Comparative Effectiveness in Thyroid Cancer: Key Questions and How to Answer Them

Elliot A. Asare and Tracy S. Wang

Abstract

Controversies in treatment of thyroid cancer remain despite numerous published studies. Robust comparative effectiveness studies examining: (1) the role of prophylactic central compartment neck dissection (pCCND) in patients with papillary thyroid cancer (PTC); (2) the use of post-operative radioactive iodine (RAI) ablation therapy following total thyroidectomy; (3) use of low versus high doses of I-131 in RAI therapy; (4) thyroid hormone withdrawal (THW) versus recombinant thyroid stimulating hormone (rhTSH) prior to RAI; and (5) the role of routine measurement of serum calcitonin levels are needed to help strengthen existing treatment recommendations. Reasons for the controversies and suggestions for quality comparative effectiveness studies are discussed.

Keywords

Thyroid cancer · Prophylactic central compartment neck dissection · Recombinant thyroid stimulating hormone · Radioactive iodine ablation · Thyroid hormone withdrawal · Calcitonin · Thyroid nodules

Contents

E.A. Asare · T.S. Wang (✉)
Department of Surgery, Medical College of Wisconsin, Milwaukee, WI, USA
e-mail: tswang@mcw.edu

E.A. Asare
e-mail: easare@mcw.edu

K.Y. Bilimoria et al. (eds.), *Comparative Effectiveness in Surgical Oncology*,
Cancer Treatment and Research 164, DOI 10.1007/978-3-319-12553-4_5

1 Comparative Effectiveness in Thyroid Cancer: Key Questions and How to Answer Them

In the United States (U.S.), the prevalence of clinically palpable thyroid nodules in adults over age 50 is approximately 5 % [1]. Autopsy, intraoperative and ultrasound findings estimate the prevalence of thyroid nodules in adults in the U.S. at near 50 % [2–4]. The female to male prevalence ratio of thyroid nodules is 4:1, with most nodules being benign [1].

Thyroid cancer is the 9th most common cancer in the United States, with an incidence of 12.2 per 100,000 per year and a mortality rate of 0.5 per 100,000 [5]. The estimated lifetime risk of being diagnosed with thyroid cancer is 1.1 % and the relative 5-year survival is 97.7 % [5]. The three primary histologic types are differentiated (papillary, follicular, Hurthle cell), medullary, and anaplastic thyroid cancer. Papillary thyroid cancer (PTC) accounts for over 80 % of all cases of thyroid cancer [1, 6].

The absolute increase in the incidence of thyroid cancer is estimated to be 9.4 per 100,000 individuals, with PTC accounting for the majority of these cases [7]. With such a significant increase in the incidence of thyroid nodules and thyroid cancer, robust evidence-based guidelines to provide all providers with a framework for the management of the patient with thyroid cancer is critical. Topics in the treatment of differentiated thyroid cancer (DTC) where comparative effectiveness studies would help strengthen the level of evidence-based recommendations include: (1) the role of prophylactic central compartment neck dissection (pCCND) in patients with PTC; (2) the use of post-operative radioactive iodine (RAI) ablation therapy following total thyroidectomy; (3) use of low versus high doses of I-131 in RAI therapy; and (4) thyroid hormone withdrawal (THW) versus recombinant thyroid stimulating hormone (rhTSH) prior to RAI. The role of routine measurement of serum calcitonin levels in patients with thyroid nodules also will be discussed.

2 Prophylactic Central Compartment Neck Dissection (pCCND) for Papillary Thyroid Cancer

The incidence of macroscopic cervical lymph node metastases, detectable by physical examination, cervical ultrasonography, or visual inspection at the time of surgery, in patients with PTC is between 20 and 50 %, while the incidence of micrometastasis approaches 90 % [2]. The central neck compartment (level VI) is the most common site of lymph node metastases in patients with PTC [8, 9]. The central compartment is bounded by the hyoid bone (superior), carotid artery (lateral), sternal notch or innominate artery (inferior), Fig. 1 [10].

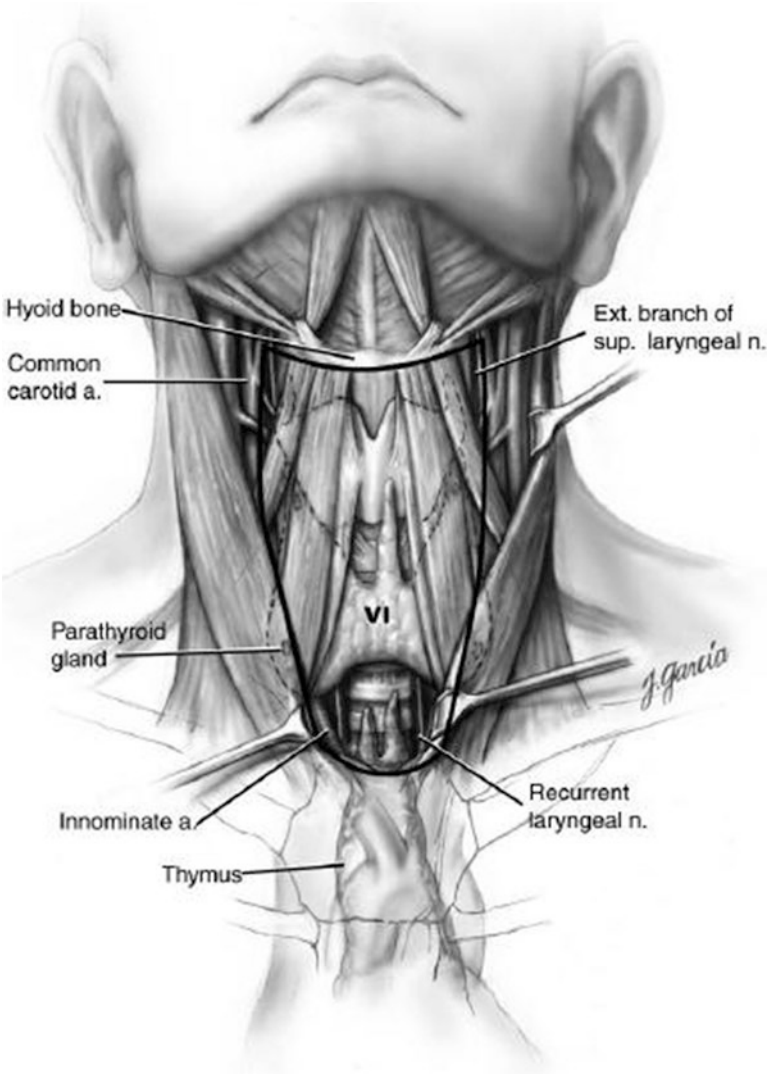

Fig. 1 The central compartment of the neck (reprinted with permission from Carty et al.) [10]

Table 1 Common prognostic factors for differentiated thyroid carcinoma [12, 37, 88]

Name of prognostic grouping	Components
AMES	**A**ge, **M**etastases, **E**xtent of disease, **S**ize of tumor
AGES	**A**ge, **G**rade, **E**xtent of disease, **S**ize of tumor
MACIS	**M**etastases, **A**ge, **C**ompleteness of resection, **I**nvasion, **S**ize of tumor
TNM	**T**umor, **N**ode, **M**etastasis, Age

The American Thyroid Association (ATA) defines central compartment neck dissection (CCND) as "the comprehensive, compartment-oriented removal of the prelaryngeal, pretracheal and at least one paratracheal lymph node basin" [2]. There is consensus that patients with clinically apparent (N1a) central compartment lymph nodes should undergo total thyroidectomy with therapeutic CCND [2]. However, in view of the prevailing contradictions on the effect of lymph node status on recurrence and survival, there is no consensus on the role of routine pCCND in patients with PTC and no clinical evidence of lymph node metastases (clinically N0), either by physical examination, preoperative ultrasonography, or intraoperative inspection at the time of thyroidectomy. As level C evidence, the current ATA guidelines on the management of patients with DTC recommends that patients with advanced primary tumors (T3 or T4) with clinically negative lymph nodes may undergo pCCND while patients with small tumors (T1 or T2) with no clinically apparent lymph nodes may be spared CCND [2]. This section will highlight some of the pros and cons of pCCND with regards to locoregional recurrence, survival, and postoperative complications based on studies from various single institution, multi-institution and large administrative databases. The reasons for the persistent controversies and how they could be effectively resolved will also be discussed.

Generally accepted prognostic factors for PTC include age, tumor size, completeness of resection, extrathyroidal extension, and the presence of distant metastases (Table 1) [11–14]. The effect of locoregional lymph node metastases on rates of recurrence and survival in patients with PTC remains controversial.

2.1 Recurrence

Single and multi-institution studies estimate the locoregional recurrence rate of patients with PTC to be 6–59 % [15–18]. The central compartment is the most common site of recurrence [16]. There is increased cost and morbidity in patients with recurrent disease, given that reoperative cervical surgery is associated with higher rates of recurrent laryngeal nerve injury and hypoparathyroidism, both transient and permanent [19–21]. The probability of recurrence is influenced by the lymph node status of the patient, with clinically node-positive patients having a higher rate of recurrence [22]. Studies on the role of pCCND in decreasing tumor recurrence have yielded contradictory results [9, 23–25].

The sensitivity of high-resolution ultrasonography in detecting cervical lymph node metastases is reported to be 52 % with a false negative rate of 58 % [26]. While ultrasonography has a higher detection rate than physical exam alone in the detection of metastatic lymphadenopathy, the overall detection rate remains low. Given the difficulty in predicting the presence of metastatic lymphadenopathy preoperatively, one would expect that reliance on only therapeutic CCND at the time of thyroidectomy would miss a significant number of patients with micrometastatic lymphadenopathy [27]. As a result, failure to remove microscopic metastases at the time of initial thyroidectomy would theoretically place patients at a higher risk for recurrent DTC and need for further treatment, including reoperative surgery [22, 28].

Early locoregional recurrence of DTC may be due to existing nodal metastases which was not recognized pre- or intraoperatively and thus not removed at the index operation, if routine pCCND was not performed [28]. In addition, routine pCCND and resection of micrometastatic nodal disease may influence the need for, and dosage of I-131 given at the time of subsequent RAI, although data are conflicting [27, 29, 30]. Some studies have found that patients in whom the true nodal status is unknown because they did not undergo pCCND may be under-treated and subsequently are more likely to have a locoregional recurrence; this is in part due to the fact that identification of micrometastasis 'upstages' PTC from Nx to N1a disease, in the American Joint Committee on Cancer (AJCC) staging system and N1a PTC is considered "Stage III" PTC in patients >45 years [27, 29, 31, 32]. Other studies, however, suggest that performance of pCCND and identification of micrometastasis may preclude the need for RAI in patients with undetectable serum thyroglobulin levels and no evidence of disease on whole body prescans performed at the time of RAI [30].

Serum thyroglobulin is a postoperative marker for recurrent PTC and higher rates of athyroglobulinemia have been reported among patients who underwent total thyroidectomy with ipsilateral pCCND [33]. A meta-analysis of 11 published studies with a total of 2,318 patients revealed a lower trend toward recurrence in patients treated with total thyroidectomy and prophylactic central neck dissection, although statistical significance was not reached, OR 0.59 (95 % CI 0.33–1.07) in favor of total thyroidectomy with pCCND [34]. The pooled recurrence rate for total thyroidectomy with pCCND was 4.7 % compared to 7.9 % in the total thyroidectomy group [34].

Contrary to the studies reporting favorably on the effect of pCCND on recurrence, some studies have not found more aggressive surgery to correlate with decreased recurrence [16, 35]. A single institution, retrospective cohort review of patients with PTC over a 60 year period found the recurrence rate among clinically node negative patients to be 0.8 % compared to a recurrence rate of 16 % in patients who had clinically positive lymph nodes at presentation [16]. There was no increased risk of mortality from thyroid cancer in the cohort that experienced tumor recurrence. Another single institution study in which all surgeries were performed by a single surgeon, did not find any central neck recurrence in patients who received total thyroidectomy with CCND, however, lateral neck recurrences were observed in 5 patients who had more than 5 metastatic central neck lymph nodes on

therapeutic CCND only [36]. These findings would suggest that pCCND offers no benefit to patients with clinical N0 disease [36].

Contrary to other studies, another single institution retrospective cohort study in which both groups received post-operative 131-I therapy found similar levels of serum thyroglobulin levels at 1-year follow-up in both patients who underwent total thyroidectomy alone versus total thyroidectomy with pCCND [27].

2.2 Survival

Both single-institution, retrospective cohort studies and those using larger administrative databases, such as Surveillance, Epidemiology, and End Results (SEER) have reported no effect of metastatic cervical lymph nodes on survival [26, 37, 38]. In one study using the SEER database, multivariable analysis of the factors predictive of survival in patients with PTC did not find the effect of cervical lymph node metastasis to be statistically significant [38].

In contrast, a separate study also utilizing the SEER database reported a relative risk of 1.3 (1.20–1.5) in patients with positive cervical lymph node metastasis when multivariable analysis was performed for prognostic factors of survival [39]. The role of pCCND on survival is hard to evaluate given the relatively long-term survival in patients with PTC. A prospective cohort study of patients with PTC who received total thyroidectomy with microdissection in the city of Göteborg showed that over a median follow-up of 13 years, 1.6 % died from thyroid cancer compared to 8.4 and 11.1 % with median follow-up of 10 and 11.4 years from Bergen and Helsinki respectively where patients underwent "node picking" or no information on lymph node dissection was provided [40]. In a thorough systematic review evaluating the effect of CCND on survival [23], studies from various institutions across the world reported conflicting results. A retrospective cohort study from Hannover, Germany in which 342 patients with PTC were analyzed, found improved survival in the cohort who received systematic compartment oriented dissection compared to the cohort who received selective node removal [24]. On the contrary, another single institution retrospective cohort review of 139 patients with DTC did not find lymphadenectomy to improve survival [41]. No higher level evidence exists to conclusively settle on the effect of pCCND on survival among patients with DTC [23].

2.3 Morbidity

The potential complications of CCND include hypoparathyroidism (transient or permanent), recurrent laryngeal nerve injury (transient or permanent), esophageal injury, tracheal injury, seroma, hematoma and wound infection [42]. Transient hypoparathyroidism is the most common complication of both thyroidectomy and CCND, whether performed as a therapeutic or prophylactic procedure [9, 43].

Table 2 Complications and incidence rates for total thyroidectomy with or without central compartment neck dissection [42]

Complication	Incidence (%)
Permanent hypoparathyroidism	1.2
Transient vocal cord palsy	1.1
Permanent vocal cord paralysis	3.4
Hemorrhage	1–2

In a meta-analysis of 5 studies with a total of 1,132 patients with DTC, transient hypoparathyroidism was an increased adverse event in patients undergoing thyroidectomy and CCND compared to thyroidectomy alone [42]. The reported incidence of transient hypocalcemia for thyroidectomy with or without CCND ranges from 1.6 to 53.6 % [20]. The rates of permanent hypoparathyroidism (1.2 %), transient vocal cord palsy (3.4 %), permanent vocal cord paralysis (1.1 %) and hemorrhage (1–2 %) were similar between those who underwent total thyroidectomy alone compared to recipients of total thyroidectomy with CCND, Table 2 [42]. Furthermore, different single institution studies report increased risk of hypoparathyroidism and recurrent laryngeal nerve injury in reoperative CCNDs, suggesting that prevention of reoperative surgery, perhaps by performing prophylactic CCND at the time of initial surgery, may be appropriate [23, 28, 44].

Still other studies, both single institution retrospective and prospective cohort studies, have found the complication rates of initial pCCND to be comparable to reoperative CCND [9, 45], thus suggesting that if patients experience a recurrence, they can be operated on safely and therefore they should not undergo CCND at first operation if cervical nodes are clinically negative. A large single institution retrospective review of 295 patients at a high-volume center in which 189 patients had initial total thyroidectomy with pCCND and 106 patients underwent reoperative surgery reported the following rates of complications when comparing the two cohorts: permanent hypoparathyroidism (0.5 % vs. 0.9 %), neck hematoma (1.1 % vs. 0.9 %), permanent hoarseness (2.6 % vs. 1.9 %) [9]. Furthermore, in contrast to the previously discussed meta-analysis by Chisholm et al. [42] in which patients undergoing total thyroidectomy and pCCND had only transient hypoparathyroidism as a worse outcome compared to total thyroidectomy alone, others have reported increased rates of permanent hypoparathyroidism [23, 46]. A systematic review of multiple single institution cohort studies by White et al. concluded that the rate of permanent hypoparathyroidism may be higher in patients who undergo CCND [23]. The sub-samples analyzed in the cohort studies to derive the incidence of permanent hypoparathyroidism were small and the reported rates of permanent hypoparathyroidism ranged from 1.4 to 4 % among the cohort who underwent total thyroidectomy with CCND [23]. These data would suggest that pCCND may place patients at higher risk of postoperative morbidity.

The majority of previous studies investigating the issue of pCCND in patients with PTC have been case reports, case series, prospective, or retrospective review of single or national databases, although some meta-analyses have recently been performed. Another weakness of the single institution studies is that, they are

usually done at high-volume centers where surgeries are done by very experienced surgeons; hence the findings may not be generalizable. Furthermore, much of the existing literature comparing postoperative morbidity in patients undergoing total thyroidectomy with or without CCND do not accurately distinguish between prophylactic and therapeutic CCND and the extent of lymphadenectomy performed is difficult to assess in a retrospective manner. None of the studies on this controversial issue has a level of evidence better than III, Grade C. Despite the benefit of large sample size in studies using Surveillance, Epidemiology and End Results (SEER) data, the lack of a robust randomized controlled clinical trial to effectively compare thyroidectomy alone versus thyroidectomy with pCCND has left this controversy unresolved. A randomized, controlled study examining postoperative calcium supplementation in patients following total thyroidectomy did not identify patients undergoing CCND, prophylactic or therapeutic, to be at higher risk of postoperative hypoparathyroidism, although this study was not designed to look specifically at the issue of CCND [47].

2.4 Challenges to Obtaining a Higher Level of Evidence

There are several challenges to conducting a randomized controlled trial to address the role of pCCND in patients with PTC. The low incidence of PTC, the overall low morbidity associated with pCCND and the favorably long survival necessitates a very large sample size and long follow-up time in order to detect statistically significant differences in outcome [45]. The feasibility of a multicenter randomized controlled trial is also constrained by the high budgetary estimate of $20 million [45]. Existing studies are limited by multiple factors. First, there is heterogeneity of the histology of study participants. In some studies, there are no separate subgroup analyses between PTC and follicular thyroid cancer; follicular thyroid cancer does not typically spread via the lymphatic channels and therefore, pCCND has little clinical utility in this subset of patients. Second, earlier studies may not meet the current ATA definition of a pCCND, making the extent of lymphadenectomy difficult to determine. Next, most existing studies did not have a control group of patients who did not undergo CCND and there is wide variability in inclusion/exclusion criteria and confounding factors, thus making it difficult to examine the direct effect of pCCND. Finally, temporal trends in knowledge, imaging, diagnosis, surgical technique and patient preferences call for a more robust, contemporary study.

2.5 How High Quality Evidence May Be Obtained

Large healthcare systems with integrated electronic health records such as American College of Surgeons National Surgical Quality Improvement Program (ACS NSQIP) regional collaboratives may be able to implement a prospective cohort study

to compare patients with cN0 who receive total thyroidectomy with age-matched patients with cN0 who undergo total thyroidectomy with pCCND. In such a study, standardized definitions of variables would be used thus decreasing the variability that has characterized most existing studies. Given the favorable long-term survival in patients with PTC, these cohort studies would examine short to medium term outcomes such as complications and recurrence. Also, the findings are likely to be more generalizable since the spectrum of hospital volume and surgeon experience will reflect the real world as opposed to a single institution. While this type of prospective cohort study may not be as robust as RCT, it may not be hampered by the same barriers that make RCT infeasible [45].

3 Postoperative Radioactive Iodine Therapy for Papillary Thyroid Cancer

RAI using 131-I is an important adjunct in the treatment of patients with PTC. Given the high avidity of thyroid tissue for iodine, administered 131-I enters remnant thyroid tissue where it kills tissues. Controversy exists regarding: (1) whom should undergo additional postoperative treatment with RAI; (2) THW versus recombinant TSH (rhTSH) stimulation prior to remnant ablation; and (3) the optimal dose of 131-I.

3.1 Indications for Administration of RAI in Patients with PTC

RAI is used for remnant thyroid tissue ablation resulting in the [2, 48] (i) destruction of microscopic remnants of thyroid tissue with the goal to decreasing tumor recurrence (ii) facilitation of follow-up and early detection of persistent or recurrent disease based on serum thyroglobulin levels (iii) facilitation in identifying previously undiagnosed or persistent disease when the post-ablation therapy scan is performed. ^{131}I may also be used for adjuvant therapy after complete surgical resection [2].

There remains debate about the use of postoperative RAI in patients with PTC, particularly in patients at low-risk for disease recurrence. Factors predictive of low-risk versus high-risk for disease recurrence and mortality are shown in Table 3 [49].

The ATA has made recommendations for use of RAI ablation based on the AJCC TNM staging criteria for PTC, Table 4 [2]. With the exception of patients with metastatic disease, no level A evidence exists to guide the recommendations, hence the persistent variation in the use of RAI therapy, although studies have shown an increasing trend in RAI usage [50]. A recent retrospective review of the SEER database found that for every 3 years, there is an average increase in RAI use by 1.5 % [50].

Table 3 Factors predictive of high versus low risk of recurrence and mortality (adopted and modified from Mazzaferri and Kloos) [49]

High risk features	Low risk features
Age <15 years or >45 years	Age 15–45 years
Male sex	Female sex
Family history of thyroid cancer	
Size >4 cm in diameter	Size <4 cm
Bilateral disease	Unilateral disease
Vascular invasion	No vascular invasion
Extrathyroidal extension	No extrathyroidal extension
Cervical/mediastinal lymph node metastasis	No lymph node metastasis
High histologic grade	Low histologic grade
Poor concentration of radioiodine in tumors or metastasis	Tumors with high radioiodine avidity
Distant metastasis	No metastasis

Table 4 Factors, recommendations and level of evidence regarding radioiodine remnant ablation (adopted and modified from ATA guidelines) [2]

Factors	Description	Recommendation	Strength of evidence
T1	1 cm or less, intrathyroidal or microscopic multifocal	No	E
	1–2 cm, intrathyroidal	Selective use	I
T2	>2–4 cm, intrathyroidal	Selective use	C
T3	>4 cm		
	<45 years old	Yes	B
	≥45 years old	Yes	B
	Any size, any age, minimal extrathyroidal extension	Selective use	I
T4	Any size with gross extrathyroidal extension	Yes	B
Nx, N0	No metastatic nodes documented	No	I
N1	<45 years old	Selective use	C
	>45 years old	Selective use	C
M1	Distant metastatic disease	Yes	A

3.2 Does RAI Decrease Recurrence and Improve Survival?

The effect of RAI on recurrence and survival has been debated. Some cohort studies and case series have reported decreased recurrence and improved disease-specific mortality in patients treated with RAI after thyroidectomy [2, 15, 51, 52]. Decreased rates of pulmonary metastases has been reported in patients treated with

surgery and 131-I compared to those treated with surgery alone [49]. Also, a single institution cohort study found decreased rates of recurrence in patients with microscopic residual disease treated with RAI [53]. A review of a single institution data by Mazzaferri and Kloos [49], in which recurrences were examined in a large cohort over a 40 year period revealed that patients who received total thyroidectomy with RAI and L-thyroxine therapy had fewer recurrences compared to those who had total thyroidectomy with L-thyroxine but without RAI. An older single institution study which reviewed a large cohort of patients with well DTC in which 736 patients received surgery and RAI therapy versus 863 who received surgery only, concluded that RAI treatment was the single most important prognostic factor for recurrence ($p < 0.0001$) [52].

However, there is no higher level evidence based on robust randomized controlled trials to support the claim of decreased disease recurrence and improved disease specific survival among patients who receive post-surgical RAI ablation [48]. A thorough systematic review and meta-analysis has not found consistent benefit of RAI therapy in decreasing disease recurrence and disease specific mortality.

Due to the inconsistent results from single institution studies on the benefits of RAI use on disease-specific survival and tumor recurrence, some have questioned if RAI therapy for some risk groups with PTC are necessary [54, 55]. Increased rate of secondary malignancies (absolute risk of 2 % for second primary malignancy, absolute risk of 0.4 % for leukemia) [56], sialoadenitis (estimated incidence of 2.8–33 %) [57, 58] and decreased quality-of-life are some of the adverse effects of RAI therapy [54, 59]. Studies reporting these negative effects of postoperative RAI therapy are single institution retrospective reviews, case reports or case series and hence lack the strength of evidence to sway proponents of RAI therapy.

3.3 Thyroid Hormone Withdrawal Versus Recombinant TSH Prior to Remnant Ablation

TSH stimulation is required before postoperative RAI ablation of the remnant thyroid tissue. TSH stimulation could be either via withholding of exogenous thyroid hormone (withdrawal) or administration of exogenous rhTSH [2]. rhTSH is a synthetic analog of endogenous TSH, which is produced by the anterior pituitary gland. Unlike endogenous TSH, which is both sialylated and sulfated, rhTSH is only sialylated [60]. rhTSH binds to the TSH receptor on normal thyroid follicular cells or well-differentiated thyroid cells where the adenylate cyclase and the phosphatidylinositol signaling pathways are activated and therefore mimics the hypothyroid state [60].

THW induces hypothyroidism in patients, which may lead to symptoms such as decreased cognitive function, altered emotional state, and physical discomfort. Randomized controlled trials and a number of prospective cohort studies have

demonstrated the decreased quality-of-life in patients who undergo THW prior to postoperative RAI [61–64]. In a single institution randomized controlled trial, there was a statistically significant difference in a quality-of-life survey comparing use of rhTSH versus THW prior to RAI. Patients in the rhTSH arm demonstrated better scores on each of the following measures: symptoms and signs of hypothyroidism, duration of symptoms, impact on daily and social life, mood changes and cognitive dysfunction and genital dysfunction [61]. Furthermore, use of rhTSH avoids the need to induce hypothyroidism and is invaluable in clinical situations where THW is contraindicated prior to postoperative RAI therapy, such as congestive heart failure, hyponatremia, and adrenal insufficiency [65]. Initial doubts about the effectiveness of rhTSH on successful tumor ablation have been answered by a number of studies using randomized controlled, prospective cohort and retrospective study designs [66–68]. A retrospective review of a single institution study comparing 74 patients who underwent THW before remnant ablation versus 320 patients treated with rhTSH before remnant ablation reported similar time to recurrence in the two groups as well as similar rates of disease recurrence (4 % in rhTSH group vs. 7 % in the THW group, $p = 0.1$) [68].

Questions remain about the appropriate dose of 131-I to utilize when administering postoperative RAI with rhTSH. Some studies have reported comparable outcomes with low-dose RAI after TSH stimulation using rhTSH or THW in patients at low-risk for recurrent PTC [61, 67, 69]. A single institution prospective study of 162 patients with DTC followed for 10 years after post-surgical therapy with rhTSH or THW before remnant ablation with 1.1 GBq (30 mCi) found no statistically significant difference in disease recurrence between those who received rhTSH and the THW group [69]. This result differs from that done by a prospective cohort study with a control group in which patients treated with 30 mCi (low dose) of RAI had significantly lower ablation rates [70]. This was a prospective cohort study with controls that compared the success of remnant ablation (assessed by 131-I WBS) in a cohort treated with rhTSH before remnant ablation versus cohort who underwent THW before remnant ablation. Findings showed successful remnant ablation rate of 54 % in the group who received rhTSH compared to 84 % in the THW group [70].

Initial concerns about the cost-effectiveness of using rhTSH compared to THW have recently been addressed. Cost-effectiveness studies have concluded that despite the high cost of rhTSH, avoidance of hypothyroidism and associated decreased quality-of-life which may impair productivity and safety afforded by rhTSH make the cost equivalent to THW [62, 71]. A study in which 236 patients were surveyed (61 % response rate) examined comparative cost-effectiveness of rhTSH versus THW withdrawal using a pharmacoeconomic model on the following measures; medical cost, missed work time or decreased productivity and accident and concluded that costs to society associated with THW exceeded that of rhTSH by 25 % [62]. Another cost- effectiveness study found that differences in societal cost between rhTSH and THW were dependent on days of work lost, cost of rhTSH, duration of THW, rates of failure of remnant ablation and patient's utility in the first 12 weeks after thyroidectomy [71].

Current ATA guidelines on the management of patients with DTC state that "remnant ablation can be performed following thyroxine withdrawal or rhTSH stimulation" [2].

3.4 Low- Versus High-Doses of 131-I in Administration of RAI for Patients with DTC

The optimal dosage of 131-I to use for remnant ablation continues to be an area of controversy. Because of increased side-effects such as sialoadenitis and increased second primary tumors with "high" doses of 131-I [56, 58], as well as the long-term risk of developing pulmonary fibrosis with large cumulative doses of RAI, some have questioned the use of "high" doses of 131-I by citing studies in which "low" doses have achieved similar outcome as "high" doses [72, 73]. A meta-analysis of 9 randomized controlled trials concluded that remnant ablation with 30 mCi was as successful as 100 mCi with associated fewer adverse events [73]. However, some of the individual randomized controlled trials included in the study had different thresholds for "low-dose" versus "high-dose", as well as different criteria for evaluating success of ablation, making interpretation of the results difficult to generalize [73]. Additionally, the individual studies had relatively low sample sizes (range 40–752 patients). On the contrary, a double blind randomized controlled trial from a single institution in which 341 patients were randomized to treatment with 100 mCi ("high") versus 30 mCi ("low") showed that patients in the "low" dose group often required a second dose, leading to increased cumulative activity (median dose of 130 mCi vs. 100 mCi, $p < 0.0001$) and had longer inpatient stay (median of 4 days vs. 3 days) [74].

3.5 Challenges to Obtaining a Higher Level of Evidence

The controversy regarding post-surgical RAI use persists due to some issues that affect the quality of previously published studies. Some of the prospective cohort studies and retrospective cohort studies from single institutions did not have control arms to allow for effective comparison of treatment effect. Also, in studies comparing surgical therapy alone versus surgical therapy plus RAI, some participants in the latter group may have received additional therapy such as hormonal therapy thus making it difficult to attribute treatment effect to RAI therapy only. Further, the degree of surveillance for recurrence may vary from institution to institution and thus the reported recurrence rates may not be generalizable. Additionally, variation in RAI dosage among various institutions does not allow for accurate comparison of studies to allow for a definitive conclusion to be drawn. Finally, different methods of assessing success of remnant ablation have been used in different studies thus affecting their comparability.

3.6 How High Quality Evidence May Be Obtained

A large, multicenter randomized controlled trial comparing outcomes in patients who receive low-dose RAI with high-dose RAI may help resolve this controversy. The ideal study protocol would use generally agreed upon standard definitions and end-points in order to avoid ambiguity which would decrease the validity of the results; it would be particularly important to utilize standard definitions of disease persistence and recurrence. Participating centers would agree on a single dosage for "low" and "high" respectively and on use of rhTSH versus THW. Short- and intermediate-term outcomes such as success of remnant ablation, based on serum thyroglobulin and/or follow-up radiographic studies, salivary gland dysfunction, lacrimal gland dysfunction, and patient quality-of-life could be assessed with a multicenter RCT.

Given the favorably long-term survival among patients with PTC, a prospective cohort study of patients in an ideal geographic region with easy access to healthcare and well established follow-up system may enable an assessment of the effect of post-operative RAI therapy on recurrence and disease specific survival. The quality of such a prospective cohort study will be improved if standards for "low-dose", "high-dose", and methods of assessing response to treatment are determined before start of study.

Also, to address the controversy surrounding appropriate dosing of 131-I in patients stimulated with rhTSH, a large multicenter randomized controlled trial with well-defined inclusion and exclusion criteria, as well as standard defined "low dose" versus "high dose", and end-points that can be assessed with standard techniques or lab measurements would be ideal.

4 Routine Serum Calcitonin Screening for Thyroid Nodules

Medullary thyroid carcinoma (MTC) comprises 2–4 % of the incidence of all thyroid cancers [75, 76]. Among patients with thyroid nodules, the prevalence of medullary thyroid cancer is estimated between 0.4 and 1.4 % [77–80]. It is relatively more aggressive than PTC and has a reported overall relative survival of 75 % at 10 years [75]. MTC may be inherited as autosomal dominant in 20–25 % of cases or occur sporadically in the rest of cases [81]. Prognostic factors for medullary thyroid cancer include age at diagnosis, extent of tumor, nodal disease, extent of surgical resection and distant metastases [81, 82]. Given the poor prognosis associated with late stage MTC, efforts to aid early diagnosis are being pursued.

Routine serum calcitonin levels in all patients with thyroid nodules in order to screen for possible MTC is common practice in most European countries, [77] in large part because of the inability to appropriately interpret indeterminate values [2]. While serum calcitonin levels <10 pg/mL is considered normal and >100 pg/mL is nearly diagnostic for MTC, serum calcitonin levels can be elevated in patients with elevated

serum gastrin levels, follicular neoplasms, Hashimoto's thyroiditis, renal failure, and with alcohol or tobacco use. In Europe, indeterminate serum calcitonin levels (20–100 pg/mL) can be stimulated with pentagastrin to determine the risk of MTC. However, in the United States, pentagastrin is not available and calcium stimulation is a far less reliable method. As a result, current ATA guidelines do not endorse routine screening of serum calcitonin levels in patients with thyroid nodules [2, 81].

A number of prospective, non-randomized studies have shown that serum calcitonin is the most sensitive screening test for diagnosing occult medullary thyroid cancer in thyroid nodules [83–86]. Some of the reasons for the difference in practice patterns on the use of routine serum calcitonin screening in the United States include: lack of a robust randomized controlled trial, the reliance of screening on pentagastrin to increase specificity in patients with indeterminate levels, questions about assay performance, and the cost-effectiveness of screening for a rare disease [2]. A cost-effectiveness study from North America concluded that routine serum calcitonin screening was appropriate and comparable to colonoscopy and mammography [87]. A limitation of this study was the inclusion of patients with micromedullary carcinoma and C-cell hyperplasia in the prevalence estimate [2]. Barriers to conducting a randomized controlled trial to evaluate the role of routine serum calcitonin screening on early detection of MTC include: (i) rarity of MTC, leading to difficulties with accrual and adequate power; (ii) unavailability of pentagastrin in North America; and (iii) variability in assay preparation.

A randomized controlled trial in the United States does not appear to be feasible, given the lack of an accurate way to interpret serum calcitonin levels and the relative rarity of this disease. Any attempt to evaluate the effectiveness of routine calcitonin screening in human subjects in the US is limited by the unavailability of pentagastrin. While some of the European studies evaluating the role of routine calcitonin in diagnosing MTC are of high quality, comparable studies cannot be conducted in the U.S. due to Food and Drug Administration (FDA) regulation and hence this issue will remain unresolved for a while.

References

1. Tuttle RM, Ball DW, Byrd D, Dilawari RA, Doherty GM, Duh QY et al (2010) Thyroid carcinoma. J Nat Compr Cancer Netw 8(11):1228–1274. PubMed PMID: 21081783. Epub 2010/11/18. eng
2. American Thyroid Association Guidelines Taskforce on Thyroid nodules, Differentiated Thyroid cancer, Cooper DS, Doherty GM, Haugen BR, Kloos RT et al (2009) Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid 19(11):1167–1214. PubMed PMID: 19860577
3. Ezzat S, Sarti DA, Cain DR, Braunstein GD (1994) Thyroid incidentalomas. Prevalence by palpation and ultrasonography. Arch Intern Med 154(16):1838–1840. PubMed PMID: 8053752. Epub 1994/08/22. eng
4. Stark DD, Clark OH, Gooding GA, Moss AA (1983) High-resolution ultrasonography and computed tomography of thyroid lesions in patients with hyperparathyroidism. Surgery 94 (6):863–868. PubMed PMID: 6648798. Epub 1983/12/01. eng

5. Kim MS, Lee SY, Cho WH, Song WS, Koh JS, Lee JA et al (2008) Tumor necrosis rate adjusted by tumor volume change is a better predictor of survival of localized osteosarcoma patients. Ann Surg Oncol 15(3):906–914
6. Sherman SI (2003) Thyroid carcinoma. Lancet 361(9356):501–511. PubMed PMID: 12583960. Epub 2003/02/14. eng
7. Davies L, Welch HG (2014) Current Thyroid cancer trends in the United States. JAMA Otolaryngol—Head Neck Surg. PubMed PMID: 24557566. Epub 2014/02/22. eng
8. Kouvaraki MA, Shapiro SE, Fornage BD, Edeiken-Monro BS, Sherman SI, Vassilopoulou-Sellin R et al (2003) Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. Surgery 134(6):946–954; discussion 54-5. PubMed PMID: 14668727
9. Shen WT, Ogawa L, Ruan D, Suh I, Kebebew E, Duh QY et al (2010) Central neck lymph node dissection for papillary thyroid cancer: comparison of complication and recurrence rates in 295 initial dissections and reoperations. Arch Surg 145(3):272–275. PubMed PMID: 20231628. Epub 2010/03/17. eng
10. American Thyroid Association Surgery Working Group, American Association of Endocrine Surgeons, American Academy of O-H, Neck S, American H, Neck S et al (2009) Consensus statement on the terminology and classification of central neck dissection for thyroid cancer. Thyroid 19(11):1153–1158. PubMed PMID: 19860578
11. Stephen B, Edge CCC, Fritz AG, Greene FL, Trotti III A, Byrd D (eds) (2011) AJCC cancer staging manual, 7th edn. Springer, New York
12. Cady B, Sedgwick CE, Meissner WA, Wool MS, Salzman FA, Werber J (1979) Risk factor analysis in differentiated thyroid cancer. Cancer 43(3):810–820. PubMed PMID: 427722. Epub 1979/03/01. eng
13. Roh JL, Kim JM, Park CI (2011) Central compartment reoperation for recurrent/persistent differentiated thyroid cancer: patterns of recurrence, morbidity, and prediction of postoperative hypocalcemia. Ann Surg Oncol 18(5):1312–1318. PubMed PMID: 21140230. Epub 2010/12/09. eng
14. Gimm O, Rath FW, Dralle H (1998) Pattern of lymph node metastases in papillary thyroid carcinoma. Br J Surg 85(2):252–254. PubMed PMID: 9501829. Epub 1998/03/21. eng
15. Mazzaferri EL, Jhiang SM (1994) Long-term impact of initial surgical and medical therapy on papillary and follicular thyroid cancer. Am J Med 97(5):418–428. PubMed PMID: 7977430. Epub 1994/11/01. eng
16. Hay ID, Hutchinson ME, Gonzalez-Losada T, McIver B, Reinalda ME, Grant CS et al (2008) Papillary thyroid microcarcinoma: a study of 900 cases observed in a 60-year period. Surgery 144(6):980–987; discussion 7-8. PubMed PMID: 19041007. Epub 2008/12/02. eng
17. McConahey WM, Hay ID, Woolner LB, van Heerden JA, Taylor WF (1986) Papillary thyroid cancer treated at the Mayo Clinic, 1946 through 1970: initial manifestations, pathologic findings, therapy, and outcome. Mayo Clinic Proceed 61(12):978-96. PubMed PMID: 3773569. Epub 1986/12/01. eng
18. Cranshaw IM, Carnaille B (2008) Micrometastasis in thyroid cancer. An important finding? Surg Oncol 17(3):253–258. PubMed PMID: 18504121. Epub 2008/05/28. eng
19. Chao TC, Jeng LB, Lin JD, Chen MF (1997) Reoperative thyroid surgery. World J Surg 21(6):644–647. PubMed PMID: 9230664. Epub 1997/07/01. eng
20. Pattou F, Combemale F, Fabre S, Carnaille B, Decoulx M, Wemeau JL et al (1998) Hypocalcemia following thyroid surgery: incidence and prediction of outcome. World J Surg 22(7):718–724. PubMed PMID: 9606288. Epub 1998/06/20. eng
21. Kim MK, Mandel SH, Baloch Z, Livolsi VA, Langer JE, Didonato L et al (2004) Morbidity following central compartment reoperation for recurrent or persistent thyroid cancer. Arch Otolaryngol–Head Neck Surg 130(10):1214–1216. PubMed PMID: 15492172. Epub 2004/10/20. eng
22. Conzo G, Docimo G, Pasquali D, Mauriello C, Gambardella C, Esposito D et al (2013) Predictive value of nodal metastases on local recurrence in the management of differentiated

thyroid cancer. Retrospective Clin Study. BMC Surg 13(2):S3. PubMed PMID: 24267409. Pubmed Central PMCID: Pmc3851192. Epub 2013/12/07. eng
23. White ML, Gauger PG, Doherty GM (2007) Central lymph node dissection in differentiated thyroid cancer. World J Surg 31(5):895–904. PubMed PMID: 17347896. Epub 2007/03/10. eng
24. Scheumann GF, Gimm O, Wegener G, Hundeshagen H, Dralle H (1994) Prognostic significance and surgical management of locoregional lymph node metastases in papillary thyroid cancer. World J Surg 18(4):559-67; discussion 67-8. PubMed PMID: 7725745. Epub 1994/07/01. eng
25. Shah MD, Hall FT, Eski SJ, Witterick IJ, Walfish PG, Freeman JL (2003) Clinical course of thyroid carcinoma after neck dissection. Laryngoscope 113(12):2102–2107. PubMed PMID: 14660910. Epub 2003/12/09. eng
26. Shaha AR, Shah JP, Loree TR (1996) Risk group stratification and prognostic factors in papillary carcinoma of thyroid. Ann Surg Oncol 3(6):534–538. PubMed PMID: 8915484. Epub 1996/11/01. eng
27. Hughes DT, White ML, Miller BS, Gauger PG, Burney RE, Doherty GM (2010) Influence of prophylactic central lymph node dissection on postoperative thyroglobulin levels and radioiodine treatment in papillary thyroid cancer. Surgery 148(6):1100-6; discussion 006-7. PubMed PMID: 21134539. Epub 2010/12/08. eng
28. Simon D, Goretzki PE, Witte J, Roher HD (1996) Incidence of regional recurrence guiding radicality in differentiated thyroid carcinoma. World J Surg 20(7):860-6; discussion 6. PubMed PMID: 8678963. Epub 1996/09/01. eng
29. Moo TA, McGill J, Allendorf J, Lee J, Fahey T, 3rd Zarnegar R (2010) Impact of prophylactic central neck lymph node dissection on early recurrence in papillary thyroid carcinoma. World J Surg 34(6):1187–1191. PubMed PMID: 20130868. Epub 2010/02/05. eng
30. Wang TS, Evans DB, Fareau GG, Carroll T, Yen TW (2012) Effect of prophylactic central compartment neck dissection on serum thyroglobulin and recommendations for adjuvant radioactive iodine in patients with differentiated thyroid cancer. Ann Surg Oncol 19(13):4217–4222. PubMed PMID: 23010732. Epub 2012/09/27. eng
31. Popadich A, Levin O, Lee JC, Smooke-Praw S, Ro K, Fazel M et al (2011) A multicenter cohort study of total thyroidectomy and routine central lymph node dissection for cNo papillary thyroid cancer. Surgery 150(6):1048–1057. PubMed PMID: 22136820. Epub 2011/12/06. eng
32. Laird AM, Gauger PG, Miller BS, Doherty GM (2012) Evaluation of postoperative radioactive iodine scans in patients who underwent prophylactic central lymph node dissection. World J Surg 36(6):1268–1273. PubMed PMID: 22270997. Epub 2012/01/25. eng
33. Sywak M, Cornford L, Roach P, Stalberg P, Sidhu S, Delbridge L (2006) Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer. Surgery 140(6):1000–1005; discussion 5-7. PubMed PMID: 17188149. Epub 2006/12/26. eng
34. Wang TS, Cheung K, Farrokhyar F, Roman SA, Sosa JA (2013) A meta-analysis of the effect of prophylactic central compartment neck dissection on locoregional recurrence rates in patients with papillary thyroid cancer. Ann Surg Oncol 20(11):3477–3483. PubMed PMID: 23846784. Epub 2013/07/13. eng
35. Gyorki DE, Untch B, Tuttle RM, Shaha AR (2013) Prophylactic central neck dissection in differentiated thyroid cancer: an assessment of the evidence. Ann Surg Oncol 20(7):2285–2289. PubMed PMID: 23417435. Epub 2013/02/19. eng
36. Pereira JA, Jimeno J, Miquel J, Iglesias M, Munne A, Sancho JJ et al (2005) Nodal yield, morbidity, and recurrence after central neck dissection for papillary thyroid carcinoma. Surgery 138(6):1095–1100, discussion 100-1. PubMed PMID: 16360396. Epub 2005/12/20. eng
37. Hay ID, Bergstralh EJ, Goellner JR, Ebersold JR, Grant CS (1993) Predicting outcome in papillary thyroid carcinoma: development of a reliable prognostic scoring system in a cohort of 1779 patients surgically treated at one institution during 1940 through 1989. Surgery 114(6):1050–1057; discussion 7-8. PubMed PMID: 8256208. Epub 1993/12/01. eng

38. Bhattacharyya N (2003) A population-based analysis of survival factors in differentiated and medullary thyroid carcinoma. Otolaryngol–Head Neck Surg (official journal of American Academy of Otolaryngology-Head and Neck Surgery) 128(1):115–123. PubMed PMID: 12574769. Epub 2003/02/08. eng
39. Podnos YD, Smith D, Wagman LD, Ellenhorn JD (2005) The implication of lymph node metastasis on survival in patients with well-differentiated thyroid cancer. Am Surg. 71(9):731–734. PubMed PMID: 16468507. Epub 2006/02/14. eng
40. Tisell LE, Nilsson B, Molne J, Hansson G, Fjalling M, Jansson S et al (1996) Improved survival of patients with papillary thyroid cancer after surgical microdissection. World J Surg 20(7):854–859. PubMed PMID: 8678962. Epub 1996/09/01. eng
41. Steinmuller T, Klupp J, Rayes N, Ulrich F, Jonas S, Graf KJ et al (2000) Prognostic factors in patients with differentiated thyroid carcinoma. Euro J Surg = Acta Chir 166(1):29–33. PubMed PMID: 10688213. Epub 2000/02/25. eng
42. Chisholm EJ, Kulinskaya E, Tolley NS (2009) Systematic review and meta-analysis of the adverse effects of thyroidectomy combined with central neck dissection as compared with thyroidectomy alone. Laryngoscope 119(6):1135–1139. PubMed PMID: 19358241. Epub 2009/04/10. eng
43. Cheah WK, Arici C, Ituarte PH, Siperstein AE, Duh QY, Clark OH (2002) Complications of neck dissection for thyroid cancer. World J Surg 26(8):1013–1016. PubMed PMID: 12045861. Epub 2002/06/05. eng
44. Segal K, Friedental R, Lubin E, Shvero J, Sulkes J, Feinmesser R (1995) Papillary carcinoma of the thyroid. Otolaryngol–Head Neck Surg (official journal of American Academy of Otolaryngology-Head and Neck Surgery) 113(4):356–363. PubMed PMID: 7567004. Epub 1995/10/01. eng
45. Carling T, Carty SE, Ciarleglio MM, Cooper DS, Doherty GM, Kim LT et al (2012) American Thyroid Association design and feasibility of a prospective randomized controlled trial of prophylactic central lymph node dissection for papillary thyroid carcinoma. Thyroid (official journal of the American Thyroid Association) 22(3):237–244. PubMed PMID: 22313454. Epub 2012/02/09. eng
46. Conzo G, Pasquali D, Bellastella G, Esposito K, Carella C, De Bellis A et al (2013) Total thyroidectomy, without prophylactic central lymph node dissection, in the treatment of differentiated thyroid cancer. Clinical retrospective study on 221 cases. Endocrine 44(2):419–425. PubMed PMID: 23334946. Epub 2013/01/22. eng
47. Cayo AK, Yen TW, Misustin SM, Wall K, Wilson SD, Evans DB et al (2012) Predicting the need for calcium and calcitriol supplementation after total thyroidectomy: results of a prospective, randomized study. Surgery 152(6):1059–1067. PubMed PMID: 23068088. Epub 2012/10/17. eng
48. Sawka AM, Brierley JD, Tsang RW, Thabane L, Rotstein L, Gafni A et al (2008) An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. Endocrinol Metab Clin North Am 37(2):457–480, x. PubMed PMID: 18502337. Epub 2008/05/27. eng
49. Mazzaferri EL, Kloos RT (2001) Clinical review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 86(4):1447–1463. PubMed PMID: 11297567. Epub 2001/04/12. eng
50. Goffredo P, Roman SA, Sosa JA. Have 2006 ATA practice guidelines affected the treatment of differentiated Thyroid cancer in the United States? Thyroid 24(3):463–471. PubMed PMID: 23978295. Epub 2013/08/28. eng
51. DeGroot LJ, Kaplan EL, McCormick M, Straus FH. Natural history, treatment, and course of papillary thyroid carcinoma. J Clin Endocrinol Metab 71(2):414–424. PubMed PMID: 2380337. Epub 1990/08/01. eng
52. Samaan NA, Schultz PN, Hickey RC, Goepfert H, Haynie TP, Johnston DA et al (1992) The results of various modalities of treatment of well differentiated thyroid carcinomas: a

retrospective review of 1599 patients. J Clin Endocrinol Metab 75(3):714–720. PubMed PMID: 1517360. Epub 1992/09/01. eng
53. Tsang RW, Brierley JD, Simpson WJ, Panzarella T, Gospodarowicz MK, Sutcliffe SB (1998) The effects of surgery, radioiodine, and external radiation therapy on the clinical outcome of patients with differentiated thyroid carcinoma. Cancer 82(2):375–388. PubMed PMID: 9445196. Epub 1998/01/28. eng
54. Nixon IJ, Shah JP (2014) Well differentiated thyroid cancer: are we over treating our patients? Euro J Surg Oncol (the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology) 40(2):129–132. PubMed PMID: 24373300. Epub 2014/01/01. eng
55. Hay ID, Thompson GB, Grant CS, Bergstralh EJ, Dvorak CE, Gorman CA et al (2002) Papillary thyroid carcinoma managed at the Mayo clinic during six decades (1940–1999): temporal trends in initial therapy and long-term outcome in 2444 consecutively treated patients. World J Surg 26(8):879–885. PubMed PMID: 12016468. Epub 2002/05/23. eng
56. Sawka AM, Thabane L, Parlea L, Ibrahim-Zada I, Tsang RW, Brierley JD et al (2009) Second primary malignancy risk after radioactive iodine treatment for thyroid cancer: a systematic review and meta-analysis. Thyroid (official journal of the American Thyroid Association) 19(5):451–457. PubMed PMID: 19281429. Epub 2009/03/14. eng
57. Almeida JP, Sanabria AE, Lima EN, Kowalski LP (2011) Late side effects of radioactive iodine on salivary gland function in patients with thyroid cancer. Head Neck 33(5):686–690. PubMed PMID: 21484917. Epub 2011/04/13. eng
58. Alexander C, Bader JB, Schaefer A, Finke C, Kirsch CM (1998) Intermediate and long-term side effects of high-dose radioiodine therapy for thyroid carcinoma. J Nucl Med: (official publication, Society of Nuclear Medicine) 39(9):1551–1554. PubMed PMID: 9744341. Epub 1998/09/23. eng
59. Lang BH, Wong IO, Wong KP, Cowling BJ, Wan KY (2012) Risk of second primary malignancy in differentiated thyroid carcinoma treated with radioactive iodine therapy. Surgery 151(6):844–850. PubMed PMID: 22341041. Epub 2012/02/22. eng
60. Gramza A, Schuff KG (2009) Recombinant human thyroid stimulating hormone in 2008: focus on thyroid cancer management. Onco Targets Ther 1:87–101. PubMed PMID: 21127756. Pubmed Central PMCID: Pmc2994210. Epub 2009/01/01. eng
61. Lee J, Yun MJ, Nam KH, Chung WY, Soh EY, Park CS (2010) Quality of life and effectiveness comparisons of thyroxine withdrawal, triiodothyronine withdrawal, and recombinant thyroid-stimulating hormone administration for low-dose radioiodine remnant ablation of differentiated thyroid carcinoma. Thyroid (official journal of the American Thyroid Association) 20(2):173–179. PubMed PMID: 20151824. Epub 2010/02/16. eng
62. Luster M, Felbinger R, Dietlein M, Reiners C (2005) Thyroid hormone withdrawal in patients with differentiated thyroid carcinoma: a one hundred thirty-patient pilot survey on consequences of hypothyroidism and a pharmacoeconomic comparison to recombinant thyrotropin administration. Thyroid (official journal of the American Thyroid Association) 15(10):1147–1155. PubMed PMID: 16279848. Epub 2005/11/11. eng
63. Dow KH, Ferrell BR, Anello C (1997) Quality-of-life changes in patients with thyroid cancer after withdrawal of thyroid hormone therapy. Thyroid (official journal of the American Thyroid Association) 7(4):613–619. PubMed PMID: 9292951. Epub 1997/08/01. eng
64. Taieb D, Sebag F, Cherenko M, Baumstarck-Barrau K, Fortanier C, Farman-Ara B et al (2009) Quality of life changes and clinical outcomes in thyroid cancer patients undergoing radioiodine remnant ablation (RRA) with recombinant human TSH (rhTSH): a randomized controlled study. Clin Endocrinol 71(1):115–23. PubMed PMID: 18803678. Epub 2008/09/23. eng
65. Roberts CG, Ladenson PW (2004) Hypothyroidism. Lancet 363(9411):793–803. PubMed PMID: 15016491. Epub 2004/03/16. eng
66. Robbins RJ, Driedger A, Magner J (2006) Recombinant human thyrotropin-assisted radioiodine therapy for patients with metastatic thyroid cancer who could not elevate endogenous thyrotropin or be withdrawn from thyroxine. Thyroid (official journal of the

American Thyroid Association) 16(11):1121–1130. PubMed PMID: 17123339. Epub 2006/11/25. eng
67. Barbaro D, Boni G, Meucci G, Simi U, Lapi P, Orsini P et al (2006) Recombinant human thyroid-stimulating hormone is effective for radioiodine ablation of post-surgical thyroid remnants. Nucl Med Comm 27(8):627–632. PubMed PMID: 16829763. Epub 2006/07/11. eng
68. Tuttle RM, Brokhin M, Omry G, Martorella AJ, Larson SM, Grewal RK et al (2008) Recombinant human TSH-assisted radioactive iodine remnant ablation achieves short-term clinical recurrence rates similar to those of traditional thyroid hormone withdrawal. J Nucl Med (official publication, Society of Nuclear Medicine) 49(5):764–770. PubMed PMID: 18413378. Epub 2008/04/17. eng
69. Molinaro E, Giani C, Agate L, Biagini A, Pieruzzi L, Bianchi F et al (2013) Patients with differentiated thyroid cancer who underwent radioiodine thyroid remnant ablation with low-activity (1)(3)(1)I after either recombinant human TSH or thyroid hormone therapy withdrawal showed the same outcome after a 10-year follow-up. J Clin Endocrinol Metab 98(7):2693–2700. PubMed PMID: 23626005. Epub 2013/04/30. eng
70. Pacini F, Molinaro E, Castagna MG, Lippi F, Ceccarelli C, Agate L et al (2002) Ablation of thyroid residues with 30 mCi (131)I: a comparison in thyroid cancer patients prepared with recombinant human TSH or thyroid hormone withdrawal. J Clin Endocrinol Metab 87 (9):4063–4068. PubMed PMID: 12213846. Epub 2002/09/06. eng
71. Wang TS, Cheung K, Mehta P, Roman SA, Walker HD, Sosa JA. To stimulate or withdraw? A cost-utility analysis of recombinant human thyrotropin versus thyroxine withdrawal for radioiodine ablation in patients with low-risk differentiated thyroid cancer in the United States. J Clin Endocrinol Metab 95(4):1672–1680. PubMed PMID: 20139234. Epub 2010/02/09. eng
72. Caglar M, Bozkurt FM, Akca CK, Vargol SE, Bayraktar M, Ugur O et al (2012) Comparison of 800 and 3700 MBq iodine-131 for the postoperative ablation of thyroid remnant in patients with low-risk differentiated thyroid cancer. Nucl Med Commun 33(3):268–274. PubMed PMID: 22205241. Epub 2011/12/30. eng
73. Cheng W, Ma C, Fu H, Li J, Chen S, Wu S et al (2013) Low- or high-dose radioiodine remnant ablation for differentiated thyroid carcinoma: a meta-analysis. J Clin Endocrinol Metab 98(4):1353–1360. PubMed PMID: 23436920. Epub 2013/02/26. eng
74. Fallahi B, Beiki D, Takavar A, Fard-Esfahani A, Gilani KA, Saghari M et al (2012) Low versus high radioiodine dose in postoperative ablation of residual thyroid tissue in patients with differentiated thyroid carcinoma: a large randomized clinical trial. Nucl Med Commun 33 (3):275–282. PubMed PMID: 22124360. Epub 2011/11/30. eng
75. Hundahl SA, Fleming ID, Fremgen AM, Menck HR (1998) A National Cancer data base report on 53,856 cases of thyroid carcinoma treated in the U.S. 1985–1995 (see commetns). Cancer 83(12):2638–2648. PubMed PMID: 9874472. Epub 1999/01/05 21:59. eng
76. Enewold L, Zhu K, Ron E, Marrogi AJ, Stojadinovic A, Peoples GE et al (2009) Rising thyroid cancer incidence in the United States by demographic and tumor characteristics, 1980–2005. Cancer Epidemiol, Biomark Prev (a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology) 18(3):784–791. PubMed PMID: 19240234. Pubmed Central PMCID: Pmc2676561. Epub 2009/02/26. eng
77. Elisei R (2008) Routine serum calcitonin measurement in the evaluation of thyroid nodules. Best Pract Res Clin Endocrinol Metab 22(6):941–953. PubMed PMID: 19041824. Epub 2008/12/02. eng
78. Bondeson L, Ljungberg O (1981) Occult thyroid carcinoma at autopsy in Malmo, Sweden. Cancer 47(2):319–323. PubMed PMID: 7459819. Epub 1981/01/15. eng
79. Bondeson L, Ljungberg O (1984) Occult papillary thyroid carcinoma in the young and the aged. Cancer 53(8):1790–1792. PubMed PMID: 6697317. Epub 1984/04/15. eng
80. Bergholm U, Adami HO, Telenius-Berg M, Johansson H, Wilander E (1990) Incidence of sporadic and familial medullary thyroid carcinoma in Sweden 1959 through 1981. A nationwide study in 126 patients. Swedish MCT study group. Acta Oncol (Stockholm, Sweden) 29(1):9–15. PubMed PMID: 2310607. Epub 1990/01/01. eng

81. Kloos RT, Eng C, Evans DB, Francis GL, Gagel RF, Gharib H et al (2009) Medullary thyroid cancer: management guidelines of the American Thyroid Association. Thyroid (official journal of the American Thyroid Association) 19(6):565–612. PubMed PMID: 19469690. Epub 2009/05/28. eng
82. Baloch ZW, LiVolsi VA (2001) Prognostic factors in well-differentiated follicular-derived carcinoma and medullary thyroid carcinoma. Thyroid (official journal of the American Thyroid Association) 11(7):637–645. PubMed PMID: 11484892. Epub 2001/08/04. eng
83. Daniels GH (2011) Screening for medullary thyroid carcinoma with serum calcitonin measurements in patients with thyroid nodules in the United States and Canada. Thyroid (official journal of the American Thyroid Association) 21(11):1199–1207. PubMed PMID: 21936671. Epub 2011/09/23. eng
84. Vierhapper H, Niederle B, Bieglmayer C, Kaserer K, Baumgartner-Parzer S (2005) Early diagnosis and curative therapy of medullary thyroid carcinoma by routine measurement of serum calcitonin in patients with thyroid disorders. Thyroid (official journal of the American Thyroid Association) 15(11):1267–1272. PubMed PMID: 16356091. Epub 2005/12/17. eng
85. Costante G, Meringolo D, Durante C, Bianchi D, Nocera M, Tumino S et al (2007) Predictive value of serum calcitonin levels for preoperative diagnosis of medullary thyroid carcinoma in a cohort of 5817 consecutive patients with thyroid nodules. J Clin Endocrinol Metab 92(2):450–455. PubMed PMID: 17119000. Epub 2006/11/23. eng
86. Pacini F, Fontanelli M, Fugazzola L, Elisei R, Romei C, Di Coscio G et al (1994) Routine measurement of serum calcitonin in nodular thyroid diseases allows the preoperative diagnosis of unsuspected sporadic medullary thyroid carcinoma. J Clin Endocrinol Metab 78(4):826–829. PubMed PMID: 8157706. Epub 1994/04/01. eng
87. Cheung K, Roman SA, Wang TS, Walker HD, Sosa JA (2008) Calcitonin measurement in the evaluation of thyroid nodules in the United States: a cost-effectiveness and decision analysis. J Clin Endocrinol Metab 93(6):2173–2180. PubMed PMID: 18364376. Epub 2008/03/28. eng
88. Hay ID, Grant CS, Taylor WF, McConahey WM (1987) Ipsilateral lobectomy versus bilateral lobar resection in papillary thyroid carcinoma: a retrospective analysis of surgical outcome using a novel prognostic scoring system. Surgery 102(6):1088–1095. PubMed PMID: 3686348. Epub 1987/12/01. eng