Thyroid cancer

An update on diagnosis and management

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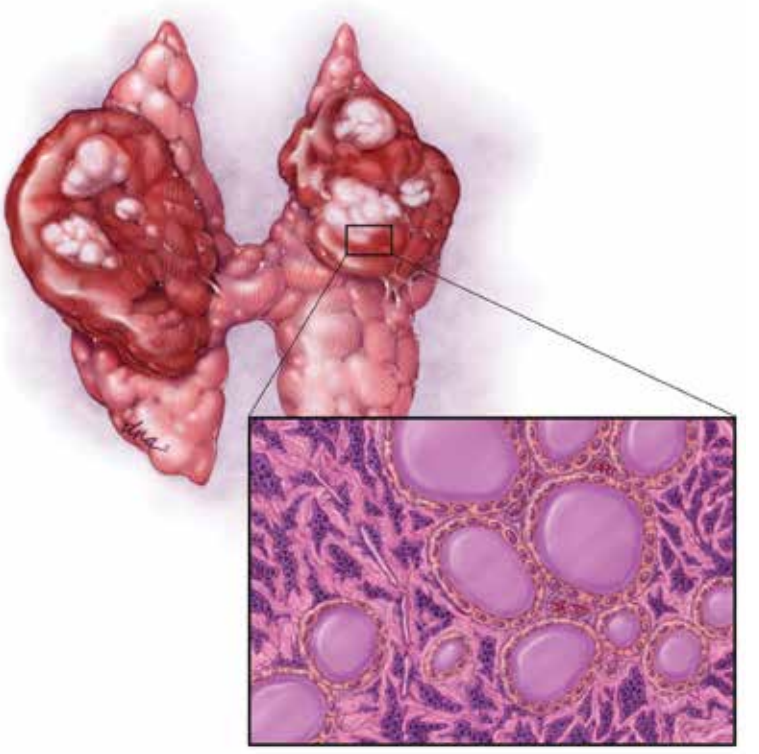

Thyroid nodules are being increasingly detected, and most thyroid cancers in Australia are now diagnosed by ultrasound before they become clinically apparent as palpable nodules. Management is individualised and dynamic, involving identifying and accurately risk stratifying malignant nodules so the most appropriate treatment is selected for each patient.

Key points

- **Thyroid nodules should be carefully assessed for suspicious ultrasound features and these in addition to nodule size and growth rate determine the need for biopsy.**
- **Most thyroid cancers in Australia are now diagnosed by ultrasound before they become clinically apparent as a palpable nodule.**
- **The management approach is individualised; the goal is to identify and accurately risk stratify malignant nodules to select the most appropriate treatment for each patient, avoiding over-investigating and over-treating.**
- **The American Thyroid Association 2015 evidence-based guidelines for the management of thyroid nodules and thyroid malignancy (which are generally followed in Australia) provide an individualised management plan rather than a 'one size fits all' approach. Ongoing management at all stages involves dynamic risk assessment.**
- **Post-thyroidectomy thyroid-stimulating hormone levels are kept suppressed below the normal range in high-risk patients but in other patients are kept in the low normal range.**
- **Serum thyroglobulin measurement has minimal use in patients with an intact thyroid but is important in thyroid cancer follow up.**

Thyroid nodules are very common and an increasing incidence with age has long been recognised.[1] Approximately 5% of people have a palpable nodule, but the prevalence of nodules detected on ultrasound increases to about 70% after middle age.[2] The clinical significance of thyroid nodules relates to the need to exclude thyroid cancer, occurring in 7 to 15% of cases, depending on factors such as age, gender, radiation exposure and family history.[2] GPs commonly encounter the clinical scenario of a patient with a thyroid nodule detected by ultrasound before it becomes palpable. This article discusses the identification of malignant nodules, their risk stratification and the most appropriate treatments, with the aim of avoiding over-investigation and over-treatment.

Types of cancer and prognosis

The four main types of thyroid cancer are papillary, follicular, medullary and anaplastic. Prognosis depends on the type of thyroid cancer, whether it is confined to the thyroid or if there have been metastases to the lymph nodes or elsewhere, and the patient's age (whether 45 years or older, or younger). Staging will depend on diagnosis, histology and imaging findings and the time course of events.

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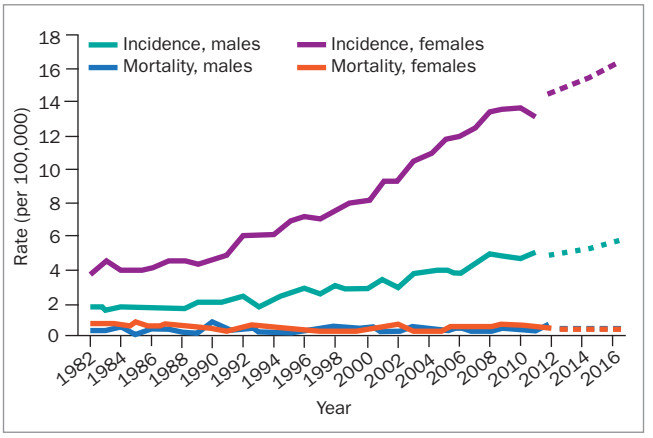

Figure 1. Incidence and mortality of thyroid cancer 1982-2016 (age-standardised rates).
Based on Australian Institute of Health and Welfare material.

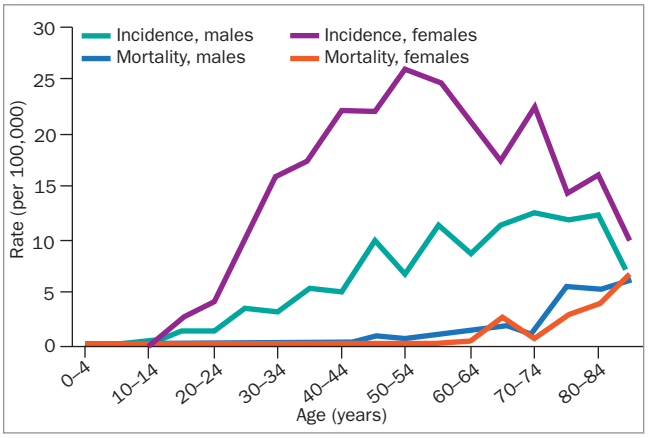

Figure 2. Incidence (2011) and mortality (2012) of thyroid cancer, by age group.
Based on Australian Institute of Health and Welfare material.

Incidence and mortality

The incidence of thyroid cancer has increased threefold since 1975 and significantly more females than males are affected. In 2011, the age standardised incidence was 5.1 for males and 13.1 for females in Australia (Figure 1).[3] The peak incidence for cancer is around the ages of 45 to 55 years for women and 60 to 80 years for men (Figure 2).[3]

Although the incidence of thyroid cancers has been increasing, in Australia (and other countries) mortality remains unchanged (at about 0.5 per 100,000 population per year, age-standardised) in Australia in 2012.[3] Most of the increased incidence is accounted for by early stage papillary thyroid cancers and is a result of higher rates of medical imaging.[4] In Korea, for example, routine population screening with thyroid ultrasound has led to a 15-fold increase in thyroid cancer incidence with no associated increase in mortality, although a large burden on service provision has ensued.[5] Identifying and accurately risk stratifying malignant nodules to enable the most appropriate treatment for each patient helps reduce over-investigation and over-treatment.

Presentation

Thyroid nodules may be detected by patients, imaging or as a result of investigation of clinical or biochemical thyroid dysfunction. Symptoms suspicious for malignancy in palpable nodules include change in voice and difficulty swallowing. Cervical lymphadenopathy should prompt consideration of thyroid cancer.

Many nodules, and hence cancers, are detected incidentally by the widespread use of neck ultrasound for the investigation of symptoms such as neck pain or discomfort, possible lymphadenopathy or presumed carotid vascular disease.[6] A number are found as 'incidentalomas' on functional fluoro-deoxyglucose positron emission tomography (FDG-PET scan), which is now being performed increasingly for diagnosis and staging or surveillance of other malignancies. There is a 33% risk these 'hot spots' will represent thyroid cancers.[7] There is a higher chance a nodule will be found to harbour malignancy if the affected patient was exposed to radiation before the age of 20 years (e.g. post-therapy for haemopoietic malignancy or prior therapy for acne). High-risk clinical features are summarised in the Box.

Tailored management

The recently revised 2015 American Thyroid Association (ATA) guidelines for the management of thyroid nodules and differentiated thyroid cancer in adults are generally followed in Australia, where possible.[2] They explain the levels of evidence and support an individualised or tailored management plan rather than a 'one size fits all' approach. Management is dynamic and includes ongoing review of the patient. It involves initial risk assessment, consideration of response to treatment and acknowledgement of maintenance of remission over time or restratification in the event of recurrence.

Thyroid cancer: high-risk clinical features

History

- Male
- Age younger than 20 years or older than 70 years
- History of head/neck irradiation
- Symptoms of compression causing dysphagia, dyspnoea, cough, dysphonia or hoarseness
- Family history of medullary thyroid cancer or multiple endocrine neoplasia type 2
- Rapid growth of nodule

Physical examination

- Nodule larger than 4 cm
- Firm/hard nodule
- Fixed to adjacent structures
- Vocal cord paralysis
- Regional lymphadenopathy
- Palpable increase in firmness and size

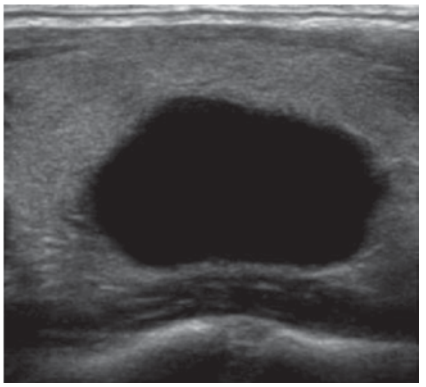

Figure 3. A cystic thyroid nodule – benign.

Work up

Work up of all patients with thyroid nodules begins with thyroid-stimulating hormone (TSH) screening and then ultrasound examination, aided by fine needle aspiration (FNA) biopsy where indicated. Sometimes early specialist referral is helpful to decide which nodule(s) require FNA biopsy.

Serum thyroglobulin measurement has minimal use in patients with an intact thyroid but is important in follow up of patients with thyroid cancer and will be discussed in detail later. Measurement of thyroid antibodies may be helpful if autoimmune thyroid disease is suspected.

Confirm nodule

Autoimmune thyroid disease, including both Graves' and Hashimoto's diseases, may cause confusion in the reporting of thyroid sonography. Increased vascularity and heterogeneous echotexture are both seen in autoimmune thyroid disease and may give the appearance of multiple small nodules.

Nodule risk assessment

A considered history on the radiology request form will aid in sonographic assessment. Where clinical features (history and examination) are suspicious for malignancy, the request should be for assessment of the thyroid and cervical lymph nodes and FNA biopsy of any suspicious nodules and nodes.

The approach is individualised. Suspicious ultrasound features are a hypoechoic lesion with microcalcifications (spiculated rather than eggshell calcification), border irregularity or central vascularity.[8] Associated lymphadenopathy is always concerning. Cystic lymphadenopathy can be seen in metastatic papillary thyroid cancer.

Much work has been done on describing patterns of ultrasound findings that denote high-risk thyroid nodules. The detail of sonographic assessment is comprehensively reported in recommendation 8 of the ATA 2015 guidelines.[2] At one end of the spectrum, purely cystic nodules are almost always benign and confer a less than 1% risk of malignancy; biopsy is not required for these nodules (Figure 3). At the other extreme, a solid and hypoechoic, or the solid hypoechoic portion of a cystic nodule, that has any of irregular margins, microcalcifications or being taller than it is wide is suspicious (Figure 4). The malignant risk of such nodules is 70 to 90% and biopsy must be undertaken (Figure 4).

Thyroid radioisotope scans are not routinely performed unless thyroid function tests are toxic (i.e. low TSH). If a nodule is 'hot' or autonomous, this reduces the likelihood of malignancy, and may influence the specialist's decision as to whether FNA is necessary.

FNA biopsy if appropriate

Ultrasound-guided FNA biopsy is recommended for thyroid nodules that are 10 mm or larger in size and have a suspicious sonographic appearance; there is generally no role for biopsy of nodules less than 10 mm in size (recommendation 8, ATA 2015 guidelines).[2] The aspirated material is sent for cytological assessment.

In patients with multiple nodules or a multinodular goitre, ATA 2015 guidelines typically recommend biopsy of the largest nodule and any other nodule with suspicious features.[2] Recent literature suggests that ultrasound features themselves are more indicative than size or serial change in growth.[9]

The cytological results of thyroid biopsy are classified according to the Bethesda classification system, with a correlative risk of malignancy and suggested management (Table 1 and below).[10]

The endocrinologist guides the decision as to whether surgery or active surveillance is most appropriate. Surgery in specialised endocrine surgery units is ideal if readily available. Robotic transaxillary thyroidectomy is an 'off-label' procedure used only by a handful of surgeons simply for cosmetic outcome in patients trying to avoid a prominent neck scar; it is currently not standard of care.

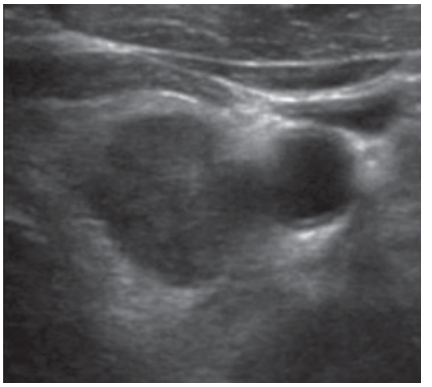

Figure 4. A solid hypoechoic thyroid nodule with irregular margins – highly suspicious of thyroid cancer.

Bethesda cytology and correlated histopathology

New recommendations in the ATA 2015 guidelines for thyroid nodules and cancer management clarify the details to be included in the specialist pathology report, which helps risk stratification and management.[2] These include American Joint Committee on Cancer TNM (tumour size, lymph nodes affected, metastases) cancer staging system criteria, vascular invasion, number of lymph nodes examined and involved, size of the largest metastatic lymph node (LN) focus, extranodal extension and variants with unfavourable outcomes (e.g. tall cell or Hurthle cell variant of papillary thyroid cancer).[2,11-16]

The management of the various categories of Bethesda lesions are detailed in Table 1. Bethesda III and IV lesions remain a challenge and treatment must be individualised. The classic papillary thyroid cancer has typical nuclear features of malignancy that allow definitive diagnosis (categories V and VI). However, benign lesions such as follicular adenoma are very difficult to distinguish from a follicular carcinoma. FNA biopsy of either can yield an atypical pattern (categories III and IV). In Western society there has been a trend to diagnostic hemithyroidectomy for both category III and IV lesions.

Bethesda V lesions are managed with

lobectomy or total thyroidectomy. The guidelines are now in favour of more conservative surgery for smaller lesions with no lymph node involvement (ATA 2015 guidelines recommendation 35).[2]

Bethesda VI lesions require surgery. This is lobectomy or total thyroidectomy with or without central or lateral neck dissection depending on preoperative evaluation (further details beyond the scope of this article).

Thyroid surgery

Where a surgical lobectomy (hemithyroidectomy) or total thyroidectomy is undertaken, the final histopathology result will further refine the risk profile and the need for further surgery such as completion thyroidectomy (removal of any thyroid tissue that remains after a less than total thyroidectomy) and lymph node clearance. Clinically involved lymph nodes (palpable or sonographically suspicious with needle biopsy confirming malignant cells) mandate an appropriate nodal dissection at the time of thyroid surgery (ATA 2015 guidelines recommendation 36).[2,17]

In cases of confirmed thyroid malignancy in a patient who has had a lobectomy, completion thyroidectomy may be undertaken. For example, a patient determined on histopathology after lobectomy to have a follicular thyroid cancer, which is considered higher risk than papillary thyroid cancer, will require completion thyroidectomy.

Aggressive management is not required for the new category of papillary thyroid cancer known as noninvasive follicular thyroid neoplasm with papillary-like nuclear features that has been added recently, after refinement of histopathological reporting.[18]

There is now good evidence that not all patients with FNA-proven thyroid cancer require immediate thyroidectomy. Studies from Japan have followed small (<10 mm diameter) classic papillary thyroid cancers without surgery to document the natural history, and have shown that generally progression is slow in these cases without initial nodal involvement.[19] Elderly patients with these thyroid cancers may therefore defer thyroidectomy (especially if they have other comorbidities) as the disease is unlikely to cause morbidity or mortality in their lifetime.

Table 1. Bethesda cytological category for thyroid cancer, malignancy risk and suggested management[2]

Bethesda diagnostic category	Malignant risk (%)	Suggested approach
I – Nondiagnostic or unsatisfactory sample	1 to 4	Repeat ultrasound-guided FNA biopsy
II – Benign	0 to 3	Conservative approach. Six- to 12-monthly clinical surveillance, with ultrasound follow up if necessary (determined by risk stratification of ultrasound pattern), for two years, then less frequent but ongoing GP/specialist review, including concerning clinical symptoms and/or neck signs
III – Atypia or follicular lesion of undetermined significance	5 to 15	Repeat ultrasound-guided FNA, may require diagnostic surgery
IV – Follicular neoplasm or suspicious for follicular neoplasm	15 to 30	Surgical lobectomy, with or without completion thyroidectomy
V – Suspicious for malignancy	60 to 75	Lobectomy or total thyroidectomy
VI – Malignant	97 to 99	Total thyroidectomy

Abbreviation: FNA = fine needle aspiration.

Similarly, for patients with asymptomatic papillary thyroid cancers diagnosed incidentally on staging FDG-PET scans performed for other cancers, it is reasonable to defer thyroid surgery if the prognosis from the other malignancy is guarded.

There is also good quality evidence that supports active observation rather than immediate surgical intervention for papillary thyroid cancer diagnosed in a nodule less than 10 mm in size (i.e. micropapillary thyroid cancer).[20]

Currently cytology/histology remains superior to somatic genetic biomarker analysis for detection of thyroid cancer. It had been hoped that genetic biomarkers, such as *BRAF* oncogene analysis, would assist clinically, however low cost–benefit ratios and specificity/sensitivity issues remain problematic for gene panel cytology in Australia.

Thyroid surgery complications

Surgical complications of thyroidectomy and general management principles are summarised in Table 2.

Postsurgical and ongoing management considerations

Decisions for further treatment after thyroid surgery are best made in an endocrinologist-led multidisciplinary team. In such a meeting, the usefulness of radioactive iodine (RAI) remnant ablation or RAI treatment of presumed (adjuvant therapy) or known (therapy) residual or metastatic disease can be determined by considering the relevant risk category (low, intermediate or high). Gross extrathyroidal extension and the presence of distant metastases are the only absolute indications for RAI therapy (ATA 2015 guidelines recommendation 51).[2]

RAI remnant ablation

RAI remnant ablation is an ingested targeted therapy facilitating the ablation of any residual thyroid bed tissue or cancer cells. The treatment must be given with a stimulated TSH (>30 IU/L), usually achieved by the administration of recombinant TSH (thyrotropin alfa). (High levels of TSH stimulate cancerous thyroid cells, which normally absorb only small

Table 2. Thyroid surgery complications and their management

Complication	Management	Comments
Bleeding	Rarely patient returns to theatre for evacuation of haematoma	Risk of any surgery
Temporary hypoparathyroidism	Generally, weekly serum calcium measurements are required and supplements are usually weaned rapidly	Common due to the interruption to the parathyroid vascular supply from trauma due to intra-operative handling. Parathyroid glands noted to have compromised blood supply at the time of surgery are auto-transplanted (reimplanted into the sternocleidomastoid muscle or forearm) with hopeful return of function
Permanent hypoparathyroidism	Calcium supplementation and calcitriol (1,25-dihydroxyvitamin D)	Authors' own observation is that mild or borderline hypoparathyroidism is under-recognised in the long term. Intercurrent illness can then cause problematic hypocalcaemia (perioral tingling, nonspecifically unwell, etc) if the patient is not taking (nonadherence) or absorbing their usual supplementation
Recurrent laryngeal nerve paralysis (RLNP) – temporary or permanent (persists longer than 12 months), unilateral or bilateral	Voice check preoperatively is advised. Common practice is to use intraoperative neural monitoring to mitigate risk of laryngeal nerve injury. Patients undergoing bilateral or redo (or reoperative) surgery and those with variant anatomy are most at risk	Nerve injury rates are variable and often higher than thought/acknowledged. Method of voice assessment (clinical or by nasoendoscopy) is variable. The average incidence of temporary RLNP after thyroid operations is 9.8% and the incidence of permanent RLNP is 2.3%[21]

amounts of iodine, to take up more iodine.) Randomised studies now support the use in most patients of lower doses (e.g. 1 GBq [25 MCi]) than used in the past, which also minimises long-term toxicity (such as salivary gland damage, bone marrow exposure and second primary malignancy from cumulative doses.[2,22,23] RAI doses are tailored by the multidisciplinary team discussion.

Surveillance

Surveillance of patients after surgery is through a combination of clinical assessment, serum TSH, serum thyroglobulin (Tg) levels (along with serum thyroglobulin antibody; TgAb) and both functional and anatomical imaging.

Thyroid-stimulating hormone

Traditionally thyroxine was prescribed in suppressive doses to all thyroid cancer patients irrespective of age, stage or remission status. The rationale was to suppress tumour growth, and for advanced cases there was good evidence of benefit. However, thyroxine doses high enough to suppress TSH levels will increase the risk of bone loss and cardiac arrhythmia, especially in older patients.

ATA guidelines now suggest a tailored approach. For low-risk patients who are cured of thyroid cancer the TSH is maintained in the normal range, albeit at the low end of normal.[2] GPs need to be aware that patients with persistent disease or high risk of recurrence are often managed with a target TSH level below the reference range, and care should be taken that the thyroxine dose is not reduced unless in consultation with the treating endocrinologist.

Thyroglobulin and thyroglobulin antibodies

Serum Tg is a useful tumour marker and is measured at around six weeks after total thyroidectomy and regularly thereafter (at least annually). TgAb should always be measured when Tg is measured and vice versa. This is because of the presence of TgAb falsely lowers the serum Tg result and can give false reassurance. Serum Tg measurements are occasionally useful in patients with an intact thyroid. Serum TgAb levels are not useful in post-thyroidectomy patients in the absence of Tg levels. Positive TgAb results are challenging to interpret. They are sometimes used by endocrinologists as a surrogate tumour marker and require careful interpretation to assess their disease burden. It is now apparent that the trend rather than single values are important in monitoring, as initial therapies (RAI therapy) can have ongoing benefit years later.[24]

Imaging

Functional whole body radioiodine scanning is performed at the time of RAI ablation and, depending on the clinical scenario, may be used in surveillance. Anatomical imaging with targeted neck ultrasound looking at the thyroid bed and cervical lymph nodes has an increasingly important role, with the benefit of no preparation and no radiation exposure. Rarely, cross-sectional imaging (with CT, avoiding iodine contrast if RAI therapy is imminent) and FDG-PET may be required.

Surgical recurrence

The risk of thyroid cancer recurrence in the long term can be as high as 20 to 30% in low to intermediate risk papillary thyroid cancer cases. Although overall cure can still be

achieved, further neck surgery may be required to remove residual or recurrent nodal disease.

Distant metastatic disease

Multiple doses of RAI therapy at appropriate intervals are given while there is evidence of iodine uptake in distant metastases.

There have been major advances in the management of progressive iodine-refractory metastatic differentiated thyroid cancer with the advent of targeted therapies such as the tyrosine kinase inhibitors (TKIs). Phase III trials of TKIs vandetanib and lenvatinib have now been conducted around the world (including Australia). Both are TGA-approved and lenvatinib became available on the PBS for locally advanced or metastatic differentiated thyroid cancer in December 2016.

Significant improvement in progression-free survival has been demonstrated with use of vandetanib and lenvatinib, but further studies are needed to demonstrate overall survival benefit. Lenvatinib has a spectrum of toxicity that GPs should be aware of, including that significant fatigue and hypertension are seen in over half of patients taking the drug. Its other toxicities are skin rash, mouth soreness, plantar and palmar desquamation, reduced appetite and diarrhoea. Lenvatinib must be prescribed by an experienced endocrinologist or oncologist.

Management of women around the time of pregnancy

There are no contraindications to pregnancy (or breastfeeding) in women who have been successfully treated for thyroid cancer as long as conception is delayed for at least six months (preferably 12) after RAI ablation. Careful monitoring of TSH levels is needed because the thyroxine dose requirement may increase by 30% (or more) early in the first trimester. Patients are advised to adjust their thyroxine dose as soon as pregnancy is confirmed and to have monthly TSH testing up to 20 weeks' gestation, and second-monthly testing thereafter, maintaining target TSH levels of 2.5 mIU/L or below in the first and second trimesters and then 3.0 mIU/L or below in the third trimester. Postpartum adjustment of thyroxine down to prepregnancy doses will usually be required. Doses for thyroidectomised patients are generally higher than for patients with intact thyroids and autoimmune thyroid disease. Patients who are pregnant or planning pregnancy should discuss management of their thyroid disease with their endocrinologist.

Women may present with thyroid nodules during pregnancy. If nodules are seen on ultrasound but have no worrying features then FNA biopsy may be deferred to the postpartum period. However, if the nodule appearance is concerning then FNA biopsy may be performed during pregnancy. Surgery for small papillary thyroid cancers with no apparent lymph node spread or growth can be delayed to the postpartum period. Occasionally surgery in the second trimester is necessary, although RAI therapy will need to be delayed until after pregnancy.[2]

Conclusion

Thyroid cancer is a common diagnosis and important to consider. Thyroid cancer management is individualised and dynamic, involving identifying and accurately risk stratifying malignant nodules so the most appropriate treatment is selected for each patient. It is important to involve endocrinologists as part of a wider multidisciplinary team for optimal patient outcomes. **ET**

References

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

COMPETING INTERESTS: None.

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