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13.3.2 Thyroid cancer Kristien Boelaert and Anthony P. Weetman **ESSENTIALS** Thyroid cancers are the most common endocrine malignancies and their incidence is rising globally, largely due to significant increases in small, incidentally detected low-risk tumours. Follicular epithelial cell cancer—the commonest type; usually well differentiated tumours with an excellent prognosis but occasionally highly undifferentiated; may be induced by exposure to ionizing radiation; typically present with asymptomatic thyroid enlargement; usually diagnosed by ultrasonography and fine needle aspiration biopsy; treatment is typically by hemi- or total thyroidectomy, followed by radioiodine ablation (administered to remove any remaining thyroid tissue) and short- to longer-term thyroid-stimulating hormone suppression depending on clinical risk stratification Medullary thyroid carcinoma—arises from parafollicular C cells; comprises 3–5% of all thyroid cancers; hereditary autosomal dominant forms associated with germline point mutations in the RET proto-oncogene; occurs in 20% as part of multiple endocrine neoplasia (MEN) type 2A or 2B, or as isolated familial medullary carcinoma; typically presents with a solitary thyroid nodule, accompanied in 50% of cases by cervical lymphadenopathy; can be associated with unusual hormonal effects, including secretory diarrhoea; diagnosis often made by fine needle aspiration biopsy and by raised serum calcitonin concentration; treatment is by total thyroidectomy (requiring long-term thyroid hormone replacement) and neck dissection (if required), followed by monitoring of serum calcitonin levels and tyrosine kinase inhibitors in advanced cases; Genetic testing for the presence of RET mutations allows family testing, with prophylactic thyroidectomy recommended for affected individuals. Rare thyroid tumours—include (1) anaplastic carcinomas—present as a rapidly enlarging and fixed thyroid masses, sometimes with local pain; rapidly fatal; (2) sarcomas; and (3) primary lymphomas—usually present as a rapidly enlarging thyroid mass in a patient with Hashimoto’s thyroiditis. Primary thyroid follicular epithelial tumours

Aetiology Differentiated thyroid cancers are the most common tumours arising from thyroid follicular epithelial cells and account for 95% of all thyroid carcinomas (Table 13.3.2.1). Papillary carcinomas Around 85% of all thyroid cancers are papillary carcinomas, and these carry the best prognosis. Most of these tumours are indolent and harbour mutually exclusive mutations of genes encoding effectors that signal through the mitogen-activated protein kinase (MAPK) pathway. BRAF V600E accounts for 60% of these mutations, followed by RAS (15%) and chromosomal rearrangements (12%) including RET, NTRK, and ALK resulting in aberrant expression of BRAF or of receptor tyrosine kinases. The remaining 13% have no known driver mutations. Different mutations are associated

13.3.2 Thyroid cancer 2303 with varying histological subtypes of papillary thyroid cancers and confer distinct patterns of gene expression, signalling, and clinical characteristics. BRAF-mutated papillary thyroid cancers tend to be more aggressive with high frequency of lymph node metastases and recurrence rates. Exposure to ionizing radiation is a risk factor for the development of papillary thyroid cancer and sharp increases in the incidence of these tumours, especially in young children, were observed following the nuclear reactor accident in Chernobyl in 1986 and following the atomic bomb explosions in Hiroshima and Nagasaki in 1945. Radiation-induced papillary cancers have a high prevalence of fusion oncogenes activating RET or NTRK and RET/PTC3 is particularly linked to radiation. Low-dose external beam radiation (10–1500 cGy) to the head and neck increases the risk of papillary thyroid cancer over 10 to 30 years. Higher thyroid

radiation doses, including those arising from radio-iodine given for treatment of hyperthyroidism, are not associated with an increased risk of malignancy because thyroid cells are destroyed rather than transformed. Mutations in the TERT gene have been identified in more aggressive subsets of papillary cancers. Follicular carcinomas Follicular thyroid cancers account for 2–5% of thyroid cancers and usually harbour mutations of either RAS or the PAX8-PPARG fusion oncogene. These tumours are also more prevalent in areas of iodine-deficiency and excessive stimulation of thyroid cell growth by thyrotropin (TSH) plays a role in their pathogenesis. Rarely follicular carcinomas are associated with activating mutations of the genes encoding the TSH receptor or Gs α protein, similar to those found in toxic adenoma, and it is thought that some follicular carcinomas arise from adenomas. The prognosis of patients with follicular cancers depends on the size of the tumour, the patient's age, and the degree of angioinvasion which predicts the risk of distant metastases. Hürthle cell cancers These are classified as a variant of follicular carcinomas and are genetically distinct. They may be widely invasive and may behave aggressively, with lung and bone metastases and refractoriness to radio-iodine. Anaplastic carcinomas These may arise from and can coexist with differentiated cancers but can also occur de novo. They have been linked to mutations in TP53 (p53 tumour suppressor gene), the TERT promoter, effectors of the phosphatidylinositol 3-kinase (PI3K)-AKT, mammalian target of rapamycin (mTOR), and genes involved in epigenetic regulation. Germline mutations Several germline variations in chromosomes 9q22.23 and 14q13.3 have been linked with high risk of differentiated thyroid cancers, due to their proximity to genes encoding proteins involved in regulating thyroid development and differentiation including FOXE1 and NKX2-1. Familial forms of papillary and follicular carcinomas exist but are unusual (3–9% of cases), including Cowden's disease (multiple hamartoma syndrome associated with PTEN mutations OMIM 158350), familial adenomatous polyposis, including the Gardner syndrome variant (associated with loss of function mutations in the APC gene OMIM 175100), and Werner's syndrome (adult progeria associated with mutation in the WRN gene). Other familial forms may be found in Peutz-Jeghers syndrome (OMIM 175200), the Carney complex (OMIM 160980), and ataxia-telangiectasia (OMIM 208900). Epidemiology Thyroid cancer incidence rates have increased dramatically in most Westernized countries and between 2014–2016 there were an average of 3527 new diagnoses annually in the United Kingdom, representing more than 155% rise since the early 1990s. In the United States, the incidence of thyroid cancer has more than tripled from 1975 through to 2015, and it is estimated that there will be 52 070 new thyroid cancer cases and 2170 deaths from the disease in 2019. Thyroid cancer is about three times more common in women than in men, and the peak incidence is between 30 and 50 years of age. Most of the recent increase in disease burden is due to the incidental detection of small, low-risk tumours, although there is some evidence that other factors including ionizing radiation, obesity, and environmental pollutants may be contributing factors. Papillary microcarcinomas, defined as tumours less than 1 cm in diameter, occur in up to 36% of autopsy specimens and up to 24% of surgical thyroidectomies. Clearly most of these do not significantly impact on long-term outcomes and life expectancy. Clinical features Most patients present with thyroid enlargement in the form of a thyroid nodule, which is often asymptomatic. This may be noticed by the patient or their relatives, or sometimes the abnormality is detected during physical examination for another complaint. The difficulty for diagnosis arises because thyroid nodules are frequent, and only about 5% of palpable thyroid nodules are malignant. Diffuse or multinodular thyroid enlargement occurs in around 10% of the population and is four times more common in women than in men. Between 4 and 7% of adults have visible thyroid nodules and these are usually hyperplastic or colloid nodules. Overall, the prevalence of malignancy in thyroid nodules is

estimated between 4 and 6.5%. There are usually no symptoms or signs to distinguish benign from malignant nodules because most cancers progress slowly and Table 13.3.2.1 Classification of thyroid malignancies Primary thyroid follicular epithelial tumours Differentiated (papillary, follicular, Hürthle cell) Poorly differentiated Undifferentiated (anaplastic) C-cell epithelial tumours (medullary carcinoma) Primary nonepithelial tumours Lymphoid origin (lymphoma, plasmacytoma) Mesenchymal cell origin (sarcoma) Other (teratoma) Secondary nonthyroidal tumours Metastases Extension of tumour from adjacent structures

SECTION 13 Endocrine disorders 2304 present before disease is advanced. Clinical parameters associated with increased risk of malignancy include male sex and being at the extremes of age (less than 20 or over 60 years). Previous exposure to radiation and a family history of thyroid cancer should also arouse suspicion. A carcinoma is more likely if thyroid enlargement has grown recently or is hard, irregular, or fixed on palpation. Clinical assessment should include careful examination of the cervical, submental, and supraclavicular lymph nodes. Late-presenting features include hoarseness, dysphagia, or dyspnoea which may indicate local invasion, but these symptoms can occasionally occur with an enlarging benign goitre. Rarely the diagnosis only becomes apparent when metastatic disease is detected in bone or lung. The relatively indolent presentation of papillary and follicular thyroid carcinoma contrasts with that of anaplastic carcinoma, in which a rapidly enlarging and fixed thyroid mass occurs, sometimes with local pain. Extension to the oesophagus, trachea, and/or recurrent laryngeal nerves is frequent, and the overlying skin may also be infiltrated. Pathology Papillary carcinomas There are several variants of papillary thyroid carcinoma united by their characteristic cytological features. The nuclei are large, clear ('Orphan Annie', after the eyes of the cartoon character), and have longitudinal grooves and invaginations of cytoplasm causing a papillary growth pattern (Fig. 13.3.2.1a). One-half of papillary carcinomas contain degenerate calcified papillae, termed psammoma bodies. The tumour is multicentric in up to 80% of cases if the resected thyroid is examined carefully. Metastasis is via the lymphatics and local lymph nodes are infiltrated in 40 to 50% of cases (more in young patients). Distant metastases are found in less than 5% of patients at presentation, with the lung being the most common site. There are more than 10 different variants of papillary thyroid cancer and those with a less favourable outcome include tall cell, columnar cell, and hobnail variants. These tumours generally present at a later age and more advanced stage than classical-type papillary thyroid cancer. Data regarding outcomes of solid variant and sclerosing (including diffuse sclerosing) variants remain controversial. The follicular variant of papillary thyroid carcinoma is a tumour composed of neoplastic follicles rather than papillae, but with follicular cells showing nuclear features characteristic of papillary thyroid cancer. There are two main subtypes: infiltrative (non-encapsulated) and encapsulated. The latter form has increased in incidence by an estimated 2-to 3-fold over the past two to three decades and makes up 10–20% of all thyroid cancers currently diagnosed in Europe and North America. These tumours have a very low risk of adverse outcomes and are now termed noninvasive follicular thyroid neoplasm with papillary-like nuclear features (NIFTP). No additional treatment with surgery or radio-iodine ablation is required for these tumours, and no further pathological staging is needed. Follicular carcinomas Follicular carcinoma is characterized by follicular differentiation with a solid growth pattern and without the nuclear features of papillary carcinoma. The tumour is encapsulated, but there is invasion of the capsule and vessels, thereby distinguishing it from a follicular adenoma (Fig. 13.3.2.1b). They may be minimally invasive when there is only microscopic capsular invasion, or angioinvasive when there is vascular invasion. The former are indolent

tumours with 10-year mortality rates of less than 5%, whereas the latter are associated with mortality rates of 5–30% depending on the number of invaded blood vessels. (a) (b) (c)

Fig. 13.3.2.1 Histopathological features of thyroid follicular epithelial carcinoma. (a) Papillary carcinoma, with psammoma bodies and typical nuclear appearance. (b) Metastatic follicular carcinoma, eroding vertebral bone. (c) Anaplastic carcinoma showing pleomorphic spindle cells. All sections, original magnification $\times 200$. Photomicrographs by courtesy of Dr K. Suvarna.

13.3.2 Thyroid cancer 2305 Hürthle cell cancers Oncocytic (Hürthle cells) cells are characterized by oxyphilic staining due to mitochondrial accumulation, resulting in abundant eosinophilic granular cytoplasm and hyperchromatic nuclei. They are classified into Hürthle cell adenomas or Hürthle cell carcinomas, depending on the presence or absence of capsular and vascular invasion. Poorly differentiated and anaplastic carcinomas Poorly differentiated thyroid cancers are aggressive tumours with partial loss of features of thyroid differentiation occupying a position between well-differentiated thyroid tumours and completely dedifferentiated anaplastic cancers. They are associated with poor outcomes and 10-year survival rates are around 50%. In anaplastic carcinoma there is no capsule, the cells are atypical, including spindle, multinuclear, and squamoid forms, and mitoses are frequent (Fig. 13.3.2.1c). Investigation and diagnosis Blood tests Thyroid epithelial cancers generally fail to affect thyroid function, but this should be evaluated in all patients presenting with a thyroid nodule; a low circulating TSH concentration strongly suggests an autonomous benign nodule. Anaplastic carcinoma may occasionally cause hypothyroidism, but the most frequent cause of an elevated TSH concentration with a hard, nodular thyroid is Hashimoto's thyroiditis. Some of the glands in these cases are so irregular that the presence of malignancy may be suspected. Differentiated thyroid cancer is more common in patients with autoimmune thyroid disease—both Graves' disease and Hashimoto thyroiditis—and thyroid lymphoma almost always occurs in association with autoimmune thyroiditis. Any dominant or atypical area in a Hashimoto's goitre therefore requires careful evaluation. Thyroid peroxidase and/or thyroglobulin antibodies are raised in about one-quarter of patients with thyroid follicular epithelial carcinoma, coincident with the presence of a lymphocytic infiltrate which, in turn, is associated with a slightly more favourable prognosis. Although measurement of serum thyroglobulin concentrations is extremely useful in follow-up, as discussed next, this investigation is unhelpful in diagnosing thyroid cancer; levels may not be elevated in some patients and, even when elevated, cannot be causally distinguished from those that occur in benign adenoma, multinodular goitre, Graves' disease, destructive thyroiditis, or Hashimoto's. Imaging Thyroid nodules may be detected in up to 60% of adults when using high resolution ultrasonography, and they are found incidentally in 16% of cross-sectional CT or MRI scans, 10% of carotid Doppler investigations, and 2–3% of positron emission tomography (PET) scans. FDG-PET positive nodules carry a higher risk of malignancy and require further evaluation. Several ultrasonographic criteria are associated with a higher suspicion for malignancy: current guidelines combine these into algorithms guiding practitioners regarding the selection of thyroid nodules that warrant further evaluation with fine needle aspiration biopsy. Ultrasonography High-resolution ultrasonography is a very sensitive tool to diagnose thyroid malignancy and may be specific for the identification of papillary thyroid cancer. Most current guidelines recommend ultrasonography, performed by a competent operator, as the first line imaging tool in patients presenting with thyroid enlargement (Figs. 13.3.2.2 and 13.3.2.3). Ultrasonographic features associated with a higher risk of malignancy are illustrated in Table 13.3.2.2. Ultrasonographic features should be used in summation to identify thyroid lesions that may be malignant and warrant fine needle aspiration biopsy (FNAB). Ultrasonography also

increases the yield of FNAB. The presence or absence of abnormal cervical lymph nodes should be documented when undertaking thyroid ultrasonography. Fig. 13.3.2.2 Ultrasound appearances of a cystic thyroid nodule with tiny echogenic foci with subtle 'ring-down' or 'comet tail' artefact (arrow) due to inspissated colloid. From Scoutt LM, Hamper UM, Angtuaco TL (eds) (2016). Ultrasound. By permission of Oxford University Press, USA. Fig. 13.3.2.3 Ultrasound appearances of papillary thyroid carcinoma. There is a large, solid nodule in the inferior pole of the right lobe of the thyroid with punctate echogenic, nonshadowing microcalcifications (arrows); T, normal thyroid parenchyma. From Scoutt LM, Hamper UM, Angtuaco TL (eds) (2016). Ultrasound. By permission of Oxford University Press, USA.

SECTION 13 Endocrine disorders 2306 In the United Kingdom, a scoring system of U1-5 is recommended to classify thyroid nodules based on ultrasound findings: U1: normal thyroid; U2: benign thyroid lesion; U3: indeterminate thyroid lesion (likely follicular lesion); U4: suspicious thyroid lesion; U5: diagnostic for thyroid cancer. Nodules graded as U3-5 warrant further cytological evaluation. The US guidelines recommend use of similar system classifying thyroid nodules as benign, very low, low, intermediate, or high risk of malignancy, and also take nodule size into account when selecting nodules that warrant FNAB. Radionuclide scanning Radionuclide scanning with ^{99m}Tc pertechnetate or radio-iodine (¹²³I or ¹³¹I) may be indicated if patients have thyroid enlargement and a low serum TSH concentration. The presence of a 'hot' nodule taking up significant amounts of radionuclide with failure of the surrounding tissue to take up the tracer is consistent with the presence of an autonomous nodule which is almost invariably benign. Most thyroid cancers fail to take up radionuclide ('cold' nodules), but benign lesions may behave in a similar way. Overall radionuclide scanning is not routinely recommended to diagnose thyroid cancer. Fine needle aspiration biopsy Fine needle aspiration biopsy and subsequent cytological evaluation remains the gold standard for the diagnosis of thyroid cancer, with sensitivity and specificity rates of more than 90%. This is now usually performed under ultrasound guidance. In the United Kingdom, the use of the 'THY classification' is recommended: THY1: nondiagnostic (insufficient cells sampled); THY2: nonneoplastic; THY3: neoplasm possible, which is further subdivided into THY3a: atypical features present, and THY3f: follicular neoplasm; THY4: suspicious of malignancy and THY5: diagnostic of thyroid cancer. US guidelines recommend the use of the Bethesda classification, which is very similar to the United Kingdom system. Surgery is usually required for lesions classified as THY3f, THY4, and THY5 and repeat biopsy should be undertaken for THY1 and THY3a nodules. In all cases the clinical, ultrasonographic, and cytological findings should be considered together and where appropriate should be discussed in a multidisciplinary team (MDT) setting, especially if there is nonconcordance between findings. Papillary carcinoma is readily diagnosed by fine needle aspiration biopsy, and medullary carcinoma and lymphoma can also be detected by the use of immunohistochemical staining, although lymphoma frequently requires core or open biopsy for confirmation. Follicular carcinomas cannot be distinguished cytologically from follicular adenomas and are usually labelled as THY3F. Many patients with these lesions will undergo diagnostic hemithyroidectomy. However, there is a rapidly growing body of literature describing the use of gene expression classifiers, mutation analysis panels, and protein expression chips to distinguish benign from malignant follicular lesions. Some centres, especially in the United States, use molecular analysis of FNAB specimens routinely in decision-making processes regarding the recommendation of surgery for these indeterminate lesions, although this is not common practice in the United Kingdom and most European countries. Thyroid cysts are usually benign and may be aspirated during biopsy, although reaccumulation of fluid is common

and may indicate presence of malignancy; if this occurs, surgery is usually required for definitive diagnosis. Management of differentiated thyroid cancer Surgical excision The initial form of treatment is surgery, which should be performed by a surgeon with the required training and expertise who is a core member of the multidisciplinary team. Assessment of extrathyroidal extension and presence (or absence) of central compartment and lateral neck lymph node disease through ultrasonography and cross-sectional imaging with CT or MRI is recommended. Thyroid lobectomy is recommended for patients with unifocal papillary microcarcinoma (<1 cm) with no other risk factors. Total thyroidectomy and central compartment lymph node dissection is recommended for patients with tumours greater than 4 cm in diameter or tumours of any size if associated with any of the following characteristics: multifocal disease, bilateral disease, extrathyroidal spread (pT3 and pT4a), positive familial history, clinically or radiologically involved lymph nodes and/or distant metastases. Tumours between 1 and 4 cm in maximum diameter may be treated with lobectomy or total thyroidectomy, depending on judgement by the multidisciplinary team taking additional risk factors into account. Lobectomy is deemed sufficient and central lymph node dissection unnecessary for tumours between 1 and 4 cm in patients aged less than 45 years, with unifocal classical type papillary cancer, without a positive family history, and without extrathyroidal spread or lymph node metastases. Neck dissection is indicated if there is clinical or radiological evidence of lateral compartment lymph node involvement. Postoperative risk stratification UK and US guidelines recommend postoperative staging using the TNM classification (Table 13.3.2.3)/AJCC (American Joint Commission on Cancer) system (Table 13.3.2.4). This classification system predicts the risk of death from disease and is a valuable indicator of overall prognosis, but it does not take individual responses to treatment into account, which may alter prognosis or the risk of recurrence. The British and American Thyroid Association guidelines therefore recommend the use of a three-tier system to predict postoperative risk of recurrence (Table 13.3.2.5).

Table 13.3.2.2 Ultrasonographic features of benign and malignant thyroid nodules

Benign nodule	Malignant nodule
Follicular lesion	Spongiform/ honeycomb
Solid and hypoechoic	Hyperechoic/ homogeneous halo
benign	Purely cystic
Irregular margin	Hypoechoic/loss of halo
suspicious	Egg shell calcification
Intranodular vascularity	Iso/hyperechoic (hypoechoic halo)
Absence of halo	Peripheral vascularity
Taller than wide	Microcalcifications

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for differentiated thyroid cancer After surgery, radio-iodine is usually administered to remove any remaining thyroid tissue, which then allows thyroglobulin or ¹³¹I total body scanning to be used in follow-up to detect metastases. This treatment may also destroy occult carcinoma and, by scanning after ablation, metastatic disease is revealed. Similar to the multidisciplinary approach recommended for decision-making regarding the extent for surgery, a risk-based approach is now recommended when selecting patients requiring radio-iodine remnant ablation. Patients in the definite indications category are those with tumours more than 4 cm or tumours of any size with gross thyroidal extension (pT4) or distant metastases. Remnant ablation is not indicated in patients with tumours not more than 1 cm, unifocal or multifocal, and in cases where histology reveals classical papillary or follicular variant or minimally invasive follicular tumours (i.e. without capsular or angioinvasion). Indications to treat tumours between 1 and 4 cm with ¹³¹I ablation remain uncertain and MDT discussion and decision-making is required. Factors favouring intervention include tumours more than 2 cm, unfavourable histological subtype, widely invasive tumours, more than five resected metastatic lymph nodes, resected lymph nodes more than 6

mm in maximum diameter, ratio of positive/negative nodes more than 0.7 and extracapsular nodal involvement. Results from two large randomized controlled trials have shown that an ablative ¹³¹I dose of 1.1 GBq is as effective as 3.7 GBq for low to intermediate risk tumours, with fewer adverse effects in the 1.1 GBq group. It is recommended that patients with T1-2 and R0 resection should receive the lower dosage. For patients with pT3 and/or N1 disease, the activity of ¹³¹I should be decided by the MDT on an individual case basis taking all prognostic factors into account. Iodine exposure, including iodine-containing contrast media, may prevent accumulation of ¹³¹I during treatment. Guidelines regarding implementation of a low iodine diet prior to radio-iodine ablation have recently been devised in the United Kingdom (see 'Further reading'). High levels of stimulation by TSH (>30 mU/litre) are required to produce maximum uptake of ¹³¹I. This may be achieved by levothyroxine withdrawal for 4 weeks, resulting in development of severe hypothyroid symptoms, or by the administration of recombinant human TSH (rhTSH) for 48 hours prior to administration of radio-iodine, thereby avoiding the need for cessation of thyroid hormone replacement. If thyroid hormone withdrawal is used, patients are usually switched to the shorter-acting liothyronine (20 µg three times daily) as replacement therapy 28 days before ¹³¹I ablation and this treatment is then discontinued 14 days before radio-iodine administration.

Randomized controlled trials have shown Table 13.3.2.3 TNM classification of thyroid cancer (adapted from 2014 BTA Guidelines for the management of thyroid cancer) Primary tumour—T Tx Primary tumour cannot be assessed T0 No evidence of primary tumour T1 Tumour ≤2 cm limited to the thyroid T2 Tumour >2 cm but ≤4 cm limited to the thyroid T3 Tumour >4 cm limited to the thyroid or any tumour with minimal extrathyroidal extension T4a Tumour of any size beyond the thyroid capsule and invading surrounding tissues T4b Tumour invades prevertebral fascia or encases carotid artery or mediastinal vessels Regional lymph nodes (cervical and upper mediastinal)—N Nx Regional lymph nodes cannot be assessed N0 No regional lymph node metastases N1 Regional lymph node metastases N1a Metastases to Level VI (pretracheal, paratracheal, and prelaryngeal/ Delphian lymph nodes) N1b Metastases to unilateral, bilateral, or contralateral cervical (levels I, II, III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (level VII) Distant metastases—M M0 No distant metastases M1 Distant metastases Residual tumour—R Rx Cannot assess presence of residual primary tumour R0 No residual primary tumour R1 Microscopic residual primary tumour R2 Macroscopic residual primary tumour Based on the TNM classification tumours are then staged as follows (AJCC/UICC staging system, Table 13.3.2.4).

Table 13.3.2.4 Staging of differentiated (papillary and follicular) thyroid carcinomas (adapted from 2014 BTA guidelines for the management of thyroid cancer) Patients aged <55 Patients aged ≥55 y Stage TNM description Stage TNM description I Any T, any N, M0 I T2, N0, M0 II Any T, any N, M1 II Any T, N1, M0 III T4a, any N, M0 IVa T4b, any N, M0 IVb Any T, any N, M1 Table 13.3.2.5

Postoperative risk stratification for risk of recurrence of differentiated thyroid cancer (adapted from 2014 BTA Guidelines for the management of thyroid cancer) Low risk Intermediate risk (any) High risk (any) No local/distant metastases Microscopic tumour invasion (perithyroidal soft tissues T3) Extrathyroidal invasion All macroscopic

tumour resected

(R0/R1) Cervical lymph node metastases N1a/N1b Incomplete tumour resection (R2) No locoregional

tumour invasion No aggressive histological features Aggressive histology, e.g. Tall cell, insular or angioinvasion Distant metastases (M1)

SECTION 13 Endocrine disorders 2308 equal efficacy of ¹³¹I remnant ablation when using thyroid hormone withdrawal and rhTSH, with improved quality of life in the rhTSH group due to absence of troublesome hypothyroid symptoms. The use of rhTSH is therefore recommended in patients with low to intermediate risk tumours (pT1 to pT3, pN0 or Nx, or N1 and M0 and R0). Radio-iodine-avid thyroid cancer metastases may be treated with further radio-iodine therapy; doses between 3.7 and 5.5 GBq are usually administered. Dynamic risk stratification Patients who have undergone total thyroidectomy and remnant ablation with radio-iodine should undergo dynamic risk stratification to define the response to initial therapy. This is usually done 9–12 months following treatment, when patients are recommended to have a neck ultrasound and measurement of rhTSH stimulated thyroglobulin (Tg). Subsequent intensity and duration of follow-up, as well as targets for TSH suppression, is then based on the assignment of patients to different response groups: excellent, indeterminate, or incomplete response (Table 13.3.2.6). Long-term levothyroxine replacement therapy Following thyroidectomy, it is necessary to maintain euthyroidism through lifelong levothyroxine replacement in all patients who have undergone a total thyroidectomy and, in some patients, following lobectomy. Suppression of serum TSH is required in intermediate and high-risk patients since thyrotropin is a growth factor for thyroid cells. Following initial treatment with surgery and radio-iodine remnant ablation, and before dynamic risk stratification, serum TSH should be suppressed below 0.1 mIU/litre. It is unnecessary to suppress serum TSH in subjects who have undergone less than total thyroidectomy and in those who have not undergone remnant ablation. In patients who are stratified into the excellent response category following dynamic risk stratification, serum TSH can be maintained in the lower half of the normal reference range (0.3–2.0 mIU/litre). For historic patients who have not undergone dynamic risk stratification, it is appropriate to keep serum TSH suppressed below 0.1 mIU/litre for 5–10 years and then to allow serum TSH to rise to the lower half of the normal reference range if there is no evidence of recurrence either biochemically or structurally. The long-term consequences of serum TSH concentrations suppressed below 0.1 mIU/litre include cardiovascular morbidity and mortality as well as osteoporosis, and evaluation of probability of osteoporotic fragility fracture risk may be required. Systemic therapies for metastatic radio-iodine-refractory thyroid cancer Metastatic thyroid cancer occurs in less than 10% of patients, about two-thirds of whom ultimately present with radio-iodine refractory disease. If patients have radio-iodine avid disease, repeated administration of radio-iodine therapy every 4–6 months may be beneficial, especially if lung metastases are present. There is little benefit above a cumulative dose of 18.5 GBq. Bone metastases may respond to ¹³¹I or external beam radiotherapy, and orthopaedic intervention may be required to stabilize pathological fractures. Palliative external beam radiotherapy has a limited role in controlling locoregional disease when further surgery is ineffective or impractical. Radiotherapy can be used alone or in combination with low-dose chemotherapy. Targeted therapies Improved understanding of the molecular pathogenesis of thyroid cancer has resulted in an explosion of targeted therapies in patients with advanced metastatic thyroid cancer. Two multikinase inhibitors, sorafenib and lenvatinib, have been approved for the treatment of radio-iodine refractory tumours on the basis of prospective, double-blind randomized placebo-controlled trials that showed longer progression-free survival. Lenvatinib appears to have the greatest efficacy. Significant adverse effects of both drugs often make the maintenance of full dose therapy a challenge. Common adverse effects include hypertension, hand-foot skin reactions, diarrhoea, rash, fatigue, weight loss, and stomatitis. Longer-term effects on quality of life and cumulative toxic effects of these agents remain to be determined. Phase 2 trials using several other multikinase inhibitors have commenced, including sunitinib, pazopanib, axitinib, cabozantinib, and motesanib, all of

which have multifunctional actions including antiangiogenic properties. Targeted therapies including RAF-kinase inhibitors used alone or in combination with MEK inhibitors are also being explored in several combination trials. Treatment with selumetinib, a MAPK kinase (MEK) 1 and MEK2 inhibitor, has been shown to produce a clinically meaningful increase in radio-iodine uptake in tumours previously refractory to radio-iodine treatment through loss of the sodium iodide symporter, particularly those with a RAS mutation. This is a rapidly developing field and more trials will help address how best to stratify patients for treatment. Follow-up Lifelong follow-up is necessary for papillary and follicular cancer because they may recur many years after apparent cure. As well as monitoring the concentration of serum TSH and performing Table 13.3.2.6 Dynamic risk stratification determining response to treatment (adapted from 2014 BTA Guidelines for the management of thyroid cancer)

Excellent response	Indeterminate response	Incomplete response
All the following: Suppressed and stimulated Tg <1 mcg/litre - Neck USS without evidence of disease - Cross-sectional and/or nuclear medicine imaging negative (if performed)	Any of the following: Suppressed Tg <1 mcg/ml and stimulated Tg ≥1 and <10 mcg/litre - Neck USS with nonspecific changes or stable lymph nodes (<1 cm) - Cross-sectional and/or nuclear medicine imaging with nonspecific changes, not completely normal	Any of the following: Suppressed Tg ≥1 mcg/litre or stimulated Tg ≥10 mcg/litre - Rising Tg values - Persistent or newly identified disease on cross-sectional and/or nuclear medicine imaging USS, ultrasound scan.

13.3.2 Thyroid cancer 2309 careful neck palpation, serum thyroglobulin should be measured. Detectable levels of thyroglobulin after thyroid ablation indicate persistent or recurrent disease. Measuring thyroglobulin levels is especially valuable when the patient is not taking thyroxine replacement, or after recombinant TSH stimulation, as the rise in TSH will promote thyroglobulin production and exaggerate any increase. The use of rhTSH stimulated thyroglobulin is recommended as part of dynamic risk stratification, but for low-risk patients (i.e. those who have not undergone radio-iodine remnant ablation and those assigned to the excellent response dynamic risk stratification category), it is appropriate to measure unstimulated Tg while the patient is on levothyroxine therapy. The presence of thyroglobulin antibodies may interfere with thyroglobulin measurements on most assays, hence these antibodies should be evaluated by a quantitative method whenever serum Tg is measured. If thyroglobulin is detectable, the patient should have a total body ¹³¹I scan and any recurrent disease can then be treated with a therapeutic dose of radioactive iodine (Fig. 13.3.2.4). If the total body scan is negative and serum Tg is consistently raised, cross-sectional imaging and occasionally FDG-PET scanning is indicated. Prognosis Differentiated thyroid cancer Most papillary thyroid cancers are indolent tumours and have an excellent prognosis, with 10-year relative survival rates of more than 98% (Table 13.3.2.7). The risk of death increases with age, hence most prognostic scoring systems take age into account. The 10-year cause-specific survival rate is lower in those with follicular carcinoma, especially if angioinvasion is present, and is only 50% in those with poorly differentiated tumours. Patients who present with or develop metastatic disease (around 10–15% of patients) have poor survival rates which are less than 10% at 10 years, especially in those whose disease becomes refractory to radio-iodine. Anaplastic carcinoma Anaplastic carcinoma (Fig. 13.3.2.5) is usually rapidly fatal. Initial assessment should focus on the identification of the small proportion of patients with localized disease and good performance status that Fig. 13.3.2.4 ¹³¹I scans of three patients. Patient A had undergone near-total thyroidectomy three months previously: two foci of remnant thyroid tissue remain in the neck. Patients B and C had both had thyroidectomy followed by ¹³¹I therapy two years previously and been found to have elevated serum thyroglobulin on routine

monitoring. In patient B there are numerous iodine-avid lymph node metastases in the neck/mediastinum and bilateral pulmonary metastases. No iodine-avid disease is identified in patient C where there is physiological iodine accumulation in salivary glands, saliva, nasal secretions, and stomach, with excreted iodine in bowel and urinary tract. From Kim CK (ed) (2015). Nuclear medicine and PET/CT cases. By permission of Oxford University Press, USA. Table 13.3.2.7 Ten-year relative survival for differentiated thyroid cancer (adapted from 2014 BTA Guidelines for the management of thyroid cancer) Stage 10-year relative survival (%) I 98.5 II 98.8 III 99.0 IVA 75.9 IVB 62.5 IVC 63

SECTION 13 Endocrine disorders 2310 may benefit from surgical resection and other adjuvant therapies. Surgery may help to relieve obstructive symptoms and external beam radiotherapy is useful in palliation, but the tumour does not take up radio-iodine. The place of chemotherapy (usually doxorubicin combined with other drugs) remains unclear. The median survival time for anaplastic carcinoma is 4 to 12 months and those with distant metastases at presentation have a median survival time of only 3 months. Prevention In the event of a nuclear accident, prompt administration of stable iodine prevents the uptake of inhaled and ingested radioactive iodine isotopes. Emergency arrangements should be in place close to nuclear installations to provide for distribution of potassium iodate tablets. Advice is available from the World Health Organization (see 'Further reading'). Special problems in pregnancy A solitary nodule in a pregnant woman should be evaluated by ultrasound and fine needle aspiration biopsy. If the biopsy suggests malignancy and the nodule is growing significantly, or if lymph node metastases develop, surgery can be undertaken in the second trimester, but otherwise this is best deferred until after delivery. Regular ultrasound surveillance is required in patients with newly diagnosed thyroid cancer who do not undergo surgery during pregnancy. Breastfeeding should be discontinued at least 8 weeks before radio-iodine remnant ablation, and pregnancy should be avoided for 6 to 12 months following radio-iodine treatment. The preconception TSH goal in women with pre-existing differentiated thyroid cancer, which is determined by risk stratification, should be maintained during pregnancy. It is likely that higher doses of levothyroxine will be required to achieve this. Medullary carcinoma of the thyroid Epidemiology and pathology Medullary carcinoma accounts for 3–5% of all thyroid cancers. About 80% are sporadic with a peak incidence at 40 to 60 years of age. Hereditary autosomal dominant forms occur as part of multiple endocrine neoplasia type 2A (MEN2A) or type 2B (MEN2B) or as isolated familial medullary carcinoma. These forms are associated with germline point mutations in the RET proto-oncogene (different from those in papillary carcinoma) and preneoplastic C-cell hyperplasia (Table 13.3.2.8). (a) (b) Fig. 13.3.2.5 MRI and CT appearances of anaplastic thyroid carcinoma. Panel (a): transverse fat-saturated T2-weighted MRI image demonstrating a large right-sided mass involving the right thyroid lamina and extending around the posterior margin of the cartilage towards the larynx. Panel (b): CT (bone windows) on the same patient demonstrating the markedly abnormal involved right thyroid lamina with ill definition, permeative destruction, and reactive sclerosis. From Hoskin P, Goh V (eds) (2010). Radiotherapy in practice—imaging. By permission of Oxford University Press. Table 13.3.2.8 Types of medullary carcinoma of the thyroid Type Frequency (%) Associated lesions RET gene mutation Sporadic 80 None RET (in approximately 50%), HRAS, NRAS, or KRAS (in 0–43%) MEN2A 10 Pheochromocytoma (20–50%), hyperparathyroidism (12–30%) Hirschsprung disease or cutaneous lichen amyloidosis in some 95% of RET mutations in exon 10 (codon 609, 611, 618 or 620) or exon 11 (codon 634) MEN2B 3 Pheochromocytoma, mucosal neuromas, marfanoid habitus, typical facies, medullated corneal nerves, and aerodigestive tract ganglioneuromatosis RET M918T

mutation in more than 95% and RET A833F in the remainder Familial medullary thyroid carcinoma
7 None Broad range of RET mutations MEN, multiple endocrine neoplasia.

13.3.2 Thyroid cancer 2311 The pathological findings are of an encapsulated tumour with round, spindle-shaped, or polyhedral cells arranged in a variety of patterns that have no prognostic significance. There is variable fibrosis and three-quarters of tumours show marked deposition of amyloid—a feature associated with a good prognosis. Heterogeneous staining for calcitonin, a hormone of C cells, is associated with a poorer outcome, reflecting dedifferentiation. Even the smallest medullary tumours may be associated with local lymph node metastases. Clinical features, diagnosis, and investigation The presentation of sporadic medullary carcinoma is typically with a solitary thyroid nodule, accompanied by cervical lymphadenopathy in 50% of cases. Lung, liver, or bone metastases are present at diagnosis in 10% of cases. Symptoms due to local invasion or the paraneoplastic production of polypeptides and prostaglandins, such as flushing, diarrhoea, and Cushing's syndrome, are less common presenting features. The diagnosis is typically made through ultrasonography and fine needle aspiration biopsy. Immunohistochemical staining for calcitonin in aspirated cells or in washout fluid of the fine needle aspiration may be required. Basal serum calcitonin concentrations are almost invariably elevated and confirm the diagnosis. There is controversy over the utility of routine serum calcitonin measurement in the work-up of all thyroid nodules; most centres perform aspiration biopsy initially. Newly diagnosed patients should be screened for other evidence of MEN and a careful family history is essential. In particular, pheochromocytoma occurring as part of an inherited cancer syndrome must be excluded before surgery through measurement of serum or urine metanephrines or catecholamines. In all cases of confirmed MTC, RET mutation analysis to establish the possible genetic basis for the disease should be performed, even in the absence of a positive family history. Testing genomic DNA for RET mutations in the germline is now widely available and should ideally be carried out on leucocyte DNA from all new patients. The absence of the most common mutations, coupled with a negative family history and the absence of C-cell hyperplasia or multicentric tumours in the resected thyroid, indicates that further family testing is not warranted. When a RET mutation is detected, there is a clear benefit from family testing as prophylactic thyroidectomy in affected individuals improves outcome. However, there are some kindreds in whom familial medullary carcinoma occurs without a recognizable RET mutation and family screening must then be undertaken annually, up to the age of 35 to 40 years, using serum calcitonin and carcinoembryonic antigen (CEA) measurements as a guide to the presence of the inherited abnormality. Management Surgery is the primary treatment for patients with sporadic or hereditary medullary thyroid carcinoma and ranges from thyroid lobectomy in selected patients with sporadic disease to total thyroidectomy with central neck dissection and unilateral or bilateral lymph-node compartment dissection. In patients who have inherited a mutated RET allele, the reliable indicator for timing thyroidectomy is the serum calcitonin concentration rather than the specific mutation. Levothyroxine replacement is needed at physiological doses rather than doses that suppress TSH. After surgery, the patient should be monitored by measurement of serum calcitonin concentration. The most accurate measurement of medullary cancer progression and aggressiveness is the calcitonin or CEA doubling time (the time it takes for the marker to double). Doubling times that are less than 6 months are associated with a very poor prognosis and those that are more than 2 years are associated with much better long-term survival rates. Although many patients with metastatic or persistent medullary thyroid carcinoma can be monitored, patients with progressive or symptomatic disease should undergo further treatment. Local recurrence with identifiable lymph

node involvement should be treated surgically. Standard chemotherapy and radiotherapy regimens are largely ineffective. Profuse (secretory) watery diarrhoea is frequently a troublesome feature of extensive disease. This may respond to treatment with loperamide, whereas somatostatin analogues have an inconsistent benefit. Systemic therapy with vandetanib and cabozantinib, RET tyrosine kinase inhibitors with additional inhibitory effects on the vascular endothelial growth factor receptor, increase progression-free survival in locally advanced or metastatic progressive medullary thyroid cancer and provide relief from symptoms. Prognosis Cure, defined as a persistently normal calcitonin level, occurs in only about one-third of patients, but 80 to 90% of patients with an elevated calcitonin level and only nodal disease survive for 10 years. Age, stage and size of tumour, and completeness of surgical removal are important prognostic features. Familial medullary carcinoma has the best outcome; in contrast the tumour associated with MEN2B is very aggressive. The overall 10-year survival is around 70%, but is over 90% in those detected early by family screening. Primary thyroid lymphoma Less than 5% of thyroid malignancies are non-Hodgkin's B-cell lymphoma. The peak incidence is between 50 and 80 years of age, and women are affected three times more frequently than men. The typical presentation is a rapidly enlarging thyroid mass in a patient with Hashimoto's thyroiditis. The clinical features may suggest anaplastic carcinoma. The diagnosis can be made by fine needle aspiration biopsy and confirmed by large-needle or open biopsy. Accurate staging is then necessary to plan treatment, which is with external beam radiotherapy and anthracycline-based chemotherapy. Intensive treatment has produced 8-year survival rates of over 90%. Rituximab, a monoclonal antibody directed against B cells, has shown some evidence of therapeutic benefit.

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