of the endocrine system (Figs 1.12–1.25). Differentiated tumors (papillary [Figs 1.14–1.17] or follicular [Fig. 1.20]) are highly treatable and are usually curable. Poorly differentiated tumors (medullary [Fig. 1.23] or anaplastic) are much less common, are aggressive, metastasize early, and have a much poorer prognosis. Thyroid cancer affects women more often than men and usually occurs in people between the ages of 25 and 65. The incidence of this malignancy has been increasing over the last decade.

The World Health Organization 2004 classification is shown in Table 1.1. The prognosis for differentiated carcinoma is better for patients aged below 40 without extracapsular extension or vascular invasion. Age appears to be

**Table 1.1** World Health Organization 2004 classification of neoplasms of the thyroid

**I** Adenomas
  **A** Follicular
    **1.** Colloid variant
    **2.** Embryonal
    **3.** Fetal
    **4.** Hürthle cell variant
  **B** Papillary (probably malignant)
  **C** Teratoma
**II** Malignant tumors
  **A** Differentiated
    **1.** Papillary adenocarcinoma
      **1.** Pure papillary adenocarcinoma
      **2.** Mixed papillary and follicular carcinoma (variants including tall cell, follicular, oxyphyl, solid)
    **2.** Follicular adenocarcinomas (variants: "malignant adenoma," Hürthle cell carcinoma or oxyphil carcinoma, clear-cell carcinoma, insular carcinoma)
  **B** Medullary carcinoma
  **C** Undifferentiated
    **1.** Small cell (to be differentiated from lymphoma)
    **2.** Giant cell
    **3.** Carcinosarcoma
  **D** Miscellaneous
    **1.** Lymphoma, sarcoma
    **2.** Squamous cell epidermoid carcinoma
    **3.** Fibrosarcoma
    **4.** Mucoepithelial carcinoma
    **5.** Metastatic tumor

Courtesy of Delellis RA, Lloyd RV, Heitx PU & Eng C. (2004) Pathology and genetics of tumours of endocrine organs. *WHO Classification of Tumours*, IARC, Lyon, France.

the single most important prognostic factor. The prognostic significance of lymph node status is controversial. Adverse factors include: Older than 45 years; follicular histology; primary tumor > 4 cm (T2–T3); extrathyroid extension (T4); and distant metastases.

### Etiology and pathogenesis

#### Risk factors for thyroid cancer
The risk factors for thyroid cancer are:
- External radiation and thyroid cancer
- History of goiter
- Family history of thyroid disease
- Female gender
- Asian ethnicity

While an increased incidence of thyroid cancer in patients with Hashimoto's thyroiditis has been reported, clinical experience does not suggest a strong relationship between this relatively common disease and thyroid cancer.

### Signs and symptoms

Most frequently the tumor is discovered accidentally as a finding during an ultrasound of the neck. It may appear as a gradually enlarging, painful mass with associated symptoms of hoarseness, dysphagia, or dysphonia, or there may be difficulty breathing. Occasionally a patient arrives with metastatic nodules in the neck, pulmonary symptoms from metastases, or a pathologic fracture of the spine or hip. Usually there are no symptoms of hyper- or hypothyroidism.

Upon examination of the neck, carcinoma of the thyroid characteristically appears as an asymmetrical lump in the gland. If it is still within the confines of the gland, it will move with the gland when the patient swallows and may be moveable within the gland. If it has invaded the trachea or neighboring structures, it may be fixed in place. Lymph nodes containing metastases may be found in the supraclavicular triangles, in the carotid chain, along the thyroid isthmus, and rarely in the axillary nodes. Although carcinoma of the thyroid is typically firm or hard, rapidly growing lesions may sometimes be soft or even fluctuant.

### Diagnosis

Most patients with thyroid carcinoma are recognized because of the observation of a neck mass and the result of fine needle aspiration cytology.

#### Laboratory findings
Laboratory tests for thyroid carcinoma:
- Thyroid stimulating hormone (TSH), and free thyroxine ($FT_4$) are usually measured to verify metabolic status.
- Antithyroid peroxidase antibodies (TPOAbs) and thyroglobulin antibodies (TgAbs).

**CHAPTER 1** Thyroid

• Thyroglobulin (Tg) assay: Although Tg assay has been suggested as an important marker for thyroid cancer, practice shows that elevated Tg levels can be caused by adenoma, multinodular goiter, and other diseases; thus, the determination is of little value before operating.

• Calcitonin immunoassay: Some groups recommend this on all patients with nodules to allow preoperative diagnosis of medullary thyroid carcinoma.

### Imaging tests

Imaging tests for thyroid carcinoma include:

• Ultrasound studies, which are the most basic and useful test.

• Isotope scans (Figs 1.18a&f, 1.19, 1.21 & 1.24) have a limited role in the initial diagnosis.

• Chest X-rays may be informative but are often omitted.

• Computed tomography (CT) (Figs 1.12, 1.13, 1.22–1.25) and TC-18F-FDG positron emission tomography (PET) (Fig. 1.18d&g) scanning of the lungs and magnetic resonance imaging (MRI) of the neck can provide useful information prior to surgery in lesions that extend outside the thyroid or have metastasis.

### Treatment

In differentiated cancers contemporary medical and surgical practice depends mainly on the clinical stage of the disease rather than on the exact histologic status. The classification can be conveniently reduced to four categories that have prognostic significance and clear therapeutic relevance (Table 1.2).

• Thyroid cancer may require surgery. The possible surgical approaches range from a simple removal of the nodule to total thyroidectomy with bilateral radical neck dissection.

• Radioactive iodine-131 is used in patients with papillary or follicular thyroid cancer for ablation of residual thyroid tissue after surgery and for the treatment of thyroid cancer.

**Table 1.2** Thyroid cancer: Classification

| Clinical stage | Comparable TNM classification |
|---|---|
| I. Intrathyroidal | T0, T1, T2, N0, M0 |
| II. Cervical adenopathy | T0–T2, N0, N1a, N1b, M0 |
| III. Locally invasive disease | T3, T4a, T4b, M0 |
| IV. Distant metastases | M1 |

Courtesy of Edge SB, Byrd DR, Compton CC, et al. (eds) (2010) *AJCC Cancer Staging Manual*, 7th edn. Springer, New York, NY.

**Table 1.3** Thyroid cancer: 5-year survival rates

| Thyroid cancer type | 5-year survival (%) | | | |
|---|---|---|---|---|
| | Stage I | Stage II | Stage III | Stage IV |
| Papillary | 100 | 100 | 93 | 51 |
| Follicular | 100 | 100 | 71 | 50 |
| Medullary | 100 | 98 | 81 | 28 |
| Anaplastic | (Always Stage IV) | | | 7 |

Courtesy of Edge SB, Byrd DR, Compton CC, et al. (eds) (2010) *AJCC Cancer Staging Manual*, 7th edn. Springer, New York, NY.

Patients with medullary, anaplastic, and most Hürthle cell cancers do not benefit from this therapy.

External irradiation may be used when the cancer is unresectable, when it recurs after resection, or to relieve pain from bone metastasis.

Sorafenib and sunitinib, approved for other indications, show promise as treatments for thyroid cancer and are being used by some patients who do not qualify for clinical trials.

Survival rate for thyroid cancer is related to both type of cancer and stage at time of diagnosis (Table 1.3).

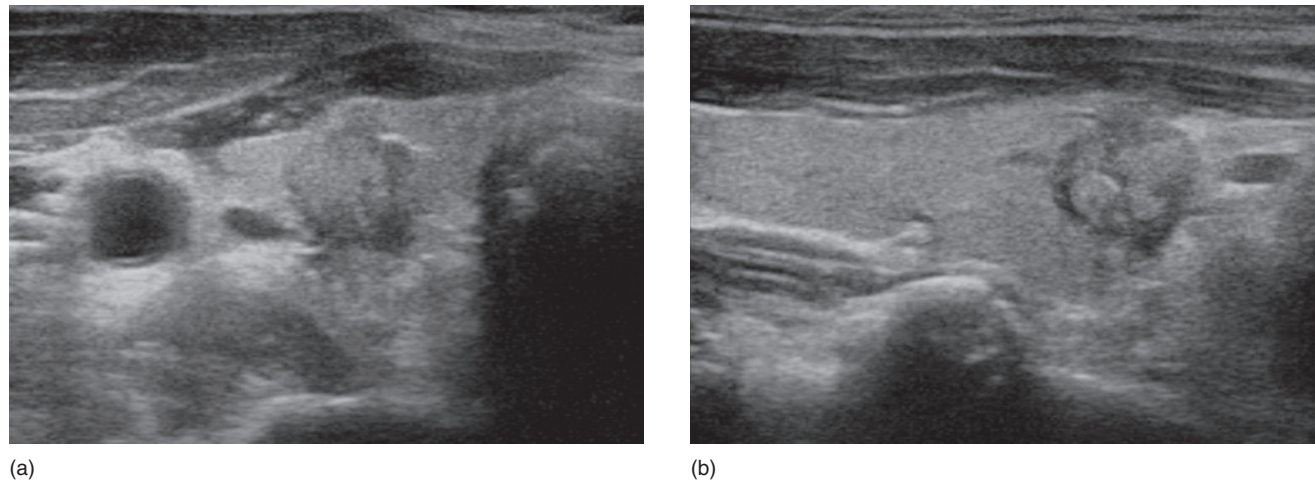**Illustrations (Figs 1.12–1.25)**



(a)



(b)

**Figure 1.12** Papillary thyroid carcinoma and cystic lymph node metastasis in a 57-year-old man. (a) Transverse sonogram of the right lobe of the thyroid shows a solitary, isoechoic, inhomogenous nodule with irregular margin. (b) Longitudinal sonogram of the same thyroid nodule.
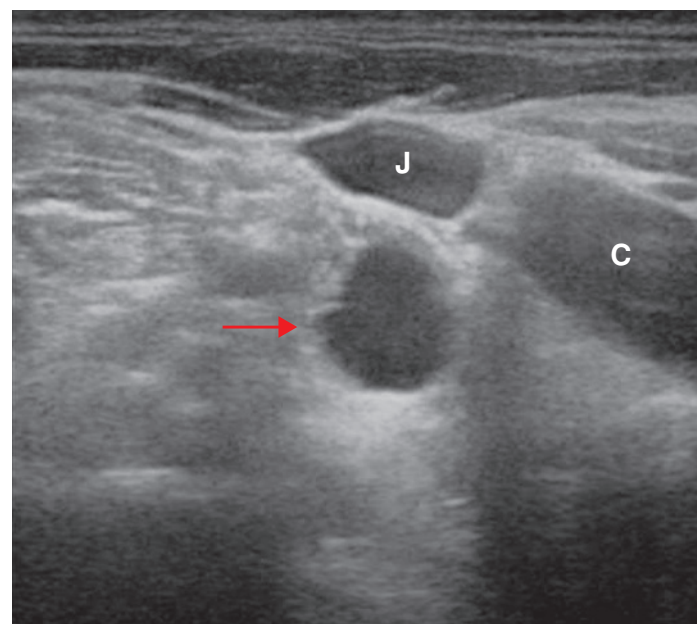


**Figure 1.13** Transverse sonogram of the right neck shows a cystic level 4 nodal (red arrow). C: carotid artery; J, jugular vein.
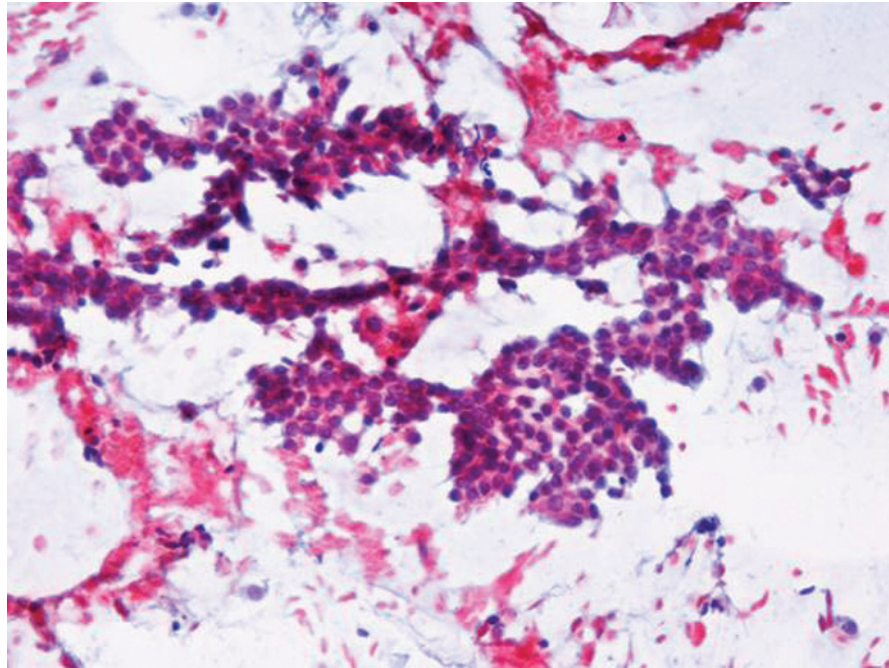
**Figure 1.14** Cytology of papillary carcinoma (Papanicolau, 20 × ). Thyrocytes are arranged in a pseudopapillary structure with nuclear irregularity.
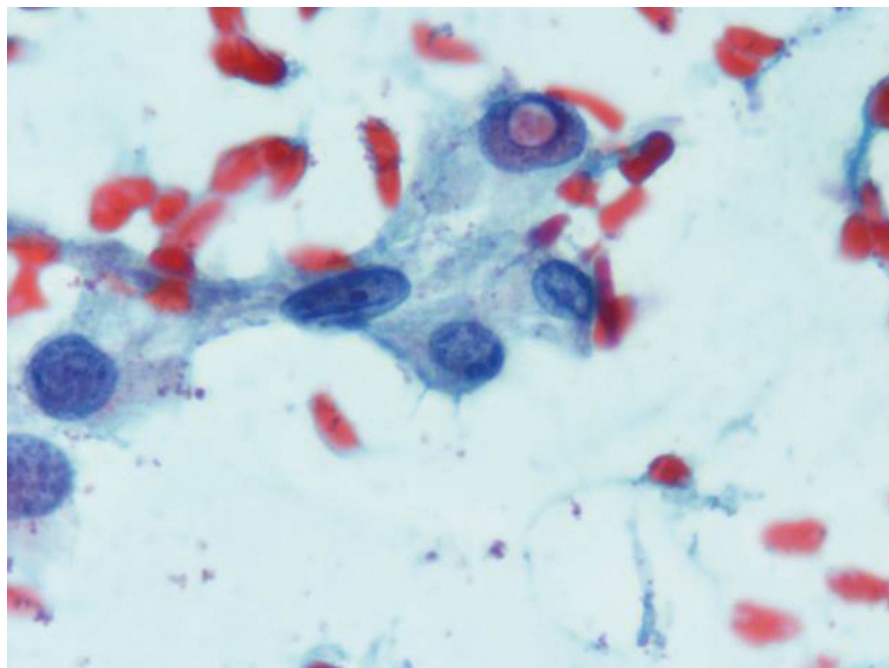


**Figure 1.15** Cytology of papillary carcinoma (Papanicolau, 40 × ). Thyrocytes with evidence of little nucleus, nuclear pseudoinclusion, and nuclear incision.

Thyroid cancer
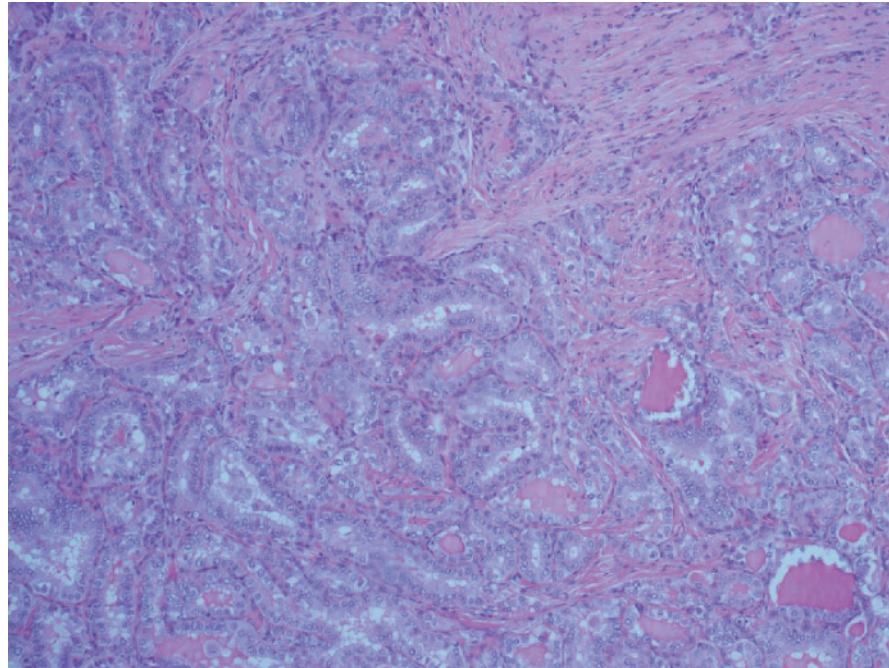


**Figure 1.16** Histology of papillary carcinoma. Papillary carcinoma with ground glass nuclei (HE, 10 × ).
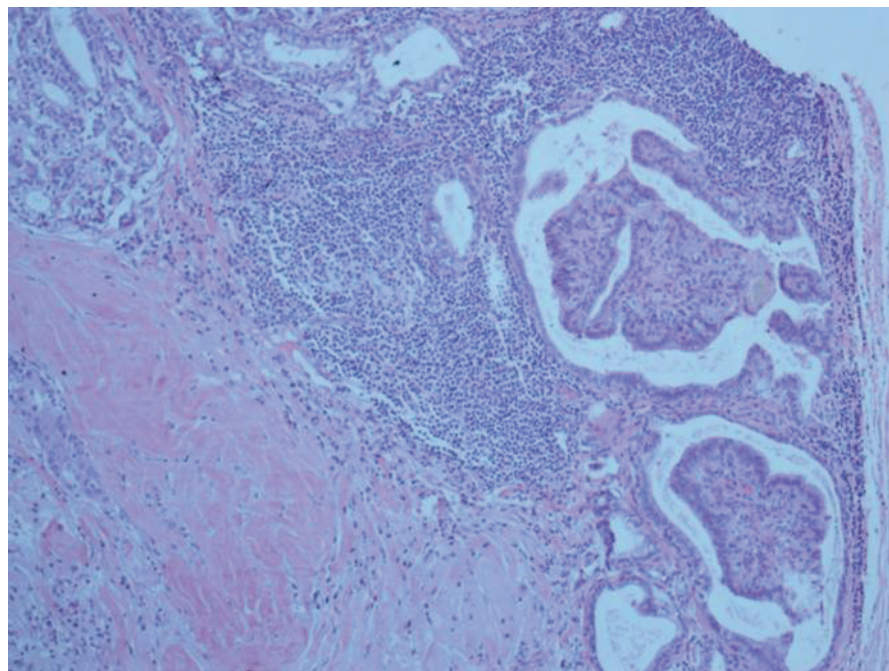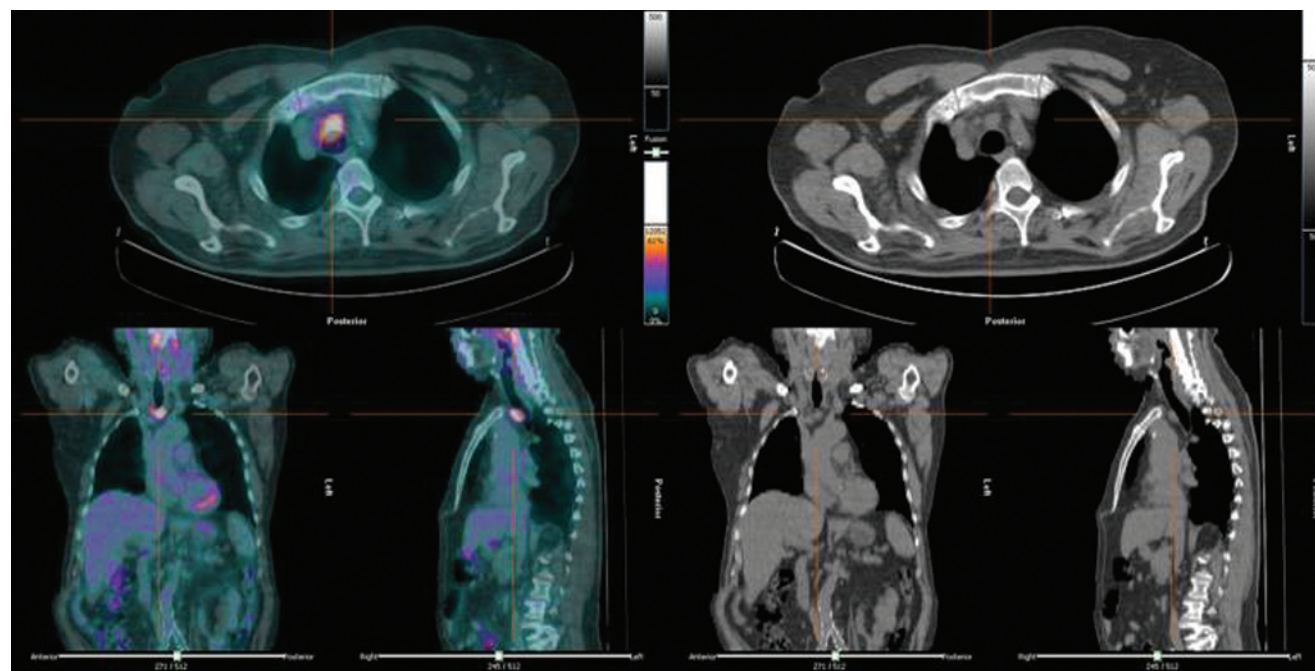


**Figure 1.17** Histology of papillary carcinoma. Metastasis in neck node (HE, 10 × ).

(a)    (b)    (c)
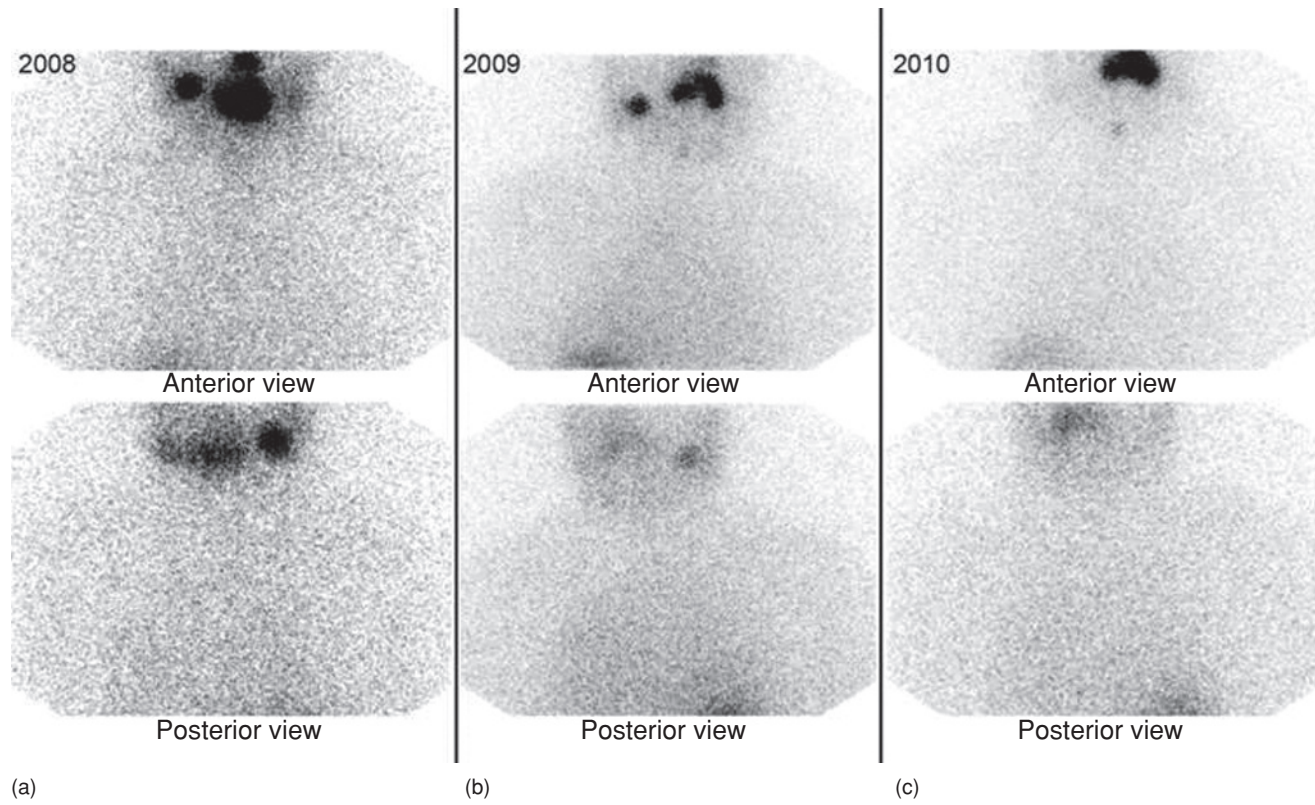


(d)

**Figure 1.18** A case of differentiated thyroid cancer: Papillary thyroid cancer infiltrating the periglandular soft tissues with lymph node metastases (pT4 N1a Mx). After several cycles of $^{131}$I therapy (a–c) the patient still had residual disease in the paratracheal lymph nodes unaffected by the iodine therapy and clearly detected by $^{18}$F-FDG positron emission tomography (PET) performed in 2008 (d) during $^{131}$I therapy and in 2009 (e) after the last $^{131}$I treatment. An increase in the size of the metastases was observed despite the iodine therapy. Iodine therapy was therefore discontinued and the patient performed an $^{111}$In-Octreoscan to verify if metastases had somatostatin receptors. The scan showed high density of somatostatin receptors (f). The patient started treatment with long-acting somatostatin analogs, with stable disease after 2 years as shown by the $^{18}$F-FDG PET scan performed for restaging 2 years after (g).
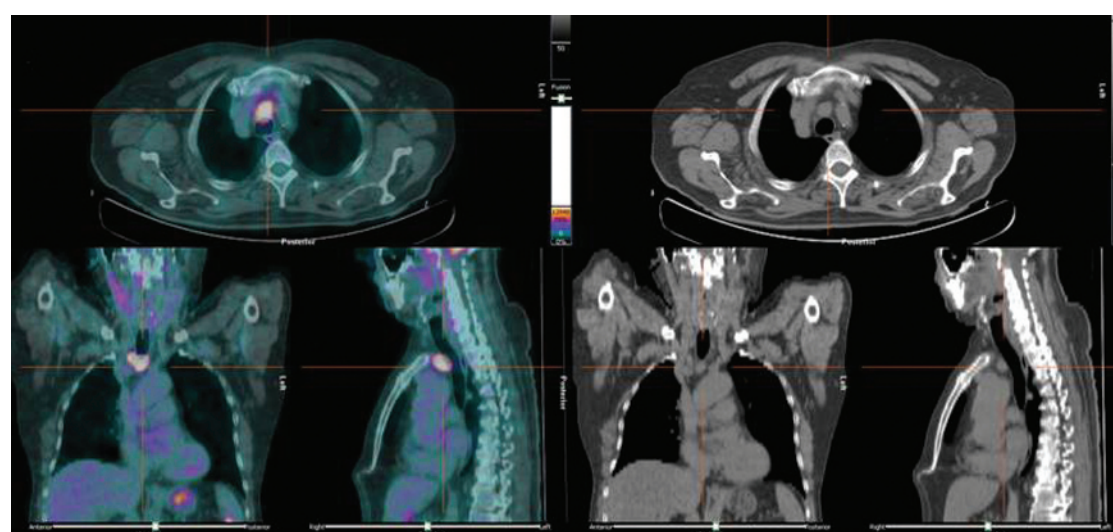
(e)



Anterior view                    Posterior view
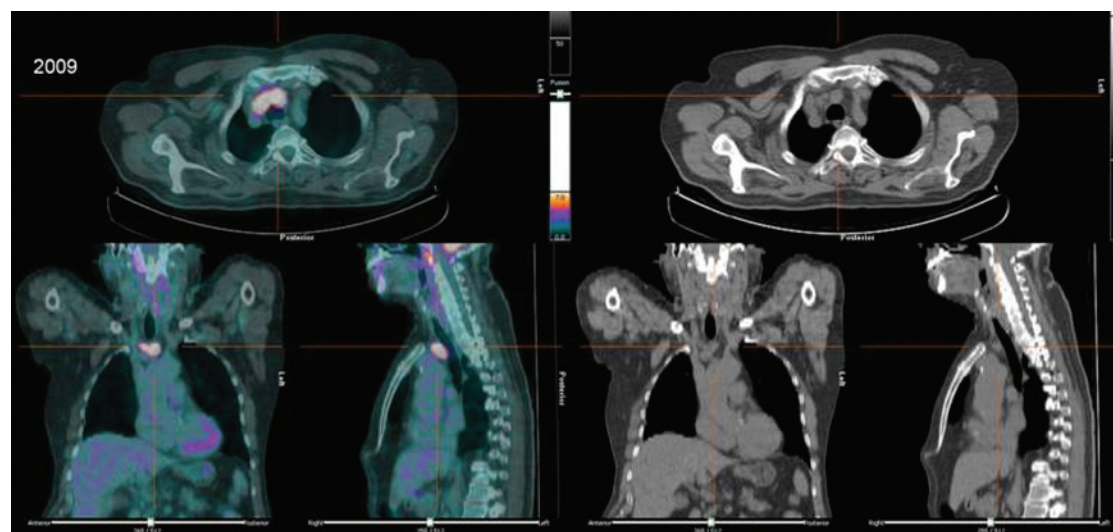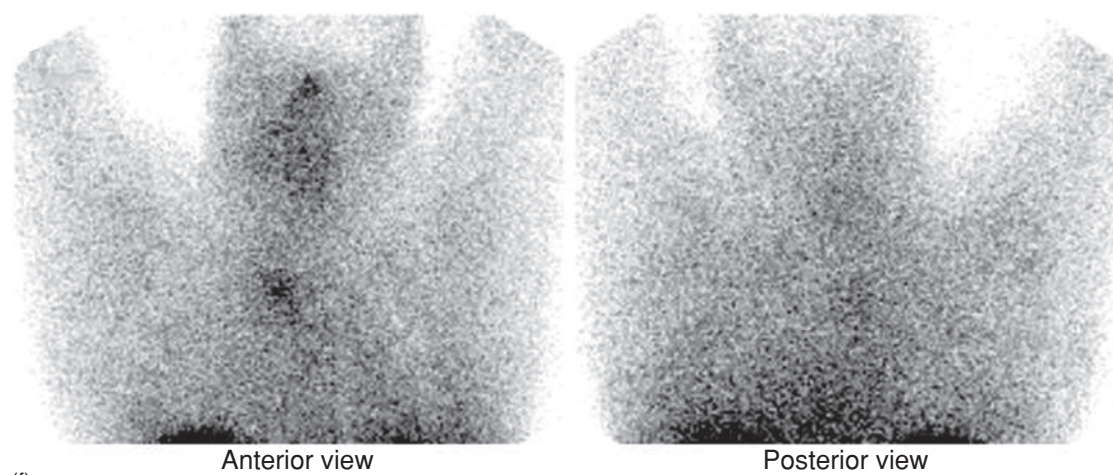
(f)



(g)

**Figure 1.18** (*Continued*)

**CHAPTER 1** Thyroid



R    L        R    L
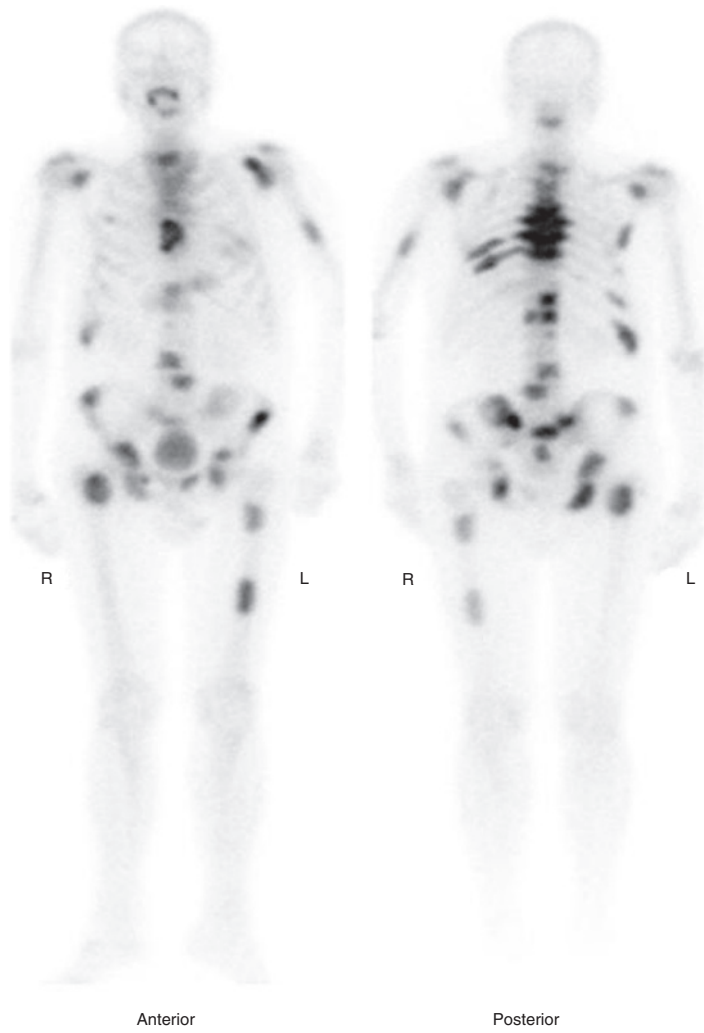
Anterior                Posterior

**Figure 1.19** A case of follicular thyroid cancer with bone metastases. Bone metastases is rare in differentiated thyroid cancer but may occur with or without $^{131}$I uptake and variable thyroglobulin (Tg) production. These metastases can be detected with $^{18}$F-FDG positron emission tomography (PET) when metabolically active, but the diagnostic exam of choice is a bone scan with $^{99m}$Tc-hydroxymethylene-diphosphonate (HDP) or $^{99m}$Tc-methyl-diphosphate (MDP) as shown in this figure. An avid bone uptake offers the treatment option with a beta-emitting isotope ($^{188}$Re-HEDP, $^{153}$Sm-EDTMP, $^{89}$Sr-Chloride, etc.).
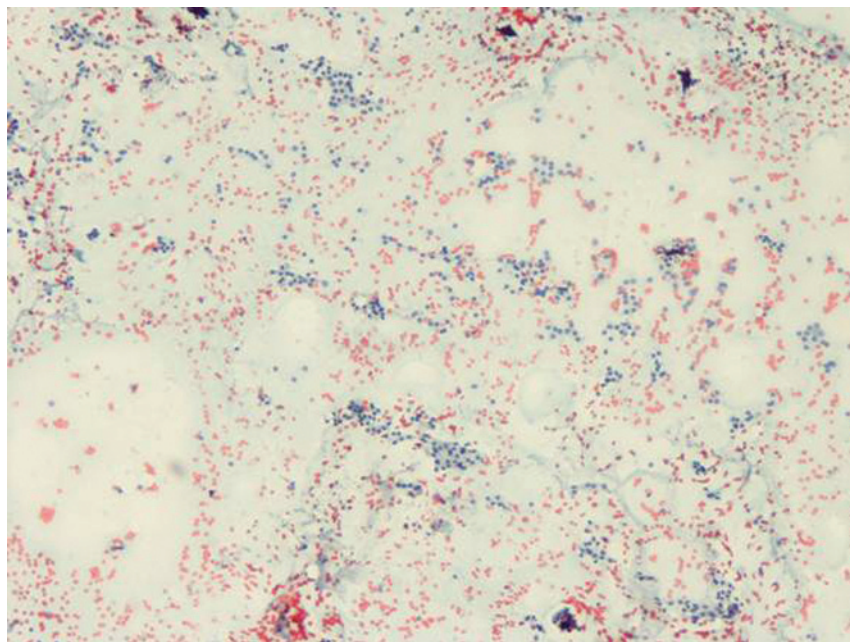


**Figure 1.20** Cytology of follicular lesion (Papanicolau, 10 ×). Thyrocytes arranged in microfollicular structure, with scant colloid.

Thyroid cancer



(aii)    Chest – anterior                Chest – posterior

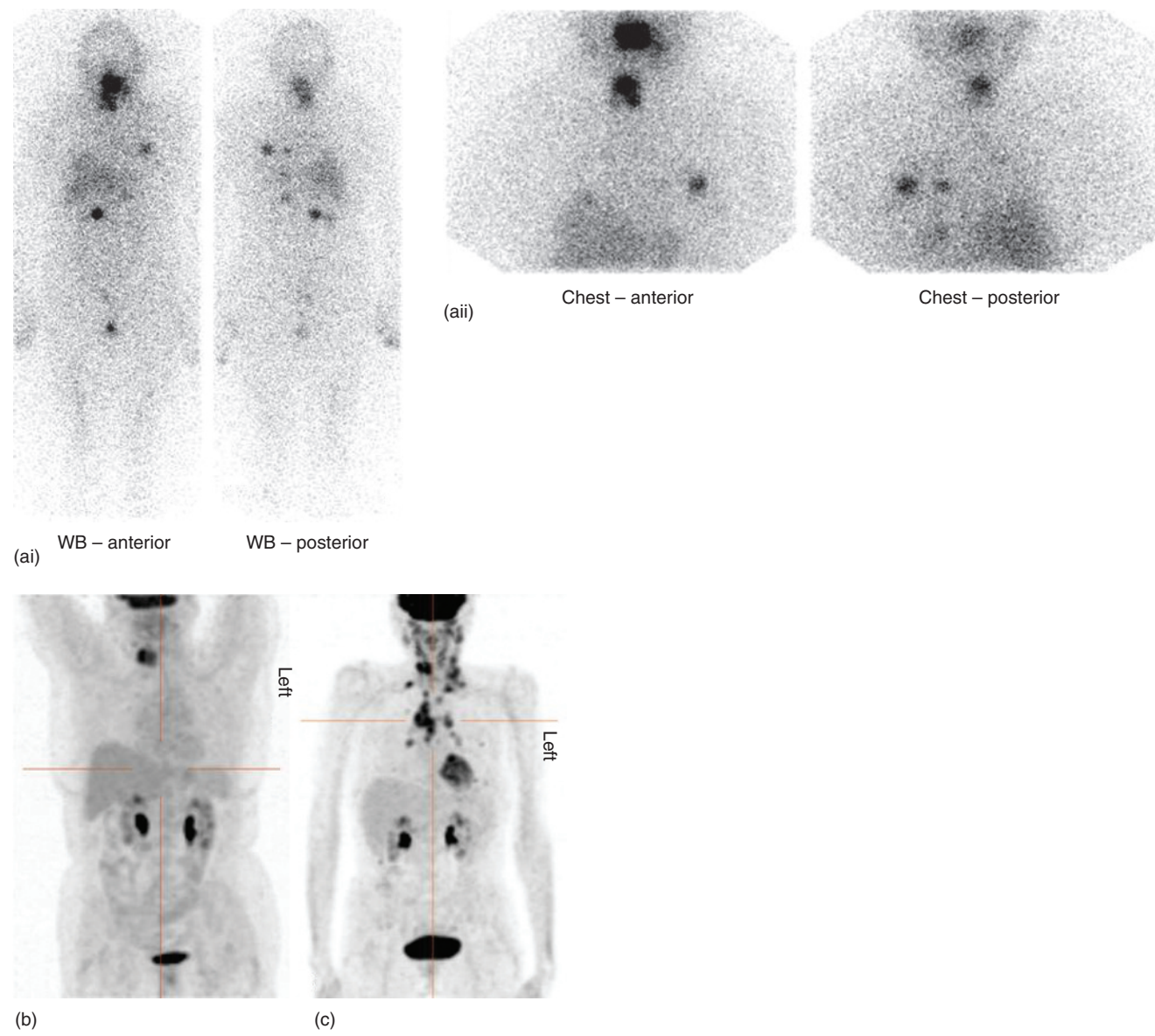(ai)    WB – anterior    WB – posterior

(b)                (c)

**Figure 1.21** A case of undifferentiated thyroid cancer: These images show the case of a 64-year-old woman who underwent several surgeries for primary and recurrent undifferentiated thyroid cancer. She also performed ^{131}I therapy and the whole body scan post-therapy showed disease recurrence in the neck and lungs (ai & aii). At the same time an ^{18}F-FDG positron emission tomography (PET) scan showed high glucose metabolism in the neck metastasis (a negative prognostic factor) but not in the other metastases (b). The patient therefore performed a salvage radiotherapy with external beam, but the following ^{18}F-FDG PET scan showed progression of the disease with multiple focal areas of increased uptake in the laterocervical lymph nodes, the mediastinum, the pulmonary parenchima, and the hilum (c).

**CHAPTER 1** Thyroid
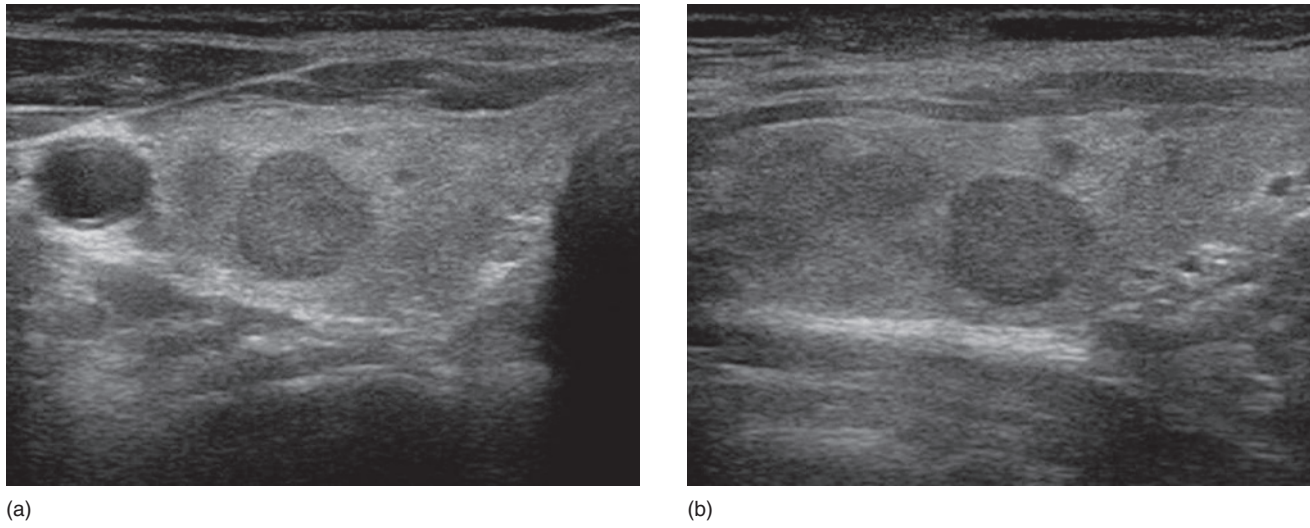


(a)                                                                    (b)

**Figure 1.22**  Medullary thyroid carcinoma in a 52-year-old woman with an elevated calcitonin value. (a) Transverse sonogram of the right lobe of the thyroid shows a solitary, hypoechoic, nodule with an irregular margin. (b) Longitudinal sonogram of the same thyroid nodule.
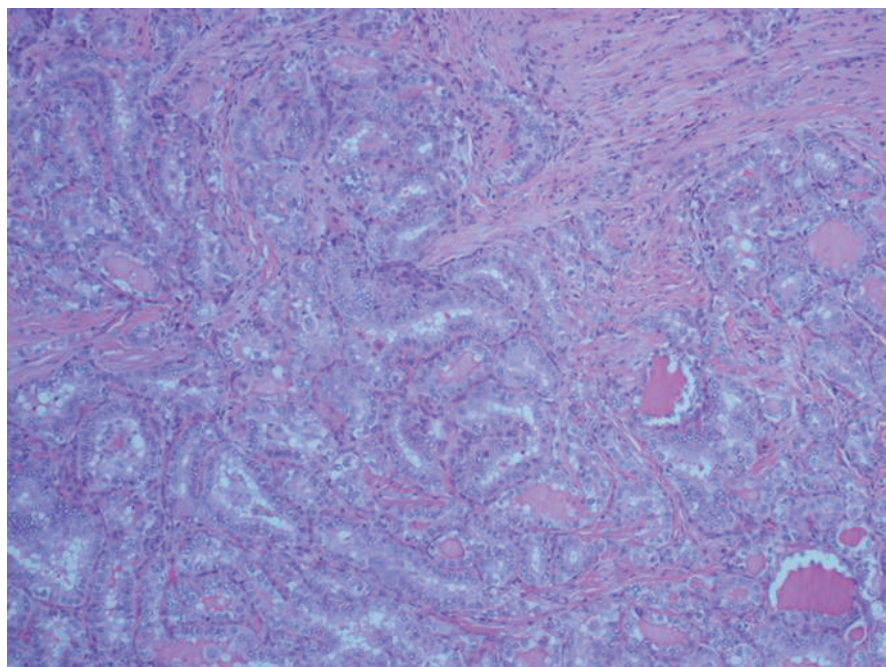


**Figure 1.23**  Histology of medullary carcinoma: Solid nests of polygonal cells associated to amyloid deposits within the stroma (HE, 20 × ).

**Figure 1.24**  A case of medullary thyroid cancer (MTC): Gamma camera images of the chest of a patient with metastatic MTC. Images were acquired 1 hour after the intravenous administration of 15 mCi of $^{99m}$Tc-HYNICTOC (a somatostatin analog that binds to type 3 receptors) before (a) and after (b) therapy with 60 mCi of $^{90}$Y-DOTATOC (the same somatostatin analog radiolabeled with a beta-emitting isotope). In MTC primary and metastatic lesions can express somatostatin receptors (SSTRs). The scintigraphic demonstration of SSTRs is therefore mandatory for both correct staging and therapy decision making. In this patient the treatment of choice was with radiolabeled somatostatin analogs, and after just one cycle of therapy the scan (b) shows large necrosis and reduction in size of all metastasis.

(a)                                              (b)

(a)                                              (b)
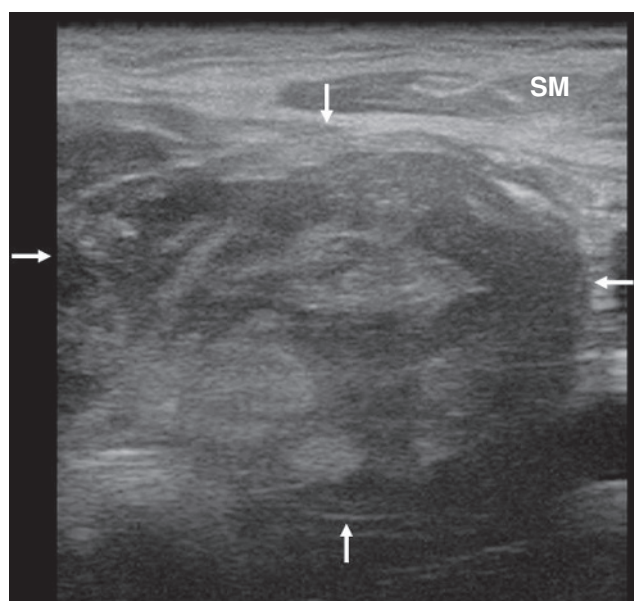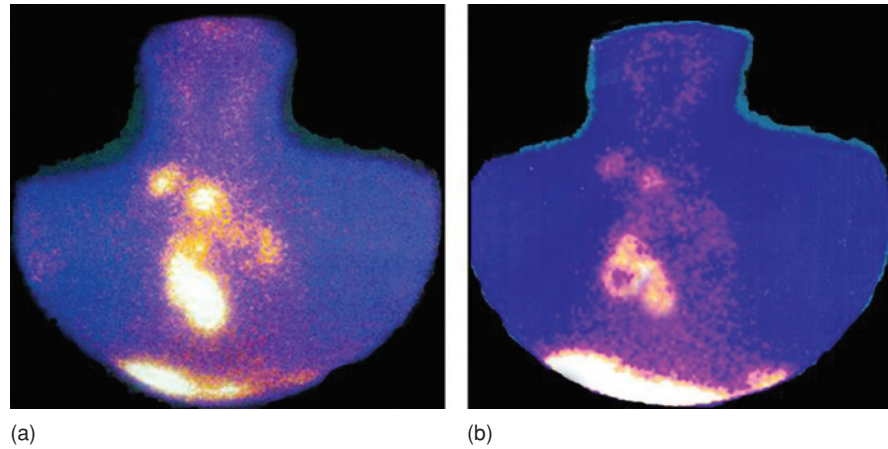
**Figure 1.25**  B-cell non-Hodgkin lymphoma of the thyroid in a 77-year-old woman with Hashimoto thyroiditis. (a) Transverse sonogram of the left lobe of the thyroid shows a large heterogeneous mass with marked hypoechogenicity when compared with the strap muscles (SM). (b) Axial contrast-enhanced computed tomography (CT) imaging shows widespread morphostructural disruption of the thyroid left lobe, replaced by hypodense solid tissue, invading adjacent muscle planes and extending to the posterior mediastinum, compressing the tracheal and esophageal lumen, and to the origin of neck vessels, significantly reducing the size of the internal jugular vein. Lymphadenopathies in the right side of the neck and in the superior mediastinum are also evident.