



Papillary thyroid cancer: the most common endocrine malignancy

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Papillary thyroid cancer has an excellent prognosis and over 90% of affected patients achieve long-term survival. Treatment is primarily by surgery and postoperative radioactive iodine ablation, which may be required to be repeated in cases of recurrence.

Key points

- The main risk factors for papillary thyroid cancer are childhood radiation exposure and a family history.
- A thorough history and examination, followed by appropriate investigations, are required when a patient presents with a neck lump suspected to be thyroid cancer.
- The initial treatment of papillary thyroid cancer consists of surgery with or without postoperative radioactive iodine ablation.
- During follow up, disease-free status is defined by: no clinical evidence of tumour; no evidence of tumour on imaging; and an undetectable serum thyroglobulin level.
- As different specialists are involved at different stages of the management of thyroid cancer, the involvement of the GP from the initial diagnosis to the long-term follow up of the patient may provide a point of contact for the patient, a source of forgotten information, and a sense of continuity of care.



The incidence of thyroid cancer has increased exponentially over the past few decades in Australia and in other countries such as the USA, Canada and France.¹⁻⁴ This steep rise is largely due to an increase in the diagnosis of papillary thyroid cancer (PTC), especially the microcarcinomas (PTC ≤ 1 cm). PTC accounts for 80% of all thyroid cancers, and is the most common subtype.

Fortunately, long-term survival rates of patients with PTC remain excellent, with a five-year relative survival of approximately 96%.^{1,5} Women are four times more likely to be diagnosed with thyroid cancer than men (Figure 1).¹ Other types of thyroid cancer include follicular thyroid cancer, medullary thyroid cancer, poorly differentiated thyroid cancer, anaplastic thyroid cancer, lymphoma and metastatic cancer to the thyroid.

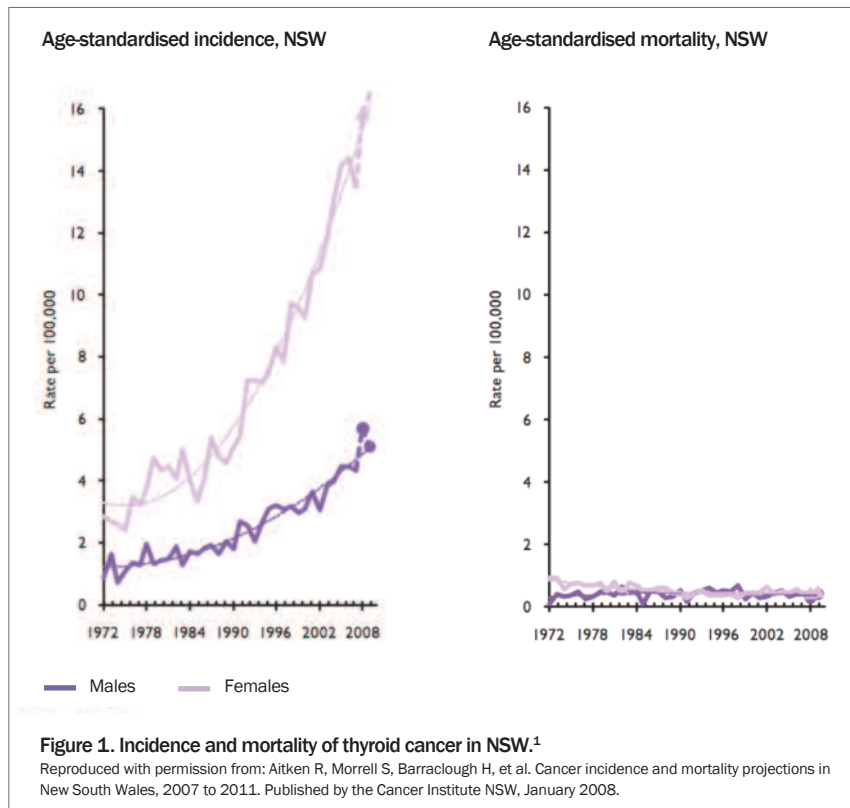
Risk factors

Although there is no distinct cause of PTC, there are a couple of major risk factors. The most well established environmental risk factor is exposure to ionising irradiation. PTC develops as a result of DNA damage by the radiation. The effect is most pronounced when the exposure occurs during childhood or adolescence, and the latency period can range from five to 45 years. History of significant radiation exposure may include:

- living in certain parts of Eastern Europe (specifically Belarus, Ukraine and the nearby region of the Russian Federation) at the time of the Chernobyl nuclear disaster in 1986
- treatment of head and neck malignancies

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Possible features of thyroid cancer⁸

High suspicion

- Family history of thyroid cancer or multiple endocrine neoplasia
- Rapid tumour growth
- Very firm thyroid nodule
- Fixation to adjacent structures
- Vocal cord paralysis (hoarse voice)
- Associated cervical lymphadenopathy
- Distant metastasis (lungs or bones)

Low suspicion

- Age less than 20 years or more than 60 years
- Male sex
- Solitary nodule
- History of head and neck irradiation
- Firm texture or possible fixation of nodule
- Nodule more than 4 cm in diameter and partially cystic
- Compressive symptoms: dysphagia, dysphonia, hoarseness, dyspnoea, cough

Adapted from: Hegedus L, et al. Management of simple nodular goitre: current status and future perspectives. *Endocr Rev* 2003; 24: 102-132.⁸

- treatment of acne by external beam irradiation
- occupational exposure.⁶

No single gene has been shown to cause hereditary PTC; however, epidemiological studies have shown that the risk of developing PTC is five to 10 times higher in patients with a first-degree relative who has the disease compared with the general population.⁷ PTC occurring in the setting of a positive family history tends to follow a more aggressive course, demonstrating features such as early age of presentation, reversed gender distribution, large tumour size, tumour multicentricity, and aggressive tumour biology or variants.⁷ These features are also clues for suspecting such kindred if present in the index case. Until specific gene(s) are identified, a detailed family history is the only way to identify the patients and families at risk.

Presentation and clinical features

Patients with PTC most commonly present with a neck lump. The lump may represent the primary tumour or neck lymph node metastasis. A small PTC nodule is often completely asymptomatic and diagnosed incidentally on imaging or when the thyroid is removed for benign conditions such as multinodular goitre or thyrotoxicity.

A thorough clinical assessment followed by appropriate investigations are required when a patient presents with a neck lump suspected to be thyroid cancer. Clinical features that should raise suspicion of thyroid cancer (not just the papillary subtype) are listed in the box above.⁸ History and examination pertaining to the functional status of the thyroid should also be included in the assessment.

Differential diagnoses for a solitary neck lump include benign thyroid lesion, skin and soft tissue lesion, lymphoma, salivary gland lesion, secondary lymphadenopathy of head and neck malignancies, and paraganglioma.

A clinical assessment of the voice not only provides clues to the potential involvement of the recurrent laryngeal nerve by the lesion, but also serves as a baseline if voice changes occur postoperatively, if management proceeds with a surgical procedure.

Investigations

Investigations of the thyroid are used to determine the likelihood and likely type of malignancy, to define anatomical extent of the disease, and to confirm the thyroid functional status. Thyroid ultrasonography and fine-needle aspirate biopsy (FNAB) of the suspicious nodule are the essential investigations for the diagnosis of PTC. Thyroid function tests may provide background information; however, they do not help in confirming the diagnosis of PTC. Thyroglobulin is a useful tumour marker of recurrent or persistent PTC; however, it too has no role in the initial diagnosis of PTC. Thyroid scintigraphy is only carried out when the TSH level is low, indicating hyperthyroidism, and has no role in the diagnosis of PTC.

Ultrasonography

Ultrasonography is the imaging of choice for the evaluation of the thyroid gland and cervical lymph nodes (Figure 2). It is accessible, inexpensive, noninvasive and well tolerated. Ultrasonic features that

are suspicious for malignancy include microcalcifications, intra-nodular hypervascularity, nodule hypoechogenicity, irregular margins and extracapsular extension. Furthermore, ultrasound-guided FNAB has been shown to produce lower rates of nondiagnostic or false-negative cytology specimens compared with FNAB performed by palpation only. A careful assessment of lateral neck lymph nodes by ultrasound is also required on confirmation of PTC by FNAB cytology.

Fine-needle aspirate biopsy

Clinical assessment, ultrasound and FNAB form the basis of the triple assessment of a thyroid nodule. Any solitary or dominant nodule over 1 cm in size should be put through the rigors of the triple assessment. Small nodules may also require FNAB if there are other clinical or ultrasound features suggestive of malignancy. The Bethesda System for reporting thyroid cytopathology is a widely adopted framework that not only categorises FNAB results but also outlines the usual management procedure within each category (see Table).⁹

The Bethesda System

The categories in the Bethesda System are summarised in the Table.⁹ It is worth noting that this reporting system is not limited to the diagnosis of PTC. Most PTCs can be diagnosed cytologically and therefore would be classified as categories V or VI in the Bethesda System. The category IV lesions that are malignant on histology are not exclusively follicular thyroid cancers, despite the label 'follicular neoplasm' used for this category. Many malignant lesions classified as an initial Bethesda category IV are the follicular variant of PTC.⁹

Laryngoscopy

Preoperative vocal cords assessment by laryngoscopy should be performed to document the baseline functional status of the vocal cords, if a surgical course of action is to be undertaken. Should there be any



Figure 2. Ultrasound of the thyroid.

change to the quality of the patient's voice postoperatively, a repeat laryngoscopy can be compared with the preoperative findings. Laryngoscopy and detailed voice assessment are usually performed by ENT surgeons with an interest in the voice.

Treatment

A multidisciplinary team

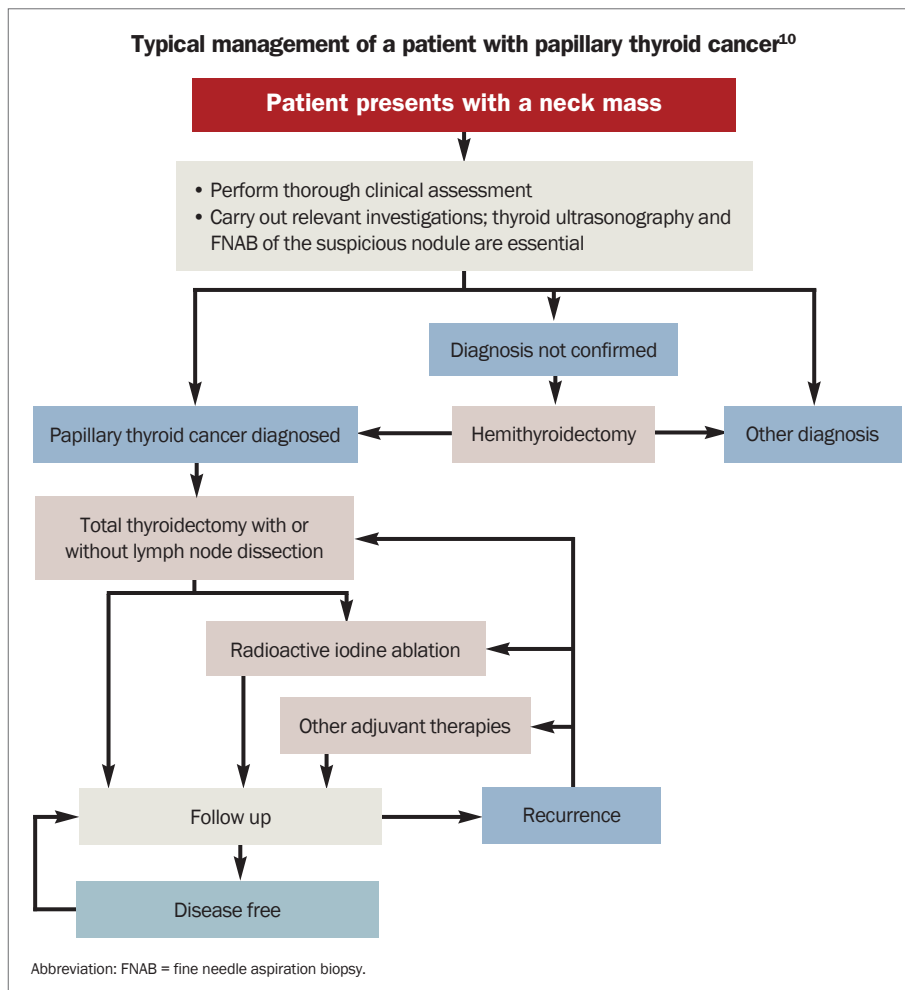
The management of patients with PTC, similar to that of many patients with other cancers, is ideally provided by a multidisciplinary team. The team typically includes an endocrine surgeon, endocrinologist, radiologist, nuclear medicine physician, pathologist, GP and allied health professionals. Concise and accurate communication among the team members, with one of the clinicians acting as the co-ordinator, underpins the effectiveness of the team.

Many hospitals run regular multidisciplinary management meetings where each patient is discussed and a consensus management plan is formulated. This plan is thus documented as part of the meeting records, and distributed to the relevant health professionals involved in the patient's care.

Table. Bethesda System for reporting thyroid cytopathology⁹

Bethesda Category	Category	Risk of malignancy	Usual management
I	Nondiagnostic or unsatisfactory	–	Repeat FNAB with ultrasound
II	Benign	<1%	Clinical follow up or ultrasound in 12 months
III	Atypia of undetermined significance or follicular lesion of undetermined significance	5–10%	Repeat FNAB in three months or refer patient for surgery (hemithyroidectomy)
IV	Follicular neoplasm or suspicious for a follicular neoplasm	20–30%	Refer patient for surgery (hemithyroidectomy)
V	Suspicious for malignancy	50–75%	Refer patient for surgery (hemi or total thyroidectomy)
VI	Malignant	99%	Refer patient for surgery (total thyroidectomy with or without lymph node dissection)

Abbreviation: FNAB = fine needle aspiration biopsy.



Surgery

The initial treatment of PTC is surgery (see the flowchart on this page showing the typical management of a patient with papillary thyroid cancer).¹⁰ Total thyroidectomy is recommended in patients with a Bethesda category V or VI with concurrent and appropriate compartmental lymph node dissection. A diagnostic hemithyroidectomy is recommended for patients with Bethesda category IV and selected patients with Bethesda category III, with completion thyroidectomy as a second-stage procedure if thyroid malignancy is confirmed.^{9,10}

PTC has the propensity to metastasise to regional lymph nodes, and some studies have shown improved disease-free survival at 12 months if prophylactic central lymph node dissection (medial to the sternomastoid muscles) is performed at the time of thyroidectomy.^{11,12} This has been shown to be achievable with minimal morbidity when performed by high volume specialist thyroid surgeons.¹³ However, the role for prophylactic central lymph node dissection is still debated. Conversely, there is agreement that lateral lymph node dissection should only be performed if there is demonstrable lymph node involvement in the lateral neck compartments (deep and lateral to the sternomastoid muscles; see Figure 3).

Radioactive iodine ablation

Radioactive iodine ablation is recommended in most patients with PTC after total thyroidectomy. However, ablation may be omitted in young patients at low risk, such as in those with solitary, small (<1 cm), well differentiated cancers confined to the thyroid with no lymph node metastasis. The recommendation for radioactive iodine and the dosages used are evolving areas of PTC management. There is now strong evidence from multicentre, randomised controlled trials to suggest that low-dose radioactive iodine (1.1 GBq) is as effective as high-dose radioactive iodine (3.7 GBq) in patients with low-risk disease requiring radioactive iodine therapy.^{14,15} Therefore, it is important for the endocrinologist, endocrine surgeon or nuclear medicine physician with an interest in managing thyroid cancer to discuss the adjuvant treatment options with all patients with PTC.¹⁶

Radioactive iodine is administered orally (as a capsule), which is then taken up by any residual thyroid epithelial cells or PTC cells. The uptake of radio-active iodine by these cells is further enhanced by having a high thyroid-stimulating hormone (TSH) level at the time of administration, either by rendering the patient hypothyroid with thyroxine

withdrawal or by injection of recombinant human TSH. The efficacy of radioactive iodine ablation under recombinant human TSH stimulation has been confirmed in large randomised trials.¹⁴ Thyroxine withdrawal and use of recombinant human TSH are usually arranged by the endocrinologist or nuclear medicine physician before the patient is admitted for radioactive iodine. The GP may assist in monitoring thyroid function and compliance during the withdrawal period, or give the recombinant human TSH injection to the patient immediately before radioactive iodine administration. Once radioactive iodine is administered, the patient is kept in an isolation room for one to three days until the radiation levels emitted from the patient are at a safe level for discharge. Some patients may find this process of isolation psychologically challenging, and appropriate counselling may reduce the level of associated anxiety.

TSH suppression therapy to decrease recurrence

As many differentiated PTCs express TSH receptors on the cell surface and respond to TSH stimulation with increasing cell growth, TSH suppression therapy has been shown to decrease the risk of recurrence. Supraphysiological doses of thyroxine are used to maintain TSH level



Figure 3. Central and lateral lymph node dissections of the neck.

Abbreviations: CND = central node dissection; LND = lateral node dissection.

to below 0.1 mIU/L in patients with PTC, except in those with a very low risk of disease recurrence.¹⁰ The period and degree of TSH suppression vary between patients depending on the assessed risk of recurrence. Therefore, TSH suppression therapy is best guided by specialists.

Follow up

In a patient who has undergone total thyroidectomy and successful radioactive iodine ablation for PTC, disease-free status is defined by:

- no clinical evidence of tumour
- no evidence of tumour on imaging (scintigraphy and ultrasound), and
- undetectable serum thyroglobulin levels during TSH suppression and stimulation.¹⁰

The main modalities in following up these patients long term are therefore clinical examination, neck ultrasound, diagnostic thyroid scintigraphy and measurement of thyroglobulin levels.

Thyroglobulin measurements can be either 'stimulated' or 'unstimulated'. A stimulated thyroglobulin level is more sensitive for detection of recurrent disease, and measurement is taken with either thyroxine withdrawal or recombinant human TSH administration. Unstimulated thyroglobulin level is measured when the patient is euthyroid or during TSH suppression. All thyroglobulin results need to be interpreted with knowledge of a concomitant measurement of thyroglobulin antibodies. The presence of thyroglobulin antibodies, which occurs in approximately 25% of patients with thyroid cancer and 10% of the general population, renders the thyroglobulin results unreliable.¹⁰ Therefore, it is routine practice to always measure thyroglobulin and thyroglobulin antibody levels simultaneously.

In very low-risk patients who have not undergone radioactive iodine ablation, follow up may be more challenging as thyroglobulin levels and thyroid scintigraphy will simply reflect remnant thyroid tissue rather than recurrent PTC. However, in some instances, a

rising trend of thyroglobulin levels may still be an indication of disease recurrence.

Initial follow up

Stimulated thyroglobulin level and diagnostic radioactive iodine scan should be obtained six to 12 months after radioactive iodine ablation to confirm the absence of disease. If either of these is suggestive of persistent disease, appropriate imaging should be used to localise remaining disease. The modality of further treatment depends on the nature and location of the disease.

Long-term follow up

If the patient is disease free at the initial reassessment at six to 12 months, a yearly clinical examination, with six- to 12-monthly measurements of serum thyroglobulin levels, should be performed following total thyroidectomy and radioactive iodine ablation. Ultrasound should be the main mode of surveillance in patients who have had a less than total thyroidectomy or those who have not had radioactive iodine ablation.

As part of the long-term follow up, thyroid function should be monitored to ensure adequate thyroxine replacement or TSH suppression as appropriate. The precise role of each physician during the follow-up period depends on local practice and the dynamics within the team. However, redundant follow-up appointments should be avoided by efficient communications among physicians.

Other adjuvant therapies for PTC

In iodine-avid PTC, even in the setting of recurrence, the primary modalities of treatment are still surgery and radioactive iodine. In rare cases, external beam radiotherapy may be used as an adjunct for locally advanced PTC, or for metastases that no longer take up radioactive iodine. Traditional chemotherapy has virtually no role in the management of PTC. However, in patients with radioactive iodine refractory metastases, targeted therapies are an emerging option under trial conditions. Such therapies include tyrosine kinase inhibitors and BRAF kinase inhibitors.¹⁷

Conclusion

PTC is the most common thyroid malignancy. Although surgery is the main treatment modality, it is often supplemented by radioactive iodine ablation. Radioactive iodine not only lowers the risk of local recurrence, it also simplifies surveillance with thyroglobulin measurements and diagnostic scans. The management of PTC is best undertaken with a multidisciplinary team approach. Despite the need for specialist management and follow up, the supportive role of the GP from the initial diagnosis to the long-term follow up of these patients should not be underestimated.

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COMPETING INTERESTS: None.

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A list of references is available on request to the editorial office.

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