

CME Article

Thyroid cancer: diagnosis and management

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Thyroid cancer is the ninth most common cancer in women in Singapore. Despite an increasing incidence of thyroid cancer in the last few decades, survival has improved due to a combination of early cytological diagnosis, low-morbidity total thyroidectomy, and

postoperative radioactive iodine therapy. Thyroid cancer is one of the most curable forms of cancer. This article provides an overview of thyroid cancer and future directions in its diagnosis and treatment.

INCIDENCE

According to the Singapore Cancer Registry, thyroid cancer is the ninth and fifteenth most common cancer in women and men, respectively.⁽¹⁾ Thyroid cancer is 3.5 times more common in women than men; the reason is not known but it parallels the higher incidence of thyroid nodules in women.⁽²⁾ The age-specific incidence of thyroid cancer rises with age; however, the most common age group falls between 25 and 50 years of age, comprising about 70% of cancers. There is no predominance in any race, as reflected by the ethnic spread of thyroid cancer in 79% Chinese, 12% Malay, and 7% Indian.

The age-standardised rate (ASR) of thyroid cancer in Singapore is 8.5 per 100,000 per year; in comparison, the rate is 10.5 per 100,000 per year in the United States and 8.5 per 100,000 per year in Australia. The annual ASR has risen for females, from 4.3 per 100,000 (1968–1972) to 6.5 per 100,000 (1998–2002), an increase of about 50%, but rates appear to be fairly stable for males.⁽¹⁾ Why there is a discrepancy in gender rates and whether there is a true increase in incidence or a higher early detection rate, e.g. by thyroid ultrasound, is difficult to know. Despite this rise (in females), mortality rates have remained low and do not feature in the top 15 cancer deaths in either men or women. The annual ASR for thyroid cancer mortality (1993–1997) is 0.4 per 100,000 for males and 0.8 per 100,000 for females; so for every 100 patients detected with thyroid cancer, about 14 patients die. In contrast, the mortality rates for lung and colon cancers are about 90 and 60 patients per 100 patients, respectively.⁽¹⁾

AETIOLOGY AND PATHOLOGY

Thyroid cancer arises from thyroid follicular cells in thyroid follicles. The pathogenesis of most thyroid cancers remains largely unknown; however, certain risk factors have been identified. One factor is its higher prevalence in endemic areas where dietary iodine is deficient, which also leads to a higher prevalence of benign nodular thyroid disease. The second factor is radiation exposure. External beam radiation used in the 1950's to treat benign childhood conditions, such as enlarged thymus, tinea capitis, acne, or tonsillitis, resulted in an increased relative risk of thyroid cancer of between 4 and 15 times.⁽³⁾ Equally potent was the nuclear exposure from the atomic bombs in Hiroshima and Nagasaki in 1945 and the Chernobyl nuclear plant accident in 1986, where cases of childhood thyroid cancer in Belarus, a nearby town to Chernobyl, had increased alarmingly from five cases in 1986 to more than 60 cases in 1993.⁽⁴⁾ In Singapore, the groups of factors described above are not major factors; in fact, close to 100% of patients with thyroid cancer here do not have an identifiable risk factor.

Malignant transformations of follicular epithelial cells into one of two forms of “differentiated” thyroid cancers can occur — papillary thyroid cancer (PTC) or follicular thyroid cancer and Hurthle cell cancer (FTC) — but why one form predominates over the other is not fully understood. PTC and FTC comprise 80% and 15% of all thyroid cancers, respectively. Thus, these two types represent the vast majority of thyroid cancers.

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Some of their behavioural characteristics are outlined in Table I. Common to both cancers are their abilities to take up iodine and to secrete thyroglobulin (Tg), a protein in colloid that binds and stores iodide complexes. Both cancers exhibit histological subtypes, some of which behave more aggressively, e.g. tall cell in PTC, and widely-invasive cancers in FTC. Both PTC and FTC have the ability to dedifferentiate into a poorly differentiated, or anaplastic thyroid cancer (ATC), with a transformation of behaviour into an aggressive, rapidly growing cancer that invades locally. In general, these cancers occur in older patients, are resistant to therapy and results in early death.

A fourth category of thyroid cancer, the medullary thyroid cancer (MTC), arises not from follicular cells but from parafollicular cells (C cells). The behaviour of MTC, is therefore different from that of PTC, FTC, and ATC — they do not take up iodine but secrete calcitonin. Also, in contrast to PTC and FTC, up to a third of MTC are familial while the rest develop sporadically.⁽⁵⁾ This autosomal inheritance can result in a combination of MTC with other diseases in multiple endocrine neoplasia syndromes (MEN 2a or 2b), characterised by pheochromocytoma, parathyroid neoplasia, or multiple neuromas. The genetic basis of inheritable MTC is explained by a germline mutation in the RET (REarranged during Transfection) proto-oncogene on chromosome 10 that encodes a member of the tyrosine kinase receptor, leading to medullary cell hyperplasia and eventually neoplastic transformation.⁽⁶⁾

Not all thyroid cancers and their behaviours can be explained by such molecular studies; however, some discoveries cast light on the development of thyroid cancers. For example, RET/PTC3 rearrangements and recently B type Raf kinase activating mutations have been identified in PTC, and overexpression of the p53 gene has resulted in more aggressive tumours and anaplastic cancers.⁽⁷⁾

Table I. Characteristics of different types of thyroid cancers.

Cancer type	Proportion of cancers (%)	Characteristics	Other features	Ten-year survival (%)
Papillary cancer	80	Multifocal foci (25%) Lymph node spread (66%)	Secretes Tg RAI uptake	> 90
Follicular cancer	15	Unifocal tumours Metastatic spread to lungs, bone (25%)	Secretes Tg RAI uptake	80–90
Medullary cancer	2	Familial inheritance (20%) Both local and metastatic spread	Secretes calcitonin No RAI uptake	70–80
Anaplastic cancer	2	Widespread local invasion and metastases	Poor RAI uptake	0
Others, e.g. lymphoma, metastatic cancers	1			

Tg = Thyroglobulin; RAI = Radioactive iodine

PRESENTATION

The risk of cancer in a solitary thyroid nodule is about 10%, and a similar malignancy rate is found in a dominant nodule of a multinodular goitre. However, in more than 80% of cases, thyroid cancer presents as a solitary thyroid nodule. A rapidly growing lump is suggestive of a neoplasm; the history taking should also include family history or previous exposure to ionising radiation. A malignant nodule typically feels firm to hard within the thyroid lobe. Occasionally, the lump may not be obvious if located in a posterior or inferior position. In such situations, ultrasonography (US) will help delineate the nodule. There is no screening programme for thyroid cancer; however, the neck should be examined for any goitre during routine health examination.

Findings that suggest more aggressive behaviour include: (a) fixity of the nodule, which indicates possible invasion of local structures, e.g. muscle or the aerodigestive tract; (b) recent hoarseness that indicates recurrent laryngeal involvement and vocal cord paralysis, or laryngeal invasion; (c) encompassed jugular veins or retrosternal extension resulting in prominent veins and congestion; (d) cervical lymphadenopathy from regional metastases (particularly in PTC); and (e) distant metastases to bone, lung, or brain. Each situation requires a different operative approach and management in addition to thyroidectomy. Rarely do distant metastases present as the first sign of thyroid cancer, although metastatic follicular cancers to bone in elderly patients have been described to present earlier and more prominently than the goitre itself.⁽⁸⁾ Most patients with thyroid cancer are euthyroid, but thyrotoxicosis can rarely occur due to toxic neoplasms or from thyroid gland destruction with the subsequent release of thyroid hormones.⁽⁹⁾ Clinical examination alone is not accurate in determining the type of thyroid cancer pathology.

DIAGNOSTIC TESTS

The main aim in evaluating a solitary thyroid nodule or a prominent nodule of a multinodular goitre is to determine the presence or absence of malignancy. The best preoperative test available today is the fine-needle aspiration cytology (FNAC), which can be performed in the clinician's office. It is a safe, simple and well-tolerated test that provides rapid and accurate results. Provided the cytology yield is good, the sensitivity and specificity of the test for malignancy is high and ranges from 80% to 95%;⁽¹⁰⁾ it is particularly accurate in the diagnosis of PTC (Fig. 1). However, its limitation is in the assessment of follicular neoplasms because FTC cannot be distinguished from benign follicular adenomas — capsular and vascular invasion of malignancy is not demonstrated on cytology but on histology (i.e. surgery is required). The cytology report in such a situation is “suspicious for malignancy”.

FNAC supersedes two previous methods of assessing malignancy — nuclear thyroid scan that detects “cold” or “hot” nodules but has an overall accuracy less than FNAC (malignant nodules are frequently “cold” on isotope scan), and intraoperative frozen section, which is now used less frequently since the implementation of FNAC. FNAC can also be used to evaluate enlarged cervical lymph nodes for recurrent or metastatic thyroid cancer. Also, for non-palpable lumps detected incidentally on US, US-guided FNAC can be performed for lesions larger than 1–1.5 cm in diameter.⁽¹¹⁾ Patients with malignant or suspicious diagnoses should undergo surgery. To improve on the already high yield of FNAC, perhaps in the future, cytology could be combined with molecular analysis of follicular tumours.⁽¹²⁾

All patients should have their thyroid function tests checked for hypo- or hyperthyroidism. Thyroid US is useful in identifying features suspicious, although not sensitive or specific, for malignancy, namely: tumour microcalcification, thyroid capsule that is breached by the cancer, tumour vascularity, and cervical lymphadenopathy (Fig. 2). Computed tomography is performed to define substernal extension or local invasion. Rarely, median sternotomy is required for a cancer that extends inferiorly into the anterior mediastinum. If vocal cord paresis due to recurrent laryngeal nerve involvement is suspected, direct laryngoscopy should be performed for documentation.

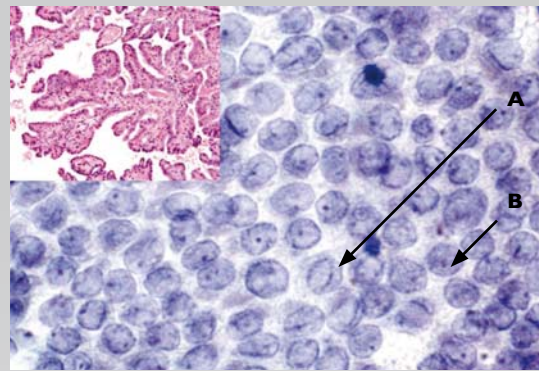


Fig. 1 Papillary thyroid cancer (PTC) cytology shows characteristic microscopic features of intranuclear grooves (A) and intranuclear inclusions (B). Inset shows papillary appearance of PTC on histology.

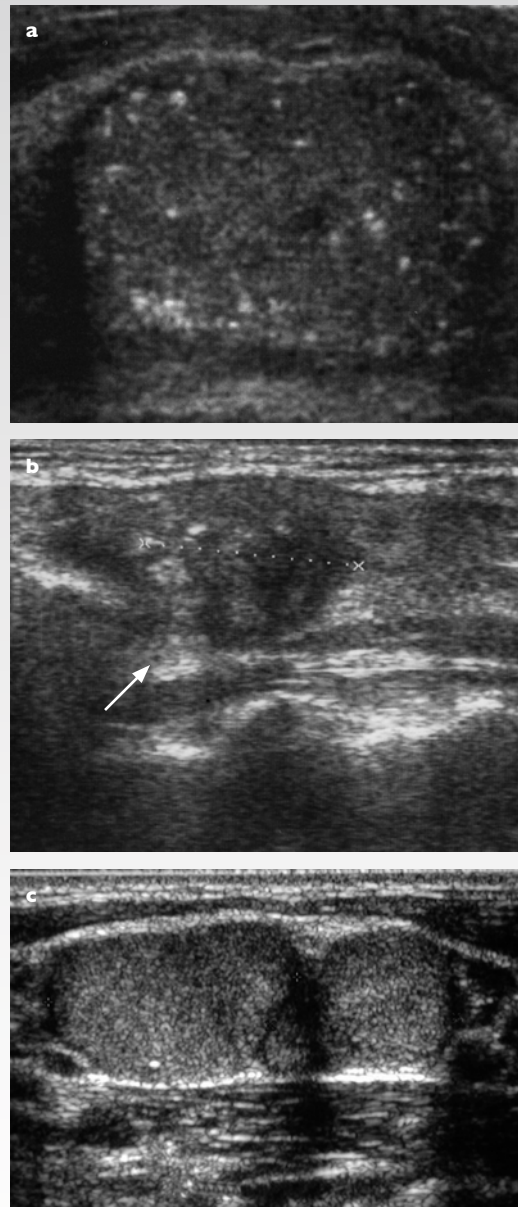


Fig. 2 Thyroid US images show (a) PTC with tumour microcalcification; (b) thyroid capsular breach by tumour (indicated by arrow); and (c) cervical lymphadenopathy.

THYROIDECTOMY

Thyroid cancer is operable in more than 90% of cases and thyroidectomy remains the main effective modality of therapy. The only exception is in ATC where extensive invasion of adjacent structures make complete resection impossible. For PTC, FTC, and MTC, thyroidectomy removes the tumour, thyroid gland, and adjacent lymph nodes in the paratracheal region (Fig. 3). There has been controversy over the extent of initial surgery for thyroid cancer, especially for PTC and FTC which comprise the majority of cancers. Evidence (levels II to III – non-randomised, well-designed studies) suggests that lesions with the best prognosis — those under 1 to 1.5 cm with no evidence of local or distant metastases (Tumour, node, metastases [TNM] stage, T1N0M0) — can probably be treated with hemithyroidectomy (total lobectomy) alone,⁽¹³⁾ but not partial lobectomy because

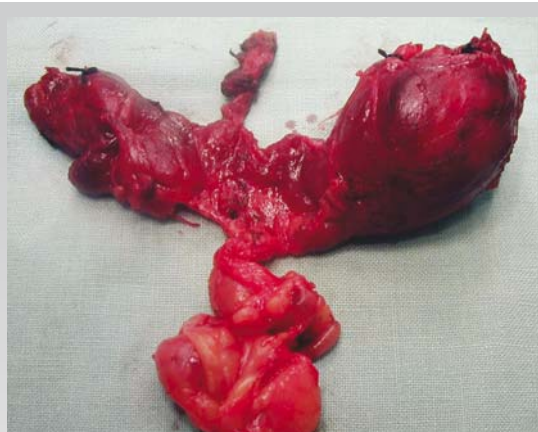
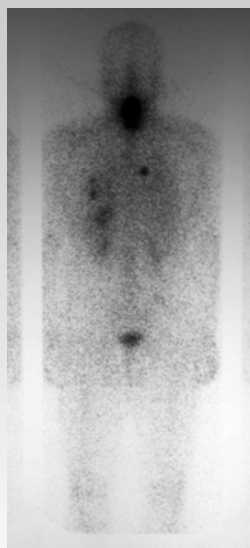


Fig. 3 Photograph of a total thyroidectomy specimen with cancer in the left thyroid lobe, and paratracheal lymph nodes (inferior to thyroid gland). The pyramidal lobe is attached to the upper part of the right thyroid lobe.

of the high risk of cancer recurrence. Because most cancers at detection are larger than 1.5 cm, total thyroidectomy is the preferred choice for two main reasons: (a) it removes all local disease, especially multifocal microcancers that occur in about 25% of PTC, even in the contralateral lobe, and (b) it improves surveillance for and treatment of recurrent or metastatic cancers through radioactive ¹³¹-iodine (RAI) therapy and serum thyroglobulin measurement.

Important aspects of total thyroidectomy are: (a) outcome is dependent upon adequate resection. In a group of 700 patients with PTC and FTC and tumours larger than 1 cm, with a median follow-up period of ten years, total thyroidectomy improved outcome and reduced the risk of cancer recurrence and death by 2.5-fold and 2.2-fold, respectively, compared to subtotal resection.⁽¹⁴⁾ For MTC, initial thorough surgery, i.e. total thyroidectomy, is also particularly essential because no adjuvant treatment such as RI2 can be used. And, (b) it is vital to minimise complications of thyroidectomy, such as permanent recurrent laryngeal nerve palsy or hypoparathyroidism, which when performed by experienced thyroid surgeons should not exceed an overall rate of 2%–3%.⁽¹⁵⁾

Other forms of surgery include modified radical neck dissection (cervical lymphadenectomy) for metastatic lymph nodes, and rarely, radical resection for advanced cancer invading the aerodigestive tract, for example, tracheal resection, laryngectomy.⁽¹⁶⁾ Hospitalisation for such extensive procedures are more prolonged than for routine total thyroidectomy where patients stay an average of about two to three days postoperatively.



RADIOACTIVE IODINE THERAPY AND THYROID HORMONE REPLACEMENT

Iodine is taken up into the thyroid follicular cells, and not other cells in the body, by an active transport process. Because of this unique characteristic, radiolabelled isotopes such as ¹³¹-iodine can be used not only to scan for but also to effectively treat metastases. PTC and FTC take up iodine, unlike MTC, and a post-therapy scan detects residual thyroid tissue in the neck, metastatic nodes, and distant metastases (Fig. 4).

Postoperative RAI treatment is indicated for patients with more advanced disease, i.e., large papillary or follicular cancers (> 2 cm) or with evidence of extrathyroidal extension or metastatic disease. A large therapy dose (30–200 mCi ¹³¹-iodine) is effective in ablating residual or metastatic disease. For RAI to be effective, total thyroidectomy and a high thyroid stimulating hormone (TSH) level, usually over 25 mU/L, is essential for follicular cells to take up iodine. This high level of TSH is achieved by one of three ways in preparation for RAI treatment and scan — withholding of L-thyroxine for 4–6 weeks after surgery; giving liothyronine (T3) for four weeks and then stopping the medication for two weeks; or giving injectable recombinant human

Fig. 4 RAI scan shows pulmonary metastases from follicular thyroid cancer, while chest radiograph failed to detect the metastases (uptake in the neck shows residual thyroid tissue that was ablated with RAI).

TSH (rhTSH) without the withdrawal of thyroid hormone, thus avoiding the discomfort of transient hypothyroidism. The latter method may become more established in the future if trials determine its efficacy in the detection and treatment phases with RAI therapy and Tg measurement.⁽¹⁷⁾

The treatment scans are repeated at intervals of 6–12 months until no further uptake is observed. In a study of more than 1,300 patients over a 40-year period, RAI therapy reduced the likelihood of cancer recurrence and death by at least half compared to those not receiving radioiodine.⁽¹⁸⁾ Cumulative high doses (above 500 mCi) of RAI, however, may put patients at risk of pancytopenia or leukaemia,⁽¹⁹⁾ and RAI is contraindicated in pregnancy. After RAI treatment, the patient is then maintained on replacement therapy with levothyroxine, 2–2.5 mcg/kg body weight to be taken daily for life, to suppress serum TSH to undetectable levels (< 0.1 mU/L) without making the patient overtly thyrotoxic. A high TSH level stimulates thyroid cancer cell growth.

External beam radiotherapy has a limited role to play in patients with thyroid cancer. Indications for radiotherapy include locally invasive and nonresectable disease in the neck, or painful bone metastases. Chemotherapy also has a limited role but may be used as palliative treatment in anaplastic cancers.

FOLLOW-UP

Follow-up surveillance includes regular neck examination for recurrent masses in the neck or cervical lymphadenopathy, and if detected, confirmed on ultrasound and FNAC. Serum thyroglobulin, a valuable tumour marker for PTC and FTC, when measured every six-monthly to yearly, is a sensitive and cost-effective method to identify patients with residual disease. After total thyroidectomy and RAI therapy, the Tg level should be less than 3–5 ng/ml; a high or increasing level indicates persistent or recurrent disease that should be investigated and treated with RAI and/or surgery. Measurement of Tg is inaccurate in the presence of circulating autoantibodies to Tg (Tg Ab). If the lesions do not take up RAI, i.e. detectable Tg but negative whole body RAI imaging, which occurs in less than 10%–15% of cases, then positron emission tomography (PET) is useful for tumour localisation.⁽²⁰⁾ In MTC, the marker for recurrence is serum calcitonin and all patients with MTC should be screened for RET proto-oncogene mutation, and if positive, their families should similarly be screened for the carrier state, so that early diagnosis and treatment can be instituted, leading to improved survival.⁽⁵⁾

PROGNOSIS

For both PTC and FTC, good prognosis is dependent on several factors, namely: (a) age younger than 40–45 years, (b) tumour size smaller than 1.5 cm, (c) absence of extra-thyroidal invasion, and (d) absence of metastases, in a study of 1,500 patients followed over an average of 16 years.⁽²¹⁾ Additionally, outcome is also dependent upon adequate therapy; survival is improved following (a) total or near-total thyroidectomy compared to lesser surgery, and (b) RAI therapy compared to those not receiving RAI.⁽¹⁸⁾ Interestingly in PTC, cervical lymph node metastases found at initial surgery were associated with higher recurrence rates but not higher mortality rates, unlike FTC and MTC where nodal metastases signified a worse prognosis than absent nodes.

The TNM system of the International Union Against Cancer and the American Joint Committee on Cancer is used for staging thyroid cancer. The cause-specific mortality rate in PTC and FTC were: Stage 1, 1.7%; Stage 2, 15.8%; Stage 3, 30%; and Stage 4, 60.9%, with an overall mortality rate of 8.4%.⁽¹⁴⁾ In other words, more than 90% of patients survive longer than 10–20 years, making it one of the most curable cancers. The high rate of survival reflects the concentrated pool of patients (> 80%) in Stages 1 and 2. Other risk-stratification systems such as the AMES (patient age, metastases, extrathyroid invasion, and tumour size) and MACIS (metastases, age, completeness of resection, local invasion, and size) have classified patients into high- or low-risk for cancer recurrence and death in order to guide treatment strategies.⁽²²⁾ The cause-specific causes of death in thyroid cancer are local invasion in a third of cases, distant metastases in a third, and both local and metastatic disease in the remaining third of cases.⁽²³⁾

SUMMARY

Papillary and follicular cancers occur in more than 95% of thyroid cancers, and much of the discussion is applicable to this group of cancers. The combination of total thyroidectomy, followed by RAI therapy, and thyroid hormone replacement therapy to suppress TSH, works effectively in most cases to achieve a high and prolonged survival rate. New diagnostic approaches such as rhTSH and PET have recently emerged to add to the growing multidisciplinary field in the management of this disease.

ACKNOWLEDGEMENT

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SINGAPORE MEDICAL COUNCIL CATEGORY 3B CME PROGRAMME
Multiple Choice Questions (Code SMJ 200702A)

	True	False
Question 1. The following describe thyroid cancer pathology:		
(a) Papillary thyroid cancer is the most common form and has a propensity to spread to regional lymph nodes.	<input type="checkbox"/>	<input type="checkbox"/>
(b) Anaplastic cancer can arise from long-standing goitre and is often non-resectable.	<input type="checkbox"/>	<input type="checkbox"/>
(c) Medullary thyroid cancer is not common and can be familial.	<input type="checkbox"/>	<input type="checkbox"/>
(d) Papillary thyroid cancer has the best prognosis and is caused by radiation in most cases.	<input type="checkbox"/>	<input type="checkbox"/>
Question 2. The following diagnostic tests are performed for thyroid cancer:		
(a) Fine-needle aspiration cytology is the most accurate of all tests in detecting thyroid cancer.	<input type="checkbox"/>	<input type="checkbox"/>
(b) Ultrasound-guided fine-needle aspiration cytology cannot be performed for lesions smaller than 1.5 cm.	<input type="checkbox"/>	<input type="checkbox"/>
(c) Ultrasound that shows fine microcalcification in a nodule is diagnostic of a benign nodule.	<input type="checkbox"/>	<input type="checkbox"/>
(d) Ultrasound of a thyroid nodule and an enlarged cervical lymph node is highly suspicious of papillary thyroid cancer.	<input type="checkbox"/>	<input type="checkbox"/>
Question 3. The following statements describe treatment of thyroid cancer:		
(a) Partial lobectomy is an adequate treatment for papillary thyroid cancer.	<input type="checkbox"/>	<input type="checkbox"/>
(b) Total thyroidectomy enables accurate measurement of serum thyroglobulin as surveillance for thyroid cancer recurrence.	<input type="checkbox"/>	<input type="checkbox"/>
(c) Complications of total thyroidectomy include recurrent laryngeal nerve palsy and hypoparathyroidism and should be less than 5%.	<input type="checkbox"/>	<input type="checkbox"/>
(d) Radioactive iodine therapy can be used after hemithyroidectomy to detect metastases.	<input type="checkbox"/>	<input type="checkbox"/>
Question 4. The following statements describe ways to achieve a high level of thyroid stimulating hormone (TSH) in preparation for radioactive iodine therapy:		
(a) Withholding L-thyroxine for 6 weeks.	<input type="checkbox"/>	<input type="checkbox"/>
(b) Giving liothyronine for four weeks and stopping for two weeks.	<input type="checkbox"/>	<input type="checkbox"/>
(c) Giving injectable recombinant human TSH together with L-thyroxine withdrawal.	<input type="checkbox"/>	<input type="checkbox"/>
(d) Ingesting TSH 2 weeks beforehand.	<input type="checkbox"/>	<input type="checkbox"/>
Question 5. The following statements describe treatment and follow-up of thyroid cancer:		
(a) Radioactive iodine therapy may not be necessarily given if the tumour is smaller than 2 cm.	<input type="checkbox"/>	<input type="checkbox"/>
(b) Replacement thyroxine, to be taken life-long after total thyroidectomy, should be given at a dose that suppresses the thyroid stimulating hormone level to more than 1.0 mU/L.	<input type="checkbox"/>	<input type="checkbox"/>
(c) During follow-up, the appropriate tests to perform if a cervical lymph node is palpated are fine-needle aspiration cytology and ultrasound.	<input type="checkbox"/>	<input type="checkbox"/>
(d) The overall mortality rate of thyroid cancer is less than 15% and is one of the most curable forms of cancer.	<input type="checkbox"/>	<input type="checkbox"/>

Doctor's particulars:

Name in full: _____
MCR number: _____ Specialty: _____
Email address: _____

SUBMISSION INSTRUCTIONS:

(1) Log on at the SMJ website: www.sma.org.sg/cme/smj and select the appropriate set of questions. (2) Select your answers and provide your name, email address and MCR number. Click on "Submit answers" to submit.

RESULTS:

(1) Answers will be published in the SMJ April 2007 issue. (2) The MCR numbers of successful candidates will be posted online at www.sma.org.sg/cme/smj by 15 April 2007. (3) All online submissions will receive an automatic email acknowledgment. (4) Passing mark is 60%. No mark will be deducted for incorrect answers. (5) The SMJ editorial office will submit the list of successful candidates to the Singapore Medical Council.

Deadline for submission: (February 2007 SMJ 3B CME programme): 12 noon, 25 March 2007