

Thyroid cancer an update

Papillary and follicular cancers are the more common types of thyroid cancer and generally have a very good prognosis. The increasing use of recombinant thyroid stimulating hormone means patients do not need to stop taking thyroxine and be rendered temporarily hypothyroid during adjuvant radioactive iodine therapy and follow-up thyroglobulin monitoring.

RON BOVA

MB BS, MS, FRACS

ANDREW WEISSBERGER

MB BS, FRACP, MD

Dr Bova is a Consultant Head and Neck Oncology Surgeon and Dr Weissberger is a Consultant Endocrinologist at St Vincent's Hospital, Sydney, NSW.

Thyroid cancer is a relatively uncommon malignancy that appears to be increasing in incidence. The spectrum of thyroid tumours ranges from well-differentiated cancers (papillary and follicular), which generally have a very good prognosis, to highly aggressive tumours such as anaplastic carcinoma, which are lethal malignancies (Figure 1). Patients with thyroid cancer require comprehensive

evaluation, multimodality treatment and long-term multidisciplinary follow up.

Although the often life-long follow up is, in most cases, primarily managed by an endocrinologist, the GP has an important role in assisting with management. Hence an understanding of the treatment and follow up considerations is important.

IN SUMMARY

- When thyroid nodules are detected, the challenge facing GPs is to distinguish patients with malignancy who require referral for surgical management from patients who have benign nodules that can be followed up nonsurgically.
- Although thyroid fine needle aspiration (FNA) is a sensitive and accurate diagnostic test, false-negative results do occur. Hence, if there are suspicious clinical findings from the history and/or examination that increase the probability of a nodule being malignant then these should override the FNA result.
- Surgery is the mainstay of treatment and total thyroidectomy is indicated in most patients. Radioactive iodine ablation and long-term thyroid stimulating hormone (TSH) suppression therapy are useful adjuvant therapies.
- GPs should be aware of the target TSH level set by the endocrinologist to avoid inadvertently reducing the thyroxine dose because of the mistaken interpretation that the TSH is too low.
- The increasing use of recombinant TSH is obviating the need for patients ceasing thyroxine and being rendered temporarily hypothyroid during investigation for residual or recurrent thyroid cancer.
- Patients with recurrent or progressive disease need comprehensive work-up and treatment in centres with expertise in treating thyroid cancer.

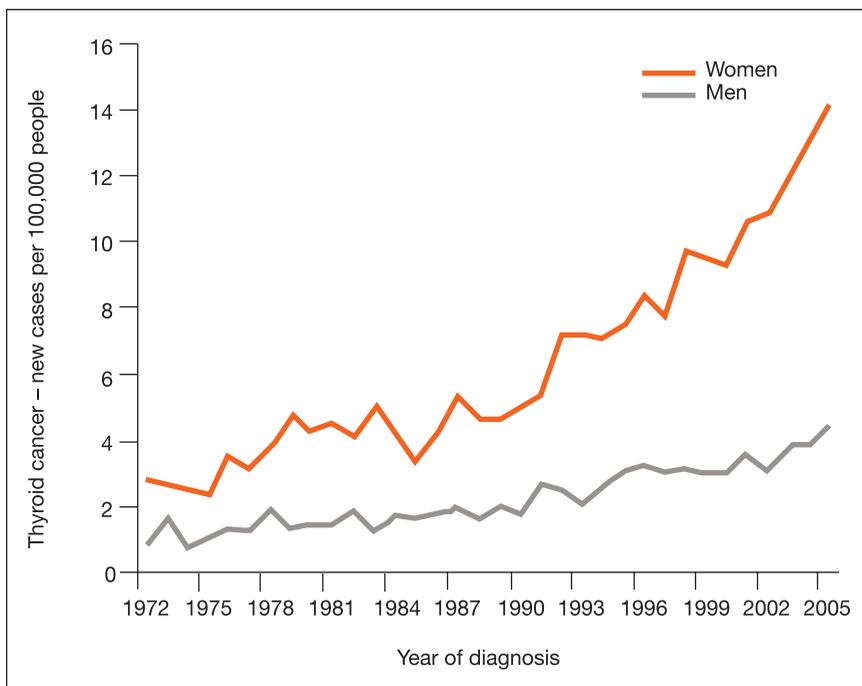


Figure 2. Age-standardised incidence of thyroid cancer in New South Wales, 1972 to 2005.¹

about 50%. The overwhelming majority (95%) of thyroid nodules are benign (colloid nodules, cysts, thyroiditis and benign follicular adenoma).

Most thyroid cancers present clinically with a palpable thyroid nodule, and are usually asymptomatic. About half of thyroid cancers are initially noticed by the patient, and about half are detected during routine physical examination, by serendipity on imaging studies often for unrelated medical conditions, or during surgery for benign thyroid disease.

When thyroid nodules are detected, the challenge facing the GP is to distinguish patients with malignancy who require referral for surgical management from patients who have benign nodules that can be followed up non-operatively.

Although most patients with thyroid cancer are asymptomatic, certain clinical findings should alert the GP to a higher probability of a thyroid nodule being malignant (Table 2). These clinical features include:

- large nodules (more than 4 cm)
- firm or hard nodules, especially if fixed to adjacent neck structures
- hoarseness due to vocal cord paralysis
- rapidly growing nodules
- nodules associated with enlarged cervical lymph nodes (lateral neck lump).

Ultrasound findings that are suspicious for malignancy include:

- nodules with irregular borders
- central hypervascularity
- microcalcification within the nodule.

Investigating a thyroid nodule

The work-up for a patient presenting with a thyroid nodule is summarised in Table 3 and the flowchart on page 30.

TSH assay and ultrasound scan

All patients with a thyroid nodule should have a routine thyroid stimulating hormone (TSH) assay and also a thyroid ultrasound scan.

The vast majority of patients with thyroid malignancy are clinically and

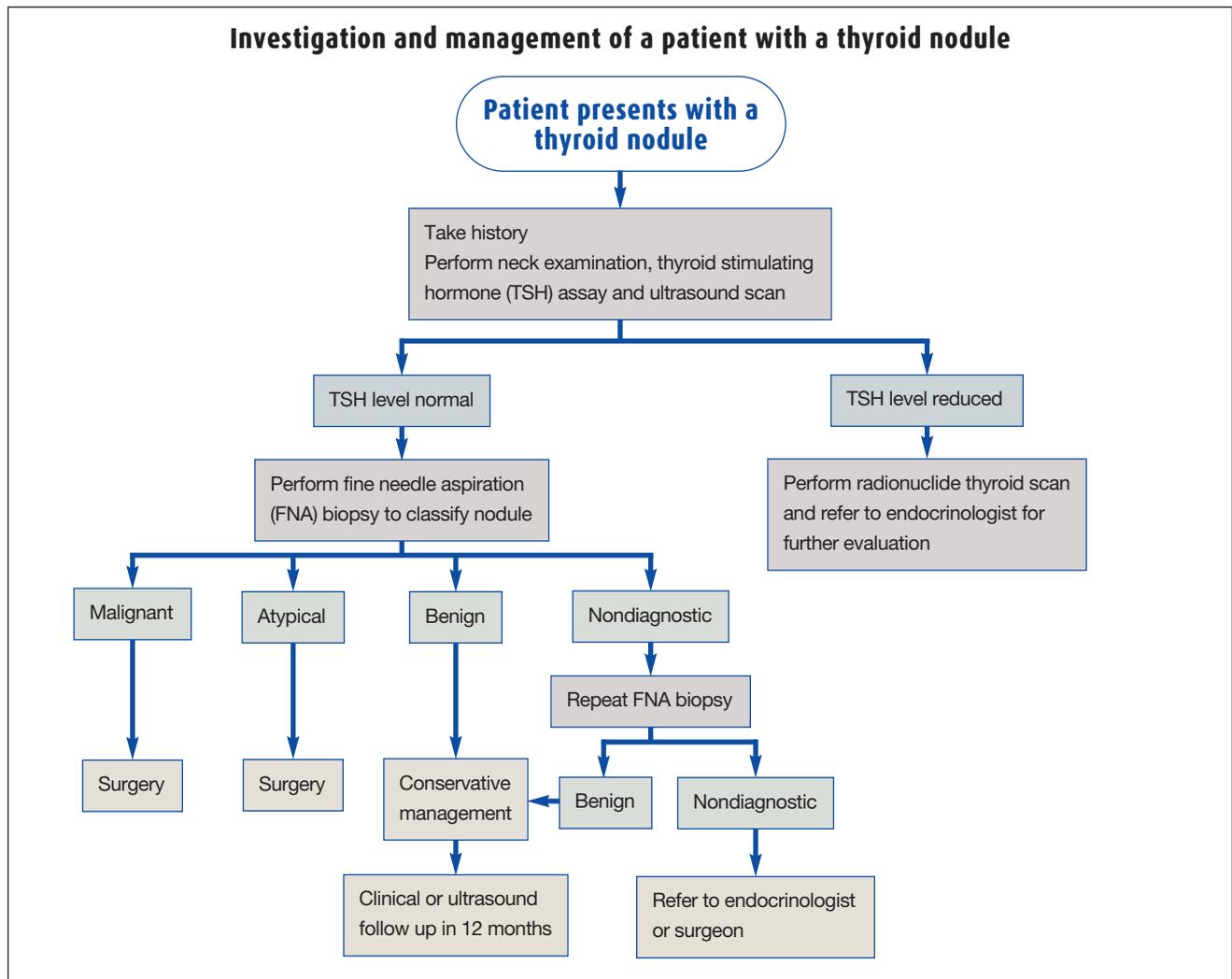
Table 2. Red flags for thyroid malignancy

- Male gender
- Extremes of age (younger than 20 or older than 65 years)
- Exposure to ionising radiation, especially during childhood
- Family history of thyroid cancer
- Large solitary thyroid nodule
- Hard thyroid nodules or with fixation to adjacent neck tissues
- Symptoms of local invasion (neck pain, hoarseness or dysphagia)
- Thyroid nodules that grow rapidly over weeks or months
- Thyroid nodules associated with enlarged cervical neck nodes

Table 3. Investigating a patient with a thyroid nodule

- History
- Physical examination of thyroid and neck
- Thyroid ultrasound scan
- Serum thyroid stimulating hormone (TSH) level measurement
- Fine needle aspiration of dominant or suspicious nodules
- Radionuclide scan indicated only if the patient is hyperthyroid (suppressed TSH); routine use in euthyroid patients should be avoided

biochemically euthyroid. Hyperthyroidism is rarely associated with malignancy; hence if the TSH is suppressed (indicating hyperthyroidism) in a patient with a thyroid nodule, the diagnostic possibilities include a solitary autonomous toxic thyroid nodule (hyperfunctioning adenoma), toxic multinodular goitre



and a solitary nodule in Grave's disease. These patients should have a radionuclide thyroid scan and be referred to an endocrinologist for further evaluation. In these cases, FNA should be withheld as the inflammatory component of these hypercellular toxic nodules can result in an atypical cytologic appearance. A comprehensive review of the management of hyperthyroidism and hypothyroidism was published in the May 2006 issue of *Medicine Today*.²

Fine needle aspiration

FNA has emerged as the investigation of choice for the routine diagnosis and

management of thyroid nodules. It is the most cost-efficient diagnostic test and has an accuracy rate of 95% in differentiating between benign and malignant nodules. Large nodules can be biopsied without ultrasound but smaller nodules are best localised and biopsied under ultrasound guidance. The use of ultrasound has been shown to increase the diagnostic accuracy of thyroid FNA compared with when performed using direct palpation.³

Cytopathology evaluation of an FNA biopsy specimen categorises a thyroid nodule into several diagnostic groups, which guides the clinician towards

specific further investigation or a therapeutic course of action.

Although thyroid FNA is a sensitive and accurate diagnostic test, false-negative results do occur in 1 to 2% of cases. Therefore, any suspicious clinical findings from the history and/or examination that increase the probability of a nodule being malignant should override the FNA result.

Classification of thyroid nodules

The diagnostic groups into which thyroid nodules are classified according to the FNA findings are listed below (see also Table 1).

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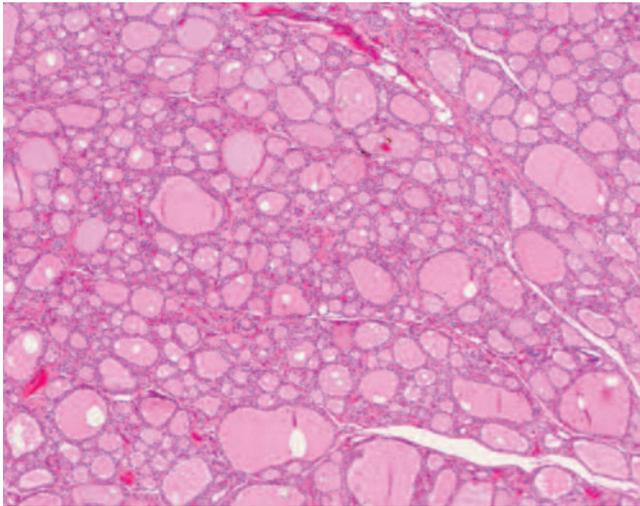


Figure 3 (above left). Normal thyroid histology showing well-formed follicles containing plentiful thin colloid.

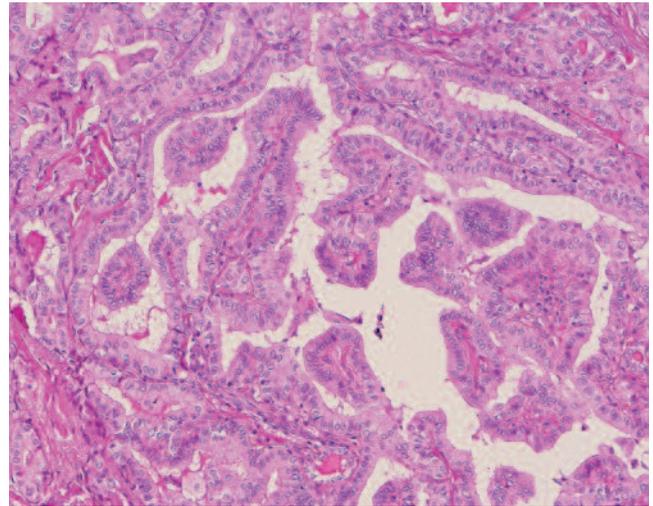


Figure 4 (above right). Papillary carcinoma showing tumour cells forming papillary structures. Note the 'coffee bean' appearance of the nuclei.

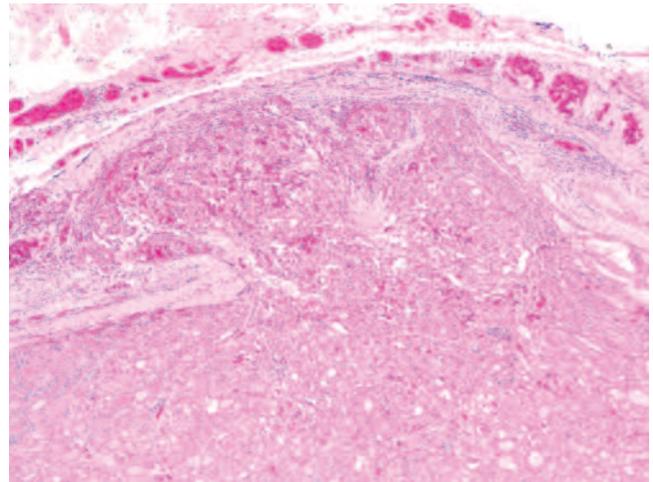


Figure 5 (right). Follicular carcinoma with tumour infiltrating through the tumour capsule.

- **Nondiagnostic.** This implies that the pathologist has not received enough cellular material to make a diagnosis, and a repeat FNA is warranted. If a repeat FNA is nondiagnostic then diagnostic hemithyroidectomy may be indicated.
- **Benign.** Normal follicular cells scattered in regular groups with macrofollicular structures and abundant thin colloid are typically found in benign nodules (Figure 3). Patients with these nodules can be treated conservatively unless there is another indication to proceed with surgery (such as a large nodule with compressive symptoms).

There is a small risk of false-negative FNA results (less than 5%) with these nodules and long-term clinical follow up of patients is advised. Nodules that are easily palpable can be clinically assessed annually whereas those that are small or difficult to palpate can be assessed with repeat ultrasound after 12 months. If there is clinical or ultrasonic evidence of nodule growth (20% increase in nodule diameter), repeat FNA is appropriate. If nodule size remains stable, yearly clinical follow up is recommended.

- **Malignant.** Unequivocal cytological features of papillary, medullary or

anaplastic carcinoma warrant surgical intervention. Cytological features of papillary carcinoma include an increased degree of cellularity with cells arranged in papillary groups and nuclei that are irregularly shaped and grooved, giving them a 'coffee bean' appearance (Figure 4).

- **Atypical.** This is often reported as 'suspicious', 'atypical follicular pattern', 'follicular lesion' or 'follicular neoplasm'. Unfortunately, cytology cannot distinguish between benign follicular adenoma and follicular carcinoma (Figure 5). An atypical follicular pattern is associated with a 20% risk of malignancy, hence

patients with these findings are usually considered for diagnostic hemithyroidectomy.

Staging of thyroid carcinoma

The variable natural history of this relatively rare cancer combined with its excellent prognosis in most patients makes it difficult to perform randomised controlled trials. Studies would require very large patient cohorts with follow-up periods spanning decades in order to obtain meaningful data.

Our current treatment recommendations are based on retrospective studies, and the ideal treatment for thyroid cancer continues to be a source of controversy. Although there is no dispute that surgery is the treatment of choice for thyroid cancer, controversy surrounds the following areas:

- the extent of necessary surgery required, both to the thyroid and to adjacent lymph nodes, particularly for small primary cancers
- the routine use of adjuvant radioactive iodine ablative therapy for low risk patients (e.g. a patient with a small – subcentimetre – papillary carcinoma)
- the role of adjuvant external beam radiotherapy
- the role of TSH suppression therapy in low risk patients.

Hundreds of publications focusing on epidemiological, clinical and pathological data have been devoted to defining prognostic parameters for papillary and follicular carcinoma. Various classification systems based on pretreatment prognostic indicators have been devised in an attempt to predict outcome and to help tailor treatment. Although multiple factors ultimately influence the outcome for patients with papillary and follicular carcinoma, the two most important and consistently demonstrable factors are patient age at the time of initial therapy and tumour stage. It is beyond the scope of this article to discuss staging systems in detail but prognostic factors

Key aspects of thyroid cancer treatment and follow up

- Surgery is the mainstay of treatment and total thyroidectomy is indicated in most patients with papillary or follicular cancer of the thyroid. Experienced thyroid surgeons should perform the surgery.
- Radioactive iodine ablation and long-term thyroid stimulating hormone (TSH) suppression using thyroxine are useful adjuvant therapies. GPs need to be aware of the target TSH level determined by the endocrinologist to avoid inadvertently reducing the thyroxine dose because of the mistaken interpretation that the TSH is too low.
- The increasing use of recombinant TSH (rhTSH) is obviating the need for patients having to stop taking thyroxine and being rendered temporarily hypothyroid so they can have stimulated thyroglobulin (Tg) levels measured and/or have follow-up whole body radioisotope thyroid scans to monitor for residual or recurrent thyroid cancer. Use of rhTSH also avoids the patient being hypothyroid between thyroidectomy and radioactive iodine ablation.
- External beam radiotherapy and chemotherapy are rarely indicated.

associated with poorer survival include the following:

- older age (more than 40 years)
- family history of thyroid cancer
- large tumour size (more than 4 cm)
- tumour extension beyond thyroid capsule
- bilateral lymph node metastases
- distant metastases
- aggressive histology (tall cell or columnar cell papillary carcinoma, widely invasive or poorly differentiated follicular carcinoma)
- incomplete tumour resection
- delayed treatment (for more than one year).

Papillary and follicular thyroid cancers

Treatment

Most patients with papillary or follicular cancer of the thyroid are treated with a combination of surgery, adjuvant radioactive iodine ablation and long-term TSH suppression therapy (see the box on this page).

Surgery

Surgery is the primary treatment for all patients with thyroid cancer and should

be performed by experienced thyroid surgeons.

Total thyroidectomy is indicated for most patients with thyroid cancer. Hemithyroidectomy alone may be considered for small solitary low-risk papillary cancers, although when a preoperative diagnosis of papillary carcinoma is made total thyroidectomy is generally recommended. Because preoperative FNA cannot differentiate between follicular carcinoma and benign follicular adenoma, patients classified as having an atypical nodule on FNA are initially treated with hemithyroidectomy and then proceed to completion total thyroidectomy if the final pathology confirms carcinoma. If there are overt signs of malignancy or the patient has a multinodular goitre and an atypical FNA on one side, initial total thyroidectomy is generally recommended.

Central compartment node dissection is commonly performed for most papillary carcinomas to remove the first echelon drainage nodes, which lie in the tracheoesophageal groove. Selective neck dissection is performed when metastatic cervical nodes are identified preoperatively. More radical resection of adjacent

structures (larynx, trachea and oesophagus) is sometimes required for advanced stage thyroid cancers invading the upper aerodigestive tract.

Radioactive iodine therapy

Radioactive iodine ablation is administered to most patients with thyroid cancer; however, its use in patients with small (less than 1.5 cm) solitary tumours is controversial. The radioactive iodine (I^{131}) is administered following total thyroidectomy and is taken up by any residual normal and malignant thyroid cells, resulting in their death. Eradicating microscopic residual postoperative tumour cells decreases local recurrence and mortality rates. Also, by eradicating any residual tumour and normal thyroid tissue, the serum thyroglobulin (Tg) level should be undetectable and therefore subsequent serum Tg levels can be used to monitor for tumour recurrence. (Tg is the protein precursor of the thyroid hormones and is produced by normal thyroid cells and by thyroid cancer cells).

High levels of TSH are required to stimulate the uptake of I^{131} into residual normal and thyroid tumour cells. This can be achieved by either of the methods below.

- Temporarily withholding thyroxine (T4) replacement for five to six weeks following total thyroidectomy until the TSH level rises sufficiently to facilitate radioactive iodine therapy. This renders patients very hypothyroid in the weeks preceding the radioactive iodine therapy, which can have an adverse effect on their ability to work and a negative impact on their quality of life. To minimise the period of hypothyroidism, patients are given tri-iodothyronine (T3; in the form of the L-isomer, liothyronine sodium), which is short-acting, for several weeks after thyroidectomy, its use being ceased two weeks before radioactive iodine therapy.
- Administering rhTSH – as two

intramuscular injections on the days preceding radioactive iodine therapy while patients are taking their regular thyroxine replacement therapy. This avoids the disruption of maintenance thyroid replacement therapy and prevents the discomfort of a period of hypothyroidism.

TSH suppression therapy

After ablation therapy, patients are commenced on long-term thyroxine therapy to suppress the TSH level so that any remaining thyroid tissue is not stimulated to grow. The TSH level should be suppressed to just below the normal range and the T4 level maintained in the high normal range but without rendering the patient thyrotoxic. A greater degree of TSH suppression is recommended for higher risk patients, especially those with metastatic disease.

TSH suppressive therapy is best supervised by an endocrinologist, who will normally advise the GP of the target TSH level.

External beam radiotherapy

Radiotherapy is occasionally used in patients with advanced thyroid cancer. This is especially so in those who are older (aged over 45 years) and have gross extrathyroidal extension at the time of surgery or positive margins, particularly if the tumour does not concentrate I^{131} thus limiting the utility of radioactive iodine ablation.

Radiotherapy is also used as palliation for unresectable disease or inoperable metastatic bone, brain or spinal disease.

Follow up

All patients with thyroid cancer require long-term follow up by a multidisciplinary team including a GP, endocrinologist, surgeon and nuclear medicine physician. Papillary and follicular thyroid cancers have a long natural history and about 5 to 20% of patients will develop local recurrence in the thyroid bed or

regional cervical lymph nodes, with one-third of these recurrences occurring 10 or more years after treatment. Unlike other malignancies, where local recurrence portends a poor prognosis, local recurrences in patients with thyroid carcinoma are readily amenable to treatment with curative intent.

The intensity of follow up will vary according to the initial tumour stage but the principles of long-term management include those listed below.

- Examination of the thyroid bed and neck, looking for evidence of local recurrence or regional recurrence in cervical lymph nodes.
- Regular thyroid function tests to assess the adequacy of TSH suppression. The treating endocrinologist will normally determine the frequency of testing and the recommended TSH level required to achieve adequate suppression.
- Serum thyroglobulin (Tg) assay. As Tg is normally only made by cells in the thyroid, it serves as a useful 'tumour marker' and has a high degree of sensitivity and specificity after total thyroidectomy and remnant ablation. A detectable Tg level is suggestive of residual or recurrent tumour. Tg is usually measured after cessation of thyroxine therapy for several weeks to allow the TSH level to increase, stimulating Tg release from any thyroid cancer cells remaining in the body. Alternatively, rhTSH can be used, which obviates the need for discontinuation of thyroxine therapy, as previously mentioned. Tg levels are measured at six and 12 months and then yearly if patients are apparently free of disease. Tg antibodies should always be measured in conjunction with serum Tg because their presence can affect the reliability of the Tg assay.
- Diagnostic whole body radioisotope scans (DWBS) are commonly used in conjunction with serum Tg assay

to monitor for thyroid cancer recurrence (Figure 6). A small amount of radioactive iodine is administered, which is usually readily taken up by any normal or malignant thyroid cells. Once again, patients either are withdrawn from their thyroxine replacement therapy or have rhTSH prior to having a DWBS. Repeat DWBS are performed at six- to 12-month intervals with concomitant radioactive iodine ablation should a persistent tumour be identified. A negative DWBS and undetectable serum Tg are generally both required for a patient to be considered in remission. Patients with low-risk small cancers and those demonstrated to be disease-free can often be followed up with serum Tg assay alone, without the need for additional DWBS.

- Sometimes patients have tumours that fail to take up radioactive iodine. They may have an elevated serum Tg level with a negative DWBS. This combination of positive serum Tg and negative DWBS can also occur in low-volume recurrent disease because Tg is generally more sensitive than DWBS in detecting disease. These patients require comprehensive imaging (neck ultrasound, chest CT, bone scan or PET scan) to try to detect the site of recurrent disease.

Patients with recurrent or progressive disease need comprehensive work-up and treatment in centres with expertise in treating thyroid cancer.

Prognosis

The overall prognosis of patients with papillary or follicular carcinoma is excellent when they are managed according to current best practice guidelines. Those who are younger than 45 years of age at the time of diagnosis with small papillary tumours (less than 4 cm) contained within the thyroid and who have no evidence of distant metastatic disease have a five-year survival rate of 99% and a

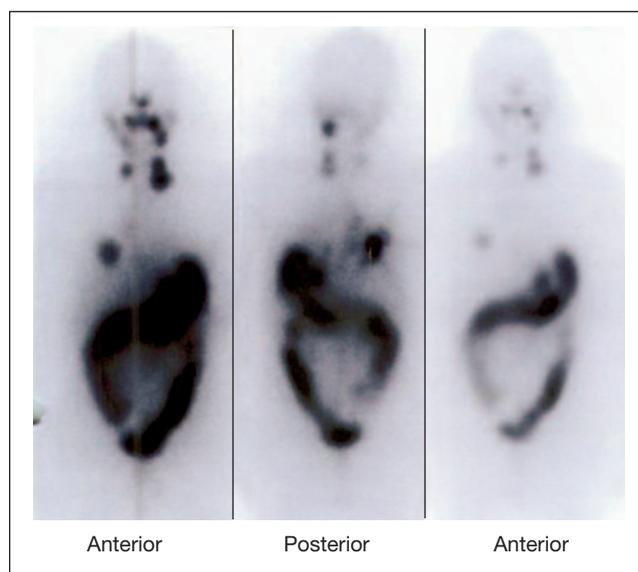


Figure 6. Diagnostic whole-body radioisotope (I^{131}) scan demonstrating multiple foci of avid iodine uptake in lower neck and chest consistent with metastatic thyroid cancer.

10-year survival rate of 98%. Even when distant metastatic disease is present at the time of diagnosis in these patients, the five and 10-year survival rates are still 99% and 85%, respectively.

Medullary thyroid carcinoma

Medullary thyroid carcinoma (MTC) arises from the neuroendocrine parafollicular calcitonin secreting cells of the thyroid, which are located predominantly in the upper portion of each thyroid lobe. Patients typically present with thyroid upper lobe nodules, and metastatic cervical adenopathy is present in about half of patients at initial presentation. An elevated serum calcitonin level confirms the diagnosis.

Most cases of MTC are sporadic; however, about a quarter are hereditary in origin. Hereditary MTC arises as a result of mutation of the *RET* proto-oncogene, which leads to the expression of a mutated receptor tyrosine kinase (an enzyme involved in the regulation of cell growth and development). Hereditary MTC occurs in three forms:

- multiple endocrine neoplasia 2a (MEN2a) – characterised by MTC in combination with phaeochromocytoma and hyperparathyroidism

- multiple endocrine neoplasia 2b (MEN2b) – characterised by MTC in combination with phaeochromocytoma, multiple mucosal neuromas and marfanoid habitus
- familial MTC – characterised by the absence of other endocrinopathies or neural abnormalities in any affected family member.

Patients with newly diagnosed MTC require a detailed work-up before surgery, including:

- serum calcitonin level determination
- neck, chest and abdominal CT looking for metastatic disease, and 24-hour urinary catecholamine screening to exclude a concurrent phaeochromocytoma
- serum parathyroid hormone level determination to exclude coincident hyperparathyroidism
- genetic screening looking for the *RET* mutation (results of genetic screening do not influence initial treatment and can be performed before or after surgery).

Radioactive iodine ablation cannot be used because MTC does not take up radioiodine. Surgery involves total thyroidectomy with bilateral neck dissection in most patients, as these patients have a

continued

high incidence of bilateral metastatic cervical nodal disease.

If patients carry the germline *RET* mutation then genetic testing after appropriate counselling should be performed on all family members. Prophylactic thyroidectomy is usually recommended in early childhood for known carriers of the *RET* gene mutation.

Anaplastic thyroid carcinoma

Anaplastic carcinoma of the thyroid is a highly lethal malignancy that is rapidly progressive and nearly always incurable. It tends to occur in elderly patients and is thought to arise from dedifferentiation of a longstanding papillary or follicular carcinoma. It usually presents with a rapidly expanding thyroid mass with extensive infiltration, and airway obstruction is a common presenting symptom.

It has a poor prognosis, with a mortality rate of 95% within two years of diagnosis. Thyroidectomy is rarely possible and palliation using radiotherapy and chemotherapy is standard treatment. Palliative tracheostomy is sometimes required.

Conclusion

Most patients with papillary and follicular thyroid cancer have a very good prognosis. Because most patients diagnosed with this cancer initially present with a thyroid nodule, GPs have to be alert to this possibility when assessing patients with thyroid nodules. Once thyroid cancer is diagnosed, the patient should be referred promptly to a thyroid surgeon for further assessment. Total thyroidectomy and adjuvant radioactive iodine thyroid remnant ablation therapy is indicated for most patients. Long-term follow up, with input from the endocrinologist, surgeon, nuclear medicine physician and GP, is required to monitor for recurrence. **MT**

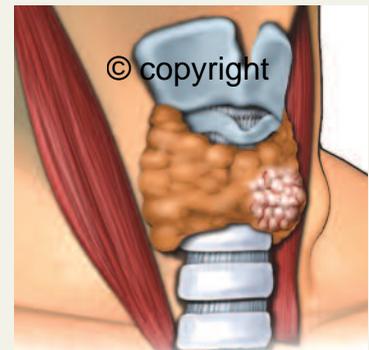
References

1. Tracey E, Baker D, Chen W, Stavrou E, Bishop J. Cancer in New South Wales: incidence, mortality and prevalence report 2005. Sydney: Cancer Institute NSW; 2007. p. 146-149.
2. McCormack AI, Learoyd DL. A guide to thyroid dysfunction. *Med Today* 2006; 7(5): 28-35.
3. Rosen IB, Azadian A, Walfish PG, et al.

Ultrasound-guided fine-needle aspiration biopsy in the management of thyroid disease. *Am J Surg* 1993; 166: 346-349.

COMPETING INTERESTS: None.

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