Update on Certain Aspects of the Evidence-based Clinical Practice Guidelines on Thyroid Nodules (Focused on the Diagnosis and Management of Well-Differentiated Thyroid Cancer)

Ida Marie Tabangay-Lim, M.D., F.P.C.S.; Arlene T. Fajardo, M.D., F.P.C.S.; Marwin Emerson V. Matic, M.D. and Alfred Philip O. de Dios, M.D., F.P.C.S. *for the Philippine Academy of Head and Neck Surgeons, Inc.*

Fernando L. Lopez, M.D., F.P.C.S. and Nilo C. De los Santos, M.D., F.P.C.S. *for the Philippine Society of General Surgeons*

Ma. Luisa D. Aquino, M.D., F.P.C.S.; Ma. Cheryl L. Cucueco, M.D., F.P.C.S.; Leonardo O. Ona III, M.D., F.P.C.S. and Jose Modesto B. Abellera III, M.D., F.P.C.S. *for the Philippine College of Surgeons Committee on Surgical Research*

The Philippine College of Surgeons (PCS) through its Committee on Surgical Research, in cooperation with the Philippine Society of General Surgeons (PSGS) and the Philippine Academy of Head and Neck Surgery, Inc. (PAHNSI) published the Evidence-based Clinical Practice Guideline on Thyroid Nodules in 2008 (PJSS Vol 63 No. 3). This guideline covers the comprehensive management of thyroid nodules -both benign and malignant. After five years, the PCS through its Committee on Cancer and Committee on Surgical Research, again in cooperation with the PAHNSI and the PSGS worked on updating its guidelines particularly those pertaining to the management of thyroid cancer, which is among the top ten cancers in the Philippines. This update focuses on the diagnostic and therapeutic aspects of the management of well-differentiated thyroid cancer including postoperative surveillance. It is based on the most recent available scientific evidence and the views of local experts. It is intended to guide surgeons (fellows, resident trainees) and general physicians involved in the management of thyroid cancer and practicing in the Philippines.

Technical Working Group:

For PAHNSI:
Alfred Philip O. de Dios, MD
Arlene T. Fajardo, MD
Marwin Emerson V. Matic, MD
Ida Marie Tabangay-Lim, MD

For PCS:
Ma. Luisa D. Aquino, MD
Jose Modesto B. Abellera III, MD
Cheryl L. Cucueco, MD
Leonardo O. Ona III, MD

For PSGS:
Fernando L. Lopez, MD
Nilo C. de los Santos, MD

The research questions from the 2008 guidelines were reviewed and modified as needed, focusing on well-differentiated thyroid cancer. Important new issues to update the working list of research questions were discussed and developed by the members of the TWG and the PCS Committee on Surgical Research. These include the role of thyroid ultrasound in detecting malignancy and the role of central node dissection in the management of well-differentiated thyroid cancer.

The search of the available literature included publications from 2007 onwards using the same electronic database used in the 2008 PCS EBCPG: Pubmed(Medline) plus Cochrane database and manual search of the following libraries: UST,UP and De La Salle Health Sciences. The search was guided by the clinical research questions using MESH terms as applicable . All existing clinical practice guidelines on thyroid cancer were likewise searched, and the references used in these guidelines were reviewed if applicable. A total number of 50 articles were used as reference for this update.

The evidences were appraised, and the initial draft of recommendations was prepared together with the PCS Committee on Surgical Research last October 13, 2012. The group agreed to apply the Levels of Evidence of the Oxford Centre for Evidence-Based Medicine, 2011 for the new recommendations.(See Appendix A)

The initial draft was presented to a multidisciplinary panel of experts and members of the PCS Board of Regents during the PCS Annual Clinical Congress on December 5, 2012, for some revisions, and for the strength of the recommendations.

The final draft was presented in a public forum during the Philippine Society of General Surgeons Annual Meeting on August 1, 2013 held at the SMX Convention Hall.

Categories of Recommendations

Category A   At least 75 percent consensus by expert panel present

Category B   Recommendation somewhat controversial and did not meet consensus

Category C   Recommendation caused real disagreements among members of the panel

Members of the Expert Panel:

 1. Alejandro C. Dizon, MD
 2. Jose Macario V. Faylona, MD
 3. Ramon S. Inso, MD
 4. George G. Lim, MD
 5. Ramoncito C. Magnaye, MD
 6. Maximo B. Nadala, MD
 7. Enrico P. Ragaza, MD
 8. Rhoel de Leon, MD
 9. Mark R. Kho, MD
10. Daniel L. de la Paz, MD
11. Edgardo R. Cortez, MD
12. Rodney B. Dofitas, MD
13. Joselito F. David, MD
14. Juan P. Sanchez Jr., MD
15. Ray I. Sarmiento, MD
16. Jose Roberto V. Claridad, MD
17. Rowen Yolo, MD
18. Jonas Y. Santiago, MD
19. Sjoberg A. Kho, MD
20. Bien J. Matawaran, MD
21. Ruben L. Carreon, MD
22. Lino Santiago S. Pabillo, MD

List of Clinical Questions:

1. What is the appropriate diagnostic work-up in a patient with thyroid nodule ?
    1.1 What is the role of thyroid function tests (TSH, T3, T4, FT4)?
    1.2 What is the role of ultrasonography ?
        1.2.1 Who should undergo ultrasonography?
        1.2.2 What are the indications for doing ultrasound guided fine needle aspiration biopsy?
    1.3 What is the role of radioisotope scan?
    1.4 What is the role of fine needle biopsy (FNAC)?
    1.5 What is the role of frozen section in the intraoperative diagnosis of thyroid nodule?

2. What is the recommended treatment for well-differentiated thyroid cancer (WDTC)?
   2.1 What is the recommended surgical procedure for the treatment of WDTC?
   2.2 What is the role of central node dissection in the management of patients with well-differentiated thyroid cancer in improving overall and disease-free survival?
       2.2.1 What is the role of therapeutic central node dissection?
       2.2.2 What is the role of prophylactic central node dissection?
   2.3 What is the role of radioactive iodine remnant ablation therapy in the treatment of WDTC?
   2.4 What is the role of completion thyroidectomy in the treatment of WDTC?
   2.5 What is the role of external beam radiation in the treatment of WDTC?
   2.6 What is the role of TSH suppression therapy in the treatment of WDTC?

3. What is the recommended postoperative surveillance for patients with WDTC?
   3.1 What is the role of thyroglobulin assay for postoperative surveillance in patients with WDTC?
   3.2 What is the role of TSH for postoperative surveillance in patients with WDTC?
   3.3 What is the role of ultrasonography for postoperative surveillance in patients with WDTC?
   3.4 What is the role of whole body scan for postoperative surveillance in patients with WDTC?

Recommendations with no new evidence:

After search of the literature was done, no new evidence was found regarding the following research questions of the PCS EBCPG on Thyroid Nodules published in 2008, hence their recommendations remain the same:

1. What is the appropriate diagnostic work up for a patient with a thyroid nodule?
   1.1 Role of thyroid function tests: TSH, T3, T4
   1.3 Role of radioisotope scan in the diagnosis of thyroid nodule

   1.4 Role of fine needle biopsy (FNAC) in the diagnosis of thyroid nodule
   1.5 Role of frozen section in the intraoperative diagnosis of a thyroid nodule.

2. What is the recommended treatment for well-differentiated thyroid cancer?
   2.4 Role of completion thyroidectomy in the treatment of WDTC
   2.5 Role of external beam radiation in the treatment of WDTC

3. What is the recommended postoperative surveillance for patients with WDTC?
   3.3 What is the role of ultrasonography for postoperative surveillance in patients with WDTC?
   3.4 Role of whole body scan in the postoperative surveillance of patients with WDTC?

Recommendations with updated evidence:

1. What is the appropriate diagnostic work-up in a patient with thyroid nodule?
   1.2 What is the role of ultrasonography in the diagnosis of thyroid nodule?
       1.2.1 Who should undergo ultrasonography?
       1.2.2 What are the indications for doing ultrasound guided fine needle aspiration biopsy?

2. What is the recommended treatment for well-differentiated thyroid cancer?
   2.1 What is the recommended surgical procedure for well differentiated thyroid cancer?
   2.2 What is the role of central node dissection in the management of patients with well-differentiated thyroid cancer in improving overall and disease free survival?
       2.2.1 What is the role of therapeutic central node dissection?
       2.2.2 What is the role of prophylactic central compartment dissection?
   2.3 What is the role of radioactive iodine remnant ablation therapy in the treatment of WDTC?
   2.4 What is the role of TSH suppression therapy in the treatment of WDTC?

3. What is the recommended postoperative surveillance for patients with WDTC?
   3.1 What is the role of thyroglobulin assay in the postoperative surveillance of patients with WDTC?
   3.2 What is the role of TSH in the postoperative surveillance of patients with WDTC?

Recommendations

1. What is the appropriate diagnostic work-up in a patient with thyroid nodule?

1.2 What is the role of ultrasonography in the diagnosis of thyroid nodule?

   1.2.1 Who should undergo ultrasonography?

Thyroid ultrasound is not recommended as a screening test for the general population.

It is recommended for the following:

1. Evaluation of the patient with nodular goiter.
2. Those with adenopathy suggestive of a malignant lesion.
3. Screening of High-risk patients (patients with history of familial thyroid cancer, previous diagnosis of MEN2, childhood cervical irradiation).

Level 5, Category B

Summary of Evidence

High-resolution ultrasound is the most sensitive test available to detect thyroid lesions, measure their dimensions accurately, identify their structure and evaluate diffuse changes in the thyroid gland. Ultrasound can identify thyroid nodules that have been missed on physical examination, isotope scanning and other imaging techniques. This study, however, should not be performed on an otherwise normal thyroid gland nor used as a substitute for a physical examination. The role of ultrasound as a screening test for thyroid nodules is limited.[1] Due to the high prevalence of thyroid nodules and the high survival rate and good prognosis, the consensus made by the AACE is that a screening test for thyroid malignancy is not justified.[2]

In all patients with palpable thyroid nodules or MNG, ultrasound should be performed to accomplish the following: help with the diagnosis in difficult cases (as in Hashimoto's thyroiditis), look for coincidental thyroid nodules, detect ultrasound features suggestive of malignant growth and select the lesions to be recommended for fine-needle aspiration (FNA) biopsy.

The physical finding of adenopathy suspicious for malignant involvement in the anterior or lateral neck compartments warrants ultrasound examination of the lymph nodes and thyroid gland because of the risk of a lymph node metastatic lesion from an otherwise unrecognized papillary microcarcinoma.

Ultrasound should be performed in all patients with a history of familial thyroid cancer (Familial Medullary Thyroid Carcinoma and Familial Non-medullary Thyroid Carcinoma), Multiple Endocrine Neoplasia type 2, or childhood cervical irradiation, even if palpation yields normal findings.

Familial non-medullary thyroid carcinoma (NMTC) refers to those neoplasms originating from the thyroid epithelial cell, and includes papillary thyroid carcinoma (PTC), follicular thyroid carcinoma (FTC), anaplastic thyroid carcinoma, and insular thyroid carcinoma.

In patients with non-specific symptoms (cervical pain, dysphagia, persistent cough, voice changes), ultrasound evaluation of the thyroid gland should be performed only on the basis of findings on physical examination and the results of appropriate imaging and laboratory tests.

Standardized ultrasound reporting criteria should be followed, indicating position, shape, size, margins, content, echogenic pattern, and, whenever possible, the vascular pattern of the nodule.[2] For multiple nodules, detail the nodule(s) bearing the ultrasound characteristics associated with malignancy (hypoechoic pattern and/or irregular margins, a more-tall-than-wide shape, microcalcifications, or chaotic intranodular vascular spots).[3] rather than describing the largest ("dominant") nodule.

Nodules with malignant potential should be identified, and fine needle aspiration biopsy should be suggested to the patient.

References

1. Won-Jin Moon, Jung Hwan Baek, So Kyung Jung, et al. Ultrasonography and the ultrasound-based management of thyroid nodules: Consensus statement and recommendations. Korean J Radiol 2011; 12(1): 1-14.
2. Gharib H, Papini E, Valcavi R, et al. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi Medical guidelines for clinical practice for the diagnosis and management of thyroid nodules. Endocr Pract 2010; 16 (1).
3. Lopez FL, Ampil IDE, Aquino MLD, et al. The PCS-PSGS-PAHNSI evidence-based clinical practice guidelines on thyroid nodules. PJSS 2008; 63(3): ____.
4. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid [Erratum (2010)20:674-675] 2009; 19: 1167-214.

1.2.2. What are the indications for doing ultrasound guided fine needle aspiration biopsy?

Ultrasound-guided fine needle aspiration biopsy is indicated for:

1. Multinodular goiter with suspicious ultrasound findings for malignancy
2. Complex (mixed cystic-solid) appearing nodule/s
3. Posteriorly located nodule/s
4. Ultrasound detected solitary nodule with malignant findings
5. Nodules greater than 1cm with indeterminate ultrasound findings
6. Nodules that are less than 1cm with indeterminate ultrasound findings which increase in size in a 6-18 months interval (more than a 50% change in volume or a 20% increase in at least two nodule dimensions with a minimal increase of 2 mm in solid nodules or in the solid portion of mixed cystic-solid nodules)

Level 3, Category A

Summary of Evidence

With the advent of technology advancement, the application of ultrasound-guided fine needle aspiration biopsy has been deemed as both reasonable and appropriate as part of the diagnostic armamentarium of a general surgeon in the management of a possible thyroid malignancy.

Studies abroad have demonstrated that it is accurate and efficient in determining malignancy in a thyroid nodule.[1,2,3]

Locally, a retrospective study by Young, et al.[3] in 2011 involving 2,239 nodules from 1,737 patients who underwent ultrasound guided FNAB showed that the procedure had a sensitivity of 70.3%, a specificity of 92.8%, a positive predictive value of 76.5%, a negative predictive value of 90.4%, and an accuracy rate of 87.2%.

The use of ultrasound becomes more apparent with its ability to detect characteristics that are suspicious for malignancy at its smallest/earliest dimension. In a retrospective study by Sahin, et al.[1] in 2006 involving 145 patients, they were able to demonstrate the ability of the ultrasound to diagnose microcarcinoma (less than 1 centimeter in diameter) with a sensitivity of 96.3%, a specificity of 71.2%, a negative predictive value of 44.8%, a positive predictive value of 98.8% and an accuracy rate of 76.1%.

However, studies by Kim[4] and Mazaferri[5] have recommended not to biopsy nodules smaller than 5 mm in size because of a high rate of false positive US findings as well as a high rate of inadequate cytology.

A retrospective study by Kim, et al. in 2009[4] involving 438 thyroid nodules that have been divided into groups A (<5mm), B (>5mm ≤ 10mm), and C (>10mm), demonstrated a decrease in sensitivity (85.7% vs 97.7% vs 100%), negative predictive value (94.9% vs 100% vs 100%), and accuracy (96.1% vs 99.1% vs 99.4%) in group A compared to the other groups.

Mazzaferri[5] cites that doing a needle biopsy in such small nodules evokes major patient anxiety and is likely to yield cytology that is insufficient for diagnosis, especially when done by those lacking in technical experience. Their study recommends periodic ultrasound examination as likely to be a better option for such patients since their small nodules may spontaneously disappear or fail to grow over time.

However, in a retrospective study by Ga Ram Kim, et al.[6], of 1,238 nodules with cytology and/or histologic confirmation which analyzed the ultrasound

characteristics of large (> 10mm) versus small nodules (< 10mm) , they found that there is a difference in the sonographic characteristics predictive of malignancy between small and big nodules. On multivariate analysis, the following sonographic features were shown to be independent factors for PTC in large nodules :irregular margin (OR = 37.788, P < 0.001), microcalcifications (OR = 17.799, P <0.001), microlobulated margin (OR =10.385, P < 0.001), and no vascularity (OR = 5.975, P< 0.001) . On the other hand, the following were noted to be independent factors in small lesions : irregular margin (OR = 7.185, P <0.001), microlobulated margin (OR = 5.952, P < 0.001), microcalcifications (OR = 3.722, P<0.001), marked hypoechogenicity (OR = 2.873, P = 0.004), and taller than wide shape (OR = 2.698, P<0.001. Hence, the need to do FNAC should be based on sonographic features and not on nodule size alone.

Woon-Jin Moon, et al.[7] recommend that if a nodule has indeterminate findings on US and is larger than 1 cm in diameter, ultrasound guided FNA should be performed due to the fact that the possibility of malignancy cannot be ruled out. If a nodule has indeterminate findings and it is 1 cm or less in size, a follow-up US would be appropriate, 6-18 months following the initial.[5] A growing nodule (more than a 50% change in volume or a 20% increase in at least two nodule dimensions with a minimal increase of 2 mm in solid nodules or in the solid portion of mixed cystic-solid nodules) necessitates a USFNA.[5]

When multiple nodules are found on US, not all of the nodules have to be biopsied. The risk of malignancy for patients with multiple thyroid nodules is not greatly different from that for patients with a single thyroid nodule. According to the ATA guideline[8], in the presence of two or more nodules 1-1.5 cm or more in size, a FNA biopsy is recommended for nodules with suspicious US findings. If none of the nodules has suspicious US findings, then FNA should be done for the largest one.

References

1. Sahin M, Sengul A, Berki Z, Tutuncu NB, Guvener ND. Ultrasound-guided fine-needle aspiration biopsy and ultrasonographic features of infracentimetric nodules in patients with nodular goiter: correlation with pathological findings. Endocr Pathol 2006; 17: 67-74.

2. Cai XJ, Valiyaparambath N, Nixon P, Waghorn A, Giles T, Helliwell T. Ultrasound guided fine needle aspiration cytology in the diagnosis and management of thyroid nodules. Cytopathology 2006; 17.

3   Young JK, Lumapas CG, Mirasol R. Sonographically guided fine-needle aspiration biopsy of thyroid nodules: Correlation between cytologic and histopathologic finding. Phil J Int Med 2011; 49(1).

4. Kim DW, Lee EJ, Kim SH, et al. Ultrasound-guided fine-needle aspiration biopsy of thyroid nodules: comparison in efficacy according to nodule size. Thyroid 2009; 19: 27-31.

5. Mazzaferri EL, Sipos J. Should all patients with subcentimeter thyroid nodules undergo fine-needle aspiration biopsy and preoperative neck ultrasonography to define the extent of tumor invasion? Thyroid 2008; 18: 597-602.

6. Ga Ram Kim, Myung Hyun Kim, Hee Jung Moon, et al. Sonographic characteristitcs suggesting papillary thyroid carcinoma according to nodule size. Ann Surg Oncol 2013; 20: 906-13.

7. Won-Jin Moon, Jung Hwan Baek, So Kyung Jung, et al. Ultrasonography and the ultrasound-based management of thyroid nodules: Consensus statement and recommendations. Korean J Radiol 2011; 12(1): 1-14.

8. Cooper DS, Doherty GM, Haugen BR, et al. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. Thyroid [Erratum (2010) 20: 674-675] 2009; 19: 1167-214.

2. What is the recommended treatment for well differentiated thyroid cancer (WDTC) that will improve overall and/or disease free survival?

   2.1 What is the recommended surgical procedure for well differentiated thyroid cancer that will improve overall and/or disease free survival?

The recommended surgical procedure for the treatment of WDTC is near-total or total thyroidectomy.

A lobectomy with isthmusectomy may be considered for selected low risk T1 and T2 tumors

Level 3, Category A

Summary of Evidence

The general slow progression of well-differentiated carcinoma has limited the production of randomized controlled trials with regards to the extent of surgery of well-differentiated thyroid cancer. Review of cohort

studies has produced much controversy which is yet unresolved.

In the PCS Thyroid Guidelines of 2008, the recommendation regarding total or near total thyroidectomy as the surgical procedure of choice was based mainly on the works of Udelsman and Mazzaferri.[1,2,3]

For papillary and follicular thyroid cancers, Mazzaferri, et al.[2] reported that lobectomy alone resulted in a 5%-10% recurrence rate in the opposite lobe, a high tumor recurrence rate, and a high (11%) incidence of pulmonary metastases. They stated that bilateral thyroidectomy and I_{131} ablation is justified by the high recurrence rates in patients with cervical LN metastasis and multicentric tumors. The 20-year rates for local recurrence and nodal metastasis after lobectomy were 14 and 19 percent, respectively, significantly higher (P=0.0001) than the 2 and 6 percent rates seen after bilateral thyroid resection. Patients treated with total or near-total thyroidectomy plus I_{131} ablation and L-thyroxine had significantly fewer recurrences and distant recurrences than those treated with any other combination (Figure 1). However, some have stated that the increase in recurrence rate and decrease in survival were found to have an independent effect on survival on multivariate analysis. Mazzaferri, et al. also chose to exclude patients with lesions under 1.5cm from the analysis.[4]

After total thyroidectomy, serial serum thyroglobulin measurements become a useful marker for recurrence. Postoperative iodine 131 (I_{131}) scans can be performed to diagnose recurrent or metastatic disease, and I_{131} can be used to ablate residual thyroid bed uptake or distant metastases. In addition, the total dose of I_{131} required for ablative therapy is far less following total thyroidectomy. Importantly, the local recurrence rate following total thyroidectomy is decreased, and the re-operative thyroid surgery with its inherently increased risks is minimized.

Recent cohort studies however, suggest the possibility of performing a less than total thyroidectomy for selected patients. With the increase in performing ultrasound as a diagnostic test for thyroid lesions, small thyroid cancer lesions can be easily detected. Barney, et al.[4] conducted a 19-year study of 23,605 subjects with well-differentiated cancer. They concluded that performing total thyroidectomy produced improved 10-year overall survival (OS) and cause-specific survival rates (CSS). However, performing lobectomy only produced higher OS and CSS but they were not statistically different (Figures 2 & 3).

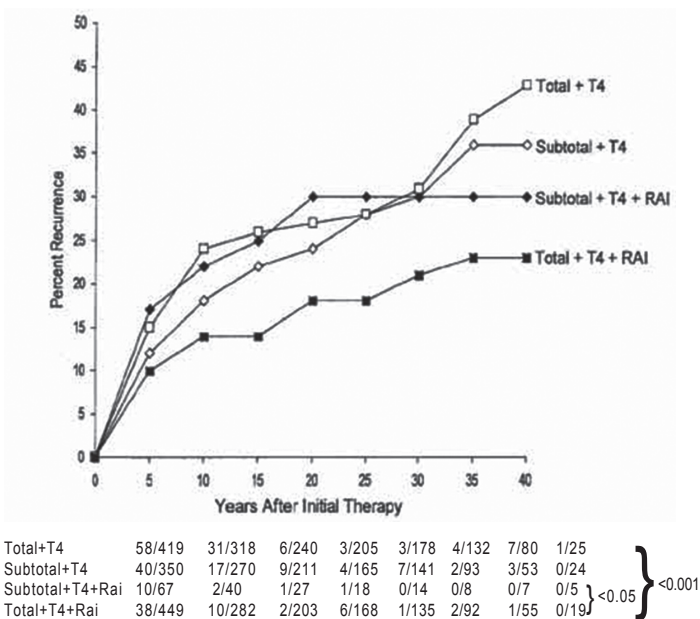|								
Total+T4	58/419	31/318	6/240	3/205	3/178	4/132	7/80	1/25
Subtotal+T4	40/350	17/270	9/211	4/165	7/141	2/93	3/53	0/24
Subtotal+T4+Rai	10/67	2/40	1/27	1/18	0/14	0/8	0/7	0/5
Total+T4+Rai	38/449	10/282	2/203	6/168	1/135	2/92	1/55	0/19

<0.05 <0.001

Figure 1. Recurrence rates following thyroid surgery and hormonal suppression +/- RAI.
Source: Mazzaferri and Kloos. Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metabol 2001; 86: 4.
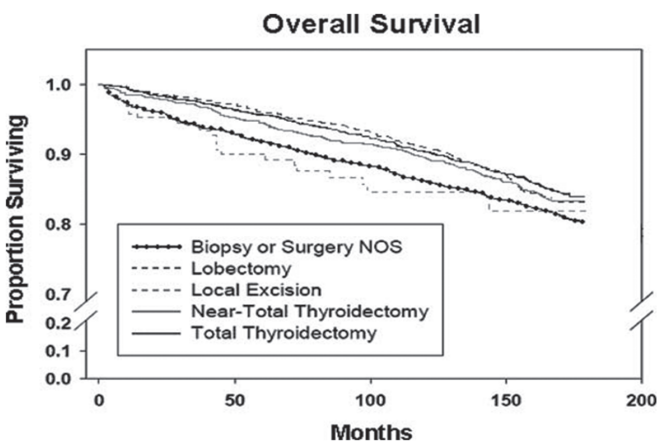

Figure 2. Overall survival by extent of surgery. NOS, not otherwise specified (Barney, 2011).
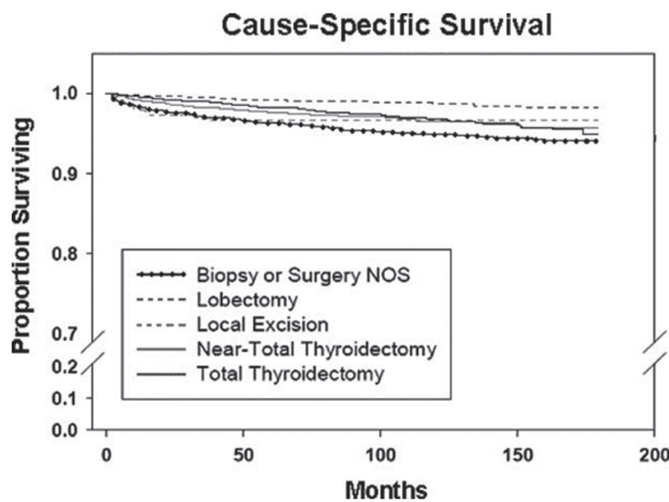
Figure 3. Cause-specific survival by extent of surgery. NOS, not otherwise specified.

This was supported by a study of Nixon, et al.[5] in 2012 of 889 patients of Memorial Sloan Kettering Cancer Center with T1 and T2 tumors with a follow-up of 99 months(Table 1). Univariate analysis showed that that there was no significant difference in the 10-year overall survival according to extent of surgery. There was also no difference in local (0% for both)and regional recurrence (0% vs 0.8 % P = .96) between total thyroidectomy and subtotal thyroidectomy groups. Age over 45 and male gender were the independent predictors of poor overall survival. Based on the results of the above studies, thyroid lobectomy with isthmusectomy may be considered as a safe alternative to total thyroidectomy for T1 and T2 well-differentiated tumors (Table 2).

Another study by Mendelsohn, et al.[6] was conducted among 22,724 patients with papillary thyroid carcinoma.

Table 1. Patient characteristics, tumor characteristics and outcomes stratified by surgical group (Nixon, 2012).

Variable	Lobectomy n = 361 n (%)	Total thyroidectomy n = 528 n (%)	P value
Age			
<45 yr	185 (54)	230 (44)	.002
>45 yr	166 (46)	298 (56)	
Gender			
Male	82 (23)	106 (20)	.345
Female	279 (77)	422 (80)	
pT stage			
pT1	249 (69)	388 (73)	.143
pT2	112 (31)	140 (27)	
RAI			
No	360 (99.7)	333 (63)	<.001
Yes	1 (0.3)	195 (27)	
Pathology			
Papillary Ca	310 (86)	490 (93)	<.001
Follicular Ca	36 (10)	16 (3)	
Hurthle cell Ca	15 (4)	22 (4)	
10-yr local recurrence	0 (0)	0 (0)	1
10-yr neck recurrence	0 (0)	5 (0.8)	.96
10-yr distant recurrence	0 (0)	5 (3)	.05
10-yr deaths of any cause	18 (7)	27 (9)	.64
10-yr disease-specific deaths	0 (0)	1 (1.5)	.245

RAI, Radioiodine ablation

Table 2. 10 year overall survival for lobectomy and total thyroidectomy groups stratified by pT,pT size and risk group. (Nixon, 2012)

		Overall 10-yr survival (%)		
Variable	n (%)	Lobectomy	Total thyroidectomy	P value
pT stage				
T1	632 (71)	92	89	.78
T2	252 (29)	96	94	.62
pT size (cm)				
<1	354 (40)	89	93	.27
1–2	283 (32)	94	87	.11
2–3	164 (18)	98	94	.93
3–4	88 (10)	94	92	.53
Risk group				
Low	374 (42)	97	96	.58
Intermediate	457 (51)	90	85	.36
High	58 (7)	90	96	.35

Among these, 5,964 patients underwent only lobectomy. Even by performing subgroup analysis for tumors 1 cm or larger, they found no significant difference in the overall survival and disease-specific survival between the groups of lobectomy versus thyroidectomy (P = .05 for OS and P = .09 for DSS) (Table 4).

Despite recent data supporting performing a less than total thyroidectomy for small thyroid carcinomas, caution must be exercised and proper selection of such candidates is needed since it was found in a retrospective medical record review done in Canada that Filipino patients experienced a thyroid cancer recurrence rate of 25% compared with 9.5% for non-Filipino patients (OR, 3.20; 95% CI, 1.23-7.49; P = .004).[7]

A retrospective study by Pellegriti, et al.[8] found that approximately 20 percent of small (< 1.5%) papillary thyroid cancer had extra thyroid invasion and/or bilateral foci which might have been overlooked in most previous studies where microcarcinoma patients where treated with lobectomy. This is important because multifocal thyroid cancers have a relapse rate higher than unifocal cancers, which is also true for microcarcinomas (8.6% vs. 1.2%).

The study showed that although small papillary cancers have a favorable outcome, it might present with signs of aggressiveness including multifocality (30%), LN metastases (30%), vascular invasion (4.7%), and even distant metastases (2.7%). Moreover, 77 (25.7%) of their patients showed evidence of persisting/relapsing disease during the follow-up period of 12.2 to 252.4

Table 3. Cox proportional HRs for overall and disease specific survival (Mendelsohn,2010).

	Overall Survival		Disease-Specific Survival	
Characteristic	HR (95% CI)	P Value	HR (95% CI)	P Value
Tumor size	1.07 (1.03-1.10)	<.001	1.56 (1.44-1.69)	<.001
Extent, localized (vs extrathyroidal)	1.46 (1.33-1.62)	<.001	3.25 (2.56-4.12)	<.001
Node status, referent: negative	1.50 (1.35-1.67)	<.001	2.49 (2.04-3.05)	<.001
Age	1.09 (1.08-1.09)	<.001	1.08 (1.07-1.09)	<.001
Male sex	1.24 (1.18-1.30)	<.001	1.06 (0.95-1.17)	.27
Race, white (vs all other races)	1.06 (0.95-1.19)	.30	0.87 (0.69-1.10)	.24
Surgical type, lobectomy (vs thyroidectomy)	0.93 (0.84-1.03)	.16	0.91 (0.71-1.15)	.41
External beam radiation therapy (vs no radiation)	1.71 (1.42-2.07)	<.001	4.48 (3.30-6.06)	<.001
Isotopes or implants (vs no radiation)	0.92 (0.88-0.97)	.002	1.21 (1.07-1.36)	.002
Histologic subtype, papillary not otherwise specified (vs follicular)	1.01 (0.92-1.11)	.85	0.89 (0.72-1.11)	.31

Abbreviations: CI, confidence interval; HR, hazard ratio.

Table 4. Recurrences according to treatment carried out for each classification system(Hurtado-Lopez,et al. 2011)

	AMES (n = 184) χ2 = 9.98 p = 0.0016		MACIS (n = 170) χ2 = 11.28 p = 0.0008		DeGroot (n = 92) χ2 = 5 p = 0.0254		TNM (n = 150) χ2 = 7.6 p = 0.0058	
	n	%	n	%	n	%	N	%
Total Thyroidectomy	7/161	4.3	5/146	3.4	2/73	2.7	7/128	5.5
Hemithyroidectomy	5/23	21.7	5/24	20.8	3/19	15.8	5/22	22.7

months (median of 45.2). This study recommended near-total or total thyroidectomy as the first choice surgical treatment.

Studies done in other countries recently have supported the need for total thyroidectomy for low risk papillary thyroid cancer. An observational study by Hurtado, et al.[9] involving 128 low risk papillary thyroid cases with 10 year follow up showed higher recurrence rates for those who have undergone hemithyroidectomy only as shown on Table 4. The recurrences were mainly regional metastases.

In another study in Romania by Varcus[10], which retrospectively reviewed 228 patients who had completion thyroidectomy after histological confirmation of thyroid cancer in the ipsilateral lobe. Only one patient with cancer < 1cm in ipsilateral lobe had malignant lesions in the contralateral lobe (4/7%). However, in patients with tumors > 1cm, the frequency of malignant lesions in the contralateral lobe was between 42.8% and 47.6%. This again supports the recommendation of doing a total thyroidectomy for tumors > 1cm.

Minimal invasive and endoscopic techniques for thyroidectomy have already been performed in our country. More studies are desired before any guidelines can be recommended for such procedures.

References

1. Udelsman R, Lakatos E, Ladenson P. Optimal surgery for papillary thyroid carcinoma. World J Surg 1996; 20: 88-93.
2. Mazzaferri EL, Kloos RT. Clinical Review 128: Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metab 2001; 86: 1447-1463.
3. Lopez FL, Ampil IDE, Aquino MLD, etal. The PCS-PSGS-PAHNSI evidence-based clinical practice guidelines on thyroid nodules. Phil J Surg Spec 2008; 63(3).
4. Barney BM, Hitchcock YJ, Sharma P, Shrieve DC, Tward JD. Overall and cause-specific survival for patients undergoing lobectomy, near-total, or total thyroidectomy for differentiated thyroid cancer. Head Neck 2011; 35 (5): 645-9.
5. Nixon IJ, Ganly I, Patel SG, Palmer FL, Whitcher MM, Tuttle RM, Shaha A, Shah JP. Thyroid lobectomy for treatment of well differentiated intrathyroid malignancy. Surgery 2012; 151 (4): 571-9.
6. Mendelsohn AH, Elashoff DA, Abemayor E, St John MA. Surgery for papillary thyroid carcinoma: is lobectomy enough? Arch Otolaryngol Head Neck Surg 2010; 136(11): 1055-61.
7. Kus LH, Shah M, Eski S, Walfish PG, Freeman JL. Thyroid cancer outcomes in Filipino patients. Arch Otolaryngol Head Neck Surg 2010; 136(2): 138-42.
8. Pellegriti G, Scollo C, Lumera G, Regalbuto C, Vigneri R, Belfiore A. Clinical behavior and outcome of papillary thyroid cancers smaller than 1.5 cm in diameter: Study of 299 cases. J Clin Endocrinol Metab 2004; 89(8): 3713-3720.
9. Hurtado-López LM, Melchor-Ruan J, Basurto-Kuba E, Montes de Oca-Durán ER, Pulido-Cejudo A, Athié-Gutiérrez C. Low-risk papillary thyroid cancer recurrence in patients treated with total thyroidectomy and adjuvant therapy vs. patients treated with partial thyroidectomy. Cirujiya y cirujanos. 2011; 79 (2): 118-25.
10. Varcus F, Bordos D, Cornianu M, Nicolicea A, Coman A, Lazar F. Thyroid cancer--the malignant lesions in the contralateral lobe. Chirurgia (Bucur). 2011; 106 (6): 765-8.

2.2 What is the role of central node dissection in the management of patients with well differentiated thyroid cancer in improving overall and disease free survival?

2.2.1   What is the role of therapeutic central compartment lymph node dissection (CLND)?

Therapeutic CLND is recommended for those with clinically palpable or ultrasonographically detected nodes.

Level 2, Category A

Summary of Evidence

Clinically evident lymph node involvement is a well-established indication for therapeutic dissection. The removal of involved cervical lymph nodes is part of loco-regional control of the disease. Two systematic reviews[1,2] showed higher rates of persistent and recurrent disease on follow-up for patients with lymph node metastases. Compartment-oriented lymph node dissection is shown to result to lower recurrences as compared to 'berry picking'. There are no clear evidences for its impact on over-all survival.

References

1. Hughes DT, Doherty GM. Central neck dissection for papillary thyroid cancer. Cancer Control 2011; 18(2): 83-8.
2. Sakorafas GH, Sampanis D, Safioleas M. Cervical lymph node dissection in papillary thyroid cancer: current trends, persisting controversies and unclarified uncertainties. Surg Oncol 2010; 19: e57-e70.

2.2.2 What is the role of prophylactic central compartment lymph node dissection?

Prophylactic central node dissection is not recommended because it does not improve overall and disease free survival.

Level 2, Category A

Summary of Evidence

Fifteen journal articles (1 prospective cohort, 11 retrospective cohorts, 2 systematic reviews and 1 meta-analysis) reported on the incidence of metastasis in the harvested nodes among patients who underwent prophylactic central lymph node dissection (CLND), or on the recurrence rate or disease-free survival against complication rates of the added procedure. Also noted was the effect of the procedure on the parameters used for surveillance.

The incidence of micrometastases in central compartment nodes ranges from as low as 45.8%[1] to as high as 60.9%.[2] Most micrometastases can be found in the pretracheal (40%) and ipsilateral (34.5%) group of nodes while the contralateral group showed an incidence of 17.4%.[2]

Several studies showed no significant difference in the recurrence rate between patients undergoing total thyroidectomy with CLND and those undergoing a total thyroidectomy only.[2,3] But the best evidence comes from two systematic reviews[4,5] which concluded that prophylactic CLND does not improve cancer survival and that there is no significant difference in recurrence rate in patients having total thyroidectomy and prophylactic CLND versus total thyroidectomy alone.

As to the complication rates, majority of studies showed an increased incidence of transient hypocalcemia and parathyroid autotransplantation among patients who underwent an additional CLND to their surgical treatment. The incidence of transient hypocalcemia ranges from 18%-51.9% for bilateral CLND, 20.5%-36.1% for unilateral CLND and 0.5%-27.7% for those without CLND.[3,6,7,8,9,10] Wong[4] gave the same conclusion and Chisholm[11] gave a risk difference of 0.13 translating into one incident of temporary hypocalcemia for every 7.7

CLNDs performed. Moreover, White, et al.[12] showed an increased incidence of permanent hypocalcemia and recurrent laryngeal nerve paralysis in patients undergoing total thyroidectomy and CLND. They reported a further increased risk of hypocalcemia and unintentional nerve injury, if the CLND was done as a second procedure. Giordano[10] showed a higher incidence of transient hypocalcemia if a bilateral CLND instead of just an ipsilateral CLND was performed (51.9% vs 36.1%). It should be noted that most of these studies employed patients whose procedures were performed by endocrine surgeons.

References

1. Chae BJ, Jung CK, Lim DJ, et al. Performing contralateral central lymph node dissection in papillary thyroid carcinoma: a decision approach. Thyroid 2011; 21(8): 873-7. Epub 2011 Jul 11

2. Wada N, Duh QY, Sugino K, et al. Lymph node metastasis from 259 papillary thyroid microcarcinomas: frequency, pattern of occurrence and recurrence, and optimal strategy for neck dissection. Ann Surg 2003; 237: 399-407.

3. Shen WT, Ogawa L, Ruan D, et al. Central neck lymph node dissection for papillary thyroid cancer. Arch Surg 2010; 145(3): 272-5.

4. Wong KP and Lang HH. The role of prophylactic central neck dissection in differentiated thyroid carcinoma: Issues and controversies. J Oncol 2011; Article ID 127929

5. Sakorafas GH, Sampanis D, Safioleas M. Cervical lymph node dissection in papillary thyroid cancer: current trends, persisting controversies and unclarified uncertainties. Surg Oncol 2010; 19:e57-e70.

6. Palestini, et al. Is central neck dissection a safe procedure in the tx of papillary thyroid cancer? Our experience. Langenbecks Arch Surg 2008; 393: 693-8.

7. Lee YS, Kim SW, Kim SW, et al. Extent of routine central lymph node dissection with small papillary thyroid carcinoma. World J Surg 2007; 31: 1954-9.

8. Lang BH, Wong KP, Wan KY, Lo CY.Impact of routine unilateral central neck dissection on preablative and postablative stimulated thyroglobulin levels after total thyroidectomy in papillary thyroid cancer. Ann Surg Oncol 2012; 19: 60-7.

9. Sywak M, Cornford L, Roach P, Stalberg P, Sidhu S, Delbridge L. Routine ipsilateral level VI lymphadenectomy reduces postoperative thyroglobulin levels in papillary thyroid cancer. Surgery 2006; 140: 1000-7.

10. Giordano D, Valcavi R, Thompson GB, et al.Complications of central neck dissection in patients with papillary thyroid carcinoma: results of a study on 1087 patients and review of literature. Thyroid. 2012; 22(9): 911-7.

11. Chisholm EJ, Kulinskaya E, Tolley NS. Systematic review and meta-analysis of the adverse effects of thyroidectomy combined with central neck dissection as comopared with thyroidectomy alone. Laryngoscope 2009; 119: 1135-9.

12. White ML, Gauger PG, Doherty GM. Central lymph node dissection in differentiated thyroid cancer. World J Surg 2007; 31: 895-904.

13. Yoo D, Ajmal S, Gowda S, Machan J, Monchik J, Mazzaglia P. Level VI lymph node dissection does not decrease radioiodine uptake in patients undergoing radioiodine ablation for differentiated thyroid cancer. World J Surg 2012; 36(6): 1255-61.

14. Alvarado R, Sywak MS, Delbridge L, Sidhu SB. Surgery. Central lymph node dissection as a secondary procedure for papillary thyroid cancer: Is there added morbidity? 2009; 145: 514-8.

15. So YK, Seo MY, Son YI. Prophylactic central lymph node dissection for clinically node-negative papillary thyroid microcarcinoma: Influence on serum thyroglobulin level, recurrence rate and postoperative complications. Surgery 2012; 151: 192-8.

2.3 What is the role of radioactive iodine remnant ablation therapy in improving overall and disease-free survival?

Radioactive iodine remnant ablation therapy is beneficial in decreasing locoregional recurrence and distant metastases.

For low risk patients who underwent total thyroidectomy, there is no benefit in giving RAI remnant ablation therapy in terms of improving disease-free survival.

Level I, Category A

Summary of Evidence

A meta-analysis by Sawka, et al in 2004[1] showed that RAI ablation may be beneficial in decreasing recurrence of WDTC. Although no randomized controlled studies were obtained, 23 studies were included out of 267 full-text papers independently reviewed. Pooled analysis showed a statistically significant treatment effect of ablation for the following 10-year outcomes: Locoregional recurrence (RR of 0.31); and distant metastases (absolute risk reduction of 3%) (Figures 1 & 2).
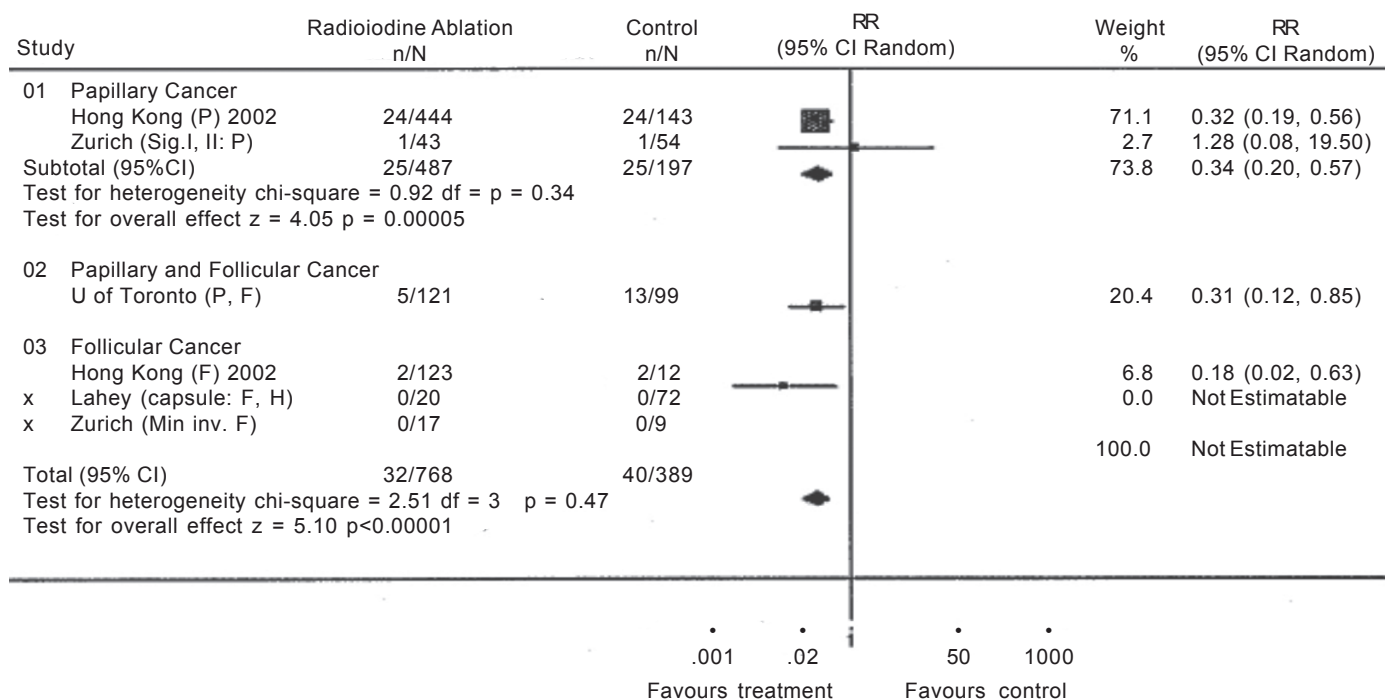
Figure 1. Random effects pooled estimate of RR reduction of RAI ablation on development of locoregional recurrence at 10 yr. n, Number of events; N, size of population studied; P, papillary; F, follicular; H, Hurthle cell; Stg I, II, stage I or II; Min inv, minimally invasive; capsule, only capsular invasion.

Source: Sawka A, Thephamongkhol K, Brouwers M, Thabane L, Browman G, Gerstein H. Clinical Review 170: A systematic review and meta-analysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. J Clin Endocrinol Metab 2004; 89(8): 3668-76.

However, Sawka, et al.[2] in 2008, published an updated systematic review on the effectiveness of RAI in well-differentiated thyroid cancer.[2] They stated that the benefit of RAI is unclear among low risk patients who underwent total or near-total thyroidectomy and are receiving thyroid hormone suppressive therapy. A similar conclusion was reported by another systematic review by Sacks, et al. in 2010.[3] Majority of very low-risk and low-risk patients who underwent post-operative RAI ablation did not demonstrate increased survival or disease-free survival.

This is further supported by a randomized phase 3 trial done by Schlumberger, et al.[4] in 2012. A total of 752 patients were enrolled and 92% of the cases had papillary cancer. Their results showed that a low dose of post-operative RAI ablation may be sufficient for low risk cancer to lessen the complications brought about by radiation exposure.

However, it is important to consider that for the subsequent follow-up of patients who did not receive post-operative RAI ablation, monitoring through the use of serum Tg levels will be complicated.

The decision to give RAI ablation must be individualized, based on the risk profile of the patient, as well as patient and physician preference, while balancing the risks and benefits of such therapy.

References

1. Sawka A, Thephamongkhol K, Brouwers M, Thabane L, Browman G, Gerstein H. Clinical Review 170: A systematic review and meta-analysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. J Clin Endocrinol Metab 2004; 89(8): 3668-76.

Study	Radioiodine Ablation n/N	Control n/N	RR (95% CI Random)	Weight %	RR (95% CI Random)
01 Papillary Cancer					
Hong Kong (P) 2002	4 / 444	5 / 143		21.1	-0.03 (-0.08, 0.01)
Zurich (Stg. IU: P)	0 / 43	0 / 54		12.9	0.00 (0.04, 0.04)
Subtotal (95% CI)	4 / 487	5 / 197		34.0	-0.22 (0.04, 0.01)
Test for heterogeneity chi-square = 1.13 df =1 p = 0.28					
Test for overall effect z = 1.17 p = 0.2					
02 Papillary and Follicular Cancer					
Ohio, USAF 2001	2 / 230	34 / 769		80.3	-0.03 (0.05, -0.02)
03 Follicular Cancer					
Hong Kong (F) 2002	9 / 123	1 / 12		0.8	0.01 (-0.17, 0.15)
Lahey (capsule: F,)	0 / 20	0 / 72		4.5	0.00 (-0.07, 0.07)
Zurich (Min inv. F)	0 / 17	1 / 9		0.4	-0.11 (-0.07, 0.05)
Subtotal (95% CI)	9 / 180	2 / 93		5.7	-0.01 (-0.07, 0.05)
Test for heterogeneity chi-square = 0.90 df = 2 p = 0.54					
Test for overall effect z = 0.29 p = 0.8					
Total (95% CI)	15 / 877	41 / 1079		100.0	-0.03 (-0.04, -0.01)
Test for heterogeneity chi-square = 3.51 df = 5 p = 0.62					
Test for overall effect z = 3.83 p = 0.0003					

.001   .02   0   50   1000
Favours treatment   Favours control

Figure 2. Random effects model examining the RD of RAI ablation on development of distant metastases at 10 yr. n, Number of events; N, size of population studied; P, papillary; F, follicular; H, Hurthle cell; Stg I, II, stage I or II; Min inv, minimally invasive; capsule, only capsular invasion; node+, including cervical lymphadenopathy.

Source: Sawka A, Thephamongkhol K, Brouwers M, Thabane L, Browman G, Gerstein H. Clinical Review 170: A systematic review and metaanalysis of the effectiveness of radioactive iodine remnant ablation for well-differentiated thyroid cancer. J Clin Endocrinol Metab 2004; 89(8): 3668-76.
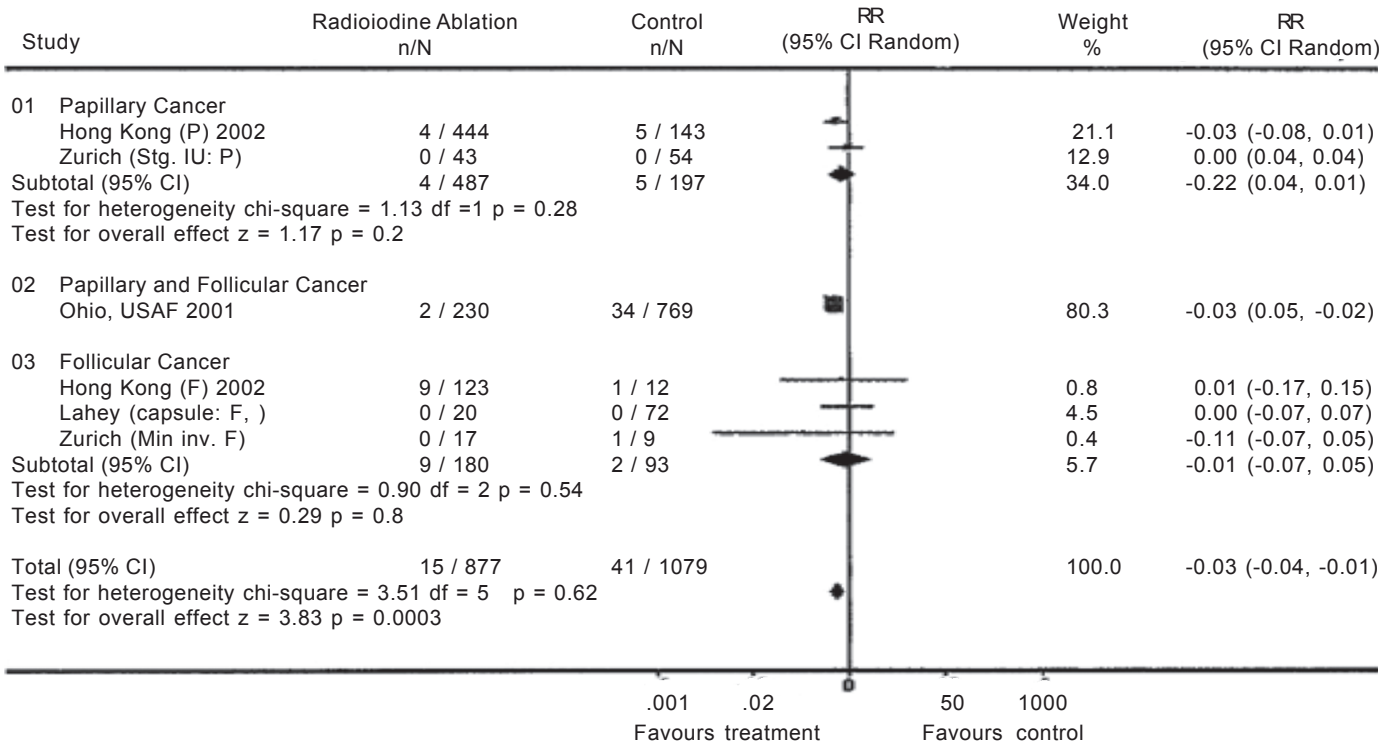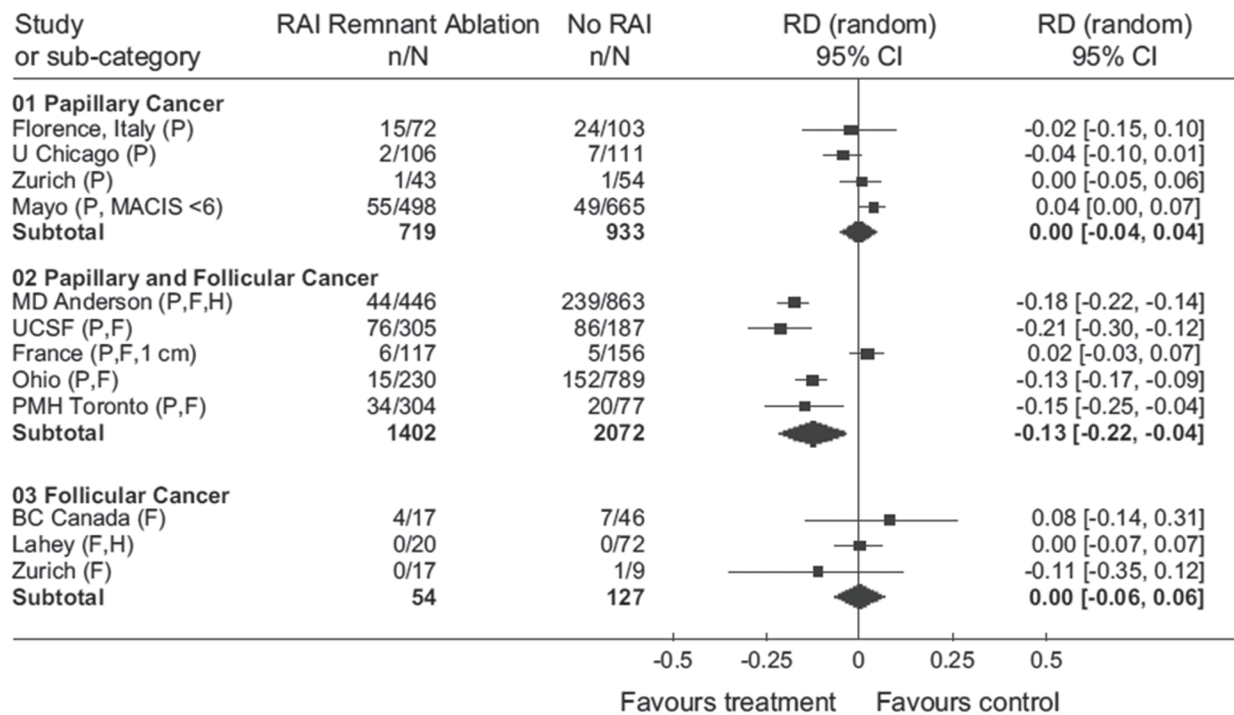
Study or sub-category	RAI Remnant Ablation n/N	No RAI n/N	RD (random) 95% CI	RD (random) 95% CI
01 Papillary Cancer				
Florence, Italy (P)	15/72	24/103		-0.02 [-0.15, 0.10]
U Chicago (P)	2/106	7/111		-0.04 [-0.10, 0.01]
Zurich (P)	1/43	1/54		0.00 [-0.05, 0.06]
Mayo (P, MACIS <6)	55/498	49/665		0.04 [0.00, 0.07]
Subtotal	**719**	**933**		**0.00 [-0.04, 0.04]**
02 Papillary and Follicular Cancer				
MD Anderson (P,F,H)	44/446	239/863		-0.18 [-0.22, -0.14]
UCSF (P,F)	76/305	86/187		-0.21 [-0.30, -0.12]
France (P,F,1 cm)	6/117	5/156		0.02 [-0.03, 0.07]
Ohio (P,F)	15/230	152/789		-0.13 [-0.17, -0.09]
PMH Toronto (P,F)	34/304	20/77		-0.15 [-0.25, -0.04]
Subtotal	**1402**	**2072**		**-0.13 [-0.22, -0.04]**
03 Follicular Cancer				
BC Canada (F)	4/17	7/46		0.08 [-0.14, 0.31]
Lahey (F,H)	0/20	0/72		0.00 [-0.07, 0.07]
Zurich (F)	0/17	1/9		-0.11 [-0.35, 0.12]
Subtotal	**54**	**127**		**0.00 [-0.06, 0.06]**

-0.5   -0.25   0   0.25   0.5

Favours treatment   Favours control

Figure 3. Pooled analysis examining risk difference for any thyroid cancer recurrence after radioactive iodine ablation (Sawka 2008).

Study or sub-category	RAI Remnant Ablation n/N	No RAI n/N	RD (random) 95% CI	RD (random) 95% CI
01 Papillary				
Zurich (P)	1/43	1/54		0.00 [-0.05, 0.06]
Hong Kong QE (P)	24/444	24/143		-0.11 [-0.18, -0.05]
Subtotal	**487**	**197**		**-0.05 [-0.20, 0.09]**
02 Papillary and Follicular				
PMH Toronto (P,F)	21/230	16/77		-0.12 [-0.21, -0.02]
Subtotal	**230**	**77**		**-0.12 [-0.21, -0.02]**
03 Follicular				
Lahey (F,H)	0/20	0/72		0.00 [-0.07, 0.07]
Zurich (F)	0/17	0/9		0.00 [-0.15, 0.15]
Hong Kong QE (F)	2/123	2/12		-0.15 [-0.36, 0.06]
Subtotal	**160**	**93**		**-0.03 [-0.13, 0.07]**

-0.5   -0.25   0   0.25   0.5

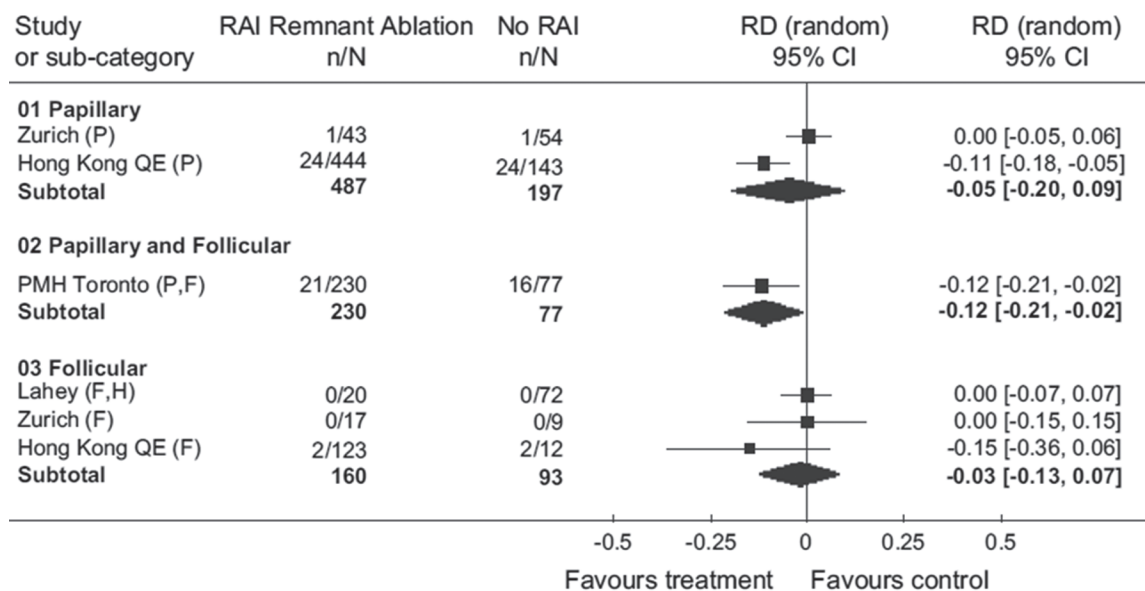Favours treatment   Favours control

Figure 4. Pooled analysis examining the risk difference for loco-regional thyroid cancer recurrence after radioactive iodine remnant ablation (Sawka 2008).

2. Sawka AM, Brierley JD, Tsang RW, Thabane L, Rotstein L, Gafni A, Straus S, Goldstein DP. An updated systematic review and commentary examining the effectiveness of radioactive iodine remnant ablation in well-differentiated thyroid cancer. Endocrinol Metab Clin North Am 2008; 37(2): 457-80.

3. Sacks W, Fung CH, Chang JT, Waxman A, Braunstein GD. The effectiveness of radioactive iodine for treatment of low-risk thyroid cancer: a systematic analysis of the peer-reviewed literature from 1966 to April 2008. Thyroid 2010; 20(11): 1235-45.

4. Schlumberger M, Catargi B, Borget I, et al. Strategies of radioiodine ablation in patients with low-risk thyroid cancer. N Engl J Med 2012; 366(18): 1663-73.

2.6 What is the role of TSH suppression therapy in the treatment of WDTC?

Thyroid hormone suppression therapy following a risk stratified approach may reduce recurrence and improve thyroid cancer-specific mortality rates and overall survival rate among high risk patients or those with stage III or IV disease.

Considering the adverse effects of TSH suppression therapy, there is no significant benefit for low risk patients especially for those with no residual or active disease.

Level 2, Category A

Specific Recommendations:

For high risk and intermediate risk* thyroid cancer patients , initial TSH suppression to below 0.1mU/L is recommended for 3 - 5 years.

For low risk* thyroid cancer patients who either received or did not receive remnant ablation, maintenance of the TSH at or slightly below the lower limit of normal (0.1-0.5 mU/L) is adequate so as to minimize the toxic effects of aggressive thyroid suppression therapy.
(*According to the Risk Stratification for Recurrence, ATA 2009)

Level 5, Category A

Summary of Evidence

Thyroid hormone suppression therapy after surgery with or without remnant ablation is an important part of the multimodal treatment of thyroid cancer. Theoretically, it is effective in stopping the growth of microscopic thyroid cancer cells or residual thyroid cancer.[1]

A prospective cohort (n=2938) which stratified patients into low risk (Stage I and II by NTCTCSG criteria) or high risk (stage III and IV) compared overall survival, disease-specific, and disease-free survival according to treatment received including degree of thyroid hormone suppression therapy. Aggressive thyroid hormone suppression therapy was found to be associated with longer overall survival among high risk patients. Moderate thyroid hormone suppression therapy predicted improved over-all survival in stage II patients. There was no impact of thyroid hormone suppression therapy among stage I patients.[2]

In a retrospective cohort of patients with metastatic differentiated carcinoma who received initial treatment and follow up in a single institution, DTC-specific survival was found to be significantly better in patients with a median TSH level of ≤ 0.1 mU/l (median survival 15.8 years) than those with a non-suppressed TSH level (median survival 7.1 years; $p<0.001$). However, suppressing TSH further (≤ 0.03 mU/l; $p=0.24$) did not result in improved survival.[3]

A randomized controlled trial comparing patients with papillary thyroid cancer who received TSH suppression therapy with those who did not, showed that disease-free survival was not inferior by more than 10% among those whose did not receive TSH suppression.[4]

There are still ongoing discussions on the duration of suppression therapy. According to the current guidelines by ESMO[5], low-risk patients who are disease-free after initial treatment may be shifted from suppressive to replacement LT4 therapy, with the goal of maintaining serum TSH level within the low normal range. However, for patients determined as high risk at the time of diagnosis but has been determined to be disease free on their first follow up after initial treatment, it is advisable to maintain them on suppressive doses of LT4 therapy (TSH < 0.1 uUI/ml) for 3-5 years because the risk of relapse in this subset of patients on long-term follow-up may still be significant.

Biondi and Cooper[6] proposed initial serum TSH targets based on the ATA risk stratification for cancer recurrence and progression[7], as well as the patients' risk

from adverse effects of LT4. The following must be taken into account: the age of the patient, and the presence of preexisting cardiovascular and skeletal risk factors that might predispose to the development of long-term adverse cardiovascular or skeletal outcomes, particularly increased heart rate and left ventricular mass, atrial fibrillation, and osteoporosis. Using this scheme, nine potential patient categories can be defined, with differing TSH targets for both initial and long-term L-T4 therapy (Tables 1 & 2).

Table 1. Suggested initial thyrotropin targets in thyroid cancer patients according to risk assessment (Biondi, 2010).

	Risk of cancer recurrence and progression		
Risk from T4 therapy	High	Intermediate	Low
High	<0.1mU/L a	0.1mU/La	0.5-1mU/L
Intermediate	<0.1mU/L b	<0.1mU/Lb	0.5-1mU/L
Low	<0.1mU/L	<0.1mU/L	0.1-0.5mU/L

a With high risk from L-T4: consider cardiovascular drugs, calcium, vitamin D, and antiresorptive drugs.
B With intermediate risk from L-T4 and high or intermediate risk of tumor progression: consider b-adrenergic blocking drugs, calcium, and vitamin D.
L-T4, levothyroxine.

Table 2. Suggested thyrotropin targets in thyroid cancer patients according to risk assessment during follow-up (Biondi, 2010).

	Risk of cancer recurrence and progression		
Risk from T4 therapy	High	Intermediate	Low
High	<0.1mU/L persistent or metastatic disease; 0.1-0.5mU/L if disease free for 5-10 years (a)	0.5-1mU/L if disease free for 5-10 years, then 1-2mU/L	1-2mU/L
Intermediate	<0.1mU/L persistent or metastatic disease b; 0.1-0.5mU/L if disease free for 5-10 years	0.1-0.5mU/L if disease free for 5-10 years, then 1-2mU/L	1-2mU/L
Low	<0.1mU/L persistent or metastatic disease c; 0.1-0.5mU/L if disease free for 5-10 years	0.1-0.5mU/L if disease free for 5-10 years, then 0.3-2mU/L	0.3-2mU/L

a With high risk from L-T4 with persistent=metastatic disease: TSH suppression should be adapted to the clinical situation.
b With intermediate risk from L-T4 with persistent=metastatic disease: consider cardiovascular drugs, calcium, and vitamin D.
c With low risk from L-T4 with persistent=metastatic disease: periodic cardiovascular and BMD assessment.

References

1. Brabant G. Thyrotropin suppressive therapy in thyroid carcinoma: what are the targets? J Clin Endocrinol Metab 2008; 93: 1167-9.
2. Jonklaas J, Sarlis NJ, Litofsky D, et al. Outcomes of patients with differentiated thyroid carcinoma following initial therapy. Thyroid 2006; 16: 1229-42.
3. Diessl S, Holzberger B, Mäder U, et al. Impact of moderate vs stringent TSH suppression on survival in advanced differentiated thyroid carcinoma. Clin Endocrinol (Oxf). 2012; 76(4):586-92. doi: 10.1111/j.1365-2265.2011.04272.x. PubMed PMID: 22059804.
4. Sugitani I, Fujimoto Y. Does postoperative thyrotropin suppression therapy truly decrease recurrence in papillary thyroid carcinoma? A randomized controlled trial. J Clin Endocrinol Metab 2010; 95(10): 4576-83. Epub 2010 Jul 21. PubMed PMID: 20660039.
5. Pacini1 F, Castagna MG, Brilli L and Pentheroudakis G. On behalf of the ESMO Guidelines Working Group on Thyroid Cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 (Supplement 5): v214-9.
6. Biondi B, Cooper DS. Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer. Thyroid 2010; 20(2):135-46.
7. Cooper DS, Doherty GM, Haugen BR, et al. Task force on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. The American Thyroid Association (ATA) Guidelines. Thyroid 2009; 19(11).

3. What is the recommended postoperative surveillance for patients with well-differentiated thyroid cancer?

Postoperative surveillance with the goal of detecting recurrence among disease free patients and progression of disease among those with residual disease can be accomplished by utilizing serum thyroglobulin, serum TSH, thyroid ultrasound, with or without whole body scan, according to the patient's risk stratification for recurrence and/or death.

Level 5, Category A

Summary of Evidence

After initial surgery and remnant ablation, the risk for recurrence and mortality in patients with well differentiated thyroid cancer should be determined based on the ATA 2009 risk stratification into low, intermediate, or high risk, and the AJCC TNM staging respectively (Table 1).[1] This can be used as a guide in determining the need and frequency of doing surveillance tests.

The diagnostic tests employed for post operative surveillance of patients with WDTC should have a high negative predictive value, so that patients who are unlikely to experience disease recurrence could be identified, hence, less aggressive management strategies which are more cost effective and safe can be used. Similarly, patients with a higher risk of recurrence should be monitored more aggressively for early detection of recurrent disease, which offers the best opportunity for effective treatment.[2]

Table 1. ATA initial risk of recurrence classification (ATA 2009):

Low-risk patients have the following characteristics:

1. no local or distant metastases;
2. complete removal of macroscopic tumor
3. there is no tumor invasion of locoregional tissues or structures nor vascular invasion
4. the tumor does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma)
5. and, if 131I is given, there is no 131I uptake outside the thyroid bed on the first posttreatment whole-body RAI scan (RxWBS)

Intermediate-risk patients have any of the following:

1. microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery;
2. cervical lymph node metastases or
3. I_{131} I uptake outside the thyroid bed on the RxWBS done after thyroid remnant ablation
4. tumor with aggressive histology or vascular invasion

High-risk patients have:

1. macroscopic tumor invasion,
2. incomplete tumor resection,
3. distant metastases, and possibly
4. thyroglobulinemia out of proportion to what is seen on the posttreatment scan

References

1. Tala H, Tuttle RM. Contemporary post surgical management of differentiated thyroid carcinoma. Clin Oncol (R Coll Radiol). 2010; 22(6):419-29. Epub 2010 Jun 1.
2. Cooper DS, Doherty GM,Haugen BR,et al. Task force on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. The American Thyroid Association (ATA) Guidelines. Thyroid 2009; 19(11).

3.1 What is the role of thyroglobulin assay for postoperative surveillance in patients with well differentiated thyroid cancer in detecting recurrence or progression of disease?

Serum thyroglobulin monitoring is essential in the follow up of patients with well differentiated thyroid cancer who underwent total thyroidectomy and radioactive iodine ablation to help detect recurrence or progression of disease

Level 2, Category A

Specific Recommendations:

1. To ensure an accurate and reliable measurement of serum Tg, an immunometric assay calibrated against the CRM- 457 international standard is recommended. If this is not possible, measurements in individual patients over time should be performed in the same laboratory and using the same assay. Quantitative determination of thyroglobulin antibodies should be likewise be done with every measurement of serum Tg.

Level 2, Category A

2. For low risk who underwent less than total thyroidectomy or total thyroidectomy without remnant ablation: periodic TSH-suppressed Tg and cervical ultrasound, followed by TSH-stimulated serum Tg measurements if the TSH- suppressed Tg testing is undetectable should be done. The change (increase) in Tg values over time should be used as a basis to work up a patient for possible progression or recurrence of disease rather than specific cut off levels of Tg (whether on TSH suppression or stimulation).

Level 4, Category A

3. For low risk DTC who underwent total thyroidectomy with remnant ablation with negative ultrasound and undetectable suppressed Tg within 1 year from treatment, TSH stimulated Tg (by hormone withdrawal or rhTSH) should be measured 1 year after the ablation to verify absence of disease. This subset of patients may be followed up with yearly clinical exam and serum Tg measurements while on hormone replacement.

Level 3, Category A

Summary of Evidence

Standardization thyroglobulin assays have not yet been achieved even with the development of an international standard which is the Certified Reference Material 457 (CRM -457). A study by Lee, et al.[1] compared the concordance of three immunoradiometric assays (IRMA) to CRM-457, and suggested that laboratories should adopt IRMAs standardized to CRM - 457.

In a retrospective analysis of 290 consecutively diagnosed cases of low risk DTC treated with thyroidectomy alone and followed up with yearly neck ultrasound and serum thyroglobulin, final Tg levels were found to be undetectable (<1 ng/ml) in 274/290 (95%) of RRA negative patients. This was not significantly different compared to a matched group of 495 RRA positive patients who had undetectable levels of Tg in 492 cases (99%) after a median follow up of 5 years. It was concluded that in most RRA negative patients, serum thyroglobulin levels spontaneously drop to undetectable levels within 5-7 years after thyroidectomy.[2] Thus, serum thyroglobulin may be useful even in patients who did not undergo RRA.

Another retrospective study reported on 312 consecutively diagnosed papillary thyroid microcarcinoma (T1NOMO) patients classified as very low risk (no family history, no history of head and neck irradiation, unifocal, no extracapsular extension and classic papillary

types) who underwent total thyroidectomy, with radioactive remnant ablation in 44 percent of the subjects. Yearly follow-up with neck ultrasound and serum thyroglobulin was done with a median follow up of 6.7 years, which showed that final serum thyroglobulin levels were undetectable (< 1 ng/ml) in all patients with RAI ablation and in 93% of those who did not receive RAI. The first neck ultrasound (6-12 months after surgery) and the last sonograms were all negative. The study proves that strict selection and classification of patients according to their risk for recurrence could help guide a cost-effective follow up protocol.[3]

References

1. Lee JI, Kim JY, Choi JY, et al. Differences in serum thyroglobulin measurements by 3 commercial immunoradiometric assay kits and laboratory standardization using Certified Reference Material 457 (CRM-457). Head Neck. 2010; 32(9):1161-6.
2. Durante C, Montesano T, Attard M, et al. On behalf of the PTC Study Group. Long-term surveillance of papillary thyroid cancer. Patients who do not undergo postoperative radioiodine remnant ablation: Is there a role for serum thyroglobulin measurement? J Clin Endocrinol Metab 2012; 7.
3. Durante C, Attard M, Torlontano M, et al. Papillary Thyroid Cancer Study Group. Identification and optimal postsurgical follow-up of patients with very low-risk papillary thyroid microcarcinomas. J Clin Endocrinol Metab 2010; 95(11): 4882-8. Epub 2010 Jul 21. PubMed PMID: 20660054.

5.2 What is the role of TSH for postoperative surveillance in the patient with WDTC?

Serum TSH level monitoring is recommended as part of postoperative surveillance to determine the adequacy of suppression to maximize the benefits while minimizing the risks associated with TSH suppression therapy.

Level 5, Category A

Summary of Evidence

Thyroid hormone suppression therapy is an essential part of the postoperative management of patients with well-differentiated thyroid cancer. The level of suppression following a risk stratified approach may reduce recurrence and improve thyroid cancer-specific mortality rates and overall survival rate among high risk patients. It also has adverse effects on the bone (osteoporosis) and the heart (arrhythmias). Thus, it is also important to monitor its levels so as to maximize its benefits while minimizing treatment related morbidity.

According to the American Thyroid Association (ATA) and European Thyroid Association ETA), TSH should be indefinitely maintained at subnormal levels (<0.1 mU/L) in patients with persistent disease in the absence of contraindications (cardiac problem or osteoporosis). In patients initially classified as high risk but have become clinically and biochemically free of disease, ATA recommends TSH levels between 0.1-0.5 mU/l for for 5-10 years . For ETA,however, TSH should be maintained at < 0.1mU/L for 3 -5 years for this subset of patients to avoid possible recurrence during this period. Thereafter, TSH may be maintained at low normal levels (0.1 - 0. 5 mU/L). In patients initially classified as low risk, serum TSH may be maintained between 0.1-0.5 mU/L . If they remain disease -free on follow up, TSH levels may be maintained in the low normal range (0.3 - 2 mU/L).[1,2,3]

Biondi, et al. (2010) proposed a stratified approach in giving TSH suppression therapy according to the risk of cancer recurrence and progression as well as the risk of adverse side effects from LT4 therapy with age, cardiovascular status and skeletal factors taken into consideration. (See Table 2 under Recommendation 2.6).[3]

References

2. Cooper DS, Doherty GM,Haugen BR,et al. Task force on Thyroid Nodules and Differentiated Thyroid Cancer. Revised American Thyroid Association management guidelines for patients with thyroid nodules and differentiated thyroid cancer. The American Thyroid Association (ATA) Guidelines. Thyroid 2009; 19(11).
2. Pacini F, Castagna MG, Brilli L and Pentheroudakis G. On behalf of the ESMO Guidelines Working Group Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2010; 21 (Supplement 5): v214-v9.
3. Biondi B, Cooper DS. Benefits of thyrotropin suppression versus the risks of adverse effects in differentiated thyroid cancer. Thyroid 2010; 20(2): 135-46.

Appendix A. Oxford centre for evidence-based medicine 2001 levels of evidence.

Question	Step 1 (Level 1*)	Step 2 (Level 2*)	Step 3 (Level 3*)	Step 4 (Level 4*)	Step 5 (Level 5)
How common is the problem?	Local and current random sample surveys (or censuses)	Systematic review of surveys that allow matching to local circumstances**	Local non-random sample**	Case-series**	n/a
Is this diagnostic or monitoring test accurate? (Diagnosis)	Systematic review of cross sectional studies with consistently applied reference standard and blinding	Individual cross sectional studies with consistently applied reference standard and blinding	Non-consecutive studies, or studies without consistently applied reference standards**	Case-control studies, or "poor or non-independent reference standard**	Mechanism-based reasoning
What will happen if we do not add a therapy? (Prognosis)	Systematic review of inception cohort studies	Inception cohort studies	Cohort study or control arm of randomized trial*	Case-series or case-control studies, or poor quality prognostic cohort study**	n/a
Does this intervention help? (Treatment Benefits)	Systematic review of randomized trials or n-of-1 trials	Randomized trial or observational study with dramatic effect	Non-randomized controlled cohort/follow-up study**	Case-series, case-control studies, or historically controlled studies**	Mechanism-based reasoning
What are the COMMON harms? (Treatment Harms)	Systematic review of randomized trials, systematic review of nested case-control studies, n-of-1 trial with the patient you are raising the question about, or observational study with dramatic effect	Individual randomized trial or (exceptionally) observational study with dramatic effect	Non-randomized controlled cohort/follow-up study (post-marketing surveillance) provided there are sufficient numbers to rule out a common harm. (For long-term harms the duration of follow-up must be sufficient.)**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning
What are the RARE harms? (Treatment Harms)	Systematic review of randomized trials or n-of-1 trial	Randomized trial or (exceptionally) observational study with dramatic effect			
Is this (early detection) test worthwhile? (Screening)	Systematic review of randomized trials	Randomized trial	Non -randomized controlled cohort/follow-up study**	Case-series, case-control, or historically controlled studies**	Mechanism-based reasoning

* Level may be graded down on the basis of study quality, imprecision, indirectness (study PICO does not match questions PICO), because of inconsistency between studies, or because the absolute effect size is very small; Level may be graded up if there is a large or very large effect size.

** As always, a systematic review is generally better than an individual study.