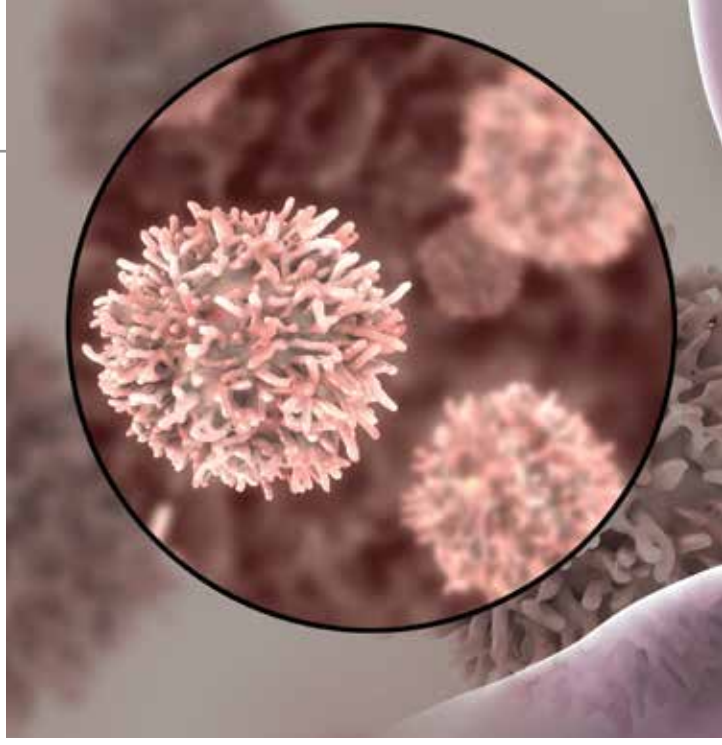


Thyroid cancer

How to achieve optimal patient outcomes

SARAH Y. QIAN MB BS(Hons)
DUNCAN J. TOPLISS MD, FRACP, FACE

Thyroid cancer is the most common endocrine malignancy, with a rising global incidence. A structured evaluation of thyroid nodules is recommended for accurate diagnosis and management. A multidisciplinary approach with shared care between specialists and GPs ensures optimal care.

The global incidence of thyroid cancer is increasing and it is predicted to be the seventh most common cancer diagnosed in women in Australia in 2017.[1] This is largely because of a greater number of incidental small cancers detected by neck imaging, as well as an increase in advanced stage papillary thyroid cancer (PTC).[2]

Thyroid cancers are a heterogeneous group of malignancies with a natural history that ranges from indolent to highly aggressive. People with thyroid cancer usually present with a thyroid nodule, but thyroid nodules are highly prevalent and mostly benign. A structured clinical approach is therefore important to identify at-risk patients, establish the diagnosis and plan management.

Classification and presentation

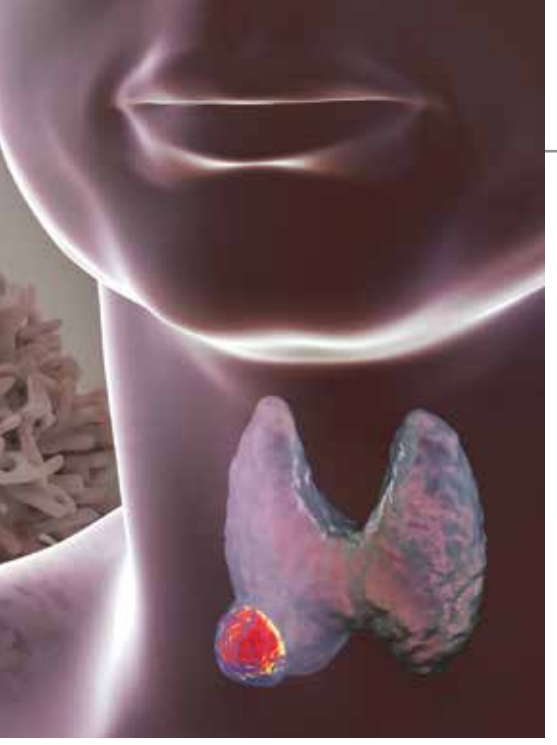
Thyroid cancer is classified according to cellular origin and degree of differentiation. Differentiated thyroid cancer arises from thyroid follicular epithelial cells and includes PTC, follicular thyroid cancer and poorly differentiated thyroid cancer usually of follicular thyroid cancer origin. These account for more than 95% of all thyroid cancers, and PTC accounts for about 90% of all differentiated thyroid cancers.[3,4] Anaplastic thyroid cancer is a rare malignancy (<1% of thyroid cancers) that also arises from follicular cells and has a very aggressive clinical course.[5] Medullary thyroid carcinoma arises from neural crest-derived parafollicular C cells, accounting for 1 to 2% of all thyroid cancers, and may occur as part of a genetic tumour syndrome (e.g. multiple endocrine neoplasia).[6] Case finding of medullary thyroid carcinoma by measurement of serum calcitonin levels during nodule evaluation is not yet part of routine care.[3] It is important to distinguish anaplastic thyroid cancer from primary thyroid lymphoma, which is a rare presentation of B-cell lymphoma usually occurring on the background of Hashimoto's thyroiditis. This is managed similarly to lymphoma at other sites. This article will

KEY POINTS

- The incidence of thyroid cancer is increasing worldwide.
- Structured assessment of a thyroid nodule consists of exclusion of hyperthyroidism, followed by neck ultrasonography and cytological examination of nodules that have a suspicious ultrasonographic appearance.
- Surgery (lobectomy or total thyroidectomy) is the first-line treatment of highly suspected or cytologically confirmed thyroid cancer.
- Adjuvant therapy, including radioactive iodine and thyroid-stimulating hormone suppression with levothyroxine therapy, is determined by evidence-based risk criteria.
- Dynamic staging and routine surveillance with thyroid ultrasound and measurement of thyroglobulin levels are important in the subsequent management of thyroid cancer.
- Optimal care involves multidisciplinary specialist management and a fully informed GP.

MedicineToday 2017; 18(12): 28-35

Dr Qian is a Registrar in the Department of Endocrinology and Diabetes at The Alfred, Melbourne. Professor Topliss is Director of the Department of Endocrinology and Diabetes at The Alfred, Melbourne; and Professor of Medicine at Monash University, Melbourne, Vic.



not discuss the management of anaplastic thyroid cancer, medullary thyroid carcinoma or thyroid lymphoma.

Clinically apparent thyroid nodules are present in 4 to 7% of the population but nodules detected on ultrasound are present in 17 to 68% of the population, with an incidence that increases with age.[3] History and physical examination help to characterise suspicious features of thyroid nodules, including size and growth. However, most thyroid cancers are not diagnosed clinically unless the disease is advanced. Features of local invasion include hoarseness of voice (laryngeal nerve dysfunction), dysphagia, airway symptoms, haemoptysis, lymphadenopathy and fixation to surrounding tissue on examination. Known risk factors for thyroid cancer, including previous external beam radiation to the neck and familial thyroid cancer, are uncommon in the Australian community.[3]

Basic investigations

Following detection of a thyroid nodule, levels of serum thyroid-stimulating hormone (TSH) should be measured to detect hyperthyroidism. If the TSH level is suppressed (TSH <0.01 mU/L), the nodule should be evaluated by radionuclide thyroid scanning for autonomy (a 'hot' nodule).[3] Autonomously functioning nodules have an extremely low risk of malignancy and therapy should thereafter focus on treatment of hyperthyroidism. Routine measurement of serum thyroglobulin levels for initial evaluation of thyroid nodules is not recommended.[3]

Neck ultrasound should be performed for all thyroid nodules to confirm size and location, identify suspicious internal features and assess for cervical lymphadenopathy. These features help to guide further management (Table 1). The ultrasound findings with highest specificity for malignancy include microcalcifications, irregular margins and shape taller than wider on recumbent transverse view.[3] Structured evidence-based systems such as the thyroid imaging and reporting data system are increasingly used to assist management decisions.[7]

For nodules considered to be sufficiently high-risk based on ultrasonographic features, fine needle biopsy is an accurate and cost-effective method of evaluation. The cytopathology is reported according to the Bethesda criteria to assist subsequent investigation and management (Table 2).[3]

Initial steps of management

If the diagnosis of thyroid cancer is confirmed or highly suspected, first-line treatment is surgical resection. Thyroidectomy by a specialist thyroid cancer surgeon performing at least 30 thyroidectomies annually is recommended.[8]

Complete surgical resection is an important factor in overall prognosis and outcome. Traditionally, a total thyroidectomy was routinely performed for all cancers larger than 1 cm in diameter; however, more recent evidence suggests that in certain cases, clinical outcomes are similar between conservative and radical approaches. Currently, total thyroidectomy is recommended for a confirmed PTC that is large (>4 cm), with extrathyroidal extension or metastases. For cancers between 1 and 4 cm in diameter without evidence of local or distant metastases, either total or subtotal thyroidectomy is appropriate.[3] Focal papillary thyroid microcarcinomas (<1 cm in diameter) generally pursue an indolent course and can be managed conservatively,[9] although lobectomy may be preferred. However, thyroidectomy should be performed if there is local invasion or metastatic spread.[10,11]

Neck dissection is performed if there is clinical or biopsy evidence of cervical lymph node disease. Therapeutic central compartment (level VI) neck dissection should be undertaken for patients with clinically involved central nodes concomitant with total thyroidectomy. Therapeutic lateral neck compartmental lymph node dissection should be performed for patients with biopsy-proven metastatic lateral cervical lymphadenopathy. Prophylactic central neck lymph node dissection is not generally recommended, as it has not been shown to reduce local recurrence or improve survival and carries additional risks of recurrent laryngeal nerve damage and hypoparathyroidism.[3] It is nevertheless practised in some high-throughput Australian centres where the morbidity is equivalent to that of thyroidectomy alone.

Histopathological features and tumour behaviour

Key histopathological features are tumour type and size, lymphovascular invasion and extrathyroidal extension. Involvement of the resection margin and lymph nodes also increases the likelihood of disease recurrence and poor prognosis.[3]

PTCs often have a papillary growth pattern and are characterised by nuclear features including clearing, grooves and inclusions. Several subtypes of PTC are described, including follicular variant PTC and tall cell variant, which has a more aggressive phenotype.[12] Recently, the noninvasive encapsulated follicular variant of PTC has been redefined as noninvasive follicular thyroid neoplasm with papillary-like nuclear features. This can be regarded as a form of carcinoma in situ and does not require total thyroidectomy or radioiodine ablation.[13] PTC metastases tend to occur regionally to cervical lymph nodes before distant spread.

Follicular thyroid cancers lack the characteristic nuclear features of PTC and commonly show transcapsular or vascular invasion. Follicular thyroid cancer can develop distant metastatic disease in the

TABLE 1. ULTRASONOGRAPHIC FEATURES OF THYROID NODULES, RISK OF MALIGNANCY AND FURTHER MANAGEMENT[3]

	Risk of malignancy	Features	Recommendations
Benign	<1%	• Cystic nodules	Observation
Very low suspicion	<3%	• Spongiform or partially cystic nodules	FNA if ≥2 cm or observation
Low suspicion	5–10%	• Partially cystic nodules with eccentric solid areas • Solid isoechoic or hyperechoic nodules	FNA if ≥1.5 cm
Intermediate suspicion	10–20%	• Solid hypoechoic nodules with smooth margins	FNA if ≥1 cm
High suspicion	>70–90%	• Solid hypoechoic nodules or solid hypoechoic components of partially cystic nodules with one or more of the following: – irregular margins – microcalcifications – taller than wide shape – rim calcifications – extrathyroidal extension – suspicious lymph nodes	FNA if ≥1 cm

Abbreviation: FNA = fine needle aspiration.

absence of local spread.[12] Encapsulated follicular tumours with only microscopic capsular invasion and no angioinvasion are designated as minimally invasive follicular thyroid cancer. The prognosis of minimally invasive follicular thyroid cancer is excellent.

Risk stratification and dynamic staging

Thyroid cancer staging follows the American Joint Committee on Cancer (AJCC) guidelines, which consider patient age, tumour size and the presence of extrathyroidal extension, lymph node and distant metastases (TNM system; see Table 3 and the Box).[14] These guidelines have recently been updated to more accurately reflect the overall low risk of mortality from thyroid cancer, while emphasising factors such as patient age, gross extrathyroidal extension and distant metastases, which are most likely to influence mortality.

The American Thyroid Association (ATA) considers similar features in its clinicopathological risk stratification system, classifying tumours into low, intermediate and high risk based on the likelihood of disease persistence or recurrence (Table 4).[3]

The risk of thyroid cancer recurrence after initial treatment is an evolving concept factoring in the features present at diagnosis (AJCC and ATA classification) and the response to therapy. Post-therapy response is classified as excellent, biochemically incomplete, structurally incomplete or indeterminate (Table 5). The revision of risk based on response to treatment forms the basis of dynamic staging, which is a key concept underlying the ongoing surveillance and treatment of thyroid cancer.[15]

TABLE 2. BETHESDA SYSTEM AND CYTOLOGY DIAGNOSTIC CATEGORIES FOR THYROID CANCER[3]

Bethesda diagnostic criteria		Risk of malignancy	Recommendations
I	Nondiagnostic/unsatisfactory	1–4%	Repeat fine needle aspiration
II	Benign	0–3%	Surveillance
III	Atypia or follicular lesion of undetermined significance	5–15%	Surveillance or surgery
IV	Follicular neoplasm or suspected follicular neoplasm	15–30%	Surveillance or surgery
V	Suspicious for malignancy	60–75%	Surgery
VI	Malignant	97–99%	Surgery

Adjuvant treatment

A multidisciplinary approach

Following surgical excision of the primary tumour, the focus of management shifts to minimisation of disease recurrence and spread, using additional therapy including radioactive iodine (RAI or 131I) and levothyroxine to provide TSH suppression. Best results are achieved by a multidisciplinary approach involving endocrinologists, endocrine and ENT surgeons, nuclear medicine physicians, radiation oncologists and anatomical pathologists, with a GP fully informed about the management plan.

TABLE 3. STAGING FOR DIFFERENTIATED THYROID CANCER[14]*

Age at diagnosis (years)	Stage	Primary tumour (T category)	Regional lymph nodes (N category)	Distant metastases (M category)
<55	I	Any T	Any N	M0
	II	Any T	Any N	M1
≥55	I	T1	N0, NX	M0
		T2	N0, NX	M0
	II	T1	N1	M0
		T2	N1	M0
		T3a, T3b	Any N	M0
	III	T4a	Any N	M0
	IVA	T4b	Any N	M0
	IVB	Any T	Any N	M1

* See the Box for TNM staging definitions. Modified from Tuttle RM, et al. Updated American Joint Committee on cancer/tumor-node-metastasis staging system for differentiated and anaplastic thyroid cancer (8th edition). Thyroid 2017; 27: 751-756.[14]

Radioactive iodine

RAI can be delivered with two different intentions. RAI ablation (generally 30 mCi) targets remnant normal thyroid tissue to improve accuracy of surveillance, whereas RAI therapy (about 100 mCi) is used to treat persistent or recurrent disease. If residual disease after initial surgery is suspected, ablation and therapy are combined in a dose of about 100 mCi. Doses up to 150 mCi can be used. Some centres may use dosimetry to avoid bone marrow depression with higher dose therapy (200 to 400 mCi) but proof of better outcome is lacking.

Postsurgical RAI ablation is recommended based on AJCC TNM classification and ATA staging (Table 5). In low-risk patients, RAI ablation is not routinely recommended but can be considered in the presence of risk factors. RAI therapy is generally favoured in patients with intermediate-risk disease, particularly if there are high-grade histological features or vascular invasion. In high-risk patients, routine RAI therapy is recommended.[3]

RAI ablation and therapy requires TSH stimulation, as a high TSH level (>30 mU/L) is needed for radioiodine concentration by remnant thyroid and cancer tissue. To achieve a high TSH level in patients receiving levothyroxine for TSH suppression, preparation with recombinant human TSH or three to four weeks of levothyroxine withdrawal before RAI is required. A post-therapy RAI whole body scan is performed to document RAI avidity of any structural disease. SPECT imaging is obtained to precisely localise uptake and clarify disease staging.[3]

Before administering RAI, several factors need to be considered. RAI is contraindicated in pregnancy, and conception should be avoided for six months after therapy. In women who are breastfeeding, treatment should be deferred until three months after breastfeeding has stopped or until there is no uptake into breast tissue on a low-activity technetium-99m scan. It is important to avoid iodine excess (e.g. radiological contrast administration) for two months before a dose of RAI.

Gonadal tissue can be exposed to radioiodine from circulating blood and from urine in the adjacent bladder. High-dose RAI (100 mCi) can cause temporary amenorrhoea or oligomenorrhoea in women and a reduction in sperm count in men; however, there are no documented

TNM STAGING DEFINITIONS FOR PRIMARY TUMOUR, LYMPH NODE STATUS AND DISTANT METASTASES[14]

T category and criteria

TX = primary tumour cannot be assessed
T0 = no evidence of primary tumour
T1 = tumour ≤2 cm limited to thyroid
- T1a = tumour ≤1 cm without ETE
- T1b = tumour >1 cm but ≤2 cm without ETE

T2 = tumour >2 cm but ≤4 cm without ETE
T3 = tumour >4 cm limited to thyroid or gross ETE invading only strap muscles
- T3a = tumour >4 cm limited to thyroid
- T3b = any size tumour with gross ETE invading only strap muscle

T4 = includes gross ETE into major neck structures
- T4a = any size tumour with gross ETE invading subcutaneous tissue, larynx, trachea, oesophagus or recurrent laryngeal nerve
- T4b = any size tumour with gross ETE invading prevertebral fascia or encasing carotid artery or mediastinal vessels

N category and criteria

NX = regional lymph nodes cannot be assessed
N0 = no evidence of regional lymph node metastases
N1 = metastases to regional nodes
- N1a = metastases to level VI or VII (pretracheal, paratracheal, prelaryngeal or upper mediastinal) lymph nodes (unilateral or bilateral disease)
- N1b = metastases to level I, II, III, IV, V or retropharyngeal lymph nodes (unilateral, bilateral or contralateral)

M category and criteria

M0 = no distant metastases
M1 = distant metastases

Modified from Tuttle RM, et al. Updated American Joint Committee on cancer/tumor-node-metastasis staging system for differentiated and anaplastic thyroid cancer (8th edition). Thyroid 2017; 27: 751-756.[14]

Abbreviation: ETE = extrathyroidal extension.

TABLE 4. RISK STRATIFICATION SYSTEM FOR DIFFERENTIATED THYROID CANCER AT TIME OF PRIMARY TREATMENT[3]

	Low risk	Intermediate risk	High risk
	• ≤5% recurrence	• 5–20% recurrence	• >20% recurrence
Papillary thyroid cancer	• Intrathyroidal tumour • Clinical N0 or ≤5 lymph node micrometastases (<0.2 cm) • Absence of aggressive histology (tall cell, hobnail, columnar)	• Minimal ETE • Aggressive histology • Vascular invasion • N1 or >5 lymph node metastases (<3 cm)	• Gross ETE • Lymph node metastases ≥3 cm • Distant metastases
Follicular thyroid cancer	• Intrathyroidal tumour • Capsular invasion and <4 foci of vascular invasion		• >4 foci of vascular invasion
Subsequent management	• Adjuvant RAI not routinely recommended • If RAI ablation is given and Tg is undetectable, maintain a TSH level of 0.5–2.0 mU/L • If RAI ablation is given and Tg is detectable but low level (e.g. Tg ≥0.2–1.0mcg/L), maintain a TSH level of 0.1–0.5mU/L • If lobectomy is performed and no RAI ablation, maintain a TSH level of 0.5–2.0 mU/L • Regular Tg and TgAb measurements and neck ultrasound	• Consider adjuvant RAI • Initial TSH goal: 0.1–0.5 mU/L • Regular Tg and TgAb measurements and neck ultrasound	• Adjuvant RAI routine • Initial TSH goal: <0.1 mU/L • Regular Tg and TgAb measurements and neck ultrasound

Modified from Haugen BR, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2016; 26: 1-133.[3]

Abbreviations: ETE = extrathyroidal extension; N0 = no metastatic nodes; N1 = metastases to regional nodes; RAI = radioactive iodine; Tg = thyroglobulin; TgAb = thyroglobulin antibody; TSH = thyroid-stimulating hormone.

long-term risks of infertility, miscarriage or fetal malformations.[3] The risk of bone marrow and secondary malignancies is increased with total RAI doses greater than 600 mCi. This risk is minimised by limiting the size of individual doses and maximising dosing intervals, and needs to be balanced against efficacy of treatment for thyroid cancer.[3]

RAI treatment itself is generally well tolerated. Brief hospitalisation is required to protect the patient's family and the community from radiation and occasionally there is nausea and transient xerostomia. With repeated doses, chronic xerostomia can occur.

Thyroxine suppression

Differentiated thyroid cancers express TSH receptors and therefore TSH can stimulate growth. For this reason, targeting a subnormal or suppressed TSH level by administering a supraphysiological dose of thyroxine can reduce disease recurrence. Initial TSH targets are determined by ATA risk categorisation and are then guided by clinical progress (Table 4).[3] This needs to be balanced against the risks of TSH suppression, including cardiac arrhythmia and bone loss. In general, for differentiated thyroid cancer that is stage II or higher, an initial TSH target of below 0.1 mU/L is appropriate.[3] The length and degree of thyroxine suppression is dependent on staging and treatment response, and should be guided by the managing endocrinologist. Ongoing TSH suppression is not required for low-risk patients in remission.

Surveillance

Routine surveillance after thyroidectomy for differentiated thyroid cancer includes neck ultrasonography and measurement of serum thyroglobulin levels. In general, surveillance in the first few years will be maintained by the endocrinologist or the surgeon or both. Persistent or recurrent disease requires long-term specialist follow up. The GP should be kept informed of the results of surveillance and any change in management. It is usually best for imaging, especially neck ultrasonography, to remain in one expert centre. Thyroxine dose adjustment should remain with the endocrinologist. Any suspected recurrence between routine surveillance assessments should be communicated to the endocrinologist or surgeon promptly.

Thyroglobulin is a large protein synthesised only by follicular thyroid cells. Although thyroglobulin is not a true tumour marker, as it is produced by normal thyroid tissue, it can function as a tumour marker in cases where there is no residual normal thyroid tissue (e.g. after total thyroidectomy and RAI ablation). Measurement of thyroglobulin levels is not recommended preoperatively as it is an insensitive and nonspecific test for thyroid cancer. Levels should be measured at least three to four weeks after thyroidectomy or RAI ablation to better reflect a true nadir level.[3]

Valid thyroglobulin values require absence of thyroglobulin antibodies (TgAb). TgAb are present in 25% of patients with thyroid cancer and 10% of the general population, and their presence can falsely lower thyroglobulin levels. In general, a thyroglobulin level below 0.2 mcg/L on suppressive levothyroxine

TABLE 5. RISK STRATIFICATION SYSTEM FOR DIFFERENTIATED THYROID CANCER DURING FOLLOW UP[3]

	Excellent response	Indeterminate response	Biochemical incomplete response	Structural incomplete response
Risk of recurrence or persistence	• 1–4%	• 15–20% structural disease during follow up	• 20% structural disease during follow up	• 50–85% persistent disease despite additional therapy
Disease-specific death rate	• <1%	• <1%	• <1%	• 11% with locoregional metastases • 50% with structural distant metastases
Imaging	• Imaging negative for disease recurrence	• Nonspecific finding on imaging	• Imaging negative for disease recurrence	• Structural or functional evidence of disease
Tg, TgAb	• Nonstimulated Tg <0.2 mcg/L • Stimulated Tg <1 mcg/L	• Nonstimulated Tg <1 mcg/L • Stimulated Tg <10 mcg/L • TgAb stable or decreasing	• Nonstimulated Tg >1 mcg/L • Stimulated Tg >10 mcg/L • Increasing TgAb concentrations	• Any Tg level

Modified from Haugen BR, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer. Thyroid 2016; 26: 1-133.[3]
Abbreviations: Tg = thyroglobulin; TgAb = thyroglobulin antibody.

therapy (TSH <0.1 mU/L) correlates well with the absence of differentiated thyroid cancer. Neck ultrasonography is useful to detect residual or recurrent disease of the thyroid bed and neck lymph nodes. This is especially useful in PTC, given the tendency for local recurrence and spread. Initially, thyroglobulin measurements and neck ultrasonography should be performed every six to 12 months, with subsequent frequency determined by staging.

Whole body RAI scanning is no longer routine but may be appropriate in certain cases – for example, in high-risk patients with follicular thyroid cancer because neck ultrasonography that is negative for local disease does not exclude distant metastases, in patients with uninformative serum thyroglobulin levels due to the presence of TgAb, or in those with a high or rising serum thyroglobulin level.

Other imaging, including CT, MRI or fluorodeoxyglucose positron emission tomography (FDG-PET), is not recommended routinely, but is used to investigate clinically suspected metastatic disease. CT with contrast is most sensitive for micrometastases of the lung, whereas MRI with gadolinium contrast is preferred to delineate the aerodigestive tract. FDG-PET should be considered in cases where residual or metastatic disease is suspected, but RAI uptake scan is negative. De-differentiated and high-risk thyroid cancer is FDG-PET positive but RAI uptake negative.[3]

Management of persistent and metastatic disease

Active surveillance versus surgical management

Disease that is asymptomatic, stable or minimally progressive on follow up is unlikely to rapidly develop clinical complications and can be treated conservatively with levothyroxine to suppress TSH and serial imaging every three to 12 months.[3] In persistent or recurrent disease that is biopsy proven, surgical excision can be considered for symptomatic relief. Repeat surgery generally has a higher risk of complications with a lower chance of success.

Other treatment options in nonresectable local disease include RAI therapy for RAI avid local or metastatic disease. In such cases, repeated dosing up to a yearly frequency may be required. External beam radiation therapy is another therapeutic modality to treat locoregional disease. Radiofrequency ablation and alcohol injection of cytologically confirmed malignant cervical lymph nodes have also been used for high-risk surgical patients.

The treatment of metastatic differentiated thyroid cancer, even without disease eradication, is associated with reduced morbidity through alleviation of local symptoms and has been shown to improve survival. Treatment response is demonstrated by a significant reduction in serum thyroglobulin levels or in the size and rate of growth of metastases.[3]

Systemic therapy

Conventional chemotherapeutic agents (e.g. doxorubicin) are no longer recommended in thyroid cancer, as they are toxic and generally ineffective. Systemic therapy with tyrosine kinase inhibitors has been shown to improve progression-free survival and to induce durable tumour regression. Sorafenib and lenvatinib are approved by the Therapeutic Goods Administration for the treatment of advancing noniodine avid differentiated thyroid cancer.[16]

Lenvatinib antagonises vascular endothelial growth factor receptor kinases and other tumour growth factors. In Australia, it is available on the Pharmaceutical Benefits Scheme (authority required) for patients with progressive metastatic differentiated thyroid cancer that is refractory to RAI and in whom surgery or radiotherapy is not suitable. A randomised

controlled trial of lenvatinib in this population showed an overall response rate of 64.8% and an increased progression-free survival of 14.7 months compared with placebo. Because of the crossover design of the trial, demonstration of improved overall survival was not demonstrated but seems likely.[17]

Tyrosine kinase inhibitors have significant side effects of hypertension, proteinuria, diarrhoea, fatigue, nausea and hand–foot skin reactions. Severe toxicities include thrombosis, bleeding, heart failure, QTc prolongation causing ventricular arrhythmia and gastrointestinal fistula formation with intestinal perforation.[3,17] Side effects are dose related and can generally be managed by dose reduction or temporary suspension.

Systemic therapy with tyrosine kinase inhibitors is indicated in progressive disease not amenable to other treatment and should be initiated and supervised by an experienced endocrinologist or oncologist. Patients with progressive disease who are taking an initial tyrosine kinase inhibitor can be considered for second-line tyrosine kinase inhibitor therapy in the context of a clinical trial. In the case of asymptomatic disease, it is reasonable to continue conservative management rather than risk the side effects of tyrosine kinase inhibitor therapy.[3]

Conclusion

Thyroid nodules are common although most are benign. Thyroid cancer is the most common endocrine malignancy and has a rising incidence. The diagnosis of thyroid cancer requires structured evaluation of thyroid nodules using ultrasonographic and cytological characteristics. Management of established cancer involves detailed individual risk assessment to guide initial treatment, and ongoing surveillance using evidence-based guidelines that are still evolving. Optimal patient outcomes are achieved through a multidisciplinary and collaborative approach between specialists and primary care physicians. MT

References

A list of references is included in the online version of this article (www.medicinetoday.com.au).

COMPETING INTERESTS: Dr Qian: None. Dr Topliss has received personal fees from Eisai and Bayer, and grants from Eisai.

Thyroid cancer

How to achieve optimal patient outcomes

SARAH Y. QIAN MB BS(Hons); **DUNCAN J. TOPLISS** MD, FRACP, FACE

References

1. Australian Institute of Health and Welfare (AIHW). Cancer in Australia 2017. Canberra: AIHW; 2017.
2. Lim H, Devesa SS, Sosa JA, Check D, Kitahara CM. Trends in thyroid cancer incidence and mortality in the United States, 1974-2013. JAMA 2017; 317: 1338-1348.
3. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association management guidelines for adult patients with thyroid nodules and differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on Thyroid nodules and differentiated thyroid cancer. Thyroid 2016; 26: 1-133.
4. Cabanillas ME, McFadden DG, Durante C. Thyroid cancer. Lancet 2016; 388: 2783-2795.
5. Smallridge RC, Ain KB, Asa SL, et al. American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid 2012; 22: 1104-1139.
6. Wells SA, Jr, Asa SL, Dralle H, et al. Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma. Thyroid 2015; 25: 567-610.
7. Tessler FN, Middleton WD, Grant EG, et al. ACR thyroid imaging, reporting and data system (TI-RADS): white paper of the ACR TI-RADS Committee. J Am Coll Radiol 2017; 14: 587-595.
8. Al-Qurayshi Z, Robins R, Hauch A, Randolph GW, Kandil E. Association of surgeon volume with outcomes and cost savings following thyroidectomy: a national forecast. JAMA Otolaryngol Head Neck Surg 2016; 142: 32-39.
9. Miyauchi A. Clinical trials of active surveillance of papillary microcarcinoma of the thyroid. World J Surg 2016; 40: 516-522.
10. Sugitani I, Toda K, Yamada K, Yamamoto N, Ikenaga M, Fujimoto Y. Three distinctly different kinds of papillary thyroid microcarcinoma should be recognized: our treatment strategies and outcomes. World J Surg 2010; 34: 1222-1231.
11. Yu XM, Wan Y, Sippel RS, Chen H. Should all papillary thyroid microcarcinomas be aggressively treated? An analysis of 18,445 cases. Ann Surg 2011; 254: 653-660.
12. Katoh H, Yamashita K, Enomoto T, Watanabe M. Classification and general considerations of thyroid cancer. Ann Clin Pathol 2015; 3: 1045-1054.
13. Nikiforov YE, Seethala RR, Tallini G, et al. Nomenclature revision for encapsulated follicular variant of papillary thyroid carcinoma: a paradigm shift to reduce overtreatment of indolent tumors. JAMA Oncol 2016; 2: 1023-1029.
14. Tuttle RM, Haugen B, Perrier ND. Updated American Joint Committee on Cancer/tumor-node-metastasis staging system for differentiated and anaplastic thyroid cancer (eighth edition): what changed and why? Thyroid 2017; 27: 751-756.
15. Scott E, Learoyd D, Clifton-Bligh RJ. Therapeutic options in papillary thyroid carcinoma: current guidelines and future perspectives. Future Oncology 2016; 12: 2603-2613.
16. Gild M, Topliss DJ, Learoyd D, et al. Clinical guidance for radioiodine refractory differentiated thyroid cancer. Clin Endocrinol 2017; doi: 10.1111/cen.13508 [Epub ahead of print].
17. Schlumberger M, Tahara M, Wirth LJ, et al. Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med 2015; 372: 621-630.