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Title: Randomized Controlled Trial of Total Thyroidectomy with and without Prophylactic Central Neck Lymph Node Dissection in Patients with Low-risk Papillary Thyroid Cancer

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PRÉCIS

Background:

- Thyroid cancer is the most common endocrine malignancy and papillary thyroid cancer (PTC) accounts for more than 80% of thyroid cancer.
- The incidence of thyroid cancer has risen over the past decades.
- Central neck lymph node metastasis (LNM) is common in PTC and preoperative imaging studies do not identify all involved lymph nodes in the central neck.
- It remains controversial if prophylactic central neck lymph node dissection (pCND) in patients with low-risk PTC results in lower rates of persistent/recurrent disease and higher complication rates as there has been no randomized controlled trial addressing these issues to date.
- Serum thyroglobulin (Tg), especially when TSH-stimulated, is a very sensitive and specific marker for persistent/recurrent PTC, in the absence of interfering anti-Tg antibodies.
- Retrospective studies have compared the postoperative TSH-stimulated Tg levels between those who underwent pCND and those who did not with conflicting results. A randomized trial is needed.
- Health-related quality of life (QOL) is a well-accepted tool to measure the outcome of cancer treatments. SF-36 v2 questionnaire has been frequently used to evaluate the QOL in patients with thyroid cancer. There is no study evaluating the difference in QOL in patients with low-risk PTC undergoing total thyroidectomy (TT) with and without pCND.

Objectives:

- To determine and compare biochemical cure rates in patients with low-risk PTCs undergoing total thyroidectomy (TT) with and without pCND as measured by postoperative TSH-stimulated serum thyroglobulin (stim-Tg) at 3 months (prior to RAI treatment).

Eligibility:

- Patients ≥ 18 years who have thyroid nodule(s) ≥1 cm but ≤ 4 cm in size with either:
    - inconclusive thyroid cytology positive for *BRAF* V600E mutation or *RET/PTC* rearrangement or
    - cytologically suspicious for or consistent with PTC
- Absence of extrathyroidal extension or lymphadenopathy suggesting metastatic PTC on physical examination and neck ultrasound.

Design:

- Prospective, single-blinded, randomized controlled clinical trial.

- Cytology will be reviewed by Laboratory of Pathology, NCI or a pathology laboratory at the enrolling institution. Once patients provide written informed consent, they will receive routine history, physical, radiographic (neck ultrasonography (USG), and/or other indicated tests) examinations as well as blood tests. Preoperative fine needle aspiration for cytology and *BRAFV600E* mutation will be performed if participant has not had either test performed.
- Preoperative assessment of QOL using standardized questionnaire (SF-36 v2) will be obtained within 30 days prior to surgery
- Preoperative vocal cord assessment will be done by flexible laryngoscopy.
- Participants will be randomized after clinical staging, including ultrasonography, to receive TT and pCND or TT alone and will be blinded from the result of randomization and treatment. Patients will remain blinded from treatment assignment for the duration of the study except for patients assigned to TT alone but found to have lymph node metastases as described below.
- If participants in TT alone group are found to have lymph node metastasis at the time of the operation by frozen section analysis, a therapeutic CND will be performed. Participants will remain in the intention to treat (TT alone) group. TT patients will be informed if a therapeutic CND is indicated and as such the blind will be broken for these patients prior to study completion.
- All participants will have intact parathyroid hormone (PTH), calcium and electrolytes checked preoperatively, in the morning after surgery, 2 weeks, and 6 months postoperatively.
- Postoperative flexible laryngoscopy will be performed on postoperative day 1 (or postoperative day 2, if it cannot be performed on the first postoperative day) and 6 months postoperatively if vocal cord abnormality is found on postoperative day 1
- Postoperative assessment of QOL will be done on day 1, 2 weeks, 3 months and 6 months, 1, 5 and 10 years postoperatively.
- Participants with postoperative hypoparathyroidism (low PTH and hypocalcemia) will be treated with calcium replacement with or without vitamin D analogue. Serum PTH and electrolytes will be monitored until resolved.
- Stim-Tg will be checked at 3 months postoperatively (prior to RAI scan/ablation, if indicated) and at 1 year postoperatively or 1-year post-remnant ablation. 1 year stim-Tg evaluation will be performed in patients enrolled at the NIH but is optional in patients enrolled at non-NIH site(s). Unstimulated Tg, thyroid function tests, and anti-thyroglobulin antibodies will be checked annually for 10 years.
- Soft tissue neck ultrasonography will be performed in all patients preoperatively and every year postoperatively for the first 10 years.
- If biochemical evidence of tumor recurrence occurs, patients will undergo appropriate radiographic studies and/or nuclear scintigraphy. Tissue biopsy of suspicious lesion(s) will be performed if clinically indicated.

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1. INTRODUCTION

1.1 STUDY OBJECTIVES

1.1.1 Primary Objective:

- To determine biochemical cure rates in patients with low-risk PTCs undergoing total thyroidectomy (TT) with and without pCND as measured by postoperative TSH-stimulated serum thyroglobulin (stim-Tg) at 3 months (prior to RAI treatment).

1.1.2 Secondary Objectives:

- To determine biochemical cure rates in patients with low-risk PTCs undergoing total thyroidectomy (TT) with and without pCND as measured by postoperative TSH-stimulated serum thyroglobulin (stim-Tg) at 1 year postoperatively in patients who will not receive RAI or 1 year post remnant ablation.
- To determine the following outcome measures in patients undergoing TT with and without pCND:
    a. The QOL of patients with low-risk PTCs undergoing TT and pCND to those undergoing TT alone using the SF-36v2 standardized questionnaire (preoperative, postoperative day 1, 2 weeks, 3 and 6 months, 1, 5 and 10 years postoperatively).
    b. Neck pain (preoperative, postoperative day 1, 2 weeks, and 6 months postoperatively).
    c. Subjective voice quality, swallowing impairment (preoperative, postoperative day 1, 2 weeks, and 6 months postoperatively) as well as objective vocal cord dysfunction (preoperative and postoperative day 1 and 6 months postoperatively only if abnormality is found on postoperative day 1) and requirement for intervention.
    d. Rate and duration of both symptomatic and asymptomatic hypoparathyroidism including requirement and duration of postoperative oral or IV calcium replacement as well as vitamin D analogue for hypoparathyroidism (preoperative PTH, postoperative day 1, 2 weeks and 6 months postoperatively).
    e. Rate of cervical wound complications (hematoma, seroma, and surgical site infection) and intervention(s) required.
    f. The use of radioactive iodine.
    g. Oncologic outcome:
        I. Radiographic evidence with biopsy or pathology proven recurrent disease.
        II. Thyroid cancer-related death.
    h. The impact of BRAF V600E mutation status on lymph node metastasis in patients with low-risk PTC undergoing TT with or without pCND. In addition, we will compare the rate of disease recurrence in patients undergoing pCND to those who will not undergo pCND, by BRAF V600E mutation status.

1.2 BACKGROUND AND RATIONALE

Thyroid cancer is the most common endocrine malignancy and it accounts for 3.8% of all new cancer diagnoses(1). Over 90% of thyroid cancers originate from follicular cells and are commonly well-differentiated thyroid cancer. These cancers include variants of papillary (PTC) and follicular thyroid cancer (FTC) (2). PTC is the most common type and it accounts for over 80% of thyroid malignancies, followed by FTC, Hürthle cell, medullary and anaplastic thyroid cancer(3). While overall prognosis of classical PTC and FTC are excellent, 10%-15% of thyroid cancers have histologic subtypes that have been shown to have more aggressive behavior. These include tall cell variant, columnar cell variant, diffuse sclerosing variant PTC as well as insular and Hürthle cell cancers(4). Although lymph node metastasis in FTC is rare (2%), lymph node metastasis (LNM) is common in PTC (~50%) and is significantly more common in aggressive PTC variants such as tall-cell variant PTC and diffuse sclerosing variant PTC (~70%)(5-7). LNM is known to be an independent risk factor for local-regional recurrence in patients with thyroid cancer. Despite an overall good prognosis for PTC, Mazzaferri et al. reported 40-year disease recurrence to be approximately 35%, two-third of which occurred within the first decade. Local recurrence comprised 68% of the disease recurrences in this study. Half of the patients with distant metastasis (32% of all recurrences) died of thyroid cancer(8). Population-based studies have also shown that patients with LNM have higher rate of cancer-related death and decreased survival. (9, 10) The effect of surgical treatment for subclinical LNM in patients with low-risk PTC on both recurrence and survival remains unclear. The rise in thyroid cancer incidence, and improved sensitivity of radiographic studies and laboratory tests to detect persistent or early recurrent disease present a significant clinical problem as the number of patients with recurrent disease is expected to grow. Unfortunately, there has been a lack of good clinical evidence to guide appropriate treatment for patients with low-risk PTC that reduces persistent/recurrent disease and thyroid cancer-associated mortality.

1.2.1 Epidemiology

The American Cancer Society estimates that there will be more than 63,000 new cases of thyroid cancer and over 2,800 cases of thyroid cancer-related death in 2014. Thyroid cancer is currently the fifth most common cancer diagnosed in women, following breast, lung, colorectal, and uterine cancers(1).

The age and gender adjusted incidence of thyroid cancer has increased faster than any malignancy in the recent years(11). The American Cancer Society has reported a remarkable increase in the incidence of thyroid cancer since the mid-1990s. The incidence has increased 5.6% per year in men and 7.0% per year in women since 2004, which represents the largest annual percentage increase of any cancer in both men and women(12). The vast majority (87%) of the excess thyroid cancers detected in the past 15 years are attributed to an increase in small cancers (less than 2 cm in diameter)(13). Unfortunately, several aspects of management in growing number of patients with low-risk thyroid cancer remain controversial including the surgical management of PTC with clinically negative lymph node.

1.2.2 Management of papillary thyroid cancer

The debate regarding the optimal management of differentiated thyroid cancer continues due to the lack of good quality data. Current recommendations are largely based on level III evidence, consisting predominantly of retrospective studies. However, it was estimated that a randomized

study to detect a 10% reduction in thyroid cancer mortality at 25 years after treatment such as radioiodine ablation would require 4,000 patients per arm and the results would not be ready for 35 years, thus demonstrating the difficulty of performing such clinical trials with a primary endpoint of overall survival(14). Current therapeutic options for patients with PTC include total or near total thyroidectomy with or without lymphadenectomy, and adjuvant therapy including radioactive iodine ablation and thyroid stimulating hormone (TSH) suppression with thyroid hormone.

The majority of patients with thyroid cancer have low-risk disease and the optimal management of such patients continues to be a subject of debates due to the lack of high quality data. There has been a growing interest in utilizing molecular diagnostic markers such as *BRAF*V600E mutation and *RET/PTC* rearrangement to improve preoperative diagnostic accuracy of fine needle aspiration and to enhance patient risk stratification. *RET/PTC* rearrangement can help identify PTC in indeterminate nodules as almost all thyroid nodules positive for clonal *RET/PTC* mutations were proved to be PTC.(15) *BRAF*V600E mutation is the most common genetic alteration found in PTC (~50%). Although the presence of *BRAF*V600E mutation confers a 100% risk of malignancy and was associated with aggressive features such as extrathyroidal extension, lymph node metastasis (LNM), more advanced tumor stage in some studies (16, 17), it remains controversial if *BRAF* V600E mutation can be used as an independent prognostic factor for thyroid cancer mortality(18-20). A number of studies suggest the utility of *BRAF* V600E mutation testing is to select patients who may benefit from more extensive initial surgery such as pCND because of higher rates of LNM and recurrent/persistent disease associated with this mutation(21-24). On the other hand, several investigators have observed an association of *BRAF* mutation with overt and occult LNM (21, 25, 26) and in up to 80% of occult (microscopic) PTC which are associated with near normal life expectancy. Moreover, the superior outcome of more extensive surgery in patients with *BRAF* mutation positive PTC has never been demonstrated. There is still insufficient data to support pCND on the basis of *BRAF* mutation alone in patients with low-risk PTC(27). Because the use *BRAF* V600E mutation status to guide the extent of surgery, particularly pCND, has never been evaluated in a prospective study, this study will evaluate the impact *BRAF* V600E mutation status on lymph node metastasis and postoperative stim-Tg in patients with low-risk PTC undergoing TT with pCND. In addition, we will compare the rate of disease recurrence in patients undergoing pCND to those who will not undergo pCND, by *BRAF* V600E mutation status.

1.2.2.1 Surgical therapy

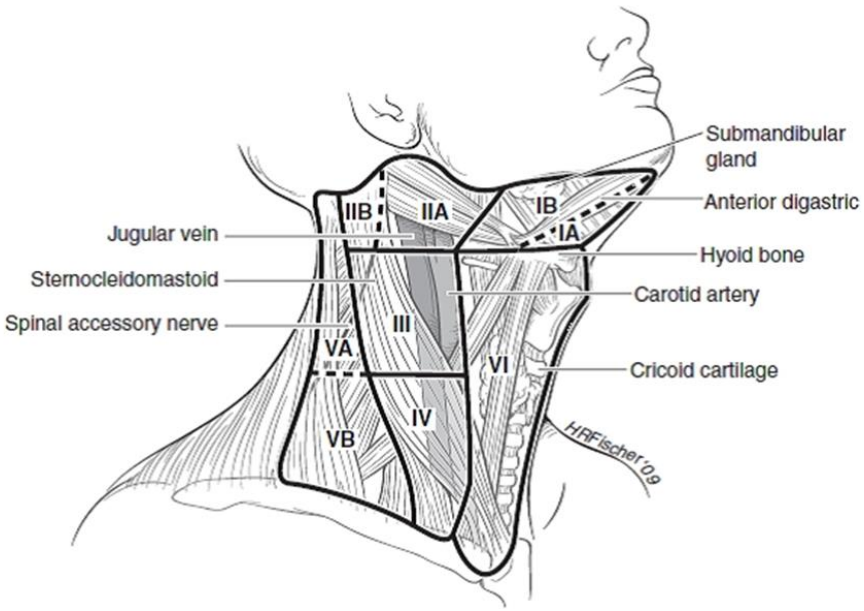
When PTCis identified preoperatively, near-total or total thyroidectomy (TT) is recommended for patients whose primary tumor size is larger than 1 cm or have other risk factors, such as contralateral thyroid nodules, regional and distant metastasis, a history of radiation exposure, a first-degree family history of thyroid cancer. Thyroid lobectomy alone may be sufficient treatment for small (<1 cm), low-risk, unifocal, intrathyroidal PTC in the absence of risk factors(11). A near-total or total thyroidectomy is also recommended in older patients (>45 years) with 1-1.5cm PTC because of higher recurrence rates in this age group(11). A population-based study of over 50,000 patients with PTC demonstrated that TT was associated with lower recurrence and survival rates for tumors > 1.0 cm on multivariate analysis. Patients with small PTCs (1.0–2.0 cm) who underwent lobectomy, had a 24% higher risk of recurrence and a 49% higher risk of thyroid cancer mortality(28). Thus, the standard of care for PTC ≥ 1cm. is TT.

1.2.2.2 Prophylactic central neck lymph node dissection and outcome

The central lymph node compartment, commonly referred to as level VI, is the most common site for LNM in patients with PTC. The boundaries of the central neck lymph node compartment include the hyoid bone superiorly, the common carotid arteries laterally, and sternal notch or the brachiocephalic artery inferiorly (**Figure 1**).

Figure 1. Cervical lymph node compartments.

Figure 1



While it is well accepted that therapeutic central neck lymph node dissection (CND) is indicated for PTC with clinical or radiographic evidence of metastatic lymph nodes, neither clinical examination nor imaging studies are reliable to detect central neck LNM. Neck ultrasound is the most commonly used diagnostic tool for patients with thyroid masses but the accuracy of neck ultrasonography (USG) in detecting metastatic central neck lymph nodes is limited because the paratracheal lymph nodes are often very small, located beneath the thyroid gland, and air-filled trachea presents an additional barrier to detect these lymph nodes preoperatively by USG. CND can be technically challenging as it requires a meticulous dissection to remove lymph nodes along recurrent laryngeal nerves while preserving parathyroid glands and their blood supply.

Because reoperation of central neck in the presence of scar tissue from previous surgery is often difficult and can result in high rates of morbidities such as transient and permanent recurrent laryngeal nerve injury and hypoparathyroidism(29), pCND at the initial operation seems logical as a significantly higher rate of reoperation in the central compartment was observed in patients who did not undergo pCND(30, 31). More recently it has been shown in three retrospective studies that pCND can reduce the doses of ^{131}I administered— or obviate it entirely—for low-risk patients shown to have no LMN (pN0)(32-34). Thus, pCND may be beneficial in some patients (pN0) by avoiding or reducing doses of ^{131}I and in others (pN1) by decreasing the risk of

reoperative surgery in the central compartment. Complications of initial pCND include increased risk of transient and permanent hypoparathyroidism in contrast to what is seen with TT alone (35), although a recent meta-analysis has shown that experienced surgeons can perform pCND safely with similar complication rates(36).

Because LNM to central neck compartment (level VI) is common in PTC and the progression of level VI LNM to lateral neck compartment has been suggested (37), some surgeons advocate routine prophylactic central neck dissection (pCND) for PTC. However, there is no consensus on patient selection for pCND based on preoperative information. While a formal compartment-oriented lymph node dissection is indicated in clinically suspicious or confirmed metastatic lymph node(s), pCND in patient with no evidence of LNM in the central neck continues to be a subject of great debates because of the lack of randomized controlled trials to address the controversy. It is inconclusive if TT with pCND would reduce the risk of locoregional recurrence compared to patients undergoing TT alone as a randomized clinical trial would require over 5,000 patients to have sufficient statistical power to detect 25% reduction in clinically identifiable tumor recurrence(38). Most studies to date have been retrospective, relatively underpowered with insufficient follow-up periods. A recent meta-analysis of 14 studies (n=3,331) demonstrated a 35% risk reduction of locoregional recurrence in patients who underwent TT and pCND but this was compared to historical controls with longer follow up time in the TT alone. Also, it remains unclear if or how much of the risk reduction is associated with the increased use of radioiodine ablation in upstaged patients as a result of detecting subclinical LNM or patient selection bias in studies examined(39).

Because thyroglobulin (Tg) is produced solely by thyroid follicular cells, measuring TSH-stimulated thyroglobulin (stim-Tg) helps in the detection of persistent/recurrent metastatic disease. Measurement of serum Tg levels is an important modality to monitor patients with differentiated thyroid cancer. In the absence of anti-thyroglobulin antibody, serum Tg has a high sensitivity and specificity to detect differentiated thyroid cancer of follicular cell origin after total thyroidectomy, and especially after thyroid remnant ablation with radioiodine. Postoperative stim-Tg levels have been shown to predict disease remission with 95% negative predictive value(40), clinical recurrence in low-risk patients (41), distant metastasis (42), disease-free survival and death(43).

To assess the completeness of surgery, some studies have compared the postoperative stim-Tg level between those who underwent pCND and those who did not with conflicting results (34, 44-46). Hughes et al. retrospectively compared stim-Tg levels at pre and 1-year post remnant ablation in143 patients with clinical node-negative PTC who underwent TT with and without pCND and found no significant difference(34). Retrospective studies from Hong Kong showed a significant lower stim-Tg before remnant ablation and higher rate of patients with undetectable thyroglobulin in TT and pCND group but no difference was observed at 6 months post remnant ablation(44). Another study reported that post-ablative stim-Tg was inversely correlated with the number of lymph nodes removed from pCND, suggesting pCND resulted in more complete eradication of (microscopic) tumor foci (45). A large retrospective study (n=447) by Sywak et al. demonstrated a significantly lower post-ablative stim-Tg and higher rates of athyroglobulinemia in patients who had TT with pCND(46). These discordant results highlight the need for randomized trial that is free of selection bias and all participants undergo the same treatment

protocol. A summary of the controversial results surrounding the effects of pCND is demonstrated in **Table 1**.

Table 1. A summary of the controversial effects of pCND[1] on the various clinical parameters in patients with PTC.

Outcome measures	Study authors	Type of study	Sample size (n)	Results	Remarks
Biochemical cure rate measured by stim-Tg[2]	Hughes et al. (34)	Retrospective	143	No difference in stim-Tg before or 1 year post-RAI[(3)]	
	Sywak et al. [(46)]	Retrospective	447	Lower post-RAI stim-Tg and higher rate of athyroglobulinemia	
Locoregional recurrence	Lang et al. (39)	Meta-analysis	3,331	35% reduction in risk of locoregional recurrence	Data from retrospective studies, confounded by selection bias and the use of RAI
	Wada et al.(47)	Retrospective	390	No difference	Probably underpowered
The use of RAI	Vaisman et al. (48)	Prospective	104	Decrease use of RAI due to higher rate of athyroglobulinemia	
	Hughes et al. (34)	Retrospective	143	Increase RAI dosage due to upstaging	

Postoperative complications	Giordano et al. [35]	Retrospective	1,087	Increase rate of transient and permanent hypoparathyroidism	
	Chisholm et al. (36)	Meta-analysis	1,132	Low rate of hypoparathyroidism and nerve injuries	
Postoperative quality of life	Not available			Unknown	
Voice quality and swallowing	Not available			Unknown	

[1]pCND: Prophylactic central neck lymph node dissection

[2]stim-Tg: Stimulated serum thyroglobulin

[3]RAI: Radioactive iodine ablation therapy.

The current American Thyroid Association (ATA) guidelines suggest that pCND can be performed in patients with advanced primary thyroid tumors (T3 or T4), as patients with tumors >4 cm in diameter have a 2–6-fold higher risk of central lymph node involvement than patients with tumors ≤4 cm (T1 or T2). (11) However, the rate of occult central neck LNM in PTC < 2cm (T1) ranged from 36% to 61% when pCND is performed[46]. The impact of a small-volume residual disease on tumor recurrence remains not fully characterized. Locoregional recurrence rate of 2%-5% were observed in patients with <5 subclinical, small (<0.2cm), LNM and median locoregional recurrence rate of 19% (range: 7%-21%) when >5 subclinical LNM(49).

This will be the first level 1 evidence that answers an important clinical question regarding the extent of initial surgery in patients with low-risk PTC. Thus, a higher rate of athyroglobulinemia in the pCND group would convince many surgeons to perform pCND and would alter current treatment guidelines. Most importantly, it would preclude the need for adjuvant radioiodine therapy and streamline the follow up management of patients. Lastly, it would be important to patients who are thyroid cancer survivors (over 500,000 patients) that they are likely "cured" of their disease. All of these have significant ramifications to the cost of care and patient outcome and survivorship.

Voice quality of patients undergoing TT and CND may be more compromised than patients who have TT alone despite no clinical evidence of recurrent laryngeal nerve injury (50). This may be caused by transient nerve conduction disorders induced by more manipulation around recurrent laryngeal nerves or the disturbance of venous and lymphatic drainage from CND(50). The Voice Handicap Index-10 (VHI-10), a self-administered questionnaire to assess patients' voice quality, was validated and published by Rosen et al.(51) . The VHI-10 has been used to assess subjective voice quality after thyroidectomy by several groups.(52, 53)(**Appendix A**)

Swallowing impairment is frequently reported following thyroidectomy and is often self-limited(54). Because CND requires more extensive dissection and manipulation around the esophagus, it may result in more pronounced swallowing impairment. However, there is no study evaluating the impact of CND on symptoms of swallowing impairment. Swallowing Impairment Score (SIS-6) (**Appendix B**) is a self-administered questionnaire which has been validated and used to assess post-thyroidectomy dysphagia(53, 54).

1.2.2.3 Radioactive iodine ablation (RAI)

RAI is used to eliminate the postsurgical thyroid remnant which may facilitate the early detection of tumor recurrence by measuring serum Tg and/or RAI whole body scan. In addition, posttherapy scan performed at the time of remnant ablation can provide more accurate initial staging as undiagnosed metastases may be visualized. Furthermore, RAI may be used as *adjuvant therapy* to ablate remaining thyroid cancer cells in patients with microscopic or gross clinical residual disease. A selective use of RAI is recommended in patients with high-risk disease known metastases, gross extrathyroidal extension, primary tumor >4 cm or in patients whose tumors are 1-4 cm with other higher risk features such as lymph node metastases, or a combination of age, tumor size, lymph node status and histology that predicts intermediate to high risk of recurrence or death from thyroid cancer. There was no clear benefit such as reduction in mortality or recurrence rates observed when RAI was used in low-risk patients (stage I without high-risk features)(11).

A selective use of RAI based on postoperative stim-Tg level has been reported to reduce the rate of RAI use, compared to the rate of RAI use proposed by ATA. Vaisman et al. did not use a routine RAI in patients with stim-Tg <1 ug/L and routinely administered RAI in patients with stim-Tg >5ugl/L. Patients with stim-Tg 1-5 ug/L were given the option to defer RAI and only 17% of these patients received RAI. Overall, only 15.4% of patients in this protocol received RAI. There was no persistent or recurrent disease in patients who did not receive RAI (mean follow-up=3 years)(48).

1.2.2.4 TSH suppression therapy

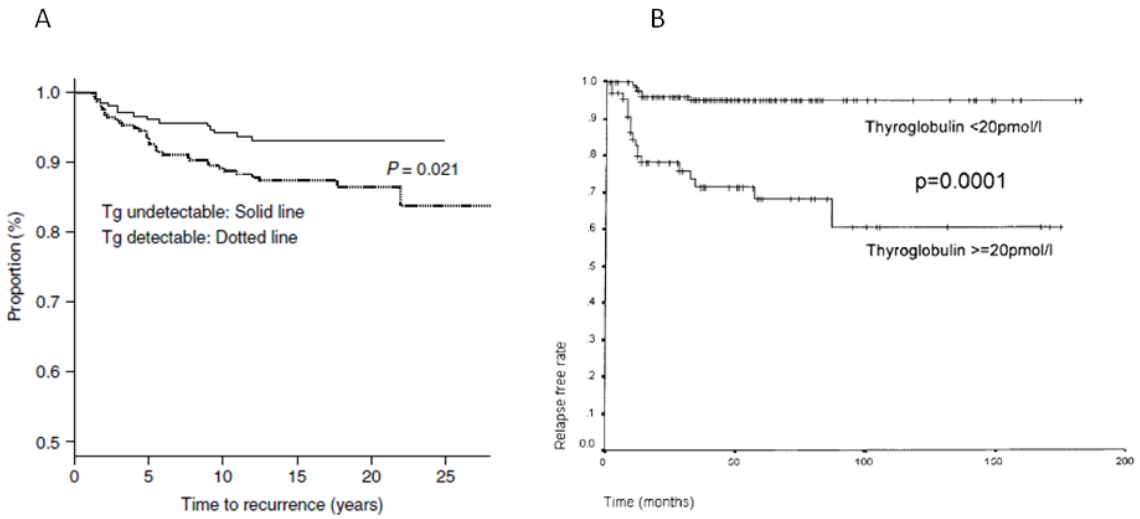
Because differentiated thyroid cancer of follicular cell origin express the TSH receptor and respond to TSH stimulation by increasing cell proliferation, the suppression of TSH by supra-physiologic dose of thyroid hormone is commonly used to decrease the risk of recurrence. The ATA guidelines recommended an initial level of TSH suppression to below 0.1 mIU/L for high-risk and intermediate-risk thyroid cancer patients, while maintenance of the TSH at or slightly below the lower limit of normal (0.1–0.5 mIU/L) is appropriate for low-risk patients. Similar recommendations apply to low-risk patients who have not undergone remnant ablation, i.e., serum TSH 0.1–0.5 mIU/L (11).

1.2.2.5 Serum thyroglobulin and postoperative surveillance

An undetectable stim-Tg (< 0.5 ng/mL) in the absence of anti-Tg antibody has an approximately 98–99.5% likelihood of identifying patients completely free of tumor on follow-up(55, 56). Detectable Tg after RAI ablation is associated with higher rate of disease recurrence (**Figure 2A)** (57). In addition, Tg level is typically higher in patients with distant metastasis and is correlated with tumor burden. (58, 59) However, stim-Tg may fail to identify patients with clinically significant tumor burden in the presence of anti-Tg antibody or in patients with poorly differentiated or other aggressive thyroid cancer subtypes, due to low Tg expression. Approximately 20% of patients who have no clinical evidence of disease with serum Tg levels < 1ng/mL during thyroid hormone suppression of TSH (60) will have a serum Tg level > 2ng/mL after rhTSH stimulation or thyroid hormone withdrawal at 12 months after initial therapy with surgery and RAI. In this patient population, one third will have identification of persistent or recurrent disease and of increasing Tg levels, and the other two thirds will remain free of clinical disease and will have stable or decreasing stim-Tg levels over time (61). Using a current highly sensitive Tg assay, undetectable unstimulated Tg (≤ 0.1 ng/ml) has a very high negative predictive value to identify patients without evidence of disease when stim-Tg is used as a benchmark(62, 63).

Figure 2. Serum thyroglobulin and outcomes of thyroid cancer: **A:** detectable post-ablative Tg is associated with higher recurrent rate; **B:** Disease-free survival in patients with stim-Tg levels ≤20 pmol/L and >20 pmol/L, 3 months after total thyroidectomy for well-differentiated thyroid cancer (1 ng/ml of thyroglobulin= ~1.515 pmol/L).

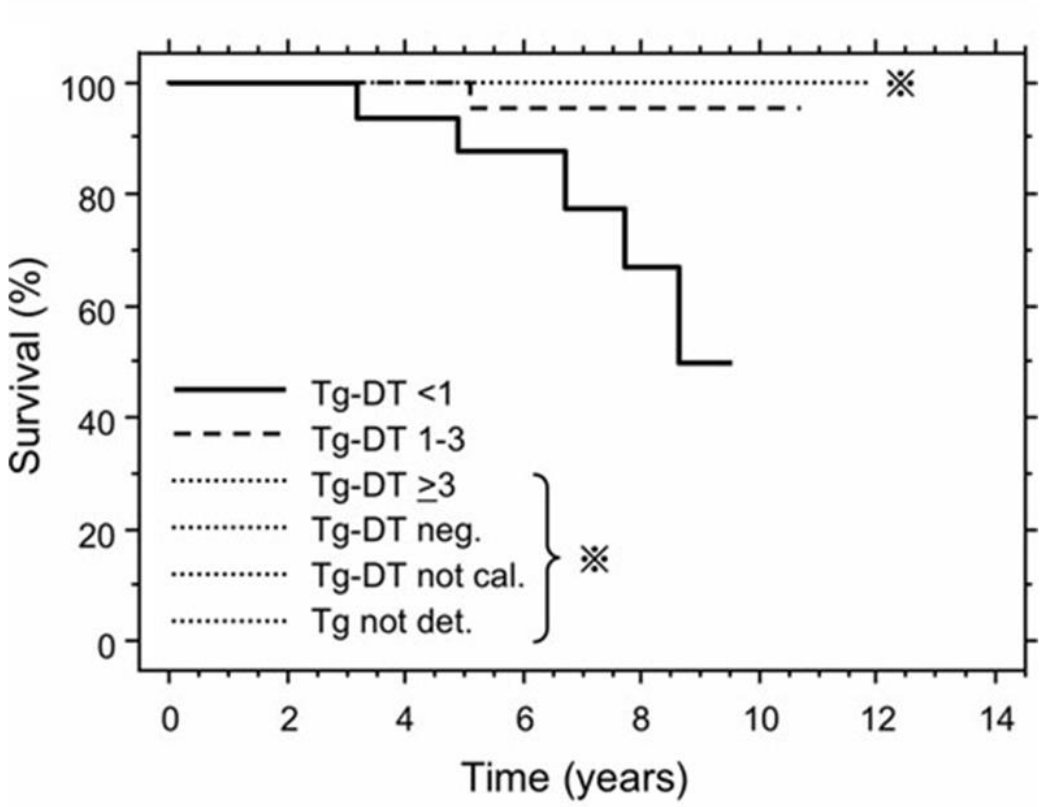
Figure 2



Although several studies suggest that a Tg cutoff level above 2 ng/ml following rhTSH stimulation is highly sensitive in identifying patients with persistent tumor (64-69), the clinical significance of minimally detectable Tg levels in the absence of clinical evidence of disease remains unclear. Patients with postoperative stim-Tg > 20pmol/L (~13 ng/ml) are at increased risk of disease recurrence (**Figure 2B**)(70). In these patients, the trend in serum Tg over time will typically identify patients with clinically significant residual or recurrent disease. A rising unstimulated or stim- Tg indicates disease that is likely to become clinically apparent(61, 71). Tg doubling time has been identified as a reliable marker for recurrent disease as well as prognostic indicator in patients with and without remnant ablation(72). Patients with Tg doubling time less than 1 year had significantly shorter thyroid cancer-specific survival, compared to those with Tg doubling time more than 1 year (**Figure 3**) (72). The ATA recommended a diagnostic whole body radioiodine scan (DxWBS) to detect recurrent or persistent disease for Tg >0.3 ng/ml or stimulated Tg > 2 ng/ml (in the absence of anti-Tg antibody) at 6-12 months after remnant ablation. Most patients with stim-Tg >5 ng/ml have clinically identifiable disease.(64, 73) If stim-Tg >5-10 ng/ml and whole body RAI scan is negative, cross-axial imaging studies and/or FDG PET/CT should be performed(11).

Figure 3. Thyroglobulin doubling time less than 1 year is associated with worse survival.

Figure 3



A follow-up of patients with low-risk differentiated thyroid cancer who have undergone total or near-total thyroidectomy *without* RAI remnant ablation may be challenging because the source of Tg can be from a thyroid remnant. A cohort of 80 patients with papillary thyroid microcarcinoma who underwent a near-total or total thyroidectomy (11 had CND) *without* RAI remnant ablation demonstrated that recombinant human TSH-stim-Tg was ≤ 1ng/ml in 56% of patients and whole body RAI scan was not useful to identify persistent or recurrent disease. The detectable stim-Tg levels mainly depended on the size of thyroid remnant shown in DxWBS(74). For those with thyroid remnant and detectable Tg, a rising Tg can be useful to detect recurrent disease.

Based on the studies cited above, stim-Tg <2 ng/ml and unstimulated Tg ≤ 0.2 ng/ml have been associated with biochemical cure or remission in patients with differentiated thyroid cancer and stim-Tg<2 ng/ml will be used in this protocol as a cut-off for biochemical cure. Stim-Tg >5 ng/ml or unstimulated Tg >0.3 ng/ml has been associated with persistent and recurrent disease(11, 48, 75, 76), and therefore, will be used in this protocol as a cut-off for biochemical persistent/recurrent disease.

Serum Tg is used to guide postoperative radioiodine therapy, level of TSH suppression and the extent of surveillance for recurrent/persistent disease(77).

1.2.2.6 Postoperative surveillance in patients with PTC and anti-thyroglobulin antibodies

The frequency of anti-Tg antibodies in patients with differentiated thyroid cancer is approximately 20-25% depending on the study population and assay used (78-80). The prevalence of anti-Tg antibodies in the general population is approximately 10%(81). Although the presence of anti-Tg antibodies can cause inaccurate Tg measurement, thereby limiting its usefulness, there has been growing evidence that the antibody levels themselves may serve as a surrogate biochemical marker of persistent/recurrent disease. However, the kinetics of anti-Tg antibodies in response to treatment differ from those of Tg levels in patients without antibodies. For example, an initial transient rise in anti-Tg antibodies can be observed following remnant ablation and it takes on average of 2-3 years for anti-Tg levels to become undetectable(82). It is important to recognize that anti-Tg antibody levels can fluctuate and a clear trend requires repetition of the tests over time. Furthermore, a variability between different assays can cause inconsistent results for antibody levels, thus it is recommended that anti-Tg antibodies are measured by the same facility using the same assay(82). Patients with declining anti-Tg antibody levels (over 50% from pretreatment value) over 6-12 months had significant lower recurrence rate than those with a lower reduction or increased levels(83). In contrast, patients with rising anti-Tg antibodies or those who convert negative antibody levels to positive ones are more concerning for progressive/recurrent thyroid cancer and a more aggressive imaging is generally performed(82). Therefore, a conversion or a rise in anti-Tg antibodies will be used to diagnose biochemical persistent/recurrent disease in this protocol.

1.2.3 Prognosis and outcome

Postoperative staging of PTC is crucial for determining the need for adjuvant radioactive iodine (RAI) therapy, the degree of TSH-suppressive therapy with levothyroxine, the methods and intensity of follow-up, as well as prognosis. Thyroid cancer staging is based on the American Joint Committee on Cancer (AJCC) TNM staging system which is intended for prediction of thyroid cancer-related mortality, and not for recurrence. In a study by Hundahl and colleagues, the outcome of 42,687patients who underwent thyroidectomy for thyroid cancer between 1985 and 1995 was determined. The majority of the patients had stage I (56.9%) or stage II disease (14.4%). Overall, patients with PTC had the best 10-year survival rate (93%) when compared with follicular (85%), Hurthle cell (76%), medullary (75%), and anaplastic (10%) cancers (3). Based on the 7th edition AJCC Cancer Staging system, the 5-year disease-specific survival rates for PTC are 100% for stages I and II, 93% for stage III, and 51% for stage IV (84). The incorporation of patient age into the AJCC system favors patients younger than 45 years of age. Even in the presence of systemic metastases, patients younger than 45 years are classified under stage II disease. Although the long-term survival of patients with PTC is usually excellent, the clinically detectable (positive imaging findings or a positive biopsy) recurrence rate is significant, up to 35% during 40-year follow-up(8). This may be an underestimation of the true rate of recurrence because patients with an elevated serum Tg level but no clinical detectable recurrences were excluded. Mazzaferri et al. demonstrated that approximately half of all recurrences occurred during the first 5 years following definitive surgical treatment and 75% within the first 10 years; therefore, a long-term follow-up is necessary. Two-third of the recurrences occurred in the neck whereas the one-third occurred in distant sites(67). Patients at the extremes of age (<20 or >60 years) had higher recurrence rates. Half of thyroid cancer related deaths are from PTC due to its high prevalence. Approximately half of the patients with PTC die

within 5 years once distant metastases are detected. Younger patients with systemic metastases survive longer(85). Common sites of systemic metastases for thyroid cancer are lungs (50%), bones (20%), and multiple organ involvement (16%). Higher rates of distant metastasis were observed in patients with Hurthle cell cancer and FTC than PTC. Five and ten-year overall mortality rates after the diagnosis of metastases were 65% and 75%, respectively(85).

1.2.4 Quality of life after treatment for thyroid cancer

It is increasingly recognized that the diagnosis and treatment of cancer can have a major impact on all aspects of a patient's quality of life (QOL). The QOL of patients with thyroid cancer can be affected by multiple different modalities of treatments and their complications. There have been only a limited number of studies addressing the QOL of patients with thyroid cancer. The QOL of patients with thyroid cancer can be affected by outcomes of various treatments including modified radical neck dissection (53), hypoparathyroidism (86), and hypothyroidism in preparation for radioactive iodine ablation(87). The QOL in patients undergoing thyroid surgery for cancer can be affected by the complications and other postoperative changes such as neck pain, dysphagia, and voice changes without evidence of nerve injury. Because more extensive surgery such as in patients undergoing TT and pCND may have more negative impact on QOL therefore, it should be assessed in conjunction to potential oncologic benefit to fully understand the risks and benefits of the procedure. Currently, there is no randomized controlled trial assessing the QOL in patients with PTC undergoing TT and pCND compared to TT alone.

The Short Form 36 Health Survey version 2.0 (SF-36) (**Appendix C**) has been widely used to assess the QOL of patients with various diseases, including cancer. It is a tool that measures health-related QOL according to an inclusive standard and not a disease-specific standard. The score is expressed numerically by the provided scoring algorithm. The SF-36 is a comprehensive short-form instrument with 36 questions that can be self-administered to yield a health profile. It comprises of 8 domains: physical functioning, role limitations caused by physical problems, bodily pain, general health, vitality, social functioning, role limitations caused by emotional problems, and mental health. The SF-36 is capable of capturing the impact of treatments on patient's QOL including complications from surgery, the effects of preparation for radioiodine treatment and its side effects, and the length of follow-up(87-89).

2 ELIGIBILITY ASSESSMENT AND ENROLLMENT

2.1 ELIGIBILITY CRITERIA

2.1.1 Inclusion Criteria

2.1.1.1 Patients must have histologically or cytologically confirmed at least 1 thyroid nodule that is ≥1 cm but ≤ 4 cm measured in greatest dimension and confirmed by the Laboratory of Pathology, NCI or confirmed by the pathology laboratory of the enrolling institution:

- Indeterminate thyroid biopsy per Bethesda System for reporting thyroid cytopathology(90) (**Appendix D**: Bethesda system for reporting thyroid cytopathology

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

Diagnostic Category	Risk of Malignancy (%)	Usual Management[†]
Nondiagnostic or Unsatisfactory	1-4	Repeat FNA with ultrasound guidance
Benign	0-3	Clinical follow-up
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	~5-15[‡]	Repeat FNA
Follicular Neoplasm or Suspicious for a Follicular Neoplasm	15-30	Surgical lobectomy
Suspicious for Malignancy	60-75	Near-total thyroidectomy or surgical lobectomy[§]
Malignant	97-99	Near-total thyroidectomy[§]

FNA, fine-needle aspiration.
[*] Adapted with permission from Ali and Cibas.[3]
[†] Actual management may depend on other factors (eg, clinical, sonographic) besides the FNA interpretation.
[‡] Estimate extrapolated from histopathologic data from patients with "repeated atypicals."
[§] In the case of "Suspicious for metastatic tumor" or a "Malignant" interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.

- Appendix E) with BRAF V600E mutation or *RET/PTC* rearrangement
- Cytologically or histologically suspicious or confirmed PTC per Bethesda System for reporting thyroid cytopathology(90) (**Appendix D**: Bethesda system for reporting thyroid cytopathology

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

Diagnostic Category	Risk of Malignancy (%)	Usual Management†
Nondiagnostic or Unsatisfactory	1-4	Repeat FNA with ultrasound guidance
Benign	0-3	Clinical follow-up
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	~5-15‡	Repeat FNA
Follicular Neoplasm or Suspicious for a Follicular Neoplasm	15-30	Surgical lobectomy
Suspicious for Malignancy	60-75	Near-total thyroidectomy or surgical lobectomy§
Malignant	97-99	Near-total thyroidectomy§

FNA, fine-needle aspiration.
* Adapted with permission from Ali and Cibas.[3]
† Actual management may depend on other factors (eg, clinical, sonographic) besides the FNA interpretation.
‡ Estimate extrapolated from histopathologic data from patients with "repeated atypicals."
§ In the case of "Suspicious for metastatic tumor" or a "Malignant" interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.

- Appendix E)

2.1.1.2 Age ≥18 years. Because PTC occurs rarely in patients <18 years of age, children are excluded from this study.

2.1.1.3 Absence of radiographic evidence of extrathyroidal extension.

2.1.1.4 Absence of abnormal lymphadenopathy suggesting metastatic PTC on physical examination and/or imaging studies.

2.1.1.5 ECOG performance status ≤2 (Karnofsky ≥60%, see **Appendix G**).

2.1.1.6 Patients must have adequate organ function to safely undergo general anesthesia and thyroidectomy. Laboratory values obtained ≤ 4 weeks prior to surgery must demonstrate adequate bone marrow function (Hb ≥ 6.0 mmol/L, absolute neutrophil count ≥ 1.5 x 10^9/L, platelets ≥ 80 x 10^9/L), liver function (serum bilirubin ≤ 2 x ULN, serum transaminases ≤ 3 x ULN). Patients with chronic kidney disease who are on chronic renal replacement therapy are allowed. Other tests, such as pulmonary function tests, cardiac echocardiogram or stress test, will be performed if clinically indicated.

2.1.1.7 Ability of subject to understand and the willingness to sign a written informed consent document.

2.1.1.8 Women must not become pregnant prior to surgery or during the first 3 months after surgery. Women who can become pregnant will be asked to practice an effective form of birth control for up to 3 months after surgery.

2.1.2 Exclusion Criteria

2.1.2.1 Patients who have had previous thyroid surgery

2.1.2.2 Patients whose tumors are deemed unresectable by clinical/imaging criteria.

2.1.2.3 Patients with known synchronous distant metastatic disease.

2.1.2.4 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

2.1.2.5 Pregnant women are excluded because we do not want to expose the unborn child to the procedures necessary to perform the surgery.

2.2 SCREENING EVALUATION

Study candidates will undergo the following evaluations which may be performed within 4 weeks prior to enrollment.

a. Detailed demographic data will be collected from the medical record and patient interview, physical examination for each participant. Data will be securely stored in a computerized database.

b. All participants with thyroid nodule(s) that have not been biopsied or non-diagnostic nodule(s) will undergo USG-guided preoperative fine needle aspiration following the ATA guidelines (**Appendix E**). The specimen(s) will be sent for cytology.

c. Cytology will be reviewed by Laboratory of Pathology, NCI or the laboratory of pathology at the enrolling institution at any time prior to enrollment.

d. Laboratory evaluation includes:

- CBC with differential
- Chemistries: Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Ionized Calcium, Magnesium total (Mg), Inorganic Phosphorus, Alkaline Phosphatase, ALT/GPT, AST/GOT, Total Bilirubin, Direct Bilirubin, LD, Total Protein.
- PT/PTT
- Thyroid Stimulating Hormone (TSH), Free T4 and T3 (only if TSH is abnormal), intact parathyroid hormone (PTH), anti-thyroglobulin antibodies, thyroglobulin

e. Radiographic evaluation includes

- Thyroid and soft tissue neck ultrasonography (USG)
- Computerized tomography (CT scan) without contrast of neck or chest and/or other tests will be done if clinically indicated.

2.3 REGISTRATION PROCEDURES

Authorized staff must register an eligible candidate with NCI Central Registration Office (CRO) within 24 hours of signing consent. A registration Eligibility Checklist from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov. Verification of Registration will be forwarded electronically via e-mail to the research team. A recorder is available during non-working hours.

2.3.1 For Participating Site Registration

Registration will be a two-part process as patients are screened on this protocol. A protocol registration form will be supplied by the CCR study coordinator and updates will be provided as needed. Subject eligibility and demographic information is required for registration. To initially register a subject, after the participant has signed consent, complete the top portion of the form and send to CCR study coordinator. Once eligibility is confirmed, after completion of screening studies, complete the remainder of the form which is the eligibility checklist, indicating that the patient is being registered for treatment and send to CCR study coordinator. In addition, source documents supporting the eligibility criteria must be sent to the CCR study coordinator. The CCR study coordinator will notify you either by e-mail or fax that the protocol registration form has been received which will include the unique patient/subject ID number. Questions about eligibility should be directed to the CCR study coordinator or PI. Questions related to registration should be directed to the CCR study coordinator.

Subjects that do not meet screening criteria should be removed from the study following the procedure in Section **3.3.4**

2.4 RANDOMIZATION (OR STRATIFICATION) PROCEDURES

After confirmation of eligibility at Central Registration Office, CRO staff will provide the research team with the randomized treatment assignment. Patients will be randomized to receive TT alone or TT+ pCND. Randomization will be conducted a 1:1 fashion using variable block sizes. Written confirmation of registration to the protocol and the randomization arm selected will be obtained from the CRO and placed on the patient's research record.

2.5 BASELINE EVALUATION

2.5.1 Preoperative evaluation

a. Participants will fill out the following questionnaires which will be conducted within 4 weeks prior to surgery to establish the baseline status of:
   - QOL using SF-36 v2 questionnaire (**Appendix C**)
   - Neck pain (scale 0 (no pain) to 10 (unimaginable, unspeakable pain))
   - Voice quality using Voice Handicap Index-10 questionnaire (**Appendix A**)
   - Swallowing symptoms using Swallowing Impairment Score (SIS-6) questionnaire (**Appendix B**)

b. All participants will undergo flexible laryngoscopy to establish baseline vocal cord functions.

c. Urine or serum pregnancy test.

3 STUDY IMPLEMENTATION

3.1 STUDY DESIGN

This is a prospective, randomized, single-blinded, controlled trial in patients with a suspicious or confirmed PTC $\leq$ 4 cm without clinical evidence of lymphadenopathy or extrathyroidal extension on imaging. Preoperative evaluation will be performed to establish the baseline status of participant's QOL, neck pain (scale 1 to 10), subjective voice and objective vocal cord function, and swallowing status using standardized questionnaires (see below). *BRAF* V600E mutation status of the tumor will be assessed in all patients after thyroidectomy. Enrolled participants will be randomly assigned preoperatively to receive either TT alone or TT with pCND. Participants and their families will be blinded from the results of randomization. If a patient who is assigned to TT alone group is found to have LNM intraoperatively by frozen section, a CND will be performed and the patient will remain in TT alone group (intention to treat). Participants in both groups will receive uniform, routine postoperative care and follow-up evaluation per protocol (see below). Stim-Tg will be measured in <u>all</u> participants prior to remnant ablation at 3 months postoperatively (prior to remnant ablation, if indicated). Stim-Tg at 1-year post-remnant ablation or 1 year postoperatively if participants do not receive remnant ablation will be performed in patients enrolled at the NIH but is optional in patients enrolled at non-NIH site(s). Tg and anti-thyroglobulin antibodies will be measured annually for 10 years. The postoperative complications and QOL of participants will be assessed during preoperative evaluation, postoperative day 1, 2 weeks, 3 and 6 months, 1, 5 and 10 years postoperatively. Surgical outcome will be evaluated at postoperative day 1, 2 weeks, and 6 months postoperatively. Participants will have an evaluation for radioactive iodine ablation by the

endocrinology service. The standardized protocol will be used based on histologic findings and patient's risk of recurrence per NIDDK protocol. (**Table 2**) Similarly, participants will be managed using a standardized protocol for TSH suppression therapy based on the risk of recurrence.

Table 2. Post-operative risk stratification: Guideline for management of patients with clinical characteristics that modify initial assessment of risk[1]

Clinical factor	**Postoperative Stim-Tg (ng/ml)**	**^{131}I ablation/preparation[2]**	**Thyroid hormone goal**
T1-T2, Nx or N0	<5	No remnant ablation	TSH low normal[3]
T1-T2, Nx or N0	≥5	30 mci(91)/WD or rhTSH	TSH low normal
T3, Nx or N0 <45 years old	<5	No remnant ablation	TSH subnormal[4]
	≥5	50-100 mCi/ WD or rhTSH	TSH subnormal
T3, Nx or N0 ≥45 years old	<5	No remnant ablation	TSH subnormal
	≥5	100 mCi/ WD or rhTSH	TSH subnormal
T4, Any N	Any	150 mCi/WD	TSH suppressed[5]
N1 <45 years old	<5	No remnant ablation	TSH subnormal
	≥5	50-100 mCi/ WD or rhTSH	TSH subnormal
≥45 years old	<5	No remnant ablation	TSH suppressed

Clinical factor	**Postoperative Stim-Tg (ng/ml)**	**^{131}I ablation/preparation[2]**	**Thyroid hormone goal**
	≥5	100 mCi/ WD or rhTSH	TSH suppressed
M1	Any	≥ 150 mCi/WD	TSH suppressed
Histologic variants	Any	≥ 150 mCi/WD	TSH suppressed
Tall cell			
Diffuse Sclerosing			
Hurthle			
Insular			
Anaplastic/ Dedifferentiated			

WD: withdrawal of thyroid hormone; rhTSH; recombinant human TSH

[1]The management may vary individually based on patient's risk factors and investigator's discretion

[2] All follow 2-week low iodine diet

[3] Low normal goal: TSH 0.5 to 1 mU/L

[4] Subnormal goal: TSH 0.1 to 0.5 mU/L

[5]Suppressed goal: TSH <0.1 mU/L

Biochemical cure or remission in this study is defined as stim-Tg < 2 ng/ml or unstimulated Tg ≤ 0.2 ng/ml. Biochemical persistent or recurrent disease is suspected when stim-Tg ≥5 ng/ml or unstimulated Tg >0.3 ng/ml or a conversion or a rise in anti-Tg antibodies.

An interim analysis will be performed after 90 who do not have anti-thyroglobulin antibody patients are enrolled (See Section 7), including a subgroup analysis based on *BRAF* V600E mutation status.

3.2 STUDY CALENDAR

Test	Screen	Baseline (Preop)	1 day postop	2 weeks postop	3 months postop	6 months postop	1 year Postop	Annually (M24-M120)
History/Physical examination	x		x	x	x	x	x	x
QOL Questionnaire		x	x	x	x	x	x	M60 and M120
Neck pain		x	x	x		x		
VHI-10		x	x	x		x		
SIS-6		x	x	x		x		
Labs[1]	x		x	x	x	x	x	x
Tg and thyroid antibodies	x				x	x	x	x
Neck USG	x				x	x	x	x
FNA thyroid		x						
Flexible laryngoscopy		x	x[2]	As needed		x[3]		
Thyroid hormone replacement or suppression therapy			x	x	x	x	x	x

Test	Screen	Baseline (Preop)	1 day postop	2 weeks postop	3 months postop	6 months postop	1 year Postop	Annually (M24-M120)
Thyroid hormone withdrawal or recombinant TSH for stim-Tg					x		x[6]	
DxWBS					x[5]		x[5]	
Urine or Serum Pregnancy Test		x						
Advance Directive (NIH only)[4]		x						

1. Intact PTH, Chemistries including Calcium, albumin, ionized calcium, inorganic phosphorous, thyroid function tests (except on day 1 postoperatively) and other labs as indicated.
2. Flexible laryngoscopy can be performed within 2 weeks after surgery, if it cannot be performed in the first day postoperatively
3. Only if vocal cord abnormalities are found on postoperative day 1flexible laryngoscopy.
4. As indicated in Section **9.3,** all subjects will be offered the opportunity to complete an NIH advance directives form. This should be done preferably at baseline but can be done at any time during the study as long as the capacity to do so is retained. The completion of the form is strongly recommended, but is not required
5. Optional for participating sites

3.3 SURGICAL GUIDELINES

Patients who are randomized to receive TT and pCND will undergo standard TT. pCND will be performed on the ipsilateral side to the dominant tumor by removal of lymphoid and fibrofatty tissue from the hyoid area to the innominate/subclavian vessels and from ipsilateral common carotid sheath medially, including the pretracheal and ipsilateral paraesophageal lymph nodes. If participant has bilateral biopsy-proven PTC, bilateral pCND will be performed in those who are randomized to receive TT and pCND. Care will be taken to preserve the parathyroid glands and their blood supply. If the parathyroid gland is devascularized, it will be autotransplanted into the sternocleidomastoid muscle pocket.

Uniform postoperative care and monitoring will be provided to participants in both groups equally.

3.3.1 Postoperative Care

3.3.1.1 Postoperative day 1, participants will be seen in-house and will:

a. Fill out the following questionnaires.
   - QOL using SF-36 v2 questionnaire
   - Neck pain (scale 0 (no pain) to 10 (unimaginable, unspeakable pain))
   - Voice quality using Voice Handicap Index-10 questionnaire
   - Swallowing symptoms using Swallowing Impairment Score (SIS-6) questionnaire

b. Undergo flexible laryngoscopy to assess vocal cord functions. This can be performed within 2 weeks postoperatively, if it cannot be done on the first postoperative day.

c. Receive laboratory evaluation at 6 hours postoperatively and AM of postoperative day 1which includes Calcium total, Ionized Calcium, Magnesium total (Mg), Inorganic Phosphorus, and intact PTH.

d. Receive thyroid replacement therapy per standard of care.

3.3.1.2 Two weeks postoperatively (± 2 days), participants will be seen in clinic and will

a. Fill out the following questionnaires.
   - QOL using SF-36 v2 questionnaire
   - Neck pain (scale 0 (no pain) to 10 (unimaginable, unspeakable pain))
   - Voice quality using Voice Handicap Index-10 questionnaire
   - Swallowing symptoms using Swallowing Impairment Score (SIS-6) questionnaire

b. Receive laboratory evaluation prior to a clinic visit which includes Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Ionized Calcium, Magnesium total (Mg), Inorganic Phosphorus, and intact PTH.

c. Have index tumor from pathology specimen tested for *BRAF* V600E mutation in either the Clinical Center Laboratory or the laboratory of the participating site

d. Undergo flexible laryngoscopy, if clinically indicated.

e. Receive TSH suppression therapy, if indicated, per standardized protocol (
f. **Table** 2)

3.3.1.3 Three months postoperatively (± 2 weeks)

- To assess the primary endpoint of the study, all participants will be seen in clinic, and will either receive recombinant TSH injections or start thyroid hormone withdrawal.
- Participants will be evaluated by endocrinology service for stim-Tg measurement and DxWBS per standardized protocol (optional in patients enrolled at non-NIH site):

a. Laboratory evaluation includes: (stimulated) Tg, anti-thyroglobulin antibodies, TSH, FT4, T3, Calcium total, Ionized Calcium, Magnesium total (Mg), Inorganic Phosphorus, and intact PTH.
b. DxWBS or RAI with post therapy scan will be performed as needed. If DxWBS is indicated patients should start and maintain a low iodine diet two weeks prior to the scan.
c. Baseline neck USG.
d. QOL using SF-36 v2 questionnaire

3.3.1.4 Six months postoperatively (± 2 weeks), participants will be seen in clinic and will

a. Fill out the following questionnaires.
   - QOL using SF-36 v2 questionnaire
   - Neck pain (scale 0 (no pain) to 10 (unimaginable, unspeakable pain))
   - Voice quality using Voice Handicap Index-10 questionnaire
   - Swallowing symptoms using Swallowing Impairment Score (SIS-6) questionnaire
b. Undergo flexible laryngoscopy only if there were impaired vocal cord function(s) on postoperative day 1 or 2.
c. Receive laboratory evaluation which includes CBC with differential, Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Ionized Calcium, Magnesium total (Mg), Inorganic Phosphorus, TSH, FT4, T3, Tg, anti-thyroglobulin antibodies, and intact PTH.
d. Undergo soft tissue neck USG. Any suspicious lymph node(s) or lesion(s) will be biopsied for cytology and Tg wash.

3.3.1.5 One year postoperatively (± 2 weeks) for participants who do not receive remnant ablation **or one year post-remnant ablation**, they will be seen in clinic and

a. Participants who undergo remnant ablation will either receive recombinant TSH for 2 consecutive days or will undergo thyroid hormone withdrawal for 4 weeks, followed by laboratory evaluation. Participants who do not undergo remnant ablation will receive only recombinant TSH for 2 consecutive days, followed by laboratory evaluation which includes Sodium (Na), Potassium (K), Chloride (Cl), Total CO2 (bicarbonate), Creatinine, Glucose, Urea nitrogen (BUN), Albumin, Calcium total, Ionized Calcium, Magnesium total (Mg), Inorganic Phosphorus, TSH, FT4, T3, Tg (stimulated), anti-thyroglobulin antibodies. Recombinant TSH-stimulated thyroglobulin is optional in patients enrolled at non-NIH site.
b. Iodine free 24hr urine collection
c. DxWBS will be performed in all participants enrolled at NIH Clinical Center and is optional in patients enrolled at non-NIH site. Patients must start and maintain a low iodine diet two weeks prior to the scan.

d. All participants will undergo soft tissue neck USG. Any suspicious lymph node(s) will be biopsied if clinically indicated.
e. Participant who develops elevated unstimulated or stimulated Tg with or without suspicious neck lesion on USG will undergo metastatic work up per 2009 ATA guidelines (11) (**Appendix F**).
f. QOL using SF-32 v2 questionnaire.

3.3.2 Recurrent Disease

Surveillance for persistent or recurrence disease will be performed every year for 10 years. The study blind will be broken after the 10 year visit unless medically necessary for the patient's continued care. Work up includes:

a. Detailed history and physical examination in clinic.
b. Calcium total, Ionized Calcium, Magnesium total (Mg), Inorganic Phosphorus, TSH, Tg (while on levothyroxine), anti-thyroglobulin antibodies.
c. Soft tissue neck USG.
d. Other radiographic imaging or nuclear scintigraphy as clinically indicated.
e. QOL using SF-36 v2 questionnaire will be assessed at 5 and 10 years postoperatively.

3.3.3 Off Study Criteria

- Absence of thyroid cancer in final pathology
- Participant requests to be withdrawn from study
- Completion of 10-year assessment
- Lost to follow-up
- Investigator discretion
- Screen failure
- Death

3.3.4 Off Protocol Therapy and Off-Study Procedure

Authorized staff must notify Central Registration Office (CRO) when a subject is taken off protocol therapy and when a subject is taken off-study. A Participant Status Updates Form from the web site (http://home.ccr.cancer.gov/intra/eligibility/welcome.htm) main page must be completed and sent via encrypted email to: NCI Central Registration Office ncicentralregistration-l@mail.nih.gov.

For participating sites:

The Participant Status Updates Form will be supplied by the CCR study coordinator. Send the completed form to the CCR study coordinator.

4 BIOSPECIMEN COLLECTION

4.1 CORRELATIVE STUDIES FOR RESEARCH

Patients will be co-enrolled on protocol 09-C-0242. Biospecimens will be collected as specified in protocol 09-C-0242.

For participating sites:

Biospecimens will not be collected at participating sites.

5 DATA COLLECTION AND EVALUATION

5.1 DATA COLLECTION

The PI at each site will be responsible for overseeing entry of data into a password protected electronic system (NCI C3D) and ensuring data accuracy, consistency and timeliness. Clinical data will be entered into the NCI C3D at least once every two weeks when patients are enrolled on the trial. Protocol-specific eCRFs will be developed for this trial in C3D. The principal investigator, associate investigators/research nurses and/or a contracted data manager will assist with the data management efforts. All data obtained during the conduct of the protocol will be kept in secure network drives or in approved alternative sites that comply with NIH security standards. Primary and final analyzed data will have identifiers so that research data can be attributed to an individual human subject participant.

The NCI investigators will be responsible for the collection, maintenance, and quality control of the study data.

End of study procedures: Data will be stored according to HHS, FDA regulations and NIH Intramural Records Retention Schedule as applicable.

Loss or destruction of data: Should we become aware that a major breach in our plan to protect subject confidentiality and trial data has occurred, the IRB will be notified.

5.1.1 Data Quality Assurance

The research team will monitor each patient's dataset throughout the study. Source document review will be made against entries on the eCRF and a quality assurance check will be performed to ensure that the investigator is complying with the protocol and regulations. In addition, after the research team (data managers) completes the CRFs a research nurse or physician at the NCI will review and verify the data.

5.2 DATA SHARING PLANS

5.2.1 Human Data Sharing Plan

What data will be shared?

I will share human data generated in this research for future research as follows:

- Coded, linked data in an NIH-funded or approved public repository.
- Coded, linked data in BTRIS (automatic for activities in the Clinical Center)

- Identified or coded, linked data with approved participating sites under appropriate agreements.

How and where will the data be shared?

Data will be shared through:

- An NIH-funded or approved public repository, clinicaltrials.gov
- BTRIS (automatic for activities in the Clinical Center)
- Publication and/or public presentations.

When will the data be shared?

- Before publication.
- At the time of publication or shortly thereafter.

5.3 TOXICITY CRITERIA

The following adverse event management guidelines are intended to ensure the safety of each patient while on the study. The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40).

6 SAFETY REPORTING REQUIREMENTS/DATA AND SAFETY MONITORING PLAN

No experimental treatments or procedures are performed as a part of this protocol and therefore no adverse events are expected. In the unlikely event that an adverse event occurs that is attributable to the research, CTCAE v. 4.0 will be used for grading such events. Patients who meet the standard of care criteria for resection of their disease will undergo a major operative procedure and may receive extensive care in the ICU. The principal investigator or designee will closely monitor and document the clinical care and treatment of each patient as per standard of care at the NIH Clinical Center. As per NIH Clinical Center standards of practice, the Occurrence Reporting System will be used to report any clinical events meeting these reporting criteria.

6.1 DEFINITIONS

6.1.1 Adverse Event

Any untoward medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

6.1.2 Suspected adverse reaction

Suspected adverse reaction means any adverse event for which there is a reasonable possibility that the research procedure caused the adverse event. For the purposes of safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the research procedure and the adverse event. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a research procedure.

6.1.3 Unexpected adverse reaction

An adverse event or suspected adverse reaction is considered "unexpected" if it is not consistent with the risk information described in the general investigational plan or elsewhere in the current application.

6.1.4 Serious

An Unanticipated Problem or Protocol Deviation is serious if it meets the definition of a Serious Adverse Event or if it compromises the safety, welfare or rights of subjects or others.

6.1.5 Serious Adverse Event

An adverse event or suspected adverse reaction is considered serious if in the view of the investigator or the sponsor, it results in any of the following:

- Death,
- A life-threatening adverse drug experience
- Inpatient hospitalization or prolongation of existing hospitalization
- Persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect.
- Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

6.1.6 Disability

A substantial disruption of a person's ability to conduct normal life functions.

6.1.7 Protocol Deviation (NIH Definition)

Any change, divergence, or departure from the IRB-approved research protocol.

6.1.8 Non-compliance (NIH Definition)

The failure to comply with applicable NIH Human Research Protections Program (HRPP) policies, IRB requirements, or regulatory requirements for the protection of human research subjects.

6.1.9 Unanticipated Problem

Any incident, experience, or outcome that:

- Is unexpected in terms of nature, severity, or frequency in relation to

  (a) the research risks that are described in the IRB-approved research protocol and informed consent document; Investigator's Brochure or other study documents, and

  (b) the characteristics of the subject population being studied; **AND**
- Is related or possibly related to participation in the research; **AND**
- Suggests that the research places subjects or others at a *greater risk of harm* (including physical, psychological, economic, or social harm) than was previously known or recognized.

6.2 NIH INTRAMURAL IRB AND CLINICAL DIRECTOR REPORTING

6.2.1 NIH Intramural IRB and NCI CD Expedited Reporting of Unanticipated Problems and Deaths

The Protocol PI will report in the NIH Problem Form to the NIH Intramural IRB and NCI Clinical Director:

- All deaths, except deaths due to progressive disease
- All Protocol Deviations
- All Unanticipated Problems
- All non-compliance

Reports must be received within 7 days of PI awareness via iRIS.

6.2.2 NIH Intramural IRB Requirements for PI Reporting at Continuing Review

The protocol PI will report to the NIH Intramural IRB:

1. A summary of all protocol deviations in a tabular format to include the date the deviation occurred, a brief description of the deviation and any corrective action.
2. A summary of any instances of non-compliance
3. A tabular summary of the following adverse events:
   - All Grade 2 **unexpected** events that are possibly, probably or definitely related to the research;
   - All Grade 3 and 4 events that are possibly, probably or definitely related to the research;
   - All Grade 5 events regardless of attribution;
   - All Serious Events regardless of attribution.

   NOTE: Grade 1 events are not required to be reported.

6.3 NCI GUIDANCE FOR REPORTING EXPEDITED ADVERSE EVENTS FOR MULTI-CENTER TRIALS

The site PI must immediately report to the coordinating center PI any serious adverse event, whether or not considered treatment related, including those listed in the protocol and must include an assessment of whether there is a reasonable possibility that the treatment caused the event within 24 hours of PI awareness of the event. The site PI will use CCR Problem report form (**Appendix I**). The Site PI must also report any protocol deviations to the coordinating center PI within 7 days of PI awareness. Participating centers must also submit the report to their IRB in accordance with their institutional policies.

6.4 DATA AND SAFETY MONITORING PLAN

6.4.1 Principal Investigator/Research Team

The clinical research team will meet on a regular basis when patients are being actively treated on the trial to discuss each patient. Decisions about dose level enrollment and dose escalation if applicable will be made based on the toxicity data from prior patients.

All data will be collected in a timely manner and reviewed by the principal investigator or a lead associate investigator. Adverse events will be reported as required above. Any safety concerns, new information that might affect either the ethical and or scientific conduct of the trial, or protocol deviations will be immediately reported to the IRB using iRIS.

The principal investigator will review adverse event and response data on each patient to ensure safety and data accuracy. The principal investigator will personally conduct or supervise the investigation and provide appropriate delegation of responsibilities to other members of the research staff.

6.4.2 Data Safety Monitoring Board (DSMB)

This protocol requires monitoring by the NCI CCR Data Safety Monitoring Board (DSMB) as described in Section 7. Interim outcome results will not be revealed to the investigators of the trial; results will be presented to the investigators prior to final accrual to the trial only if the DSMB recommends early termination of the trial.

7 STATISTICAL CONSIDERATIONS

The primary goal of this study is to determine if there is a difference in biochemical cure rates based on postoperative stimulated thyroglobulin levels (stim-Tg) at 3 months, primarily focusing on the rates of athyroglobulinemia, in patients with clinically node negative PTC undergoing TT and with and without pCND. Serum Tg, especially when TSH-stimulated, is a very sensitive and specific marker for residual thyroid tissue, persistent or recurrent differentiated thyroid cancer of follicular cell origin, in the absence of anti-Tg antibodies. Because patients with differentiated thyroid cancer whose Tg and/or stim-Tg becomes undetectable after treatment(s) are typically considered free of disease in the absence of radiographic evidence of tumor, we use athyroglobulinemia as a surrogate for biochemical remission. We conservatively estimate that there should be at least a 20% higher rate of athyroglobulinemia in patients undergoing TT and pCND (θ_2 =0.4) compared to TT alone (θ_1=0.2) during early postoperative period. With a total of 180 evaluable participants (approximately n=90 for each arm) who have no anti-thyroglobulin

antibody, the trial will have 80% power (beta=0.20) to detect the difference between 0.2 and 0.4 using a Fisher's exact test with two-sided significance level (alpha) of 0.05.

The protocol will not have any stratification at the time of randomization because there are no known factors associated with athyroglobulinemia. Because this study only enrolls patients with low-risk PTC, it is unlikely that there would be many patients with advanced age and advanced PTC that may be unevenly distributed which may confound with the results of the study.

This study will be monitored by the NCI/CCR Data Safety and Monitoring Board, both for toxicity as well as efficacy and futility with respect to the primary endpoint.

Beginning in the first spring after twenty total patients have been randomized and treated on the trial, the study will be monitored by the DSMB on an annual basis to evaluate the safety of the two arms. The SAEs (typically grade 3 toxicities, or greater) will be reported according to type of toxicity, and maximal grade noted per patient, for toxicities with at least a possible attribution to the therapy provided on that arm. Comparisons will be made between the two arms using a Cochran-Armitage test for trend, or other appropriate methods, to determine if there is increased toxicity associated with either arm.

In addition, at the first DSMB meeting held following the point at which half of the required total subjects have been enrolled and evaluated, an interim evaluation for greater than expected difference in fractions with athyroglobulinemia will be performed. Specifically, after 90 total patients who do not have anti-thyroglobulin antibody have been evaluated, using an O'Brien-Fleming approach, if the two-tailed p-value for a comparison of the two rates is <0.0054, then the trial will be stopped at that time and a significant difference declared. While invoking this boundary at an interim point will technically require that the final p-value be 0.0492 or less for the overall significance level to be retained at a 0.05 level, as a practical matter, $p<0.05$ will still be required to declare a significant result.

In addition, a single interim evaluation for futility will also take place after 90 evaluable patients accrued. At the same DSMB meeting as the single interim evaluation for efficacy, the study will be evaluated for futility as follows: if the fraction with athyroglobulinemia on the arm with TT + pCND is identical to or lower than that of the TT alone arm, then accrual will stop because of very small probability of achieving a statistically significant difference in favor of the combination arm if the trial were to be completed.

Data on QOL, swallowing and pain will be collected at baseline and at several postoperative time points indicated using the tools described in the protocol. Changes from baseline to the postoperative values will be determined, normally by subtraction, and the resulting changes over time will be compared between the two randomized arms using appropriate non-parametric tests such as a Wilcoxon rank sum test. Other statistical methods may be used as appropriate for the data obtained. As these are secondary evaluations, the results will not be formally adjusted for multiple comparisons, but any results with p-values <0.05 may be interpreted as needed in the context of the number of such tests being performed.

The trial will have an accrual ceiling of 225 participants in order to allow for a 20% rate of patients with PTC that have anti-thyroglobulin antibody, [86-88] which limits the use of postoperative Tg and stim-Tg and thus cannot be included in the 180 required for evaluation. It is anticipated that accrual time will be approximately 6 to 7 years as the investigators currently

perform 25-30 cases of preoperative suspicious or confirmed PTC per year and anticipate a higher accrual rate once the protocol is open and publicized.

8 COLLABORATIVE AGREEMENTS

8.1 MULTI-INSTITUTIONAL GUIDELINES

8.1.1 IRB Approvals

The PI will provide the NIH Intramural IRB with a copy of the participating institution's approved yearly continuing review. Registration will be halted at any participating institution in which a current continuing approval is not on file at the NIH Intramural IRB.

8.1.2 Amendments and Consents

The CCR PI will provide the NIH Intramural IRB with copies of all amendments, consents and approvals from each participating institution.

9 HUMAN SUBJECTS PROTECTIONS

9.1 RATIONALE FOR SUBJECT SELECTION

All participants who meet the eligibility criteria will be enrolled regardless of gender, race, ethnicity or other socioeconomic or demographic factors. However, the cohort is expected to comprise predominantly female participants as the incidence of thyroid cancer is higher in women.

9.2 PARTICIPATION OF CHILDREN

Because PTC is rare in children and presents at more advanced stage, we will exclude children (age <18 years) from the study to ensure that our cohort represents the majority of patients with PTC.

9.3 PARTICIPATION OF SUBJECTS UNABLE TO GIVE CONSENT (FOR NCI ONLY)

Adults unable to give consent are excluded from enrolling in the protocol. However re-consent may be necessary and there is a possibility, though unlikely, that subjects could become decisionally impaired. For this reason and because there is a prospect of direct benefit from research participation (Section **9.4**) all subjects will be offered the opportunity to fill in their wishes for research and care, and assign a substitute decision maker on the "NIH Advance Directive for Health Care and Medical Research Participation" form so that another person can make decisions about their medical care in the event that they become incapacitated or cognitively impaired during the course of the study.

Patients may experience personal benefit even during the follow-up period because they will be closely monitored and treated as needed.

Note: The PI or AI will contact the NIH Ability to Consent Assessment Team (ACAT) for evaluation as needed for the following: an independent assessment of whether an individual has the capacity to provide consent; assistance in identifying and assessing an appropriate surrogate when indicated; and/or an assessment of the capacity to appoint a surrogate For those subjects that become incapacitated and do not have pre-determined substitute decision maker, the procedures described in MAS Policy 87-4 and NIH HRPP SOP 14E for appointing a surrogate

decision maker for adult subjects who are (a) decisional impaired, and (b) who do not have a legal guardian or durable power of attorney, will be followed.

9.4 Evaluation of Benefits and Risks/Discomforts

Participants will likely experience direct benefit from the study because all will undergo total thyroidectomy for PTC which is considered a standard of care. Furthermore, there is the potential reduction in locoregional recurrence rate in those undergoing pCND.

Risks and discomforts that participants will experience are from the surgical procedures (TT with or without pCND) and their complications, which are the standard of care. These include, but not limited to, postoperative pain, surgical site bleeding or infection, voice and/or swallowing impairment with or without recurrent laryngeal nerve injury or external branch of superior laryngeal nerve injury, symptoms of hypocalcemia and discomforts from the treatment of hypoparathyroidism. Participants will like require 1 week of recovery before returning to work or routine daily activities with minimal restriction. These benefits and risks will be discussed in details with all participants. In addition, participants who require thyroid hormone withdrawal in preparation for RAI will experience symptoms of hypothyroidism up to 4 weeks prior to treatment. Those with low-risk for recurrence who require rhTSH in preparation for RAI will experience discomfort from injection sites. All of these are related to the standard of car of any patients with PTC.

9.5 Risks/Benefits Analysis for All Patients

The main risk of participation is related to the risk of complications from pCND. The addition of pCND to thyroidectomy is still considered a safe procedure with less than 1% of major complications. The transient hypoparathyroidism can occur up to 25% of patients undergoing TT and pCND, most patients are asymptomatic once the calcium replacement therapy is optimized. Permanent hypoparathyroidism following pCND occurs less than 1%. The benefit of pCND in addition to TT may include a reduction in disease recurrence.

Patients who receive TT and pCND may be upstaged may be more likely to receive RAI due to the discovery of a subclinical lymph node metastasis. The risks of RAI include temporary dry mouth, dry eyes, loss or change of taste, and may have increased risk of second primary cancers in young adults. (92) However, the benefits would outweigh the risks in participants at risk for recurrence.

9.6 Consent Process and Documentation

Each procedure/test that the patient will undergo will be explained to the patient, and the associated risks and benefits will be reviewed prior to the intervention. Participants must be able to give informed consent. The consent form will be kept in the participant's permanent medical record. The Principal Investigator, research nurse, or associate investigator is responsible for completing the consent process and a copy of the consent is offered to the patient. It will be stated clearly that participation in the research study is voluntary and that participants can withdraw from the study without losing benefits they would otherwise be entitled to. Participants will be enrolled after the consent document has been signed. Separate consents will be obtained for all surgical procedures. Because all participants will not know the results of randomization, initial consent would indicate a possibility of CND.

9.6.1 Procedure for Reconsent via Telephone

The informed consent document will be sent to the subject. An explanation of the study will be provided over the telephone after the subject has had the opportunity to read the consent form. The subject will sign and date the informed consent. A witness to the subject's signature will sign and date the consent.

The original informed consent document will be sent back to the consenting investigator who will sign and date the consent form with the date the consent was obtained via telephone.

A fully executed copy will be returned via mail for the subject's records.

The informed consent process will be documented on a progress note by the consenting investigator and a copy of the informed consent document and note will be kept in the subject's research record.

9.6.2 Informed consent of non-English Speaking Subjects (NCI Only)

We anticipate the enrollment of Spanish speaking research participants into our study. The IRB approved full consent document will be translated into that language in accordance with the Clinical MAS Policy M77-2.

If there is an unexpected enrollment of a research participant for whom there is no translated extant IRB approved consent document, the principal investigator and/or those authorized to obtain informed consent will use the Short Form Oral Consent Process as described in MAS Policy M77-2, OHSRP SOP 12 and 45 CFR 46.117 (b) (2). The summary that will be used is the English version of the extant IRB approved consent document. Signed copies of both the English version of the consent and the translated short form will be given to the subject or their legally authorized representative and the signed original will be filed in the medical record.

Unless the PI is fluent in the prospective subject's language, an interpreter will be present to facilitate the conversation (using either the long translated form or the short form). Preferably someone who is independent of the subject (i.e., not a family member) will assist in presenting information and obtaining consent. Whenever possible, interpreters will be provided copies of the relevant consent documents well before the consent conversation with the subject (24 to 48 hours if possible).

We request prospective IRB approval of the use of the short form process for non-English speaking subjects and will notify the IRB at the time of continuing review of the frequency of the use of the Short Form.

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11 APPENCIES

11.1 APPENDIX A: VOICE HANDICAP INDEX-10

		0	1	2	3	4
1	My voice makes it difficult for people to hear me.					
2	People have difficulty understanding me in a noisy room.					
3	My voice difficulties restrict personal and social life.					
4	I feel left out of conversations because of my voice.					
5	My voice problem causes me to lose income.					
6	I feel as though I have to strain to produce voice.					
7	The clarity of my voice is unpredictable.					
8	My voice problem upsets me.					
9	My voice makes me feel handicapped.					
10	People ask, “What’s wrong with your voice?”					

11.2 APPENDIX B: SWALLOWING IMPAIRMENT SCALE (SIS-6)

		0	1	2	3	4
1.	It requires great effort to swallow					
2.	I feel a throat obstacle during swallowing					
3.	I feel pharyngeal annoyance during bolus transit					
4.	I cough during bolus transit					
5.	I feel a sensation of a foreign body in my pharynx					
6.	I have some difficulties swallowing fluids					

11.3 APPENDIX C: SF 36 HEALTH SURVEY

SF36 Health Survey

INSTRUCTIONS: This set of questions asks for your views about your health. This information will help keep track of how you feel and how well you are able to do your usual activities. Answer every question by marking the answer as indicated. If you are unsure about how to answer a question please give the best answer you can.

1. In general, would you say your health is: (Please tick **one** box.)
   - Excellent ☐
   - Very Good ☐
   - Good ☐
   - Fair ☐
   - Poor ☐

2. Compared to one year ago, how would you rate your health in general now? (Please tick **one** box.)
   - Much better than one year ago ☐
   - Somewhat better now than one year ago ☐
   - About the same as one year ago ☐
   - Somewhat worse now than one year ago ☐
   - Much worse now than one year ago ☐

3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much? **(Please circle one number on each line.)**

	Activities	Yes, Limited A Lot	Yes, Limited A Little	Not Limited At All
3(a)	**Vigorous activities**, such as running, lifting heavy objects, participating in strenuous sports	1	2	3
3(b)	**Moderate activities**, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	1	2	3
3(c)	Lifting or carrying groceries	1	2	3
3(d)	Climbing **several** flights of stairs	1	2	3
3(e)	Climbing **one** flight of stairs	1	2	3
3(f)	Bending, kneeling, or stooping	1	2	3
3(g)	Waling **more than a mile**	1	2	3
3(h)	Walking **several blocks**	1	2	3
3(i)	Walking **one block**	1	2	3
3(j)	Bathing or dressing yourself	1	2	3

4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health? **(Please circle one number on each line.)**

		Yes	No
4(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
4(b)	Accomplished less than you would like	1	2
4(c)	Were **limited** in the **kind** of work or other activities	1	2
4(d)	Had **difficulty** performing the work or other activities (for example, it took extra effort)	1	2

5. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (e.g. feeling depressed or anxious)? **(Please circle one number on each line.)**

		Yes	No
5(a)	Cut down on the **amount of time** you spent on work or other activities	1	2
5(b)	Accomplished less than you would like	1	2
5(c)	Didn't do work or other activities as **carefully** as usual	1	2

6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbours, or groups? (Please tick **one** box.)

- Not at all ☐
- Slightly ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

7. How much physical pain have you had during the past 4 weeks? (Please tick **one** box.)

- None ☐
- Very mild ☐
- Mild ☐
- Moderate ☐
- Severe ☐
- Very Severe ☐

8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)? (Please tick **one** box.)

- Not at all ☐
- A little bit ☐
- Moderately ☐
- Quite a bit ☐
- Extremely ☐

9. These questions are about how you feel and how things have been with you during the past 4 weeks. Please give the one answer that is closest to the way you have been feeling for each item.

	(Please circle one number on each line.)	**All of the Time**	**Most of the Time**	**A Good Bit of the Time**	**Some of the Time**	**A Little of the Time**	**None of the Time**
9(a)	Did you feel full of life?	1	2	3	4	5	6
9(b)	Have you been a very nervous person?	1	2	3	4	5	6
9(c)	Have you felt so down in the dumps that nothing could cheer you up?	1	2	3	4	5	6
9(d)	Have you felt calm and peaceful?	1	2	3	4	5	6
9(e)	Did you have a lot of energy?	1	2	3	4	5	6
9(f)	Have you felt downhearted and blue?	1	2	3	4	5	6
9(g)	Did you feel worn out?	1	2	3	4	5	6
9(h)	Have you been a happy person?	1	2	3	4	5	6
9(i)	Did you feel tired?	1	2	3	4	5	6

10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting with friends, relatives etc.) (Please tick **one** box.)

- All of the time ☐
- Most of the time ☐
- Some of the time ☐
- A little of the time ☐
- None of the time ☐

11. How TRUE or FALSE is each of the following statements for you?

	(Please circle one number on each line.)	**Definitely True**	**Mostly True**	**Don't Know**	**Mostly False**	**Definitely False**
11(a)	I seem to get sick a little easier than other people	1	2	3	4	5
11(b)	I am as healthy as anybody I know	1	2	3	4	5
11(c)	I expect my health to get worse	1	2	3	4	5
11(d)	My health is excellent	1	2	3	4	5

Thank You!

11.4 APPENDIX D: BETHESDA SYSTEM FOR REPORTING THYROID CYTOPATHOLOGY

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

Diagnostic Category	Risk of Malignancy (%)	Usual Management[†]
Nondiagnostic or Unsatisfactory	1-4	Repeat FNA with ultrasound guidance
Benign	0-3	Clinical follow-up
Atypia of Undetermined Significance or Follicular Lesion of Undetermined Significance	~5-15[‡]	Repeat FNA
Follicular Neoplasm or Suspicious for a Follicular Neoplasm	15-30	Surgical lobectomy
Suspicious for Malignancy	60-75	Near-total thyroidectomy or surgical lobectomy[§]
Malignant	97-99	Near-total thyroidectomy[§]

FNA, fine-needle aspiration.
[*] Adapted with permission from Ali and Cibas.[3]
[†] Actual management may depend on other factors (eg, clinical, sonographic) besides the FNA interpretation.
[‡] Estimate extrapolated from histopathologic data from patients with "repeated atypicals."
[§] In the case of "Suspicious for metastatic tumor" or a "Malignant" interpretation indicating metastatic tumor rather than a primary thyroid malignancy, surgery may not be indicated.

11.5 APPENDIX E: REVISED AMERICAN THYROID ASSOCIATION MANAGEMENT GUIDELINES FOR FINE NEEDLE ASPIRATION OF THYROID NODULE

TABLE 3. SONOGRAPHIC AND CLINICAL FEATURES OF THYROID NODULES AND RECOMMENDATIONS FOR FNA

Nodule sonographic or clinical features	*Recommended nodule threshold size for FNA*
High-risk history[a]	
Nodule WITH suspicious sonographic features[b]	>5 mm Recommendation A
Nodule WITHOUT suspicious sonographic features[b]	>5 mm Recommendation I
Abnormal cervical lymph nodes	All[c] Recommendation A
Microcalcifications present in nodule	≥1 cm Recommendation B
Solid nodule	
AND hypoechoic	>1 cm Recommendation B
AND iso- or hyperechoic	≥1–1.5 cm Recommendation C
Mixed cystic–solid nodule	
WITH any suspicious ultrasound features[b]	≥1.5–2.0 cm Recommendation B
WITHOUT suspicious ultrasound features	≥2.0 cm Recommendation C
Spongiform nodule	≥2.0 cm[d] Recommendation C
Purely cystic nodule	FNA not indicated[e] Recommendation E

[a]High-risk history: History of thyroid cancer in one or more first degree relatives; history of external beam radiation as a child; exposure to ionizing radiation in childhood or adolescence; prior hemithyroidectomy with discovery of thyroid cancer, ^{18}FDG avidity on PET scanning; MEN2/FMTC-associated RET protooncogene mutation, calcitonin >100 pg/mL. MEN, multiple endocrine neoplasia; FMTC, familial medullary thyroid cancer.
[b]Suspicious features: microcalcifications; hypoechoic; increased nodular vascularity; infiltrative margins; taller than wide on transverse view.
[c]FNA cytology may be obtained from the abnormal lymph node in lieu of the thyroid nodule.
[d]Sonographic monitoring without biopsy may be an acceptable alternative (see text) (48).
[e]Unless indicated as therapeutic modality (see text).

11.6 APPENDIX F: ALGORITHM FOR MANAGEMENT OF DIFFERENTIATED THYROID CANCER AT 1 YEAR AFTER RAIREMNAT ABLATION [11]

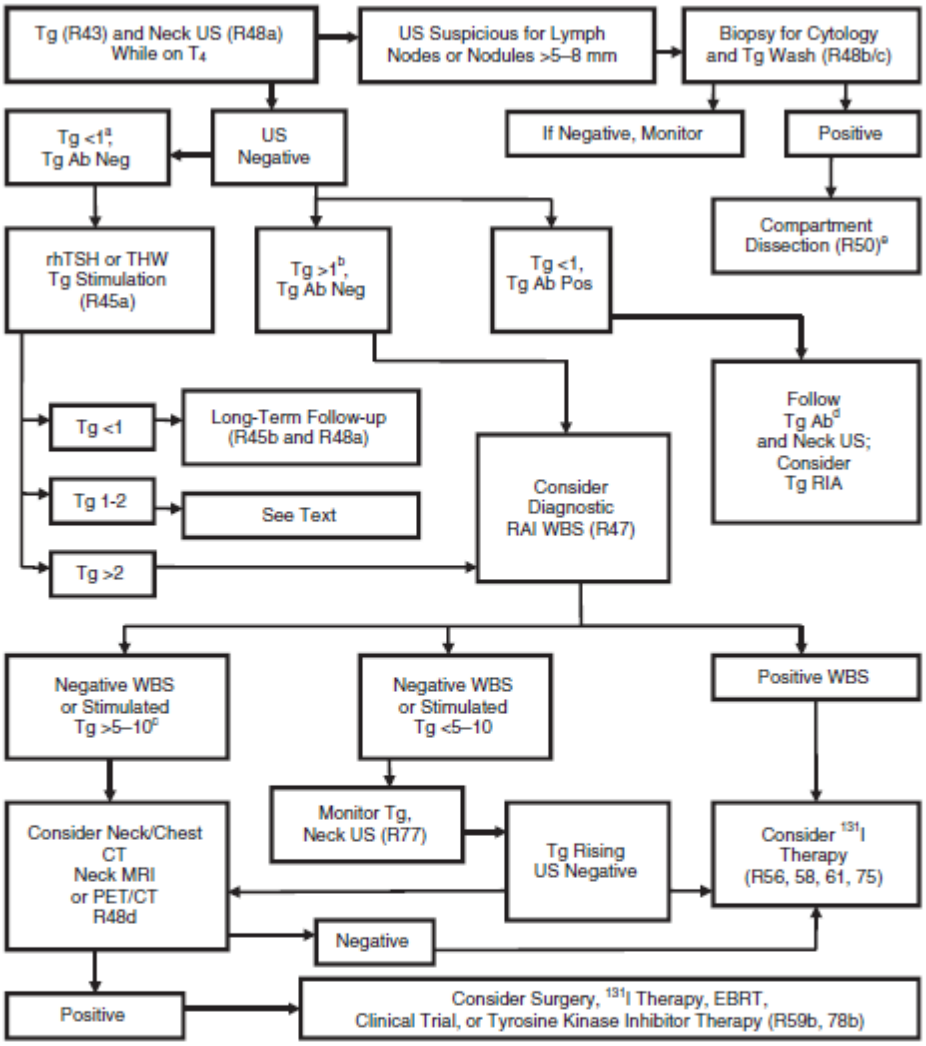
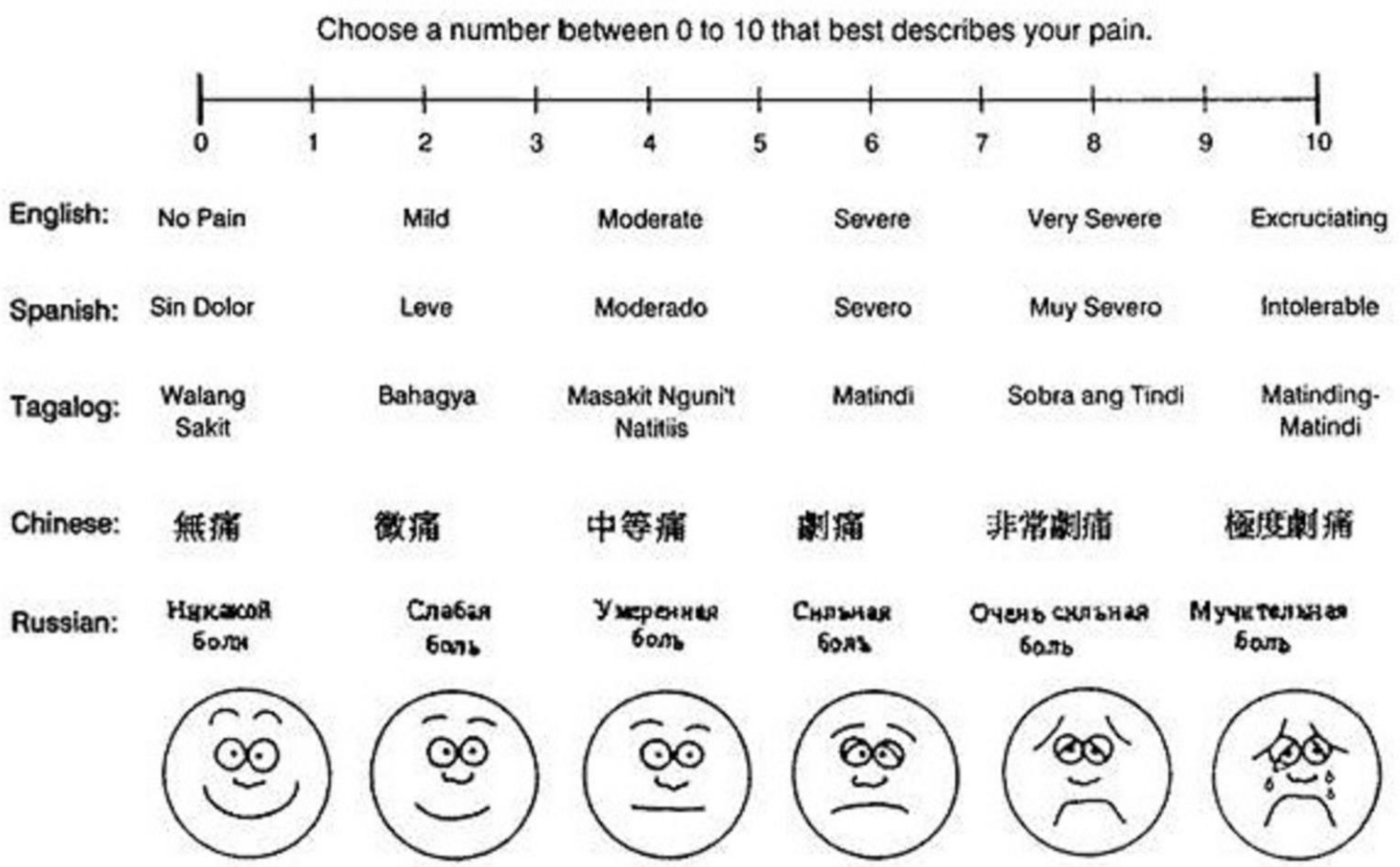


FIG. 4. Longer term follow-up of patients with differentiated thyroid carcinoma.
[a]TgAb is anti-thyroglobulin antibody usually measured by immunometric assay.
[b]Heterophile antibodies may be a cause of falsely elevated serum Tg levels (436,437). The use of heterophile blocking tubes or heterophile blocking reagents have reduced, but not completely eliminated this problem. Tg that rises with TSH stimulation and falls with TSH suppression is unlikely to result from heterophile antibodies.
[c]See text concerning further information regarding levels of Tg at which therapy should be considered.
[d]Tg radioimmunoassay (RIA) may be falsely elevated or suppressed by TgAb. Tg results following TSH stimulation with rhTSH or thyroid hormone withdrawal are invalidated by TgAb in the serum even when Tg is measured by most RIA tests. TgAb levels often decline to undetectable levels over years following surgery (306). A rising level of TgAb may be an early indication of recurrent disease (305).
[e]See text for decision regarding surgery versus medical therapy, and surgical approaches to locoregional metastases. FNA confirmation of malignancy is generally advised. Preoperative chest CT is recommended as distant metastases may change management.

11.7 APPENDIX G: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		**Karnofsky Performance Scale**	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

11.8 APPENDIX H: NECK PAIN SCALE



11.9 APPENDIX I: CCR PROBLEM REPORT FORM

NCI Protocol #:	**Protocol Title:**
	Report version: *(select one)* ____Initial Report ____Revised Report ____Follow-up
Site Principal Investigator:	
Date of problem:	**Location of problem:** *(e.g., patient's home, doctor's office)*
Who identified the problem? *(provide role (not name of person): nurse, investigator, monitor, etc…)*	
Brief Description of Subject *(if applicable)* (*Do NOT include personal*	Sex: ___ Male ___ Female Age: ___ Not applicable (more than subject is involved)

identifiers)	
Diagnosis under study:	
Name the problem: *(select all that apply)* [ ] Adverse drug reaction [ ] Abnormal lab value [ ] Death [ ] Cardiac Arrest/ code [ ] Anaphylaxis [ ] Sepsis/Infection [ ] Blood product reaction [ ] Unanticipated surgery/procedure [ ] Change in status (e.g. increased level of care required) [ ] Allergy (non-medication) [ ] Fall [ ] Injury/Accident (not fall) [ ] Specimen collection issue [ ] Informed consent issue [ ] Ineligible for enrollment [ ] Breach of PII [ ] Tests/procedures not performed on schedule	

[ ] Other, brief 1-2 word description: _____ **Detailed Description of the problem:** (*Include any relevant treatment, outcomes or pertinent history*):
***Is this problem unexpected?** *(see the definition of unexpected in the protocol))* __YES __NO **Please explain:**
***Is this problem related or possibly related to participation in the research?** __YES __NO **Please explain:**
***Does the problem <u>suggest</u> the research places subjects or others at a greater risk of harm than was previously known or recognized?** __YES __NO **Please explain:**
Is this problem? (*select all that apply*) [ ] An Unanticipated Problem* that is: [ ] Serious [ ] Not Serious [ ] A Protocol Deviation that is: [ ] Serious [ ] Not Serious [ ] Non-compliance

**Note if the 3 criteria starred above are answered, "YES", then this event is also a UP.*
Is the problem also *(select one)* [ ] AE [ ] Non-AE
Have similar problems occurred on this protocol at your site? __YES __NO **If "Yes", how many? ____ Please describe:**
Describe what steps you have already taken as a result of this problem:
In addition to the NCI IRB, this problem is also being reported to: (*select all that apply*) [ ] Local IRB [ ] Study Sponsor [ ] Manufacturer : _____ [ ] Institutional Biosafety Committee [ ] Data Safety Monitoring Board [ ] Other: _____ [ ] None of the above, not applicable

INVESTIGATOR'S SIGNATURE:	**DATE:**