PRINCESS MARGARET CANCER CENTRE
CLINICAL PRACTICE GUIDELINES

ENDOCRINE

THYROID
# Endocrine Site Group – Thyroid

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1. **INTRODUCTION & SUMMARY OF RECOMMENDATIONS**

Thyroid cancer incidence is rising in both genders but especially women. The thyroid gland is composed of follicular cells, parafollicular cells, and connective tissue with occasional lymphocytes. Each of these cell types can give rise to histologically distinct tumors that differ significantly in behavior, prognosis and response to treatment. Tumors derived from follicular epithelial cells account for more than 95% and are classified as differentiated (papillary and follicular), poorly differentiated (insular) and undifferentiated (anaplastic). Medullary thyroid cancers are derived from parafollicular cells. The 10 year survival rates are approximately 95% and 85% for papillary and follicular carcinomas, 75% for medullary thyroid cancer, 50% for poorly differentiated carcinomas, and less than 5% for the anaplastic variant (1; 2). Thyroid cancer is the commonest endocrine malignancy, representing from 1 to 2% of all cancers (LiVolsi 1990; Murray 1998; Asa and Bedard 2000; Baloch and LiVolsi 2002). It is about three times more common in women than in men and currently represents the 10th most common malignancy in women (Greenlee et al. 2000).

**i. Access to a multidisciplinary thyroid cancer team**

a. Management of differentiated thyroid cancer and of medullary thyroid cancer is the responsibility of a specialized multidisciplinary team, membership of which will normally be comprised of an endocrinologist, pathologist, surgeon, and radiation oncologist, with support from a specialist nurse, all with expertise and interest in the management of thyroid cancer

b. Patients will normally be seen by one or more members of the multidisciplinary team; a combined clinic is recommended, and all members of the multidisciplinary team should maintain continued professional development on an on-going basis.

**ii. Patient focus**

a. Patients should be offered full informed consent about their condition and their treatment

b. Patients should have continued access to a multidisciplinary team for guidance, support and follow up.

**iii. Surgery**

a. The surgeon should have training and expertise in the management of thyroid cancer and be a member of the multidisciplinary team

**iv. Pathology**

a. Pathologists dealing with thyroid tumors should have expertise and interest in thyroid cytology, histopathology, and molecular biology of thyroid tumors.

b. All patients should be staged by clinical and pathological TNM staging. Pathology reporting should be synoptic and comprehensive.
c. Risk group assignment. Patients should be assigned to appropriate risk groups as per the guidelines by the department of radiation oncology at Princess Margaret Hospital. These are detailed below under the RADIATION Section 6.

v. Aims of Treatment

The aims of treatment are the removal of all tumour, the elimination of clinical, radiological or biochemical evidence or recurrence and minimization of unwanted side-effects.

vi. Summary of management of differentiated thyroid cancer

a. All new patients should be seen by a member of the multidisciplinary team and treatments plans should be discussed and endorsed by the multidisciplinary team. Complex cases should be reviewed at multidisciplinary tumour boards prior to any intervention
b. Fine needle aspiration cytology should be used in the planning of surgery
c. Patients with a papillary carcinoma more than 1 cm in diameter or with high risk follicular cell-derived thyroid cancer should undergo total thyroidectomy. Patients with low risk follicular cell-derived thyroid cancer or papillary thyroid cancer less than 1 cm in diameter may be treated with thyroid lobectomy alone.
d. Following surgery, patients will require levothyroxine therapy at a dose sufficient to suppress serum thyroid stimulating hormone to less than 0.1 mIU/L. For patients confirmed to be low risk, a serum TSH of less than 0.5 mIU/L is acceptable.

vii. Follow-up of differentiated thyroid cancer

Follow-up should be life-long as the disease has a long natural history; late recurrences are uncommon but not unheard of and can be treated successfully. Regular surveillance is necessary for monitoring of treatment, particularly to ensure TSH suppression and for treatment of hypocalcemia. Suppression of serum TSH is one of the main components of treatment in high risk cases.

Surveillance for recurrence of disease is essential and is based on annual clinical examination, annual measurement of serum thyroglobulin and TSH, annual cervical neck ultrasound, other diagnostic imaging, and fine needle aspiration biopsy where indicated.

viii. Medullary thyroid cancer

The initial evaluation of suspected medullary thyroid cancer includes fine needle aspiration biopsy, measurement of plasma calcitonin and CEA. The patient with medullary thyroid cancer should have access to clinical genetic services and RET genetic testing. All patients with medullary thyroid cancer should be offered genetic counseling and RET mutational analysis. In patients with medullary thyroid cancer, associated endocrinopathies should be identified (MEN2A and 2B) including pheochromocytoma and primary multiglandular hyperparathyroidism. These can be excluded in new patients with medullary thyroid cancer by
measuring 24 urinary catecholamines including metanephrines and serum calcium as well as parathyroid (PTH) hormone.

Minimum treatment is total thyroidectomy and level six nodal dissections. Life long follow-up is essential, including monitoring of the tumour markers calcitonin and CEA.
2. PREVENTION

Prevention is possible when genetic information can provide sensitive and specific information. In general, Mendelian genetics forms the basis for gene-informed risk assessment and management for patients and their families. This is the true meaning of 21st century personalized medicine, yet it has not occurred with some specific exceptions.

In the case of thyroid cancer, germline mutations in the RET proto-oncogene, encoding a receptor tyrosine kinase, cause >90% of familial medullary thyroid carcinoma (FMTC) and multiple endocrine neoplasia type 2 (MEN 2), an autosomal dominant disorder characterized by medullary thyroid cancer, pheochromocytoma, and hyperparathyroidism. This knowledge provides the basis for evidence-based molecular diagnosis, predictive testing, genetic counseling, and gene-informed cancer risk assessment. However, it is quite likely that many other syndromic endocrine neoplasias will fall under this category with other candidate genes including mutations in Von Hippel-Lindau (VHL), or Succinate dehydrogenase (SDHB-D). The familial risk associated with epithelial (nonmedullary) thyroid carcinoma is among the highest of all solid tumors, yet only a few highly penetrant heritable thyroid carcinomas are currently recognized. This is illustrated by Cowden syndrome, an autosomal dominant disorder characterized by breast, thyroid, and other cancers, caused by germline mutations in PTEN, encoding a phosphatase, and to a lesser frequency by SDHB/SDHD gene variants.

In the next sections we will review the molecular basis of what causes thyroid cancer and how this relates to the different types of morphologic forms of this neoplasia. Undoubtedly, this information will prove critical in the design of specific screening and prevention guidelines.
3. SCREENING, EARLY DETECTION, AND FINE NEEDLE ASPIRATION

3.1 Screening and prevention

3.1.1 Etiology

The etiology of most thyroid tumors is not known. A small minority is due to inherited genetic defects. MEN-2 and FMTC are a rare example of inheritance of a mutant proto-oncogene. The gene responsible for this disease encodes the transmembrane receptor tyrosine kinase ret (Mulligan and Ponder 1995). Please see figure below. The identification of an activating ret mutation in members of kindreds is now accepted as an indication for prophylactic thyroidectomy in early childhood, since these individuals will develop medullary thyroid carcinoma that can metastasize and is lethal in more than half of patients. Moreover, distinct ret mutations are associated with distinct clinical phenotypes (Fig. 1). Mutations in exons 10 and 11 that encode the extracellular domain of the ret protein are implicated as the cause of familial medullary thyroid carcinoma alone. Specific mutations, usually in exon 11 involving codon 634, are associated with MEN-2A and specifically codon 634 mutations replacing cysteine with arginine are more often associated with parathyroid disease and pheochromocytoma that characterize this disease complex. Activating mutations in exon 16 that replace a codon 918 methionine with threonine alter the tyrosine kinase domain of ret and result in MEN-2B, a more aggressive variant of MEN-2 with mucosal neuromas and a marfanoid habitus in addition to tumors of thyroid C cells, parathyroids and adrenal medulla.

![Fig. 1: Ret Mutations in MEN2 & MTC](image)

The etiology of thyroid carcinomas of follicular epithelial cells is not entirely known, but there is evidence of a causal role for radiation (Kondo et al. 2006). This is true of radiation therapy, for
example in patients who have received external beam radiotherapy for malignancies of the head and neck as well as for cosmetic therapy for facial acne. It is also true in populations exposed to radioactive fallout from nuclear disasters, such as in Japan after the nuclear bomb disasters and in Ukraine and Belarus after the Chernobyl episode. The exposure to radioactivity has its highest impact in the young, and the disease is more often multifocal than in sporadic cases, however, the prognosis in patients who have been exposed to radiation does not appear to differ from those with no history of radiation (Brierley and Asa 2001). Radiation has been implicated as causative of ret/PTC gene rearrangements that are thought to play a role in the genesis of thyroid carcinomas (Nikiforova et al. 2000). Recently, another chromosomal rearrangement involving the BRAF kinase (AKAP-BRAF) representing yet another form of paracentric inversion has been identified in radiation-associated thyroid cancers (Ciampi et al. 2005). Regardless of the mode of activation, these recent data indicate that pharmacologic targeting of the BRAF kinase should provide more support for the critical contribution of this effector in tumorigenic signaling in the thyroid. Diet has been implicated in the development of thyroid cancer as well; populations with low iodine intake develop goiters and have a higher incidence of follicular carcinoma, but most investigators now recognize dietary iodine insufficiency as the reason for a higher incidence of follicular as opposed to papillary carcinomas. In other words, there is no evidence that it increases the incidence of cancer; rather it alters the morphological variant of well-differentiated thyroid carcinoma.

Screening for thyroid tumors has really only been applied systematically in cases of familial disease. Members of kindreds have traditionally been screened using biochemical analysis of hormone hypersecretion. More recently, the addition of genetic information has allowed earlier and definitive identification of carriers in families with known mutations. Patients with activating mutations of the ret proto-oncogene will almost certainly develop medullary thyroid carcinoma, a disease that is lethal if not detected early or prevented, and therefore current guidelines recommend prophylactic thyroidectomy in childhood, usually by age 5 for those with MEN-2A or FMTC, and at or around age 1 year for those with the more aggressive mutation of MEN-2B. Some families have unidentified mutations and hormonal screening remains the standard mechanism of tumor detection, with the addition of radiological investigation where indicated.

Screening for thyroid tumors is usually part of the physical examination since the thyroid is readily accessible on palpation of the neck. When a thyroid nodule is detected, the most valuable technique to evaluate these lesions is the cytological examination of a fine needle thyroid aspirate (Murray 1998; Asa and Bedard 2000; Baloch and LiVolsi 2002). It can clearly identify some patients who will require surgery and most of those who are unlikely to require surgery. Cytologic examination can very quickly impart a diagnosis of papillary carcinoma, medullary carcinoma, lymphoma, anaplastic carcinoma or metastatic carcinoma. In contrast to these clearly malignant lesions, the majority of thyroid aspirates yield a benign diagnosis, which is either thyroiditis or a follicular lesion, a benign proliferative process usually associated with abundant colloid storage. Nevertheless, there is a population of patients whose thyroid aspirates yield abundant follicular epithelial cells with atypia consistent with a neoplastic process; these lesions cannot be classified based on cytology alone and surgery is required to allow thorough histopathological analysis to identify or exclude invasive behavior that distinguishes benign from malignant neoplasms.
3.2 Methods of Screening

There are currently two methods of screening for thyroid cancer, genetic testing and thyroid cytology.

3.2.1 Genetic testing

Genetic screening should be focused on patients with a suggestive family history or other features of multiple endocrine neoplasia. The genetic approach relies on peripheral blood sampling for DNA mutational analysis. At this stage of our knowledge this applies mainly to medullary thyroid cancer. The patient with medullary thyroid cancer should have access to clinical genetic services and RET genetic testing. All patients with medullary thyroid cancer should be offered genetic counseling and RET mutational analysis. Hence, evaluation of suspected medullary thyroid cancer includes fine needle aspiration biopsy, measurement of plasma calcitonin and CEA. In patients with medullary thyroid cancer, associated endocrinopathies should be identified (MEN2A and 2B) including pheochromocytoma and primary multiglandular hyperparathyroidism. These can be excluded in new patients with medullary thyroid cancer by measuring 24 urinary catecholamines including metanephrines and serum calcium as well as parathyroid (PTH) hormone. Minimum treatment is total thyroidectomy and level six nodal dissection. Life long follow-up is essential, including monitoring of the tumour markers calcitonin and CEA.

Prophylactic surgery should be offered to disease-free carriers of germline RET mutations identified by genetic screening programs. The possibility of future surgery should be discussed with parents before considering testing their children. The timing of prophylactic thyroid surgery is beyond the scope of this protocol.

3.2.2 Fine Needle Aspiration

The second major diagnostic approach involves testing on the tumor sample itself. This often performed by cytologic and DNA and/or RNA testing on cells obtained from a fine needle aspirate.

Image-guided Thyroid Biopsies

Thyroid nodules should be biopsied, whenever possible, by palpation. Listed below are the criteria for image-guided biopsies.

A. Irrespective of size
- Marked hypoechoigenicity
- Presence of microcalcifications
- Nodule taller than width (AP dimensions > side to side dimension)
- Spiculated margins

B. Nodules larger than 1.0 cm
Any of criteria met under “A” and:
- Hypoechogeticity (compared to background of the thyroid)
- Macrocalcification

C. Nodules larger than 4.0 cm

Any of criteria met under “A” and:
- Predominantly cystic (>80-90% cystic) and if the solid component does not have any of the above characteristics. If solid component displays any of the characteristics mentioned in the first 2 groups, then they would be classified under the above mentioned groups.
- Uniformly isoechoic / Hyperechoic
- Spongiform

In the presence of a morphologically abnormal neck node, biopsy of the most significant ipsilateral thyroid nodule will be performed as per the criteria above.

Patients with high risk factors (family history, prior neck irradiation, type 2 MEN), nodules may requiring sampling irrespective of imaging characteristics.

Biopsies will not be performed for diffuse thyroid disease, but for any nodule in background of diffuse disease based on ultrasound characteristics described above.

In multi-nodular goiters nodule(s) to be biopsied will be selected based on the criteria above. Only up to 2 nodules are typically sampled in one sitting. If the patient needs 3 or more nodules to be sampled based on the criteria above, this maybe scheduled at a future date.

3.2.3. Thyroid Cytopathology

Current general FNA diagnostic criteria

- General diagnostic category
  - 6 tiered scheme
    - Non-diagnostic or Unsatisfactory
    - Benign
    - Follicular lesion (Atypia) of undetermined significance
    - Neoplasm (or suspicious for neoplasm)
      - Follicular neoplasm
      - Hürthle cell neoplasm
    - Suspicious for malignancy
    - Malignant

1. NON-DIAGNOSTIC ASPIRATES:

- Non-diagnostic or Unsatisfactory
For application to:
- Limited cellularity
- Poor fixation and preservation
- Cyst contents
  - BUT, unsatisfactory with cyst contents to be separated from the unsatisfactory due to low cellularity (but not cystic)

E. Cibas (AJCP 2009;132:658-665 & Thyroid 2009;19:1159-1165)
- Advocates epithelial quantitation
  - 6 groups of epithelial cells, each composed of at least 10 cells

Non-diagnostic or Unsatisfactory management
ATA recommendation 6
- (a) US guidance should be used when repeating the FNA procedure for a nodule with an initial non-diagnostic cytology result {evidence based strong}
- (b) Partially cystic nodules that repeatedly yield non-diagnostic aspirates need close observation or surgical excision. Surgery should be more strongly considered if the cytologically non-diagnostic nodule is solid {evidence based fair}

2. BENIGN ASPIRATES:

Benign
- Low risk of malignancy (0-3%)
- Subcategories:
  - “Consistent with benign follicular nodule”
    - Nodular goiter, colloid nodule, hyperplastic/adenomatoid nodule (follicular nodular disease)
  - “Consistent with lymphocytic (Hashimoto) thyroiditis in proper clinical context”
  - “Consistent with granulomatous (subacute) thyroiditis”
  - Other

Benign nodule management
ATA Recommendation 11
- If the nodule is benign on cytology, further immediate diagnostic studies or treatment are not routinely required {evidence based strong}

ATA recommendation 14
- (a) …all benign thyroid nodules be followed with serial US examinations 6-18 months after initial FNA.
  - If stable (no more than 50% change in volume or <20% increase in at least 2 nodule dimensions) the next follow-up US every 3-5 years {expert opinion}
• (b) …if there is evidence for growth (more than 50% change in volume or 20% increase in at least 2 nodule dimensions) FNA should be repeated, preferably with US guidance {evidence based fair}

ATA recommendation 15
• Recurrent cystic thyroid nodules with benign cytology should be considered for surgical removal or ablative ethanol injection based on compressive symptoms and cosmetic concerns {evidence based fair}

3. INDETERMINATE OR FOLLICULAR LESION OF UNDETERMINED SIGNIFICANCE (FLUS):

➢ Follicular Lesion of Undetermined Significance
  ❖ This is abbreviated as “FLUS”
  ❖ Alternative name “Atypia of Undetermined Significance” (AUS)
  ❖ Cytomorphology
    • “Not benign” or “not neoplasm” or “not suspicious”
    ❖ Situations in which it may be used
      – Samples with technically compromised morphology
        » Nuclear morphology is not discernible
        » Much of the epithelium is obscured by blood or other artifact
      • (Cibas & Ali. Thyroid 2009;19:1159-1165.)
        – Microfollicular predominant pattern, but not enough for follicular neoplasm (i.e. in sparsely cellular FNA)
        – Predominance of Hürthle cells in sparsely cellular FNA with scant colloid
        – Moderate to marked cellularity, exclusively Hürthle cells, yet clinical setting suggests benign Hürthle cell nodule (Hashimoto’s thyroiditis or multi-nodular goiter)
        – Focal features of papillary carcinoma (grooves, enlarged nuclei, pale chromatin, altered nuclear contour/shape) in an otherwise benign appearing sample
          » Especially in Hashimoto or with abundant colloid
        – Cyst-lining cells with grooves, prominent nucleoli, nuclear elongation and/or intranuclear inclusions in an otherwise predominantly benign appearing sample
        – Minor population of follicular cells with nuclear enlargement and prominent nucleoli
        – Atypical lymphoid infiltrate, (in which repeat aspirate for flow cytometry is desirable) but not sufficient to consider suspicious for malignancy

➢ Follicular Lesion of Undetermined Significance
  ❖ Used in approximately 3-18% of reports
• But varies widely
• Recommendations to “try to limit its use to approximately 7% or fewer of all thyroid FNA”
• AUS/Malignancy ratio between 1.0 and 3.0
  ▶ Risk of malignancy 5-15%

➢ FLUS management
  ▶ Clinically FLUS gets lumped with the other “indeterminates”
    • Follicular neoplasm
    • Hürthle cell neoplasm
  
  ▶ ATA recommendation 9
    • If the cytology reports *follicular neoplasm*, a $^{123}$I thyroid scan may be considered, especially if serum TSH is in the low-normal range. If concordant autonomously functioning nodule is not seen, lobectomy or total thyroidectomy should be considered *(expert opinion)*

  ▶ ATA recommendation 8
    • ….molecular markers (e.g. BRAF, RAS, RET/PTC, Pax8-PPARγ or galectin-3) may be considered for patients with indeterminate cytology on FNA *(expert opinion)*

4. NEOPLASTIC ASPIRATES:

➢ Hürthle cell neoplasm management
  ▶ ATA recommendation 10
    • If Hürthle cell neoplasm, a radionuclide scan is not needed, and either lobectomy or total thyroidectomy is recommended, depending on the lesion’s size and other risk factors *(evidence based strong)*

5. SUSPICIOUS ASPIRATES:

➢ Suspicous for malignancy
  ▶ Suspicous for papillary carcinoma
    • The bulk of cases will be suspicious for papillary ca
  
  ▶ Suspicous for __________
    • Medullary carcinoma
    • Lymphoma
    • Metastasis
    • Others
  
  ▶ Risk of malignancy: 50-75%

➢ Suspicous for papillary carcinoma management
  ▶ ATA recommendation 7
    • If a cytology result is diagnostic of or suspicious for PTC, surgery is recommended *(evidence based strong)*
ATA recommendation 10
• If suspicious for papillary carcinoma, a radionuclide scan is not needed, and either lobectomy or total thyroidectomy is recommended, depending on the lesion’s size and other risk factors [evidence based strong]

6. MALIGNANT ASPIRATES:

- Malignant
  - Risk of malignancy 97-99%
- Papillary carcinoma management
  - ATA recommendation 7
    • If a cytology result is diagnostic of or suspicious for PTC, surgery is recommended [evidence based strong]
3.2.4 Section References:

1. **Kim criteria** *(AJR 2002 178:687-91)*
Any single of the criteria below irrespective of size:
- Marked hypo-echogencity
- Irregular or microlobulated margins
- Microcalcification
- Taller than wide

All hypoechoic nodules + one of following features:
- Irregular margins
- Intranodular vascularity
- Longer than wide
- Microcalcification

- >1cm if micro calcification present
- >1.5cm if solid, or macrocalcification
- >2cm, if mixed solid/cystic or cystic with mural nodule
  - If nodule has grown substantially

4. **American Thyroid Association** *(J Clin Endocrinol Metab 2008; 93:3037-3044)*
All nodules 1cm or larger unless TSH is low
For <1cm, based on ultrasound features.

5. Presence or absence of growth is not a reliable marker of the malignant or benign nature of a nodule *(Endocr Pract 2006; 12:63-102, Thyroid 2006; 16:109-142, AJR 2010; 194:31-37)*

6. Prevalence of thyroid cancer does not differ between nodules larger or smaller than 1cm. Also, microcarcinoma can have an aggressive course including extracapsular growth and nodal metastases *(JCEM 2002; 87:1941-46 & Clin Endocrinol (Oxf) 2004; 60:21-28)*

7. AJR 2010; 194:31-37
9. Radiographics 2007; 27:847-865
11. AJR 2011; 196:655-660
12. JCEM 2002; 87:1941-46
13. JCEM 2009; 94:1748-51
4. DIAGNOSIS AND PATHOLOGY

4.1 Diagnostic Surgical Pathology

_Tumors of thyroid follicular cell derivation_ are the most common neoplasms of the endocrine system. They include benign follicular adenomas, well-differentiated papillary or follicular carcinomas, poorly differentiated "insular" carcinomas, and dedifferentiated anaplastic carcinomas. Among human malignancies, they include the most benign and non-lethal occult papillary microcarcinomas that are found incidentally in up to 24% of the adult population, and one of the most rapidly lethal malignancies, the anaplastic carcinomas that frequently result in death by strangulation in less than 6 months.

_Follicular Nodules of the Thyroid_

Follicular nodules may be hyperplastic, benign follicular adenomas or malignant lesions which include follicular carcinoma and follicular variant papillary carcinoma.

Like in parathyroid and adrenal cortex, _hyperplasia_ may be extremely difficult to distinguish from _neoplasia_. Although there are rigid criteria for this distinction, in many instances the disease is not as defined as classical teaching has suggested. Generally speaking, hyperplasia is a multifocal disorder in which lesions are poorly encapsulated. The nodules of nodular hyperplasia exhibit architectural as well as cytologic heterogeneity and this is truly the hallmark of this disease. In contrast, a follicular neoplasm generally represents a solitary encapsulated lesion that is uniform both in cytology and architecture. Architecturally these lesions may be macrofollicular, in which case they are somewhat difficult to distinguish from hyperplastic nodules; microfollicular lesions are more cellular and worrisome but may also represent part of the spectrum of hyperplasia. Clonality studies have indicated that classical teaching may, in fact, be wrong. Although multinodular hyperplasia is expected to be a polyclonal disease, the dominant nodules in multinodular goiters are often monoclonal, raising serious doubts about our diagnostic criteria. Moreover, the evidence of clonal proliferation in sporadic nodular goiter indicates that the thyroid is a site for the hyperplasia-neoplasia sequence. Nevertheless, clinical experience has shown us that the vast majority of these lesions remain entirely benign. The terminology "Follicular Nodular Disease" is recommended to avoid the use of inappropriate terminology for this disorder (Boerner and Asa 2010).

The criteria for the diagnosis of _malignancy in a follicular neoplasm_ require the presence of vascular or capsular invasion. Nuclear and cellular atypia and mitotic figures may be present in adenomas as well as in carcinomas and therefore cytologic characteristics are not helpful in this regard. Follicular carcinomas cannot, therefore, be distinguished from follicular adenomas by fine needle aspiration cytology. However, there are additional tools that are facilitating this diagnosis; for example a novel marker of malignancy in these lesions is HBME-1, a monoclonal antibody directed against an unknown epitope that is expressed in malignancy but not benign thyroid follicular epithelial cells. More recently, another marker of follicular carcinoma is the detection of PPARγ that is aberrantly expressed due to a gene rearrangement that places PPARγ under the control of the thyroid transcription factor Pax 8 in follicular carcinoma (Kroll et al. 2000).

Follicular carcinomas exhibit a wide range of biologic behaviours that are reflected by morphologic criteria. Capsular invasion is usually divided into two groups. _Widely invasive follicular carcinomas_, which are usually identifiable as invasive grossly, and certainly are not difficult to recognize as invasive microscopically, carry a poor prognosis with a 25-45% ten-year
survival. In contrast, the more common scenario is that of minimal capsular invasion. This requires very careful and thorough examination of the entire capsule of the follicular neoplasm by the pathologist. *Minimally invasive follicular carcinoma* is identified by total thickness invasion through the capsule superficially into the adjacent parenchyma but not widely beyond the capsule. Borderline lesions include those with invasion into the capsule beyond the bulk of the lesion but not through the full thickness of the capsule or situations in which islands of tumor are trapped within a capsule, associated with perpendicular rupture of collagen. The finding of nests, cords, or individual tumor cells within a tumor capsule leads some pathologists to the diagnosis of minimally invasive follicular carcinoma, however, this may represent an artifact in a patient who has undergone fine needle aspiration biopsy, with trapping by fibrosis or displacement of tumor cells into the capsule. The pathologist is therefore advised to carefully search for evidence of fine needle aspiration biopsy in the adjacent tissue. This would include finding focal hemorrhage, deposition of hemosiderin-laden macrophages, the presence of granulation tissue and/or fibrosis, all of which would indicate a needle biopsy site and the possibility of artifactual invasion rather than true invasion.

The careful search for minimally invasive carcinoma is time consuming and difficult for even the most diligent pathologist. Recent data suggest that this search may be unnecessary since it would appear that patients with minimally invasive carcinoma have almost 100% ten-year survival rates and therefore some argue that this disease does not need to be distinguished from follicular adenoma. Nevertheless, the investigators that have reported these data have treated their patients for carcinoma rather than for benign disease. Rather than endorsing a cavalier approach that would entail less work for the pathologist, it behooves us to recognize the presence of potential malignancy, to treat the patient appropriately, but also to identify the excellent prognosis that these lesions carry after appropriate management.

*Angioinvasive follicular carcinomas* are aggressive and require management accordingly. The criteria for angioinvasion are controversial but a recent publication defines the criteria in use at this institution (Mete and Asa 2011). Using these criteria, the identification of vascular invasion predicts a high likelihood of distant metastasis (Mete and Asa 2011) that should provoke a more aggressive management protocol.

The last few decades have seen a decrease in the incidence of follicular thyroid carcinoma, probably due to dietary iodine supplementation. However, misdiagnosis of this tumor continues. Benign lesions, such as partly encapsulated hyperplastic nodules or nodules exhibiting pseudo-invasion after fine needle aspiration, are often over-diagnosed as malignant; papillary carcinomas with follicular architecture are often misinterpreted as follicular carcinoma. The clinical features, pathophysiology, and biological behavior of follicular cancer differ significantly from those of the entities with which it is often confused. Only careful histopathologic classification will permit accurate evaluation of treatment options and prognosis.

**Papillary Lesions**

Papillary nodules of the thyroid are usually malignant but occasional benign papillary tumors are identified.

*Papillary Hyperplasia*

Papillary lesions are seen focally in *nodular goiter* with or without associated hyperfunction; "hot" nodules are usually associated with increased uptake on radionucleotide scan.
The so-called "papillary hyperplastic nodule" most likely represents a benign neoplasm of the thyroid. These are said to occur most commonly in teenage girls. They present as solitary nodules and may be associated with clinical hyperfunction. Benign papillary neoplasms in adults may result in clinical toxicity and a "hot" nodule on radionuclide scanning. These lesions are encapsulated, often show central cystic change and have subfollicle formation in the centers of broad edematous papillae. They are distinguished from papillary carcinoma by lack of nuclear atypia (see below).

**Papillary Carcinoma**

Papillary carcinoma comprises more than 80% of thyroid epithelial malignancies in countries where goiter is not endemic. The name "papillary carcinoma" is historic and often is misleading. In fact, the architecture of these neoplasms varies from an almost pure papillary pattern to a pure follicular pattern; many tumors have a mixed papillary and follicular pattern. It is now recognized that the diagnosis of papillary carcinoma is based on cytologic criteria, as specified in the WHO classification on thyroid tumors, "a distinctive set of nuclear characteristics." No one specific feature is absolutely diagnostic of papillary carcinoma; usually one relies on a constellation or combination of nuclear features for the diagnosis. These nuclear features may be accompanied by more easily recognized psammoma bodies and the presence of high molecular weight cytokeratins, which are readily localized in formalin-fixed paraffin-embedded tissue when microwave antigen retrieval is applied. Identification of high molecular weight cytokeratins confirms the suspected diagnosis of papillary carcinoma in approximately 60% of cases. Other markers of papillary carcinoma include HBME-1 (see follicular lesions, above) and ret. The ret tyrosine kinase, that is expressed in thyroid C cells and exhibits somatic activating mutations in medullary thyroid carcinomas and germline activating mutations in MEN-2, is usually not expressed in thyroid follicular epithelial cells. However, there are several variants of gene rearrangements, known as ret/PTC, that result in expression of the carboxy terminus of ret in papillary carcinoma. Detection of such a rearrangement by immunostaining for ret can facilitate diagnosis in difficult cases.

Thyroid tumors exhibiting the nuclear characteristics of papillary carcinoma diffusely or multifocally should be diagnosed as papillary carcinoma rather than as follicular carcinoma. These lesions share certain clinical characteristics such as biological indolence and an excellent prognosis with a 20-year survival rate of 95% or better. Papillary carcinomas invade lymphatics, leading to a high percentage of regional lymph node metastases. Metastases beyond the neck are unusual in common papillary carcinoma and probably only occur in about 5 to 7% of cases. The criteria for angioinvasion are controversial but a recent publication defines the criteria in use at this institution (Mete and Asa 2011). Using these criteria, the identification of vascular invasion in a differentiated papillary carcinoma predicts a high likelihood of distant metastasis (Mete and Asa 2011) that should provoke a more aggressive management protocol.

**Aggressive Tumors of Follicular Cell Derivation**

Specific morphologic features can identify tumors that are more aggressive than the usual well differentiated follicular or papillary malignancies derived from follicular epithelial cells. For example, the tall cell variant of papillary carcinoma is recognized to behave in a much more aggressive fashion. These tumors have a height to width ratio that exceeds 3:1. Tumors that exhibit this feature in more than 30% of the tumor mass generally are found in older patients who have extra-thyroidal extension and these patients have a guarded prognosis.
The identification of insular dedifferentiation marks a tumor that requires much more aggressive management. Insular carcinoma, also known as poorly differentiated carcinoma, is a tumor that exhibits a behaviour intermediate between well differentiated thyroid cancer and anaplastic carcinoma. These lesions are identified by their architectural growth pattern; they form solid nests of epithelial cells that resemble neuroendocrine carcinoma more than a follicular lesion, however, they generally contain thyroglobulin immunoreactivity to characterize their differentiation.

Anaplastic thyroid carcinomas are composed of undifferentiated cells that may exhibit three general patterns but most tumors manifest mixed morphology. The most common type is the giant cell variant; as the name suggests, these tumors are composed predominantly of large cells with abundant cytoplasm and bizarre, often multiple, hyperchromatic nuclei. The squamoid variant is composed of large cells that form nests, resembling squamous carcinoma. Spindle cell anaplastic carcinomas have a fascicular architecture and dense stromal collagen with spindle-shaped tumor that may resemble fibrosarcoma (LiVolsi 1990). In all three variants, mitotic figures and atypical mitoses are frequent. There is usually extensive necrosis and in some cases, necrosis may be so extensive that the only viable tumor is around blood vessels. Anaplastic carcinomas are highly infiltrative, destroying thyroid tissue and invading skeletal muscle, adipose tissue and other peri-thyroidal structures. Blood vessel invasion and thrombosis with or without tumor cell involvement is frequent. These lesions usually have no immunoreactivity for markers of thyroid cells and are often a diagnosis of exclusion.

The reported association between well-differentiated thyroid carcinoma and anaplastic carcinoma ranges from 7% to 89% of cases, however, the lower figures are likely underestimates, attributable to inadequate sampling. The data suggest that anaplastic carcinoma originates most often in an abnormal thyroid; the tumor has a higher incidence in regions of endemic goiter and a history of goiter is reported in over 80% of cases. As stated above, nodular goiter is often the site of monoclonal proliferation, the first step in the hyperplasia-neoplasia sequence. However, it is difficult to document transformation of a benign lesion to a malignant tumor. Insular carcinoma appears to be intermediate in the spectrum, and may represent a transition form. The association of papillary carcinoma, particularly the more aggressive tall cell variant, with anaplastic tumors has also been described. The factors underlying dedifferentiation in thyroid tumors remain to be established; age and radiation have been implicated. Clearly, the vast majority of well-differentiated thyroid lesions do not undergo such transformation. A pattern of genetic mutations resulting in oncogene activation or loss of tumor suppressor gene activity has been proposed to correlate with the stepwise progression from adenoma to carcinoma and through the de-differentiation process in thyroid. The significance of microscopic anaplastic change is controversial; some people have suggested that focal microscopic anaplastic dedifferentiation does not alter prognosis but others have shown that this finding alone is statistically significant as a marker of aggressive behaviour.

4.2 Prognostic factors

Prognostic factors in neuroendocrine tumors are generally extent of disease and sometimes involve patterns of hormone production. Some genetic factors are also predictive; for example, familial medullary thyroid carcinoma (FMTC) with or without the association of MEN-2A syndrome has a better survival than that associated with MEN-2B syndrome and has been associated with better survival than sporadic medullary thyroid carcinoma. However, in patients
matched for age, extent of tumor and lymph node involvement, survival is similar for those with the hereditary and sporadic medullary thyroid carcinomas. Any differences in survival of hereditary and sporadic cases may be due to earlier diagnosis in high-risk patients that are screened for hereditary medullary thyroid cancers. Although presenting at an earlier age, patients with MEN-2B have more advanced disease and poorer survival than those with MEN-2A. Younger age and female gender are generally reported as favorable prognostic indicators in this disease. The presence of lymph node involvement affects survival adversely, as does extension through the thyroid capsule. The most important predictive factor for survival is biochemical cure, measuring calcitonin after surgery. However a decrease in the calcitonin level may indicate progression to a poorly differentiated tumor. Carcinoembryonic antigen (CEA) has also been used as a marker for disease progression in medullary thyroid carcinoma, a short CEA doubling time is associated with rapidly progressive disease.

The most useful prognostic markers in well-differentiated carcinomas of thyroid follicular epithelium are patient variables, tumor size and extent of disease. Age is the single most important prognostic factor. Patients under the age of 45 usually have an excellent prognosis; in contrast those over 45 years of age generally have a poorer outlook. Sex has also been said in the past to be an important determinant of tumor biology but more recent studies have suggested that there is no major difference in the behavior of these carcinomas in men compared to women. Tumor size is exceedingly important. Tumors less than 1 cm are common and appear to be different biologically than larger tumors; a recent study has shown that occult papillary carcinomas are identified in up to 24% of the population in thyroids that are removed for non-malignant or unrelated disease. In contrast, tumors greater than 1 cm are thought to be of clinical significance and those larger than 3 cm generally have a poorer prognosis than do smaller tumors. The presence of cervical lymph node metastases, whether microscopic or identified clinically, is thought to increase the risk of recurrence of disease but has been shown to have no impact on mortality. Extra-thyroidal extension, in contrast, predicts a worse prognosis and the presence of distant metastases is the hallmark of an aggressive tumor that will bear the potential for high mortality. In patients who have metastatic disease, the site of metastases, the size of metastases and the ability to take up radioiodine are important factors. The value of novel molecular markers in determining the prognosis of differentiated thyroid cancer remains to be established. Alterations in cell cycle control elements including cyclin D1 over-expression and under-expression of the cyclin-dependent kinase inhibitor p27 predict regional metastatic thyroid cancer growth (Khoo et al. 2002; Kondo et al. 2006) Cheng et al 2011) and positivity for biomarkers including HBME-1, CK19 and galectin-3 also predict lymph node metastases and more aggressive local behavior.

4.3 Section References:


LiVolsi VA (1990) Surgical Pathology of the Thyroid. W.B. Saunders: Philadelphia, P.A


5. MANAGEMENT

5.1 Early Stage Cancer

Surgical treatment of differentiated thyroid cancer

The relationship between volume of thyroid surgery by individual surgeons and outcomes is complicated, however there is a strong case for patients with thyroid cancer to be operated on and treated by clinicians who have appropriate training, experience and continued practice in this area.

Regular audit of outcomes and complications of surgery undertaken by members of the multidisciplinary team will help in the maintenance of skill and professional development.

5.1.1 Preparation for Surgery

Informed consent: should be obtained from all patients after full discussion of treatment options. The operating surgeon should normally obtain this consent.

The specific complications of thyroid surgery, as well as those complications which can occur during any surgical procedure, should be documented in the patient’s chart. The patients should be provided with appropriate information sheets.

Prophylactic heparin: preparations are not required for routine use in patients undergoing thyroid surgery. VTE prophylactics should be used in patients at high risk of thromboembolic events.

5.1.2 Surgical treatment options

Thyroid surgery – the main stay of treatment for differentiated thyroid cancer of surgery; the following terminology should be used:

Lobectomy: the complete removal of one lobe of the thyroid

Hemithyroidectomy: the complete removal of one lobe of the thyroid including isthmus

Near total Lobectomy: total lobectomy leaving behind only the smallest amount of thyroid tissue (less then 1 gram) to protect the recurrent laryngeal nerve.

Near total thyroidectomy: the complete removal of one thyroid lobe (lobectomy) and the near total lobectomy on the contralateral side or a bilateral near total procedure. This should be clearly defined in the operative notes.

Total thyroidectomy: the removal of both thyroid lobes, isthmus, and pyramidal lobe of the thyroid gland.
The terms sub-total lobectomy and sub-total thyroidectomy are imprecise and should be avoided. The classically described sub-total lobectomy or sub-total thyroidectomy procedures are inappropriate for the treatment of thyroid cancer.

The recurrent laryngeal nerve should be identified and preserved in virtually all instances, permanent damage to a recurrent laryngeal nerve should occur in significantly less then 5% of patients who have undergone surgery for thyroid cancer; bilateral injuries are extremely rare. Of note – nerve injury rates are higher after re-operative procedures.

Attempts should be made to preserve the external branch of the supralaryngeal nerve, by ligation of the superior thyroid vessels at the capsule of the thyroid gland. Parathyroid glands should, whenever possible, be identified and preserved if their vascular supply is deemed to be compromised. The glands should be excised, biopsied, and re-planted into muscle.

It is of note that formal lymph node dissection of the central compartment of the neck (level VI) is associated with an increased risk of post-operative hypoparathyroidism, both transient and permanent.

**5.1.3 Indications for Surgery for Papillary Thyroid Carcinoma**

a. An adequate fine needle aspiration, as discussed above, should reliably diagnose the majority of papillary thyroid carcinomas. A definitive cytologic diagnosis mandates the appropriate surgery as below. There is no indication for intraoperative consultation once the diagnosis is established as the false positive rate of cytology is exceedingly low. In cases where cytology is “suspicious” for papillary carcinoma, the surgery should be determined in consultation with the patient, explaining the potential need for a second operation.

b. Patients with node-negative cancer of 1 cm diameter or less can be adequately treated by lobectomy followed by thyroid hormone therapy.

c. In most patients, especially in those with tumors greater than 1cm in diameter, multifocal disease, extrathyroidal spread, familial disease, those with clinically involved nodes, total thyroidectomy is indicated. Total thyroidectomy is also indicated where there is a history of prior neck radiation exposure in childhood.

**5.1.4 Indications for completion thyroidectomy and neck node dissection**

d. If the diagnosis of thyroid cancer has been made after thyroid lobectomy, completion of thyroidectomy should be considered at 8-12 weeks following histologic diagnosis of malignancy. In patients with clinically uninvolved nodes, but who are deemed to be at higher risk (age greater than 45 yrs, tumors greater than 4 cm in diameter, extracapsular or extrathyroidal extension, poor differentiation or lymphovasular invasion, total thyroidectomy and level VI node dissection on the ipsilateral side should be performed (see Figure 2). Palpable disease at level VI nodes discovered at surgery is treated by a level VI central neck
node dissection. When suspicious or clinically-involved nodes are apparent preoperatively, or encountered at surgery in the lateral neck, then a selective neck dissection (level IIA to VB) is recommended to preserve the accessory nerve, sternocleidomastoid muscle and internal jugular vein. See diagram below:

Fig. 2: Levels of neck lymph node involvement in Thyroid Cancer
5.2 Surgery for Follicular Thyroid Carcinoma

A fine needle aspiration cannot distinguish thyroid follicular adenoma from follicular carcinoma; therefore a cytologic diagnosis of follicular neoplasm usually mandates lobectomy as the minimal surgical procedure.

Frozen section examination is of no value when the fine needle aspiration biopsy is that of a follicular neoplasm. If definitive histology reveals a follicular adenoma or hyperplastic nodule, no further treatment is required. Follicular carcinoma under 1 cm in diameter with minimal capsular invasion should be treated by lobectomy alone. Patients with follicular carcinoma showing evidence of vascular invasion should be treated by total thyroidectomy. Patients with follicular carcinomas more than 4 cm in diameter should be treated by total thyroidectomy.

Clear recommendations for low risk patients with tumors 1-4 cm in diameter showing minimal capsular invasion only must be individualized and should be at the discretion of the multidisciplinary team.

Palpable or suspicious cervical lymph nodes are dealt with in an identical manner to papillary carcinoma.

5.2.1 Surgery for Papillary Thyroid Microcarcinoma

Patients with well-differentiated thyroid carcinoma less then 1 cm in diameter have an exceedingly low risk of mortality from thyroid cancer, and therefore can be treated adequately by partial thyroidectomy, provided that:

1) there is no evidence of metastasis
2) there is no evidence of vascular invasion
3) there is no evidence of lymph nodal involvement.

5.2.2 Management of Medullary Thyroid Cancer

Types of Surgery

The aims of first time surgical treatment of medullary thyroid cancer are local regional control and to obtain biochemical and well as clinical cure.

All patients with established medullary thyroid cancer should undergo total thyroidectomy, bilateral central compartment node dissection, with the superior limit of the dissection being the thyroid cartilage, the inferior limit the brachial cephalic vein, and the extent laterally the medial boarder of the carotid artery.

Neck node dissection

Patients with pT2 tumors and higher or palpable lymph nodes in the central or lateral compartment or radiologic suspicion of nodal involvement should undergo additional selective
neck dissection of levels IIA to VB on the affected side. In the absence of direct invasion the sternocleidomastoid muscle, internal jugular vein and accessory nerve should be conserved.

Routine dissections of levels I, IIB and VA is not required unless palpable or suspicious nodes at these site. When there is a strong suspicion or evidence of mediastinal nodal involvement below the brachiocephalic vein, the patient should be considered for further surgery, which would require a sternotomy in most cases.

Patients with distant metastasis at presentation often have prolonged survival. Even in the presence of disseminated disease, total thyroidectomy and central compartment node dissection, should be considered to prevent subsequent compromise of the airway, esophagus and recurrent laryngeal nerve.

5.2.3 Clinico-pathologic Risk Stratification

**Low-risk patients exhibit the following characteristics:**

1) No local or distant metastases;

2) All macroscopic tumor has been resected;

3) There is no tumor invasion of loco-regional tissues or structures;

4) The tumor does exhibit aggressive histologic features such as: tall cell, insular, columnar, cell carcinoma) or vascular invasion;

5) and if 131I is given, there is no 131I uptake outside the thyroid bed on the first post-treatment whole-body RAI scan (RxWBS)

**Intermediate-risk patients include those who have any of the following:**

1) microscopic invasion of tumor into the peri-thyroidal soft tissues at surgery;

2) cervical macroscopic lymph node metastases

3) 131I uptake outside the thyroid bed on the whole body scan performed following thyroid remnant ablation

4) tumor with aggressive histology or vascular invasion

5) On-going controversies and other caveats.
The Endocrine Site Group acknowledges that there is a spectrum of severity of lymph node disease, in terms of prediction of thyroid cancer recurrence (See ATA Surgical Affairs guidelines Oct 2012). In particular, low volume central neck nodal disease - < 5 nodes [microscopic or small] with no extranodal extension), are typically associated with relatively good prognosis. This is particularly relevant if there is no evidence of residual disease (ie. negative lateral neck ultrasound, Tg undetectable – although specific Tg cutoff remain unclear. The group acknowledges the importance of neck ultrasound and thyroglobulin levels in assessing risk and in follow up. The group also acknowledges the importance of considering patient treatment preferences, particularly in situations where evidence for or against RAI remains unclear. This includes low risk disease or small volume central neck nodal disease.
RADIATION THERAPY

6.1 Papillary, follicular-variant papillary, and follicular histologies.

Patient Eligibility: Any patient with confirmed histologic diagnosis of classic papillary, follicular-variant papillary, or follicular thyroid carcinoma. Histology should be reviewed, whenever possible, in all patients.

Background: There have been limited randomized controlled trials to guide the management of these tumours. Treatment recommendations are therefore based on retrospective studies and continually updated as new evidence emerges.

The treatment of low risk patients is controversial with little data to support the use of RAI in low risk patients (3). In some centers all patients with tumours greater than 1 –1.5 cm may be treated with thyroidectomy and RAI (4; 5) but some experts recommend that low risk patients (i.e. < 45 years old with tumours < 4 cm and no additional poor prognostic features) may be treated by total thyroidectomy or lobectomy without RAI (6-10) and this is supported by our own data and data from the National Thyroid Cancer Treatment Study Group (11; 12) and recognized by the American Thyroid Association Guidelines (13). Several recent randomized controlled studies have shown that for patients in whom the aim of iodine administration is remnant ablation 30 mCi of 131-I RAI is equally as effective as 100 mCi.

It is important to emphasize that the rate of initial successful remnant ablation following the administration of 100 mCi of I-131 varies significantly between reported clinical trials. This ranged from 64% in the trial from Fallahi et al. (Fallahi 2012), 56% in the trial from Maenpaa et al (Maenpaa 2008), 89% in the trial from Mallick et al (Mallick 2012), 67% in the trial from Pilli et al. (Pilli 2007), 60% in the trial from Zaman et al. (Zaman 2006), to 94% in the latest trial from Schlumberger et al. (Schlumberger 2012).

Moreover, at least one recent RCT comparing low vs. high dose RAI, indicated that the rate of initial successful ablation was 51.6% being 39.2% in the low-dose group and 64.1% in the high-dose group. The relative risk (RR) of unsuccessful ablation for the low-dose versus high-dose was 1.695 [95% confidence interval (CI), 1.34–2.14]. In the low-dose group, more patients needed a second dose of I-131, resulting in a higher cumulative activity (Nucl Med Commun. 2012: 33:275–282).

In another study of 309 DTC patients (285 women and 24 men) 30 mCi of 131I was applied in 86 patients, 60 mCi in 128 and 100 mCi in 95 patients with median follow-up of 10 years (2-12). No significant differences in the 5 years efficacy of thyroid remnant radioiodine ablation using 30, 60, and 100 mCi were observed in low-risk DTC patients. However, patients treated initially with 30 mCi, required second course of radioiodine in 22% compared to 13.3% and 11.2% of those treated with 60 mCi and 100 mCi (Kukulskka et al. Thyroid Research 2010, 3:9).

The general PMH/UHN policy for management of these tumours is guided by risk stratification and includes any combination of the following:

• Total or completion thyroidectomy
• Radioactive iodine (RAI)
• TSH suppression
• External beam radiation in patients at high risk of local relapse

**Objectives:**
• 1. Ablate remnant thyroid tissue with 131-RAI to aid follow up
• 2. Adjuvant 131I-RAI to reduce recurrence in patients at high risk of recurrence
• 3. Therapy with 131I-RAI in patients with documented residual or metastatic disease
• External radiation for extra-thyroidal extension to improve local control.

**Staging:** UICC 7th Edition

**Investigations:** TSH, Free T3, Free T4, thyroglobulin, anti-thyroglobulin antibodies, corrected calcium, and PTH
Pathology review as necessary.
Ultrasound of the lateral neck if not performed before surgery
Whole body iodine scan (WBS) after therapeutic RAI administration
CT scan neck and thorax after RAI if known or suspected gross residual disease
CT scan thorax if WBS shows lung or other metastases

**Treatment Policy:** Gross Tumour Present
• Reassess for feasibility of surgical excision
• RAI if total thyroidectomy performed
• External beam radiotherapy (XRT)
Gross Tumour Absent

**Risk Definition:**
The prognostic factors for survival in differentiated thyroid cancer are well-recognized. The major factors are (14; 1; 2; 15):
• Age (greater than 50)
• Primary tumor size
• Local extent of involvement
• Vascular invasion
• Lymphovascular invasion
• Differentiation (presence of tall cell, insular, or poor differentiation)
In addition for local recurrence:
• Lymph node involvement. Macroscopic metastatic nodes are of greater concern for risk of recurrence.

**Risk stratification**
Although there are known risk definition tools for survival but not recurrence (MACIS, AGES, AMES) none are ideal. MACIS has the advantage of being based on the largest series.

**6.1.1 LOW RISK:**
In low risk patients the aim of RAI is to ablate remnant thyroid tissue and aid follow up with thyroglobulin and imaging studies but its value in terms of a favorable benefit:risk ratio in many cases remain uncertain.
There is no good evidence to support benefit from RAI in T1N0 tumours, particularly if the tumor size is < 1.5 cm. RAI is not recommended for T1N0 tumors. For T2 and T3 tumors, in the absence of randomized data and conflicting conclusions from retrospective reviews and the known risks of radioactive iodine ablation (3; 16-19) treatment is to be individualized and decided on discussion with patient.

*Low risk may be sub-grouped as follows:
A. RAI is not recommended
T1N0 carcinomas.

B. Those who probably do not require ablation but if it is the patient’s preference to proceed with RAI, 29.9 mCi will be prescribed
– Under age of 50 T2 (without clinical and histological extra-thyroidal extension and without unfavorable histological features*)
(Some N1a with microscopic local nodal involvement)
– Over age of 50 T2 (MACIS < 6)

C. Those who may benefit from RAI ablation with 29.9 mCi
– Under age of 50 T3 MACIS < 6, or any N1a disease (with microscopic nodal involvement)
– Over age of 50 T2, pT3 (<4 cm with histological minimal extra-thyroidal extension but no evidence of clinical extra-thyroidal extension), or any N1a disease
- Any age T1 tumors with unfavorable histological features* or macroscopic multifocal disease in the thyroid gland.
*Unfavorable histologic features include any one of the following: tall cell, hobnail cell, columnar cell change in a significant part of the tumor (>30% of tumor), solid growth (>30%), widely invasive growth, angio-invasive, any level of dedifferentiation and intrathyroidal psammomatous dissemination.

Our suggested approaches include:

A. Lobectomy only performed

• thyrroxine replacement without complete suppression of TSH
 OR
• Completion thyroidectomy
 and
• thyrroxine replacement without complete suppression of TSH
 or
• RAI 29.9 mCi-RAI and thyrroxine replacement without complete suppression of TSH

B. Total thyroidectomy performed

• Thyrroxine replacement without complete suppression of TSH
 or
• RAI 29.9 mCi I131 and thyrroxine replacement without complete suppression of TSH

6.1.2 INTERMEDIATE RISK:
For 70-125mCi
These are patients who are:
– Under age of 50: N1a with macroscopic lymph nodes, or T4a extrathyroidal extension
– Over age of 50: clinical T3 with extra-thyroidal extension (ETE), T4 or N1a
– Any age: N1b (please see surgical section for anatomic illustration)
– Any age: MACIS >6
– Any age: T2 with poor histologic features*

The influence of nodal disease on prognosis is controversial. Although the Mayo report did not find nodal involvement influenced survival risk, analysis of our PMH/UHN data suggested that nodal involvement affected recurrence risk (9, 21). There may be a difference in prognosis depending on site of nodal involvement. N1a disease is more commonly seen as surgeons perform more unilateral and bilateral central compartment dissection. By extension from the Mayo data surveillance without RAI may be appropriate for patients with N1a disease especially if nodal disease is microscopic and otherwise good prognosis.3

Our suggested approach is as follows:
Lobectomy only performed
• Completion thyroidectomy
• RAI 70-125 mCi and TSH suppression

Total thyroidectomy performed
• RAI 70-125 mCi and TSH suppression

6.1.3 HIGH RISK:
The use of adjuvant XRT is controversial but our data from the PMH/UHN and elsewhere suggest it is beneficial in selected patients, especially older patients with clinical Stage (cT4) disease, i.e. gross extra-thyroidal extension but may be beneficial in highly selected younger patients i.e. T4b or extensive T4a disease and poor histological features (12, 20-22).

Our suggested approaches are as follows:
Lobectomy only performed
• Completion thyroidectomy
• RAI 125 – 200 mCi-I131
• TSH suppression
• XRT (who meet the criteria described above)

Total thyroidectomy performed
• RAI 125 – 200 mCi-I131
• TSH suppression
• XRT (who meet the criteria described above)

6.1.4 RECURRENT DISEASE:
• Surgical resection whenever possible
• RAI unlessrecurred after 2nd administration of RAI and no evidence of uptake
• XRT to thyroid bed or cervical and upper mediastinal nodes if nodal recurrence despite adequate previous RAI therapy

METASTATIC DISEASE:
Lung
RAI 200 mCi-I131 (consider reducing to 150 mCi if widespread lung metastases)
Bone
RAI 200 mCi-I131
Consider surgical resection if isolated metastases
If not resectable for XRT 50 Gy in 25 fractions

6.1.5 EXTERNAL BEAM TECHNIQUE
Thyroid Bed
Dose
56 Gy in 33 fractions to CTV56 to large volume and
66 Gy in 33 fractions to CTV 66 to reduced volume encompassing GTV with a 1cm margin
adjusted to take into account barriers to invasion (e.g. bone, air)

or
Microscopic residual 50 Gy in 25 fractions over 5 weeks
In selected poorer performance patients consider hypofractionation
Microscopic disease: 40 Gy in 16 fractions

Gross residual disease: 50 Gy in 20 fractions
Volumes Patient simulated in the supine position with extended neck.
Planning CT scan performed and the below contoured
• HTV if preoperative imaging of GTV available
• GTV if gross residual tumour
• CTV defined as the thyroid bed from the hyoid to the suprasternal notch the prevertebral fascia
to the anterior aspects of the transverse processes, laterally to mid sternocleidomastoid,
    encompassing the carotid artery and jugular vein, ensuring adequate coverage of the
    tracheoesophageal groove, the jugular and posterior cervical lymph nodes within the
    limits defined above (including level III, IV, VI, and partially level V nodal regions).
• Adjustments of the encompassed volume are made relative to pre-surgical diagnostic imaging
    and operative reports.
• Submandibular salivary glands and parotid salivary glands
Technique IMRT
Thyroid bed, unilateral or bilateral neck, and superior mediastinum
The whole cervical lymph node chain is rarely treated. The parotid glands should be spared if
possible. Indications for cervical nodal irradiation include gross extracapsular extension
and recurrence post RAI therapy
Dose: Microscopic disease: 50 Gy in 25 fractions over 5 weeks.
Or
56 Gy in 33 fractions to CTV56 to large volume and
66 Gy in 33 fractions (CTV 66) to reduced volume encompassing GTV with a 1 cm margin
adjusted to take into account barriers of tumor spread (i.e. bone, air) and distance from
skin.
Technique: IMRT throughout
Follow-Up:
• Shared among involved physicians and surgeons, including the PMH Endocrine Oncology
  Clinic.
• Monitor with serum thyroglobulin levels.
• Iodine scans 6-12 months following radioiodine therapy with recombinant TSH (rhTSH; Thyrogen) or withdrawal.
• Low risk and some intermediate risks may be followed by thyroglobulin on thyroxine if thyroglobulin is less than 2 μg/L at the time of RAI therapy and there was minimal uptake in the thyroid bed and ultrasound confirms the absence of suspicious lymph nodes.
• Patients treated by lobectomy and TSH suppression may be followed up with neck ultrasound (U/S).
• Other imaging, U/S, CT, MRI, PET scan as appropriate

6.2 Medullary thyroid cancer (MTC) histology

Objectives: To define the role of external beam radiation therapy in MTC.
To identify individuals at risk of developing MTC and prevent with prophylactic thyroidectomy.

Patient Eligibility: All patients with MTC.
Staging: UICC 7th edition
Minimum Investigations: CBC, calcitonin, CEA, Calcium (total & ionized), phosphate, liver function tests, and CXR.
Blood to DNA diagnostic laboratory to detect the RET oncogene in all cases.
CT of the neck, CT of thorax, & liver, bone scan.
Pathology review.

Treatment Policy: Reassess for feasibility of surgical excision if gross tumour present or further lymph node dissection if calcitonin and/or CEA are persistently elevated.
After complete excision and a normal calcitonin: no further treatment (24).
If calcitonin is high and no evidence of metastatic disease but T4a or T4b tumour or extensive lymph node involvement consider external radiation (25-27; 22; 28).
For gross unresectable residual disease: post-operative external radiation.

RT technique: Tumour volume: thyroid bed, bilateral neck, superior mediastinum (mini-mantle).
IMRT Dose: Microscopic residual 50 Gy in 25 fractions over 5 weeks
Gross residual: 56 Gy in 33 fractions (CTV56) to large volume and
66 Gy in 33 fractions to gross disease (CTV66), usually a reduced volume encompassing GTV with a 1cm margin adjusted to take into account barriers of tumor spread (i.e. bone, air), and distance from skin.

Follow-Up: Monitor clinically, biochemically with calcitonin and CEA levels, and radiographically with CT scanning.
The outcome measures are local and distant disease-free state.

6.3 Anaplastic Thyroid Cancer Histology

Background: Anaplastic carcinoma accounts for <5% of malignant thyroid neoplasms. They are frequently lethal despite aggressive therapy. Trials of combined modality therapy (surgery, radiation therapy, chemotherapy) have not improved the poor 5-year survival
rate of about 5-10%. Local disease progression often causes distressing symptoms, with or without distant metastases(29). Because of their poor prognosis, all anaplastic carcinomas are classified as Stage IV by UICC.

**Objectives** : To define a tolerable regimen of accelerated hyperfractionated radiation therapy aiming at local tumor control, while keeping treatment-related toxicity to an acceptable level.

**Patient Eligibility** : All patients with Anaplastic Thyroid Cancer.

**Staging** : UICC 7th edition

Minimum

**Investigations** : CBC, thyroid indices, liver function tests.

CT Neck and Thorax

Bone scan (for patients being considered for radical intent).

Pathology review.

Surgical Oncology opinion as to resectability and adequacy of airway.

**Treatment**

**Policy** : Giant and spindle cell anaplastic cancers: radical radiotherapy following grossly total excision or patients with unresectable local disease, with no evidence of distant spread and good performance status

Hyperfractionated radiotherapy (60 Gy/40 fractions, bid) over 4 weeks.

In older patients or patients with poor performance status 50 Gy in 20 daily fractions over 4 weeks.

Other patients: palliative radiation therapy, dose/fractionation as dictated by patient condition: e.g. 20 Gy/5 fractions, with the option of a second course 4 week later for responding patients (28; 29).

Disease unresponsive to radiotherapy or if distant metastases present: trial of chemotherapy.

Small cell anaplastic thyroid: chemotherapy x 3 (as for small cell lung CA), then radiotherapy (40 Gy/20 fractions).

Radioactive iodine has no role in the management of anaplastic carcinoma, except perhaps in cases where the predominant histology is differentiated (papillary or follicular) with only small foci of anaplastic change(s).

**RT technique** : The target volume should include the known local disease, the thyroid bed, and the immediate peri-thyroidal lymph nodes. No attempt will be made to cover the entire neck or mediastinum in radical treatments unless disease is documented in these sites.

IMRT for all patients except for emergency when treatment can be started as AP:PA especially if 2 phase. Second phase may be IMRT or other technique to spare the spinal cord.

**Follow-up** : Shared among involved physicians and surgeons, including the PMH Endocrine Oncology Clinic. Tumor response usually assessed adequately by physical examination in the clinic.
6.4 Section References:

10. Jonklaas J, Sarlis NJ, Litofsky D, Ain KB, Bigos ST, Brierley JD, Cooper DS, Haugen BR, Ladenson PW, Magner J, Robbins J, Ross DS, Skarulis M, Maxon HR, Sherman SI 2006 Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid 16:1229-1242.
Additional key references:


7. Other therapies:

7.1 Thyroid hormone replacement and suppression

Patients who have received a total thyroidectomy or those who have had a sub-total thyroidectomy but require thyrotropin (TSH) suppression should be placed on synthetic thyroid hormone.

**Low risk patients:** TSH should be in the low normal range (~0.1-0.5 mIU/L).
**Intermediate risk patients:** TSH should be below normal or undetectable with a normal free T4, but can be relaxed after a negative follow up scan and stimulated thyroglobulins.
**High risk patients:** TSH should be undetectable with a normal free T4.

7.2. Targetted therapy with receptor tyrosine kinase inhibitors

As indicated under Sections 3 and 4, thyroid cancer is considered to be a disease driven by intragenic mutations resulting in selective signaling activation. As such, recent efforts have focused on the use of receptor tyrosine kinase (RTK) inhibitors in the control of disease progression. Such agents are currently reserved for those in whom all other therapies have failed. Due to the risk of toxicities such therapies should be medically supervised in the context of a research protocol or other structured monitoring setting.
8. Oncology Nursing Practice and supportive care

8.1 Nursing Patient Care

Refer to general oncology nursing practice

8.2 Patient Education

*Thyroid Cancer Canada* is working towards creating an environment in which people who are dealing with thyroid cancer, especially the newly diagnosed, are met with support and information. *Thyroid Cancer Canada* draws on the medical community to provide a consistent and high standard of support for all individuals dealing with the disease.

TCC’s goals & objectives include facilitating communication among thyroid cancer patients, providing credible information about the disease, providing emotional support, and assisting thyroid cancer patients with voicing their needs to health care professionals and those who are responsible for health care policy.

TCC liaises with groups with similar or corresponding mandates.

TCC governs itself within the values and principles outlined in its By-Laws and Terms of Reference (available by request).

For more information please check: www.thyroidcancer.org

8.3 Psychosocial Care

Refer to general oncology psychosocial care
9. Follow-up Care

Follow-up should be life-long as the disease has a long natural history; late recurrences are uncommon but not unheard of and can be treated successfully. Regular surveillance is necessary for monitoring of treatment, particularly to ensure TSH suppression and for treatment of hypocalcemia. Suppression of serum TSH is one of the main components of treatment in high-risk cases.

Surveillance for recurrence of disease is essential and is based on annual clinical examination, annual measurement of serum thyroglobulin and TSH, annual cervical neck ultrasound, other diagnostic imaging, and fine needle aspiration biopsy where indicated. In patients with particularly high-risk of disease recurrence (i.e. >T1) stimulated thyroglobulin measurements following thyroid hormone withdrawal or following recombinant human TSH (rhTSH; thyrogen) is advised on an annual basis. This is typically carried out for at least 5 years where indicated.