Clinical Practice Guidelines of the Philippine General Hospital for the Management of Thyroid Nodules and Well-differentiated Thyroid Carcinoma (2008)

PGH Working Group on Thyroid Cancer

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I. INTRODUCTION

The development of a hospital-based clinical practice guideline (CPG) on thyroid nodules and well-differentiated thyroid cancers presents enormous challenges, mainly because thyroid diseases are managed by a diverse field of health professionals. Endocrinologists, surgeons, otorhinolaryngologists, and nuclear medicine specialists all play a role in the management of both thyroid nodules and well-differentiated thyroid cancers. Hence, this CPG was developed by an interdisciplinary panel of experts from the Section of Endocrinology, Department of Surgery, Department of Otorhinolaryngology, and Section of Nuclear Medicine. Consultants from the Department of Radiology, Department of Pathology, and the Section of Medical Oncology were likewise consulted on key issues. This involvement of a varied group of health professionals assures a more widespread acceptability of the clinical use of these guidelines as well as uniformity in the standards of care within the hospital. Most importantly, this will ensure that the patient will receive the best possible care.

The main objective of this endeavor is to formulate guidelines for the appropriate management of thyroid cancer patients seen at Philippine General Hospital. With the guidelines in place, we intend to: 1) improve the outcome and quality of care of well-differentiated thyroid cancer in the Philippine General Hospital; 2) develop a model for the multidisciplinary management of well-differentiated thyroid cancer; 3) develop an algorithm appropriate for PGH for the treatment of well-differentiated thyroid cancer based on available clinical evidence and expert opinion; 4) improve the referral system for future management of thyroid cancer; and 5) develop a database of thyroid cancer patients for future audit and research.

Clinical practice guidelines are usually systematically developed from current available scientific evidence and accepted approaches to treatment. The literature on thyroid nodules and differentiated thyroid cancer is replete with controversies in many areas. Among these are the most cost-effective approach to diagnostic evaluation of thyroid masses, the extent of surgery for thyroid cancer, and the role of radioactive iodine therapy. The insidious clinical course of the disease as well as the ethical issues inherently involved in studies involving cancer patients contribute to the dearth of reliable local and international data from randomized, controlled trials. Thus, in addition to the available published evidence, there is a need to rely on experience and expert clinical judgment to resolve issues and arrive at a consensus.

These guidelines are intended to assist in decision making on the management of thyroid nodules and well-differentiated thyroid cancers. Ultimately, however, it is the well- informed patient who makes the choice as to which treatment option is most appropriate.

II. EXECUTIVE SUMMARY

To develop the guidelines, the Sections of Endocrinology, Nuclear Medicine, and Medical Oncology from the Department of Medicine, the Division of Head and Neck Surgery of the Department of Surgery, and the Departments of Otorhinolaryngology, Radiology, and Pathology convened as a body on June 21, 2005 to formulate a set of objectives. On the subsequent meeting on July 5, 2005, protocols from each department were presented and issues that needed to be resolved were identified. A core group of surgeons and endocrinologists, designated as the Technical Working Group (TWG), was formed and tasked to set up consensus meetings and gather available evidence. An extensive literature search on the management of thyroid nodules and well-differentiated thyroid cancer was undertaken. On-line databases (National Library of Medicine – MEDLINE 1990-2005, using Medical Subject Heading terms and free text; EMBASE 1990 – 2005; Cochrane Library; National Guideline Clearinghouse; Department of Science and Technology – Philippine Council for Health Research and Development) were searched via the internet using the term well-differentiated thyroid cancer. Succeeding meetings involving lectures on the role of radioactive iodine by Dr. Jerry Obaldo, standardization of fine needle aspiration biopsy (FNAB) by Dr. Avila, and the role of thyroid ultrasound by Dr. Lazaro were held on August 30, 2005, October 25, 2005, and February 21, 2006, respectively. Key issues were then discussed and resolved at the section/department level from July to September 2006 prior to the plenary meeting held on November 7, 2006. During the plenary meeting, the first draft of the CPG was presented to all involved specialties for modification and/or approval. Suffice it to say that this manuscript consists of a summary of the strongest evidence that addresses the clinical questions and recommendations each department and section has discussed.

LEVELS OF EVIDENCE

I - Evidence from at least one properly designed randomized, controlled trial or meta-analysis

II - Evidence from at least one well-designed clinical trial without prior proper randomization, from prospective cohort or case-control analytic studies (preferably from one center), from multiple time-series studies, or from dramatic results in uncontrolled experiments

III - Evidence from opinions of respected authorities on the basis of clinical experiences, descriptive studies, or reports of expert committees

CATEGORIES OF RECOMMENDATIONS

A - Recommendations that were approved by consensus (75% of the multi-sectoral expert panel).

Strongly recommends (Homogenous evidence from multiple well-designed randomized controlled trials with sufficient statistical power; homogenous evidence from multiple well-designed cohort controlled trials with sufficient statistical power; at least one conclusive level 1 publication demonstrating benefit outweighs risk)

B - Recommendations that were somewhat controversial and did not meet consensus

Recommends (Evidence from at least 1 well designed clinical trial, cohort, or case-controlled analytic study or meta-analysis; non-conclusive level 1 publication; at least one conclusive level 2 publication demonstrating benefit outweighs risk)

C - Recommendations that caused real disagreements among members of the panel

Recommendation is based on expert opinion (Evidence based on clinical experience, descriptive studies, or expert consensus opinion; no conclusive level 1 or 2 publication; at least 1 conclusive level 3 publication demonstrating benefit outweighs the risk)

ISSUES IDENTIFIED

A. Definition of Terms

A. With regard to biopsy
1. Non-diagnostic biopsy
2. Indeterminate cytology

B. With regard to surgery
1. Total thyroidectomy
2. Near total thyroidectomy
3. Subtotal thyroidectomy

C. Absence of persistent tumor

D. Aggressive histopathologic subtypes

E. High/Low risk patient for disease morbidity and mortality

B. Thyroid Nodule Evaluation: What is/are the appropriate diagnostic test/s for evaluation of clinically evident or incidentally discovered thyroid nodules? What are the roles of the following:
A. Thyroid function tests
B. Fine needle aspiration biopsy (FNAB)
C. Cervical Ultrasound

C. Primary Therapy
A. What is the appropriate **extent of initial surgery** for well-differentiated thyroid cancer?
B. What is the role of intra-operative **frozen section**?
C. What is the type of **lymph node dissection** that should be performed?
D. When should **completion thyroidectomy** be performed?

D. Staging System: What postoperative staging system should be used?

E. Adjunctive Therapy
A. What is the role of postoperative **radioactive iodine** remnant ablation?
1. Is there a need for pre-therapy whole body I^{131} scintigraphy?
2. How should patients be prepared for radioiodine ablation?
3. What activity of I^{131} should be used for radioiodine ablation?
B. What is the role of **TSH suppression therapy**?
C. What is the role of **radiotherapy**?
D. What is the role of **chemotherapy**?

F. Follow up and Monitoring: What diagnostic examination/s should be performed in the follow up of patients with well-differentiated thyroid cancer? What are the roles of the following:
A. Thyroglobulin Measurements
B. Whole Body I^{131} Scan
C. Cervical Ultrasound

G. Administrative Issues
A. What is the clinical pathway for patients with well-differentiated thyroid cancer?
B. Where would data be stored and how can it be utilized?

SUMMARY OF RECOMMENDATIONS

III. DEFINITION OF TERMS[1]

Non-diagnostic biopsy - Failure to meet specified criteria for adequacy that have previously been established

Indeterminate cytology - Reported as "suspicious", "follicular lesion", "follicular neoplasm", or "Hurthle cell neoplasm"

Total thyroidectomy - Removal of all grossly visible thyroid tissue

Near total thyroidectomy - Leave less than 1 gram of tissue adjacent to the insertion of the recurrent laryngeal nerve into the cricothyroid muscle

Subtotal thyroidectomy - Leave more than 1 gram of tissue with the posterior capsule on the involved side

Absence of Persistent Tumor - In a patient who has undergone total or near total thyroidectomy and thyroid remnant ablation with radioactive iodine, disease free status comprises *all* of the following:
a) No clinical evidence of tumor
b) No imaging evidence of tumor (No tumor uptake outside the thyroid bed on the initial post-treatment whole body I^{131} scan, on a recent diagnostic scan or neck ultrasound)
c) Undetectable serum thyroglobulin levels during TSH suppression and stimulation, in the absence of interfering antibodies

Aggressive histopathologic subtypes - tall cell, columnar cell, insular carcinoma

IV. THYROID NODULE EVALUATION

*What is/are the appropriate **diagnostic test/s** for evaluation of clinically evident or incidentally discovered thyroid nodules?*

CONSENSUS: All patients with a thyroid nodule shall undergo serum TSH determination, thyroid ultrasound, and fine needle aspiration biopsy (FNAB) as initial evaluation. Ultrasound guided biopsy is recommended for non-diagnostic and indeterminate cytology biopsies, nodules that are more than 50% cystic, and nodules with a posterior location.

V. PRIMARY THERAPY

A. *What is the appropriate extent of **initial surgery** for well-differentiated thyroid cancer?*

CONSENSUS: Total or near total thyroidectomy is recommended for a thyroid nodule which is proven malignant by fine needle aspiration biopsy and has a size greater than 1 cm. Thyroid lobectomy may be sufficient treatment for lesions less than 1 cm, isolated intrathyroidal well-differentiated carcinomas in the absence of cervical nodal metastases.

B. *What is the role of intra-operative **frozen section**?*

CONSENSUS: A frozen section shall be performed for

non-diagnostic preoperative fine needle aspiration biopsy results.

C. *What is the type of **lymph node dissection** that should be performed?*

CONSENSUS: Depending on the clinical situation, an appropriate node dissection shall be performed.

D. *When should **completion thyroidectomy** be performed?*

CONSENSUS: Completion thyroidectomy shall be advised for lesion size greater than 1 cm, multi-focal disease, nodal metastases, involved resection margins, extrathyroidal or vascular invasion, and/or aggressive histologies and to those with nodules in the contralateral remaining lobe.

VI. STAGING SYSTEM

*What postoperative **staging system** should be used?*

CONSENSUS: The 6th edition of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) TNM classification shall be used for all patients with differentiated thyroid cancer because of its utility in predicting disease mortality and its requirement for cancer registries.

VII. THERAPY

A. *What is the role of postoperative remnant ablation with **radioactive iodine**?*

CONSENSUS: Ablative radioactive iodine-131 therapy shall be given postoperatively to all patients with well-differentiated thyroid carcinoma assessed to be at risk for disease morbidity and mortality

1. *Who are the patients indicated for radioactive iodine therapy?*

CONSENSUS: Candidates for radioactive iodine therapy are those patients with lesion size greater than 1 cm, multi-focal disease, nodal metastases, involved resection margins, extrathyroidal or vascular invasion, and/or aggressive histologies.

2. *Is there a need for pre-therapy whole body scintigraphy with I^{131}?*

CONSENSUS: Due to potential problems with detection sensitivity and post-imaging thyroid stunning, a routine pre-therapy whole body I^{131} scan is not recommended.

3. *How should patients be prepared for radioiodine ablation?*

CONSENSUS: Ideally, post-op radioactive iodine therapy should be given within 4 – 6 weeks after the surgery. Low iodine diet should be prescribed. Levothyroxine should not be given post-operatively, prior to radioactive iodine therapy. For subsequent radioactive iodine therapy, levothyroxine therapy shall be withdrawn for at least three weeks prior to the time of therapy. Recombinant human TSH may be given to patients with contraindications to levothyroxine withdrawal.

4. *What activity of I^{131} should be used for remnant ablation?*

CONSENSUS: An I^{131} dose of 100 mCi shall be given to patients with no nodal extension, perithyroidal extension, or distant metastases. A dose of 150 mCi shall be given to patients with nodal metastases and to patients with distant metastases on their first radioiodine therapy. Subsequent radioiodine ablation of patients with distant metastases shall use a dose of 200 mCi, in the absence of diffuse lung metastases.

B. *What is the role of **TSH suppression therapy**?*

CONSENSUS: Maintenance of TSH at or slightly below the lower limit of normal (0.1 to 0.5 mU/L) is appropriate for patients at risk for developing complications from thyroid hormone suppressive therapy, in the absence of contraindications (e.g., decreased bone mineral density, atrial fibrillation, or myocardial ischemia).

C. *What is the role of **radiotherapy**?*

CONSENSUS: External beam radiation therapy shall be reserved for the management of the following situations: unresectable gross residual cervical disease, painful bone metastases, metastatic lesions in critical locations likely to result in fracture, neurological or compressive symptoms not amenable to surgery, painful pleural-based lesions, and recurrent hemoptysis.

D. *What is the role of **chemotherapy**?*

CONSENSUS: The routine adjunctive use of chemotherapy is not recommended. However, it may be considered in patients who have surgically unresectable disease and are unresponsive to radioactive I^{131} or external beam radiation therapy. It may also be offered to patients who are not amenable to external beam radiotherapy.

VIII. FOLLOW UP AND MONITORING

A. *What is the role of **thyroglobulin** measurements?*

CONSENSUS: In patients with well-differentiated thyroid cancer that have undergone total or near-total thyroidectomy and postoperative radioiodine ablation, TSH stimulated serum thyroglobulin should be measured every 6 – 12 months by an immunometric assay, ideally in the same laboratory and using the same assay. Concurrent determination of thyroglobulin antibodies should be done at least once during follow up to determine the reliability of the thyroglobulin levels obtained. A basal and stimulated thyroglobulin level of 1 ng/ml and ≤ 2 ng/ml, respectively, are indicative of absence of persistent disease.

Routine serum thyroglobulin determination is not recommended in patients who have undergone less than total thyroidectomy and in patients who had total thyroidectomy but did not undergo ablative radioactive iodine treatment.

B. *What is the role of whole body I^{131} scintigraphy?*

CONSENSUS: A post-treatment whole body I^{131} scan shall be done within 3 to 7 days in all patients who have undergone ablative radioactive iodine therapy. Thereafter, patients with negative stimulated thyroglobulin levels, anti-thyroglobulin levels and cervical ultrasound do not require routine diagnostic whole body scan during follow up.

C. *What is the role of **cervical ultrasound**?*

CONSENSUS: Cervical ultrasound to evaluate the thyroid bed, central and lateral node compartments should be performed at 6 and 12 months postoperatively, then annually for at least 3 to 5 years for high risk patients.

IX. ADMINISTRATIVE ISSUES

A. *What is the clinical pathway for patients with well-differentiated thyroid cancer?*

CONSENSUS: All patients with a complaint of thyroid nodule shall be evaluated based on the agreed protocol and shall form the patient database. The guidelines shall be applicable to patients in both charity and pay services.

B. *Where would data be stored and how can it be utilized?*

CONSENSUS:

1. Only one set of data collection forms will be disseminated for use in evaluating and managing patients with thyroid nodules at the Philippine General Hospital.
2. The data obtained shall comprise the Thyroid Cancer Registry of the Philippine General Hospital, which shall be initiated and maintained by the Thyroid Cancer Study Group. This registry shall be available to all members of the Thyroid Cancer Study Group and to other interested parties after appropriate permission has been secured.
3. The Extension Research Office shall be the repository of the Thyroid Cancer Registry.
4. All research/investigations that will be developed from the guidelines and from the ensuing database will have to ask permission and technical approval from the Thyroid Cancer Study Group.

X. EVIDENCE FOR RECOMMENDATIONS

1) All patients with a thyroid nodule shall undergo serum TSH determination, thyroid ultrasound, and fine needle aspiration biopsy (FNAB) as initial evaluation.

Although there is a lack of clinical trials supporting the routine use of serum thyrotropin determination in the initial evaluation of a thyroid nodule, expert opinion recommends such a practice. A subnormal TSH level associated with a hot nodule on radionuclide thyroid scan precludes the need for further cytologic evaluation, since functioning nodules rarely harbor a malignancy. On the other hand, FNA is the most accurate and cost-effective method for evaluation of thyroid nodules.[1]

Thyroid ultrasound plays an ancillary role in the cytologic evaluation of thyroid nodules. Nodules that are more than 50% cystic or located posteriorly decrease the accuracy of fine needle aspiration biopsy performed with palpation.[3-4] In addition, thyroid ultrasound can confirm if there is truly a nodule and if there are other nodules present that have signs of malignancy (e.g., solid, hypoechoic, vascular, calcifications) and therefore warrant a biopsy.[5-7] For multi-nodular goiters, sonographic characteristics are superior to nodule size for identifying nodules that are more likely to be malignant.[8-9] Furthermore, preoperative UTZ identifies suspicious cervical adenopathy in 20-31% of cases, potentially altering surgical approach.[10-11] However, prospective studies are needed. Baseline thyroid measurements will also be useful for follow up of nodules with benign or indeterminate cytologic findings, since the accuracy of physical examination for nodule size is inferior to that of ultrasound.[7] The database that will be generated from this protocol will allow us to prove, or disprove, the utility of such routine evaluation in our setting.

2) **Total or near total thyroidectomy is recommended for a thyroid nodule which is proven malignant by fine needle aspiration biopsy and has a size greater than 1 cm. Thyroid lobectomy may be sufficient treatment for small, low risk, isolated intrathyroidal papillary carcinomas in the absence of cervical nodal metastases.**

Subtotal thyroidectomy has been shown to be an inappropriate operation for thyroid cancer.[13] Increased extent of primary surgery may improve survival for high risk patients.[14-16] Rates of recurrence are reduced by total or near total thyroidectomy even among low risk patients[17-19] In the Asia Pacific region expert consensus, bilateral total or near-total thyroidectomy is recommended when papillary, follicular, or Hurthle cell cancer is known or suspected preoperatively.[2] Additional criteria for preoperative total or near total thyroidectomy were: age greater than 45 years old, tumor more than 2 cm in diameter, extra thyroidal extension, regional lymph node involvement, multi-focality, history of neck irradiation, family history of cancer, and known distant metastases. For apparently low-risk patients, in light of the varying surgical expertise, decision-making about lobectomy versus thyroidectomy must be weighed against the minimally lower risk of disease recurrence versus sometime higher rates of postoperative hypoparathyroidism and recurrent laryngeal nerve injury.[2]

3) **A frozen section shall be performed for non-diagnostic preoperative fine needle aspiration biopsy results.**

Results from studies in the Asia-Pacific region show no consistent agreement between frozen section and final histopathologic findings.

4) **Depending on the clinical situation, an appropriate node dissection shall be performed.**

Regional lymph node metastases are present in 20-90% of patients with papillary CA.[20-21] In many cases, these lymph nodes do not appear abnormal to inspection.[22] Bilateral central node dissection may improve survival compared to historical controls and reduce risk for nodal recurrence.[22-23] This central compartment dissection can be done with low morbidity by experienced surgeons.[24-27] In the report from the Asia-Pacific region, selective central neck dissection is usually performed at initial surgery. Lateral neck dissections are reserved for cases in which additional disease is detected either pre- or intraoperatively.[2]

5) **Completion thyroidectomy after lobectomy shall be advised for high risk patients and to those with nodules in the contralateral remaining lobe.**

In the report from the Asia-Pacific region, completion thyroidectomy is advised for patients with large tumor size, local extrathyroidal invasion, involved resection margins, extensive cervical node metastases, aggressive histology, multifocal tumors, vascular invasion, and nodules in the contralateral remaining lobe. These characteristics are believed to confer an increased risk of disease recurrence. In addition, experts prefer surgical excision of remaining tissue to the multiple I^{131} doses typically required to ablate an entire remaining lobe.[2] Completion thyroidectomy likewise allows for an improved efficacy of postoperative ablative radioiodine therapy. The surgical risks of a two-stage thyroidectomy has been shown to be similar to those of a near total or total thyroidectomy.[61-62]

6) **The American Joint Committee on Cancer/ International Union Against Cancer (AJCC/UICC) TNM staging shall be used for all patients with differentiated thyroid cancer because of its utility in predicting disease mortality and its requirement for cancer registries.**

Post-op staging is used for prognostication, decision making on adjunctive therapy, to determine frequency and intensity of follow up, and to enable accurate communication between health care professionals. No scheme has demonstrated clear superiority.[12] Each of the schemes allows accurate identification of 70-85% of patients at low risk of mortality. The AJCC/UICC TNM staging employs a shorthand method and is used for hospital cancer registries and epidemiologic studies (APPENDIX). However, it doesn't take into account several independent prognostic variables[1]

7) **Ablative radioactive iodine-131 therapy shall be given postoperatively to all patients with well-differentiated thyroid carcinoma assessed to be at high risk for disease morbidity and mortality**

Goals of postoperative radioiodine remnant ablation include to destroy residual thyroid tissue and thereby decrease locoregional recurrence, and to facilitate long-term surveillance with whole-body iodine scans and/or stimulated Tg measurements.[1, 28,29] Large, retrospective trials show significant decrease in disease recurrence[30-33] and cause-specific mortality.[15-16,30-32] Benefit appears to be restricted to those with tumor size greater 1.5 cm or with residual disease after surgery. Lower risk patients do not show evidence for benefit.[15,17,34] No prospective studies have been performed to address this problem. Hence, in the Asia-Pacific expert consensus, some low risk patients may not receive

radioiodine, particularly if the prospects for reliable long-term follow up are good.[2]

8) Due to potential problems with detection sensitivity and post-imaging thyroid stunning, a routine pre-therapy whole body scintigraphy with ^{131}I is not recommended.

In the presence of a large thyroid remnant, the whole body I^{131} scan is dominated by uptake within the remnant, potentially masking the presence of extrathyroidal disease within locoregional lymph nodes, the upper mediastinum, or even at distant sites.[34] In addition, there is an increasing trend to avoid pre-therapy radioiodine scans due to concerns over I^{131} induced stunning of the thyroid cancer.[35] Stunning will produce a reduction in the uptake of the I^{131} therapy dose. This occurs most prominently with higher I^{131} doses (5-10 mCi) and with increasing time between the diagnostic dose and therapy.[36-37] Although stunning is not visually appreciated at doses of 1 – 3 mCi, the accuracy of low dose scans has been questioned.[1] Furthermore, even if studies have shown excellent concordance between I^{123} and I^{131} for tumor detection, routine use of I^{123} is not recommended for the following reasons: 1) optimal I^{123} activity and time to scan after I^{123} administration is not known; 2) I^{123} is expensive and not universally available; 3) the short half-life ($t_{1/2}$ = 13 hours) of I^{123} makes handling this isotope more difficult; 4) stunning may also occur, although to a lesser degree than I^{131}.[37] Hence, in the Asia-Pacific report of experts, typically no pre-treatment diagnostic scan is performed. Instead, a post-treatment scan is usually obtained to define the amount and site(s) of remaining thyroid tissue.[2]

9) Levothyroxine therapy shall be withdrawn for at least three weeks prior to the time of therapy. Recombinant human TSH may be given to patients with contraindications to levothyroxine withdrawal.

An arbitrary serum TSH concentration of 25-30 mU/l or more has been established as the optimal level to perform reliable 131-I whole body scans (WBS) or radioablative therapy.[63-66] Several studies have shown that adequate TSH levels are commonly achieved by the third week of hormone withdrawal in 89-97% of patients[66-71]

The inconvenience of symptomatic hypothyroidism and the theoretical probability that prolonged periods of hyperthyrotropinemia could stimulate cancer cell growth have prompted strategies aimed at reducing or eliminating the time these patients must spend without thyroid hormone. Use of recombinant human TSH is probably the best solution to avoid hypothyroidism. However, it is expensive and is not proven cost-effective for routine use.[72] Recombinant human TSH is not approved in the United States for remnant ablation[1,72] but is approved in Europe. Although the shift to liothyronine for 2 – 4 weeks followed by a 2 week withdrawal is another alternative,[1] this drug is no longer available in the country.

10) An I^{131} dose of 100 mCi shall be given to patients with no nodal extension, perithyroidal extension, or distant metastases. A dose of 150 mCi shall be given to patients with nodal metastases and to patients with distant metastases on their first radioiodine therapy. Subsequent radioiodine ablation of patients with distant metastases shall use a dose of 200 mCi.

Successful remnant ablation, usually defined as absence of visible radioiodine uptake on a subsequent diagnostic radioiodine scan, is generally achieved with doses of I^{131} between 30 and 100 mCi.[73-76] However, higher activities tend to have higher success rates.[77] A dose of 100 – 200 mCi may be appropriate if residual macroscopic disease is suspected or documented or if there is an aggressive tumor histology.[1] In the Asia-Pacific report, I^{131} doses used for therapy typically range from 50 – 150 mCi. Those with iodine-avid distant metastases receive larger doses of 150 – 200 mCi.[2]

11) Initial thyrotropin suppression to below 0.1 mU/L is recommended for high risk patients in the absence of contraindications such as decreased bone mineral density, atrial fibrillation, or myocardial ischemia. Maintenance of TSH at or slightly below the lower limit of normal (0.1 to 0.5 mU/L) is appropriate for low risk patients and for high-risk patients at risk for developing complications from thyroid hormone suppressive therapy.

The purported goals of thyroid hormone therapy are to restore euthyroidism and suppress circulating TSH to reduce the risk of tumor recurrence. A meta-analysis has suggested an association between thyroid hormone suppression therapy and reduction of major adverse clinical events.[56] There is a study that showed a TSH $\leq$ 0.05 mU/L is associated with longer relapse-free survival,[57] while another large study did not show correlation between disease progression and TSH suppression.[58] On the other hand, the potential benefit from thyroid hormone suppression should be weighed against the risk of complications from such treatment. There is a solid association with the development of atrial fibrillation when the TSH is less than 0.10 mU/L, whereas the evidence for risk of atrial fibrillation

with a serum TSH of 0.1 to 0.3 mU/L is limited.[78] The risk for atrial fibrillation can be anywhere from 2.8 fold over 2 years or 3 fold in 10 years.[79-80] The strength of association with cardiac dysfunction and reduced bone mineral density in postmenopausal women is fair.[78]

The appropriate degree of TSH suppression by levothyroxine is still unknown. In the Asia-Pacific report, the precise intensity of TSH suppression depends on the patient's disease stage and the sensitivity of available TSH assays. Some clinicians reduce the intensity of TSH suppression after several years in patients with no evident disease, particularly if there are symptoms of thyrotoxicosis, declining bone mineral density, risk of atrial fibrillation or myocardial ischemia. It is likewise advisable to reduce the intensity of TSH suppression in low risk patients with no recurrent disease 2 years postoperatively. However, in high-risk patients and in those with residual disease, beta blockers may be necessary to permit the adequate TSH suppression.[2]

12) **External beam radiation therapy shall be reserved for the management of the following situations: unresectable gross residual cervical disease, painful bone metastases, metastatic lesions in critical locations likely to result in fracture, neurological or compressive symptoms not amenable to surgery.**

Due to the efficacy of radioactive I^{131} therapy, external beam radiation is infrequently used in the management of well-differentiated thyroid cancer. Its role is limited to palliation of unresectable disease.[81] Furthermore, it is not known whether external beam radiation might reduce the risk for recurrence in the neck after adequate primary surgery and/or radioactive iodine therapy.[1]

13) **The routine adjunctive use of chemotherapy is not recommended. However, it may be considered in patients who have surgically unresectable disease and are unresponsive to radioactive I^{131} or external beam radiation therapy. It may also be offered to patients who are not amenable to external beam radiotherapy.**

Doxorubicin monotherapy may produce partial response or stable disease in up to 40% of patients,[38-41] but durable responses are uncommon. Most studies of combination chemotherapy show no advantage over monotherapy.[42]

14) **In patients with well-differentiated thyroid cancer that have undergone total or near-total thyroidectomy and postoperative radioiodine ablation, TSH stimulated serum thyroglobulin should be measured every 6 – 12 months by an immunometric assay, ideally in the same laboratory and using the same assay. Concurrent determination of thyroglobulin antibodies should be done at least once during follow up to determine the reliability of the thyroglobulin levels obtained. A basal and stimulated thyroglobulin level of 1 ng/ml and 2 ng/ml, respectively, are indicative of absence of persistent disease.**

Routine serum thyroglobulin determination is not recommended in patients who have undergone less than total thyroidectomy and in patients who had total thyroidectomy but did not undergo ablative radioactive iodine treatment.

Serum thyroglobulin has a high sensitivity and specificity in detecting thyroid cancer, especially after total thyroidectomy and remnant ablation with I^{131}. The highest degree of sensitivity is noted when a TSH concentration of 25-30 mU/l or more has been reached, commonly after thyroid hormone withdrawal for at least 3 weeks.[63-66] Although thyroglobulin determination may be done in patients undergoing thyroid hormone suppression, a negative result (i.e., less than 1 ng/mL) will necessitate repeating the test under TSH stimulation to avoid missing patients with relatively small amounts of residual tumor.[1,47,50] Patients not amenable to or with contraindications to thyroid hormone withdrawal may use recombinant human TSH.[1,2] According to the panel of experts in the Asia-Pacific report, TSH-stimulated serum thyroglobulin testing alone, without whole-body scanning, may be sufficiently sensitive to monitor thyroid cancer patients who have previously had a negative radioiodine scan. This approach is recognized to be more cost-effective and convenient in settings were whole body ^{131}I scintigraphy is logistically difficult and expensive.[2]

The presence of thyroglobulin antibodies, found in 25% of thyroid cancer patients,[83] will falsely lower serum thyroglobulin measurements in immunometric assays.[84] Nonetheless, serial serum anti-thyroglobulin antibody measurements may serve as an imprecise surrogate marker of residual thyroid tissue.[85-86] Less commonly, defective or absent production of immunoreactive thyroglobulin by tumor cells may fail to identify patients with clinically significant tumors, even when thyroglobulin determination is done under TSH stimulation.[82] Small cervical lymph node metastases and less differentiated tumors are other sources of false negative thyroglobulin results.[87,88]

15) A post-treatment whole body I^{131} scan shall be done within 3 to 7 days in all patients who have undergone ablative radioactive iodine therapy. Thereafter, low risk patients with negative stimulated thyroglobulin levels and cervical ultrasound do not require routine diagnostic whole body scan during follow up.

A diagnostic whole body I^{131} scan is most useful during follow up when there is little or no remaining thyroid tissue. Stunning and accuracy are two issues that have to be addressed. Low risk patients who are clinically free of residual tumor, have undetectable serum thyroglobulin levels, and negative cervical ultrasound usually do not require diagnostic pretreatment scans. On the other hand, the post-treatment scan, due to the larger doses of I^{131} used, may occasionally visualize disease not seen on pretreatment scan.[51-55] Historically, it has been the practice in many centers in the Asia- Pacific region to do radioiodine scanning every 6 – 12 months until two sequential negative scans are obtained. With wider implementation of basal and TSH-stimulated thyroglobulin monitoring, a single negative whole-body scan is now considered sufficient to cease further scanning unless thyroglobulin levels are rising or are unreliable due to the presence of autoantibodies.[2]

16) Cervical ultrasound to evaluate the thyroid bed, central and lateral node compartments should be performed at 6 and 12 months postoperatively, then annually for at least 3 to 5 years for high risk patients.

Cervical ultrasound is highly sensitive in the detection of cervical metastases in patients with differentiated thyroid cancer, especially when combined with serum thyroglobulin determinations.[59] It may occasionally detect metastasis even when TSH-stimulated thyroglobulin is negative. In the Asia-Pacific region, cervical ultrasound plays an ancillary role in the follow up of patients who are at high risk for disease recurrence. However, this should be performed and interpreted by individuals with significant training and experience in sonographic imaging.

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APPENDIX

TNM CLASSIFICATION FOR DIFFERENTIATED THYROID CARCINOMA

Definition	
T1	Tumor diameter 2 cm or smaller
T2	Primary tumor diameter > 2 and up to 4 cm
T3	Primary tumor diameter > 4 cm, limited to the thyroid bed, or with minimal extrathyroidal extension
$T4_a$	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve
$T4_b$	Tumor invades prevertebral fascia or encases carotid artery or mediastinal vessels
Tx	Primary tumor size unknown, but without extrathyroidal invasion
N0	No metastatic nodes
$N1_a$	Metastases to level VI (pretracheal, paratracheal, prelaryngeal/Delphian lymph nodes)
$N1_b$	Metastases to unilateral, bilateral, contralateral, cervical or superior mediastinal nodes
Nx	Nodes not assessed at surgery
M0	No distant metastasis
M1	Distant metastasis
MX	Distant metastasis not assessed

STAGE	PATIENT AGE <45 YEARS	PATIENT AGE > 45 YEARS
I	Any T, any N, M0	T1, N0, M0
II	Any T, any N, M1	T2, N0, M0
III	-	T3, N0, M0
		T1, $N1_a$, M0
		T2, $N1_a$, M0
		T3, $N1_a$, M0
		$T4_a$, N0, M0
IVA	-	$T4_a$, $N1_a$, M0
		T1, $N1_b$, M0
		T2, $N1_b$, M0
		T3, $N1_b$, M0
		$T4_a$, $N1_b$, M0
IVB	-	$T4_b$, any N, M0
IVC	-	Any T, any N, M1