The management of thyroid cancer in adults: a review of new guidelines

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ABSTRACT – The management of thyroid cancer has been facilitated by the recent publication of the *Guidelines for the management of thyroid cancer in adults* under the auspices of the British Thyroid Association and the Royal College of Physicians. This is a consensus document that has been developed by a number of key investigators in the field. The central tenet of the guidelines is that thyroid cancer is a disease which requires specialist care from a multidisciplinary team, including an endocrinologist, nuclear medicine physician, thyroid surgeon and endocrine pathologist. The guidelines are comprehensive and detailed, covering differentiated (papillary and follicular) and medullary cancer of the thyroid. They have been written in sections aimed at thyroid cancer specialists, primary care physicians, patients and their families. The guidelines are greatly welcomed and represent a major step forwards in the co-ordination of specialist care for thyroid cancer in the UK.

KEY WORDS: follicular carcinoma of thyroid, medullary carcinoma of thyroid, papillary carcinoma of thyroid, thyroid cancer

Although rare, thyroid cancer is the commonest cause of endocrine cancer. It accounts for about 1% of all malignant disease. In contrast, thyroid nodules occur in 5–10% of the population. The timely identification of malignant disease renders this condition curable in most cases.

The incidence shows a geographical variation and is more common in women (2.4/100,000 UK) than in men (0.9/100,000 UK). The median age at diagnosis is 45–50 years. Neoplasms of the thyroid follicular cell encompass a wide spectrum of phenotypes, from benign follicular adenomas to follicular, papillary and anaplastic carcinomas. The prevalence of follicular carcinoma and anaplastic cancers depends partly on the iodine intake in particular geographic areas, being more common in areas of iodine deficiency[1]. In iodine sufficient areas, papillary carcinomas account for about 80% of thyroid tumours. In areas of iodine deficiency, as the prevalence of follicular carcinoma rises, the prevalence of papillary carcinoma falls to 35–55%. Previous neck irradiation in childhood and nuclear fall-out are well recognised predisposing factors to the development of papillary carcinoma[2]. Discrete tumours of less than 1cm diameter are associated with a 10-year survival of over 90%. The survival falls with increasing tumour size, metastatic spread and age (>40 years). Even so, 10-year survival in patients below 40 years with metastatic disease can be up to 80%[3]. There are two major reasons for the favourable prognosis: first, thyroid cancer tends to be an indolent disease and, secondly, thyroid cancer cells usually retain a degree of differentiation in that they are able to take up iodide and are thus amenable to radio-iodine therapy. This means that even metastatic disease remains eminently treatable.

Guidelines for the management of thyroid cancer in adults

The management of thyroid cancer has been greatly facilitated by the publication of *Guidelines for the management of thyroid cancer in adults* under the auspices of the British Thyroid Association[4]. (Similar guidelines have been published in the USA[5].) This detailed consensus document has been developed by a number of key opinion leaders in the field, including endocrinologists, surgeons, pathologists, radiologists, biochemists and patient advocates. Differentiated (papillary and follicular) and medullary cell cancer of the thyroid (MCT) are covered, and all aspects of patient management discussed. From the outset, the guidelines emphasise the central role of the specialist multidisciplinary team in the management of thyroid cancer. This team should comprise an endocrinologist, thyroid surgeon, nuclear medicine physician, pathologist, radiologist, biochemist and, in most cases, a specialist thyroid cancer nurse.

The guidelines provide details of the pre-operative, operative and postoperative management of thyroid cancer patients, and also discuss the management of thyroid cancer in pregnancy.

The role of the primary care physician

A particularly useful section concentrates on the role of the primary care physician in the assessment of a thyroid nodule. All patients should be referred to a

specialist thyroid clinic. Indications for early referral are:

- a thyroid nodule in a very young (<10 years) or elderly (>65 years) patient
- a previous history of exposure to radiation
- a positive family history
- associated symptoms/signs, particularly a fixed, non-mobile nodule/mass, hoarseness (recurrent laryngeal nerve involvement), cervical lymphadenopathy, stridor, bone pain.

Patients with euthyroidism may have malignant disease. Those with hypo- or hyperthyroidism can usually have a routine referral to the thyroid clinic.

Key Points

Thyroid cancer is the commonest form of endocrine cancer, accounting for about 1% of malignant disease

Thyroid nodules are common, occurring in 5–10% of the population. The majority are benign. All thyroid nodules should be examined initially by fine needle aspiration cytology

Thyroid cancer should be managed by a specialist multidisciplinary team

Timely identification and appropriate management render thyroid cancer curable in the majority of patients

Laboratory tests

Serum calcitonin may be measured if there is a suspicion of MCT. All patients referred with thyroid nodules should undergo fine needle aspiration cytology (FNAC). This should be carried out only by an experienced operator in conjunction with a cytologist with a particular interest in thyroid disease. If the pathology shows benign results, the biopsy should be repeated 3–6 months later. Indeterminate or inadequate cytology should result in repeat FNAC. Positive cytology indicates immediate referral for surgery.

There is a caveat: follicular neoplasms cannot be differentiated into benign or malignant without formal histological examination. For this reason, follicular neoplasms are initially treated by lobectomy, followed by completion thyroidectomy in the event of malignant disease.

Papillary and follicular thyroid cancer

Treatment of papillary and follicular thyroid cancer is total thyroidectomy, together with removal of all lymph nodes in the central compartment of the neck. Lymph nodes lying along the carotid sheath and internal jugular vein are also removed if there is evidence of disease involvement. Small tumours (<1 cm diameter) may be treated by lobectomy, followed by suppressive thyroxine (T4) therapy. This has the disadvantage that it renders serum thyroglobulin redundant as a means of monitoring the patient for recurrent disease (see below). Because of this, some centres still use the conventional approach to management for all patients, regardless of prognostic grouping.

Radio-iodine therapy

Patients who have undergone total thyroidectomy are usually referred for ablative ^{131}I therapy to destroy any remaining normal and malignant thyroid cells. Ablative radiotherapy reduces local recurrence and improves survival[3]. Patients may remain off thyroid hormone replacement and receive ^{131}I treatment 3–4 weeks postoperatively. More frequently, however, the radio-iodine treatment is delayed for 2–3 months, during which time patients are treated with triiodothyronine (T3) or T4. T3 is usually the treatment of choice because it has a shorter half-life than T4. It is stopped about 14 days before ^{131}I treatment. T4 needs to be stopped for four weeks. This will result in elevation of serum thyroid-stimulating hormone (TSH) (should be >30 mU/l) which facilitates the uptake of radio-iodine into thyroid tissue.

Radio-iodine treatment can be given only in specialised centres which form part of the multidisciplinary team. Patients are treated in screened rooms specially designed for radiotherapy. Most patients are admitted for 3–5 days with a postablation scan normally carried out prior to discharge to assess whether or not there is any residual thyroid uptake either in the thyroid bed or elsewhere. Patients are then maintained on a suppressive dose of T4 (TSH <0.15 mU/l) to prevent TSH stimulation of any recalcitrant cells which have escaped the previous treatment.

The guidelines recommend that a diagnostic radio-iodine scan should be carried out about six months following ^{131}I ablation. As for the first scan, the patient either stops T4 for four weeks or switches to T3, which is stopped about 14 days before the scan. Serum thyroglobulin is measured at the same time. In the absence of residual thyroid tissue, thyroglobulin levels should remain undetectable. Measurable thyroglobulin levels in the absence of antibodies indicate the likelihood of residual or recurrent disease. Uptake of radio-iodine and/or elevated serum thyroglobulin are indications for a further treatment dose of ^{131}I. Whole-body scans are carried out three days after treatment to determine sites of uptake. If there is evidence of residual disease, the patient should be scanned again six months later.

Recombinant human thyroid-stimulating hormone

A new addition to the treatment armamentarium is recombinant human TSH[6]. This enables patients to undergo radio-iodine scans or ^{131}I treatment without having to stop thyroid hormone therapy. It is effective, although scans are slightly less sensitive than following conventional thyroid hormone withdrawal. Its main drawback is cost. It should be used for patients with hypopituitarism who lack endogenous TSH drive. It is also useful in patients with severe ischaemic heart disease in whom thyroid hormone withdrawal is likely to cause difficulties.

All patients require lifelong follow-up on suppressive T4 therapy. It is important to monitor carefully the long-term consequences, such as atrial fibrillation. Serum thyroglobulin can be routinely measured on T4 therapy although, in the absence of

TSH stimulation, recurrent disease cannot be completely excluded.

Medullary cell cancer of the thyroid

MCT accounts for 5–10% of all thyroid cancers and about one-quarter of the cases have a familial autosomal dominant component. This neoplasm arises from the calcitonin-producing parafollicular C cells of the thyroid. The disease is usually multifocal on a background of hyperplasia. MCT may arise as part of either multiple endocrine neoplasia (MEN) 2A (MCT, phaeochromocytoma, primary hyperparathyroidism) or MEN 2B (MTC, phaeochromocytoma, together with mucosal neuromas). It can also occur as familial isolated MTC or as sporadic disease. Hirschsprung's disease is occasionally associated with MEN 2. Patients may present with a thyroid nodule, cervical lymphadenopathy or humoral effects such as flushing or diarrhoea. There may be symptoms and/or signs of phaeochromocytoma or hypercalcaemia.

The approach to MCT is different from that for the treatment of papillary and follicular thyroid cancer. All patients require specialist endocrine assessment for associated endocrine disease. The tumour is not treatable by radio-iodine and is relatively radio-insensitive. It is therefore paramount that the disease be identified at the earliest possible opportunity so that the patient can undergo curative surgery.

Screening for familial disease

The management of these patients has been made easier by the identification of discrete point mutations in the *RET* proto-oncogene in over 90% of patients with familial disease[7]. This has enabled families to be screened before the disease becomes clinically manifest. A negative family history does not exclude the possibility of a germline (inheritable) mutation. All patients with germline mutations (leucocyte DNA) of *RET* must be referred for genetic counselling. In the rare situation in which there is a family history in the absence of a demonstrable *RET* mutation, screening can be carried out by calcium-pentagastrin-stimulated calcitonin testing.

The current recommendation is for children to undergo genetic screening at an early age (below 5 years). If the screening is positive, they should undergo surgery. The standard approach to the surgical management of MCT is total thyroidectomy, together with central node dissection. Subsequent follow-up is by clinical monitoring and measurement of serum calcitonin levels. However, the disease is relatively indolent and patients can survive for many years, even with a significant tumour load. The basic approach to recurrent disease is surgical resection, where applicable. Radiotherapy is reserved to control local symptoms in patients with inoperable disease.

General information

Patient information – A useful inclusion in the guidelines is patient information, with sections on:

- the thyroid gland and thyroid cancer
- thyroid surgery – things you need to know about having a thyroidectomy
- radio-iodine ablation treatment.

Thyroid cancer database – There is a suggested thyroid cancer data set, based upon a data set which has been in use in one centre for the last decade. It is suggested that this is used for clinical management and audit. The ultimate aim for thyroid cancer management, as for all malignant disease, however, must be the registration and follow-up of all patients on a national database.

Conclusions

The publication of these guidelines is an important step forward in the management of thyroid cancer patients. The guidelines really represent a series of separate books aimed at thyroid cancer specialists, primary care physicians, patients and their families.

General physicians and surgeons should also be aware of the guidelines, the central tenet of which is that thyroid cancer is a disease which requires specialist care from a multidisciplinary team. The importance of this cannot be overemphasised. All clinicians should recognise that the *ad hoc* management of patients outside a multidisciplinary team framework is entirely inappropriate.

The guidelines also represent a major step forward in the aim of establishing co-ordinated specialist care for the management of thyroid cancer in this country. They provide the framework that will 'lead to better care and subsequent improvement in survival for patients with thyroid cancer in England and Wales'.

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