



DIAGNOSIS AND MANAGEMENT OF THYROID CANCER

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Introduction

Each year, approximately 17 000 new cases of thyroid cancer are diagnosed and 1300 thyroid-related deaths occur in the United States.¹ Cancers of the thyroid are classified based on cell type origin: follicular cell-derived carcinoma (FCDC) arises from thyroid follicle cells, and medullary thyroid carcinoma (MTC) arises from the parafollicular cells, also called C cells. Follicular cell-derived cancers are further categorized as differentiated or undifferentiated (anaplastic). The differentiated cancers of the thyroid, papillary and follicular, are the most prevalent types, occurring in approximately 75% and 10% of cases, respectively.² These cancers undergo slow growth or no growth over long periods of time. Medullary thyroid cancer occurs in 6%-8% of all thyroid cancers.¹ Undifferentiated thyroid carcinoma makes up less than 10% of all thyroid cancers.³

Diagnosis

Thyroid cancer is typically presented as a palpable mass, and it is often found on routine examination of the neck.¹ Fine needle aspiration (FNA) biopsy is considered to be the most effective method for assessing the status of a thyroid nodule before surgery.^{2,4} Thyroid nodules are classified as benign, malignant, nondiagnostic, or inadequate. If the FNA biopsy indicates a nodule is malignant, identification of the type of carcinoma present is verified by pathocytologic examination.¹

Management

Though the management of differentiated FCDC, MTC, and anaplastic carcinomas differ, thyroid cancer management generally occurs in 3 phases.^{1,5} In phase 1, the extent of the disease is determined and surgery is performed to remove malignant tissue. Patients are assigned to risk-groups for cancer recurrence following initial surgery and postoperative staging of the tumor. In phase 2, patients are examined for any signs of recurrent disease and treated accordingly. In phase 3, disease-free survivors are re-examined at regular intervals to test for disease recurrence. The high risk of recurrence in some cancers may require that phase 3 management continue for as many as 30 years following initial diagnosis and treatment. Management of patients with thyroid carcinoma requires a multidisciplinary approach involving endocrinologists, surgeons, pathologists, oncologists, and nuclear medicine specialists.⁵

Recurrence Risk Stratification

Postoperatively, patients with FCDC or MTC are stratified into low, intermediate, or high recurrence risk groups depending on age at diagnosis, primary tumor size and extent, the presence of distant metastases, and regional lymph node involvement.¹ Risk stratification dictates follow-up management of each patient.

Differentiated Thyroid Carcinoma

Papillary Carcinoma

A papillary thyroid tumor appears as an unencapsulated, firm nodule with ill-defined margins.¹ Papillary thyroid cancer commonly metastasizes to neck and lymph nodes, and less than 5% of patients will have distant metastases. When metastases occur, they are usually found in the lungs.

Follicular or Hürthle Cell Carcinoma

A follicular thyroid tumor appears as a relatively soft mass, usually solitary and encapsulated.¹ Follicular thyroid cancer can spread to the bones, lungs, and central nervous system, but does not normally spread to the lymph nodes. Hürthle cell carcinoma is a variant of follicular carcinoma that occurs in about 3% to 5% of all thyroid cancer cases. It is more aggressive and difficult to treat than other follicular cancers.

Surgical Management of Differentiated Thyroid Carcinomas

The extent of thyroidectomy is controversial for patients with differentiated thyroid tumors smaller than 1.0 cm that do not extend beyond the thyroid capsule and are not metastatic. Some surgeons recommend ipsilateral thyroid lobectomy with isthmusectomy in these cases.^{1,2} However, others suggest that most, if not all, patients with differentiated thyroid cancer should undergo total or near total thyroidectomy because of the multifocality and high recurrence rate of these cancers.⁶ Total or near total thyroidectomy is associated with lower recurrence rates and an increase in survival.^{2,6} It also allows for whole-body radioiodine scanning (WBS) and serum thyroglobulin (Tg) testing to detect recurrent local or metastatic disease at follow-up.^{1,2,6} However, total thyroidectomy can lead to complications that are not seen after lobectomy, including hypothyroidism,² hypoparathyroidism, and recurrent laryngeal nerve palsy.⁶ Patients who undergo either lobectomy or total thyroidectomy will require levothyroxine sodium (LT₄) therapy. High risk patients (based on age, presence of metastases, and extent and size of tumor) or patients with bilateral nodules or cancer should always undergo total or near total thyroidectomy.¹

Postoperative Management of Differentiated Thyroid Cancer

After total or near total thyroidectomy, many patients with differentiated FCDC undergo ¹³¹I radioactive iodine (RAI) ablation of residual thyroid tissue within 4 weeks following surgery.^{1,2,7} Radioactive iodine ablation destroys remnants of normal thyroid tissue, destroys residual cancer cells, and identifies distant metastases. Because the thyroid is the only source of Tg, the removal and destruction of all thyroid tissue by radioiodine ablation maximizes the sensitivity of serum Tg testing to detect residual or recurrent disease at follow-up.^{1,2,6,8}

Because TSH stimulates FCDC cell growth, patients will require suppression of TSH secretion by the pituitary using LT₄ following initial surgery and radioiodine ablation.^{1,2,7} The TSH target range for most patients with no evidence of persistent disease is 0.1 to 0.4 mIU/L. For high-risk patients or those patients with persistent or recurrent disease, TSH levels should be maintained at low or undetectable levels (less than 0.1 mIU/L). For very low-risk patients and long-term survivors, TSH levels can be maintained at low to normal levels, between 0.5 to 1.0 mIU/L. Serum TSH and free T₄ should be measured in 6 to 8 weeks.

After surgery, patients should be followed up within 6 to 12 months with a WBS.^{1,7} In order for thyroid tissue to take up ¹³¹I in the WBS, serum TSH levels must be increased to >30 mIU/L.^{2,6} This can be achieved either through LT₄ withdrawal for 4 to 6 weeks prior to scanning² or administration of recombinant human TSH (rhTSH).^{1,9} Serum Tg testing to detect recurrent disease may be carried out in conjunction with either LT₄ withdrawal or rhTSH-stimulated WBS as part of follow-up management.^{2,7,8} Serum Tg test results can be affected by the presence of anti-Tg antibodies; screening for these antibodies is necessary to interpret falsely low Tg results.² The levels of circulating Tg following total thyroidectomy and RAI ablation should be less than 1.0 ng/mL (undetectable) with rhTSH stimulation or LT₄ withdrawal.⁶ The degree of local or

metastatic disease detected by WBS, Tg testing, and neck ultrasound will dictate whether further surgery or RAI ablation is needed. Patients typically undergo combination WBS, Tg testing, and ultrasound yearly as part of their long-term follow-up.² Both Tg and TSH testing are recommended every 6 months for the first 3 years following surgery and then yearly thereafter.²

Persistent or recurrent local disease and large metastases are usually treated by surgical excision; RAI therapy or external beam radiotherapy may be needed to treat recurrent metastatic disease.^{1,6}

Medullary Thyroid Carcinoma

Medullary thyroid cancer arises from the calcitonin-secreting C cells of the thyroid gland.¹ Approximately 75% of MTC cases are sporadic and 25% are due to autosomal dominant disease.² Medullary cancers have a mortality rate of 10% to 20% at 10 years, with cervical lymph node metastases occurring early. Tumors larger than 1.5 cm are likely to metastasize, often to bone, lungs, liver, and the central nervous system. Metastases usually contain calcitonin and stain for amyloid.

Preoperative testing for, and removal of, pheochromocytomas should be performed prior to thyroid surgery.^{1,2} Patients with MTC should undergo total thyroidectomy and central compartment lymph node dissection or unilateral modified radical neck dissection.^{1,2} Serum calcitonin levels should be checked within 8 to 12 weeks of the surgery to detect residual disease.¹ Because C cells do not respond to TSH, patients with MTC will likely require thyroid hormone replacement but not suppressive therapy as part of their management.¹

Recurrent disease should be surgically resected; if resection is not possible, external beam radiotherapy may be used.² Chemotherapy is not usually effective for treating MTC.

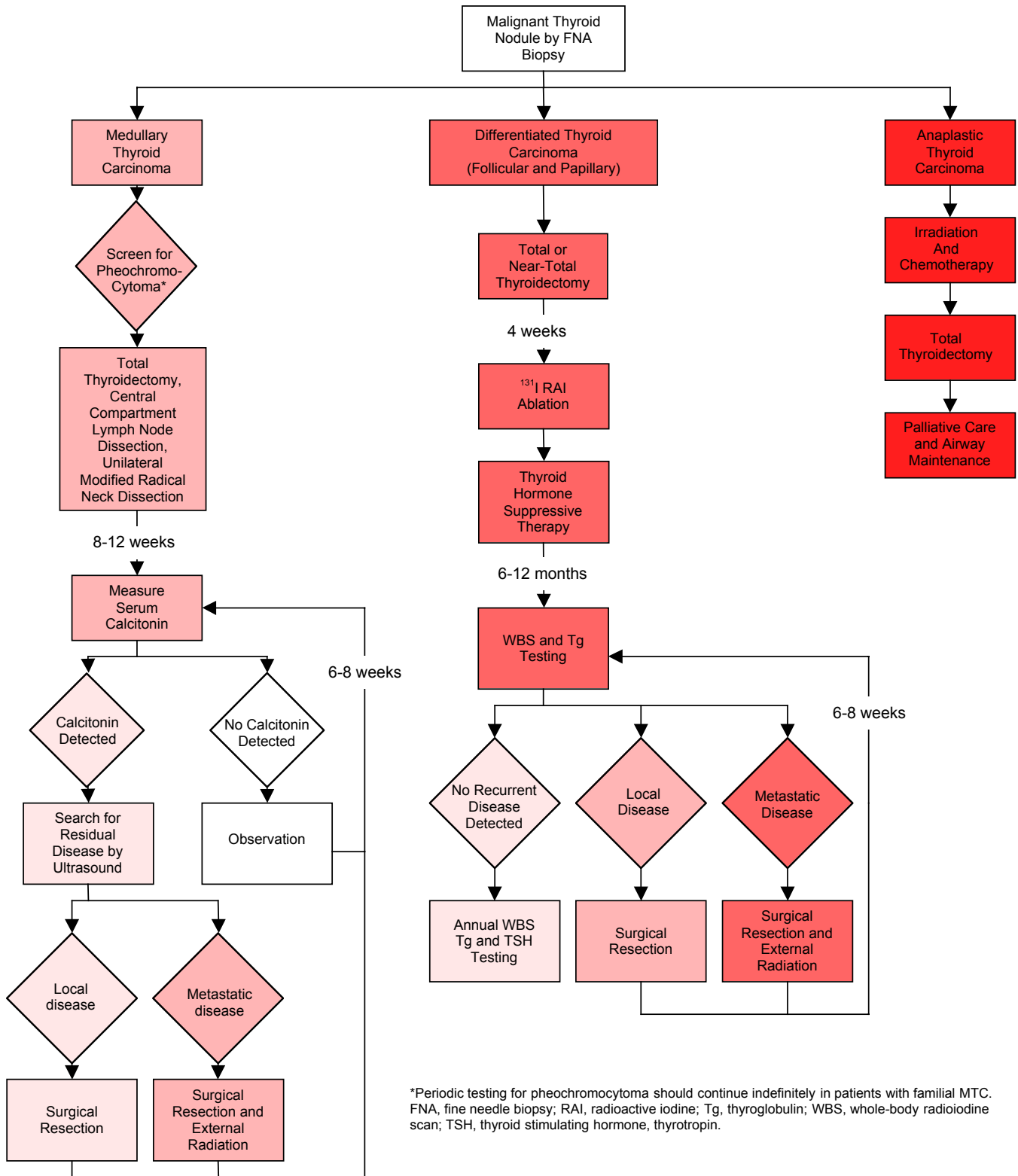
Undifferentiated (Anaplastic) Thyroid Carcinoma

Anaplastic thyroid cancer is extremely aggressive and exceptionally virulent, and consists primarily of undifferentiated cells. Anaplastic thyroid tumors are typically hard, poorly circumscribed, and fixed to surrounding structures, with areas of necrosis and hemorrhage.¹ At diagnosis, anaplastic tumors are often larger than 5 cm and are multiple or bilateral. These cancers are more prevalent in older populations (greater than 65 years of age). Primary resection of the tumor may be necessary to protect the airway. Survival of patients may be extended through the use of external beam radiotherapy and resection to control local disease in conjunction with chemotherapy.^{1,2} Care of patients with undifferentiated thyroid carcinoma primarily requires palliative measures and maintenance of the airway.

National Comprehensive Cancer Network Factors Predictive of High Risk of Thyroid Cancer Recurrence and Risk ⁶	
Age <15 or >45 years	Vascular invasion
Male sex	Lymph node metastases
Family history of thyroid cancer	Certain tumor subtypes
Tumor >4 cm in diameter	Histologic grade
Bilateral disease	Poor concentration of iodine
Extrathyroidal extension	Distant metastases

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*Periodic testing for pheochromocytoma should continue indefinitely in patients with familial MTC. FNA, fine needle biopsy; RAI, radioactive iodine; Tg, thyroglobulin; WBS, whole-body radioiodine scan; TSH, thyroid stimulating hormone, thyrotropin.