Revised American Thyroid Association
Management Guidelines for Patients with
Thyroid Nodules and Differentiated Thyroid Cancer
Adapted for Nova Scotia

Full Version
Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer Adapted for Nova Scotia

Objectives:

The purpose of this guideline is to provide recommendations for differentiated (papillary and follicular) thyroid cancer care in Nova Scotia based on the Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer in order to:

- Improve the long-term overall and disease-free survival for thyroid cancer patients in Nova Scotia;
- Enhance the health related quality of life of adult patients with thyroid cancers;
- Improve communication of clinically important medical information amongst the health care team through structured reporting and standardized terminology;
- Provide the basis for initial discussion with patients regarding management options;
- Provide a consistent approach to areas of practice variation based on current evidence and expert opinion of thyroid cancer clinicians in Nova Scotia.

This guideline does not address medullary nor anaplastic thyroid cancer in adults or thyroid cancers in the pediatric population. For information about the management of medullary thyroid cancer, see Medullary Thyroid Cancer: Management Guidelines of the American Thyroid Association (http://www.thyroid.org/professionals/publications/documents/MTC_Guidelines.pdf).

Preamble:

Practice guidelines are intended to assist health care professionals with decisions throughout the spectrum of the cancer experience. Guidelines should never replace specific decisions for individual patients, and do not substitute for the shared decisions between any patient and doctor (or other health professional) which are unique to each circumstance. However, guidelines do provide evidence-based background information, consensus-based recommendations for similar problems, and a context for each individual decision.

This guideline provides an overview of recommendations and rationale for the multidisciplinary management of differentiated (papillary and follicular) thyroid cancer in Nova Scotia. Healthcare systems vary and these recommendations may not be applicable in other jurisdictions.

This guideline was developed through a partnership between the Queen Elizabeth II Health Sciences Centre (QEII HSC) Interprofessional Thyroid Oncology Clinic team and Cancer Care Nova Scotia. It is designed for family physicians, surgeons, pathologists, radiologists, other community-based specialist physicians and other health professionals involved with thyroid cancer patients and includes recommendations on:


2 The ATA provides a tool for calculating volume change in nodule on its website (Change in Thyroid Nodule Volume Calculator www.thyroid.org/professionals/calculators/CINV.php)
• Pre-surgical evaluation of thyroid nodules;
• Surgical treatment and complications;
• Pathology reporting, grading and tumour staging (TNM);
• Risk prognostic systems;
• Post-surgical radioactive iodine (RAI) therapy;
• Protocols for lab and diagnostic follow-up;
• Management of local and regional recurrences;
• Early and long-term follow-up; and
• Supportive and palliative care management.

This guideline will be reviewed and revised when the American Thyroid Association guideline is revised. Current versions of this guideline will be available on the Cancer Care Nova Scotia website (http://www.cancercare.ns.ca)

Comment on Clinical Trials:

An important component of treatment decision-making for any patient is the potential for enrollment in relevant clinical trials. The guideline writing team is committed to advancing patient care, through participation in clinical trials. At any point in time, there may be a clinical trial opportunity for any component of this guideline. As specific trials become available, eligible patients may be offered the opportunity to enroll in the relevant trial. Patients are encouraged to discuss clinical trials opportunities with their cancer specialist. Current clinical trials in Canada are listed at www.canadiancancertrials.ca.

Acknowledgements:

Sections of this guideline are adapted with permission from the Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer (Cooper et al., 2009) referred to from this point forward as the ATA Guidelines.

The guideline writing team recognizes that the ATA Guidelines are well-developed and widely accepted guidelines for thyroid cancer. Modifications were limited and were only made under the following conditions:

• The recommended approach is not currently available in Nova Scotia
• Where the evidence was equivocal and/or the ATA panel was unable to make a recommendation for or against a practice, the Nova Scotia panel made a recommendation for a preferred approach
• To provide clarity within the Nova Scotia context
• Where issues of importance to thyroid cancer management in Nova Scotia are not addressed by the ATA Guideline (e.g., recommendations for consistent reporting templates)

The order of the recommendations has changed from the ATA original. All ATA recommendations are clearly indicated in the text and when modifications have been made, these have been clearly indicated as well. A cross-reference of the ATA recommendations to the order in the Nova Scotia guideline as well as explanation for modifications can be found in Appendix 12 (available on the CCNS website). Readers interested in the evidence or rationale behind the ATA recommendations are referred to the original ATA Guideline.

In addition, the European Consensus Statement on the Management of Patients with Differentiated Thyroid Carcinoma of the Follicular Epithelium (Pacini et al., 2006), and The
British Thyroid Association/Royal College of Physicians Guidelines for the Management of Thyroid Cancer in Adults (British Thyroid Association, 2007), were important references.

The development of this guideline was a collaborative effort with input from Surgical Oncologists, Head and Neck Surgeons, Medical and Radiation Oncologists, Endocrinologists, Nuclear Medicine physicians, Radiologists, and Pathologists in Nova Scotia and was sponsored by Cancer Care Nova Scotia. The authors thank everyone involved for their participation and interest in this project.

For More Information:

For further information on this or any other Practice Guideline, please contact Cancer Care Nova Scotia by telephone (902) 473-4645 or 1-866-599-2267, or by e-mail: info@CCNS.nshealth.ca.

Guideline Approval Process:

Cancer Care Nova Scotia, Chief Medical Director - June 2014


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Part I Introduction

Overview of Thyroid Cancer

Although thyroid cancer is relatively rare (less than 1% of all cancers), it has some distinct characteristics:

- While there is a high prevalence of thyroid nodules, only a small proportion are malignant
- The incidence of thyroid cancer is increasing the most rapidly of all major cancers
- Unlike most other cancers, thyroid cancer mainly affects a relatively young (under age 50) population
- Most thyroid carcinomas are indolent and can recur decades later
- It is generally associated with good prognoses with low mortality rates
- However, a notable proportion of cases exhibit aggressive characteristics with significantly higher recurrence and mortality rates
- Unlike other cancers, there is a paucity of clinical trial evidence on which recommendations can be based

As a result, clinicians, patients and the health care system must address a number of unique issues:

- Rapidly increasing volume of patients who require assessment; specialized, multidisciplinary treatment; and long-term monitoring straining the existing cancer system resources
- As a relatively rare cancer, there remains limited knowledge among clinicians about optimal work-up and management
- Wide variations in practice exist based on consensus opinions and historical data
- Thyroid cancer patients face different life challenges than those with other cancers (e.g., mid-career; issues of fertility and raising young families) requiring different aspects of supportive care
- Despite the overall good prognosis, there is significant anxiety and morbidity associated with thyroid cancer diagnosis, management and follow-up
- Judicious and efficient processes are required for diagnosing malignant thyroid nodules and identifying patients who require more aggressive therapy and intense follow-up

The over-riding challenge is to balance the toxicity of initial management and morbidity of long-term follow-up while minimizing recurrence rates and facilitating the early detection of recurrence. Furthermore, this needs to be tailored to the individual patient using a dynamic risk stratification strategy pre-operatively, post-operatively and at the time of assessment of response to adjuvant therapy.

Management of Thyroid Cancer

There are regional differences in recommendations for managing differentiated (papillary and follicular) thyroid carcinoma for initial surgery, radioactive iodine (RAI) therapy (Sawka et al., 2007) and thyroxine suppression therapy in both Canada and the United States. These variations exist due to a lack of clear direction from limited clinical data, particularly prospective randomized trials. Guidance for management of thyroid cancer is derived primarily from studies of large patient cohorts in which therapy has not been randomized.

Most patients can be cured when properly treated by a team of experienced physicians and
surgeons. The initial treatment of choice is surgery with or without thyroxine replacement therapy. Subsequently, only close follow-up is necessary for patients who have pathologically early stage disease without any other adverse factors. The remainder should be considered for post-operative adjuvant therapy with RAI and TSH suppression. External beam radiation and systemic therapy are utilized in more advanced stage disease.

The majority of thyroid cancer cases responsible for the rapidly rising incidence consist of patients with early stage disease. In order to avoid over-treatment and unnecessary treatment toxicity in a patient population with an overall good prognosis, increasing importance is being placed on prognostic factors and risk stratification pre-operatively, post-operatively and at the time of assessment of response to adjuvant therapy. The clinical management of differentiated thyroid cancer has been evolving in the last decade, as advances in diagnosis and therapy become available such as highly sensitive assays for serum thyroglobulin measurement, improved neck ultrasound technology, and the increasing use of recombinant human thyrotropin (rhTSH) (Pacini et al., 2006). Applying a dynamic risk-adapted approach with the incorporation of more cost effective, less invasive and highly-sensitive testing procedures will lead to optimal management of thyroid cancer and provide the best quality of life for patients. Development of efficient strategies for diagnosis, therapy, and surveillance are critical in thyroid cancer care where mortality rates remain low and life-long follow-up care is required.

Need for Coordinated Interdisciplinary Care

Differentiated Thyroid Cancer (DTC) patients require management by a variety of specialists, which can lead to inconsistent and fragmented care, as borne out of studies from various centers (Sawka et al., 2007). Surveys of both thyroid cancer patients and specialists indicate that there is significant variation in care between specialists and facilities. Two-hundred and thirteen (213) participants at the 5th Biennial Course of Management of Thyroid Nodular Disease and Cancer were asked multiple-choice questions and the responses were analyzed by specialty (endocrinology, general surgeons, otolaryngologists, and pathologists). Statistically significant inter-specialty differences were observed in 12 of 19 questions (63%), particularly in the operative and post-operative follow-up of thyroid cancer (Clark & Freeman, 2005).

In the Canadian-specific results of an international survey of thyroid cancer patients conducted in 2010, it was noted there is inconsistency in the identification of thyroid cancer; wait times in Canada to see thyroid cancer specialists and start treatment, particularly in Nova Scotia, were longer than in other countries; there were marked differences in surgical approaches across provinces and variation across treatment centres as to whether patients had RAI treatment, and the use of RhTsh (Thyrogen) preparation in the treatment and testing of thyroid cancer patients varied. From this survey of the Canadian thyroid cancer patient experience, it was ultimately concluded, “Measures should be taken to standardize care across the country to optimize patient care.” (Thyroid Cancer Canada, 2010, p 2)

Thyroid cancer patient focus groups have also confirmed poor and inconsistent coordination of thyroid cancer care among different caregivers (Sawka et al., 2009). Patients with thyroid cancer require interdisciplinary assessment and care early in their cancer journey. Over the past decade, several centers of excellence have developed models of interdisciplinary teams comprising surgeons, radiologists/nuclear medicine physicians, pathologists, radiation oncologists, endocrinologists and allied specialists to deliver coordinated care within hospitals ensuring that individual patients get appropriate and consistent treatment recommendations (Imran & Rajaraman, 2011). Access to a dietitian is important for many patients for assistance with low-iodine diet. Nurses, nuclear medicine technologists and social workers also have key roles in the education and care of thyroid cancer patients. Furthermore, family physicians caring for thyroid cancer patients require support from the interdisciplinary thyroid cancer team at the
time of diagnosis and during long-term follow-up through evidence-based guidelines.

Poor communication between the various specialties can lead to delays in care or less than optimal care if key information is not communicated. Thyroid cancer specialists require information from multiple sources to develop an optimal management plan for each individual that will lead to a rational, risk-based approach to initial and adjuvant therapy, and follow-up studies. Ultrasound, surgical and histological findings may all influence risk stratification, decisions about adjuvant treatment, and follow-up strategy (Carty et al., 2012). As part of this guideline development process, standardized templates for pathology and ultrasound reporting have been developed for Nova Scotia and a goal is to implement these across the province with the expectation that patient care will be improved. At the same time, Nova Scotia is implementing surgical synoptic reporting, which will address the need for standardized surgical information.

In Nova Scotia, diagnosis and surgical management of thyroid cancer is provided across the province but RAI therapy is only available at the through the Interdisciplinary Thyroid Oncology Clinic (ITOC), QEII HSC, in Halifax.

The ITOC was established in 2005 and accepts referrals for differentiated and other forms of thyroid cancer for interdisciplinary assessment and management. In 2010, an evaluation of the ITOC demonstrated improved coordination of care and the provision of consistent recommendations and resulted in improved patient and health provider satisfaction (Rajaraman, Imran, Barnes, & McLean, 2010).

**Epidemiology of Thyroid Carcinoma**

**Incidence**

Thyroid cancers represent approximately 2% of all new cases of cancer in Canada (Public Health Agency of Canada, 2010). Thyroid carcinoma is as prevalent as multiple myeloma, twice as common as Hodgkin’s disease and comparable in frequency to cancers occurring in the esophagus, larynx, mouth and uterus (Cobin et al., 2001). For unknown reasons, women are affected about three times more often than men.

According to the Canadian Cancer Society in 2014, “The incidence rate of thyroid cancer is the most rapidly increasing incidence rate among all major cancers. There was a 6.2% per year increase in males since 2001 and a 4.3% per year increase in females between 2005 and 2010”. (Canadian Cancer Society’s Advisory Committee on Cancer Statistics, 2014, p 21)

Similar increases have been noted in Europe and the United States. Despite the increase in incidence, mortality rates remain low and stable (Canadian Cancer Society’s Steering Committee, 2010).

Possible explanations for the increase in incidence include:

- Earlier stage, asymptomatic cancers being found as a result of improved early detection practices and technologies (e.g., ultrasound and needle biopsy).
- Increased exposure to diagnostic ionizing radiation
- Another unidentified risk factor (Canadian Cancer Society’s Advisory Committee on Cancer Statistics, 2014; How & Tabah, 2007; Kent et al., 2007).

In Nova Scotia, the age-standardized incidence rate in 2014 was 15/100,000 for women and
5/100,000 for men, with 120 new cases estimated (Canadian Cancer Society’s Advisory Committee on Cancer Statistics, 2014).

Thyroid cancer has an unusual age distribution: about 5% of all thyroid cancers occur in patients less than 25 years of age, and incidence rises comparatively slowly with age (Public Health Agency of Canada, 2010). Whereas overall cancer incidence increases with age, with more than half of all diagnoses occurring after age 65, thyroid cancer incidence rates in females sharply increase from early 20s to mid-30s, continue to rise less steeply to mid-40s, remain relatively stable through mid-50s and then decreases. In males, thyroid cancer incidence rates steadily increase from age 20 to mid-70s when they sharply decrease (Public Health Agency of Canada, 2010). Data from the United States Surveillance, Epidemiology, and End Results (US SEER) Program of the National Cancer Institute (NCI) indicates that between 1975 and 2000, thyroid cancer was the fourth most common cancer for those aged between 15-29 (Waguespack, Wells, Ross, & Bleyer, 2006). Recent US SEER data indicates the median age for diagnosis of thyroid cancer was 50 (National Cancer Institute). Thyroid cancer is at least four times more common in women than men under age 50 (Cancer Care Ontario, 2005).

**Thyroid Cancer Incidence NS over time** (Cancer Care Nova Scotia Surveillance and Epidemiology Unit, 2014)
**Female Thyroid Cancer Incidence by Age** (Cancer Care Nova Scotia Surveillance and Epidemiology Unit, 2014)

![Age-Specific Incidence Rate, Thyroid Cancer, Females, Nova Scotia, 2008-2012](image)

**Female All Cancer Incidence by Age** (Cancer Care Nova Scotia Surveillance and Epidemiology Unit, 2014)

![Age-Specific Incidence Rate, All Cancers, Females, Nova Scotia, 2008-2012](image)

**Recurrence**

While thyroid cancer has low mortality rates, recurrence rates are still of concern in a subset of patients. There is continued evolution of the prognostic factors used to identify those at significant risk for recurrence, which can happen in up to 30% of patients, and one-third may have recurrence up to 30 years after diagnosis (Mazzaferri & Jhiang, 1994).
Mortality

Despite the increase in incidence, thyroid cancer mortality rates have remained low and stable. Nova Scotia’s age-standardized mortality rate from thyroid cancer for the period 2007 to 2011 (both sexes) was 0.32 deaths/100,000 with an average of five deaths per year (Cancer Care Nova Scotia Surveillance and Epidemiology Unit, 2014). The Nova Scotia mortality rate is similar to the Canadian rate.

Histology and Pathology

Follicular Cell Derived Thyroid Cancer:

The majority of thyroid cancers are derived from follicular cells, which are responsible for producing thyroglobulin. Each tumour type differs substantially relative to initial mode of spread, pattern of recurrence and metastatic involvement (Cobin et al., 2001). Papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) are considered well-differentiated thyroid cancers, which generally have a good prognosis, although the course is unpredictable in any given case. PTC accounts for 80-85% of all thyroid cancers and FTC for 5-10%. PTC is recognized by characteristic nuclear features; it tends to spread via lymphatics. PTC has many variants, some of which have a worse prognosis (e.g. tall cell and columnar cell variants). FTC tends to spread via blood vessels rather than lymphatic vessels, and is therefore more likely to give rise to distant metastases, such as to bone. It also has variants, the commonest of which is the Hurthle cell or oncocyctic variant.

Poorly differentiated thyroid carcinoma is an uncommon type of thyroid cancer with a prognosis between that of PTC/FTC and anaplastic carcinoma (described below). These tumors retain some features of thyroid follicular cells, but are aggressive and tend to show extrathyroidal extension and high metastatic potential.

Anaplastic thyroid carcinoma is a rare highly aggressive form of thyroid cancer that usually affects older individuals. It may arise on a background of well differentiated thyroid carcinoma. It has a tendency for rapid growth, replacing the thyroid and extending into other neck structures. The prognosis is very poor, with most patients dying within a few months of diagnosis.

Medullary Thyroid Cancer:

Medullary thyroid carcinoma (MTC) is derived from the parafollicular or C cells, which are responsible for producing the hormone calcitonin. Fewer than five percent of patients have MTC, which is sometimes familial and can be associated with other endocrine malignancies (so-called multiple endocrine neoplasia syndromes). Again, treatment is with surgery, but this disease is more difficult to control because it tends to be more invasive and cannot be treated with RAI (National Institute for Clinical Excellence, 2004).

This guideline does not address medullary thyroid cancer. For information about the management of medullary thyroid cancer, see Medullary Thyroid Cancer: Management Guidelines of the American Thyroid Association. (http://www.thyroid.org/professionals/publications/documents/MTC_Guidelines.pdf)
Other types of thyroid carcinoma:

There are other rare forms of thyroid cancer, including primary thyroid lymphomas and sarcomas, as well as metastatic cancer to the thyroid (such as from kidney cancer). These types are not addressed by these guidelines.

Thyroid Cancer Histologic Distribution, 2008 - 2012

<table>
<thead>
<tr>
<th>Proposed Classification</th>
<th>Count</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary Thyroid Cancer</td>
<td>528</td>
<td>91.7</td>
</tr>
<tr>
<td>Follicular Thyroid Cancer</td>
<td>17</td>
<td>3.0</td>
</tr>
<tr>
<td>Medullary Thyroid Cancer</td>
<td>9</td>
<td>1.6</td>
</tr>
<tr>
<td>Anaplastic Thyroid Cancer</td>
<td>5</td>
<td>0.9</td>
</tr>
<tr>
<td>Other Thyroid Cancer</td>
<td>17</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>576</strong></td>
<td></td>
</tr>
</tbody>
</table>

Source: *Cancer Care Nova Scotia, June 2015*

Thyroid Carcinoma Risk Factors

Risk factors for thyroid cancer include:

- Exposure to ionizing radiation, especially during early childhood
- Female sex (women are more than twice as likely as men to develop thyroid cancer although the reason is not known)
- Deficient and/or excess dietary iodine
- Prolonged stimulation with thyroid stimulating hormone (which can be due to chronic iodine deficiency)
- Chronic lymphocytic thyroiditis (risk of lymphoma)
- A family history of thyroid carcinoma
- Genetic factors (linked with medullary thyroid cancer) (National Institute for Clinical Excellence, 2004)
Prognostic Factors

Compared to other cancers, patients treated for DTC have favourable long-term outcomes. Risk of clinically evident recurrence can be predicted with greater risk for recurrence for those with extremes of age, histology other than classic papillary thyroid cancer (PTC), and primary tumour stage (Tuttle, Leboeuf, & Shaha, 2008).

Those at lowest risk of dying are young (under 45 years of age), with tumours less than 1 cm, classic PTC histology confined to the thyroid gland and no apparent lymph node involvement or distant metastases. Conversely, those at highest risk of dying are over age 45 with large tumours (greater than 4 cm) and distant metastases. Completeness of resection is also an indicator of prognosis (Tuttle et al., 2008).

Staging

DTC is unique in that the patient’s age (older or younger than 45) affects the staging. For patients under age 45, there are only two stages (I and II) instead of the usual four. According to the American Joint Committee on Cancer/International Union for Cancer Control (AJCC/UICC) TNM staging system, Stage I is any tumour that has not metastasized (any size tumour (T), any regional lymph node involvement (N), no distant metastasis (M)) and Stage II is any tumour that has metastasized (any T, any N, distant metastasis (M1)) (see Appendix 1: Staging for the TNM staging tables) (Edge et al., 2010).
Part II Management of Thyroid Nodules

Risk of Malignancy in Thyroid Nodules

Thyroid nodules have been found in 4-8% of the general population through palpation, 19-67% of patients with the use of ultrasound and in 50% of autopsy specimens (Moon et al., 2011). Thyroid nodules are approximately four times more common in women than in men. Palpable nodules increase in frequency throughout life, reaching a prevalence of about 5% in the United States population age 50 years and older. By contrast, thyroid carcinoma is uncommon with the lifetime risk of being diagnosed approximately 1% (National Cancer Institute). Malignancies have been found in 9-15% of the nodules that were evaluated with fine needle aspiration (FNA) biopsy (Cooper et al., 2009; Moon et al., 2011; National Institute for Clinical Excellence, 2004).

The majority of malignant nodules are asymptomatic. The probability of malignancy in a thyroid nodule rises considerably with the following:

History:
- Rapid growth (more than a 50% change in volume or a 20% increase in nodule diameter with a minimum increase in two or more dimensions of 2 mm solid nodules or in the solid portion of mixed cystic–solid nodules)\(^2\) (Cooper et al., 2009)
- Hoarseness due to vocal cord paralysis
- History of thyroid cancer in one or more first degree relatives.
- Exposure to ionizing radiation (e.g., external beam radiation)
- Prior hemithyroidectomy with discovery of thyroid cancer
- Extremes of age (i.e. under 15 or older than 60)
- History of multiple endocrine neoplasia (MEN)
- Persons born in the Philippines, Hawaii, Iceland and other areas with high volcanic activity have an increased risk of thyroid cancer

Exam:
- Cervical lymphadenopathy
- Firm, irregular and fixed nodule

Investigations:
- Nodules greater than 1 cm in diameter or smaller lesions with high-risk features
- Tumour invasion into adjacent structures
- \(^{18}\)F-FDG avidity on Positron Emission Tomography (PET) scanning
- MEN2/FMTC-associated RET protooncogene mutation
- Calcitonin > 100 pg/mL
- Suspicious ultrasound findings (see Table 1: Indications for FNA of Thyroid Nodule(s) for list of suspicious features)

In an otherwise normal gland or a diffuse goiter, thyroid nodules may be solitary or multiple. Among multinodular goiters, one nodule may become clinically dominant in terms of growth,

\(^2\) The ATA provides a tool for calculating volume change in nodule on its website (Change in Thyroid Nodule Volume Calculator www.thyroid.org/professionals/calculators/CINV.php)
dimension, and functional characteristic. The risk of malignancy is similar among hypofunctioning solitary nodules and multinodular goiter (Pacini et al., 2006). The presence of microcalcification on ultrasound is suggestive of malignancy.

**Presentation**

Thyroid cancer commonly develops in women of reproductive age. It usually presents as a solitary nodule in a patient with normal thyroid hormone levels; cancer is found in about 10% of such cases. Other presentations are less common including cervical lymphadenopathy, hoarseness, difficulty in breathing or swallowing, and discomfort in the neck (National Institute for Clinical Excellence, 2004).

About half of malignant nodules are discovered during:

- Routine physical examinations
- Imaging studies for other purposes
  - Approximately 1-2% of people undergoing $^{18}$FDG-PET imaging for other reasons have thyroid nodules discovered incidentally. Since the risk of malignancy in these $^{18}$FDG-positive nodules is about 33% and the cancers may be more aggressive, such lesions require prompt evaluation (Cooper et al., 2009)
- Surgery for benign disease

The other half are usually first noticed by the patient, usually as an asymptomatic nodule.

Because differentiated thyroid cancer is difficult to distinguish from benign tumours, delay in diagnosis is common. Delayed diagnosis results in increased mortality rates (Mazzaferri & Jhiang, 1994).

**Referral Guidelines**

**Immediate and Urgent Referral**

A person presenting with symptoms of tracheal compression, including stridor due to thyroid swelling, should be referred immediately for emergency care.

A person should be referred urgently to a specialist (patient seen within 6 weeks) if they have thyroid swelling AND one or more of the following:

- A solitary nodule increasing in size either by palpation or on ultrasound (more than a 50% change in volume or a 20% increase in at least two nodule dimensions with a minimal increase of 2 mm in solid nodules or in the solid portion of mixed cystic–solid nodules)$^3$
- A history of neck irradiation
- A family history of an endocrine tumour$^4$
- Unexplained hoarseness or voice changes

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$^3$ The ATA provides a tool for calculating volume change in nodule on its website (Change in Thyroid Nodule Volume Calculator [www.thyroid.org/professionals/calculators/CINV.php])

$^4$ MEN2 (Medullary Thyroid Carcinoma, Pheochromocytoma, Parathyroid adenoma, Mucosal Neuroma) and Cowden’s Syndrome (Breast cancer, Thyroid cancer (especially follicular), Gardner’s Syndrome, Endometrial cancer, Hamartomatous intestinal polyps, Lipomas, Fibromas, Genitourinary tumours (such as kidney cancer or uterine fibroids))
- Cervical lymphadenopathy
- Very young (pre-pubertal) patients
- Patients aged 65 years and older (National Institute for Health and Clinical Excellence & National Collaborating Centre for Primary Care, 2005; New Zealand Guidelines Group, 2009)

### Routine Referral

Order thyroid function tests (TSH, free T4) in patients with thyroid swelling without stridor or any of the features listed above (National Institute for Health and Clinical Excellence & National Collaborating Centre for Primary Care, 2005). Those who require further investigation should be referred promptly (i.e. the patient is seen within 3 months).
Guidelines for Management of Thyroid Nodules

The following recommendations have been adapted, with permission, from the ATA Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer (Cooper et al., 2009). The order of the recommendations has changed from the ATA original but the original ATA numbering is provided for easy reference.

Recommendations that have been modified from the ATA original are clearly identified. Where an ATA recommendation was modified, the source for the modification is referenced, including the level of evidence if provided by the original source. Where a source is not indicated, the modification was made based on the expert opinion of the CCNS panel.

Initial Work-up

1. With the discovery of a thyroid nodule, a complete history and physical examination focusing on the thyroid gland and adjacent cervical lymph nodes should be performed (Cooper et al., 2009).

See ATA Figure 1: Algorithm for the evaluation of patients with one or more thyroid nodules Adapted for NS for work-up of thyroid nodules.

Laboratory Tests

2. Measurement of serum TSH (thyroid stimulating hormone) is indicated in the initial evaluation of a patient with a thyroid nodule. A subnormal serum TSH concentration may suggest the presence of autonomous nodule(s) and should be investigated with nuclear medicine imaging (see CCNS Recommendation 12). If serum TSH is normal or elevated, there is no routine indication for a nuclear medicine thyroid scan (ATA R1 modified).

3. Routine measurement of serum thyroglobulin (Tg) for initial evaluation of thyroid nodules is not recommended (ATA R3).

4. The routine measurement of serum calcitonin is not recommended unless there is a suspicion of MTC, family history of MTC or MEN syndromes (ATA R4 modified).

If there is a family history of medullary thyroid cancer (MTC) or MEN II, a basal serum calcitonin level should be obtained, and if it is elevated [≥ 11 pg/mL], medullary cancer is likely present. In such patients, the presence of a pheochromocytoma should also be excluded (Singer et al., 1996).
ATa Figure 1
Algorithm for the evaluation of patients with one or more thyroid nodules
Adapted For NS

Low (subnormal) TSH

99mTc pertechnetate scan (Rec 12)

Hyperfunctioning nodule
Evaluate and treat for hyperthyroidism

Nodule not hyperfunctioning
Diagnostic US (Rec 5a)

Nodule on US
Do FNA (see FNA Flowchart and Recommendations 9-16)

Results of FNA

Atypia/follicular lesion of undetermined significance
Repeat FNA

Repeat FNA
If after 1-2 results remain unsatisfactory, use US guided FNA (Rec 15a)

Results remain unsatisfactory
Close follow up OR surgery (Rec 15b)

Malignant

Suspicious for malignancy

Follicular Neoplasm or suspicious for Follicular Neoplasm

Benign (Rec 20a)

Elevated TSH
Evaluate and treat for hypothyroidism

Normal TSH
FNA not indicated

Unsatisfactory (Rec 15)

Follicular Neoplasm AND TSH low normal (0.3-2 mIU/L) (Rec 18)
Consider 99mTc pertechnetate scan

Hyperfunctioning

Normal or High TSH

History & Physical (Rec 1), TSH (Rec 2)

Follicular Neoplasm AND TSH is not low normal (>2 mIU/L)
Hurthle Cell neoplasm (Rec 19) OR Follicular Neoplasm

Surgery
Pre-op US

Follow (Rec 20b)
Imaging

Thyroid Ultrasound

Thyroid ultrasound is the most accurate imaging technique for the detection and anatomic characterization of thyroid nodules and is required when a palpable nodule is discovered.

Ultrasound (US) can accurately:

5. a) Thyroid ultrasound should be performed in all patients with one or more suspected thyroid nodules and normal or elevated serum TSH including an assessment of lymph nodes in levels I through VI (i.e. both the central and lateral compartments), the supraclavicular regions and, as possible, the retropharyngeal and parapharyngeal spaces (ATA R2 modified). An assessment of vocal cord mobility may also be undertaken, in accordance with ultrasonographer and radiologist comfort and experience.

See ATA Figure 1: Algorithm for the evaluation of patients with one or more thyroid nodules Adapted for NS.

- Identify features and size of specific thyroid nodules particularly in the context of a multinodular goiter and in relation to palpable abnormality
- Guide fine needle aspiration (FNA) biopsy
- Detect suspicious cervical lymph nodes as small as a few millimeters in diameter (Pacini et al., 2006)

5. b) It is recommended that physicians provide the following information when ordering thyroid US:

- All ultrasound requests should specify if the patient is at high or average risk for thyroid carcinoma and if considered high-risk, on what basis (Table 1A: Patient with High-risk Clinical Features lists all high-risk clinical features).
- If thyroid function and/or nuclear medicine testing results are available, they should be detailed on the request form or sent with the patient for their ultrasound appointment.
- Post-treatment thyroid cancer patient requests should indicate if there are clinically concerning features for recurrence or changes in serum thyroglobulin levels (CCNS Panel).

6. It is recommended that radiologists reporting thyroid ultrasounds use a structured template (CCNS Panel).

Such a template is being developed by the Panel and will be provided to radiologists when it is complete.
Radioisotopes play an important role in management of thyroid cancer. Assessment of the functional status of a thyroid nodule is performed with a thyroid scan using $^{99m}$Technetium ($^{99m}$Tc)-pertechnetate or $^{123}$Iodine ($^{123}$I). $^{99m}$Tc-pertechnetate is trapped by thyroid tissue, while $^{123}$I is trapped and organified. Both tracers emit gamma rays detectable by imaging cameras. In Nova Scotia only $^{99m}$Tc-pertechnetate is routinely used for evaluation of thyroid nodules.

Radioisotope therapy, either ablation of remnant thyroid tissue or adjuvant therapy of thyroid cancer is performed using large doses of $^{131}$Iodine ($^{131}$I). $^{131}$I emits beta particles which deliver local radiation therapy. $^{131}$I also emits gamma rays which can be imaged, and thus $^{131}$I is used to perform whole body scans (WBS) for thyroid cancer metastases, using either a small tracer dose for a diagnostic scan (DxWBS), or a few days following therapy using the on-board high therapeutic dose (RxWBS). Because of the higher dose, RxWBS may be more sensitive for metastases.

Both forms of radioiodine, $^{131}$I and $^{123}$I, are administered orally, whereas $^{99m}$Tc-pertechnetate is injected intravenously.

7. A nuclear medicine thyroid scan is not a routine requisite for the management of thyroid cancer (CCNS Panel).

The nuclear medicine thyroid scan is not routinely indicated. While hot nodules have a very low-risk of malignancy, the vast majority of nodules are cold on scan. The exception is when the TSH is suppressed, in which case there is an increased likelihood the nodule will be a hyperfunctioning adenoma, and thus hot on scan, obviating the need for further evaluation.

8. Clinical use of $^{18}$FDG-PET scan to improve diagnostic accuracy of indeterminate thyroid nodules is not recommended (ATA R8b modified).

PET scanning has made a substantial impact on the imaging of many cancers, though the impact is somewhat tempered in thyroid cancer. PET routinely uses the tracer 2-deoxy-2-$[^{18}$F]fluoro-D-glucose ($^{18}$FDG), a glucose analog with increased uptake in tissues with high metabolism, such as many malignancies. However, as most thyroid cancers are well differentiated, $^{18}$FDG uptake is often limited. Consequently whole body scans with $^{131}$I are routinely more sensitive for metastases. However, in some situations $^{18}$FDG-PET scanning is indicated, for example when recurrence is suspected clinically or biochemically, and the $^{131}$I scan is negative. PET scanning is performed in conjunction with a low dose CT scan (PET-CT) which further enhances the utility of PET, providing anatomic localization of areas of abnormal $^{18}$FDG uptake.
Fine Needle Aspiration (FNA) Biopsy (See Flowchart 1: Fine Needle Aspiration Biopsy)

Generally only nodules larger than 1 cm require evaluation. Occasionally there may be nodules smaller than 1 cm that require evaluation because of suspicious ultrasound findings or clinical features, as outlined in Table 1: Indications for FNA of Thyroid Nodule(s): rapid growth\(^5\), a history of head and neck irradiation or a positive family history of thyroid disease.

<table>
<thead>
<tr>
<th>9. a) FNA is the procedure of choice in the evaluation of thyroid nodules (ATA R5a).</th>
</tr>
</thead>
<tbody>
<tr>
<td>b) Thyroid FNA should preferably be performed or supervised by an experienced physician (MacKay, MacIntosh &amp; Imran, 2008; Pitman et al., 2008) (CCNS Panel).</td>
</tr>
<tr>
<td>c) Physicians should monitor their insufficiency rate and success aspirate rate (adequacy of specimen) (Ljung, et al., 2008) (CCNS Panel).</td>
</tr>
</tbody>
</table>

A low false-negative rate is dependent on high quality samples that are obtained by technically-skilled operators with sufficient quantity and quality for accurate interpretation (Pitman et al., 2008).

Aspiration may be performed by any physician or surgeon with expertise and interest in thyroid disease. However, he/she should be trained in good practice and should perform sufficient aspirates to maintain expertise (British Thyroid Association, 2007).

Immediate cytologic assessment is helpful, as it determines specimen adequacy and may improve triage of specimens to methods that optimize its diagnostic value (Layfield, Cibas, Gharib, & Mandel, 2009).

In case of conventional slide preparation, expertise in smear preparation and proper handling of samples is required. Periodic review and reporting of slide preparation quality is recommended. In some institutions, cytotechnologists may be available to provide rapid assessment of specimen quality in case repeat FNA is required.

<table>
<thead>
<tr>
<th>10. US guidance for FNA is recommended for non-palpable nodules. If the nodule is palpable, US guidance is not normally required unless it is predominantly cystic, or located posteriorly in the thyroid lobe (ATA R5b).</th>
</tr>
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</table>

<table>
<thead>
<tr>
<th>11. (a) In the presence of two or more thyroid nodules &gt;1 cm, those with a suspicious sonographic appearance should be aspirated preferentially (ATA R12a).</th>
</tr>
</thead>
</table>

Various sonographic characteristics of a thyroid nodule have been associated with a higher likelihood of malignancy. These include nodule hypoechochogenicity compared to the normal thyroid parenchyma, increased intranodular vascularity, irregular infiltrative margins, the presence of microcalcifications, an absent halo, and a shape taller than the

\(^5\) Rapid growth is defined as more than a 50% change in volume or a 20% increase in at least two nodule dimensions with a minimal increase of 2 mm in solid nodules or in the solid portion of mixed cystic–solid nodules (Cooper et al., 2009). The ATA provides a tool for calculating volume change in nodule on its website (Change in Thyroid Nodule Volume Calculator www.thyroid.org/professionals/calculators/CINV.php)
width measured in the transverse dimension. With the exception of suspicious cervical lymphadenopathy, which is a specific but insensitive finding, no single sonographic feature or combinations of features is adequately sensitive or specific to identify all malignant nodules (Cooper et al., 2009).

11. (b) If none of the nodules has a suspicious sonographic appearance and multiple sonographically similar coalescent nodules with no intervening normal parenchyma are present, the likelihood of malignancy is low and it is reasonable to aspirate the largest nodules on each side only and observe the others with serial US examinations (ATA R12b modified).
Flowchart 1
Fine Needle Aspiration Biopsy

Nodule on US
aspirate those with suspicious
sonographic features (Rec 11a)
OR
if multiple nodules >1 cm,
the largest on each side (Rec 11b)

Non-palpable OR
Predominantly cystic OR
Located posteriorly in
thyroid lobe (Rec 10a)

Palpable AND
minimal cystic
component

US guided
FNA

FNA

If after 1-2 attempts,
results remain
unsatisfactory (Rec 15a)

If the results continue as unsatisfactory

Close follow up OR
surgical excision if
high risk features
(Rec 15b)
Table 1: Indications for FNA of Thyroid Nodule(s): Threshold Size, Based on Ultrasound Characteristics

The use of US guided FNA of suspicious thyroid nodules is recommended:

- For non-palpable nodules (CCNS Recommendation 10)
- If the nodule is palpable and predominantly cystic, or located posteriorly in the thyroid lobe (CCNS Recommendation 10)
- If after one to two attempts to obtain FNA without US, results for a nodule remain “unsatisfactory” (CCNS Recommendation 15a)

<table>
<thead>
<tr>
<th>Table 1A: Patient with High-risk Clinical Features (any of the following)</th>
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<tbody>
<tr>
<td><strong>Suspicous Ultrasound Features</strong></td>
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<tr>
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<tr>
<td></td>
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<td></td>
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<tr>
<td></td>
</tr>
<tr>
<td>Microcalcifications only</td>
</tr>
<tr>
<td>High-risk feature(s) without microcalcifications (see above)</td>
</tr>
<tr>
<td><strong>No Suspicious Ultrasound Features</strong></td>
</tr>
<tr>
<td><strong>Abnormal Cervical Lymph Nodes</strong></td>
</tr>
</tbody>
</table>
### Table 1B: Patient Without High-risk Clinical Features

<table>
<thead>
<tr>
<th>Solid Nodule</th>
<th>Suspicious Ultrasound Features</th>
<th>FNA nodules &gt; 1 cm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Microcalcifications • Hypoechoic • Increased nodular vascularity • Infiltrative margins • Extracapsular extension • Coarse calcification in solitary nodule (not MNG) • Interrupted rim of calcification</td>
<td></td>
</tr>
<tr>
<td>No Suspicious Ultrasound Features</td>
<td></td>
<td>FNA nodules ≥ 1.5 cm</td>
</tr>
<tr>
<td>Mixed Cystic-Solid</td>
<td>Suspicious Ultrasound Features (see above)</td>
<td>FNA nodules ≥ 1.5 cm</td>
</tr>
<tr>
<td>No Suspicious Ultrasound Features</td>
<td></td>
<td>FNA nodules ≥ 2 cm</td>
</tr>
<tr>
<td>Spongiform</td>
<td>FNA nodules ≥ 2 cm</td>
<td></td>
</tr>
<tr>
<td>Purely Cystic</td>
<td>FNA not indicated</td>
<td></td>
</tr>
</tbody>
</table>

12. A subnormal serum TSH concentration may suggest the presence of autonomous nodule(s). A technetium $^{99m}$Tc-pertechnetate should be performed and directly compared to the US images to determine functionality of each nodule > 1.0 cm. FNA should then be considered only for those isofunctioning or non-functioning nodules, among which those with suspicious sonographic features should be aspirated preferentially (ATA R13 modified).

13. When available, molecular markers (e.g., BRAF, RA S, RET/PTC, Pax8-PPARg, or galectin-3) may be considered for patients with indeterminate cytology on FNA to help guide management (ATA R8a modified).


15. (a) If after 1-2 attempts, results for a nodule remain “unsatisfactory”, US guidance should be used (ATA R6a modified).

(b) Partially cystic nodules that repeatedly yield unsatisfactory aspirates need close observation or surgical excision. Surgery should be more strongly considered if the cytologically non-diagnostic nodule is solid or other high risk features are present (see Risk of Malignancy in Thyroid Nodules) (ATA R6b modified).

16. Thyroid cytology should be interpreted by a pathologist with an interest in thyroid disease or by one who participates in a multidisciplinary network with the possibility of cytology review. There should be correlation with any subsequent histology (British Thyroid Association, 2007). It is important the pathologist be provided with relevant history, clinical findings and imaging results at the time of specimen referral to assist with interpretation (CCNS Panel).

**Fine Needle Aspiration (FNA) Biopsy Results** (See ATA Figure 1: Algorithm for the evaluation of patients with one or more thyroid nodules Adapted for NS)

17. If a cytology result is diagnostic of or suspicious for PTC, surgery is recommended (ATA R7).
18. If the cytology reading reports a follicular neoplasm, a $^{99m}$Tc-pertechnetate thyroid scan may be considered, if not already done, especially if the serum TSH is in the low-normal range. If a concordant autonomously functioning nodule is not seen, lobectomy or total thyroidectomy should be considered (ATA R9).

19. If the cytology reading is “suspicious for papillary carcinoma” or “Hürthle cell neoplasm,” (oncocytic variant of follicular 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 (ATA R10).

20. a) If the nodule is benign on cytology, further immediate diagnostic studies or treatments are not required (ATA 11 modified). This category includes multinodular goiter and thyroiditis.

20. b) It is recommended that all benign thyroid nodules be followed with serial US examinations 6-18 months after the initial FNA. If nodule size is stable (i.e., no more than a 50% change in volume or < 20% increase in at least two nodule dimensions in solid nodules or in the solid portion of mixed cystic–solid nodules), the interval before the next follow-up clinical examination or US may be longer (e.g., every 3-5 years) (ATA R14a).

“Thyroid nodules diagnosed as benign require follow-up because of a low, but not negligible, false-negative rate of up to 5% with FNA, which may be even higher with nodules > 4 cm. While benign nodules may decrease in size, they often increase in size, albeit slowly…. Nodule growth is not in and of itself pathognomonic of malignancy, but growth is an indication for repeat biopsy” (Cooper et al., 2009, p 1175).

20. c) If there is evidence for nodule growth either by palpation or sonographically (more than a 50% change in volume or a 20% increase in at least two nodule dimensions with a minimal increase of 2 mm in solid nodules or in the solid portion of mixed cystic–solid nodules), the FNA should be repeated, preferably with US guidance (ATA R14b).

The ATA provides a tool for calculating volume change in nodule on its website, which clinicians may find useful when monitoring nodule growth (see Change in Thyroid Nodule Volume Calculator http://www.thyroid.org/professionals/calculators/CINV.php).

21. Routine suppression therapy of benign thyroid nodules in iodine sufficient populations is not recommended (ATA R16).
22. Patients with growing nodules that are benign after repeat biopsy should be considered for continued monitoring or intervention with surgery based on symptoms and clinical concern. There are no data on the use of Levothyroxine (LT4) in this subpopulation of patients (ATA R17).

Management of Thyroid Nodules in Pregnancy

23. For euthyroid and hypothyroid pregnant women with thyroid nodules, FNA should be performed. For women with suppressed serum TSH levels that persist after the first trimester, FNA may be deferred until after pregnancy and cessation of lactation, when a radionuclide scan can be performed to evaluate nodule function (ATA R19).
Part III Management of Differentiated Thyroid Cancer

Overview

It is recommended that thyroid cancer patients have their care coordinated by a specialist multidisciplinary team. Most thyroid cancer patients will be treated with total thyroidectomy and appropriate removal of lymph nodes followed by radioiodine therapy of residual normal or malignant thyroid tissue. Total thyroidectomy will require life-long management with thyroid hormone. This approach cures more than 80% of patients. Still, some die of the disease and nearly 15% have local recurrences, while another 5-10% develop distant metastases. Over 50% of recurrences appear in the first five years, but distant metastases may surface years, and sometimes decades, after initial therapy (Mazzaferri & Jhiang, 1994).

Referral

Referral for Surgery

24. Following a diagnosis of thyroid cancer, the patient should be referred to a surgeon experienced in thyroid surgery (Gourin, et al., 2010) (CCNS Panel).

Referral to Interdisciplinary Thyroid Oncology Clinic (ITOC)

25. It is strongly recommended that all patients with a diagnosis of thyroid carcinoma be referred to the ITOC for interdisciplinary review (Radiation Oncology, Endocrinology, Nuclear Medicine, Surgical Oncology and allied health professionals), patient education and supportive care. Referrals should be made within 6-8 weeks of surgery (CCNS Panel).

Patients will be assessed by the ITOC team regarding treatment options and rationale, side-effects, procedure and radioactive precautions, as required. Written information and support from the clinic staff is also provided.

Fax referrals to the Nova Scotia Cancer Centre Referrals Office at 902-473-6079 (tel. 902-473-5140) with the following documents:

- Completed legible Nova Scotia Cancer Centre Referral Form (available at www.cancercare.ns.ca Select health professionals/resources/forms) or (www.cdha.nshealth.ca/physicians/documents Select forms, Cancer Care Program Referral Form)
- Referral or consultation letter highlighting presenting signs and symptoms
- Pathology report confirming the diagnosis
- Other relevant investigations, including US report

If any tests or reports are pending, the date and the location of the procedure should be noted so that the reports may be obtained when available. To facilitate a timely appointment for the patient, send in the referral while awaiting these results.

Urgent or emergent referrals can be made through the locating service (902-473-2220).
If the referring physician would like to discuss a case with a thyroid oncology specialist, it is recommended that they call the appropriate specialist associated with the ITOC (Radiation Oncology: Dr. Mal Rajaraman, Endocrinologist: Dr. Ali Imran, or Otolaryngologist/Head and Neck Surgeon: Dr. Rob Hart) through the locating service 902-473-2220.

**Thyroid Cancer Management Guidelines**

Goals of initial therapy of DTC:

- To remove the primary tumour and any disease that has extended beyond the thyroid capsule, and involved cervical lymph nodes. Completeness of surgical resection is an important determinant of outcome, while residual metastatic lymph nodes represent the most common site of disease recurrence.

- To minimize treatment- and disease-related morbidity. The extent of surgery and the experience of the surgeon both play important roles in determining the risk of surgical complications.

- To permit accurate disease staging and recurrence risk stratification. Because disease stage and recurrence risk stratification facilitates with prognostication, disease management and follow-up strategies, accurate post-operative staging is a crucial element in the management of patients with DTC.

- To facilitate post-operative treatment with radioactive iodine (RAI), where appropriate.

- To permit accurate long-term surveillance for disease recurrence.

- To minimize the risk of disease recurrence and metastatic spread. Adequate surgery is the most important treatment variable influencing prognosis, RAI treatment, thyrotropin suppression and external beam irradiation each play adjunctive roles in at least some patients (Cooper et al., 2009, p 1177).

**Risk Stratification**

The purpose of risk stratification is to identify those patients at high-risk for recurrence or death from thyroid cancer so that they can be offered appropriate aggressive therapy and follow-up. Likewise, it is important to identify patients at low-risk of disease recurrence or mortality to avoid unnecessary treatment morbidity from over-treatment and improve cost-effectiveness. This is even more significant due to the rapidly increasing incidence rates of relatively early stage, asymptomatic DTC that have overall good prognosis which emphasizes the need to carefully weigh the risks and benefits of therapy with surgery, RAI and TSH suppression.
26. Recurrence risk varies for individual patients and is dynamic over the clinical course of the disease. In Nova Scotia, it is recommended that risk assessment for recurrence be individualized and conducted at the following points in time:

a) Pre-operative Risk Stratification to determine the surgical treatment strategy (see Risk Stratification Flowcharts 1A: Risk Stratification Pre-op Differentiated Thyroid Carcinoma (Papillary) and 1B: Risk Stratification Pre-op Differentiated Thyroid Carcinoma (Follicular)).

b) Initial Risk Stratification for patients who have undergone total thyroidectomy +/- neck dissection to determine indications for adjuvant RAI therapy and dose (see Risk Stratification Flowchart 2: Risk Stratification Post-op and Adjuvant Therapy Selection for Differentiated Thyroid Carcinoma (Papillary and Follicular)) (CCNS Panel).

c) Re-stratification of Recurrence Risk Based on Response to Therapy (6-12 months after initial therapy) to guide TSH suppression and long term follow-up (see Risk Stratification Flowchart 3: Recurrence Risk Stratification Based on Response to Therapy and Recommendations for Long-term TSH Suppression and Risk-adapted Follow-up) (CCNS Panel).

Pre-operative Staging with Diagnostic Imaging and Laboratory Tests

27. Pre-operative neck US for the contralateral lobe and cervical (central and especially lateral neck compartments) lymph nodes is recommended for all patients undergoing thyroidectomy for malignant cytologic findings on biopsy. US guided FNA of sonographically suspicious lymph nodes should be performed to confirm malignancy if this would change management (ATA R21).
28. Routine pre-operative use of other imaging studies (CT, MRI, PET) is not recommended except under specific clinical circumstances (ATA R22 modified). Clinical circumstances that warrant further imaging of the neck with enhanced\(^*\) CT or MRI are:
- Hoarseness
- Dysphagia
- Laryngeal fixation
- Respiratory symptoms
- The presence of a lateral neck mass

\(^*\)Note: contrast enhanced CT is not recommended if patients are likely to require \(^{131}\)I RAI therapy or diagnostic scan within 6 weeks (CCNS Panel).

29. Routine pre-operative measurement of serum Tg is not recommended (ATA R23).

Surgical Treatment of Thyroid Cancer

**Note:** In this guideline, only the term “total” thyroidectomy is used to prevent confusion between “near-total” and “sub-total” thyroidectomy. If less than total thyroidectomy is performed, it is recommended that descriptive terminology such as lobectomy or hemithyroidectomy (+/- isthmusectomy) is used.

**Initial Surgery**

Adequate surgery is the most important treatment variable influencing prognosis (Cooper et al., 2009).

**Pre-operative Risk Stratification to determine the surgical treatment strategy.**
(See Risk Stratification Flowcharts 1A: Risk Stratification Pre-op Differentiated Thyroid Carcinoma (Papillary) and 1B: Risk Stratification Pre-op Differentiated Thyroid Carcinoma (Follicular)).

30. The standard surgical treatment of total thyroidectomy is offered when any of the following high-risk features are present:

- The primary thyroid carcinoma is more than 1 cm,
- Contralateral thyroid nodules, regional or distant metastases, are present
- The patient has a:
  - personal history of radiation therapy to the head and neck or a
  - first-degree family history of differentiated thyroid cancer (Cooper, et al., 2009)
- Tall cell, columnar, insular, solid variants or poorly differentiated thyroid carcinoma) (National Comprehensive Cancer Network, 2013)
- Extrathyroidal extension (National Comprehensive Cancer Network, 2013)
- Older age (> 45 years) may also be a criterion for recommending total thyroidectomy because of higher recurrence rates in this age group (Cooper, et al., 2009)
Total thyroidectomy may reduce the risk for recurrence within the contralateral lobe (Cooper et al., 2009).
FNA results:
- Suspicious
- Malignant

- If not already done, Neck US (contralateral lobe and cervical lymph nodes) (Rec 27)
- IF hoarseness, dysphagia, laryngeal fixation, respiratory symptoms, lateral neck mass: further imaging (enhanced CT, MRI) (*contrast enhanced CT is not recommended if patients are likely to require ¹³¹I RAI therapy or diagnostic scan within 6 weeks) (Rec 28)

Pre-op laryngoscopy to evaluate vocal cord mobility (Rec 38b)

Total thyroidectomy if ANY of the following high risk features are present:
- older age (> 45 years)
- a personal history of exposure to ionizing radiation
- a first-degree family history of differentiated thyroid cancer
- the primary thyroid tumour is >1 cm
- contralateral thyroid nodules, regional or distant metastases
- extrathyroidal extension
- aggressive variant (tall cell, columnar cell or poorly differentiated features) (Rec 30,31)

Therapeutic central neck compartment (Level VI) lymph node dissection if clinically involved central or lateral lymph nodes (Rec 33a)

Bilateral prophylactic central-compartment neck dissection should be considered in PTC with clinically uninvolved central neck lymph nodes, especially for advanced primary tumours (T3 or T4) (Rec 33b)

Prophylactic central neck dissection should be considered for small (T1 or T2), clinically node-negative DTC (Rec 33c)

Therapeutic lateral neck compartmental lymph node dissection should be performed for patients with biopsy proven metastatic lateral cervical lymphadenopathy (Rec 34)

Lobectomy +/- isthmusectomy

IF Isolated indeterminate solitary nodule, no high risk features (indicating total thyroidectomy) and patient prefers limited surgery (Rec 32)

- Therapeutic central neck lymph node dissection should be included if the lymph nodes are clinically involved (Rec 33)
- Offer completion thyroidectomy to those patients for whom a total thyroidectomy would have been recommended had the diagnosis been available before the initial surgery (Rec 36)

Completion thyroidectomy?

- Ensure TSH remains in normal range with T4 supplementation as clinically indicated (i.e. no TSH suppression)
- Lifelong annual US for suspicious contralateral lesions (Rec 32)

go to Flowchart 2 (Risk Stratification Post-op and Adjuvant Therapy)
Risk Stratification Flowchart 1B: Risk Stratification Pre-op
Differentiated Thyroid Carcinoma (Follicular)

FNA Results:
- Repeatedly Unsatisfactory
- Follicular lesion of undetermined significance
- Follicular neoplasm (not hyperfunctioning on $^{99m}$Tc scan)

If not already done, Neck U/S (contralateral lobe and cervical lymph nodes) (Rec 27)

If hoarseness, dysphagia, laryngeal fixation, respiratory symptoms, lateral neck mass: further imaging (enhanced CT, MRI) (*contrast enhanced CT is not recommended if patients are likely to require $^{131}$I RAI therapy or diagnostic scan within 6 weeks) (Rec 28)

Pre-op laryngoscopy (Rec 38b)

Total Thyroidectomy if ANY of the following:
- Metastatic disease
- Invasive cancer
- Patient preference
- Suspicious US or FDG-PET findings
- A personal history of exposure to ionizing radiation
- A first-degree family history of differentiated thyroid cancer

Total thyroidectomy without prophylactic central neck dissection may be appropriate for most follicular cancer (Rec 33c)

If lymph nodes:
- Central neck dissection (Level VI)
- Lateral neck dissection (Levels II-IV +/- V)

Lobectomy +/- isthmusectomy

Benign

Minimally or frankly Invasive Follicular carcinoma +/-extensive vascular invasion

Observe, No TSH Suppression

If Lobectomy +/- isthmusectomy, completion thyroidectomy

Therapeutic central neck lymph node dissection should be included if the lymph nodes are clinically involved (Rec 33a)

Go to Flowchart 2 (Risk Stratification Post-Op and Adjuvant Therapy)
31. For patients with thyroid cancer > 1 cm, the initial surgical procedure should be a total thyroidectomy unless there are contraindications to this surgery. Thyroid lobectomy alone may be sufficient treatment for small (< 1 cm), low-risk, unifocal, intrathyroidal papillary carcinomas and no previous exposure to ionizing radiation or radiologically or clinically involved cervical nodal metastases (ATA R26 modified).

32. For patients with an isolated indeterminate solitary nodule (and none of the features listed above) who prefer a more limited surgical procedure, thyroid lobectomy (+/- isthmusectomy) is the recommended initial surgical approach with life-long annual US for suspicious contralateral lesion (ATA R24 modified).

Lymph Node Dissection

33. (a) Therapeutic central neck compartment (level VI) neck dissection for patients with clinically involved central or lateral neck lymph nodes should accompany total thyroidectomy to provide clearance of disease from the central neck (ATA R27a).

33. (b) Bilateral prophylactic central-compartment neck dissection should be considered in patients with PTC with clinically uninvolved central neck lymph nodes, especially for advanced primary tumours (T3 or T4). It is recommended that surgeons performing central neck dissections monitor the quality indicators found in CCNS Recommendation 40 (ATA R27b modified). Elective central neck dissection may improve staging accuracy, affect future treatment plans, and reduce surveillance burden and can be achieved with minimal complications when performed by experienced hands (Evidence level B) (Liao & Shindo, 2012).

33. (c) Total thyroidectomy with prophylactic central neck dissection should be considered for small (T1 or T2), clinically node-negative PTCs and follicular cancers in which case, a referral should be made to a surgeon experienced with central neck dissections (ATA R27c modified). This does not apply to diagnostic hemithyroidectomy (CCNS Panel).

34. Therapeutic lateral neck compartmental lymph node dissection should be performed by a Head and Neck surgeon for patients with biopsy proven metastatic lateral cervical lymphadenopathy (ATA R28).

35. It is recommended that the 2009 ATA Consensus Statement on the Terminology and Classification of Central Neck Dissection for Thyroid Cancer be used for consistent terminology (see http://www.thyroid.org/thyroid-guidelines/consensus/) (Carty, et al., 2009) (CCNS Panel).
Completion Thyroidectomy

36. Completion thyroidectomy should be offered to those patients for whom a total thyroidectomy would have been recommended had the diagnosis been available before the initial surgery. This includes all patients with thyroid cancer except those with small (< 1 cm), unifocal, intrathyroidal, node-negative, low-risk tumours. Therapeutic central neck lymph node dissection should be included if the lymph nodes are clinically involved (ATA R29 modified).

For patients who are found to have DTC post-lobectomy for benign disease, completion thyroidectomy with or without central neck dissection, should be considered except when ALL of the following features apply:

- Negative margins
- No contralateral lesion
- Less than 1 cm in size
- No suspicious lymph nodes
- Unifocal
- No extrathyroidal extension
- No previous exposure to ionizing radiation
- Age less than 45
- No family history of thyroid cancer in first degree relatives

Surgery for Thyroid Cancer in Pregnancy

37. A nodule with cytology indicating PTC discovered early in pregnancy should be monitored sonographically and if it grows substantially (as defined above in CCNS Recommendation 20b) by 24 weeks gestation, surgery should be performed at that point. However, if it remains stable by mid-gestation or if it is diagnosed in the second half of pregnancy, surgery may be performed after delivery. In patients with more advanced disease, surgery in the second trimester is reasonable (ATA R20a).

There has been no prospective study comparing the outcome of DTC in women undergoing surgery during pregnancy versus those where surgery was delayed until after delivery (Imran & Rajaraman, 2011). Currently there is no consensus about the optimum timing of surgery for DTC in pregnancy, and individualized decisions are generally based on patients’ wishes and other risk factors. Most specialists would agree that in the absence of aggressive disease, it is reasonable to delay surgery until after delivery. On the other hand, if surgery is to be considered (e.g., in case of large tumour, compressive symptoms, aggressive pathological or clinical features, rapid enlargement of tumour or patient concern), it should be performed in the second trimester before 24 weeks gestation, primarily due to an increased risk of spontaneous abortion when surgery is performed in the first trimester (Imran & Rajaraman, 2011). At the ITOC, the preference is to delay surgery until after delivery but patients are closely monitored throughout pregnancy with neck ultrasound scans during each trimester (Imran & Rajaraman, 2011).
Surgical Complications

The extent of surgery and the experience of the surgeon both play important roles in determining the risk of surgical complications (Cooper et al., 2009).

38. Surgeons should monitor their complication rate. The following indicators are recommended:

a) Completeness of surgical resection is an important determinant of outcome (Cooper et al., 2009).

b) The acceptable recurrent laryngeal nerve (RLN) injury rate is less than 1% (permanent, excluding those requiring nerve sacrifice). All surgeons should track this routinely with pre- and post-operative laryngoscopy.

Depending on the size of the primary tumour, permanent paralysis is rare (<2%) when the patient is treated by an experienced surgeon (Pacini, et al., 2006).

c) The acceptable hypoparathyroidism rate is less than 5% (permanent, relevant to uncomplicated thyroidectomy that excludes level VI).

All surgeons should track this routinely with post-operative serum calcium with albumin (or ionized calcium if available) and consider parathyroid hormone (PTH) if taking supplementary calcium (CCNS Panel).

39. If there is ongoing clinical voice dysfunction after 6 months post-operative, consider referral to voice clinic (CCNS Panel).

Transient vocal dysfunction is more frequent but resolves spontaneously in most patients within 1-6 months. Much higher rates of complications are observed when surgery is undertaken by non-dedicated surgeons. When it occurs, permanent unilateral recurrent laryngeal nerve paralysis (RLNP) is frequently well tolerated, but rarely may be life threatening by inducing aspiration pneumonia. Permanent unilateral RLNP may decrease quality of life by decreasing voice quality and by increasing vocal effort (Pacini et al., 2006).

Hypocalcemia

After total thyroidectomy with or without parathyroid transplantation, hypocalcemia occurs in one-third of cases, but persists longer than 3 months in less than 2%. Symptoms of hypocalcemia should be noted and total serum calcium, preferably ionized calcium, should be checked the day after surgery and daily until stable. Follow-up should include ionized calcium. Serum PTH measurement may be useful in borderline cases to predict the possibility of recovery from hypocalcemia (Pacini et al., 2006).

If hypocalcemia develops or the patient becomes symptomatic, calcium supplementation should be commenced, together with alfalcaldiol or other vitamin D derivates. Close monitoring of serum calcium is needed to prevent hypercalcemia (see Appendix 8.2: Hypocalcemia Management Guidelines) (Pacini et al., 2006).
Post-operative Pathology and Staging

40. The CDHA adaptation of the College of American Pathologists (CAP) Protocol for the Examination of Specimens From Patients with Carcinomas of the Thyroid Gland (Ghossein, et al., 2009) is recommended when reporting thyroid cancer pathology for nodules > 0.2 cm. Incidental solitary papillary carcinomas > 0.2 cm do not need to be reported using this template (see Appendix 4: CDHA Adaptation of the College of American Pathologists Protocol for the Examination of Specimens from Patients with Carcinomas of the Thyroid Gland) (CCNS Panel).

Pathology synoptic reports are useful for reporting results from examinations by providing a consistent format ensuring that all necessary elements are reported and making it easier for treating physicians to find information.


Post-operative Radioiodine Therapy and Recommendations for Radioactive Iodine (RAI) Remnant Therapy

The use of radioactive iodine ($^{131}$I, RAI) oral therapy in the post-surgical setting is based on the following indications:

- **Ablation** (low-risk situations where the presence of remnants makes follow-up difficult): RAI ablation of residual normal thyroid tissue (remnant) facilitates the early detection of recurrence based on serum Tg measurement and $^{131}$I DxWBS.

- **Adjuvant** (situations where the patient is considered to be at higher-risk of recurrence but is not known to have cancer at the time of treatment): RAI treatment of residual post-operative microscopic tumour foci may decrease the recurrence rate and possibly the mortality rate.

- **Therapeutic** (in patients who are known to have disease present): RAI therapy of disease known to be present.

- **Staging** (settings in which patient is suspected to have disease present): A high activity of $^{131}$I permits a sensitive post-therapy WBS (RxWBS) 3-7 days after its administration, which may reveal previously undiagnosed tumours (Pacini et al., 2006).

Who Should be Treated with RAI?

Post-thyroidectomy, patients are stratified for risk of overall mortality and recurrence (see Risk Stratification Flowchart 2: Risk Stratification Post-op and Adjuvant Therapy Selection for Differentiated Thyroid Carcinoma (Papillary and Follicular)). Patients who are at high-risk of mortality or at significant risk of recurrence (i.e. AJCC Stage III/IV or those under 45 with distant metastases, microscopic invasion of tumour into the perithyroidal soft tissues, cervical lymph node metastases (other than Level VI),
aggressive histology or vascular invasion), are treated with adjuvant RAI to improve survival, reduce recurrence rates and facilitate long-term follow-up.

While RAI appears to be a reasonably safe therapy, it is associated with a cumulative dose-related low-risk of early and late onset complications such as salivary gland damage, nasolacrimal duct obstruction, and secondary malignancies (Cooper et al., 2009). As RAI therapy is only available in Nova Scotia at the QEII HSC, there are additional impacts on quality of life including coordinated preparation with low-iodine diet and TSH stimulation (either thyroid hormone withdrawal or rh-TSH) and socio-economic costs such as travel.

For those who fall into the low-risk DTC category, there are limited data available on the efficacy of RAI as adjuvant treatment to prevent recurrences or prolong survival in patients. The use of adjuvant RAI therapy in low-risk patients (under age 45 with T1 tumours and no extrathyroidal extension or lymph node metastasis) is controversial as growing evidence suggests that there is no benefit to in reducing mortality while exposing patients to toxicity. Post-operative risk stratification is being advocated to identify patients at low-risk of recurrence who would not benefit from RAI (Brown, de Souza, & Cohen, 2011; Iyer, Morris, Tuttle, Shaha, & Ganly, 2011; Sacks, Fung, Chang, Waxman, & Braunstein, 2010; Tuttle et al., 2008; Vaisman et al., 2010).

At 6 months post-thyroidectomy, low-risk patients with the following characteristics are assessed with TSH stimulated thyroglobulin measurements (Stim-Tg):

- Low-risk PTC (including follicular variants)
- Limited to the thyroid gland
- No metastatic lymph nodes outside the central compartment (level VI)
- No evidence of extrathyroidal extension or distant metastases
- Total thyroidectomies with minimal residual thyroid tissue performed by an expert surgeon capable of removing nearly all thyroid tissue
- No detectable interfering serum anti-thyroglobulin antibodies

Patients are classified into three subgroups based on the Stim-Tg results. Those patients with undetectable (< 1.5 pmol/L) Stim-Tg levels are at lowest-risk for residual/recurrent DTC and there is no indication for immediate RAI therapy. If the Stim-Tg levels are above 7.5 pmol/L, patients are strongly advised to undergo RAI therapy. For those who have a Stim-Tg between 1.5-7.5 pmol/L, selection for RAI therapy is based on disease and patient criteria that include histology, gender, detectable metastatic Level VI lymph nodes at surgery, abnormal neck US, co-morbidities and patient preference.

After re-stratification based on response to therapy, low-risk patients who do not receive RAI must be followed on long-term thyroid hormone suppression therapy (THST) and examined at regular intervals for possible disease recurrence with annual stimulated Tg for the first 2 years and then suppressed Tg annually, annual neck ultrasound scan for 2 years, and other imaging and biopsy studies when indicated (see Risk Stratification Flowchart 3: Recurrence Risk Stratification Based on Response to Therapy and Recommendations for Long-term TSH Suppression and Risk-adapted Follow-up and Appendix 5: STIM-Tg Protocol for more details of this protocol).

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6 Based on Vaisman’s schema (Vaisman et al., 2010)
7 While the literature reports Tg levels in µg/L, the QEII HSC laboratory reports Tg levels in pmols/L and this is the unit that is used in this guideline.
41. a) RAI therapy is recommended for all patients with known distant metastases, gross extrathyroidal extension of the tumour regardless of tumour size, or primary tumour size > 4 cm even in the absence of other higher risk features (see ATA Guideline for strength of evidence) (ATA R32a modified).

b) RAI therapy is recommended for selected patients with 1-4 cm thyroid cancers confined to the thyroid, who have documented lymph node metastases, or other higher risk features when the combination of age, tumour size, lymph node status, and individual histology predicts an intermediate to high risk of recurrence or death from thyroid cancer (ATA R32b modified). Refer to Risk Stratification Flowchart 2: Risk Stratification Post-op and Adjuvant Therapy Selection for Differentiated Thyroid Carcinoma (Papillary and Follicular) for specific selection criteria and management recommendations (see ATA Guideline for detail and strength of evidence).

c) RAI therapy is not recommended for patients with cancer less than 1 cm (either unifocal or multifocal) without other high risk features (ATA R32c and d modified).

d) All other patients should be risk-stratified and considered for RAI therapy (see Risk Stratification Flowchart 2: Risk Stratification Post-op and Adjuvant Therapy Selection for Differentiated Thyroid Carcinoma (Papillary and Follicular)) (CCNS Panel).

42. Radioactive iodine therapy in lieu of completion thyroidectomy is not recommended (ATA R30 modified).

Pregnancy and RAI Therapy

RAI administration during pregnancy is contraindicated due to the sequelae of exposing the embryo or fetus to high doses of radiation which include fetal hypothyroidism, attention deficit disorders, memory impairment, mental retardation, malformations, growth changes, induction of malignancies including leukemia, and lethal changes (Imran & Rajaraman, 2011).

For more detail, refer to the Guidelines of the American Thyroid Association for the Diagnosis and Management of Thyroid Disease During Pregnancy and Postpartum (http://thyroidguidelines.net/pregnancy).
43. a) Pregnancy must be excluded before $^{\text{131}}$I therapy is given (Pacini, et al., 2006) and avoided for 6 months to a year after ablation (Sacks, et al., 2010) (ATA R73 modified).

b) RAI should not be given to nursing women due to the significant accumulation of $^{\text{131}}$I in the lactating breast and its excretion in breast milk. Depending on the clinical situation, RAI therapy could be deferred until a time when lactating women have stopped breast-feeding for at least 6-8 weeks (ATA R74a modified).

c) Dopaminergic agents might be useful in decreasing breast exposure in recently lactating women, although caution should be exercised given the risk of serious side effects associated with their routine use to suppress postpartum lactation (ATA R74b).
Refer all patients to ITOC

Total Thyroidectomy +/- Neck Dissection

AJCC Staging to stratify for overall survival/mortality risk (see Appendix 1)

Stage I/II

Risk Stratification for recurrence

Stage III/IV or age <45, M1

High-risk patients
(ATA p1180)
ANY of the following:
1) macroscopic tumour invasion (T4 extension beyond the thyroid capsule)
2) incomplete tumour resection with gross residual disease,
3) distant metastases (M1)
(Rec 41a)

Initiate Level A TSH Suppression
(Rec 59)
0.01-0.1 mIU/L

Treat with RAI using the following dosing schedule:
- N0,NX M0 100 mCi
- N+ M0 150 mCi
- M+ 200 mCi

Flowchart 3 for Restratification, Long Term TSH Suppression and Follow Up

Low-risk patients (ATA p1180 and Vaisman 2010)
ALL of the following:
1) no distant metastases;
2) no metastatic lymph nodes outside the central compartment (Level VI) (N0, N1a, Nx)
3) all macroscopic tumour has been resected;
4) pathology limited to the thyroid gland: no tumour invasion of locoregional tissues or structures; no gross or microscopic extrathyroidal extension
5) papillary or follicular variant of papillary thyroid cancer (i.e. the tumour does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma))
6) no vascular invasion
7) negative resection margins
8) no detectable interfering serum anti-Tg antibodies
9) thyroidectomy done by experienced thyroid surgeon (low total thyroidectomy complication rates (recurrent laryngeal nerve injury, post-op hypocalcemia) and minimal residual thyroid tissue) (Rec 41c)

Intermediate-risk patients (ATA p1180)
ANY of the following:
1) microscopic invasion of tumour into the perithyroidal soft tissues at initial surgery or
2) cervical lymph node metastases (other than Level VI) or
3) tumour with aggressive histology or vascular invasion
AND no features of high-risk patients (Rec 41b)

Initiate Level C TSH Suppression
(Rec 59)
0.35-2 mIU/L

6 months post op: TSH Stimulated Tg Measurement

<1.5 pmol/L

No Routine RAI Administration

1.5-7.5 pmol/L

No RAI

Consider possible RAI Administration.
Selection criteria include:
- histology
- gender
- detectable metastatic Level VI lymph nodes at surgery or neck U/S
- co-morbidities
- patient attitude including treatment preferences and fertility goals

RAI Administration
30 mCi

>7.5 pmol/L

Flowchart 3 for Restratification, Long Term TSH Suppression and Follow Up

Conversion from pmol/L to ng/ml or µg/L can be calculated by (pmol/L) ÷ 1.5
Preparation for RAI Therapy

Pre-therapy Investigations

44. Pre-therapy nuclear medicine scans and/or measurement of thyroid bed uptake are not routinely recommended, unless it will change the decision to treat with RAI or will change the dose (e.g., adequacy of surgical resection or to assess for metastases). If a pre-therapy scan is done, a low dose of 1-3 mCi $^{131}$I should be used (ATA R35 modified).

45. Patients receiving therapeutic doses of RAI should have baseline CBC and assessment of renal function (ATA R72).

All patients should have a stimulated Tg performed at the time of radioiodine ablation when their TSH levels are elevated. For those treated with hormone withdrawal, sampling can occur immediately prior to $^{131}$I therapy; those who receive rhTSH will achieve maximum stimulation Tg on the fifth day post first injection (Brigden, Driedger, Rachinsky, & Singh, 2013).

Patient Preparation
(See Appendix 6: Patient Preparation for Radioactive Iodine Scans and Therapy)

i) Patient Education

All patients undergoing RAI at the QEII HSC undergo an educational session with a nuclear medicine technologist, which includes discussions around preparation for the treatment, what the treatment involves, and radiation protection issues for the days following therapy and the provision of a written patient education package.

ii) Minimization of endogenous circulating iodine levels

The efficacy of RAI therapy depends on the radiation dose delivered to the thyroid tissue, which is maximized if circulating iodine levels are minimized. Low-iodine diets (< 50 ug/d of dietary iodine) have been recommended prior to RAI therapy to increase the effective radiation dose.

46. Patients should be advised to avoid iodine-containing medications (e.g., antiseptics, eye drops or amiodarone and iodine-containing multivitamins or mineral supplements) for 4-6 weeks prior to RAI therapy or scans (Luster, et al., 2008). Similarly, patients should not receive IV radiographic contrast for 6 weeks prior to the therapy (amiodarone metabolites may decrease sensitivity of the iodine scan) (CCNS Panel).
iii) TSH Stimulation

48. Remnant ablation can be performed following thyroxine withdrawal or rhTSH stimulation (ATA R34). See Appendix 6: Patient Preparation for Radioactive Iodine Scans and Therapy for TSH Stimulation Protocols.

Effective thyroid remnant ablation or RAI therapy of DTC lesions (e.g., palliation of metastases) requires adequate stimulation by TSH. Two methods of preparation are available: (a) thyroid hormone withdrawal (THW) and consequent hypothyroidism, or (b) administration of recombinant humanized thyrotropin (rhTSH) (thyrotropin alfa (Thyrogen®)) (Pacini et al., 2006).

While either method of TSH elevation is generally acceptable, rhTSH preparation may be indicated in selected patients:

- With underlying co-morbidities making iatrogenic hypothyroidism potentially risky
- Who are unable to raise endogenous serum TSH levels (e.g., pituitary dysfunction)
- For whom a delay in therapy might be deleterious
- Unable to tolerate prolonged hypothyroidism (rhTSH has significantly improved measures of quality of life compared to thyroid hormone withdrawal) (Luster et al., 2008)
- Unable to tolerate hypothyroidism (less symptoms and improved quality of life)
- Receiving palliative therapy
- Where the more prolonged TSH stimulation with THW is undesirable (i.e. active metastatic disease) (Luster et al., 2008)

rhTSH is obtained from the patient’s own retail pharmacy. The cost of rhTSH is substantial. Patients may have private insurance that will cover it and should check with their insurers. The patient can also obtain coverage through the Nova Scotia Pharmacare programs (e.g., Seniors Pharmacare or Family Pharmacare). Please note that rhTSH is a special authorization drug on most insurance plans and all NS Pharmacare plans.

rhTSH is approved as a single agent for preparation of radioiodine remnant ablation in patients with papillary or follicular thyroid cancer who have undergone thyroidectomy as treatment for thyroid cancer. rhTSH would be a reasonable alternate to thyroid hormone withdrawal in patients who are unable to tolerate the prolonged hypothyroidism state or who cannot achieve satisfactory elevation of endogenous TSH. rhTSH may be used in patients with previously incomplete remnant ablation or a recurrence of thyroid cancer who require therapeutic radioiodine ablation (Nova Scotia Department of Health, 2008).
It is recommended that arrangements be made to administer Thyrogen in the patient’s home community.

$^{131}$I Radioiodine Therapy

49. The minimum activity (30-100 mCi) necessary to achieve successful remnant ablation should be utilized, particularly for low-risk patients (ATA R36).

Recent randomized, prospective clinical trials (Leenhardt et al., 2011; Mallick, et al., 2012; Schlumberger et al., 2012) suggest that patients with localized disease (T1-3, N0-1, M0), favourable histology, total thyroidectomies performed by expert surgeons and no residual disease (R0) can be successfully treated with lower dose (30mCi) RAI. The benefits of using a lower dose include less time in isolation, reduction in radiation exposure with fewer early and late complications and increased cost-efficiency.

50. If residual microscopic disease is suspected or documented, or if there is a more aggressive tumour histology (e.g., tall cell, insular, columnar cell carcinoma), then higher activities (100-200 mCi) may be appropriate. See Risk Stratification Flowchart 2: Risk Stratification Post-op and Adjuvant Therapy Selection for Differentiated Thyroid Carcinoma (Papillary and Follicular) and CCNS Recommendation 79a (ATA R37).

Harmful Effects of RAI

While RAI appears to be a reasonably safe therapy, it is associated with a cumulative dose-related low-risk of early and late onset complications such as salivary gland damage, nasolacrimal duct obstruction, and secondary malignancies (see Appendix 7: Harmful Effects of Radioiodine for information on early and late effects of RAI) (Cooper et al., 2009).

51. While the evidence is insufficient to recommend for or against the routine use of preventive measures to prevent salivary gland damage after RAI therapy, in Nova Scotia, sour candies are routinely recommended 12-24 hours after oral RAI administration (Mandel & Mandel, 2003; Nakada et al., 2005) (ATA R68 modified).

52. Patients with xerostomia are at increased risk of dental caries and should discuss preventive strategies with their dentists (ATA R69).

53. Surgical correction should be considered for nasolacrimal outflow obstruction, which often presents as excessive tearing (epiphora) but also predisposes to infection (ATA R70).
54. Because there is no evidence demonstrating a benefit of more intensive screening, all thyroid cancer patients should be encouraged to seek age and gender appropriate screenings for cancer and other conditions according to routine health maintenance recommendations or as recommended by their primary care provider. Patients who receive a cumulative $^{131}I$ activity in excess of 500-600 mCi should be advised that they may have a small excess risk of developing leukemia and solid tumours in the future (ATA R71).

Post-therapy RAI Scan

55. A post-therapy scan is recommended following RAI therapy. This is typically done 3-7 days after the therapeutic dose is administered (ATA R39 modified). See Appendix 5: STIM-Tg Protocol for protocol.

Post-therapy whole body iodine scanning (DxWBS) is typically conducted approximately 3-7 days after RAI therapy to visualize metastases. In addition to planar imaging, SPECT-CT should be considered. Additional metastatic foci have been reported in 10-26% of patients scanned after high dose RAI treatment compared to the diagnostic scan. The new abnormal uptake was found most often in the neck, lungs and mediastinum, and the newly discovered disease altered the disease stage in approximately 10% of the patients, affecting clinical management in 9-15% (Cooper et al., 2009).

**TSH Suppression Therapy**

In very low-risk patients where only lobectomy +/- isthmusectomy is performed (i.e., total thyroidectomy is not done), T4 supplementation may be required to correct hypothyroidism (i.e. T4 replacement with the goal of maintaining serum TSH in the normal range of 0.35-5.5).

After initial treatment with total thyroidectomy, T4 supplementation is required for two reasons: (a) to correct the hypothyroidism (T4 replacement); (b) to inhibit the TSH-dependent growth of residual cancer cells by decreasing the serum TSH level (i.e. TSH Suppression).

56. T4 supplementation is required post-operatively for total thyroidectomy patients (CCNS Panel).

Levothyroxine (LT4) is the drug of choice. The use of T3 has no place in the long-term treatment of thyroid cancer patients and its use is limited to short-term correction of hypothyroidism or in preparation for a RAI scan or therapy (Pacini et al., 2006).

Adverse effects of subclinical thyrotoxicosis secondary to TSH suppression are represented mainly by cardiac complications and bone loss. Retrospective studies have shown that these possibilities are limited if the appropriate dose of LT4 is carefully monitored, thereby avoiding elevation of FT4 and FT3. However, in elderly patients and in patients with known cardiac disease, TSH suppression should be avoided. During subclinical thyrotoxicosis an additional matter of concern is the evidence that the majority of patients have a prothrombotic profile (Pacini et al., 2006). Patients whose
TSH levels may be chronically depressed should be counselled to ensure adequate daily intake of both calcium (1000 mg/day) and vitamin D (800 units/day) (Brigden et al., 2013).

Initial TSH Suppression Therapy (first 6-12 months)

57. In high- and intermediate-risk patients, after initial treatment with total thyroidectomy and adjuvant RAI therapy, TSH suppression to 0.01-0.1 mU/L (level A) is recommended until re-stratification at 6-12 months (see Risk Stratification Flowchart 2: Risk Stratification Post-op and Adjuvant Therapy Selection for Differentiated Thyroid Carcinoma (Papillary and Follicular)) (ATA R40 modified). See Appendix 8.1: Guidelines for Suppression of TSH in Thyroid Cancer Patients for patient instructions.

In low-risk patients after initial treatment with surgery and regardless of whether they have received adjuvant RAI therapy, serum TSH should be maintained between 0.35-2.0 mU/L until re-stratification at 6-12 months. See Risk Stratification Flowchart 2: Risk Stratification Post-op and Adjuvant Therapy Selection for Differentiated Thyroid Carcinoma (Papillary and Follicular) (ATA R40 modified). See Appendix 8.1: Guidelines for Suppression of TSH in Thyroid Cancer Patients for patient instructions.

Re-stratification of Risk Based on Response to Initial Therapy and Recommendations for TSH Suppression and Follow-up

58. Re-stratification of risk occurs 6-12 months after RAI therapy (or surgery if no RAI therapy had been administered) with the following investigations: clinical neck exam, stimulated Tg, neck ultrasound, and I\(^{131}\) DxWBS if RAI therapy had been administered (I\(^{131}\)DxWBS is not performed for low-risk patients whose post-RxWBS shows no worrisome abnormalities). See Risk Stratification Flowchart 3: Recurrence Risk Stratification Based on Response to Therapy and Recommendations for Long-term TSH Suppression and Risk-adapted Follow-up.
59. Recommended TSH suppression level is modified based on re-stratification of recurrence risk. TSH suppression levels are based on the response to initial therapy. See Risk Stratification Flowchart 3: Recurrence Risk Stratification Based on Response to Therapy and Recommendations for Long-term TSH Suppression and Risk-adapted Follow-up.

Level A suppression (TSH: 0.1-0.01 mIU/L) is recommended in patients with “Acceptable Response” or “Incomplete Response” to initial therapy indefinitely in the absence of specific contraindications.

Level B suppression (TSH: 0.1-0.5 mIU/L) for 5-10 years is recommended in patients who have an “Excellent Response” to initial therapy (are clinically and biochemically free of disease), but who had initially presented with intermediate- or high-risk disease.

Level C suppression (TSH: 0.3–2mIU/L), (i.e. low normal range), is recommended in patients free of disease, especially those at low-risk for recurrence or who have not undergone remnant ablation and have undetectable suppressed serum Tg and normal neck US (ATA R49 modified).

If patients are unable to tolerate (hyperthyroid symptoms and signs) suppressive TSH therapy, it would be appropriate to move to a lower level of suppression (i.e. A to B to C) (CCNS Panel).
Flowchart 3: Recurrence Risk Restratification
Based on Response to Therapy, and
Recommendations for Long Term TSH Suppression and Risk-Adapted Follow-up
(adapted from Tuttle Table III)

From Flowchart 2, No RAI administration
At 12 months from surgery:
• Clinical Neck Exam
• Stimulated Tg
• Neck Ultrasound (Rec 58)

Excellent Response
ALL of the following: (Tuttle 2010 Table 2)
• Neck Exam: negative
• Stimulated Tg undetectable (<1.5 pmol/L)
• Neck US without evidence of disease
• Cross-sectional and/or nuclear medicine imaging negative

Intermediate Risk

Level C suppression
TSH: 0.3-2 mIU/L
These patients may not require regular follow up through ITOC

Follow Up
(Vaisman 2010 Figure 1 and Tuttle 2008 Table IV)
Clinical neck exam annually
Stimulated Tg annually
then suppressed Tg annually
RAI Dx WBS Not required
Cross-sec imaging Not required
FDG PET scanning Not required

Intermediate high

Level A suppression
TSH: 0.1-0.01 mIU/L

If results are abnormal, investigate and manage appropriately.
Otherwise, repeat all but 131 I Whole Body Scan 12 months later.

Incomplete Response
ANY of the following: (Tuttle 2010 Table 2)
• Neck Exam: palpable nodes
• Stimulated Tg ≥ 15 pmol/L
• Rising Tg values
• Neck US: Evidence of structurally significant recurrent/persistent disease in the thyroid bed (>1cm) OR cervical lymph nodes (>1cm) OR distant mets (Tuttle 2008 Table 3)
• Persistent or newly identified disease on cross-sectional and/or nuclear medicine imaging (including post-tx WBS)

Consider additional evaluations and cross-sectional imaging, possibly FDG-PET scan and the need for additional therapy (Tuttle 2008 Table IV) and individualized follow up plan.

Initial Risk

Level B suppression
TSH: 0.1-0.5 mIU/L for 5-10 years

Assessment of the response to initial therapy
(18-24 months post-therapy)

Level A suppression
TSH: 0.1-0.01 mIU/L

From Flowchart 2, RAI administration
At 6 months post RAI:
• Clinical Neck Exam
• Stimulated Tg
• Neck Ultrasound (Rec 60)

I131 Whole Body Scan (DxWBS) for Intermediate and High Risk patients.
DxWBS not required for Low Risk patients whose post-Rx WBS shows no worrisome abnormalities. (Rec 70)

I131 Whole Body Scan (DxWBS) for Intermediate and High Risk patients.
DxWBS not required for Low Risk patients whose post-Rx WBS shows no worrisome abnormalities. (Rec 70)

N.B. Interpretation of Tg measurements should be done with caution in patients who have detectable interfering serum anti-Tg antibodies.
Other Treatment Modalities

External Beam Radiation and Chemotherapy

60. The use of external beam irradiation to treat the primary tumour should be considered in patients over age 45 with grossly visible extrathyroidal extension at the time of surgery and a high likelihood of microscopic residual disease, and for those patients with gross residual tumour in whom further surgery or RAI would likely be ineffective. The sequence of external beam irradiation and RAI therapy depends on the volume of gross residual disease and the likelihood of the tumour being RAI responsive (ATA R41).

61. There is no role for the routine adjunctive use of chemotherapy in patients with DTC (ATA R42).
Part IV Long-term Management of Differentiated Thyroid Cancer

Follow-up recommendations and long-term TSH suppression guidelines for DTC are dynamic and risk-adapted. Initial follow-up for the majority of DTC patients should be undertaken in conjunction with the ITOC team as per the re-stratification of recurrence risk based on response to therapy (see Risk Stratification Flowchart 3: Recurrence Risk Stratification Based on Response to Therapy and Recommendations for Long-term TSH Suppression and Risk-adapted Follow-up).

Tests with high negative predictive value allow identification of patients unlikely to experience disease recurrence, so that less aggressive management strategies can be used that may be more cost effective and safe. Similarly, patients with a higher-risk of recurrence are monitored more aggressively, as early detection of recurrent disease offers the best opportunity for effective treatment. Patients with persistent or recurrent disease are offered treatment to cure or to delay future morbidity or mortality. In the absence of such options, therapies to palliate by substantially reducing tumour burden or preventing tumour growth are utilized, with special attention paid to tumour-threatening critical structures (Cooper et al., 2009).

There are three goals in follow-up of DTC patients:

1. To monitor for recurrence and treatment-related sequelae, which include atrial fibrillation and osteoporosis secondary to TSH suppression and toxicity related to RAI therapy;
2. To monitor thyroxine suppression or replacement therapy;
3. To provide psychosocial support and counseling as necessary, particularly for younger patients, and in relation to pregnancy.

DTC can sometimes recur decades after the initial disease is managed and therefore mandates life-long surveillance. Depending on the individual patient’s disease specifics, recurrence risk re-stratification after assessment of response to therapy may require several years of specialist follow-up. After this time, if re-stratification deems that the patient is at low risk for recurrence and no longer requires specialist care in the ITOC, primary care practitioners will receive a Transfer of Care note from the ITOC clinic detailing patient history and recommended long-term primary care surveillance. Patients should be referred to ITOC for consultation and management if they are experiencing difficulties with thyroxine suppression/replacement therapy, significant toxicity or are suspected of having recurrent disease. A Survivorship Care Plan is available for thyroid cancer patients that describes the recommended surveillance, provides information about healthy living and lists resources for cancer survivors. This is available on the Cancer Care Nova Scotia website and is also distributed in hard copy through the ITOC clinic.

In patients who have undergone total thyroidectomy and thyroid remnant ablation, disease free status comprises all of the following:

- No clinical evidence of tumour,
- No imaging evidence of tumour (no uptake outside the thyroid bed on the initial post-RAI treatment WBS, on a recent DxDxWBS, or neck US),
- Undetectable serum thyroglobulin levels during TSH suppression and stimulation in the absence of interfering antibodies (Cooper et al., 2009).
Thyroid cancer patients have reported that primary care physicians and other health professionals sometimes failed to recognize the adverse effects of RAI treatment at follow-up (see Appendix 7: Harmful Effects of Radioiodine for information on early and late effects of radioiodine) (Sawka et al., 2009).

**Serum Thyroglobulin Assays in the Follow-up of Differentiated Thyroid Cancer**

Measurement of serum thyroglobulin (Tg) levels is an important modality to monitor patients for residual or recurrent disease. In the absence of antibody interference, serum Tg has a high degree of sensitivity and specificity to detect thyroid cancer, especially after total thyroidectomy and remnant ablation, with the highest degrees of sensitivity noted after thyroid hormone withdrawal or stimulation using recombinant human thyrotropin (rhTSH) (Cooper et al., 2009).

Serum Tg may remain detectable during the initial follow-up period, suggesting either incomplete ablation or residual tumour. For patients at intermediate- or high-risk for recurrence, where it is important to detect early recurrence, re-treatment with RAI should be considered. Ongoing follow-up of the trend in serum Tg over time will typically identify patients with clinically significant disease. A rising unstimulated or stimulated serum Tg indicates disease that is likely to become clinically apparent.

The presence of anti-Tg antibodies, which occur in approximately 25% of thyroid cancer patients and 10% of the general population, will falsely lower serum Tg determinations in immunometric assays. The use of recovery assays in this setting to detect significant interference is controversial. Serial serum anti-Tg antibody quantification using the same methodology may serve as an imprecise surrogate marker of residual normal thyroid tissue or tumour (Cooper et al., 2009).

The results of serum Tg measurements made on the same serum specimen differ among assay methods and therefore, the Tg cutoff may differ significantly among different laboratories. The Tg cutoff level above 3 pmol/L \(^8\) (2 ng/mL) following rhTSH stimulation is highly sensitive in identifying patients with persistent tumour (Cooper et al., 2009).

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62. Serum Tg should be measured by an immunometric assay that is calibrated against the CRM- 457 standard. Ideally, serum Tg should be assessed in the same laboratory and using the same assay, during follow-up of patients with DTC who have undergone total thyroidectomy with or without thyroid remnant ablation. Tg antibodies should be quantitatively assessed with every measurement of serum Tg (ATA R43). See Risk Stratification Flowchart 3: Recurrence Risk Stratification Based on Response to Therapy and Recommendations for Long-term TSH Suppression and Risk-adapted Follow-up for frequency of measurement follow-up of patients with DTC based on risk re-stratification.

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\(^8\) In Nova Scotia, all serum Tg measurements are referred to the QEII HSC laboratory and reported in units of pmols/L.
63. Periodic serum Tg measurements and expanded neck ultrasonography should be considered during follow-up of patients with DTC who have undergone less than total thyroidectomy, and in patients who have had a total thyroidectomy but not RAI ablation. While specific cutoff levels during TSH suppression or stimulation that optimally distinguish normal residual thyroid tissue from persistent thyroid cancer are unknown, rising Tg values over time are suspicious for growing thyroid tissue or cancer (ATA R44 modified). See Risk Stratification Flowchart 3: Recurrence Risk Stratification Based on Response to Therapy and Recommendations for Long-term TSH Suppression and Risk-adapted Follow-up.

64. Patients with a rising stimulated or unstimulated Tg should initially be investigated with clinical neck exam and expanded neck ultrasound and be referred to the ITOC for further evaluation (CCNS Panel).

65. Empiric RAI therapy (100-200mCi) can be considered in patients with elevated (Tg levels after T4 withdrawal of 15 pmol/L (10 ng/mL) or higher, or a level of 7.5 pmol/L (5 ng/mL) or higher after rhTSH stimulation) or rising serum Tg levels in whom imaging has failed to reveal a potential tumour source. If the post-therapy scan is negative, no further RAI therapy should be administered (ATA R75).

The sensitivity of detection of recurrence by structural or functional imaging is greater with higher levels of elevation of serum Tg therefore further imaging studies are guided by stimulated serum Tg levels and results of I\textsuperscript{131}DxWBS. It should be noted that contrast-enhanced CT studies should be deferred due to the iodine load interfering with the sensitivity of the I\textsuperscript{131}DxWBS. \textsuperscript{18}FDG-PET studies are most useful in patients with > 15pmol/L(10 ng/ml) and a negative I\textsuperscript{131}DxWBS (Cooper et al., 2009).

**Management of Thyroglobulin-positive Patients with Negative Imaging**

66. If persistent non-resectable disease is localized after an empiric dose of RAI, and there is objective evidence of significant tumour reduction, then RAI therapy should be repeated, at appropriate intervals, until the tumour has been eradicated or the tumour no longer responds to treatment. The risk of repeated therapeutic doses of RAI must be balanced against uncertain long-term benefits (ATA R76).

69. Tg-positive, RxWBS-negative patients with no structural evidence of disease can be followed with serial structural imaging studies and serial Tg measurements, with both performed more frequently if the Tg level is rising. When and how often to repeat \textsuperscript{18}FDG-PET/CT imaging in this setting is less certain (ATA R79).
68. a) If an empiric dose (100-200 mCi) of RAI fails to localize the persistent disease, \textsuperscript{18}FDG-PET/CT scanning should be considered, especially in patients with unstimulated serum Tg levels > 15-30 pmol/L (> 10-20 ng/mL) or in those with aggressive histologies, in order to localize metastatic lesions that may require treatment or continued close observation (ATA R78a).

b) Patients who are Tg-positive and had a negative first post-treatment whole body scan (RxWBS), with disease that is incurable with surgery and is structurally evident or visualized on \textsuperscript{18}FDG-PET/CT scan can be managed with thyroid hormone suppression therapy, external beam radiotherapy, chemotherapy, radiofrequency ablation, chemo-embolization, or monitoring without additional therapy if stable. Clinical trials should also be considered (ATA R78b modified).

### Diagnostic Whole Body Radioactive Iodine Scans (DxWBS), Ultrasound, and Other Imaging Techniques During Follow-up of Differentiated Thyroid Cancer

70. DxWBS is performed for intermediate and high risk patients at 6 months post RAI administration for remnant ablation. DxWBS is not performed for low-risk patients whose post-RxWBS shows no worrisome abnormalities (risk categories are defined in Risk Stratification Flowchart 2: Risk Stratification Post-op and Adjuvant Therapy Selection for Differentiated Thyroid Carcinoma (Papillary and Follicular)). See Risk Stratification Flowchart 3: Recurrence Risk Stratification Based on Response to Therapy and Recommendations for Long-term TSH Suppression and Risk-adapted Follow-up (CCNS Panel).

71. a) Following surgery, cervical US to evaluate the thyroid bed and central and lateral cervical nodal compartments including the supraclavicular regions and, as possible, the retropharyngeal and parapharyngeal spaces should be performed at 6-12 months and then periodically, depending on the patient’s risk for recurrent disease and Tg status (see Risk Stratification Flowchart 3: Recurrence Risk Stratification Based on Response to Therapy and Recommendations for Long-term TSH Suppression and Risk-adapted Follow-up) (ATA R48a). It is recommended that the US be done by a radiologist who specializes in ultrasonography.

b) If a positive result would change management, ultrasonographically suspicious lymph nodes (greater than 5-8 mm in the smallest diameter) should be biopsied for cytology (ATA R48b modified).

c) Suspicious lymph nodes less than 5-8 mm in largest diameter may be followed without biopsy with consideration for intervention if there is growth or if the node threatens vital structures (ATA 48c).
Pregnancy in the Treated Thyroid Cancer Patient

Whenever possible, pre-pregnancy counseling should be provided to women including the rationale for more frequent TSH testing, the need for dose adjustment and the possibility of reduced thyroxin absorption with commonly used pre-pregnancy supplements such as iron and calcium, and women should be advised to take these supplements separately from their thyroxin. Those who are already taking suppressive TSH therapy and are planning to get pregnant are typically advised to reduce the dose of thyroxin aiming for a TSH in the range of 0.5-2.5 mIU/L. Upon confirmation of pregnancy, the dose is increased by an additional two tablets each week if TSH is > 1.5 mIU/L, and by one tablet if TSH is < 1.5 mIU/L. Serum TSH levels are checked every 4-6 weeks and the dose adjusted to achieve and maintain TSH in the range of 0.5-2.5 mIU/L during pregnancy (Imran & Rajaraman, 2011).

At the ITOC, pregnant women with low-risk DTC who are regarded as free of disease prior to pregnancy, aside from their thyroxin dose adjustment, are followed on a 3 monthly (once in each trimester) basis with an unstimulated Tg and a thorough neck examination at each visit. Those women who have high-risk DTC or had documented recurrence of DTC prior to pregnancy are followed more rigorously on a 3 monthly basis with unstimulated Tg and neck US. Normal reference ranges for serum Tg are irrelevant for follow-up of such patients and decision regarding cancer progress is based on their pre-pregnancy Tg levels as well as US findings (Imran & Rajaraman, 2011).

Suppressive T4 therapy should continue during pregnancy. Thyroid function tests should be monitored regularly to ensure that TSH remains suppressed as T4 requirements may increase during pregnancy (British Thyroid Association, 2007).

In the event of pregnancy, the dose of LT4 may require adjustment based on the results of TSH measurements. In the case of documented stable remission, the optimal TSH level should be in the low-normal range, but, if the woman has persistent disease or is at high-risk of recurrence, serum TSH should be kept suppressed around 0.1 mU/l (Pacini et al., 2006).
Part V Management of Patients with Metastatic Disease

Patients with metastatic DTC are potentially curable if disease is limited to the neck, and even those with hematogenous distant metastases can have a significant long-term survival with appropriate early detection, management and follow-up.

The overall approach to treatment of distant metastatic thyroid cancer is based upon the following observations and oncologic principles:

1. Morbidity and mortality are increased in patients with distant metastases, but individual prognosis depends upon factors including histology of the primary tumour, distribution and number of sites of metastases (e.g., brain, bone, and lung), tumour burden, age at diagnosis of metastases, and $^{18}$FDG- and RAI-avidity.

2. Improved survival is associated with responsiveness to surgery and/or RAI therapy.

3. In the absence of demonstrated survival benefit, certain interventions can provide significant palliation or reduce morbidity.

4. In the absence of improved survival, palliative benefit or reduced potential morbidity, the value of empiric therapeutic intervention is significantly limited by the potential for toxicity.

5. Treatment of a specific metastatic area must be considered in light of the patient’s performance status and other sites of disease; e.g., 5-20% of patients with distant metastases die from progressive cervical disease.

6. Longitudinal re-evaluation of patient status and continuing re-assessment of potential benefit and risk of intervention is required.

7. The overall poor outcome of patients with radiographically evident or symptomatic metastases that do not respond to RAI, the complexity of multidisciplinary treatment considerations and the availability of prospective clinical trials should encourage referral of such patients to the Interdisciplinary Thyroid Oncology Clinic (ITOC) at the QEII HSC (Cooper et al., 2009).

The preferred hierarchy of treatment for metastatic disease (in order) is surgical excision of locoregional disease in potentially curable patients, $^{131}$I therapy, external beam radiation, watchful waiting with patients with stable asymptomatic disease, and experimental trials. Experimental trials may be tried before external beam radiation in special circumstances, in part because of the morbidity of external beam radiation and its relative lack of efficacy. A small fraction of patients may benefit from radiofrequency ablation, ethanol ablation, or chemo-embolization (Cooper et al., 2009).

Metastases discovered during follow-up are likely manifestations of persistent disease that has survived initial treatment, and are often incurable by additional $^{131}$I treatment. Some patients will have a reduction in tumour burden with additional treatments that may offer a survival or palliative benefit (Cooper et al., 2009).
Referral

75. Patients with metastatic disease should be referred to the Interdisciplinary Thyroid Oncology Clinic (ITOC) at the QEII HSC (see Referral to Interdisciplinary Thyroid Oncology Clinic (ITOC)).

76. Specialist palliative care is necessary for patients with recurrent end-stage disease. Symptoms of stridor and fear of choking are very distressing and can be alleviated by pharmacological means, palliative surgery and counseling. These patients should be referred early to their local palliative care team.

Surgical Management of Locoregional Metastases

Surgery is favoured for locoregional (i.e. cervical lymph nodes and/or soft tissue tumour in the neck) recurrences, when distant metastases are not present. Approximately one-third to one-half of patients may become free of disease in short-term follow-up (Cooper et al., 2009).

77. a) Therapeutic comprehensive compartmental lateral and/or central neck dissection, sparing uninvolved vital structures, should be performed for patients with persistent or recurrent disease confined to the neck (ATA R50a).

   b) Limited compartmental lateral and/or central compartmental neck dissection may be a reasonable alternative to more extensive comprehensive dissection for patients with recurrent disease within compartments having undergone prior comprehensive dissection and/or external beam radiotherapy (ATA R50b).

78. When technically feasible, surgery for aerodigestive invasive disease is recommended in combination with RAI and/or external beam radiotherapy (ATA R51).

Patient outcome is related to complete resection of all gross disease with the preservation of function with techniques ranging from shaving tumour off the trachea or esophagus for superficial invasion to more aggressive techniques when the trachea is more deeply invaded (e.g., direct intraluminal invasion) including tracheal resection and anastomosis or laryngopharyngoesophagectomy. Patients who are not curable may undergo less aggressive local treatment.

RAI Therapy for Locoregional or Distant Metastatic Disease

For regional nodal metastases discovered on DxWBS, RAI may be employed, although surgery is typically used in the presence of bulky disease or disease amenable to surgery found on anatomic imaging such as US, CT scanning or MRI. RAI is also used adjunctively following surgery for regional nodal disease or aerodigestive invasion if residual RAI-avid disease is present or suspected (Cooper et al., 2009).
79. a) In Nova Scotia, an empiric high-dose 150-200 mCi is chosen when RAI therapy is used in the treatment of locoregional or metastatic disease (CCNS Panel).

b) Empirically administered amounts of $^{131}$I exceeding 200 mCi that often potentially exceed the maximum tolerable tissue dose should be avoided in patients over age 70 years (ATA R52b).

c) In select cases of high dose therapy, e.g., when there is a high burden of pulmonary metastases, dosimetry calculations may be useful to establish a safe dose.

80. There are currently insufficient outcome data to recommend rhTSH-mediated therapy for all patients with metastatic disease being treated with $^{131}$I (ATA R53).

81. Recombinant human TSH-mediated therapy may be indicated in selected patients with underlying co-morbidities making iatrogenic hypothyroidism potentially risky, in patients with pituitary disease who are unable to raise their serum TSH, or in patients in whom a delay in therapy might be deleterious (see Appendix 6: Patient Preparation for Radioactive Iodine Scans and Therapy). Such patients should be given the same or higher activity that would have been given had they been prepared with hypothyroidism or a dosimetrically determined activity (ATA R54).

82. Since there are no outcome data that demonstrate a better outcome of patients treated with lithium as an adjunct to $^{131}$I therapy, the data are insufficient to recommend lithium therapy (ATA R55).

**Treatment of Distant Metastatic Disease**

**Treatment of Pulmonary Metastases**

83. Patients with radioactive iodine-avid pulmonary micrometastases or macronodular metastases should be referred to ITOC for consideration of management with RAI therapy (ATA R56, 57, 58 modified).
84. a) Evidence of benefit of routine treatment of non–RAI avid pulmonary metastases is insufficient to recommend any specific systemic therapy. For many patients, metastatic disease is slowly progressive and patients can often be followed conservatively on TSH suppressive therapy with minimal evidence of radiographic or symptomatic progression. For selected patients, however, other treatment options need to be considered, such as metastasectomy, endobronchial laser ablation, or external beam radiation for palliation of symptomatic intrathoracic lesions (e.g., obstructing or bleeding endobronchial masses), and pleural or pericardial drainage for symptomatic effusions. Referral for participation in clinical trials should be considered (ATA R59a).

b) Referral for participation in clinical trials should be considered for patients with progressive or symptomatic metastatic disease. For those patients who do not participate in clinical trials, treatment with tyrosine kinase inhibitors should be considered (ATA R59b).

Treatment of Bone Metastases

In the management of the patient with bone metastases, key criteria for therapeutic decisions include risk for pathologic fracture, particularly in a weight-bearing structure; risk for neurologic compromise from vertebral lesions; presence of pain; avidity of radioiodine uptake; and potential significant marrow exposure from radiation arising from radioiodine-avid pelvic metastases (Cooper et al., 2009).

85. Complete surgical resection of isolated symptomatic metastases has been associated with improved survival and should be considered, especially in patients <45 years old with slowly progressive disease (ATA R60).

86. RAI therapy of iodine-avid bone metastases has been associated with improved survival and should be employed, although RAI is rarely curative. Such patients should be referred to ITOC for consideration of management with RAI therapy (ATA R61 modified).

87. When skeletal metastatic lesions arise in locations where acute swelling may produce severe pain, fracture, or neurologic complications, external radiation and the concomitant use of glucocorticoids to minimize potential TSH induced and/or radiation-related tumour expansion should be strongly considered (ATA R62).

88. Painful lesions that cannot be resected can also be treated by several options individually or in combination, including RAI, external beam radiotherapy, intra-arterial embolization, radiofrequency ablation, periodic pamidronate or zoledronate infusions (with monitoring for development of possible mandibular osteonecrosis), or vertebroplasty or kyphoplasty. While many of these modalities have been shown to relieve bone pain in cancer, they have not necessarily been reported to have been used in thyroid cancer patients (ATA R63).
89. Evidence is insufficient to recommend treatment of asymptomatic, non–RAI-responsive, stable lesions that do not threaten nearby critical structures (ATA R64).

Treatment of Brain Metastases

Brain metastases typically occur in older patients with more advanced disease and are associated with a poor prognosis. Surgical resection and external beam radiotherapy traditionally have been the mainstays of therapy and may provide palliation. There are few data showing efficacy of RAI (Cooper et al., 2009).

90. Patients with DTC metastatic to the brain should be referred to the ITOC urgently. Early initiation of glucocorticoid therapy (such as Dexamethason 8-16mg divided into 2-4 doses daily) should be considered to minimize ongoing or anticipated symptoms related to the CNS metastases (CCNS Panel).

91. Complete surgical resection of CNS metastases should be considered regardless of RAI avidity, because it is associated with significantly longer survival (ATA R65).

92. CNS lesions that are not amenable to surgery should be considered for external beam irradiation. Optimally, very targeted approaches (such as radiosurgery) are employed to limit the radiation exposure of the surrounding brain tissue. Whole brain and spine irradiation could be considered if multiple metastases are present (ATA R66).

93. If CNS metastases do concentrate RAI, then RAI could be considered. If RAI is being considered, prior external beam radiotherapy and concomitant glucocorticoid therapy are strongly recommended to minimize the effects of a potential TSH-induced increase in tumour size and the subsequent inflammatory effects of the RAI (ATA R67).
External Beam Radiotherapy in Treatment of Metastatic Disease

94. External beam radiation should be used in the management of unresectable gross residual or recurrent cervical disease, painful bone metastases, or metastatic lesions in critical locations likely to result in fracture, neurological, or compressive symptoms that are not amenable to surgery (e.g., vertebral metastases, CNS metastases, selected mediastinal or subcarinal lymph nodes, pelvic metastases) (ATA R80).

Chemotherapy in the Treatment of Metastatic Disease

While surgery and the judicious use of RAI, as described in these guidelines, is sufficient treatment for the majority of patients with DTC, a minority of these patients experience progressive, life-threatening growth and metastatic spread of the disease. The recent explosion of knowledge regarding the molecular and cellular pathogenesis of cancer has led to the development of a range of targeted therapies, now undergoing clinical evaluation. Each of these targeted approaches holds promise for our future ability to treat patients with life-threatening disease unresponsive to traditional therapy. In the meantime, for appropriate patients, entry into one of the available clinical trials may be an option (Cooper et al., 2009).
Part VI Supportive Care

This section was written by the CCNS Panel in conjunction with CCNS Supportive Care Team and is not taken from the ATA Guidelines. Please refer to the Best Practice Guideline for the Management of Cancer-Related Distress in Adults for recommendations regarding screening for distress and distress management.

Introduction

Thyroid cancer patients, like all cancer patients, may have a number of supportive care needs, often including the need for psychosocial support (Roth & Holland, 1995). The psychosocial needs of patients will vary depending on whether or not they are newly diagnosed, have already been living with cancer, or are among those for whom treatment has failed. In addition, one must also attend to the impact of the cancer on the patient’s partner, family and support system as they may need assistance.

Approximately one-third of all cancer patients experience clinically significant depression, anxiety and adjustment difficulties (Howell et al., 2010). The needs of thyroid cancer patients differ from those of patients with other cancer diagnoses, as the majority of thyroid cancer patients will not have life-threatening disease. While the survival rate for thyroid cancer is high, the diagnosis and treatment can have a significant impact on the individual and his/her family. Thus, it is important that those who require psychosocial care are identified and provided with necessary supports. All cancer patients, regardless of diagnosis, may experience periods of increased distress at critical points in the cancer trajectory such as investigation/diagnosis, start and end of treatment as well as at times of recurrence or transition to palliative care (Howell et al., 2010).

It is the responsibility of the attending health care team to provide basic support through the continuum of disease, and to seek further assistance as necessary to meet the patient’s needs. Referral to interprofessional team members (such as the QEII’s Psychosocial Oncology Team) to address the patient’s concerns may be appropriate.

Supporting individuals affected by cancer requires:

- Effective communication by and with health care providers,
- A process for identifying when clinically significant levels of distress are present and
- An awareness of the individual’s unique needs or challenges so that appropriate interventions may be offered (Howes et al., 2015).

Please refer to the Best Practice Guideline for the Management of Cancer-Related Distress in Adults for information concerning effective communication, screening for distress, and distress management including referral pathways.

Supportive Care and Thyroid Cancer

Thyroid cancer patients have unique needs, particularly during periods of thyroid hormone withdrawal and during the isolation period following RAI, which must be addressed.

An online survey of international thyroid cancer patients was conducted through thyroid patient organizations in seven countries (The Thyroid Cancer Alliance (TCA): Argentina, Canada, France, Germany, USA and UK) in March 2010. In total, there were 2,398 respondents, of
which 274 (11%) were Canadian (14 respondents were from Nova Scotia; 5% of the Canadian respondents) (Thyroid Cancer Canada, 2010).

Also, Sawka, (Sawka et al., 2009) conducted focus groups with 16 DTC patients at one facility in Toronto regarding the experience of receiving a thyroid cancer diagnosis and the experience of RAI therapy.

The TCA survey and the Sawka focus group results indicated that patients reported the diagnostic stage as being a period of high anxiety, as is common in all cancer diagnoses. Being told that thyroid cancer was a “good cancer” is not necessarily reassuring, and patients can feel that their diagnosis and concerns are unimportant to their care team.

The TCA patient survey found that psychological support at diagnosis was often lacking:

<table>
<thead>
<tr>
<th>% of respondents:</th>
<th>Canada</th>
<th>International</th>
</tr>
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<tbody>
<tr>
<td>Offered support from a nurse or similar person</td>
<td>17.9%</td>
<td>20%</td>
</tr>
<tr>
<td>Offered psychological support</td>
<td>4.7%</td>
<td>5%</td>
</tr>
<tr>
<td>Given details of a patient support organization</td>
<td>15.0%</td>
<td>14%</td>
</tr>
</tbody>
</table>

When asked what was the most difficult aspect of their cancer journey, one-quarter (24%) of all TCA survey respondents said receiving a cancer diagnosis, and 22% said uncertainty/anxiety about the future (Banach et al., 2013).

Need for Information

Sixty-three percent (63.1%) of the Canadian TCA patient survey respondents were not given clear written information about their disease and its treatment. This is the same as the international experience (Banach et al., 2013).

For the focus group participants, sub-specialty physicians were the primary source of information and counselling regarding RAI treatment (Sawka et al., 2009). They reported receiving contradictory information from various sub-specialty providers and the internet. Focus group participants wanted more plain-language information about potential risks, benefits and uncertainties about RAI therapy at the time of decision making. Participants felt the disclosure of the risk of second malignancies to be important.

Patient Recommendations for Improving Thyroid Cancer Care

The focus group participants made the following recommendations for improving thyroid cancer care:

- The team should explain the rationale for RAI therapy and the potential risks, benefits and uncertainties in plain-language
- Care should be provided in a multidisciplinary team based environment
- Provide information about current clinical practice guidelines and how they relate to an individual’s case (Sawka et al., 2009).

When asked what, if anything, could their medical team have done to improve their cancer journey, almost one-half (45%) of survey respondents would have liked more information about
the disease initially, 43% wanted an introduction to a patient support group, and the same number said psychological support (Banach et al., 2013).

**Practical Support**

Cancer patients are frequently challenged by practical issues such as transportation, especially to a tertiary centre, and financial barriers including access to drugs due to lack of insurance coverage. Cancer Patient Navigators or the Medication Resource Specialist may be able to provide assistance for those in need or referrals to other agencies.

**Screening for Distress**

In Nova Scotia, it is recommended that all adults diagnosed with cancer be screened for distress at critical times (such as the start and end of cancer treatment, transition to survivorship or end-of-life care, disease progression or recurrence and other stressful times) throughout the cancer continuum (Howes et al., 2015). The formal implementation of screening for distress in cancer patients using a common, standardized tool and approach began in Nova Scotia in 2009. The service continues to be expanded and is currently available to selected patients across the province. The goal is that all newly diagnosed cancer patients in Nova Scotia will be offered screening for distress, and then will be re-screened at critical times.

The objective of screening for distress is to quickly identify those people experiencing distress. Screening allows the health care provider to determine the need for further assessment and referral to healthcare specialists for assessment, management of concerns and treatment. Assessment is a thorough examination of the individual’s concerns, conducted after screening (Howes et al., 2015).

Some of the risk factors related to patients’ distress include:

- Younger age
- A history of mental illness
- Social isolation/limited social supports
- Greater burden of illness
- Advanced stage of cancer
- Post-treatment physical changes/losses
- Multiple life stressors

**Managing Distress**

Referral pathways have been developed to assist health professionals in Nova Scotia address concerns identified through screening for distress that are beyond the abilities of the front-line caregivers. These pathways are available through the Best Practice Guideline for the Management of Cancer-Related Distress in Adults.

Approaches for the management of psychosocial and emotional difficulties include the following:

- Encouraging patients to use their constructive coping/stress management strategies
- Providing patients with information and education on their disease and treatment
- Helping patients access positive social supports
- Encouraging patients to focus on a whole-person approach to coping with their illness (i.e. physical, psychological, social, spiritual)
• Encouraging patient involvement in relevant support groups, if appropriate
• Referring patients to psychosocial oncology healthcare professionals (i.e., psychologists, psychiatrists, social workers, spiritual care workers, advanced practice nurses) for consultation and treatment (e.g., psycho-education, counseling, and psychotherapy), as appropriate. There are psychosocial oncology resources available through the QEII Cancer Care service (902-473-5140) and the Cape Breton Cancer Centre (902-567-7771) for patients registered with these programs.

Cancer Patient Navigators are a valuable resource for patients and families, and are available in all of Nova Scotia except in the Halifax area, Eastern Shore and West Hants (Central Zone). See below for contact information.

For more information about screening for distress and providing psychosocial support to thyroid and other cancer patients, please see:

• Best Practice Guideline for the Management of Cancer-Related Distress in Adults (Cancer Care Nova Scotia) (available from www.cancercare.ns.ca)

• The Pan-Canadian Practice Guideline: Screening, Assessment and Care of Psychosocial Distress (Depression, Anxiety) in Adults with Cancer (available from www.capo.ca)

Resources for Patients

There are a number of local and national resources for thyroid cancer patients living in Nova Scotia:

• A Patient's Guide to Thyroid Cancer. For those diagnosed with papillary or follicular cancers, published by Thyroid Cancer Canada (available at www.thyroidcancercanada.org or call 416-487-8267).

• Low Iodine Diet. A short-term diet to prepare for RAI treatment or scan (available at www.thyroidcancercanada.org or call 416-487-8267).

• The Canadian Cancer Society's Information Service can connect patients and families to peer support, local resources and additional sources of information, including materials in languages other than English (available at www.cancer.ca or call 1-888-939-3333).

• Cancer Care Nova Scotia, in consultation with the Canadian Cancer Society- Nova Scotia Division, maintains an Inventory of Psychosocial Resources in Nova Scotia for health care professionals who care for cancer patients, to assist them and individuals affected by cancer in more readily accessing psychosocial services when needed. The inventory includes a list of both public and private psychosocial resources, available across the province. The focus is on licensed health care professionals, who provide psychosocial and supportive care to patients. The inventory can be accessed at www.cancercare.ns.ca/psychosocialinventory.

• Patient information sheets on a wide variety of topics related to aspects of cancer care including financial issues, accessing psychosocial support, side effects and symptom management are available at www.cancercare.ns.ca Patients and Families, Patient Education, Living Well With Cancer.

• The Emotional Facts of Life with Cancer is a guide to counseling and support for patients, family members and friends (available at www.capo.ca Explore, Professional and Student Info).
• **Young Adult Cancer Canada** provides information and support to young adults living with any cancer diagnosis (available at [www.youngadultcancer.ca](http://www.youngadultcancer.ca)).

• **Thyroid Cancer Canada** provides resources and offers an online forum for thyroid cancer patients (available at [www.thyroidcancercanada.org](http://www.thyroidcancercanada.org) or call 416-487-8267).

• All patients undergoing RAI therapy at the QEII HSC undergo an **educational session with a nuclear medicine technologist**, which includes discussions around preparation for the treatment, what the treatment involves, and radiation protection issues for the days following therapy and the provision of a patient education package.

• **What Happens Now? Follow up Care for Thyroid Cancer Patients.** Cancer Care Nova Scotia. (available at through the ITOC clinic and at [www.cancercare.ns.ca](http://www.cancercare.ns.ca))

### Pain and Symptom Management

A number of resources exist for patients who need help with pain or symptom management and/or palliative care. These include the attending oncology team, the Cancer Patient Navigator, and the local palliative care team. Only a small proportion of thyroid cancer patients require specialist palliative care. However, it is particularly important to ensure that these patients are referred in a timely manner.

### Contact Information for Nova Scotia Health Authority Supportive Cancer Care and Palliative Care Services:

<table>
<thead>
<tr>
<th>Area</th>
<th>Cancer Patient Navigator</th>
<th>Palliative Care</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lunenburg and Queen's counties</td>
<td>(902) 527-5820</td>
<td>902-634-7369 or 902-354-3436</td>
</tr>
<tr>
<td>Shelburne, Yarmouth and Digby counties</td>
<td>(902) 749-1523</td>
<td>902-742-3542 ext 1481</td>
</tr>
<tr>
<td>King's and Annapolis Counties</td>
<td>(902) 690-3700</td>
<td>902-678-7381 ext 2270</td>
</tr>
<tr>
<td>Colchester and East Hants counties</td>
<td>(902) 893-2549</td>
<td>902-893-5554 ext 2306</td>
</tr>
<tr>
<td>Cumberland county</td>
<td>(902) 667-6424</td>
<td>902-667-5400 ext 6373</td>
</tr>
<tr>
<td>Pictou county</td>
<td>(902) 752-7600 ext 4922</td>
<td>902-752-7600 ext 4190</td>
</tr>
<tr>
<td>Guysborough, Antigonish, Richmond and part of Inverness counties</td>
<td>(902) 867-4500 ext 4707</td>
<td>902-867-4296 or 902-867-4436</td>
</tr>
<tr>
<td>Cape Breton Regional Municipality, Victoria and Inverness counties</td>
<td>Victoria County 902-336-2504 902-295-2112 Inverness County 902-224-4002 902-258-1129 Cape Breton 902-567-6122</td>
<td>902-567-7846</td>
</tr>
</tbody>
</table>
Contact Information for Cancer Centre Supportive Cancer Care and Palliative Care Services:

<table>
<thead>
<tr>
<th></th>
<th>Cancer Centre Psychosocial Team</th>
<th>Palliative Care</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>QEII Cancer Care services</strong></td>
<td>902-473-5140</td>
<td>902-473-3119</td>
</tr>
<tr>
<td><strong>Cape Breton Cancer Centre</strong></td>
<td>902-567-7771</td>
<td>902-567-7846</td>
</tr>
</tbody>
</table>
References


Cancer Care Nova Scotia Surveillance and Epidemiology Unit. (2014).


Thyroid Cancer Canada. (2010). Thyroid cancer patient survey: Selected results pertaining to the Canadian experience.


Appendix 1: Staging

Post-operative Staging
Post-operative staging for thyroid cancer, as for other cancer types, is used to:

1. Permit prognostication for an individual patient with differentiated thyroid carcinoma (DTC);
2. Tailor decisions regarding post-operative adjunctive therapy, including RAI therapy and thyrotropin suppression, to the patient’s risk for disease recurrence and mortality;
3. Make decisions regarding the frequency and intensity of follow-up, directing more intensive follow-up towards patients at highest-risk;
4. Enable accurate communication regarding a patient between health care professionals; and
5. Evaluate differing therapeutic strategies applied to comparable groups of patients in clinical studies (Cooper et al., 2009).

Because of its utility in predicting disease mortality, and its requirement for cancer registries, American Joint Committee on Cancer/International Union against Cancer (AJCC/UICC) staging is recommended for all patients with DTC. The use of post-operative clinicopathologic staging systems is also recommended to improve prognostication and to plan follow-up for patients with DTC (ATA R31).

Definitions of TNM

*Primary Tumour (T)*
Note: All categories may be subdivided: (s) solitary tumour and (m) multifocal tumour (the largest determines the classification).

<table>
<thead>
<tr>
<th>TX</th>
<th>Primary tumour cannot be assessed</th>
</tr>
</thead>
<tbody>
<tr>
<td>T0</td>
<td>No evidence of primary tumour</td>
</tr>
<tr>
<td>T1</td>
<td>Tumour 2 cm or less in greatest dimension limited to the thyroid</td>
</tr>
<tr>
<td>T1a</td>
<td>Tumour 1 cm or less, limited to thyroid</td>
</tr>
<tr>
<td>T1b</td>
<td>Tumour more than 1 cm but not more than 2 cm in greatest dimension, limited to the thyroid</td>
</tr>
<tr>
<td>T2</td>
<td>Tumour more than 2 cm but not more than 4 cm in greatest dimension limited to the thyroid</td>
</tr>
<tr>
<td>T3</td>
<td>Tumour more than 4 cm in greatest dimension limited to the thyroid or any tumour with minimal extrathyroid extension (e.g., extension to sternothyroid muscle or perithyroid soft tissues)</td>
</tr>
<tr>
<td>T4a</td>
<td>Moderately advanced disease</td>
</tr>
<tr>
<td></td>
<td>Tumour of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve</td>
</tr>
<tr>
<td>T4b</td>
<td>Very advanced disease</td>
</tr>
<tr>
<td></td>
<td>Tumour invades prevertebral fascia or encases carotid artery or mediastinal vessels</td>
</tr>
</tbody>
</table>
**Regional Lymph Nodes (N)**
Regional lymph nodes are the central compartment, lateral cervical, and upper mediastinal lymph nodes.

- NX: Regional lymph nodes cannot be assessed
- N0: No regional lymph node metastasis
- N1: Regional lymph node metastasis
- N1a: Metastasis to Level VI (pretracheal, paratracheal, and pylaryngeal/Delphian lymph nodes)
- N1b: Metastasis to unilateral, bilateral, or contralateral cervical (Level I, II, III, IV, V) or retropharyngeal or superior mediastinal lymph nodes (Level VII)

**Distant Metastasis (M)**
- M0: No distant metastasis
- M1: Distant metastasis

**Anatomic Stage/Prognostic Groups**
Separate stage grouping are recommended for papillary or follicular (differentiated), medullary, and anaplastic (undifferentiated) carcinoma.

<table>
<thead>
<tr>
<th>Papillary or follicular (differentiated)</th>
<th>UNDER 45 YEARS</th>
<th>45 YEARS AND OLDER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>Any T</td>
<td>N0</td>
</tr>
<tr>
<td>Stage II</td>
<td>Any T</td>
<td>N0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1</td>
<td>N0</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1a</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1a</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1a</td>
</tr>
<tr>
<td>Stage IVa</td>
<td>T4a</td>
<td>N0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N1a</td>
</tr>
<tr>
<td></td>
<td>T1</td>
<td>N1b</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1b</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>N1b</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T4b</td>
<td>Any N</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T</td>
<td>Any N</td>
</tr>
</tbody>
</table>

Revised American Thyroid Association Management Guidelines – Adapted for Nova Scotia - 61
<table>
<thead>
<tr>
<th>Stage</th>
<th>T1</th>
<th>N0</th>
<th>M0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stage I</td>
<td>T2</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td><strong>T3</strong></td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td>Stage III</td>
<td>T1</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td><strong>T3</strong></td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVA</td>
<td>T4a</td>
<td>N0</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td>T4a</td>
<td>N1a</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td><strong>T1</strong></td>
<td>N1b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td><strong>T2</strong></td>
<td>N1b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td><strong>T3</strong></td>
<td>N1b</td>
<td>M0</td>
</tr>
<tr>
<td></td>
<td><strong>T4a</strong></td>
<td>N1b</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVB</td>
<td>T4b</td>
<td>Any N</td>
<td>M0</td>
</tr>
<tr>
<td>Stage IVC</td>
<td>Any T</td>
<td>Any N</td>
<td>M1</td>
</tr>
</tbody>
</table>

Medullary carcinoma (all age groups)
Appendix 2: Template for Thyroid and Neck Ultrasound Reporting for Nova Scotia

This is being developed and is not yet available.
Appendix 3: The Bethesda System for Reporting Thyroid Cytopathology

Background

In June 2010, a consensus meeting of specialist physicians and surgeons from across Nova Scotia involved in the diagnosis and management of thyroid cancer met to review the proposed interpretation and adaptations to the American Thyroid Association (ATA) Guidelines and address ways to improve communication and monitor quality of care for thyroid cancer. This included physicians representing surgery, pathology, radiology, radiation oncology, medical oncology, as well as endocrinology specialists, nurses and a nuclear medicine technologist. This initiative was supported by Cancer Care Nova Scotia (CCNS) and included participation by CCNS staff.

Pathologists from across the province participated in a small group discussion regarding the following question: What is the best protocol and structured reporting template for cytopathological interpretation of FNA biopsy samples of thyroid nodules? The recommendation arising from the Nova Scotia consensus conference is that The Bethesda System for Reporting Thyroid Cytopathology be adopted as the template for reporting, with minor modifications.

The Recommended Diagnostic Categories are as follows:

I. Unsatisfactory
   - Cyst fluid only
   - Virtually acellular specimen
   - Other (obscuring blood, clotting artifact, etc.)

II. Benign
   - Consistent with benign follicular nodule (includes adenomatoid nodule, hyperplastic nodule, colloid nodule, etc.)

III. Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance

IV. Follicular Neoplasm
   - Specify if Hürthle cell (oncocytic) type

V. Suspicious for Malignancy
   - Suspicious for papillary carcinoma
   - Suspicious for medullary carcinoma
   - Suspicious for metastatic carcinoma
   - Suspicious for lymphoma
   - Other

VI. Malignant
   - Papillary thyroid carcinoma
   - Poorly differentiated carcinoma
   - Medullary thyroid carcinoma
   - Undifferentiated (anaplastic) carcinoma
   - Squamous cell carcinoma
   - Carcinoma with mixed features (specify)
   - Metastatic carcinoma
   - Non-Hodgkin lymphoma
   - Other
Explanatory Notes:

The Nova Scotia modifications made to the published format of the Bethesda System for Reporting Thyroid Cytopathology include elimination of Nondiagnostic as an alternative to Unsatisfactory. The participants felt that the term Nondiagnostic was confusing, as historically some pathologists have used this terminology to indicate a specimen that has adequate cellularity but is not specific for a particular lesion.

For a thyroid specimen to be satisfactory for evaluation there must be at least six groups of well visualized follicular cells, with at least 10 cells per group. Exceptions to this numeric requirement include the presence of cytologic atypia, the presence of abundant colloid, and when inflammation predominates such as in lymphocytic thyroiditis.

Specimens can also be unsatisfactory due to obscuring blood, overly thick smears, or excessive air-drying. Cyst-fluid only cases should be considered unsatisfactory, as a cystic papillary carcinoma cannot be ruled out. In the proper clinical setting, these specimens may be considered clinically adequate even though they are reported as unsatisfactory.

Benign follicular nodules, lymphocytic thyroiditis, and granulomatous thyroiditis may be included under the Benign category.

Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance can be used for thyroid FNAs that do not fit easily into the benign, suspicious, or malignant categories. This is a category of last resort and the frequency of interpretations should be in the range of 7% of all FNA interpretations. There are a number of specific examples of how this terminology can be used in the references provided.

At the consensus meeting, Suspicious for Follicular Neoplasm was not included as an alternate wording for the category Follicular Neoplasm. This overlaps somewhat with the terminology for the previous category, Follicular Lesion of Undetermined Significance and could lead to confusion regarding the management of these patients. It is useful to specify if a Hürthle cell neoplasm is suspected.

Suspicious for Malignancy is used when features are strongly suggestive of malignancy, but are not conclusive. This most commonly applies to changes suggestive of papillary carcinoma but can also be applied to features suggestive of medullary carcinoma and lymphoma.
According to The Bethesda System for Reporting Thyroid Cytopathology, each category has an implied risk of malignancy (Table 2 below), and is linked to evidence-based clinical management guidelines (see Flowchart 1: Fine Needle Aspiration in guideline).

### Table 2: The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Malignancy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic or Unsatisfactory</td>
<td></td>
</tr>
<tr>
<td>Benign</td>
<td>0-3</td>
</tr>
<tr>
<td>Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance</td>
<td>~5-15</td>
</tr>
<tr>
<td>Follicular Neoplasm or Suspicious for a Follicular Neoplasm</td>
<td>15-30</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>60-75</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99</td>
</tr>
</tbody>
</table>

Appendix 4: CDHA Adaptation of the College of American Pathologists Protocol for the Examination of Specimens from Patients with Carcinomas of the Thyroid Gland

Procedure: _

Tumour focality: _

Estimated number of tumours: _

Dominant Tumour Characteristics:
- Laterality: _
- Tumour Size: _
- Histologic type: _
- Variant: _
- Architecture (papillary carcinoma only): _
- Cytomorphology (papillary carcinoma only): _
- Margin: _
- Distance from margin: _
- Tumour capsule: _
- Tumour capsule invasion: _
- Lymph-vascular invasion: _
- Extent of LVI (fewer or more than 4 foci): _
- Extrathyroidal extension: _

Second Tumour Characteristics:
- Laterality: _
- Tumour Size: _
- Histologic type: _
- Variant: _
- Architecture (papillary carcinoma only): _
- Cytomorphology (papillary carcinoma only): _
- Margin: _
- Distance from margin: _
- Tumour capsule: _
- Tumour capsule invasion: _
- Lymph-vascular invasion: _
- Extent of LVI (fewer or more than 4 foci): _
- Extrathyroidal extension: _

Regional Lymph Nodes:
- Central (level vi): _
- Cervical or other: _
- Extranodal extension: _

Pathological Stage:
- Primary tumour: _
- Regional lymph nodes: _
- Distant metastases: _

Additional Pathologic Findings: _
Parathyroids:
- Present? _
- Number: _
- Site: _

Note. Adapted from College of American Pathologists Protocol for the Examination of Specimens from Patients with Carcinomas of the Thyroid Gland by R. Ghossein, et al., 2009.
Appendix 5: STIM-Tg Protocol: Utilization of Post-operative Stimulated Tg Levels to Guide Patient Selection in RAI Remnant Ablation in Low-risk Papillary Thyroid Carcinoma

The utility of RAI ablation in the management of well-differentiated thyroid cancer in low-risk patients remains controversial due to lack of evidence of survival benefit and weak data suggesting RAI ablation reduces disease recurrence. In this patient population, given the potential risks of RAI treatments, a selective approach to RAI ablation decision-making is recommended (see Risk Stratification Flowchart 3: Recurrence Risk Stratification Based on Response to Therapy and Recommendations for Long-term TSH Suppression and Risk-adapted Follow-up) (Vaisman et al., 2010).

Low-risk Patient Selection for RAI therapy

**Low-risk** patients (Cooper et al., 2009; Vaisman et al., 2010) **ALL** of the following:

1. no distant metastases;
2. no metastatic lymph nodes outside the central compartment (Level VI) (N0, N1a, Nx)
3. all macroscopic tumour has been resected;
4. pathology limited to the thyroid gland: no tumour invasion of locoregional tissues or structures; no gross or microscopic extrathyroidal extension;
5. papillary or follicular variant of papillary thyroid cancer (i.e. the tumour does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma));
6. no vascular invasion;
7. negative resection margins;
8. no detectable interfering serum anti-Tg antibodies;
9. thyroidectomy done by experienced thyroid surgeon (low total thyroidectomy complication rates (recurrent laryngeal nerve injury, post-op hypocalcemia) and minimal residual thyroid tissue)) (see Who Should be Treated with RAI?)

Protocol:

1. Post-thyroidectomy, patients are placed on TSH suppression.
2. Baseline measurements to confirm the absence of Tg antibodies.
3. Measure stimulated serum Tg 3 months post-operatively and stratify based on Stim-Tg level (undetectable (< 1.5 pmol/L\(^9\)), 1.5–7.5 pmol/L, and > 7.5 pmol/L).
4a. Patients with undetectable Stim-Tg measurements are followed on long-term thyroid hormone suppression therapy (THST) and examined at regular intervals for possible disease recurrence with annual Stim-Tg, annual neck US, and other imaging and biopsy studies when indicated.
4b. Patients with Stim-Tg measurements of 1.5–7.5 pmol/L are given the option of deferring immediate RAI therapy in favour of long-term surveillance. Those who do not receive RAI are followed on long-term thyroid hormone suppression therapy (THST) and examined at regular intervals for possible disease recurrence with annual Stim-Tg, annual neck US, and other imaging and biopsy studies when indicated.
4c. Patients with a Stim-Tg value > 7.5 pmol/L are strongly advised to proceed with RAI.

\(^9\) While the literature reports Tg levels in µg/L, the QEII HSC laboratory reports Tg levels in pmols/L and this is the unit that is used in this guideline.
Appendix 6: Patient Preparation for Radioactive Iodine Scans and Therapy (See Patient Preparation for more details)

**Patient Education**

All patients undergoing RAI therapy at the QEII HSC undergo an educational session with a nuclear medicine technologist, which includes discussions around preparation for the treatment, what the treatment involves, and radiation protection issues for the days following therapy and the provision of a written patient education package.

**Minimizing Endogenous Circulating Iodine Levels**

Patients should be advised to avoid iodine in the weeks preceding therapy or scanning.

<table>
<thead>
<tr>
<th>Preparation for Therapy</th>
<th>Preparation for Scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avoid iodine-containing medications, multi-vitamins or mineral supplements</td>
<td>6-8 weeks prior</td>
</tr>
<tr>
<td>Avoid IV radiographic contrast</td>
<td>6 weeks prior</td>
</tr>
<tr>
<td>Start Low-Iodine Diet</td>
<td>2 weeks prior</td>
</tr>
<tr>
<td>Resume Normal Diet</td>
<td>Full 2 days post therapy</td>
</tr>
</tbody>
</table>

**Elevating TSH:**

Effective uptake of radiiodine by the thyroid requires adequate stimulation by elevating circulating TSH. Two methods of preparation are available: (a) thyroid hormone withdrawal (THW) and consequent hypothyroidism, or (b) administration of recombinant humanized thyrotropin (rhTSH, thyrotropin alfa, Thyrogen®).

<table>
<thead>
<tr>
<th>Preparation for Therapy</th>
<th>Preparation for DxWBS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Option 1. Thyroid Hormone Withdrawal (THW)</strong></td>
<td></td>
</tr>
<tr>
<td>Stop Medications</td>
<td>4 weeks prior:</td>
</tr>
<tr>
<td></td>
<td>- stop T4 (Levothyroxine) (Synthroid®, Eltrexin®)</td>
</tr>
<tr>
<td></td>
<td>- start T3 (Liothyronine) (Cytomel®) 25 mcg PO BID x 2 weeks</td>
</tr>
<tr>
<td>2 weeks prior:</td>
<td>- stop T3 (Liothyronine) (Cytomel®)</td>
</tr>
<tr>
<td>Resume Medications</td>
<td>Full 2 days post therapy</td>
</tr>
<tr>
<td></td>
<td>4 weeks prior:</td>
</tr>
<tr>
<td></td>
<td>- stop T4 (Levothyroxine) (Synthroid®, Eltrexin®)</td>
</tr>
<tr>
<td></td>
<td>- start T3 (Liothyronine) (Cytomel®) 25 mcg PO BID x 2 weeks</td>
</tr>
<tr>
<td>2 weeks prior:</td>
<td>- stop T3 (Liothyronine) (Cytomel®)</td>
</tr>
<tr>
<td></td>
<td>1 day after completion of scan unless otherwise advised by physician</td>
</tr>
</tbody>
</table>
Option 2. Thyrotropin (rhTSH) (and Continue Thyroid Hormone Medications)

| rhTSH injections 0-9 mg IM once each day for 2 days (approximately 24 hours apart) prior to radioactive iodine (see Thyrogen® Product Monograph\(^\text{10}\)) | rhTSH injections 0-9 mg IM once each day for 2 days (approximately 24 hours apart) prior to radioactive iodine (see Thyrogen® Product Monograph\(^\text{11}\)) |

While either method of TSH stimulation is acceptable, rhTSH preparation may be indicated in selected patients. rhTSH is obtained from the patient’s own retail pharmacy. The cost of rhTSH is substantial. Patients may have private insurance that will cover it and should check with their insurers (thyrotropin alfa DIN 02246016). The patient can also obtain coverage through the NS Pharmacare programs (e.g., Seniors Pharmacare or Family Pharmacare). Please note that rhTSH is a special authorization drug on most insurance plans and all NS Pharmacare plans.

Appendix 7: Harmful Effects of Radioactive Iodine (RAI)

While RAI appears to be a reasonably safe therapy, it is associated with a cumulative dose-related low-risk of early- and late-onset complications. Therefore, it is important to ensure that the benefits of RAI therapy, especially repeated courses, outweigh the potential risks. There is probably no dose of RAI that is completely safe nor is there any maximum cumulative dose that could not be used in selected situations. However, with higher individual and cumulative doses there are increased risks of side effects (Cooper et al., 2009). Most important for patients at low-risk of recurrence and mortality, there is growing evidence that there is no survival benefit from RAI therapy while patients are exposed to toxicity. To minimize risk to patients, $^{131}$I should be given only when benefits are expected, and in these patients the minimal activity should be administered (Pacini et al., 2006).

RAI therapy can be harmful to the embryo or fetus and is contraindicated in pregnant women. RAI is also contraindicated in women who are lactating or breastfeeding (see Pregnancy and RAI Therapy).

One of the goals of long-term follow-up is to monitor for late toxicities from RAI.

Preventive Measures

To promote excretion of RAI, and minimize early side effects, all patients should be encouraged to take liberal hydration beginning immediately after oral RAI administration. To minimize radiation exposure of the salivary glands, salivary stimulants, such as sour candies, are recommended to be started 12-24 hours after oral RAI administration.

While the evidence is insufficient to recommend for or against the routine use of preventive measures to prevent salivary gland damage after RAI therapy, in Nova Scotia, sour candies are routinely recommended 12-24 hours after oral RAI administration (Mandel & Mandel, 2003; Nakada et al., 2005) (see CCNS Recommendation 51).

Possible Early Effects

Common side effects in order of frequency:

- **Nausea and vomiting** can be minimized by anti-emetic drugs
- **Sialadenitis** can be managed with hydration and non-steroidal anti-inflammatory medication
- **Abnormalities of taste and smell** are frequent but transient
- **Tear duct blockage** (xerophthalmia)
- **Radiation thyroiditis** with swelling and discomfort is more frequent in patients with large thyroid remnants and can be limited by the use of corticosteroids for a few days.
- **Hypospermia** has been observed following $^{131}$I treatment but is usually transient. Pre-treatment sperm banking should be offered to male patients if multiple activities of $^{131}$I are planned. Conception should not occur before a minimum of 4 months after $^{131}$I treatment as this allows for the life span of a sperm cell (Pacini et al., 2006).

Patients with xerostomia are at increased risk of dental caries and should discuss preventive strategies with their dentists (see CCNS Recommendation 52). A single ablation activity rarely leads to xerostomia (Pacini et al., 2006).

Surgical correction should be considered for nasolacrimal outflow obstruction, which often...
presents as excessive tearing (epiphora) but also predisposes to infection (see CCNS Recommendation 53). Dry eye is infrequent (Pacini et al., 2006).

Possible Late Effects

Secondary Malignancies:

The development of secondary primary malignancies attributable to RAI is a rare late effect (Iyer et al., 2011).

- The risk of secondary malignancies is dose related, with an excess absolute risk of 14.4 solid cancers and of 0.8 leukemias per 27 mCi of 131I at 10,000 person-years of follow-up. Cumulative $^{131}I$ activities above 500–600 mCi are associated with a significant increase in risk.
- Most long-term follow-up studies variably report a very low-risk of secondary malignancies (bone and soft tissue malignancies, including breast, colorectal, kidney, and salivary cancers, and myeloma and leukemia) in long-term survivors.
- A meta-analysis of two large multicenter studies showed that the risk of second malignancies was significantly increased at 1.19 (95% CI: 1.04–1.36; p<0.010), relative to thyroid cancer survivors not treated with RAI.
- The risk of leukemia was also significantly increased in thyroid cancer survivors treated with RAI, with a relative risk of 2.5 (95% CI: 1.13–5.53; p<0.024).
- There appears to be an increased risk of breast cancer in women with thyroid cancer. It is unclear whether this is due to screening bias, RAI therapy, or other factors. An elevated risk of breast cancer with $^{131}I$ was not observed in another study (Cooper et al., 2009).

Radiation pneumonitis and fibrosis can occur in patients with diffuse pulmonary metastases who received repeated activities of RAI over short intervals of time (Pacini et al., 2006). As previously noted (see CCNS Recommendation 79c), when there is a high burden of pulmonary metastases, dosimetry calculations may be useful to establish a safe dose.

Persistent mild decrements in white blood count and/or platelets are not uncommon in patients who have received multiple RAI therapies. Furthermore, radiation to the bone marrow is impacted by several factors, including renal function (Cooper et al., 2009).

An earlier onset of menopause has been reported after repeated courses of radioiodine (Pacini et al., 2006).
Appendix 8: Useful ITOC Handouts

8.1 Guidelines for Suppression of TSH in Thyroid Cancer Patients
8.2 Hypocalcemia Management Guidelines
8.3 How to Take Thyroid Replacement Therapy for Thyroid Cancer
FAQ
**GUIDELINES FOR SUPPRESSION OF TSH IN THYROID CANCER PATIENTS**

Your patient has been prescribed levothyroxine for management of thyroid cancer. The aim for this therapy is to suppress Thyroid Stimulating Hormone (TSH). This has been showed to reduce the risk of thyroid cancer recurrence. To achieve that:

Your patient should have serum TSH checked every 6 weeks.

a) The dose of levothyroxine should be adjusted in aliquots of 25 micrograms each time until TSH is in the recommended level (see below) on two consecutive blood tests that are drawn at least 6 weeks apart.

- □ Level A: TSH = 0.01-0.1 mIU/L
- □ Level B: TSH = 0.1-0.5 mIU/L
- □ Level C: TSH = 0.35-2 mIU/L

Once target TSH has been achieved, further blood tests should be repeated at 6 month intervals to ensure adequate TSH suppression.

With this therapy your patient may experience mild symptoms of hyperthyroidism initially, but they should subside. If these symptoms become intolerable, consider reducing the dose by 25 micrograms and contact the Multidisciplinary Clinic at (902) 473-3723.
Appendix 8.2

HYPOCALCEMIA MANAGEMENT GUIDELINES

Your patient has developed hypocalcemia after thyroid cancer surgery. These guidelines should help you manage your patient’s calcium.

1. Confirm hypocalcemia by measuring serum/ionized calcium. If ionized calcium is not yet available, you can check serum total calcium and albumin. Corrected calcium can be calculated by using the following formula:

   Corrected calcium: increase serum calcium by 0.2 mmol/L for every decrease of 10g/L (below 40 g/L) in serum albumin.

2. Check serum Mg level and if low, replace accordingly.

3. If your patient is symptomatic with hypocalcemia (numbness, unusual twitching, or tingling sensations) or serum calcium is significantly low (total calcium < 1.8 mmol/L, ionized calcium < 1.0 mmol/L) give 10mls of 10% calcium gluconate intravenously over 30 minutes and send the patient to the local Emergency Department immediately.

4. In a case of mild hypocalcemia (serum calcium > 1.8 mmol/L, ionized calcium > 1.0 mmol/L) increase oral intake of elemental calcium to 2.0g daily and recheck calcium 1 week later. If hypocalcemia persists despite a daily elemental calcium intake of 2.0g per day, add Rocaltrol 0.25mcg b.i.d. Check calcium every 2-3 days and adjust the dose of Rocaltrol until noromocalcemia is achieved.

5. In a case of resistant hypocalcemia, please contact the on-call Endocrinologist of the Multidisciplinary Thyroid Oncology Clinic at 902-473-3723.
Appendix 8.3

How to Take Thyroid Replacement Therapy for Thyroid Cancer (FAQ)

1) Which form of thyroid replacement therapy is recommended for me?

Synthetic thyroxine or T4 is the standard treatment in patients with thyroid cancer. In Canada, several formulations of T4 are currently available. Of those, the two most commonly used brand-name preparations are: Synthroid (made by Abbott) and Eltroxin (made by GSK). T4 supplied by certain manufacturers are available in more dosage sizes and may facilitate dose titration.

2) Can I switch a similar dose of one form of T4 with another?

Studies have suggested that when tablets of similar dosage, but made by different manufacturers are taken, there may be subtle differences in the actual amount of T4 that ultimately becomes available to the body. Similar differences may also occur in brand-name versus generic preparations. Therefore, it is preferable to stick with the same formulation of T4, but if the preparation must be changed, follow-up blood work should be done to confirm the adequacy of blood thyroid levels after 6-8 weeks.

3) What is the best time to take T4?

T4 should ALWAYS be taken on an empty stomach. We recommend taking T4 an hour or so before breakfast, but if that is not feasible then it should be taken at bedtime. Other medications, including many non-prescription drugs, such as iron and calcium preparations, interfere with the absorption of T4 and should not be taken at the same time as T4. If you take any other drug in addition to T4 (whether prescription, non-prescription or natural supplement), please ask your pharmacist if it will interfere with your T4 therapy.

4) Why do I need frequent blood tests and dose adjustments?

In order to minimize the risk of recurrence of thyroid cancer, your cancer team has provided you with written goals of T4 treatment. Please discuss those goals with your family physician. In order to maintain your blood levels within the recommended range, you will require continuous monitoring. Typically, you will need frequent (once every 6 weeks or so) blood testing when you start taking T4 initially. Once you have achieved your recommended target, your doctor will still continue to check your blood every 3-6 months, and if necessary, adjust your T4 dosage to ensure that you levels are adequately maintained.
Appendix 9: Abbreviations Found in Guideline

International Organizations

AJCC/UICC  American Joint Commission on Cancer/Union for International Cancer Control
ATA      American Thyroid Association

Nova Scotia Organizations

CCNS  Cancer Care Nova Scotia
ITOC  Interdisciplinary Thyroid Oncology Clinic
QEII HSC  Queen Elizabeth II Health Sciences Centre

Thyroid Cancer Related Terms

DTC  Differentiated thyroid cancer.
DxWBS  Diagnostic Whole Body Scan
FNA  Fine Needle Aspiration
MEN2  Multiple endocrine neoplasia type 2: a group of medical disorders associated with tumours of the endocrine system
MTC  Medullary Thyroid Carcinoma
PTC  Papillary thyroid cancer
PTH  Parathyroid Hormone
RAI  Radioactive Iodine
rhTSH  Recombinant human thyrotropin
RLN/RLNP  Recurrent Laryngeal Nerve Paralysis
RxWBS  Therapeutic Whole Body Scan
Stim-Tg  Stimulated Thyroglobulin
Tg  Thyroglobulin
THW  Thyroid Hormone Withdrawal
TSH  Thyroid Stimulating Hormone
US  Ultrasound
WBS  Whole Body Scan
WDTC  Well-differentiated thyroid cancer
\(^{18}\text{FDG-PET}\)  \(^{18}\text{F-Fluorodeoxyglucose positron emission tomography (PET Scan)}\)
\(^{123}\text{I}\)  Iodine-123 radioactive isotope of iodine sometimes used in nuclear medicine imaging (not used for thyroid cancer in NS)
\(^{131}\text{I}\)  Iodine-131 radioactive isotope of iodine used in thyroid cancer treatment and whole body imaging
\(^{99}\text{Tc}\)  Technetium-99 isotope of technetium used in nuclear medicine imaging
Appendix 10: Guideline Adaptation Process

The adaptation process began in February 2010 following the 2009 publication of the American Thyroid Association (ATA) Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer (ATA Guidelines). The adaptation team consisted of the Chair, Dr Murali (Mal) Rajaraman (Radiation Oncologist), Dr Ali Imran (Endocrinologist), Dr Rob Hart (Head and Neck Surgeon), Dr Steve Burrell (Nuclear Medicine) – all members of the QEII Interprofessional Thyroid Oncology Clinic (ITOC) team and affiliated with Dalhousie Medical School, and Jill Petrella (Manager of Quality and project manager of the adaptation project) and Sandra Cook (Manager of Patient Navigation and Surgical Oncology) of Cancer Care Nova Scotia (CCNS).

All members of the adaptation team completed Conflict of Interest Disclosure Declarations. The only declared conflict of interest was from the Chair, who disclosed having received funding from Genzyme Canada for database development, human resources for database support and development of software with database and clinical applications and one time involvement at a Genzyme Canada Inc Advisory Board meeting in September 2009 discussing aspects of thyroid cancer patient care and Thyrogen use.

Particular areas of concern for the writing team were the lack of consistent reporting processes and terminology when reporting thyroid cancer pathological and ultrasound findings in Nova Scotia and the lack of standardized approaches to prevent inappropriate variations in practice that might lead to poorer outcomes.

The team agreed to adapt the ATA Guidelines for Nova Scotia and received permission to adapt them from the ATA in June 2010. The team met weekly and reviewed and discussed whether to accept or adapt each ATA recommendation to meet NS context. Agreement was by consensus.

In June 2010, a consensus meeting was held with 25 participants from across Nova Scotia: surgeons, pathologists, radiologists, medical and radiation oncologists, endocrinologists, nurses and nuclear medicine technologists. Dr Sandy McEwan, well-known nationally and internationally as an experienced thyroid cancer clinician and researcher, facilitated the meeting. All participants completed a Conflict of Interest Disclosure Declarations prior to the start of the meeting.

Of the 25 participants, 3 declared conflicts:

- 1 had received honoria from various surgical and pharmaceutical companies in support of an education day on ENT topics
- 1 was a member of the Canadian Association of Pathologists Executive at the time the College of American Pathologists reporting protocols (including the thyroid protocol) were endorsed as a content standard (2009) and is a member of a Canadian Partnership Against Cancer committee which promotes the use of synoptic pathology reporting
- 1 has served as the Genzyme Canada Advisory Board Chair
- 2 have received funding from Genzyme Canada for database development, human resources for database support and development of software with database and clinical applications
- 1 reported one time involvement at a Genzyme Canada Inc Advisory Board meeting in September 2009 discussing aspects of thyroid cancer patient care and Thyrogen use.
In addition, Genzyme Canada provided the airfare and accommodation for Dr McEwan to attend the meeting.

The goal of the meeting was to develop recommendations for Nova Scotia based on the ATA Guidelines that would:

a) improve communication of clinically important medical information amongst the health care team through structured reporting and standardized terminology

b) provide the basis for a discussion with patients regarding management options while the specific treatment plan would depend on a more complete discussion of risks and benefits of proposed therapies with individual patients

Small groups based on specialty (surgery, radiology, pathology) were assigned three questions for discussion. Two questions were specific to each specialty and one question was discussed by all groups. Participants were informed in advance of the assigned questions and were given background reading. Participants who were not from these three specialties were assigned to one of the three groups. There was large group discussion of all questions at the end of the day. A full report of the meeting is available upon request.

To address the issue of improved communication, the following recommendations were made:

- **Standardized pathology reporting:** the content of the College of American Pathologists Protocol for the Examination of Specimens from Patients with Carcinomas of the Thyroid Gland with modifications as made at the meeting is recommended for use in Nova Scotia. Dr Martin Bullock, QEII HSC pathologist, led this work.
- **Standardized cytopathology reporting:** to adopt The Bethesda System for Reporting Thyroid Cytopathology (TBSRTC) with minor modifications. Dr Rebecca MacIntosh, QEII HSC pathologist, led this work.
- **Standardized ultrasound reporting:** develop a structured reporting template for US examination of thyroid nodules and of thyroid cancer for Nova Scotia. Dr Brian Psooy, QEII HSC radiologist, led this work.

In November 2010, the Adaptation Team recognized that based on emerging evidence, modification of the approach to management for low risk thyroid cancer patients should be considered (i.e. these patients might not require radioactive iodine therapy). Recommendations and flowcharts outlining this risk-stratification approach were developed.

In 2012, the Capacity Enhancement Program of the Canadian Partnership Against Cancer (CPAC) conducted an external review of the draft adapted guideline on behalf of CCNS. Feedback on the evidence and the recommendations presented in the draft guideline was sought from external reviewers across Canada. Nineteen candidate content experts representing seven provinces were contacted by email and asked to serve as external reviewers. Ten content experts agreed to participate and were sent the draft report and the link to a short online questionnaire. Eight responded. The questionnaire consisted of items evaluating the methods, presentation, and completeness of reporting of the draft guideline report, as well as the appropriateness of the draft recommendations, and barriers or enablers to guideline implementation. Written comments were invited. Overall, 43% of respondents agreed

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with the draft recommendations as stated and 57% would consider endorsement or adaptation of the draft guideline report for use in their own jurisdiction (see Appendix 11). Simultaneously, CCNS conducted a similar review with the participants from the 2010 consensus meeting and other Nova Scotia key stakeholders.

The team reviewed the feedback received from the external review and made revisions as appropriate. (see Appendix11).

The revised adapted guideline was endorsed by the Chief Medical Director for Cancer Care Nova Scotia in June 2014, and it was submitted to the Nova Scotia Department of Health and Wellness in November 2014.

**Cancer Care Nova Scotia Involvement**

As the provincial cancer agency for Nova Scotia, the mandate for Cancer Care Nova Scotia (CCNS) includes the development of provincial standards and guidelines related to cancer care and treatment. CCNS staff worked with the ITOC team members in the review of the ATA guideline by providing meeting facilitation support and organization for both the core team meetings and the consensus meeting including all communication with participants and logistical arrangements. CCNS staff also coordinated the writing and editing of the various drafts.

To facilitate the involvement of all stakeholders in the consensus meeting, CCNS removed financial barriers by providing travel and accommodation for those coming from outside Halifax and reimbursing fee for service physicians for their time during the meeting (at the approved Department of Health rate for administrative work). CCNS did not provide compensation of any kind to the members of the adaptation team.

CCNS did not influence the decision-making.

It will be the role of CCNS to work with stakeholders in implementing the guideline recommendations.
## Appendix 11: Response to External Review

<table>
<thead>
<tr>
<th>External review comment</th>
<th>Response</th>
</tr>
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<tbody>
<tr>
<td>(The recommendation numbers and page numbers referenced in these comments may not coincide with the current numbered recommendations as a result of revisions to the guideline made after the external review)</td>
<td></td>
</tr>
<tr>
<td>1. The guideline development methods are of high quality.</td>
<td></td>
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<tr>
<td>I would not describe the ATA guidelines as the &quot;gold standard&quot; in so far as the management of thyroid nodules detected at US is concerned. I might also consider the Society of Radiologists in Ultrasound Consensus Conference Statement (Radiology 2005) in this regard.</td>
<td>Changed wording to The Nova Scotia panel recognizes that the ATA guidelines are well-developed and widely accepted guidelines for thyroid cancer and chose to follow them as closely as possible</td>
</tr>
<tr>
<td>It is difficult to assess the expertise of the panel developing the guidelines since their names and experience with thyroid cancer were not included.</td>
<td>Learning for next time.</td>
</tr>
<tr>
<td>For the recommendations that differ substantially from ATA, it would be helpful for the details of evidence review/appraisal/synthesis and development of recommendations (i.e. consensus) to be more clearly described. If undertaken, any consultation with stakeholders or consideration of costs should also be more clearly described.</td>
<td>An explanation for modifications can be found in Appendix 12.</td>
</tr>
<tr>
<td>2. The guideline presentation is of high quality.</td>
<td></td>
</tr>
<tr>
<td>The general format is well organized, but more narrative and medical evidence justifying substantial changes in recommendations from ATA document would be helpful.</td>
<td>An explanation for modifications can be found in Appendix 12.</td>
</tr>
<tr>
<td>3. The completeness of reporting is of high quality</td>
<td></td>
</tr>
<tr>
<td>For the recommendations that differ substantially from ATA, it would be helpful for the details of evidence review/appraisal/synthesis and development of recommendations (i.e. consensus) to be more clearly described.</td>
<td>An explanation for modifications can be found in Appendix 12.</td>
</tr>
</tbody>
</table>
4. The guideline recommendations are appropriate for the target population.

<table>
<thead>
<tr>
<th>It is my experience that the majority of thyroid nodules are discovered incidentally at US and are not palpable. This will result in an enormous number of nodules to biopsy in your catchment area. Are you prepared to meet the demand for US guided fine needle biopsy generated by following the ATA guidelines?</th>
<th>We believe the guidelines will decrease referral to endocrinology and would deter unnecessary referrals.</th>
</tr>
</thead>
<tbody>
<tr>
<td>For the recommendations that differ substantially from ATA, it would be helpful for the details of evidence review/appraisal/synthesis and development of recommendations (i.e. consensus) to be more clearly described.</td>
<td>An explanation for modifications can be found in Appendix 12.</td>
</tr>
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</table>

5. I agree with the recommendations as stated.

<table>
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<tr>
<th>(If not, please list what areas are missing or suggest revisions)</th>
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<tr>
<td>The guidelines are made for a paying population. They are rather weak on the recommendations for low risk thyroid cancers. In a public health care system we must be more rigorous and refuse unnecessary radioactive iodine therapy for patients with low risk disease, rather than have the feeble recommendations that allow paying customers to demand unnecessary treatments for “peace of mind”</td>
</tr>
<tr>
<td>We’ve addressed issue of unnecessary RAI therapy using the risk-stratifying approach.</td>
</tr>
<tr>
<td>Would you consider including guidelines for the performance of fine needle thyroid biopsy?</td>
</tr>
<tr>
<td>Performance of FNAB is addressed in the section “Guidelines for the Management of Thyroid Nodules” (page 15).</td>
</tr>
<tr>
<td>? Re 68b, page 46: is it implied that nodes greater that 5-8mm smallest diameter are suspicious? If not, what features makes these (normal sized) nodes suspicious? Biopsy of nodes 5mm short axis diameter may be unrealistic.</td>
</tr>
<tr>
<td>This is taken straight from ATA recommendation 48b) –If a positive result would change management, ultrasonographically suspicious lymph nodes greater than 5–8mm in the smallest diameter should be biopsied for cytology with Tg measurement in the needle washout fluid. Recommendation rating: A. The only modification we made was to remove reference to the washout fluid.</td>
</tr>
<tr>
<td>Re the Thyroid and Neck US reporting template: When describing gland vascularity, how is this determined (subjectively?)? I am confused by the convention for numbering nodules. A diagram might help. I am confused about irregular vs infiltrative borders. A picture</td>
</tr>
<tr>
<td>The US reporting template continues to be revised. We will investigate possibility of incorporating diagrams and pictures.</td>
</tr>
<tr>
<td>Topic</td>
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<tr>
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</tr>
<tr>
<td>Re peripheral &quot;rim of fire&quot; vascularity: is this helpful (overlap for benign and malignant nodules). Re neck lymph node stations: a diagram may be helpful to include.</td>
</tr>
<tr>
<td>2.1 - remove rapid growth since it is usually slow growth.</td>
</tr>
<tr>
<td>2.1 Include adult when discussing exposure to radiation.</td>
</tr>
<tr>
<td>2.1 I would include ethnic background (there is a lot of literature on patients born in the Philippines, Hawaii, and Iceland) and their increased risk of thyroid cancer.</td>
</tr>
<tr>
<td>Under investigations I would include worrisome ultrasound findings (Taller&gt;wide, microca+, hypoechoic).</td>
</tr>
<tr>
<td>Also, nodules 6mm-9.9mm should be investigated if the patient has risk factors.</td>
</tr>
<tr>
<td>In 2.3.1 I would add family history of thyroid cancer.</td>
</tr>
<tr>
<td>For some of the major modifications that were made from the ATA document, more evidence justification would be needed to support routine use of the outlined approach, and some examples would include: #67 routine whole body radioactive iodine scanning 6 months after remnant ablation (no evidence cited), and radioactive iodine remnant ablation of</td>
</tr>
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</table>
low risk DTC based on elevated simulated thyroglobulin level (1 study cited for protocol presented for level of thyroglobulin determining need for treatment) (Flowchart 2). advocated to identify patients at low-risk of recurrence who would not benefit from RAI (Brown, de Souza, & Cohen, 2011; Iyer, Morris, Tuttle, Shaha, & Ganly, 2011; Sacks, Fung, Chang, Waxman, & Braunstein, 2010; Tuttle et al., 2008; Vaisman et al., 2010).

6. The barriers or enablers to the implementation of this guideline report have been identified. (If not, please identify what areas are missing)

<table>
<thead>
<tr>
<th>This area is not directly addressed by the document and will likely need to be considered prior to implementation. For instance, the &quot;Template For Thyroid And Neck Ultrasound Reporting For Nova Scotia&quot; is a wonderful idea and I am certain that surgeons and endocrinologists will be enablers of this change, but the radiologists may present a barrier as the reporting is much more comprehensive than the standard approach.</th>
<th>We are planning an educational intervention with the radiologists and US technologists to encourage their use of this template. A pilot of the reporting template will be conducted in early 2015.</th>
</tr>
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<tbody>
<tr>
<td>Potential barrier is volume of nodules for biopsy, as noted above.</td>
<td>We believe the guidelines will decrease referral to endocrinology and would deter unnecessary referrals.</td>
</tr>
<tr>
<td>It is unclear whether this guideline is intended to be used by clinicians as a stand-alone document or whether it is to be used in conjunction with the ATA document. It may be challenging for clinicians to have the time to review and implement 2 related guidelines in clinical practice. The use of the Nova Scotia guideline as a stand-alone document may be insufficient given details of the evidence base foundation are not reported to the detailed extent of the ATA document.</td>
<td>The intent is to be standalone. Those who are interested in the rationale behind the ATA recommendations will be referred to the original document.</td>
</tr>
</tbody>
</table>

Other comments:

Overall, great work that will hopefully become a standard for other provinces.
1) The preamble (below) should be corrected to use the term "surgeons" rather than "general surgeons" as Otolaryngologists - Head and Neck Surgeons perform many, and in some areas, most, of these procedures. This guideline is designed for family physicians, general surgeons, pathologists, radiologists, other community-based specialist physicians and other health professionals involved with thyroid cancer

“general” deleted
patients and includes recommendations on:

<table>
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<tr>
<th>2) Recommendation 32B has an error and should refer reader to Recommendation 36, rather than 35. (last line) (b) Bilateral prophylactic central-compartment neck dissection should be considered in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes, especially for advanced primary tumors (T3 or T4). It is recommended that surgeons performing central neck dissections monitor the quality indicators found in Recommendation 35. (ATA R27b modified)</th>
<th>Correction made</th>
</tr>
</thead>
<tbody>
<tr>
<td>3) You have suggested referral of patients with a diagnosis of thyroid cancer to an experienced thyroid surgeon (3.2) and later provide this information: If the referring physician would like to discuss a case with a thyroid oncology specialist, it is recommended that they call the appropriate specialist (Radiation Oncology: Dr Mal Rajaraman, Endocrinologist: Dr Ali Imran, or a thyroid Surgeon) through locating 902-473-2220. You have specifically identified a radiation oncologist and endocrinologist, would it be worthwhile to provide a list of thyroid surgeons with appropriate training and volume?</td>
<td>Added “call the appropriate specialist associated with the Interdisciplinary Thyroid Oncology Clinic” and added Otolaryngologist/Head and Neck Surgeon along with endocrinologist and radiation oncologist.</td>
</tr>
<tr>
<td>4) I would suggest that you recommend that any patient requiring lateral compartment dissection (see below) be referred to a Head and Neck surgeon with fellowship training and adequate volume: 33. Therapeutic lateral neck compartmental lymph node dissection should be performed for patients with biopsy proven metastatic lateral cervical lymphadenopathy. (ATA R28)</td>
<td>Added “by a H&amp;N surgeon” and provided the Cancer Care Ontario definition of H&amp;N Surgeon in a footnote.</td>
</tr>
<tr>
<td>5) Minor check box formatting error in &quot;GUIDELINES FOR SUPPRESSION OF TSH IN THYROID CANCER PATIENTS&quot;</td>
<td>Corrected</td>
</tr>
</tbody>
</table>

Page 38. In addition to the French paper, there is also Mallick et al, NEJM 2012; 366: 1674-85., in support of a lower activity of iodine treatment (30 mCi) for low risk and some intermediate risk cases. We are revising our guidelines to use more of the low dose approach.

The section on supportive care and Permission requested from NCCN
appendices are useful. Permission will likely be required from NCCN for the recommendations citing NCCN.

<table>
<thead>
<tr>
<th>Page 9; para1, line 2</th>
<th>grammatical</th>
</tr>
</thead>
<tbody>
<tr>
<td>“...specialists...which can lead to inconsistent and fragmented care as borne out...”</td>
<td>Edits made</td>
</tr>
</tbody>
</table>

| Page 12 re: distribution of papillary and follicular cancer frequencies: 54/37 is an odd distribution. Most of us see these diagnoses in a ratio of more like 90/10. Is there a reason for this high incidence of follicular cancers? | No. |

<table>
<thead>
<tr>
<th>Page 12 re: risk factors for thyroid cancer: “. Exposure to ionizing radiation, especially during early childhood”</th>
<th>Edit made</th>
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<tbody>
<tr>
<td>I note that nearly all of the excess thyroid cancers that resulted from the Chernobyl accident followed exposure of children who were less than 10 years old at the time. (See various IAEA and UNSCEAR Reports; eg: <a href="http://www.unscear.org/docs/reports/2008/11-80076_Report_2008_Annex_D.pdf">http://www.unscear.org/docs/reports/2008/11-80076_Report_2008_Annex_D.pdf</a> ).</td>
<td></td>
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</table>

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<thead>
<tr>
<th>Page 13 re: History, 4th bullet. “...or adolescence...”</th>
<th>Removed reference to childhood and adolescence based on feedback</th>
</tr>
</thead>
<tbody>
<tr>
<td>There seems to be a difference between radiation received through exposure to isotopes and external beams on account of the differences in dose rates. Further, I am not aware of any literature that holds adolescents to be more at risk than adults; the numbers from Chernobyl do not support that they are. Perhaps they just have more time to manifest the effects.</td>
<td></td>
</tr>
</tbody>
</table>

| Page 15 re: Routine Referral. Which thyroid tests are being recommended here? | TSH and free T4 have been specified |

| Page 16 re: ATA Fig 1. Two comments: a) These days more and more, both physicians and surgeons are equipped with office ultrasound machines, permitting the deployment of u/s-guided biopsy as the primary diagnostic technique. b) While pertechnetate scans are a reasonable screen for functionality, they are non-specific and both false positive and negative results occur when uptake is used as a marker for benignancy. While I realize that the delivery of ¹²³I to Halifax poses some logistic problems, this isotope is much more | a) office-based U/S machines are still rare in NS b) ¹²³I is not currently available in NS |
specific and sensitive. We did not realize until we deployed both isotopes in a number of cases how frequently discrepancies were observed.

**Page 18** re: NM thyroid scan: While the <1% false negative rate is true of iodine, there are both false positive and negative issues with pertechnetate.

| Changed “<1% risk” to “very low risk” |

**Page 19** Flowchart 1 seems redundant after ATA Fig 1.

| Intended to provide more detail on FNA |

**Page 22** re: item 18. A pertechnetate scan may be adequate if the TSH is low and autonomous function is to be excluded but $^{123}$I is preferable if the question concerns possible malignancy.

| guideline doesn’t preclude us from using $^{123}$I for a scan in the odd case. |

**Page 33** re: item 3.5 It may be helpful to think of $^{131}$I therapy as being indicated for three possible indications:

a) Low risk situations where the presence of remnants makes follow up difficult (ablation)

b) Situations where patient is considered to be at higher risk of recurrence but has not known cancer at the time of treatment (adjuvant)

c) Settings in which the patient is known to have disease present (therapeutic)

| These categories and descriptions have been added. |

**Page 33** re: Item 3.5.1 2nd para, 2nd sentence. The risk of secondary malignancies following $^{131}$I treatment is not so clear cut. There are publications showing evidence for all possible outcomes. Sawka’s meta-analysis (Sawka et al. Thyroid 19;451-7, 2009; Brown AP et al. J Clin Endo Metab 2008;89:504-15.) showed that the incidence of 8 cancers, most notably breast) was increased but does not comment at length concerning the 6 others whose incidence is significantly decreased, most notably that of lung cancer. If radiation is not believed to decrease the incidence of some cancers, why should it be assumed, short of knowing the mechanism, that radiation caused others? Bhattacharyya N & Chien W Ann Otol Rhinol Laryngol. 2006;115:607-10.) on the other hand, found no relationship between treatment for thyroid cancer and subsequent breast cancer. Both Bhattacharyya and

| we exactly quote ATA 71 |
Sawka relied heavily on the US SEER database to reach their opposing conclusions. Sandeep et al (J Clin Endo Metab 2006;91:1819-25), using a different database, found a reciprocal relationship between breast and thyroid cancers irrespective of which had occurred first. Thus, I do not consider the culpability of $^{131}I$ in the development of subsequent primary cancers as settled.

Page 36 re: Item 3.5.2 concerning subsequent pregnancies. There are several possible reasons to delay pregnancy after $^{131}I$ therapy, having primarily with the need to follow up on the efficacy of therapy and to avoid the complexity of disease recurrence during the course of a pregnancy. 15 years ago Schlumberger et al (J Nucl Med. 1996;37:606–612) suggested the spontaneous abortion was more common within the first year post ablation but their recommendation to delay pregnancy for this reason was negated by subsequent additional observations (Garsi JP et al JNucl Med 2008;49:845-52). Further, the BEIR VII Report (2005) states that there are no detectable transgenerational effects from radiation exposure experienced prior to impregnation. Thus, there seems to be no reason to avoid pregnancy post-$^{131}I$ therapy on radiological grounds.

Page 37 re: medications containing iodine. Note that amiodarone is retained in lung and fatty tissues of the body with a clearance time on the order of a year. The breakdown of each molecule releases two atoms of iodine, thus ensuring saturation of iodine-avid tissues for many months. In the case of residual cancers, the effect of amidarone will likely result in a false negative scan.

Re: rhTSH. Despite its cost, rhTSH may be a cost-effective intervention in many cases on account of reduced time lost from employment as a result of its use.

Revised Recommendation 44 to include Amiodarone metabolites may decrease sensitivity of the iodine scan.

Page 38 re: 3.5.4 dose of $^{131}I$. The recent publications concerned a heterogeneous group of patients, many with low risk disease, and the endpoint was ablation of remnants of presumably normal thyroid tissue. Many of

The point is that the recent studies show that low and high dose are equally effective for ablation.
the patients included in these trials would not have received an ablation under the terms of the protocol under discussion here. For those who are stand to benefit from adjuvant therapy and not only ablation, the best dose of $^{131}$I may be somewhat higher.

**Re: item 3.5.5 Harmful effects...**
See my earlier comments re secondary malignancies.
The two papers that recommend against immediate administration of sialogogues are, in my opinion, deeply flawed. They report only on the effect of administering or withholding sour candies and seemingly provided no other prophylaxis. The sour candies are only one aspect of the salivary gland care that should be provided, although they do reduce iodine concentration in the gland. Since the concentration of iodine in the glands depends on concurrent blood concentration and the half time of iodine in the blood is about 6-8 hours, the patient has the most to gain from sialogogues in the first hours post therapy. The other significant aspects of salivary gland care include attention to hydration, avoidance of nocturnal accumulation and the use of Prednisone for about 5 days.

**Page 39 re:3.5.6 post-therapy scan.** For those patients who were prepared with rhTSH, the increased rate of renal clearance allows for the performance of the scan within 2-5 days of therapy when renal function is normal. While the planar whole body scan of itself does sometimes show previously unsuspected disease, several publications and our own experience have shown that use of SPECT CT at this time further increases information further and may lead to changes of management in up to 25% of cases.

**Page 41 Risk management flowchart 3; top right box.** I think most experts recommend that routine follow up of an abnormal Tg should be delayed to 10-12 months since the level may continue to fall for quite a long time. On the other hand, if the original stimulated Tg was undetectable, the patient may not benefit from further stimulated tests. The sensitivity of the $^{131}$I scan is only about 60% compared with $>98\%$ for the combination

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In addition to planar imaging, SPECT-CT should be considered. |
| **Page 41** Risk management flowchart 3; top right box. I think most experts recommend that routine follow up of an abnormal Tg should be delayed to 10-12 months since the level may continue to fall for quite a long time. On the other hand, if the original stimulated Tg was undetectable, the patient may not benefit from further stimulated tests. The sensitivity of the $^{131}$I scan is only about 60% compared with $>98\%$ for the combination | Revised – dxWBS only recommended for Intermediate and High Risk patients and for low risk patients whose post-Rx WBS shows worrisome abnormalities. |
of ultrasound and stimulated TG (when needed). The ATA guideline recommends against routine use of follow up diagnostic $^{131}$I scans.

**Page 43** re 3rd goal in follow up of DTC patients. There might be an issue concerning timing of follow up interventions and pregnancies but, as noted earlier, there is no evidence that even several rounds of $^{131}$I therapy can compromise the outcome of subsequent pregnancies. As the experience with mammalian radiobiology grows, we have to unlearn some earlier conclusions that mostly came from experiments on fruit flies. See our statement 3.5.2 (R41a), exactly per ATA (6-12 months avoidance of pregnancy)

**Page 45** re: para 65b. I suspect it was intended to say that chemotherapy plays a role only in the context of a clinical trial. We quote ATA 78b

**Page 46** re: par 68. I want to emphasize my total agreement concerning the importance of quality ultrasound by dedicated colleagues. Thanks

Para 70. Re avoidance of pregnancy for 8-12 months. In patients with low risk disease who underwent $^{131}$I therapy and had a concurrent normal Tg in the absence of antibodies, there is no radiobiological reason to delay a much desired pregnancy. See our statement 3.5.2 (R41a), though this is per ATA (6-12 months avoidance of pregnancy)

**Page 50** re: para 74a. In patients with normal renal function and, especially when rhTSH is used to prepare the patient, higher doses will be well tolerated when necessary. When hypothyroidism is avoided, renal function will be up to 30% better and the non-target radiation dose is 30% lower for the same radiation dose administered to the cancer (Hanscheid H, J Nucl Med. 2006; 47:648-654). Added: In select cases of high dose therapy, for example when there is a high burden of pulmonary metastases, dosimetry calculations may be employed to establish a safe dose

**Page 75** re: patient preparation for $^{131}$I therapy. One thing I didn’t see mentioned anywhere concerns the handoff of the patient from the surgeon to the radiiodine therapist. We found that it is helpful if the surgeon places the patient on full dose hormone replacement on hospital discharge while the pathology report is pending. Thus, those patients who do not need further intervention can go back to work as soon as their incision has healed sufficiently; the others can then. Worth considering.
be scheduled for therapy according to the priority attached to their findings. Those who are prepared with rhTSH then lose no more than 2-4 additional days from work for this medical reason.

**Page 77** re: harmful effects of radiation. I take exception to the statement "There is probably no dose of radioiodine that is completely safe...". There are no data that support this statement; the assumption of LNT lies at the base of regulation but without evidence. The propagation of such statements promotes public fear without helping patients.

Re: preventive measures. See my earlier comments

**Page 78** re: secondary malignancies. While it behooves us to be conservative, the role of radioiodine in the development of secondary malignancies is unsettled as stated earlier.

Re: pulmonary fibrosis. When diffuse lung mets are known to be present, a diagnostic $^{131}\text{I}$ scan will allow semiquantitative dosimetry is helpful in the selection of an initial therapy dose.

Re: thyroid replacement para 1. Synthroid is available in more dosage sizes and, therefore, may be preferable.

**Page 82** re: thyroid replacement para 1. Synthroid is available in more dosage sizes and, therefore, may be preferable.

Re: item 3. It is probably best to advise against taking any other medication at the time of taking thyroid hormone. Tablets often contain fillers such as talc to provide adequate bulk for handling and these may compromise absorption (e.g., Tylenol).

Without naming brands, we state “T4 supplied by certain manufacturers are available in more dosage sizes and may facilitate dose titration.” As this is written for patients, it will be the physician or pharmacist who would choose the preferred brand.

We state “Other medications, including many non-prescription drugs, such as iron and calcium preparations, interfere with the absorption of T4 and should not be taken at the same time as T4. If you take any other drug in addition to T4 (whether prescription, non-prescription or natural supplement), please ask your pharmacist if it will interfere with your T4 therapy.”
Appendix 12: Cross-Reference to Original ATA Recommendations

See spreadsheet on CCNS website:

http://www.cancercare.ns.ca/site-cc/media/cancercare/changes%20from%20ATA.xls
Appendix 13: Guideline Development Acknowledgements

This guideline was written by a collaborative effort of the members of the QEII Interprofessional Thyroid Oncology Team, and was sponsored by Cancer Care Nova Scotia.

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