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The PCS-PSGS-PAHNSI Evidence-Based Clinical Practice Guidelines on Thyroid Nodules

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Starter Statement

The management of thyroid conditions involves various specialties of medicine to include internists, endocrinologists, nuclear medicine specialists, surgeons, pathologists, and radiotherapists. Since surgeons play a major role in the management of thyroid nodules especially thyroid cancer, these guidelines were developed focusing on the diagnosis and management of benign thyroid nodules and well-differentiated thyroid cancer.

Although there are other guidelines on thyroid conditions in other countries such as that of the American Thyroid Association (ATA) and the American Association of Clinical Endocrinologists (AACE), they may not be as applicable to our setting. Thyroid nodules are very common in the Philippines and there are numerous controversies related to management of this disease condition. Because of these, there is a compelling need to formulate Evidence-based Clinical Practice Guidelines (EBCPG) to guide local health practitioners in the diagnosis and treatment of the thyroid nodules.

Thus, the Philippine College of Surgeons (PCS) through its Committee on Surgical Research undertook this project in cooperation with the Philippine Society of General Surgeons (PSGS) and the Philippine Academy of Head and Neck Surgeons, Inc. (PAHNSI).

These guidelines are based on the most recent available scientific evidence and the views of local experts on current practices in the management of thyroid nodule and well-differentiated thyroid cancer. They are intended primarily to assist practitioners in clinical decision making. They are merely recommendations and are not the only acceptable methods of managing thyroid nodules. They should be modulated by patients' preferences, socio-cultural circumstances and other factors that may influence the management of individual patients. They are not intended to serve as the basis for court litigations, sanctions or related issues.

The funding for this project was provided by the PCS Foundation. Pharmaceutical companies provided assistance in the logistic and technical aspects but they were not involved in any way in the formulation of the guidelines and recommendations.

Executive Summary

The Philippine College of Surgeons (PCS) together with the Philippine Society of General Surgeons (PSGS) and the Philippine Academy of Head and Neck Surgeons, Inc. (PAHNSI) developed these Evidence-Based Clinical Practice Guidelines on Thyroid. Each was represented in the Technical Working Group (TWG).

The TWG is composed of the following:

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2. Isaac David E. Ampil II, MD (PCS)
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4. Marilou N. Agno, MD (PSGS)
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6. Randy Jesus O. Cañal, MD (PAHNSI)
7. Samantha S. Castañeda, MD (PAHNSI)
8. Jose Roberto V. Claridad, MD (PAHNSI)
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10. Joselito F. David, MD (PAHNSI)
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13. Teodoro J. Herbosa, MD (PSGS)
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15. Jose Antonio M. Salud, MD (PSGS)
16. Ray I. Sarmiento, MD (PSGS)

Important issues and a working list of research questions were discussed and developed by the members of the TWG and the PCS Committee on Surgical Research since 2006, and approved by the PCS Board of Regents last May 19, 2007. Mesh terms were used to answer the questions. Electronic database used were Pubmed (Medline) of the U.S. National Library of Medicine. This was combined with a manual search of the UST, PGH, St. Luke’s, Ateneo, Abbott, Department of Science and Technology, and Pfizer libraries to retrieve full text of some journals. A total of 678 articles were retrieved and appraised, from which 111 articles were used to answer the research questions.

The TWG held several meetings to propose a recommendation for each clinical question, based on the corresponding best scientific evidence. The group agreed to apply the Levels of Evidence of the Oxford Centre for Evidence-Based Medicine, May 2001.

Levels of Evidence

Oxford Centre for Evidence-Based Medicine, May 2001.

Level	Therapy	Diagnosis
1A	SR** with homogeneity of RCTs	SR with homogeneity of Level 1 diagnostic studies from different clinical centers
1B	Individual RCT	One clinical center
1C	All or none*	High sensitivity and specificity
2A	SR with homogeneity of cohort studies	SR with homogeneity of Level 2 diagnostic studies
2B	Individual cohort study	Cohort study
2C	Outcomes research	
3A	SR with homogeneity of case-control studies	SR with homogeneity of 3 b and better studies
3B	Individual case-control study	Non-consecutive study, or without consistently applied reference standards
4	Case series (and poor quality cohort and case-control studies)	Case-control study, poor or non-independent reference standard
5	Expert opinion	Expert opinion

To ensure acceptability to the other specialties, a multidisciplinary Panel of Experts was convened on December 3, 2007 during the PCS 63rd Annual Clinical Congress to discuss and modify the first draft, and to grade the recommendations. Recommendations were graded as follows:

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. Alex A. Erasmo, MD, FPCS
2. Alex E.L. Cerillo, MD, FPCS
3. Gabriel L. Martinez, MD, FPCS
4. Antonio S. Say, MD, FPCS
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18. Johanna Cañal, MD (PRO)
19. Jonas Y. Santiago, MD (PSNM)
20. Victor de Villa, MD (AACEP)
21. Ferdinand E. Cercenia, MD, FPCS
22. Daniel A. de La Paz Jr., MD, FPCS

Recommendations

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 and FT4)?

In the initial evaluation of a patient with a thyroid nodule, serum TSH and/or thyroid hormones are measured.

Level 5, Category A

Summary of Evidence

Cooper, et al.[1] recommend that patients with thyroid nodules should have serum TSH measurement. If serum TSH is subnormal, a radionuclide thyroid scan should be obtained to document whether the nodule is functioning, because functioning nodules rarely harbor malignancy. On the other hand, thyroid hormone levels (T3 and T4) are usually normal in the presence of a nodule, and normal thyroid hormone levels do not differentiate benign from cancerous nodules. However, the presence of hyperthyroidism or hypothyroidism favors a benign nodule.

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

Ultrasound evaluation is recommended for the following:

1. High-risk patients, (patients with history of familial thyroid cancer, previous diagnosis of MEN2, childhood cervical irradiation) .
2. Patients with suspicious nodule for cancer in the background of multinodular goiter.
3. Those with adenopathy suggestive of a malignant lesion.
4. Evaluation of the patient with nodular goiter.

Level 5, Category A

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. Due to the high prevalence of clinically inapparent, small thyroid nodules and the low-grade aggressiveness of most thyroid cancers, ultrasound should not be performed as a screening test in the general population unless well-known risk factors have been recognized.[2]

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. 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.[2]

Familial nonmedullary 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.[3]

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.

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. Nodules with malignant potential should be identified, and fine needle aspiration biopsy should be suggested to the patient.[2]

1.3. What is the role of radioisotope scan in the diagnosis of thyroid nodule?

The role of scintigraphy in the diagnostic work-up of thyroid nodules is limited to patients with subnormal serum TSH.

Level 5, Category A

Summary of Evidence

Cooper, et al.[1] showed that if serum TSH is subnormal, a radionuclide thyroid scan should be obtained to document whether the nodule is hot or cold. Functioning nodules rarely harbor malignancy. If the nodule is hot, then a biopsy is not warranted. If the nodule is cold or warm, then a biopsy should be done.

The role of thyroid scan is limited, especially in countries with iodine-rich diets, in which serum TSH measurement and thyroid ultrasound can correctly diagnose autonomous nodules in most patients, and FNA facilitates accurate diagnosis of a malignant lesion. The resolution of ultrasound is considerably greater than that of scintigraphy, and scanning has little place in the topographic assessment of nodular goiter and no place in the measurement of thyroid nodules.[2]

1.4. What is the role of fine needle biopsy (FNAC) in the diagnosis of thyroid nodule?

FNAC is recommended for the diagnosis of benign and malignant thyroid lesions.

Level 2B, Category A

Summary of Evidence

De los Santos, Gomez, Guiang, and Kintanar[4,5,6,7], in separate local studies showed that the over all diagnostic accuracy of FNAC ranges from a low of 85 percent to a high of 96 percent which is comparable to foreign studies, as indicated in Table 1.

Table 1. Summary characteristics for thyroid fine-needle aspiration: Results of local literature survey.

Author (n)	Specificity (%)	Sensitivity (%)	Diagnostic Accuracy (%)	Likelihood Ratio (+)
de los Santos ET (PGH, 1985) (61)	96.2	66.7	91.8	17.5
Gomez JA (MMC, 1995) (30)	92.3	94.4	93.5	12.25
Guiang JP (UST, 1999) (57)	85	100	96.5	6.7
Kintanar HR (QMMC, 2002) (49)	97.1	57.1	85.7	19.7

Gharib, et al.[2] reported that about 70 percent of FNA specimens are classified as benign; in addition, 5 percent are malignant, 10 percent are suspicious, and 10 percent to 20 percent are non-diagnostic or unsatisfactory. The result of FNA is important in deciding whether to manage the patient medically or surgically. Some reviews and reports have indicated that the selection of patients for surgical treatment on the basis of FNA results has increased the yield of cancer from 15 percent to 50 percent. The sensitivity and specificity of FNA performed by experienced personnel are excellent, as shown in Table 2. A major concern is the possibility of a false-negative FNA result — that is, a missed diagnosis of malignant disease. The false-negative rate is 1 percent to 11 percent (mean, 5%). Another concern is the false-positive FNA rate, defined as the percentage of patients with positive FNA results but negative histologic findings for cancer. This rate varies from less than 1 percent to 7 percent, as indicated in Table 2.

Woeber[8], in his review showed that the overall diagnostic accuracy of FNAC for benign and malignant lesions in these studies was 95 percent. The negative predictive value of a benign cytodiagnosis ranges between 89 percent and 98 percent in the seven studies with a mean of 94 percent or a false negative rate of 6 percent. The negative predictive value of an indeterminate cytodiagnosis was much lower, the false negative rate averaging 27 percent. In this study, the false positive rate of malignant cytodiagnosis was only 4 percent.

The AACE thyroid nodule guidelines state that thyroid FNA biopsy is now established as reliable and safe and has become an integral part of thyroid nodule evaluation. The central role of endocrinologists in thyroid nodule evaluation and FNA biopsy is clear, and recent surveys have emphasized that almost 100 percent of endocrinologists use FNA biopsies for diagnosis of thyroid nodules. FNA is critical in establishing benignity.[2]

Table 2. Summary characteristics for thyroid fine-needle aspiration: Results of literature survey.

Feature	Mean (%)	Range (%)	Definition
Sensitivity	83	65-98	Likelihood that patient with disease has positive test results
Specificity	92	72-100	Likelihood that patient without disease has negative test results
Positive predictive value	75	50-96	Fraction of patients with positive test results who have disease
False-negative rate	5	1-11	Fine-needle aspiration negative; histology positive for cancer
False-positive rate	5	0-7	Fine-needle aspiration positive; histology negative for cancer

Source: Gharib, et al. (2006)

1.5. What is the role of other imaging modalities such as CT scan, MRI and PET scan?

PET scan with ^{18}F-FDG is an accurate diagnostic tool in the detection of thyroid cancer in inconclusive cytologic diagnosis of thyroid nodules.

Level 1C, Category C

Magnetic Resonance Imaging (MRI) and Computed Tomography (CT) should NOT be used routinely because they are rarely diagnostic for malignant lesions in nodular thyroid disease.

Level 5, Category A

Summary of Evidence

De Geus-Oei, et al.[9], in a prospective study on 44 consecutive patients scheduled for hemithyroidectomy because of inconclusive FNAB findings showed that the pre-PET probability for cancer in this study population was 14 percent (6/44), and the post-PET probability increased to 32 percent (6/19) after a ^{18}F-FDG PET. This study showed that F-FDG PET should play an important role in the management of patients with inconclusive cytologic diagnosis of a thyroid nodule. F-FDG PET reduced the number of futile hemithyroidectomies by 66 percent. Although PET is a relatively costly procedure, this cost outweighs the costs and risks associated with unnecessary thyroid surgery.

The recommendation of Grade C was given based on the fact that PET is not only costly, it is also not available in all hospitals. It was not recommended as the test to be done in order to confirm inconclusive FNAB findings, because of its low accuracy. Rather than do a PET, it was recommended to do a repeat FNAB.

As to the use of MRI and CT, the clinical practice guidelines for Thyroid Nodules of the American Association of Clinical Endocrinologists state that they should not be used routinely because they are rarely diagnostic for malignant lesions in nodular thyroid disease.[2]

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2. What is the recommended treatment for benign thyroid nodule/s?

2.1 What is the role of medical treatment for benign thyroid nodule/s?

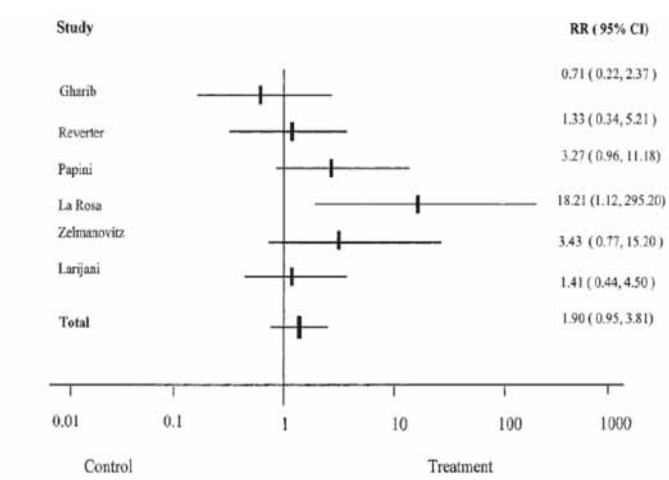
2.1.1. What is the role of TSH suppression for benign thyroid nodule/s?

TSH suppression may be considered in young patients with small (< 3 cm) cytologically benign thyroid nodules.

Level 1A, Category A

Summary of Evidence

Castro, et al.[1] did a meta-analysis which also showed that TSH suppression for 6 to 12 months resulted in a decrease in thyroid volume (22%) but was not statistically significant (relative risk= 1.9; CI: 0.95-3.81; NNT=15). The solitary nodule averaged 17.2 ml in size (Small volume – mean size single palpable 3 ml – 16 ml).



Source: Castro, et al. Effectiveness of thyroid hormone suppressive therapy in benign solitary thyroid nodules: A meta-analysis. J Clin Endocrinol Metabol 2007; 87(9): 4154–4159.

In patients with small solitary thyroid nodule, TSH suppression was shown to result in at least a 50 percent reduction in the size of the thyroid nodule. A randomized controlled trial by Wemeau, et al.[2] showed that TSH suppression for 18 months significantly reduced the growth of solitary thyroid nodules as well as prevented the development of additional nodules (relative risk=1.43; NNT=12). The volume of the thyroid nodule averaged 3.1 ml. Clinical and ultrasonographic nodule characteristics were assessed before and 3, 6, 12, and 18 months after TSH suppression. The authors concluded that 18 months of TSH suppressive L-T4 therapy was effective in reducing the growth of solitary thyroid nodules and preventing the further development of additional nodules.

Table 3. Mean changes in solitary thyroid nodule size and volume after 18 months of L-T_4 or placebo treatment.

	L-T_4	Placebo	P
Palpation			
Large nodule dimension (mm)	-3.5 $\pm$ 7	+0.5 $\pm$ 6	0.006
Ultrasonography			
Largest nodule dimension (mm)	-1.25 $\pm$ 5.57	+0.44 $\pm$ 6.9	0.07
Nodule volume (ml)	-0.36 $\pm$ 1.71	+0.62 $\pm$ 3.67	0.01

Source: Wemeau, et al. Effects of thyroid-stimulating hormone suppression with levothyroxine in reducing the volume of solitary thyroid nodules and improving extranodular non-palpable changes: A randomized, double-blind, placebo-controlled trial by the French Thyroid Research Group. J Clin Endocrinol Metabol 2002; 87(11):4928–4934.

Studies on the long-term effect of TSH suppression are lacking.

The AACE guidelines recommend levothyroxine therapy for thyroid nodules that are negative by fine needle aspiration, in patients from geographic areas with iodine deficiency, young patients with small thyroid nodules, and nodular goiters with no evidence of functional autonomy. [3]

During the public forum, "young" patients was defined to mean less than 50 years of age and premenopausal among women. It was also suggested that before starting TSH suppression therapy, baseline levels of TSH should be high.

References

1. Castro, et al. Effectiveness of thyroid hormone suppressive therapy in benign solitary thyroid nodules: A meta-analysis. J Clin Endocrinol Metabol 2007; 87(9): 4154–4159.
2. Wemeau, et al. Effects of thyroid-stimulating hormone suppression with levothyroxine in reducing the volume of solitary thyroid nodules and improving extranodular nonpalpable changes: A randomized, double-blind, placebo-controlled trial by the French Thyroid Research Group. J Clin Endocrinol Metabol 2002; 87(11): 4928–4934.
3. Gharib H, Papini E, Valcavi R, Baskin HJ, Crescenzi A, Dottorini ME, Duick DS, Guglielmi R, Hamilton Jr. CR, Zeiger MA, and Zini M. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules. Endocrinol Pract 2006; 12 (1).

2.1.2. What is the role of radioactive iodine (RAI) therapy for benign thyroid nodule/s?

Radioactive iodine (RAI) is not the primary management for benign thyroid nodule/s. However, it may be given to cases of benign non-toxic goiter patients who have cosmetic complaints or compression symptoms but who refuse surgery or who are at high risk for surgery.

Level 4, Category A

Summary of Evidence

Two case series done by Nygaard, et al.[1,2] showed that RAI may be given in cases of multinodular non-toxic goiter patients who have cosmetic complaints or compression symptoms but who refuse surgery or at high risk for surgery. Median ^{131}I dose was 555 (148-1110) MBq. The median reduction was 40 (22-48) ml (60% reduction, $p<.0001$), half of which occurred within 3 months. However, 11 patients developed hypothyroidism (cumulative 5 year risk 22%, 95% CI 4.8-38.44%). (Figure 1)

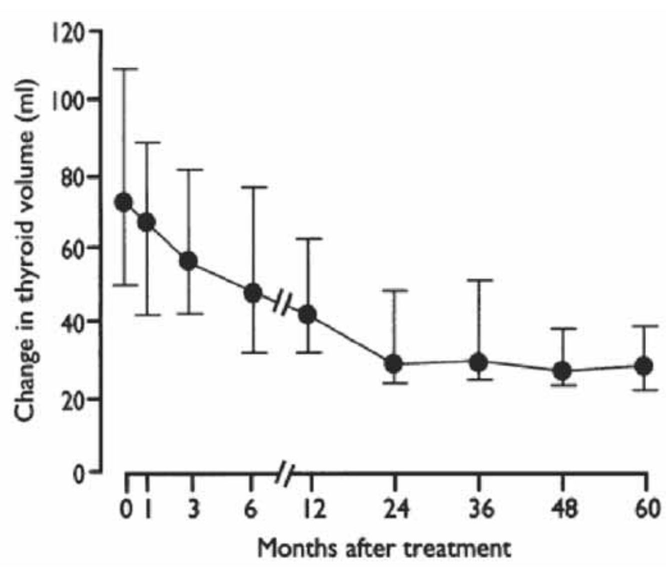


Figure 1. Median changes in thyroid volume alterations after iodine-131 treatment in 39 patients with non-toxic multinodular goitre who remained euthyroid after a single dose. Bars are quartiles.

Source: Nygaard, et al. Radioiodine treatment of multinodular non-toxic goiter. BMJ 1993; 307:828-832.

When treating toxic autonomously functioning thyroid nodules with ^{131}I, a cure rate of 75 percent within 3 months was seen. The total thyroid volume was reduced by 45 percent within 2 years, and hypothyroidism was seen in less than 10 percent. (Figure 2)

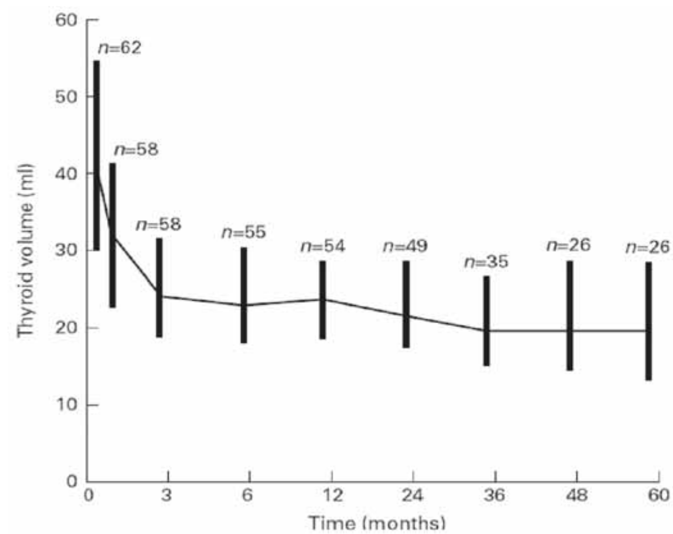


Figure 2. Radioactive iodine and thyroid size.

Source: Nygaard, et al. Long-term effect of radioactive iodine on thyroid function and size in patients with solitary autonomously functioning toxic thyroid nodules. Clin Endocrinol 1999; 50: 197–202.

References

1. Nygaard, et al. Radioiodine treatment of multinodular non-toxic goiter. BMJ 1993; 307:828-832.
2. Nygaard, et al. Long-term effect of radioactive iodine on thyroid function and size in patients with solitary autonomously functioning toxic thyroid nodules. Clin Endocrinol 1999; 50: 197–202.

2.2. What is the role of surgery in the management of benign thyroid nodule?

2.2.1. Solitary benign thyroid nodule

For a solitary benign nodule, lobectomy with isthmusectomy is sufficient.

Level 5, Category A

Summary of Evidence

According to the AACE/AME (2006) guidelines (Grade C recommendation), total or near-total lobectomy may be done, with or without isthmusectomy. A prior isthmusectomy would be of benefit in case there would be a need for a completion thyroidectomy. The latter would technically be easier if the isthmus has been resected and as such, there would be less dissection on the anterior aspect of the trachea. [1]

Reference

1. Gharib H, Papini E, Valcavi R, Baskin HJ, Crescenzi A, Dottorini ME, Duick DS, Guglielmi R, Hamilton Jr. CR, Zeiger MA, and Zini M. American Association of Clinical Endocrinologists and Associazione Medici Endocrinologi Medical Guidelines for Clinical Practice for the Diagnosis and Management of Thyroid Nodules. Endocrinol Pract 2006; 12 (1).

2.2.2. Multinodular Goiter

For multinodular goiter, the recommended surgical treatment is total or near-total thyroidectomy.

Level 1B, Category A

Summary of Evidence

A randomized study by Giles, et al.[1] on 218 patients with euthyroid multinodular goiter compared outcome following total/near-total versus bilateral subtotal thyroidectomy (Group 1: Total N=19; Near-total N=90 versus Group 2: Bilateral subtotal N=109). There were no permanent complications noted in either group. There was no difference in the incidence of temporary unilateral vocal cord dysfunction (0.9 vs 0.9%, p>0.005), but the incidence of temporary hypoparathyroidism was slightly higher in those who underwent total/near-total thyroidectomy (1.8% vs 0.9%, p>0.05%) (Table 4).

Table 4. Incidence of temporary hypoparathyroidism in 218 patients with multinodular goiter who underwent total/near-total vs bilateral subtotal thyroidectomy.

	Temporary Hypoparathyroidism (+)	(-)	
Total/Near-Total Thyroidectomy	2	107	109
Bilateral Subtotal Thyroidectomy	1	106	109

RR = 2
ARR = -0.01

Source: Giles Y, Boztepe H, Terzio T and Tezelman S. The advantage of total thyroidectomy to avoid reoperation for incidental thyroid carcinoma in multinodular goiter. Arch Surg 2004; 139:179-182.

Papillary cancer was found in 10 (9.2%) and 8 (7.3%) patients, respectively. Among these, 9 patients required RAI (5 patients in Group 1 did not undergo a second operation, 4 patients in Group 2 underwent completion thyroidectomy prior to RAI) (p=0.007) (Table 5).[1]

Table 5. Incidence of second surgery in 218 patients with multinodular goiter who underwent total/near-total vs bilateral subtotal thyroidectomy.

	Second Surgery (+)	(-)	
Total/Near-Total Thyroidectomy	0	109	109
Bilateral Subtotal Thyroidectomy	4	105	109

RR = 0

Source: Giles Y, Boztepe H, Terzio T and Tezelman S. The advantage of total thyroidectomy to avoid reoperation for incidental thyroid carcinoma in multinodular goiter. Arch Surg 2004; 139: 179-182.

Erbil, et al.[2], compared total versus near-total thyroidectomy in a randomized study of 216 patients with euthyroid multinodular goiter. There were no persistent complications, and no difference in the rate of recurrent laryngeal nerve palsy. Both procedures obviated the need for an operation for incidentally found thyroid carcinoma. For near-total thyroidectomy, the incidence of transient hypoparathyroidism (9.8 vs 26%, p<0.001) (Table 6), and asymptomatic hypocalcemia (7.4 vs 27%, p<0.001) was slightly lower.

Table 6. Incidence of transient hypoparathyroidism in 216 patients with multinodular goiter who underwent total vs near-total thyroidectomy.

	Transient Hypoparathyroidism (+)	(-)	
Total Thyroidectomy	27	77	104
Near-Total Thyroidectomy	11	101	112

RR = 2.6 ARR = - 0.16

Source: Erbil Y, Barbaros U, Salmashoglu A, Yanik B, Bozbora A and Ozarmagan S. The advantage of near-total thyroidectomy to avoid postoperative hypoparathyroidsm in multinodular goiter. Langenbecks Arch Surg 2006; 391: 567-573.

The recurrence rate of goiter was studied in a retrospective study by Ozbas, et al.[3] of 750 patients with multinodular goiter who underwent total, near-total or bilateral subtotal thyroidectomy. A 1.2 percent recurrence rate of goiter was noted in the bilateral subtotal thyroidectomy group with a median follow-up of 53 months (Table 7).

This literature review noted that the risk for recurrence of goiter in bilateral subtotal thyroidectomy is 9-43 percent, and likewise mentioned the increased surgical morbidity for reoperation. Moreover, a number of patients who underwent subtotal thyroidectomy still required thyroxine replacement following surgery.

References

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3. What is the role of frozen section in the diagnosis of thyroid CA?

Frozen section has limited utility in diagnosing thyroid malignancies if the fine needle aspiration biopsy result shows follicular neoplasm, inadequate or suspicious aspirate.

Level 1B, Category A

Summary of Evidence

Frozen section during thyroidectomy is usually requested when an initial fine-needle aspiration biopsy (FNAB) result shows follicular neoplasm, a suspicious result, or inadequate

Table 7. Complication and recurrence rates in 750 patients with multinodular goiter who underwent total, near-total or bilateral subtotal thyroidectomy.

	Total	Near-total	Bilateral subtotal
No. of patients	260	320	170
Temporary RLN palsy	5 (1.9%)	2(0.6%)	4 (2.4%)
Permanent RLN palsy	—	––	1 (0.6%)
Temporary hypoparathyroidism	78 (30%)	39 (12.2%)	14 (8.2%)
Permanent hypoparathyroidism	1 (0.4%)	––	—
Recurrence of goiter	—	––	2 (1.2%)
Hematoma	1 (0.4%)	––	—
Wound infection	—	––	1 (0.6%)
Follow-up (months)	51 (22-96)	50 (25-90)	61 (18-102)

Source: Ozbas, et al. Comparison of the complications of subtotal, near total and total thyroidectomy in the surgical management of multinodular goiter. Endocrine Journal 2005; 52(2): 199-205.

aspirate. Several studies have shown a low sensitivity of frozen section when done base on these non-confirmatory FNAB results.

A meta-analysis by Miltenburg[1] of 2204 patients who underwent both frozen section and final histopathology with FNAB of follicular adenoma showed a sensitivity of frozen section to be 87 percent, specificity of 48 percent with an accuracy of 82 percent. This meta-analysis suggests that frozen section is not a specific test and cannot be used to confidently rule out follicular carcinoma. (Figure 3)

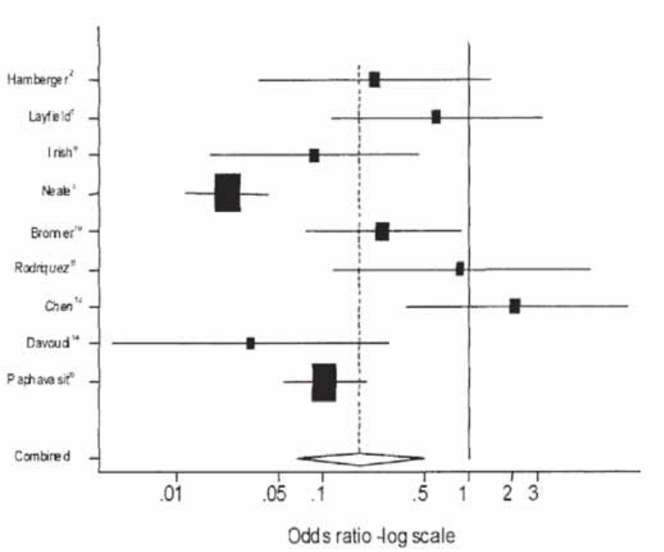


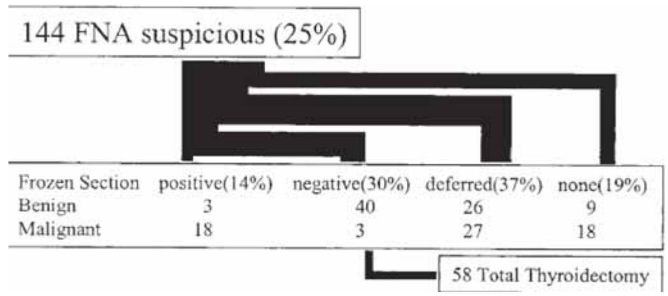
Figure 3. Frozen section Odds ratio 0.181 (95% CI 0.06-49); R = 0.01.

Source: Miltenburg, et al. The role of frozen section, gender, age, and tumor size in the differentiation of follicular adenoma from carcinoma: A meta-analysis. Surgery 2000; 128:1075-1081.

Following a suspicious FNAB, frozen section was reported by Brooks [2] to have a sensitivity of only 37.5 percent with a specificity of 57.97 percent. Furthermore, frozen section changed the management in only 5 percent. (Table 8)

Similar results were noted by Cetin[3] who reported a sensitivity of frozen section of 33.33 percent and a specificity of 93.75 percent for patients who had inadequate or suspicious FNAB. (Table 9)

Table 8. Frozen section in suspicious fine-needle aspiration biopsy.



Source: Brooks, et al. Role of fine-needle aspiration biopsy and frozen section analysis in the surgical management of thyroid tumors. Ann Surg Oncol 2001.

Table 9. Sensitivity and specificity of frozen section for patients who had inadequate or suspicious fine-needle aspiration biopsy.

	Final histopath malignant	Final histopath benign
Frozen section malignant	4	0
Frozen section deferred	5	1
Frozen section benign	3	15
Total	12	16

Source: Cetin, et al. Frozen section in thyroid surgery: Is it a necessity? Can J Surg 2004; 47(1).

A study by Alonso[4] involving 66 solitary thyroid nodules with FNAB findings of follicular neoplasm showed sensitivity of frozen section to be 13.33 percent. They concluded that the routine use of intraoperative frozen section is useless in cases of cytological diagnosis of follicular neoplasm on FNA biopsy because of the low probability of detecting a follicular carcinoma. (Table 10)

Table 10. Final diagnosis in the 66 cases studied in frozen section (64 "deferred" cases and 2 classified as follicular variant of papillary carcinoma).

	Final Pathology			
Frozen Section Category	Follicular Carcinoma	Follicular Variant of Papillary Carcinoma	Folliluar Adenoma	Nodular Hyperplasia
Malignant	0	2	0	0
"Deferred"	8	7	19	30

Source: Alonso, et al. Frozen section in a cytological diagnosis of thyroid follicular neoplasm laryngoscope 2003; 113: 563-566; 8(2):92-100.

A local study by Erese, et al.[5] also supports the above studies. Frozen section analysis of FNAB diagnosed cases of follicular adenoma yielded a sensitivity of 75 percent, specificity of 61 percent, positive predictive value of 46 percent and a negative predictive value of 85 percent when compared to the final histopathology.

The use of frozen section will not change the extent of resection. The extent of resection should be individualized based on clinical assessment and established risk factors, such as nodule size and consistency, age, metastasis, extent of involvement.

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1. Miltenburg, et al. The role of frozen section, gender, age, and tumor size in the differentiation of follicular adenoma from carcinoma: A meta-analysis. Surgery 2000; 128:1075-1081.
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4. What is the recommended treatment for well-differentiated thyroid carcinoma (WDTC)?

4.1. What is the recommended surgical procedure for the treatment of WDTC?

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

Level 2B, Category A

Summary of Evidence

According to Udelsman[1], two major points must be addressed when contemplating on the better surgical treatment for well-differentiated thyroid cancers: 1) Is the recurrence rate minimized by a more extensive procedure? and 2) Can the results of postoperative management and adjuvant therapy be improved by removing all functioning thyroid tissue?

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 reoperative thyroid surgery with its inherently increased risks is minimized.

This study reviewed the data of Mazzaferri, et al.[2] who reported on the results of 576 patients with papillary carcinoma of the thyroid who underwent surgery. The initial results were reported in 1977 with a 95 percent follow-up. The mean and median follow-up intervals were 6.9 and 6.0 years, respectively. A second report published in 1981 extended the median follow-up to 10 years 3 months. The data initially showed a significant decrease in the recurrence rate for total thyroidectomy (7.1%) as compared to less than total (18.4%) during a follow-up of 0.5 to 30 years (Table 11).

Table 11. Recurrence and death rates according to the extent of thyroidectomy: data of Mazzaferri, et al.[15,16]

Extent of Thyroidectomy	No. of Patients	Recurrence			Deaths		
		No.	%	p	No.	%	%
1977 report							
Less than total	261	48	18.4		4	1.5	
Total	310	22	7.1	<0.002	1	0.39	<0.01
1981 report							
Less than total	261	50	19.2		4	1.5	
Total	310	34	10.9	<0.01	2	0.6	NS

Source: 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.

Moreover, data from the Mayo Clinic comparing the local recurrence rates after unilateral versus total thyroidectomy for papillary thyroid carcinoma with a median follow-up of 22.8 years shows a 17.2 percent recurrence rate for unilateral lobectomy, with 1.9 percent for total thyroidectomy (Table 12).

Table 12. Recurrence rates according to the extent of thyroidectomy: Mayo Clinic Data.

Extent of Thyroidectomy	No. of Patients	Local Recurrence No.	%
Unilateral	145	25	17.2
Total	156	3	1.9

Source: 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.

The most common significant complications of surgery for thyroid cancer are permanent recurrent laryngeal nerve injury and permanent hypoparathyroidism. Transient nerve injury or short-lived hypoparathyroidism does not affect the long-term quality of life, and rare complications (eg. bleeding, infection) are not of sufficient frequency to be an issue. Published complication rates comparing total and less than total thyroidectomy vary significantly (Table 13).

Udelsman, et al.[1] calculated the weighted mean incidence of permanent recurrent laryngeal nerve injury and permanent hypoparathyroidism to be 3.0 percent and 2.6 percent respectively for total thyroidectomy and 1.9 percent and 0.2 percent for lobectomy/isthmusectomy. However, they stated that approximately 20 percent of patients who undergo initial lobectomy/isthmusectomy for thyroid carcinoma develop local recurrence, such that these patients will require completion total thyroidectomy for which the complication rate has been reported to be at least twofold higher than that for initial total thyroidectomy – for which they predicted the complication rates between the two arms to be almost similar, as follows:

Initial total thyroidectomy = 3.0% + 2.6% = 5.6%
Initial lobectomy/isthmusectomy
+ 20.0% recurrence (completion thyroidectomy)
= 1.9% + 0.2% + 20% (6.0% + 5.2%) = 4.3%

Source: Udelsman R, Lakatos E, Ladenson P. Optimal surgery for papillary thyroid carcinoma. World J Surg 1996; 20:88-93.

A retrospective study by Pellegriti, et al.[3] 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

Table 13. Complications of total and subtotal thyroidectomy.

Study	No. of Patients	Permanent Recurrent Laryngeal Nerve Injury (%)	Permanent Hypo-parathyroidism (%)
Total Thyroidectomy			
Thompson & Harness, 1970[50]	184	4.8	5.4
Perzik, 1976[65]	216	5.5	2.8
Scanlan et al. 1981[59]	245	0.4	0.8
Clark, 1982[16]	82	0	1.2
Weighted mean		3.0	2.6
Subtotal thyroidectomy			
Perzik, 1976[65]	129	3.2	0
McConahey, et al.1986[24]	722	1.9	0.3
Vickery, et al. 1987[53]	176	1.1	0
Weighted mean		1.9	0.2

Source: Udelsman R, Lakatos E, Ladenson P. Optimal surgery for papillary thyroid carcinoma. World J Surg 1996; 20:88-93.

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

This study did not address the issue whether near-total thyroidectomy or lobectomy should be used to treat small PTCs, but it indicated that a high proportion of these cancers carry one or more risk factors including bilateral foci even in tumors $\leq$ 1.5 cm. They recommend near-total thyroidectomy as the first-choice surgical therapy for these tumors.

In 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 ^{131}I 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 ^{131}I ablation and L-thyroxine had significantly fewer recurrences and distant recurrences than those treated with any other combination (Figure 4).

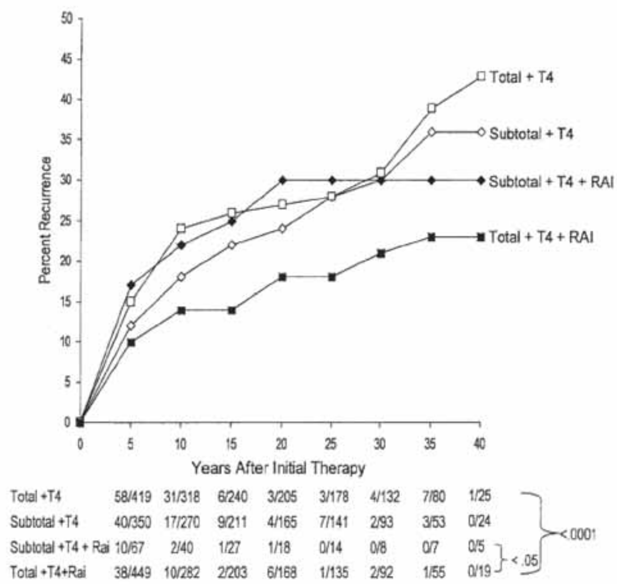

Figure 4. Recurrence rates following thyroid surgery and hormonal suppression +/- RAI.

Source: Mazzaferri and Kloos. Current approaches to primary therapy for papillary and follicular thyroid cancer. J Clin Endocrinol Metabol 2001; 86: 4.

Table 14. Histopathological characteristics of 299 small PTCs at presentation, classified in two subgroups according to the tumor size.

	All cases	Tumor size		
		< 1.0 cm	1.1 - 1.5 cm	
No.	299	187	112	Pvalue[a]
Multifocal	95 (31.7)	50 (26.7)	45 (40.2)	0.030
Bilateral	55 (18.4)	28 (15.0)	27 (24.1)	0.023
Extrathyroidal	60 (20.0)	26 (13.9)	34 (30.3)	0.000
Vascular invasion	14 (4.7)	8 (4.3)	6 (5.3)	0.456
Lymph node	90 (30.1)	46 (24.6)	44 (39.3)	0.009
Sclerosant variant	9 (3.0)	9 (4.8)	0	0.015
Distant metastases	8 (2.7)	5 (2.7)	3 (2.7)	0.746

Source: 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.

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4.2. What is the role of radioactive iodine (RAI) therapy in the treatment of WDTC?

Radioactive iodine (RAI) is beneficial for decreasing locoregional recurrence and distant metastases.

Level 2A, Category A

Summary of Evidence

A systematic review and meta-analysis by Sawka, et al.[1] showed that RAI ablation may be beneficial in decreasing recurrence of WDTC. Although no randomized controlled studies were obtained, 23 studies met the inclusion/ exclusion criteria 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 5 & 6).

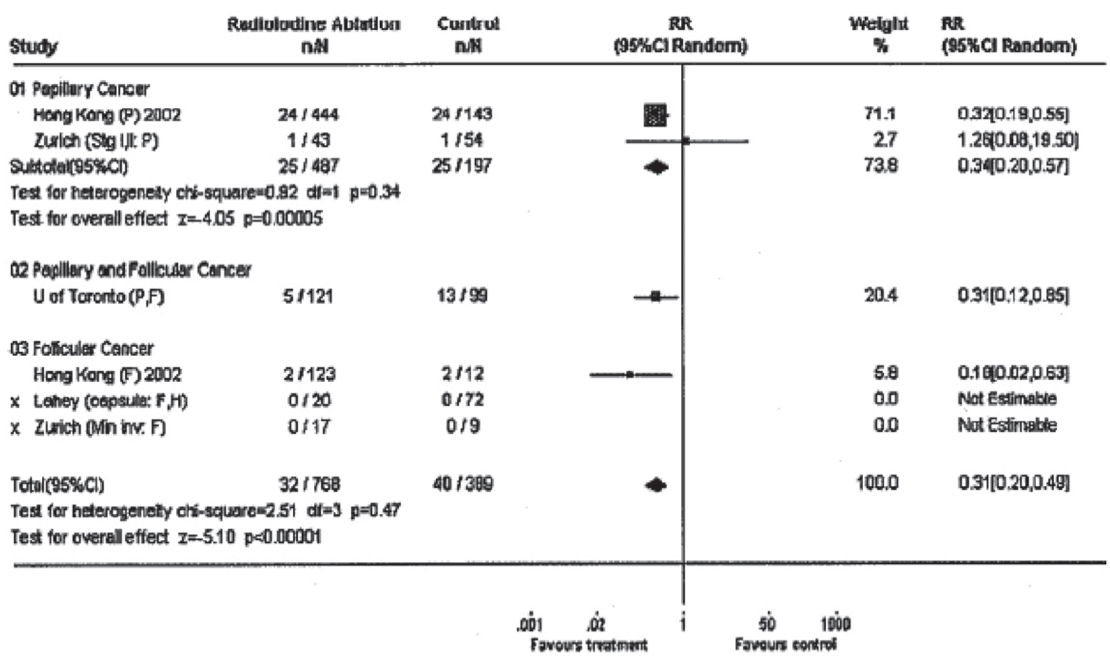

Figure 5. Random effects pooled estimate of RR reduction of RAI ablation on development of locoregional recurrence at 10 yr. n, Number of events; N, size of population studied; P, papillary; F, follicular; H, Hurthle cell; Stg I, II, stage I or II; Min inv, minimally invasive; capsule, only capsular 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):3668-3676.

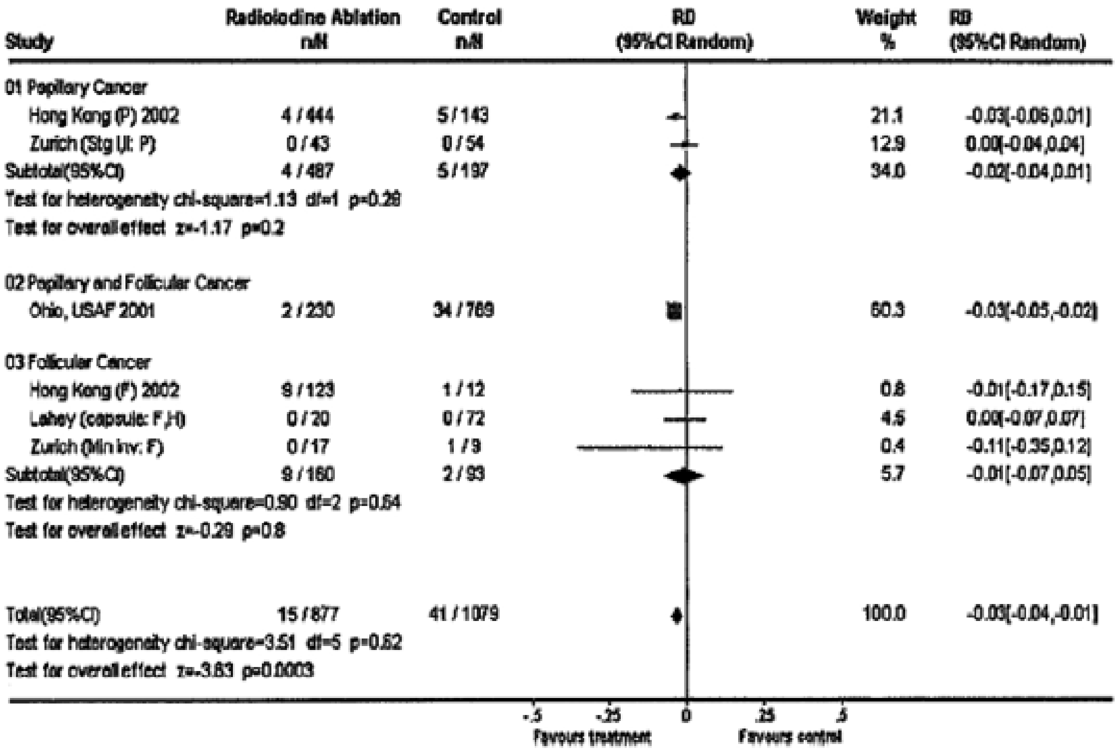

Figure 6. Random effects model examining the RD of RAI ablation on development of distant metastases at 10 yr. n, Number of events; N, size of population studied; P, papillary; F, follicular; H, Hurthle cell; Stg I, II, stage I or II; Min inv, minimally invasive; capsule, only capsular invasion; node+, 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):3668-3676.

Although there is a reasonable certainty that RAI ablation decreases recurrence, this study is proposing that only a long-term randomized controlled trial may resolve the issue, but the feasibility of a RCT examining the potential benefit of adjuvant RAI in thyroid cancer will always be limited by the tremendous number of sample size needed to really determine its benefit in terms of thyroid cancer-related mortality. In the meantime, the decision for 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.

Reference

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4.3. What is the role of completion thyroidectomy in the treatment of WDTC?

Completion thyroidectomy should be offered to those patients for whom a near-total or total thyroidectomy would have been recommended had the diagnosis been available before the initial surgery. This includes all patients with thyroid cancer except those with small (<1.5 cm), intrathyroidal, node-negative, low-risk tumors.

Level 2B, Category A

Summary of Evidence

Completion thyroidectomy may be necessary when the diagnosis of malignancy is made after lobectomy for an indeterminate or non-diagnostic biopsy. Some patients with malignancy may require completion thyroidectomy to provide complete resection of multicentric disease, and to allow radioiodine therapy. Most but not all studies on papillary cancer have observed a higher rate of cancer in the opposite lobe when multifocal ($\geq$2 foci), as opposed to unifocal, disease is present in the ipsilateral lobe. Since papillary cancer is known to be multifocal in about 30–80 per cent, initial total thyroidectomy remains an effective and safe treatment method to reduce the surgical risk of the patients and to facilitate radioactive iodine therapy.[1]

A retrospective study Kim[2] was done to determine the frequency of malignant lesions in the contralateral lobe after completion thyroidectomy and to assess the predictive factors that may anticipate the presence of a malignant lesion that may necessitate completion thyroidectomy. A total of 214 patients underwent lobectomy and isthmusectomy, with 81 patients having malignant disease in the resected lobe (53 follicular, 24 papillary, 1 Hurthle cell, 1 medullary, 1 insular, 1 anaplastic carcinoma). Completion thyroidectomy revealed malignancy in the resected contralateral lobe in 29 patients. After completion thyroidectomy, factors predicting the presence of cancer in the contralateral lobe were assessed according to clinical parameters and pathologic findings in the ipsilateral lobe. The age and sex of patients, co-existence of a benign nodule, and distribution of histological types and average size of the primary tumor, incidence of capsular extension and presence of local lymph node metastases were similar between the two groups. Cancer multifocality in the ipsilateral lobe was the only significant variable to predict the presence of additional cancer in the contralateral lobe by multivariate analysis (RR = 6.03, CI 2.23 – 16.35). Size of the cancers found in the contralateral lobe was in the range of 0.2 – 0.9 cm with a median value of 0.6 cm. The authors concluded that patients who had multifocal cancers in the ipsilateral lobe are likely to have another cancer in the contralateral lobe that must be removed by completion surgery.

The surgical risks of two-stage thyroidectomy (lobectomy followed by completion thyroidectomy) are similar to those of a near-total or total thyroidectomy. A study suggested that in cases where a completion thyroidectomy is needed, there is a significant survival advantage and a lower recurrence rate if performed within 6 months from the initial partial thyroid resection as compared to more than 6 months after the initial surgery.[2]

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4.4 What is the role of external beam radiotherapy in the treatment of WDTC?

External beam radiotherapy is indicated as part of the treatment of WDTC when there is gross residual tumor or invasion of adjacent structures, and does not concentrate RAI.

Level 2B Category A

Summary of Evidence

Postoperative adjuvant external beam radiotherapy is infrequently indicated for differentiated thyroid cancer except as a palliative treatment for locally advanced, otherwise unresectable disease. Reports on the use of external radiation to the thyroid bed or neck have had contradictory conclusions. Mazzaferri and Young[1] reported on a small group of patients who had EBRT and these patients had a higher local relapse rate than patients who did not have the treatment. Others have also reported the lack of a beneficial effect of EBRT on local control or survival. In contrast, there are reports of responses among patients with locally advanced disease who are at high risk due to residual tumor and improved relapse-free and cause-specific survival. Simpson and coworkers and others have shown that EBRT resulted in improved local control in patients considered to be at high risk for local relapse, with a 5-year overall survival rate of 78 percent.[2]

A retrospective study by Tubiana[3] involving 600 patients was done to determine the usefulness of EBRT in differentiated thyroid cancer. Patients treated with cobalt 60 or megavoltage received an average dose of 50 Gy whereas those treated with conventional x-rays (average dose, 28 Gy) or radium mold received lower doses. The authors found that the numbers of local recurrences in patients with macroscopically complete, incomplete, or dubious surgical tumor excision treated without EBRT was 21 percent (70 of 336 patients). In 180 irradiated patients, the local recurrence rate was 14 per cent. The difference in local recurrence rates between irradiated and non-irradiated patients is statistically significant ($p< 0.05$). It is much more significant when one takes into account only the 17 recurrences within the irradiated field ($p < 0.01$).

Adjuvant EBRT should be considered if there is grossly visible local extrathyroidal tumor invasion at the time of surgery so that there is a significant likelihood of having macroscopic or microscopic residual disease, especially if the residual tumor will likely fail to concentrate sufficient amounts of radioiodine, and if there is extensive T4 disease in patients older than 60 years of age in whom there is extensive extranodal spread after optimal surgery even in the absence of evident residual disease.[3]

Radiotherapy should be planned carefully, preferably using 3D conformal planning techniques, with appropriate precautions taken for prevention of radiation myelopathy. Intensity modulated radiotherapy (IMRT) may have advantages over conventionally planned radiotherapy when treating the thyroid bed and regional nodes. However, an important consideration in the adjuvant setting is that the use of intensity modulated radiotherapy with multiple fields can theoretically increase the risk of second malignancies in long-term survivors.

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

Thyroid hormone suppression therapy will significantly reduce recurrence and thyroid cancer-specific mortality rates.

Level 2A, Category A

Summary of Evidence

Differentiated thyroid cancer expresses the thyrotropin receptor on the cell membrane, and responds to TSH stimulation by increasing the expression of several thyroid-specific proteins (thyroglobulin, sodium iodide symporter) and by increasing the rates of cell growth. Suppression of TSH, using supraphysiologic doses of LT_4, is used commonly to treat patients with thyroid cancer in an effort to decrease the risk of recurrence.

A meta-analysis of 10 observational cohort studies[1] was done to evaluate the effect of thyroid hormone suppression therapy in patients with well-differentiated thyroid cancer on the likelihood of adverse clinical outcomes such as disease progression, disease recurrence and mortality. Of the combined cohort of 4,174 patients with thyroid cancer, 2,880 patients (69%) were given thyroid hormone suppression therapy. The average periods of follow-up ranged from 4.5 to 19.5 years. Patients on TSH suppression therapy had a decreased risk of adverse clinical outcomes (RR = 0.73; CI = 0.60 - 0.88; $p < 0.05$). Removal of 2 studies that failed to show a benefit from thyroid hormone suppression therapy resulted in homogeneity as well as consistent findings for the remaining cumulative cohort of 3,013 patients in 8 studies (RR = 0.38; CI = 0.292 - 0.493; $p < 0.05$). The authors concluded that thyroid hormone suppression therapy appears justified in thyroid cancer patients following initial therapy.

Although thyroid hormone suppression therapy has been shown to significantly reduce recurrence and thyroid cancer-specific mortality rates in both single institution studies and meta-analyses, the minimum degree of TSH suppression to achieve this effect remains debatable. In patients with well-differentiated thyroid cancer, the levothyroxine (LT4) dose needed to maintain serum TSH suppressed is ~2.1-2.4 µg/kg/day, as opposed to the replacement therapy doses of 1.6-1.8 µg/kg/day used in patients with hypothyroidism caused by non-malignant disease. To add more complexity to this issue, the LT4 dose required to achieve thyroid hormone suppression therapy is dependent on the subject's age, with younger patients needing higher doses per unit weight than older patients.

A retrospective study by Pujol[2] found that patients with a greater degree of TSH suppression (>90% of undetectable TSH values) had a trend toward a longer relapse-free survival than the remaining population ($p = 0.14$). The patients with a lesser degree of TSH suppression (<10% of undetectable TSH values) had a shorter relapse-free survival than the remaining patients ($p < 0.01$). In multivariate analysis that included TSH suppression, age, sex, histology, and tumor node metastasis stage, the degree of TSH suppression was an independent predictor of recurrence ($p = 0.02$). The authors concluded that a lesser degree of TSH suppression (≥ 1 µU/mL) is associated with an increased incidence of relapse compared to a constantly suppressed TSH (≤ 0.05 μU/mL). Conversely, another large study found that disease stage, patient age, and ^{131}I therapy independently predicted disease progression, but that the degree of TSH suppression did not.

A prospective study by Wang[3] was done to determine the target level of TSH suppression by analyzing the relationship between the degree of TSH suppression determined by third generation assay and thyroglobulin (TG) response over a 3 year period. The serum samples of patients who had undergone near-total thyroidectomy for WDTC, ^{131}I ablation and had no serum TG autoantibodies were analyzed. The study showed that 1) TG levels were significantly higher during the period off L-T4 therapy than on L-T4 therapy; 2) that during LT_4 therapy, the mean TG levels were significantly higher when TSH levels were normal than when TSH levels were suppressed (< 0.5 mU/L); and 3) that when TSH was suppressed below normal, there was no correlation between the relative changes in TSH and TG by individual in all 3 groups ($p > 0.05$). The authors suggest a stratified postoperative thyroid hormone management of patients with differentiated thyroid carcinoma. TSH should be lowered to below normal in patients with active disease. If patients are clinically disease free with TG levels below 2 ng/ml, TSH can be kept within the normal range.

Retrospective studies have demonstrated that TSH suppression to below 0.1 mU/L may improve outcomes in high risk patients with thyroid cancer although no such evidence of benefit has been documented in low-risk patients. Adverse effects of TSH suppression include subclinical thyrotoxicosis, exacerbation of angina in patients with ischemic heart disease, increased risk for atrial fibrillation, and increased risk of osteoporosis in postmenopausal women. Therefore, thyrotropin suppression to below 0.1 mU/L is recommended for high-risk patients with thyroid cancer, while maintenance of the TSH at or slightly below the lower limit of normal (0.1-0.5 mU/L) is appropriate for low-risk patients.

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5. What is the recommended pre-operative metastatic work up for well-differentiated thyroid carcinoma?

Locoregional Metastasis:

Pre-operative neck ultrasound is recommended to detect locoregional metastasis for WDTC .

The routine use of computed tomography (CT), and integrated CT/positron emission tomography (PET) is not recommended.

Level IB, Category A

Distant Metastasis:

Chest x-ray, HRCT and FDG-PET are not routinely recommended to detect distant metastasis for WDTC.

Level IB, Category A

Magnetic resonance imaging (MRI) is not routinely recommended preoperatively.

Level 5, Category A

Summary of Evidence

Metastastic work-up for well-differentiated thyroid carcinoma is recommended as part of preoperative staging to determine the extent of thyroid surgery and lymph node dissection. Cervical recurrence, primarily in the form of regional lymph node metastases has been a major concern since it occurs in up to 30 percent of cases after surgical treatment.[1] Appreciation of the presence lymph node metastases in microcarcinomas has led to greater awareness and concern in focusing on recurrence free survival together with the overall survival.

Loco-regional Metastasis

Recent recommendations on the operative management of lateral cervical lymph node metastasis have become more aggressive. Formerly, the American Thyroid Association stated the accepted standard of care: “A modified radical neck dissection is usually indicated for patients with clinically palpable extensive ipsilateral cervical adenopathy."[1] Similarly, the American Association of Clinical Endocrinologists and American Association of Endocrine Surgeons do not recommend prophylactic lateral neck dissections.[2] Ito, et al. suggested that with papillary microcarcinoma: 1) modified neck dissection is not necessary in patients without lateral neck nodes detected on preoperative ultrasonography; and 2) patients with preoperatively detected lateral node metastases are more likely to develop recurrence so careful neck dissection should be performed. [3]

Preoperative detection of non-palpable lateral node metastasis and extra-thyroidal extension is important. Slough, et al.[4], recommends combined use of ultrasound and contrast CT to produce an effective nodal map to direct nodal dissection at the time of surgery since lymph node involvement occurs in 30 percent of cases of papillary thyroid carcinoma, and extra-thyroidal extension occurs in 8-32 percent of cases.

The use of neck ultrasound alone can detect lymph node or soft-tissue metastases in neck compartments believed to be uninvolved by physical examination in 33-50 percent of patients. In a retrospective cohort study by Stulak, et al.[5] preoperative ultrasound done on 486 patients undergoing initial operation identified non-palpable lateral jugular lymph node metastasis (LNMs) in 70 (14.4%) and palpable nodes in 37(6.7%). In re-operative patients, non-palpable lateral LNMs were detected in 106 (64.2%), 61 (28.2%) had LNMs detected in the central neck, and 56 (25.6%) detected palpable nodes. Overall, preoperative ultrasound detected non-palpable LNMs in 231 (32.9%) of the 702 patients with papillary thyroid carcinoma who underwent ultrasound, thereby altering the operative procedure performed in 15 (40.5%) of these patients, and helped to guide the extent of lymphadenectomy. He reported the sensitivity, specificity, and positive predictive value for US were 83.5 percent, 97.7 percent, and 88.8 percent in initial patients, and 90.4 percent, 78.9 percent, and 93.9 percent in re-operative patients.

Nam-Goong, et al.[6] in a retrospective study of 267 patients who underwent ultrasound-guided fine-needle aspiration, extrathyroidal extension was observed in 44 percent, and regional lymph node metastasis in 50 percent of 36 patients with WDTC in incidentally detected impalpable thyroid nodules.

Kouvaraki, et al.[7] retrospectively compared preoperative transcutaneous ultrasonography of the neck and physical examination (PE) results in the detection of locoregional metastases (lymph node and soft tissue) in 212 patients who underwent operation for primary, persistent, or recurrent papillary (n=130), medullary (n=61), or follicular/Hurthle cell (n=21) carcinoma. Ultrasonography detected lymph node or soft-tissue metastases in neck compartments believed to be uninvolved by PE in 39 percent of patients. Ultrasound findings altered the operative procedure in 39 percent of these patients, facilitating complete resection of disease and potentially minimizing local-regional recurrence.

Table 15. Accuracy of preoperative ultrasonography in 770 patients (initial and reoperative) with papillary thyroid carcinoma.

	True Positive (%)	Sensitivity (%)	Specificity (%)	Positive Predictive (%)	Overall Accuracy (%)	Likelihood Ratio (+)
Preoperative n=486	14.7	83.5	97.7	88.8	95.2	36.3
Re-operative n=216	56.7	90.4	78.9	93.9	87.9	4.28

Source: Stulak JM, Grant CS, Farley DR, Thompson GB, van Heerden JA, Hay ID, Reading CC, and Charboneau JW. Value of preoperative ultrasonography in the surgical management of initial and reoperative papillary thyroid cancer. Arch Surg 2006; 141: 489-496.

Table 16. Accuracy of preoperative ultrasonography in the surgical management of 212 patients with thyroid carcinoma (PTC and MTC).

Compartment	Sensitivity	Specificity	Likelihood Ratio (+)
Central	52%	95%	10.4
Ipsilateral	77%	93%	11
Contralateral	79%	96%	19.75

183/ 212 had histopathologic analysis of lymph nodes and soft tissue
29/212 was (-) by PE and US.

Source: Kouvaraki, et al. Role of preoperative ultrasonography in the surgical management of patients with thyroid cancer. Surgery 2003; 134(6):946-954.

The nodes' criteria of malignancy are 1) diameter of 1 cm or more, 2) clear hypoechoic pattern or non-homogenous pattern with alternating hypoechoic and hyperechoic areas, 3) cystic appearance, 4) presence of internal calcifications 5) rounded shape with increase anteroposterior diameter and 6) long/short diameter ratio greater than 0.7 and 7) absence of hilum. When any of these criteria is present, the next step is to get a histologic diagnosis.[8]

Pre-operative ultrasonographic examination for lymph node metastasis is found to be useful in dictating the extent of lymph node dissection[2,3,5] since removal of the thyroid as well as primary tumor and accessible locoregional disease remains an important component of initial treatment even in metastatic disease.[8]

Jeong, et al.[9] in his recent prospective study of 26 patients comparing PET/CT with ultrasound and CECT revealed that at all lymph node levels (levels I-VI), PET/CT showed a sensitivity of 30.4 percent, a specificity of 96.2 percent and a diagnostic accuracy of 86.9 percent whereas US were 41.3 percent, 97.4 percent, 89.1 percent (US) and 34.8 percent, 96.2 percent, 87.2 percent (CECT). (Table 17) Considering only the lateral cervical node group (levels I-V), PET/CT showed a sensitivity of 50.0 percent, a specificity of 97.0 percent and a diagnostic accuracy of 92.3 percent, 53.9 percent, 97.9 percent, 93.5 percent (US) and 42.3 percent, 96.6 percent, 91.2 percent (CECT). (Table 18) The diagnostic results for US, CECT and PET/CT upon initial evaluation of the cervical lymph nodes did not differ significantly on a level-by-level basis. His preliminary results suggest that integrated PET/CT does not provide any additional benefit when compared to US and CECT for the initial evaluation of cervical node levels in patients with papillary thyroid carcinoma.

Table 17. Likelihood ratios of ultrasound, CECT and positron emission tomography/computed tomography scan for evaluating all cervical node levels (I-VI), compared with the final status.

Modalities and Grading	Final Status of Lymph Node Level* Disease (+)	Disease (-)	Diagnostic Values
US			+ LR = 20.05 - LR = 0.77
Test (+)	19	7	PPV: 73·7%
Test (-)	27	259	NPV: 95·0%
	Sensitivity: 53·6%	Specificity: 97·9%	Total n: 312
CECT			+LR = 9.25 - LR = 0.68
Test (+)	16	10	PPV: 61·5%
Test (-)	30	256	NPV: 89·1%
	Sensitivity: 34·8%	Specificity: 96·2%	Total n: 312
PET/CT			+ LR = 8.99 - LR = 0.72
Test (+)	14	9	PPV: 60·9%
Test (-)	32	257	NPV: 88·9%
	Sensitivity: 30·4%	Specificity: 96·2%	Total n: 312

PPV, positive predictive value; NPV, negative predictive value; *The final status of lymph node levels was determined using the following three criteria: the results of surgical pathology; the results of a 5 mCi radioactive 131I scan prior to definitive radioactive iodine ablation therapy at 2-3 months after surgery; and, the follow-up clinical examination of the neck.

Source: Jeong HS, et al. Integrated 18F FDG-PET/CT for the initial evaluation of cervical node level of patients with papillary thyroid carcinoma: Comparison with ultrasound and contrast enhanced CT. Clin Endocrinol (Oxf) 2006; 65 (3):402-407.

Table 18. Likelihood ratios of US, CECT and PET/CT scans for evaluating the lateral cervical node levels (I-V), compared with the final status.

Modalities and Grading	Final Status of Lymph Node Level*		Diagnostic Values
US	Disease (+)	Disease (-)	+ LR = 25.2 - LR = 0.47
Test (+)	14	5	PPV: 73·1%
Test (-)	12	229	NPV: 90·6%
	Sensitivity: 41.3%	Specificity: 97.4%	Total n: 260
CECT			+LR = 12.375 - LR = 0.59
Test (+)	11	8	PPV: 57·9%
Test (-)	15	226	NPV: 93·8%
	Sensitivity: 42.3%	Specificity: 96.6%	Total n: 260
PET/CT			+ LR = 16.7 - LR = 0.51
Test (+)	13	7	PPV: 65·0%
Test (-)	13	227	NPV: 94·6%
	Sensitivity: 50.0%	Specificity: 97.0%	Total n: 260

PPV, positive predictive value; NPV, negative predictive value; *The final status of lymph node levels was determined using the following three criteria: the results of surgical pathology; the results of a 5 mCi radioactive I^{131} scan prior to definitive radioactive iodine ablation therapy at 2-3 months after surgery; and, the follow-up clinical examination of the neck.

Source: Jeong HS, et al. Integrated 18F FDG-PET/CT for the initial evaluation of cervical node level of patients with papillary thyroid carcinoma: Comparison with ultrasound and contrast enhanced CT. Clin Endocrinol (Oxf) 2006; 65 (3):402-407.

Distant Metastasis

The lungs are the common site of metastases in patients with differentiated thyroid carcinoma. Chest x -ray has been primarily and routinely used because it is less expensive than the other imaging modalities. Occasionally high resolution computed tomography (HRCT) is requested to establish pulmonary metastasis in patients with well-differentiated thyroid carcinoma.

A review by Habra, et al. at M.D. Anderson Cancer Center of 333 patients over a 20-year period showed that chest x-ray abnormality developed in 22 (6.6 %) patients. Conversion to a positive Chest x-ray from papillary and follicular carcinoma was seen at an average of 66 months. Contribution of routine chest x-ray in the long-term follow-up of patients with differentiated thyroid carcinoma is limited.[10]

Bal, et al. reviewed the clinical characteristics, pattern of disease at presentation, histopathologic sub-type, treatment, course and outcome of WDTC in pediatric age group since it behaves more aggressively and presents with a high incidence of pulmonary metastasis at the time of initial diagnosis. Their series included 1,754 patients, 122 (7%) were 20 years or younger of whom 28 (23%) had pulmonary metastasis. Twenty-one (75%) had normal chest x-ray. In 15 (54%) children, metastasis was detected after first post surgery WBS, 4 (14%) post ablation I^{131} WBS. Seven cases (25%) and two (7%) were detected by first and second post-therapy scans, respectively. CT only detected micronodular pulmonary shadows in 5 (28%). They concluded that chest x-ray and HRCT have a limited role in detecting pulmonary metastasis since a large majority of the children and adolescents with confirmed pulmonary metastases could be missed. [11]

A preoperative CT/MRI should be done if the lesion is fixed or substernal (iodinated contrast should be avoided unless essential).[12] FDG - PET is not routinely done preoperatively but only after elevated serum thyroglobulin is with a negative WBS post operatively.[13] Several studies done revealed its sensitivity to range from 88 - 94.6 percent, specificity 25 – 95.2 percent and a diagnostic accuracy of 87.8 percent.

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

The recommended postoperative surveillance for patients with well-differentiated thyroid cancer is: serum thyroglobulin, serum TSH, thyroid ultrasound and whole body scan.

The major goal of recommending an effective postoperative surveillance system for patients with well-differentiated thyroid cancer is to be able to detect recurrence as early as possible as it may translate to better outcomes. When total thyroidectomy and radioiodine ablation have been the initial treatment, three powerful tools are available for follow-up: basal and stimulated serum thyroglobulin (Tg) measurement; iodine 131 whole body scan (WBS) and neck ultrasound. The utilization of these tests should be based on the risk for recurrence of progression of the disease.

The following recommendations will follow the definition of risk levels used by ATA Guidelines 2006:

Risk for recurrence/progression based on characteristics after initial surgery and remnant ablation:

Low risk:

1. No local or distant metastases
2. All macroscopic tumors have been resected
3. No tumor invasion of locoregional tissues or structures
4. Tumors have no aggressive histology (tall cell, insular, columnar carcinoma or vascular invasion)
5. If I^{131} is given, no uptake outside the thyroid bed on first post-treatment WBS

Intermediate risk:

1. Microscopic invasion of tumor into peri-thyroidal soft tissues at initial surgery with aggressive histology or vascular invasion

High risk:

1. Have macroscopic tumor invasion, incomplete tumor resection, distant metastases, or I^{131} uptakes outside the thyroid bed on the post-treatment scan done after thyroid remnant ablation

Follow up should be individualized according to risk level.

6.1. What is the role of thyroglobulin assay for postoperative surveillance in patients with well differentiated thyroid cancer?

Measurement of serum thyroglobulin is the most important initial test to monitor patients for residual or recurrent well-differentiated thyroid cancer.

Level 2A, Category A

Summary of Evidence

Serum thyroglobulin (Tg) testing is sufficiently sensitive to be used in the follow up management of low risk patients with well differentiated thyroid cancer , especially after total thyroidectomy and remnant ablation or those who are clinically free of disease. In the study of Mazzaferri, et al. 8 studies were cited which included 1028 low risk patients thought to be clinically free of disease. The thyroglobulin level was less than 1 ug/liter during THST in 784 out of 1028 patients (76%). A rise in serum Tg to >2 ug/liter in response to rhTSH in 21 percent of 784 patients revealed the presence of metastasis in 36 percent[1] (Table 19).

In general, 1 gram of normal thyroid tissue results in a serum Tg of approximately 1 ug/liter when the TSH is in the normal range and about 0.5 ug/liter when TSH is suppressed.[2] There are two ways of measuring serum Tg: one is by withdrawal from thyroid hormone suppression and the other is by using recombinant TSH. There is enough evidence that proves that the two methods used to stimulate Tg, are equally effective in detecting metastatic thyroid cancer especially when a cut off of 2 ug/liter is used.[1,3] T_3 levels should be determined 4-6 weeks after withdrawal of T_4 therapy.

There are factors that may affect the value of serum Tg. The presence of anti-thyroglobulin antibody may lead to a false negative result.[4,5] Thyroglobulin levels should be interpreted in the light of the pretest probability of clinically

Table 19. Serum thyroglobulin and whole body scan after thyroid hormone withdrawal and recombinant thyroid stimulating hormone stimulation.

First author (Ref. no.)	Total patients (n)	No. of patients with metastases[a] (%[b] [n])	THST Tg ≤ μg/liter (% [n])	rhTSH studies in patients with THST Tg ≤ 1 μg/liter: rhTSH Tg > 2 (% [n])	Yield of rhTSH testing (% [no. with metastases/no. with Tg > 2])	Metastatic disease on DxWBS[k] (% [n])	Metastatic sites (n = 58) among 728 patients with complete Tg data and follow-up
Haugen (30)	220	4 [illegible]	55 [illegible]	39 [illegible]	17 [illegible]	4 [illegible]	Locoregional [illegible] and distant metastases [illegible]
David (31)	33	6 [illegible]	88 [illegible]	7 [illegible]	100 [illegible]	0 [illegible]	Lung [illegible]
Vitale (32)	104	3 [illegible]	44 [illegible]	17 [illegible]	38 [illegible]	0 [illegible]	Locoregional [illegible] and distant metastases [illegible]
Haugen (34)	83	8 [illegible]	88 [illegible]	34 [illegible]	28 [illegible]	0 [illegible]	Lymph node neck [illegible] and chest [illegible]
Mazzaferri (33)	107	10 [illegible]	100 [illegible]	19 [illegible]	55 [illegible]	0 [illegible]	Lymph node neck [illegible], lung [illegible], and uncertain site [illegible]
Pacini (35)	72	15 [illegible]	100 [illegible]	43 [illegible]	35 [illegible]	ND	Lymph node neck [illegible] and lung [illegible]
Robbins (28)	109	15 [illegible]	63 [illegible]	14 [illegible]	68.8 [illegible]	10.1 [illegible]	Lymph nodes neck [illegible], mediastinum/cervical nodes [illegible], and lung [illegible]
Wartofsky (36)	300	3 [illegible]	89 [illegible]	10 [illegible]	ND	ND	ND
Total (%) of all patients in column	100 [1028]	6.5 [illegible]	76.3 [illegible]	21.4 [illegible]	35.8 [illegible]	2.3 [illegible]	Distant metastases [illegible] 36.2%, locoregional [illegible] 60.3%, and uncertain [illegible] 3.4%

ND, Not determined.
[a] Metastases found in low-risk patients as the result of rhTSH-stimulated studies or a DxWBS showing uptake outside the thyroid bed.
[b] Percentages rounded to the nearest integer in all but last row.
[c] Patients with baseline THST-Tg <2 μg/liter.
[d] Patients with a baseline THST-Tg ≤1 μg/liter.
[e] Patients with a baseline THST-Tg <1 μg/liter.
[f] Patients (n = 4) with baseline TSHT-Tg ≤ 2 μg/liter. Seven patients had metastases seen on DxWBS, yet 5 had rhTSH-stimulated Tg < 2 (false-negative rhTSH-stimulated Tg levels), and 9 of 16 patients with rhTSH Tg > 2 μg/liter had metastatic disease with a negative DxWBS. One patient had both neck nodes and mediastinal uptake.
[g] Patients with rhTSH-stimulated Tg ≥ 2 μg/liter.
[h] Personal communication with the authors.
[i] Patients with rhTSH-stimulated Tg > 1 μg/liter.
[j] Only limited follow-up data were reported in the Wartofsky study, and these data thus have been omitted from the table.
[k] Positive, uptake in metastases on DxWBS (not thyroid bed).
[l] DxWBS negative and Tg ≥ 2 μg/liter.

Source: Mazzaferri EL, Robbins RJ and Spencer CA. A consensus report of the role of serum thyroglobulin as a monitoring method for low risk patients with papillary thyroid carcinoma. JCEM 2003; 88(4): 1433-1441.

significant residual tumor. For example, a poorly differentiated cancer may be present despite low basal or stimulated thyroglobulin; in contrast, a minimally elevated stimulated thyroglobulin may occur in patients at risk for clinically significant morbidity.[6]

It is less sensitive in patients with small cervical lymph node metastases or less differentiated tumor.[7,8] A rising unstimulated or stimulated serum Tg may signify disease that is likely to become clinically apparent.[9]

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

Serum TSH level monitoring is recommended for postoperative surveillance of patients with WDTC to determine the adequacy of suppression.

Level 2B, Category A

Specific Recommendations:

In patients with persistent disease, the serum TSH should be maintained below 0.1 mU/L indefinitely in the absence of specific contraindications. (Level 2)

In patients who are clinically disease free but who presented with high risk disease, consideration should be given to maintaining TSH suppressive therapy to achieve serum TSH levels of 0.1 to 0.5 mU/L for 5 to 10 years. (Level 2)

In patients free of disease, especially those at low risk for recurrence, the TSH may be kept within the low normal range (0.3 to 2 mU/L). (Level 2)

Serum TSH should be monitored every 6 months to 12 months in the first year and then yearly thereafter. (Level 5)

Summary of Evidence

A study by Pujol found that patients with a greater degree of TSH suppression (>90% of undetectable TSH values) had a trend toward a longer relapse-free survival than the remaining population ($p = 0.14$). The patients with a lesser degree of TSH suppression (<10% of undetectable TSH values) had a shorter relapse-free survival than the remaining patients ($p < 0.01$) (Figures 7 & 8 and Table 20). In a multivariate analysis that included TSH suppression, age, sex, histology, and tumor node metastasis stage, the degree of TSH suppression was proven to be an independent predictor of recurrence ($p = 0.02$) (Table 21). The authors concluded that a constantly suppressed TSH (≤ 0.05 uU/ml) was associated with a longer relapse free survival than when serum TSH levels were always 1uU/ml or greater.[1]

A prospective study by Wang[2] was done to determine the target level of TSH suppression by analyzing the relationship between the degree of TSH suppression determined by third generation assay and thyroglobulin (TG) response over a 3 year period.[2] The serum samples of patients who had undergone near-total thyroidectomy for WDTC, ^{131}I ablation and had no serum TG autoantibodies were analyzed. They were classified into three groups: Group A are those with local or distant relapse, GroupB are those without clinically detectable disease but with slightly elevated TG (2ng/ml under LT4 suppression or above 3 ng/ ml off LT4 therapy and Group C are those with no active disease and Tg levels below 2 and 3 ng/ml during and off LT4 therapy,respectively. The study showed that 1) TG levels were significantly higher during the period off L-T4 therapy than on L-T4 therapy($p<0.01$); 2) that during LT$_4$ therapy the mean TG levels were significantly higher when TSH levels were normal than when TSH levels were suppressed (< 0.5 mU/L) which showed statistical significance($p=0.001$) only in the group with active disease; and 3) that when TSH was suppressed below normal, there was no correlation between the relative changes in TSH and TG by individual in all 3 groups ($p > 0.05$). The authors suggest a stratified postoperative thyroid hormone management of patients with differentiated thyroid carcinoma. TSH should be lowered to below normal in patients with active disease. If patients are clinically disease free with TG levels below 2 ng/ml, TSH can be kept within the normal range.

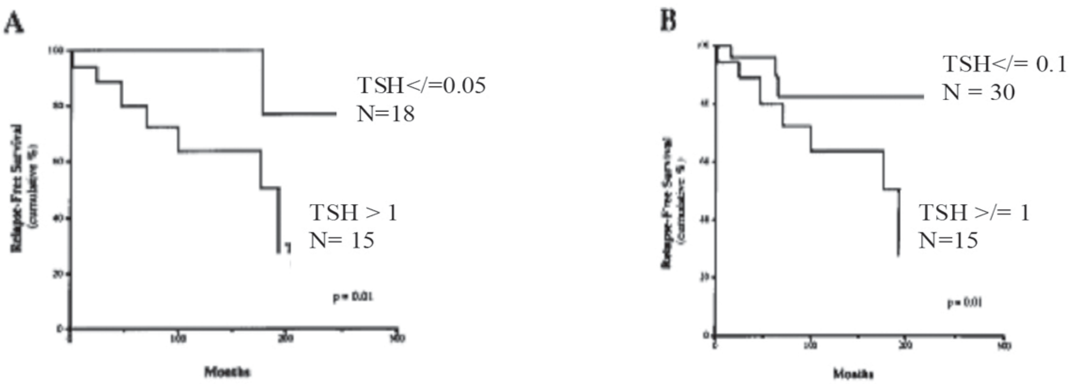

Figure 7. Recurrence free survival (RFS) in subgroups of patients with stable TSH levels over time. A, Comparison between a subgroup of patients with maximal TSH suppression during follow up (TSH < 0.05 mU/L) and a non-suppressed group (TSH > 1mU/L). B, Comparison between a subgroup of patients with a near maximal TSH suppression during the follow up (TSH ≤ 0.1 mU/L) and the non TSH suppressed group (TSH > 1mU/L).

Source: Pujol P. J Clin Endocrinol Metab 1996; 81 (12): 14318-4323.

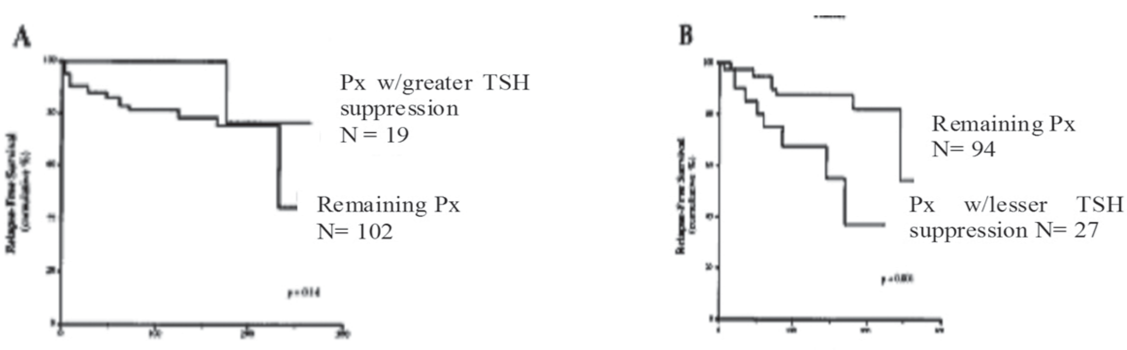

Figure 8. RFS according to the degree of TSH suppression in the overall population. A, Patients with greater TSH suppression were those with more than 90% undetectable TSH values (≤ 0.05 mU/L) over time; the remaining patients had 90% or less undetectable TSH values. B, patients with lesser TSH suppression were those with less than 10% undetectable TSH values over time; the remaining patients had 10% or more undetectable TSH values.

Source: Pujol P, et al. J Clin Endocrinol Metab 81 (12): 14318-4323.

Table 20. Analysis of recurrence-free survival according to different degrees of thyroid-stimulating hormone suppression.

Groups	No. of Patients	Median RFS(months)	No. of Relapses	P value (a)
Stable TSH*				
≥ 1mU/L	15	112	6	
Vs ≤ 0.05mU/L	18	259	1	<0.01
Vs ≤ 0.1mu/L	30	235	3	0.01
%TSH ≤ mU/L**				
> 90%	19	242	1	
vs. other patients	102	215	18	0.14
<10%	27	151	8	
vs. other patients	94	195	11	<0.01

(a) by generalized Wilcoxon (Breslow) test
* Subgroups of patients with all annual TSH values during the follow up as indicated
** percentage of undetectable TSH values during the follow up

Table 21. Multivariate Cox analysis of recurrence-free survival.

Parameters	P value	B coefficient	Relative Risk	95% CI
Stage *	<0.01	0.7	2.1**	1.1-4.2
TSH suppression***	0.02	1.1	3.2	1.2-8.6
Age(≥45 vs < 45 yr)	0.05	0.9	2.5	0.9-6.5
Histology****	NS			
Sex	NS			

95% CI, asymptomatic 95% confidence intervals
* Stage 1 vs Stage 2 vs Stage 3-4
** When stage increases from one stage to the higher stage
*** poor TSH suppression (<10% undetectable TSH values) vs the remaining patients
**** papillary vs follicular

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6.3. What is the role of ultrasonography for postoperative surveillance in the patient with WDTC?

Ultrasound is recommended for postoperative surveillance to detect recurrence in the thyroid bed and cervical nodes.

Level 1B, Category A

Summary of Evidence

Ultrasound of the neck is a reliable tool in detecting cervical nodal metastases in patients with differentiated thyroid cancer especially if confirmed by a conclusive cytological diagnosis or if analyzed in combination with thyroglobulin monitoring.[1]

The study by Simeone[2] showed that ultrasound of the neck using real time scanner with a 10 MHz transducer, has a 96 percent sensitivity and 83 percent specificity in detecting recurrent thyroid carcinoma. The examination should include the entire neck with visualization of the submandibular gland, the thyroid bed, the area deep to the clavicle and the superior mediastinum. The area lateral to the carotid artery and jugular vein should be evaluated for any lymphadenopathy.

On ultrasound examination, the normal postoperative bed should have a uniform echogenic texture owing to fibrofatty tissue. Recurrence in the thyroid bed appears as hypoechoic mass using high frequency USG (12.5 mHz). Krishnamurty performed an ultrasound guided FNA of suspicious hypoechoic mass in the thyroid bed gave a 100 percent sensitivity and 85.7 percent specificity (N= 21). However, it should be noted that there are several benign pathologies that may mimick tumor recurrence which include remnant thyroid tissue, benign reactive lymph nodes, postoperative changes and suture granulomas.[3]

In the study by Lee, et al., it was determined that among the different ultrasonographic findings suggestive of malignancy in a newly detected nodule in the thyroid bed, marginal irregularity microcalcification and a shape not parallel to the surrounding tissue plane would have the higher sensitivity and specificity for the diagnosis of neck recurrence[4] (Table 22).

The addition of neck ultrasound to rhTSH stimulated Tg, increased the sensitivity of Tg from 85 percent to 96.2 percent and the negative predictive value from 98.2 percent to 99.5 percent and decreased the false negative rate from 14.8 percent to 3.7 percent.[5] (Table 23) In combination with stimulated Tg, it has a better sensitivity than diagnostic WBS alone or combined with stimulated Tg in low risk patients (Table 24).

In the study of Torlontano which focused on determining the sensitivity of neck ultrasound to detect lymph node metastases in a cohort of 456 low risk papillary cancer patients, it was shown that ultrasound has a 100 percent sensitivity (38/38) and 100 percent specificity (418/418) giving an accuracy of 100 percent (456/456). Cervical nodal metastases may occasionally be detected by neck ultrasound even when TSH stimulated serum thyroglobulin levels remain undetectable.[1]

Table 23. Accuracy of Tg after rhTSH.

	Tumor Positive	Tumor Negative
Test positive	23 TP = 85%	0 FP = 0%
Test negative	4 FN = 14.5%	223 TN = 100%

Positive test = Tg > 1 ng/ml
PPV = 100%
NPV = 98.2%
Sensitivity = 85%
Specificity = 100%

Source: Pacini F, Molinario E, and Castagna MG. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. J Clin Endocrinol Metab 2003; 88: 3668-3673.

Table 22. Diagnostic sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and p value of the individual ultrasonographic findings suggesting malignancy.

Ultrasound-guided Findings	No (%)	Sn	Sp	PPV	NPV	Accuracy	P
Marginal irregularity	15 (78.9)	78.9	100	100	76.5	87.5	<.001
Microcalcification	14 (73.7)	73.7	84.6	87.5	68.8	78.1	.003
Taller than wide	9 (47.4)	47.4	100	100	56.5	68.8	.004
Ill-defined margin	5 (26.3)	26.3	30.8	35.7	22.2	28.1	.029
Macrocalcification	5 (26.3)	26.3	84.6	71.4	44	50	.671

Source: Lee JH, Lee HK, and Lee DH. Ultrasonographic findings of newly detected nodule on the thyroid bed in postoperative patients for thyroid carcinoma: correlation with the results of ultrasonography-guided fine needle aspiration biopsy. Clinical Imaging 2007; 31: 109-113.

Table 24. Diagnostic accuracies of recombinant human thyrotropin-stimulated serum thyroglobulin, I^{131} whole body scan and neck ultrasound for detecting or excluding metastatic disease in low and high-risk patients.

	rhTSH-Tg (%)	DxWBS (%)	rhTSH-Tg+US(%)	rhTSH Tg+WBS(%)
Low risk	85.7	4.7	100	85.7
High risk	84.6	33.3	92.3	100

Source: Pacini F, Molinario E, and Castagna MG. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. J Clin Endocrinol Metab 2003; 88: 3668-3673.

Table 25. Accuracy of Tg after rhTSH and neck ultrasound.

	Tumor Positive	Tumor Negative
Test positive	2 TP = 96.2%	0 FP = 0%
Test negative	1 FN = 3.7%	223 TN = 100%

Positive test = Tg> 1 ng/ml and/or lymph node metastases at ultrasound
PPV = 100%
NPV = 99.5%
Sensitivity = 96.2%
Specificity = 100%

Source: Pacini F, Molinario E, and Castagna MG. Recombinant human thyrotropin-stimulated serum thyroglobulin combined with neck ultrasonography has the highest sensitivity in monitoring differentiated thyroid carcinoma. J Clin Endocrinol Metab 2003; 88: 3668-3673.

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6.4. What is the role of total body scan for postoperative surveillance in patients with WDTC?

A diagnostic whole body scan has limited usefulness and is NOT necessary in low risk patients who are clinically free of residual tumor, with undetectable serum Tg and has negative neck ultrasound.

Likewise, it is NOT necessary if the Tg is elevated and ultrasound of the neck is positive, since therapeutic options (surgery or RAI ablation) are already warranted.

Level 2B, Category A

Summary of Evidence

Cailleux, et al. tried to determine whether a control I^{131}TBS should be routinely performed 1 year after initial treatment. The results of his study showed that a diagnostic WBS with 74-185 megabecquerel (MBq) performed 1 year after thyroid ablation demonstrated no abnormal uptake. Furthermore, there was no correlation with the serum Tg levels and its main use was to confirm the completeness of thyroid ablation[1] (Table 26).

Although serum thyroglobulin and diagnostic whole body scan have been previously considered complementary in identifying residual tumor, an undetectable Tg alone has been found to sufficiently do this. Little information is added by performing a diagnostic WBS in evaluating low risk patients for persistent disease.[2,3] In another study by Torlontano evaluating the diagnostic accuracy of I^{131}WBS and serum Tg obtained after rhTSH stimulation in the first follow up of patients with DTC showed that I^{131}WBS is not helpful.[4]

Table 26. Absence of relationship between the thyroglobulin level obtained after withdrawal of T4 and the presence of uptake in the thyroid bed on the control I^{131} TBS.

Tg level (ng/ml)	Diagnostic I^{131} TBS		Demonstrated disease after initial treatment	
	No detectable uptake	Uptake in thyroid bed	< 1 year	> 3 years
<1	195	15		2
1-10	29	1+1[a]		1
>10	12	3	5[b]	
Total	236	20	5	3

[a]The only one patient who had visible uptake in the thyroid bed representing 1% administered activity demonstrated lung metastases by CT scan.
Source: Cailleux AF, Baudin E, Travagli JP, Ricard M, and Sclumberger M. Is diagnostic iodine 131 scanning useful after total thyroid ablation for differentiated thyroid cancer? J Clin Endocrinol Metab 2000; 85:175-178.

If therapeutic options are already warranted, a pre-therapeutic/diagnostic scan is not recommended because of the "stunning effect" which decreases uptake of therapeutic doses of RAI.

However, a diagnostic whole body scan may be utilized in localizing the site of recurrence and metastasis, to determine dosing by bulk and to determine uptake of RAI by the tumor.

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6.5. What is the role of positron emission tomography for postoperative surveillance in patients with WDTC?

FDG PET scan is a valuable tool in detecting and localizing recurrence and metastasis in post total thyroidectomy patients with negative whole body scans and elevated thyroglobulin levels.

FDG PET scan provides prognostic information for patients with differentiated thyroid carcinoma.

Level 2B, Category A

Summary of Evidence

Elevated thyroglobulin levels are generally regarded as a sensitive indicator of recurrent or metastatic disease and are usually associated with positive whole body scans. However, around 15-20 percent of patients with elevated thyroglobulin levels will have negative whole body scans. Iodine-concentrating lesions have differentiated thyroid carcinoma cells that retain their iodine-trapping mechanism and have low glucose metabolism. Lesions that do not concentrate iodine have differentiated thyroid carcinoma cells that lose their iodine-trapping mechanism and have high glucose metabolism. The use of FDG PET scans has grown because of its ability to localize lesions with high glucose metabolism.[1] Several studies have supported the use of FDG PET scans as an important tool in detecting and localizing recurrences and metastasis in post total thyroidectomy patients with elevated thyroglobulin levels and negative whole body scans with sensitivity of 78 percent to 94.6 percent and specificity of 25 percent to 95 percent.[2-7]

A cohort study by Wang, et al. of 125 post-thyroidectomy patients showed that survival was reduced in age > 45, distant metastasis, and PET positivity, high rates of FDG uptake and high volumes of FDG-avid disease. The single strongest predictor of survival was the volume of FDG–avid disease with patients with FDG volumes more than 125 ml was having significantly reduced short term survival. The 3-year survival of patients with FDG volumes less than 125 ml was 0.96 compared with 0.18 for FDG volumes greater than 125 ml. Once distant metastasis is discovered in patients with WDTC, FDG PET scan can identify low and high-risk subsets.[8]

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6.6. What is the role of computed tomography for postoperative surveillance in patients' with WDTC?

High resolution/helical CT scan is useful in detecting lung metastasis in patients with detectable thyroglobulin and negative WBS.

Integration of CT scan increases the diagnostic accuracy of PET scan in detecting metastasis in patients with DTC.

Level 2B, Category B

Summary of evidence

A study by Ilagan, et al.[1] showed that HRCT was able to detect 81.8 percent of patients with pulmonary metastasis. Furthermore, HRCT characteristics were noted to be a significant prognostic factor. The best 5-year survival rates were seen in HRCT-negative patients, followed by patients with micronodular (<5 mm) (86 %) and nodular (5-20mm) (25%).

Review articles by Pagano, et al.[2] and Ringel, et al.[3] also advocate the usefulness of high resolution/helical CT scan in detecting pulmonary metastasis in patients with well-differentiated thyroid carcinoma.

A retrospective study by Ong, et al.[4] investigating the utility of integrated PET/CT scans in detecting recurrences and metastasis in post-thyroidectomy patients with elevated thyroglobulin levels and negative whole body scans showed sensitivity at 88.2%.

A prospective study by Palmedo, et al.[5] investigating 127 lesions in 40 patients comparing CT scan, PET scan, side by side CT and PET scan , and integrated PET/CT scan showed significant increase in diagnostic accuracy for integrated PET/CT scans (Table 27).

Table 27. Diagnostic accuracy of CT scan, PET scan, side by side CT and PET scan, and integrated PET/CT scan in 40 patients, (institution).

	PET	CT	Side by side	PET/CT
Sensitivity %	79	79	95	95
Specificity %	76	71	76	91
PPV %	75	71	78	86
NPV %	80	79	94	95
Accuracy %	78	75	85	93

Source: Palmedo H, Bucerius H, Joe A, Strunk H, Hortling N, Meyka S, Roedel R, Wolff M, Waldermann E, Biersack H, and Jaeger U. Integrated PET/CT in differentiated thyroid cancer: diagnostic accuracy and impact on patient management. J Nucl Med 2006; 47: 616-624.

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6.7. What is the role of chest x-ray for postoperative surveillance in the patient with WDTC?

Routine chest x-rays have a limited role in detecting pulmonary metastasis for patients with well-differentiated thyroid cancer.

Level 2B, Category A

Summary of Evidence

Chest x-rays were once used routinely to evaluate pulmonary metastasis. Vassilopoulou-Sellin, et al.[1] in a retrospective study found out that chest x-rays were able to detect only 58 percent (11/19) of patients with positive lung metastasis on whole body scan. Ilagan, et al.[2] likewise noted dismal chest x-ray detection of pulmonary metastasis (36.4 %). Another study by Habra, et al.[3] noted that only 6.6 percent of patients with well-differentiated thyroid carcinoma developed chest x-ray abnormalities with a median interval to chest x-ray conversion at 66 months and with most of these patients having other evidence of recurrence or metastasis.

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7. What is the recommended treatment for recurrent and metastatic WDTC?

The recommended treatment for recurrent/metastatic WDTC is surgical excision of locoregional metastasis.

Level 5, Category A

The recommended treatment distant metastatic disease in selected patients is surgery followed by I^{131} therapy.

Level 4, Category A

Radiotherapy may be used for the treatment of painful bone metastases, metastatic lesions in critical locations likely to result in fracture, or with neurological or compressive symptoms that are not amenable to surgery.

Level 4, Category A

The role of chemotherapy is unclear.

Level 4, Category A

Thyroid suppression maybe used in combination with surgery and other therapeutic modalities.

Level 4, Category A

Summary of Evidence

The ATA Guidelines states that the preferred hierarchy of treatment is surgical excision of locoregional disease in potentially curable patients, I^{131} therapy, external beam radiation, watchful waiting for stable disease and experimental chemotherapy. A small fraction may benefit from radiofrequency ablation, ethanol ablation or chemo-embolization.[1]

Surgical management of locoregional metastases is the preferred treatment when distant metastases are not present. Approximately one half to one third will remain disease free in short-term follow up. The ATA guidelines recommend complete ipsilateral compartmental dissection of involved compartments while sparing vital structures (spinal accessory nerve, internal jugular vein and sternocleidomastoid muscle). However, it is not clear if surgery of locoregional disease is beneficial if it is associated with distant metastasis except for palliation.[1]

Ninety percent of malignant nodules are well differentiated, 70-80 percent of which have the papillary type and 20–30 percent of the follicular type. Distant metastases develop in 5 -23 percent of patients and 1–4 percent have distant metastases at the time of diagnosis. Most common sites of metastases are the lung and bones, with the liver and brain rarely involved.[2]

Patients with distant metastases have an increased mortality, at least half will die of metastatic disease during the course of follow-up. The probability of survival is 60.7 percent at 5 years, 51.2 percent at 10 years and 38.4 percent at 15 and 20 years. Milhailovic reported that age less than 45 years, histological type and initial therapy instituted are significant factors, which influenced survival. Survival was higher in patients with papillary versus follicular cancer, and in those who had adequate surgery (total/ near total thyroidectomy) with neck dissection and RAI therapy.[2]

Ho Pak, et al.[3] reported the NIH experience on metastasectomy in the management of thyroid cancer. Twenty nine patients with advanced nonmedullary thyroid carcinoma underwent 47 surgeries, including resection of distant metastases (lung,skeleton,kidneys &brain) with RAI therapy. EBRT, chemotherapy and others were used selectively. Metastasectomy resulted in a 38 percent reduction in thyroglobulin levels in 23 patients. Kaplan Meyer survival curve showed cumulative survival rates of 78.5 percent at 5 years, and 50 percent at 10 years after distant metastasectomy.

Surgical resection of bone metastases was shown in retrospective studies to be a prognostic factor affecting survival.[4,5] Zettinig[6] in 41 patients identified total thyroidectomy, lymph node surgery, RAI therapy and absence of extraskeletal distant metastases as significant predictors of survival. In the subgroup of patients with distant metastases limited only to the bone, the surgical resection of the bone metastases was a significant prognostic factor affecting survival. Bernier[7] reported that in patients with bone metastases as a revealing symptom of thyroid carcinoma, without metastases from other organs, the cumulative dose of I^{131} therapy and complete bone metastases surgery in patients less than 45 years old were independent prognostic factors associated with improved survival.

The surgical resection of brain metastases has been shown to improve survival when compared to no resection in reports from the database of the Mayo Clinic (20.8 vs. 2.7 months), and MD Anderson Cancer Center (16.7 vs. 3.4 months; $p < 0.05$).[8]

The benefits of RAI therapy for metastases are reported in several case series. Schlumberger, et al.[5] noted that RAI was one of the factors, which account for survival in those patients with lung and/or bone metastases, which concentrate I^{131}. Those with complete response following treatment of distant metastasis had a 15 yr survival rate of 89 percent. In the series by Ronga[9] of patients with lung metastases, all patients underwent total thyroidectomy with or without neck dissection. I^{131} uptake by metastases was also important for survival. In the series of Massin[10] of patients with pulmonary metastasis, ten-year survival was only 25 percent for those without I^{131} uptake vs. 75 percent for those with I^{131} uptake.

The ATA Guidelines have recommendations on the use of EBRT for the treatment of painful bone metastases, metastatic lesions in critical locations likely to result in fracture, and neurological or compressive symptoms not amenable to surgery (ex, vertebral metastases, CNS metastases, selected mediastinal or subcarinal lymph nodes, pelvic metastases). Patients deemed at high risk for recurrence (older patients, with extra-thyroidal extension of tumor, with macroscopic or microscopic residual disease) appeared to benefit if given external beam radiotherapy.[1]

Several studies reviewed their results with the use of EBRT in the management of thyroid carcinoma. Tsang, et al.[4] reported their experience in the adjuvant management of patients with WDTC at high risk for recurrence using various techniques and doses of radiotherapy. These patients were older (> 45 years old), had extrathyroidal extension of tumor and had macroscopic or microscopic residual disease. Although results were not statistically significant, they concluded that cause specific survival and local control of papillary tumors with postoperative microscopic residuum may benefit from EBRT. A retrospective study by Ford [11] showed that EBRT using a total dose of at least 50 Gy may improve local recurrence rates. They used EBRT for the presence of macroscopic and microscopic residual disease, Hurthle cell variants, multiple lymph node involvement and focus of anaplastic carcinoma. Mazzarotto[12], and Brierley[13], noted that EBRT for metastatic WDTC had acceptable acute toxicity and rarely produced serious long-term complications.

The role of chemotherapy in the treatment of patients with recurrent/metastatic WDTC remains unclear. Haugen Bryan[14] summarized 10 papers reporting the use of Adriamycin, the most effective single agent, with an average response rate of 40 percent. De Besi, et al. used chemotherapy for patients with progressive symptomatic disease unresponsive to hormonal or isotopic treatment. Patients with varying histology were treated with BAP regimen (Bleomycin, Adriamycin and Platinum). Only 9/21 had objective response (2 had complete response, 7 partial response), with a median survival of 11 months. Of those with no response, 3 responded to a four drug second line regimen (Vincristine, fluorouracil, BCNU and

Methotrexate).[14] Trials are now on phase I and recruitment phase to determine the role of chemotherapy in recurrent/ metastatic disease.[16]

Thyroid suppression may be used in combination with other therapies for recurrent/metastatic WDTC. In the retrospective series of Mihailovic, et al.[2] surgery + RAI therapy + life long hormone therapy + EBRT were used in 10 patients; however, a longer survival of DTC with metastasis was achieved by adequate surgery followed by I^{131} therapy.

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