



Update on epidemiology classification, and management of thyroid cancer

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ABC article

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INTRODUCTION

Thyroid cancer represents approximately 0.5–1% of all human malignancy¹. In the UK the incidence of thyroid cancer is 2-3 per 100,000 populations². In geographical areas of low iodine intake and in areas exposed to nuclear disasters the incidence of thyroid cancer is higher. Benign thyroid conditions are much more common. In the UK approximately 8 % of the population have nodular thyroid disease². Nodular thyroid disease increases with age and is also more common in females and in geographical areas of low iodine intake. Primary thyroid malignancy can be broadly divided into 2 groups. The first group, which generally have much better prognosis, are the well-differentiated thyroid carcinoma, which includes papillary carcinoma, follicular carcinoma and Hürthle cell tumours. The second group includes the poorly differentiated thyroid carcinoma like medullary thyroid carcinoma and the anaplastic thyroid carcinoma. Other rare tumours such as sarcomas, lymphomas and the extremely rare primary squamous cell carcinoma of the thyroid should be included in the second group. Secondary or metastatic thyroid cancer can be from breast, lung, colon and kidney malignancies.

AETIOLOGY

There are many factors that are implicated in the aetiology of thyroid cancer these includes:

1) Ionising radiation:

Exposure to ionising radiation is a well-recognised factor in causing thyroid cancer. Following Chernobyl nuclear disaster in the former USSR there has been a significant increase in development of thyroid cancer among the local population including children³. Nodular thyroid

disease is also found to increase following ionising radiation exposure.

2) Genetic predisposition:

Medullary thyroid carcinoma can be familial and develop on a background of Multiple Endocrine Neoplasia (MEN) type 2a and type 2b, which are inherited as Autosomal Dominant. MEN type 2a includes medullary thyroid carcinoma, Pheochromocytoma and Parathyroid neoplasia. MEN type 2b includes medullary thyroid carcinoma, Pheochromocytoma, Marfanoid appearance with multiple mucosal neuromas of tongue and lips and ganglioneuromas of the gastrointestinal tract. Medullary thyroid carcinoma can also be inherited as a familial Non-MEN medullary thyroid carcinoma or can develop sporadically. The implicated gene is mutation of the RET proto-oncogene.

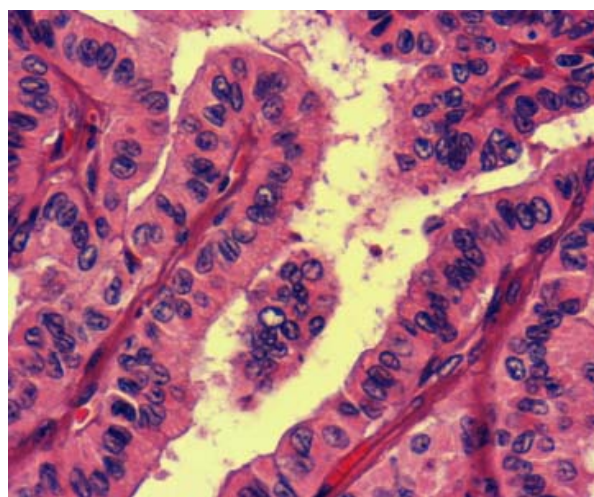


Figure 1: papillary thyroid carcinoma (H&E).
3) Chronic Lymphocytic Infiltration:

Hashimoto's Autoimmune lymphocytic thyroiditis is known to predispose to development of thyroid lymphoma.

4) Low iodine intake:

This is due to lower thyroid hormones production which consequently leads to increase production of thyroid stimulating hormone (TSH) which leads to excessive stimulation of the thyroid follicles leading to development of nodular thyroid disease and possibly promotes cancerous changes in follicular cells.

HISTOLOGICAL CLASSIFICATION

Primary malignancy of the thyroid gland can originate from any of the cellular components of the gland and is called primary thyroid malignancy which can be either differentiated or poorly-differentiated. The cellular components of the thyroid glands are follicular cells and para-follicular cells, lymphoid cells and stromal cells.

Tumours originating from thyroid follicles are called follicular cell-derived thyroid carcinoma (FCDC) (Figures 1, 2 and 3). FCDC represent the majority of thyroid carcinoma (80–90%)⁴ and includes papillary thyroid carcinoma, follicular carcinoma and Hürthle cell carcinoma. The histological appearance of papillary carcinoma is complex, branching papillae with fibrovascular cores. Nuclei are overlapping with finely dispersed optically clear chromatin (ground-glass appearance).

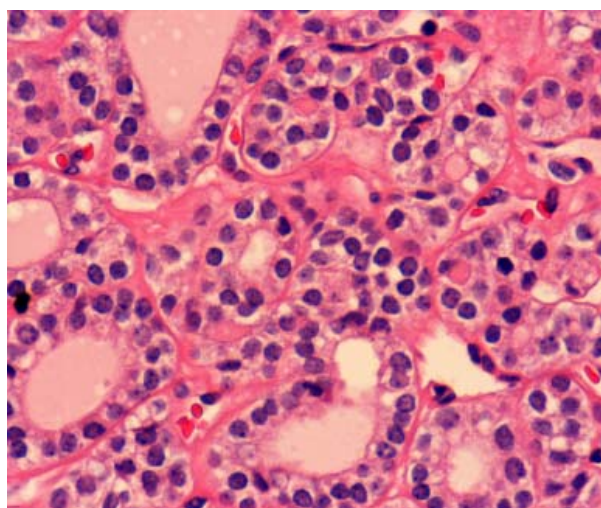


Figure 2: follicular cell carcinoma (H&E).

Psammoma bodies that represent necrosis of tumor cells with calcification can be seen in between tumor cells, and are fairly specific for

papillary carcinoma. In follicular carcinoma there is invasion of adjacent thyroid parenchyma, blood vessels or capsule with usually uniform cells with absence of nuclear features of papillary carcinoma.

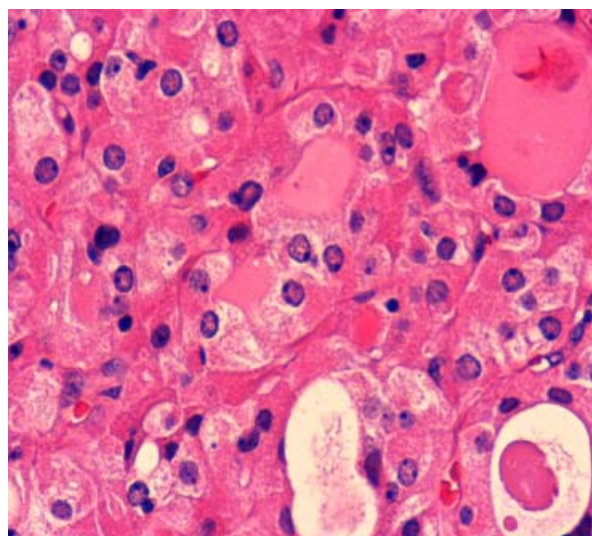


Figure 3: Hürthle cell carcinoma (H&E).

Hürthle cell carcinoma is a very rare differentiated thyroid tumour. Hürthle cells are part of follicular cells. The German histologist "Hürthle" first described them. Their role in the thyroid follicle is still not very clear. They are large, polygonal cells characterized by extensive mitochondrial content which gives it its characteristic granular, eosinophilic cytoplasm, hence the other name eosinophilic cell.

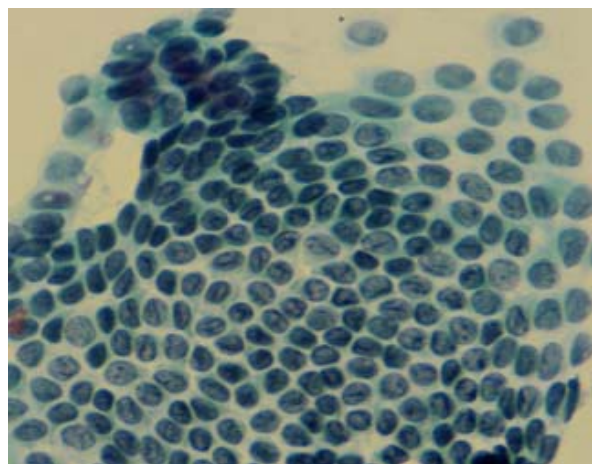


Figure 4: FNAC of papillary cell carcinoma (H&E).

Hürthle cell tumour can be either benign or malignant. Histological demonstration of capsular and vascular invasion is important in diagnosing malignancy. Para follicular C cells gives rise to

medullary thyroid carcinoma and constitute 5–10% of total thyroid cancer.

Other primary thyroid carcinomas that are much less common include malignant lymphomas, sarcomas, anaplastic carcinomas, and the very rare squamous cell carcinomas. Secondary thyroid cancer are usually due to direct spread from adjacent structure like for example cancers of the larynx or hypoharynx or can be due to haematogenous spread from cancer of the breast, colon, kidney and lungs.

CLINICAL PRESENTATION

1) Solitary thyroid nodule or dominant nodule in a multinodular goitre:

This is the most common way of presentation of thyroid cancer. A solitary thyroid nodule carries a risk of 10–20% of being malignant². The risk is higher in the very young and the elderly and those who had previous exposure to ionising radiation.

2) Pressure symptoms:

Compression to nearby structure like the oesophagus and trachea will lead to gradual and progressive dysphagia to solid food and/or shortness of breath on exertion due to limitation of airflow. Severe airway obstruction can lead to stridor, which can also be a result of vocal cords paralysis due to direct tumour infiltration.

3) Change in voice quality (Dysphonia):

This is usually due to vocal cords paralysis, which causes hoarseness of voice.

4) Regional or distant metastasis:

Cervical neck swelling due to metastasis at regional lymph nodes in the neck can be the only presenting symptom of thyroid malignancy in about 20% of patients. Distant metastasis to the lungs or bones can also be the presenting symptom in follicular thyroid carcinoma.

5) Hormonal Changes:

Thyrotoxicosis due to toxic thyroid carcinoma is extremely rare.

INVESTIGATION

1) FNAC (Fine Needle Aspiration Cytology):

Fine needle aspiration cytology is the single most important investigation to carry out in patients with a thyroid nodule⁵. It has the ability to give a diagnosis in about 85% of patients and differentiate

benign thyroid conditions from neoplastic thyroid conditions, provided a representative cellular tissues are obtained and examined by an expert cytologist; where features of cellular neoplasia are recognised like cellular and nuclear atypia, enlarged nuclei, increase mitosis and hyperchromatism. An example of FNAC in papillary thyroid carcinoma is shown in figure 4. FNAC has its limitation in follicular thyroid cancer, as it cannot differentiate between follicular adenoma and follicular carcinoma, and the report is usually read as indeterminate follicular neoplasm. Vascular and capsular invasion needs to be demonstrated histologically in order to diagnose follicular carcinoma; and for this reason core biopsy or more commonly thyroid lobectomy is required when facing this situation to obtain histological diagnosis. If the results of the FNAC are inconclusive which is usually due to insufficient material aspirated, the procedure can simply be repeated to obtain enough sample materials.

2) Thyroid Ultrasound:

Thyroid ultrasound can be helpful in differentiating solitary nodules from multinodularity seen in benign nodular thyroid disease, or can be used in guiding FNAC (Ultrasound guided FNAC). It is very important to realise that thyroid carcinoma especially follicular thyroid cancer can arise as a dominant nodule in multinodular goitre and a FNAC of the dominant nodule should be attempted.

3) Radioisotope thyroid scan:

The radioisotope thyroid scan is usually used to investigate a patient with solitary thyroid nodule to measure its activity. The isotope used for diagnostic scanning is usually Technetium pertechnetate (Tc 99m) or radioactive iodine (¹²³I or ¹³¹I). It is also useful in multinodular goitre to detect the presence of autonomous functioning nodules. A metabolically very active nodule (hot nodule) has an extremely low risk of being malignant. A metabolically inactive nodule (cold nodule) has a risk of about 10–20% of being malignant and this risk is also depends on other factors like age, gender and previous exposure to ionising radiation. The risk is higher for the very young and the elderly and for males and those with previous history of radiation exposure.

4) Other Imaging studies:

Chest X-ray can be useful in detecting pulmonary metastasis in follicular carcinoma. Both computerized tomography (CT) and magnetic resonance imaging (MRI) can have a very important role in assessing the extent of tumour spread and involvement of the local structures around the thyroid like the larynx, pharynx and the

oesophagus. This will help in planning the surgical approach and the degree of surgical resection required especially in large and extensive thyroid tumours with extra thyroid extension that are involving the nearby important structures.

5) Laboratory investigations:

Thyroid function test (TFT) and baseline thyroglobulin level can be useful in both monitoring the disease progression after treatment and to detect early recurrences. TFT should be performed regularly to ensure a low level of thyroid stimulating hormone (TSH) is achieved when adjuvant therapy with thyroxin is given in treating thyroid cancer. The presence of thyroglobulin in the blood is indicative of thyroid tissue activity in the body. Its level is used as a tumour marker and a monitoring tool to detect any active residual thyroid tissue in the body, which may require further ablation therapy with radioactive iodine; this will be discussed later. Serum calcitonin measurement is useful in case of medullary carcinoma thyroid because cancer cells secrete it so it can be used as both for diagnosis and disease monitoring.

PROGNOSIS AND STAGING OF THYROID CANCER

Several factors have been found which stratify the risk of mortality and aggressiveness of a differentiated thyroid cancer. These factors are used in planning the suitable treatment option in each patient and the aim is to cure the patient from the disease with the least morbidity and will help the clinicians to identify those high risk patients who need more aggressive treatment and adjuvant therapy and more stringent follow up. Twenty years survival rate for differentiated thyroid cancer is around 90% because most of these are papillary, which generally have excellent prognosis⁵.

The "Tumour–Node–Metastasis" system (TNM) is an internationally accepted system for tumour staging and is used in staging of thyroid cancer. TNM system was developed by the International Union Against Cancer (UICC) and the American Joint Commission on Cancer (AJCC). Age of the patient is included in the TNM staging of thyroid cancer, which is unique. Patients who are aged 45 or older do worse than those who are younger and should be treated more aggressively. The TNM staging system is demonstrated in table (1).

There are also other staging or scoring systems that have been developed to allow a means of predicting tumour behaviour, risk of recurrence and survival rate.

AGES scoring system was developed by Hay *et al* in 1987 and uses age (whether younger or older than 40 years), grade of tumour, extent of tumour (extra thyroid extension or distant metastasis), and size of primary tumour. Low risk scores are those who scores 3.99 or less^{6,7}.

Cady and Rossi developed the AMES scoring system in 1988, which is based on age, metastasis (if present), extent of primary tumour (intra thyroidal versus extra thyroidal), and size of primary tumour). The score results will stratify the patients into either low or high-risk group⁸.

Other systems include MACIS, which describes metastasis, age, completeness of primary surgical resection, invasion (presence of extra thyroidal invasion) and the size of primary tumour.

GASH scoring system has also been developed which includes gender in the risk estimation as males are known to do worse than females in thyroid cancer treatment and should be regarded as a higher risk than female counterpart. The factors used in GASH are gender, age, stage and histology².

TREATMENT OF THYROID CANCER

Treatment of Thyroid Cancer should be by multimodality treatment through multidisciplinary team approach; involving a surgeon, an endocrinologist, a radiotherapist and an oncologist. Selection of the appropriate treatment depends on the type of risk and the characteristics encountered for both the tumour as well as the patient.

1) Papillary Carcinoma Thyroid:

Papillary thyroid carcinoma is the most common differentiated thyroid cancer and constitutes about 80% of all differentiated thyroid cancer. Ten-year survival is around 98%. The treatment for low risk patients with papillary carcinoma like for example females less than 45 years old with tumour limited to the thyroid gland can be adequate with thyroid lobectomy followed by TSH suppressive therapy in the form of Thyroxin supplements and life long monitoring using thyroglobulin level with regular clinical evaluation⁹. The argument against this approach is the possibility of dealing with multifocal papillary thyroid carcinoma in small percentage of patients. For high risk patients like males and those older than 45 years old with high grade tumours should undergo total thyroidectomy followed by radioactive iodine (¹³¹I) ablation of thyroid remnants

Table 1: TNM staging of thyroid cancer		
T	Primary tumour	
Tx	Primary tumour can not be assessed	
T0	No evidence of primary tumour	
T1	Tumour 1 cm or less in greatest dimension and limited to the Thyroid	
T2	Tumour between 1 and 4 cm in greatest dimension and limited to the Thyroid	
T3	Tumour more than 4 cm in dimension but limited to the Thyroid	
T4	Tumour of any size extending beyond the Thyroid capsule	
N	Regional lymph nodes (cervical and upper mediastinal lymph nodes)	
Nx	Regional lymph nodes can not be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
N1a	Metastasis in ipsilateral cervical lymph node (s)	
N1b	Metastasis in bilateral, midline or contralateral cervical lymph nodes	
M	Distant metastasis	
Mx	Distant metastasis can not be assessed	
M0	No distant metastasis	
M1	Distant metastasis present	
	Age <45	Age > 45
Stage1	Any T, any N, M0	T1, N0, M0
Stage2	Any T, any N, M1	T2 or T3, N0, M0
Stage3	T4, N0, M0 or any T, N1, M0
Stage4	Any T, any N, M1

and any possible residual thyroid tumour using radioactive iodine (^{131}I). This is followed by TSH suppressive therapy to prevent tumour stimulation by TSH, which is achieved by giving the patient thyroxin supplement in TSH suppressive dose. Follow up for life is also required with Thyroglobulin level and regular isotope scans. Prior to performing ^{131}I radioisotope follow-up scanning, thyroxin should be stopped 4 weeks before scanning to facilitate rise in TSH to improve ^{131}I uptake by any residual tumour or thyroid tissues. Any residual tumour or thyroid tissue detected should be dealt with by ablative radioactive ^{131}I dose. Regional lymph nodes involvement should be surgically dealt with at the time of the primary surgery by selective or modified radical neck dissection depending on the severity of lymph node involvement. Unlike in cervical lymphadenopathy squamous cell carcinoma secondaries from head and neck primary sites, regional lymph nodes involvement in differentiated thyroid carcinoma does not greatly affect the overall survival.

A more radical surgery to the larynx, pharynx and the oesophagus is sometimes required to eradicate the disease when these structures are involved through direct tumour spread. This can range from tumour shaving of the thyroid cartilage, cricotracheal resection to partial or total pharyngolaryngectomy. The decision of the type of resection will depend on the part of the airway that is involved by the tumour and the residual tumour-free airway framework. External beam radiation can also be required for tumours that do not adequately take up radioactive iodine.

2) Follicular Carcinoma:

Follicular carcinoma thyroid is more aggressive than papillary carcinoma but less aggressive than medullary thyroid carcinoma. It is less common than papillary thyroid carcinoma and constitutes around 15–20% of total thyroid carcinoma¹⁰. It is a differentiated tumour arising from thyroid follicles so the majority takes up radioactive iodine. The planning of treatment is also depends on the degree of risk with lower threshold for total

thyroidectomy than in papillary thyroid carcinoma. Radioactive iodine for thyroid ablation of any residual thyroid or tumour tissue should be done and a follow up for life with clinical, radioisotope scanning and thyroglobulin level monitoring should also be done.

3) Hürthle cell carcinoma:

Hürthle cell carcinoma is now regarded by the WHO as a variant of follicular carcinoma. Although controversial, it is still generally recognised as an aggressive form of differentiated thyroid cancer. The treatment protocol will be similar to that for follicular cell carcinoma. Hürthle cell carcinoma may not concentrate radioactive iodine as good as other differentiated thyroid cancer; non the less radioactive iodine ablation of any remnant thyroid tissues should be done to allow for thyroglobulin level monitoring.

4) Medullary Thyroid Carcinoma:

Surgery in the form of total thyroidectomy and neck dissection for nodal involvement gives the best chance of cure. As these tumours originally arise from Para follicular C cells (calcitonin producing cells), so it is not a surprise that they do not concentrate radioactive iodine and so external beam radiotherapy can be offered as adjuvant treatment for more extensive disease involvement. Follow-up for life by regular clinical examination and monitoring of calcitonin level in there blood should be done. First-degree relatives should be screened for familial type of disease using calcitonin level or more accurately by detecting a mutated proto-oncogene. Family members who carry the mutated proto-oncogene should undergo elective thyroidectomy to avoid the inevitable chance of developing medullary thyroid cancer. These patients should also be screened for MEN type 2 prior to any surgical procedure where phaeochromocytoma and parathyroid hyperplasia can be associated. It is important to remember that medullary thyroid cancer can be sporadic (non familial). A familial non-MEN medullary thyroid carcinoma does also exist and it is also important to be remembered.

5) Anaplastic Thyroid Carcinoma:

This is a very aggressive malignant tumour of the thyroid, which usually present in the elderly with a very rapidly growing hard goitre that can compress the airways leading to stridor. It carries a very poor prognosis and all these tumours are considered T4. It is very important to obtain tissue for histological diagnosis as malignant lymphoma, which has a better prognosis, can have a similar presentation. The treatment is usually palliative with radiotherapy. Tracheostomy is often required to maintain the airway patency.

6) Malignant Lymphoma:

Lymphoma is treated as for any other lymphoma in the body. A histological typing and grading along with staging CT scan and a referral to a medical oncologist is required.

7) Other Rare Thyroid Tumours:

Soft tissue sarcomas and squamous cell carcinoma of the thyroid are very rare and are beyond the scope of this review.

CONCLUSION

Multidisciplinary team approach along with departmental Auditing and Quality Assurance should offer the best quality of care to thyroid cancer patients. These patient are generally requires lifelong medical care and follow-up.

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REFERENCES

1. Ahmedin J et al (2002): Cancer statistics, CA Cancer J Clin 52:23,2002.
2. Watkinson JC, Gaze MN, Wilson JA (2000): Tumours of the thyroid and parathyroid glands. In Stell & Maran's Head and Neck surgery fourth edition, 459-485, Butterworth & Heineman.
3. Pacini F et al: Post-Chernobyl thyroid carcinoma in Belarus children and adolescents: comparison with naturally occurring thyroid carcinoma in Italy and france, L Clin Endocrinol Metab 82:3563,1997.
4. Mclver B, Hay ID: Postoperative management of differentiated thyroid carcinoma. In Doherty GM, Skogseid B, editors: Surgical endocrinology, Philadelphia, 2001, Lippincott, Williams & Wilkins.
5. Gharib H, Goellner JR: Fine Needle Aspiration Biopsy of the Thyroid Gland. In Randolph GW, editor: Surgery of the Thyroid and Parathyroid Glands, 2003, Saunders.
6. Hay ID, Tayor WF, McConahey WM: A prognostic score for predicting outcome in

- papillary thyroid carcinoma, *Endocrinology* 119:T15, 1986.
7. Hay ID et al: Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring in a cohort of 1.779 patients surgically treated at one institution during 1940 through 1989, *Surgery* 114: 1050, 1993.
 8. Cady B, Rossi R: An expanded review of risk –group definition in differentiated thyroid carcinoma, *Surgery* 104: 947, 1988.
 9. Powell JG, Hay ID: Papillary Carcinoma of the Thyroid. In Randolph GW, editor: *Surgery of the Thyroid and Parathyroid Glands*, 2003, Saunders.
 10. Shaha AR, Shah JP: Follicular Carcinoma of the Thyroid. In Randolph GW, editor: *Surgery of the Thyroid and Parathyroid Glands*, 2003, Saunders.