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New Concepts in Management of Pediatric Thyroid Cancer

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Some warm up questions

Compared to adults, thyroid nodules in children are

_____

A. Less common
B. More common
C. Equally common

A. Prevalence about 2% by thyroid US, higher in older children (~15%). Prevalence in adults up to 50% by thyroid US.

Compared to adults, thyroid nodules in children are _____

A. Less likely to be malignant
B. More likely to be malignant
C. Equally as likely to be malignant

B. 25% are malignant versus 5% are malignant in adults

When histology and tumor size are controlled, children with thyroid cancer are _____ to have regional lymph node involvement, extrathyroidal extension, and pulmonary metastasis

A. Less likely
B. More likely
C. Equally likely

B.

Despite extensive disease at clinical presentation, children are _____ to die from disease than are adults.

A. Less likely
B. More likely
C. Equally likely

A.

Primer on Thyroid Cancer

Original Investigation

Current Thyroid Cancer Trends in the United States

Louise Davies, MD, MS; H. Gilbert Welch, MD, MPH

IMPORTANCE We have previously reported on a doubling of thyroid cancer incidence—largely due to the detection of small papillary cancers. Because they are commonly found in people who have died of other causes, and because thyroid cancer mortality had been stable, we argued that the increased incidence represented overdiagnosis.

OBJECTIVE To determine whether thyroid cancer incidence has stabilized.

DESIGN Analysis of secular trends in patients diagnosed with thyroid cancer, 1975 to 2009, using the Surveillance, Epidemiology, and End Results (SEER) program and thyroid cancer mortality from the National Vital Statistics System.

SETTING Nine SEER areas (SEER 9): Atlanta, Georgia; Connecticut; Detroit, Michigan; Hawaii; Iowa; New Mexico; San Francisco–Oakland, California; Seattle–Puget Sound, Washington; and Utah.

PARTICIPANTS Men and women older than 18 years diagnosed as having a thyroid cancer between 1975 and 2009 who lived in the SEER 9 areas.

INTERVENTIONS None.

MAIN OUTCOMES AND MEASURES Thyroid cancer incidence, histologic type, tumor size, and patient mortality.

RESULTS Since 1975, the incidence of thyroid cancer has now nearly tripled, from 4.9 to 14.3 per 100 000 individuals (absolute increase, 9.4 per 100 000; relative rate [RR], 2.9; 95% CI, 2.7-3.1). Virtually the entire increase was attributable to papillary thyroid cancer: from 3.4 to 12.5 per 100 000 (absolute increase, 9.1 per 100 000; RR, 3.7; 95% CI, 3.4-4.0). The absolute increase in thyroid cancer in women (from 6.5 to 21.4 = 14.9 per 100 000 women) was almost 4 times greater than that of men (from 3.1 to 6.9 = 3.8 per 100 000 men). The mortality rate from thyroid cancer was stable between 1975 and 2009 (approximately 0.5 deaths per 100 000).

CONCLUSIONS AND RELEVANCE There is an ongoing epidemic of thyroid cancer in the United States. The epidemiology of the increased incidence, however, suggests that it is not an epidemic of disease but rather an epidemic of diagnosis. The problem is particularly acute for women, who have lower autopsy prevalence of thyroid cancer than men but higher cancer detection rates by a 3:1 ratio.

CME Quiz at jamanetworkcme.com and CME Questions page 388

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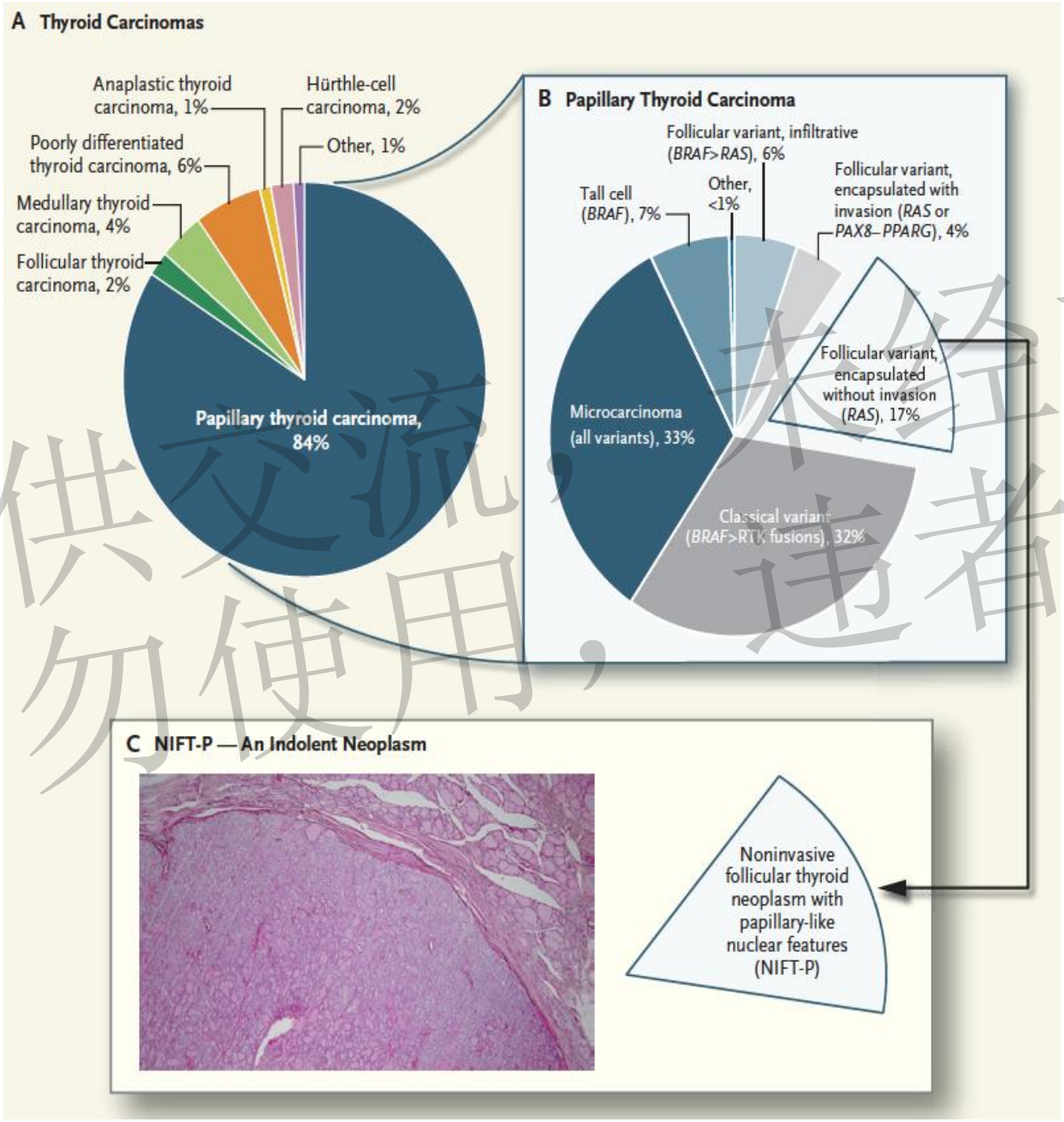
Increased incidence of thyroid cancer is directly related to more diagnoses of small papillary cancer especially in women

Overuse of thyroid US is certainly a contributing factor (epidemic of diagnosis)

Less of a problem in pediatric population where thyroid US tends to be used less often except in patients with history of radiation exposure or familial genetic syndromes

Prevalence of Thyroid Cancer Histotypes



NEJM 2016 375:1054

Prevalence of Thyroid Cancer Histotypes

JAMA Oncology | Original Investigation

Nomenclature Revision for Encapsulated Follicular Variant of Papillary Thyroid Carcinoma

A Paradigm Shift to Reduce Overtreatment of Indolent Tumors

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IMPORTANCE Although growing evidence points to highly indolent behavior of encapsulated follicular variant of papillary thyroid carcinoma (EFVPTC), most patients with EFVPTC are treated as having conventional thyroid cancer.

OBJECTIVE To evaluate clinical outcomes, refine diagnostic criteria, and develop a nomenclature that appropriately reflects the biological and clinical characteristics of EFVPTC.

DESIGN, SETTING, AND PARTICIPANTS International, multidisciplinary, retrospective study of patients with thyroid nodules diagnosed as EFVPTC, including 109 patients with noninvasive EFVPTC observed for 10 to 26 years and 101 patients with invasive EFVPTC observed for 1 to 18 years. Review of digitized histologic slides collected at 13 sites in 5 countries by 24 thyroid pathologists from 7 countries. A series of teleconferences and a face-to-face conference were used to establish consensus diagnostic criteria and develop new nomenclature.

MAIN OUTCOMES AND MEASURES Frequency of adverse outcomes, including death from disease, distant or locoregional metastases, and structural or biochemical recurrence, in patients with noninvasive and invasive EFVPTC diagnosed on the basis of a set of reproducible histopathologic criteria.

RESULTS Consensus diagnostic criteria for EFVPTC were developed by 24 thyroid pathologists. All of the 109 patients with noninvasive EFVPTC (67 treated with only lobectomy, none received radioactive iodine ablation) were alive with no evidence of disease at final follow-up (median [range], 13 [10-26] years). An adverse event was seen in 12 of 101 (12%) of the cases of invasive EFVPTC, including 5 patients developing distant metastases, 2 of whom died of disease. Based on the outcome information for noninvasive EFVPTC, the name "noninvasive follicular thyroid neoplasm with papillary-like nuclear features" (NIFTP) was adopted. A simplified diagnostic nuclear scoring scheme was developed and validated, yielding a sensitivity of 98.6% (95% CI, 96.3%-99.4%), specificity of 90.1% (95% CI, 86.0%-93.1%), and overall classification accuracy of 94.3% (95% CI, 92.1%-96.0%) for NIFTP.

CONCLUSIONS AND RELEVANCE Thyroid tumors currently diagnosed as noninvasive EFVPTC have a very low risk of adverse outcome and should be termed NIFTP. This reclassification will affect a large population of patients worldwide and result in a significant reduction in psychological and clinical consequences associated with the diagnosis of cancer.

Editorial page 1005

Supplemental content at jamaoncology.com

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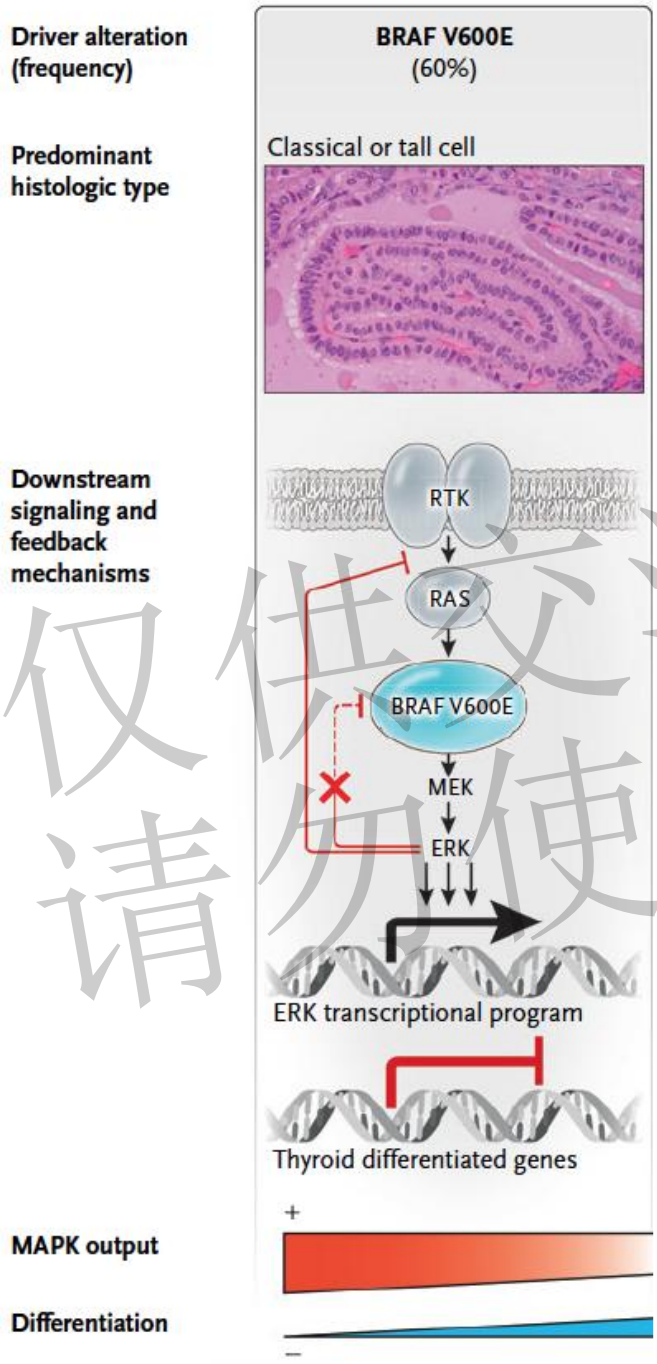
Encapsulated follicular variant of PTC is a common cause of an indeterminate cytology by FNA

Pathologist have reclassified this lesion as a benign neoplasm and renamed it

Noninvasive thyroid neoplasm with papillary-like nuclear features (NIFT-P)

Papillary Thyroid Cancer



BRAF mutation- No negative feedback. High rate of LN mets and recurrence after thyroidectomy. **Rare in Children**

RTK fusions- Common in radiation-induced damage. Low mortality. **Much more common in children especially NRTK**

RAS mutations and PAX8-PPARG fusion- Common in follicular cancer and follicular variant papillary. The degree of angio-invasiveness and size predicts mets. Hurthle-cell is a variant with more agressive behavior.

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ORIGINAL ARTICLE

Preoperative Diagnosis of Benign Thyroid Nodules with Indeterminate Cytology

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ABSTRACT

BACKGROUND

Approximately 15 to 30% of thyroid nodules evaluated by means of fine-needle aspiration are not clearly benign or malignant. Patients with cytologically indeterminate nodules are often referred for diagnostic surgery, though most of these nodules prove to be benign. A novel diagnostic test that measures the expression of 167 genes has shown promise in improving preoperative risk assessment.

METHODS

We performed a 19-month, prospective, multicenter validation study involving 49 clinical sites, 3789 patients, and 4812 fine-needle aspirates from thyroid nodules 1 cm or larger that required evaluation. We obtained 577 cytologically indeterminate aspirates, 413 of which had corresponding histopathological specimens from excised lesions. Results of a central, blinded histopathological review served as the reference standard. After inclusion criteria were met, a gene-expression classifier was used to test 265 indeterminate nodules in this analysis, and its performance was assessed.

RESULTS

Of the 265 indeterminate nodules, 85 were malignant. The gene-expression classifier correctly identified 78 of the 85 nodules as suspicious (92% sensitivity; 95% confidence interval [CI], 84 to 97), with a specificity of 52% (95% CI, 44 to 59). The negative predictive values for "atypia (or follicular lesion) of undetermined clinical significance," "follicular neoplasm or lesion suspicious for follicular neoplasm," or "suspicious cytologic findings" were 95%, 94%, and 85%, respectively. Analysis of 7 aspirates with false negative results revealed that 6 had a paucity of thyroid follicular cells, suggesting insufficient sampling of the nodule.

CONCLUSIONS

These data suggest consideration of a more conservative approach for most patients with thyroid nodules that are cytologically indeterminate on fine-needle aspiration and benign according to gene-expression classifier results. (Funded by Veracyte.)

From the Departments of Medicine (E.K.A.) and Pathology (E.S.C.), Brigham and Women's Hospital and Harvard Medical School, Boston; Veracyte, South San Francisco, CA (G.C.K., D.C., J.D., L.F., P.S.W., J.I.W., R.B.L.); the Departments of Pathology (Z.W.B., V.A.L.) and Medicine (S.J.M.), Perelman School of Medicine, University of Pennsylvania, Philadelphia; the Department of Medicine, Ohio State University College of Medicine, Columbus (R.T.K.); the Department of Pathology, University of Washington School of Medicine, Seattle (S.S.R.); Centro Diagnostico Italiano, Milan (J.R.); the Department of Surgery, University of Cincinnati College of Medicine, Cincinnati (D.L.S.); the Department of Surgery, Johns Hopkins University School of Medicine, Baltimore (M.A.Z.); and the Department of Medicine, University of Colorado School of Medicine, Aurora (B.R.H.). Address reprint requests to Dr. Alexander at the Thyroid Unit, Division of Endocrinology, Metabolism and Diabetes, Brigham and Women's Hospital, 75 Francis St., Rm. PBB-B4, Boston, MA 02115, or at ekalexander@partners.org; or to Dr. Kennedy at Veracyte, Inc.,7000 Shoreline Ct., Suite 250, South San Francisco, CA 94080, or at giulia@veracyte.com.

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Indeterminate Biopsy

A well-done RCT

Conclusion: GEC (Afirma) is a "rule out" test with a high NPV

Several authors receive compensation from Veracyte; one is on its board of directors

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Noninvasive Follicular Variant of Papillary Thyroid Carcinoma and the Afirma Gene-Expression Classifier

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Background: It is now recognized that noninvasive follicular variant of papillary thyroid carcinoma (NFVPTC) is a distinct subset of FVPTC with an exceedingly indolent clinical course. The Afirma gene-expression classifier (GEC) helps guide clinicians in the management of thyroid nodules with indeterminate fine-needle aspiration (FNA) results. Thyroid surgery is recommended for nodules with a suspicious Afirma result, whereas observation is deemed reasonable for most nodules with a benign result. The aim of this study was to confirm that the Afirma test detects NFVPTCs and to determine how many carcinomas detected by the Afirma GEC represent NFVPTCs.

Methods: From a database of 249 FNAs sent for Afirma testing between January 2012 and October 2014, a search was conducted for cases with a preceding FNA diagnosis of atypia/follicular lesion of undetermined significance (AUS/FLUS) or suspicious for a follicular neoplasm (SFN), a suspicious Afirma result, and a corresponding resection specimen reviewed at Brigham and Women's Hospital. The diagnoses of the prior FNAs and subsequent resection specimens were recorded. Slides for all resection specimens with a diagnosis of FVPTC were reviewed to identify NFVPTCs.

Results: Sixty-three cases met the inclusion criteria. The preceding FNA diagnosis was AUS/FLUS in 34 (54%) cases and SFN in 29 (46%) cases. The surgical resection specimen demonstrated 16 (25%) FVPTCs, five (8%) follicular thyroid carcinomas, one (2%) classical type PTC, and 41 (65%) benign tumors/nodules. Of the 16 FVPTCs, 14 (88%) were NFVPTCs. Thus, NFVPTCs accounted for 64% of the carcinomas in the cohort.

Conclusion: These results indicate that the Afirma GEC detects NFVPTCs and that many of the carcinomas detected by Afirma are NFVPTCs. While all care should be individualized and include clinical and sonographic assessment, these results suggest lobectomy as opposed to total thyroidectomy should be considered for nodules with a preceding AUS/FLUS or SFN on cytology and a suspicious Afirma result.

Introduction

THYROID NODULES ARE VERY COMMON in adults. However, only 7–15% are malignant (1). Ultrasound-guided fine-needle aspiration (FNA) is accepted as the diagnostic standard of care for the preoperative evaluation of nontoxic thyroid nodules (1). Although FNA accurately classifies the majority of nodules as benign or malignant, approximately 15–30% of FNAs are associated with indeterminate FNA results, defined as a cytologic diagnosis of atypia/follicular lesion of undetermined significance (AUS/FLUS), suspicious for follicular neoplasm (SFN), and suspicious for malignancy (SUS) (2,3). Because of the risk of malignancy for nodules with indeterminate cytology, surgery is often required. However, the majority of these nodules are found to be benign on surgical resection (4). The Afirma gene-expression classifier (GEC) was developed to reduce the number of diagnostic surgeries performed by further risk stratifying nodules with an indeterminate FNA diagnosis (5). The GEC interrogates the mRNA expression of 167 genes to identify nodules with a benign molecular signature. Thus, the GEC is designed to maximize accurate detection of benign rather than malignant nodules. In other words, the GEC is used as a "rule out" test. A prospective, multicenter study showed that a benign Afirma result has a negative predictive value of 95%, 94%, and 85% for nodules with a cytologic diagnosis of AUS/FLUS, SFN, and SUS, respectively (5). As a result of the lower negative predictive value associated with a nodule with a SUS diagnosis on FNA, Afirma testing is currently primarily utilized for nodules with an FNA diagnosis of AUS/FLUS or

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But wait…..

New results from the same group.

Of 63 indeterminate nodules that had Afirma testing

41/63 were benign
22/63 malignant
16/22 malignant were FVPTC

So 57/63 (90%) you should not remove…why test at all?

Use of molecular diagnostic tests in pediatric thyroid cancer patients is not justified due to lack of prospective studies in children and the realization that pediatric and adult thyroid cancers are different.

Operative approach for a biopsy diagnostic for follicular cell–derived malignancy (ATA Guidelines 2016)

RECOMMENDATION 35

(A) For patients with thyroid cancer >4 cm +/- nodes use near-total or total thyroidectomy and gross removal of all primary tumor unless contraindicated.

(B) For patients with thyroid cancer >1 cm and <4 cm +/- nodes can be either a bilateral procedure (near-total or total thyroidectomy) or a unilateral procedure (lobectomy). However, the treatment team may choose total thyroidectomy to enable RAI therapy or to enhance follow-up based upon disease features and/or patient preferences.

(C) If surgery is chosen for patients with thyroid cancer <1 cm without nodes use thyroid lobectomy unless there are clear indications to remove the contralateral lobe. Probably not sufficient in prior head and neck radiation, familial thyroid carcinoma, or clinically detectable cervical nodal metastases.

Thyroid Cancer Risk Groups (ATA Guidelines 2016)

Low Risk- Intrathyroidal DTC, ≤ 5 LN micrometastes (LN < 0.2 cm)

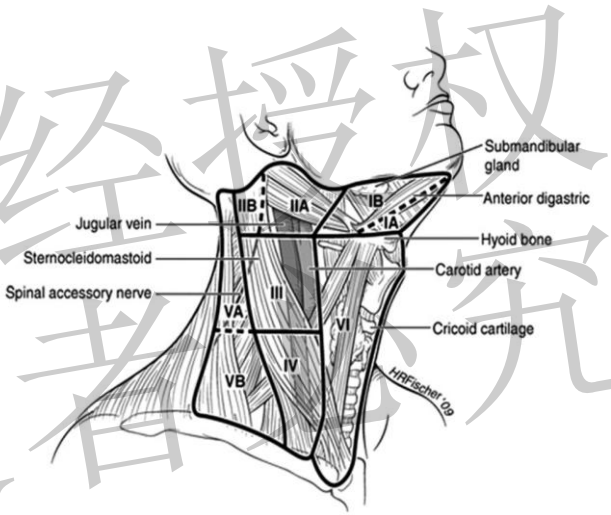
Intermediate Risk- Aggressive histology, minor extrathyroidal extension, vascular invasion. > 5 LN (all < 3 cm)

High Risk- Gross extrathyroidal extension, distant metastases, incomplete cancer resection, LN > 3 cm

Lymph Node Dissection (ATA Guidelines 2016)

RECOMMENDATION 36

(A) Therapeutic central-compartment (level VI) neck dissection for patients with clinically involved central nodes should accompany total thyroidectomy to provide clearance of disease from the central neck.



(B) Prophylactic central-compartment neck dissection should be considered in patients with PTC with advanced primary tumors (T3 [> 4cm] or T4 [invasion outside thyroid])

(C) Thyroidectomy without prophylactic central neck dissection is appropriate for small (T1 [≤ 2cm] or T2 [>2 ≤ 4 cm]), noninvasive, clinically node-negative PTC and for most follicular cancers, which are unlikely to go to nodes.

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DOI: 10.1089/thy.2011.0317

ARTICLE

American Thyroid Association Design and Feasibility of a Prospective Randomized Controlled Trial of Prophylactic Central Lymph Node Dissection for Papillary Thyroid Carcinoma

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Background: The role of prophylactic central lymph node dissection in papillary thyroid cancer (PTC) is controversial in patients who have no pre- or intraoperative evidence of nodal metastasis (clinically N0; cN0). The controversy relates to its unproven role in reducing recurrence rates while possibly increasing morbidity (permanent hypoparathyroidism and unintentional recurrent laryngeal nerve injury).
Methods and Results: We examined the design and feasibility of a multi-institutional prospective randomized controlled trial of prophylactic central lymph node dissection in cN0 PTC. Assuming a 7-year study with 4 years of enrollment, 5 years of average follow-up, a recurrence rate of 10% after 7 years, a 25% relative reduction in the rate of the primary endpoint (newly identified structural disease; i.e., persistent, recurrent, or distant metastatic disease) with central lymph node dissection and an annual dropout rate of 3%, a total of 5840 patients would have to be included in the study to achieve at least 80% statistical power. Similarly, given the low rates of morbidity, several thousands of patients would need to be included to identify a significant difference in rates of permanent hypoparathyroidism and unintentional recurrent laryngeal nerve injury.
Conclusion: Given the low rates of both newly identified structural disease and morbidity after surgery for cN0 PTC, prohibitively large sample sizes would be required for sufficient statistical power to demonstrate significant differences in outcomes. Thus, a prospective randomized controlled trial of prophylactic central lymph node dissection in cN0 PTC is not readily feasible.

Introduction

Thyroid cancer is the most common endocrine malignancy. In the United States, an estimated 44,670 new cases of thyroid cancer were diagnosed in 2010 with a total of 1690 deaths due to the disease (1). The discrepancy between the total number of cases of all endocrine cancers arising in the thyroid (95.2%) and the total proportion of endocrine cancer deaths (65.8%) reflects the long-term survival associated with thyroid malignancies, given its relatively indolent nature (1).

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What is the role of RAI (including remnant ablation, adjuvant therapy, or therapy for persistent disease) after thyroidectomy (ATA Guidelines 2016)

RECOMMENDATION 51

(A) RAI remnant ablation is not routinely recommended after thyroidectomy for ATA low-risk DTC patients (Secondary malignancy a real concern in pediatric population).

(B) RAI remnant ablation is not routinely recommended after lobectomy or total thyroidectomy for patients with unifocal papillary microcarcinoma, in the absence of other adverse features (Shouldn't do it anyway).

(C) RAI remnant ablation is not routinely recommended after thyroidectomy for patients with multifocal papillary microcarcinoma in absence of other adverse features.

(D) RAI adjuvant therapy should be considered after total thyroidectomy in ATA intermediate-risk level DTC patients.

(E) RAI adjuvant therapy is routinely recommended after total thyroidectomy for ATA high risk DTC patients.

Papillary thyroid microcarcinoma: A study of 900 cases observed in a 60-year period

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Background. *The study aims were to characterize patients with papillary thyroid microcarcinoma (PTM) and to describe post-surgical outcome.*
Methods. *Nine hundred PTM patients had initial treatment at Mayo Clinic during 1945–2004. Mean follow-up was 17.2 years. Recurrence and mortality details were derived from a computerized database.*
Results. *Median tumor size was 7 mm; 98% were intrathyroidal. 273 patients (30%) had neck nodal involvement; 3 (0.3%) had distant metastases at diagnosis. Seven-hundred and sixty-five (85%) underwent bilateral lobar resection (BLR; total-, near-total, or bilateral subtotal thyroidectomy). Regional nodes were removed by either "node picking" (27%) or compartmental dissection (23%). Tumor resection was incomplete in 5 (0.6%). Radioiodine remnant ablation (RRA) was performed in 155 (17%). Overall survival did not differ from expected for an age and gender matched control group (P = .96); 3 patients (0.3%) died of PTM. None of the 892 patients with initial complete tumor resection developed metastatic spread during 20 postoperative years. Twenty-year and 40-year tumor recurrence rates were 6% and 8%, respectively. Higher recurrence rates were seen with multifocal tumors (P = .004) and node-positive patients (P < .001). Neither more extensive surgery nor RRA reduced recurrence rates compared to unilateral lobectomy.*
Conclusion. *More than 99% of PTM patients are not at risk of distant spread or cancer mortality. RRA after BLR did not improve postoperative outcome. (Surgery 2008;144:980-8.)*

From the Divisions of Endocrinology and Internal Medicine, Biostatistics, Gastroenterologic and General Surgery, and Anatomic Pathology, Mayo Clinic and College of Medicine, Rochester, Minn

PAPILLARY THYROID CARCINOMA (PTC) is the most common thyroid follicular cell-derived malignancy.[1] Papillary thyroid microcarcinoma (PTM), defined as PTC with a maximum tumor diameter of 10 mm or less[2] has long been recognized to be present in 6-36% of autopsy studies.[3] These small tumors are being increasingly recognized *in vivo*,[4] due, in part, to the increasing use of high-resolution ultrasound, capable of permitting guided biopsies of nodules as small as 3 mm in diameter[5,6] and threatening an "epidemic of microcarcinomas."[7]

In 1992, we published a study of 535 consecutive patients with PTM treated at Mayo Clinic,[8] and concluded the following: that (1) the prognosis was excellent, if patients were managed initially by bilateral lobar resection (BLR), encompassing either total or near-total thyroidectomy, or a bilateral sub-total resection; and (2) locoregional recurrence rates in node-positive patients treated by BLR were not improved by post-operative radioactive remnant ablation (RRA). However, 16 years after this publication, there remains substantial controversy regarding the appropriate therapeutic strategy for PTM patients.[9,10]

At one extreme is a Japanese group who argue that observation without surgery is safe for small intrathyroidal PTM,[11] while some experts in the United States favor unilateral lobectomy without RRA.[12] At the other extreme are groups who consider it "reasonable to perform total thyroidectomy (possibly associated with central compartment node dissection), I-131 whole body scan (followed by I-131 therapy when necessary) and TSH-suppressive hormonal therapy" in PTM.[13,14] One recent study of PTM has suggested "always performing a total thyroidectomy followed by radiometabolic therapy in all papillary carcinomas, independent of their size."[15]

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85% had a bilateral operation

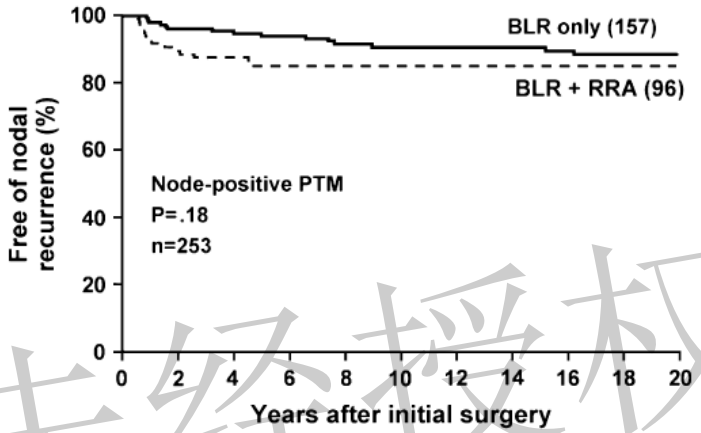

Fig 9. Lack of influence of radioiodine remnant ablation, when performed within 6 months of bilateral potentially curative surgery, on neck nodal recurrence in 253 node-positive PTM.

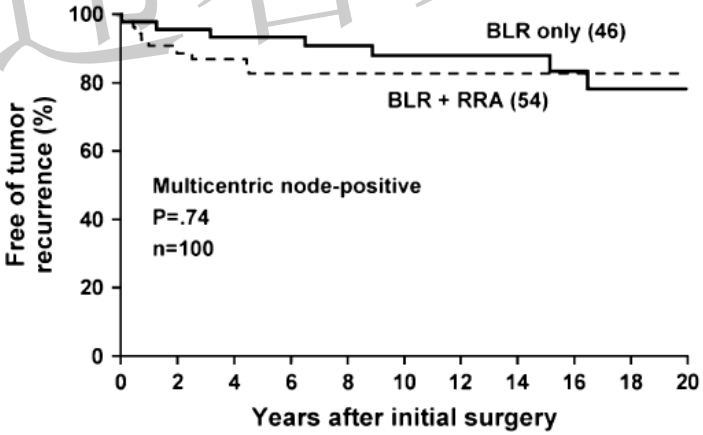

Fig 10. Lack of influence of RRA on tumor recurrences (any site) in 100 multicentric node-positive PTM patients treated at Mayo during 1945 through 2004.

Long-Term Impact of Initial Surgical and Medical Therapy on Papillary and Follicular Thyroid Cancer

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PURPOSE: To determine the long-term impact of medical and surgical treatment of well differentiated papillary and follicular thyroid cancer.

METHODS: Patients with papillary and follicular cancer (n = 1,355) treated either in U.S. Air Force or Ohio State University hospitals over the past 40 years were prospectively followed by questionnaire or personal examination to determine treatment outcomes. Outcomes were analyzed by Kaplan-Meier survival curves and Cox proportional-hazard regression model.

RESULTS: Median follow-up was 15.7 years; 42% (568) of the patients were followed for 20 years and 14% (185) for 30 years. After 30 years, the survival rate was 76%, the recurrence rate was 30%, and the cancer death rate was 8%. Recurrences were most frequent at the extremes of age (<20 and >59 years). Cancer mortality rates were lowest in patients younger than 40 years and increased with each subsequent decade of life. Thirty-year cancer mortality rates were greatest in follicular cancer patients, who were more likely to have adverse prognostic factors: older age, larger tumors, more mediastinal node involvement, and distant metastases. When patients with distant metasteses at diagnosis were excluded, follicular and papillary cancer mortality rates were similar (10% versus 6%, *P* not significant [NS]). In a Cox regression model that excluded patients who presented with distant metastases, the likelihood of cancer death was (1) increased by age ≥40 years, tumor size ≥1.5 cm, local tumor invasion, regional lymph-node metastases, and delay in therapy ≥12 months; (2) reduced by female sex, surgery more extensive than lobectomy, and ^{131}I plus thyroid hormone therapy; and (3) unaffected by tumor histologic type. Following ^{131}I therapy given only to ablate normal thyroid gland remnants, the recurrence rate was less than one third the rate after thyroid hormone therapy alone (*P* <0.001). No patient treated in this way with ^{131}I has died of thyroid cancer. Low ^{131}I doses (29 to 50 mCi) were as effective as high doses (51 to 200 mCi) in controlling tumor recurrence (7% versus 9%, *P* = NS). Following ^{131}I therapy, whether given for thyroid remnant ablation or cancer therapy, recurrence and the likelihood of cancer death were reduced by at least half, despite the existence of more adverse prognostic factors in patients given ^{131}I.

At 30 years, the cumulative cancer mortality rate following ^{131}I therapy, regardless of the reason for its use, was one third that in patients not so treated (*P* = 0.03).

CONCLUSION: Over the long term, for tumors ≥1.5 cm that are not initially metastatic to distant sites, near-total thyroidectomy followed by ^{131}I plus thyroid hormone therapy confers a distinct outcome advantage. This therapy reduces tumor recurrence and mortality sufficiently to offset the augmented risks incurred by delayed therapy, age ≥40 at the time of diagnosis, and tumors that are much larger than 1.5 cm, multicentric, locally invasive, or regionally metastatic.

We began this cohort study in 1970 to investigate the long-term impact of therapy on papillary and follicular thyroid cancer.[1,2] At the time, no prospective randomized clinical trials had been done to address the effects of therapy. None have yet been done and it is unlikely that any will be, considering the good prognosis of these tumors and the necessarily prolonged nature and potential cost of such studies. Wong et al[3] estimated that a clinical trial to address the issue of ablative radioactive iodine (^{131}I) therapy would require nearly 4,000 patients in each arm of the study to detect a 10% reduction in mortality after 25 years. If 1 in every 10 thyroid cancer patients was enrolled, enrollment would take 10 years, and the results would be available after 35 years.

Our previous studies of this cohort[1,2,4,5] have suggested that patient age at the time of diagnosis, tumor size, local tumor invasion, and regional or distant metastases were especially important prognostic factors. Although we found that treatment with near-

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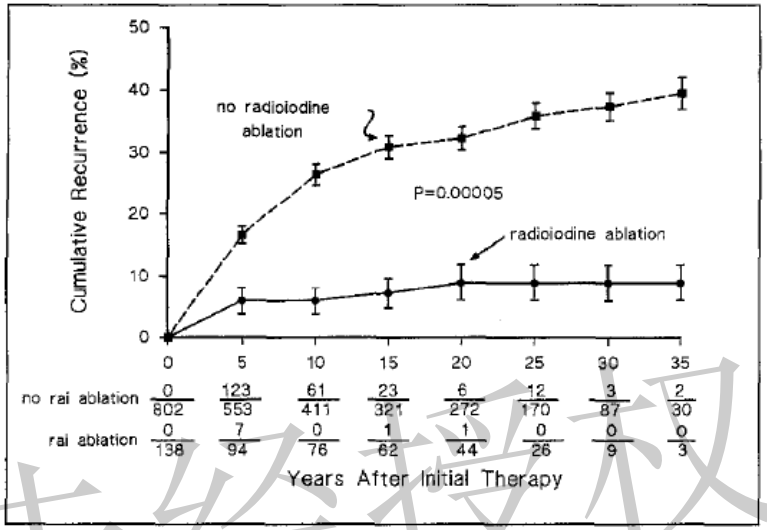

Figure 6. Cancer recurrence in patients with stage 2 or 3 tumors either treated with (n = 138) or without (n = 802) ^{131}I ablation to destroy presumably normal thyroid gland tissue without tumor. More patients treated with ^{131}I had follicular cancer (*P* <0.001). See Figure 1 legend.

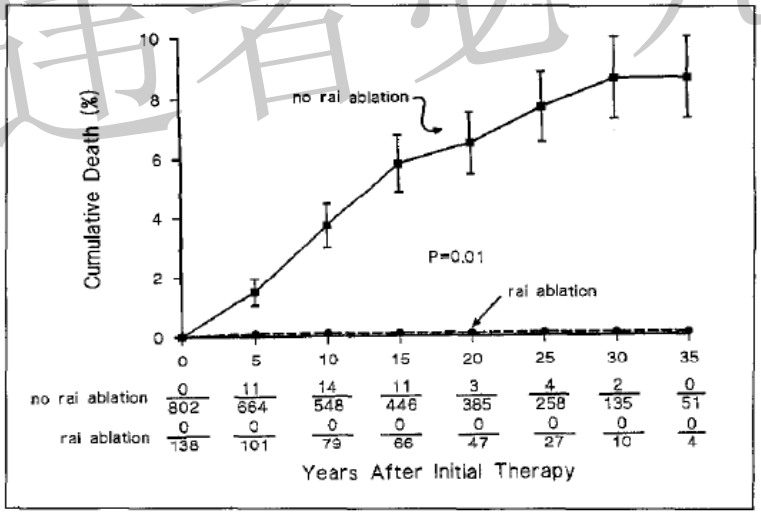

Figure 7. Cancer mortality rates in patients with stage 2 or 3 tumors treated either with (n = 138) or without (n = 802) ^{131}I remnant ablation to destroy presumably normal thyroid gland tissue without tumor. More patients treated with ^{131}I had follicular cancer (*P* <0.001). See Figure 1 legend.

This study excluded patients with distant mets

Can rhTSH (Thyrogen) be used as an alternative to thyroxine withdrawal for remnant ablation or adjuvant therapy in patients who have undergone near-total or total thyroidectomy? (ATA Guidelines 2016)

RECOMMENDATION 54

(A) In patients with ATA low- and intermediate-risk DTC without extensive lymph node involvement, in whom RAI remnant ablation or adjuvant therapy is planned, preparation with rhTSH is an acceptable alternative to thyroid hormone withdrawal for achieving remnant ablation.

(B) In patients with ATA intermediate-risk DTC who have extensive lymph node disease in the absence of distant metastases, preparation with rhTSH stimulation may be considered as an alternative to thyroid hormone withdrawal prior to adjuvant RAI treatment (Unproven in long-term follow-up studies).

(C) In patients with ATA high-risk DTC, more long-term outcome studies are needed before rhTSH preparation for RAI adjuvant treatment can be recommended.

(D) In patients with DTC of any risk level with significant comorbidity that may preclude thyroid hormone withdrawal prior to iodine RAI administration, rhTSH preparation should be considered.

First Human Trial of Thyroid Carcinoma Using rhTSH (Thyrogen)

The New England Journal of Medicine

COMPARISON OF ADMINISTRATION OF RECOMBINANT HUMAN THYROTROPIN WITH WITHDRAWAL OF THYROID HORMONE FOR RADIOACTIVE IODINE SCANNING IN PATIENTS WITH THYROID CARCINOMA

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ABSTRACT

Background To detect recurrent disease in patients who have had differentiated thyroid cancer, periodic withdrawal of thyroid hormone therapy may be required to raise serum thyrotropin concentrations to stimulate thyroid tissue so that radioiodine (iodine-131) scanning can be performed. However, withdrawal of thyroid hormone therapy causes hypothyroidism. Administration of recombinant human thyrotropin stimulates thyroid tissue without requiring the discontinuation of thyroid hormone therapy.

Methods One hundred twenty-seven patients with thyroid cancer underwent whole-body radioiodine scanning by two techniques: first after receiving two doses of thyrotropin while thyroid hormone therapy was continued, and second after the withdrawal of thyroid hormone therapy. The scans were evaluated by reviewers unaware of the conditions of scanning. The serum thyroglobulin concentrations and the prevalence of symptoms of hypothyroidism and mood disorders were also determined.

Results Sixty-two of the 127 patients had positive whole-body radioiodine scans by one or both techniques. The scans obtained after stimulation with thyrotropin were equivalent to the scans obtained after withdrawal of thyroid hormone in 41 of these patients (66 percent), superior in 3 (5 percent), and inferior in 18 (29 percent). When the 65 patients with concordant negative scans were included, the two scans were equivalent in 106 patients (83 percent). Eight patients (13 percent of those with at least one positive scan) were treated with radioiodine on the basis of superior scans done after withdrawal of thyroid hormone. Serum thyroglobulin concentrations increased in 15 of 35 tested patients: 14 after withdrawal of thyroid hormone and 13 after administration of thyrotropin. Patients had more symptoms of hypothyroidism ($P<0.001$) and dysphoric mood states ($P<0.001$) after withdrawal of thyroid hormone than after administration of thyrotropin.

Conclusions Thyrotropin stimulates radioiodine uptake for scanning in patients with thyroid cancer, but the sensitivity of scanning after the administration of thyrotropin is less than that after the withdrawal of thyroid hormone. Thyrotropin scanning is associated with fewer symptoms and dysphoric mood states. (N Engl J Med 1997;337:888-96.)

THYROID carcinoma is diagnosed in 14,000 people each year in the United States.[1] Most are effectively treated by surgery, followed often by radioiodine therapy and always by thyroid hormone therapy to suppress the secretion of thyrotropin. These patients require monitoring for recurrence of tumor, which can occur decades later.[2,3] In some patients, monitoring includes periodic discontinuation of thyroid hormone therapy for radioiodine scanning[4,5] and measurement of serum thyroglobulin[6,7] to detect residual or recurrent thyroid carcinoma. As a consequence of discontinuing thyroid hormone therapy, patients typically have symptomatic hypothyroidism, some may not have a sufficient increase in thyrotropin secretion for optimal imaging,[8] and a few patients have accelerated tumor growth.[9-11]

A solution to these problems is the administration of thyrotropin to stimulate remaining thyroid tissue.[12,13] Recombinant human thyrotropin has the properties and actions of native thyrotropin.[14-17] In a preliminary study, thyrotropin stimulated the uptake of radioiodine by residual thyroid and thyroid-cancer tissue in patients who had previously been oper-

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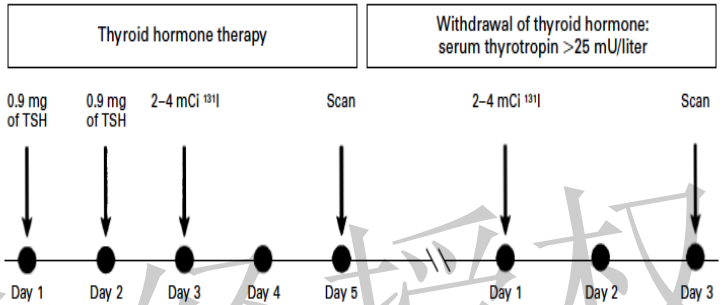


Figure 1. The Study Design.
TSH denotes intramuscular recombinant human thyrotropin.

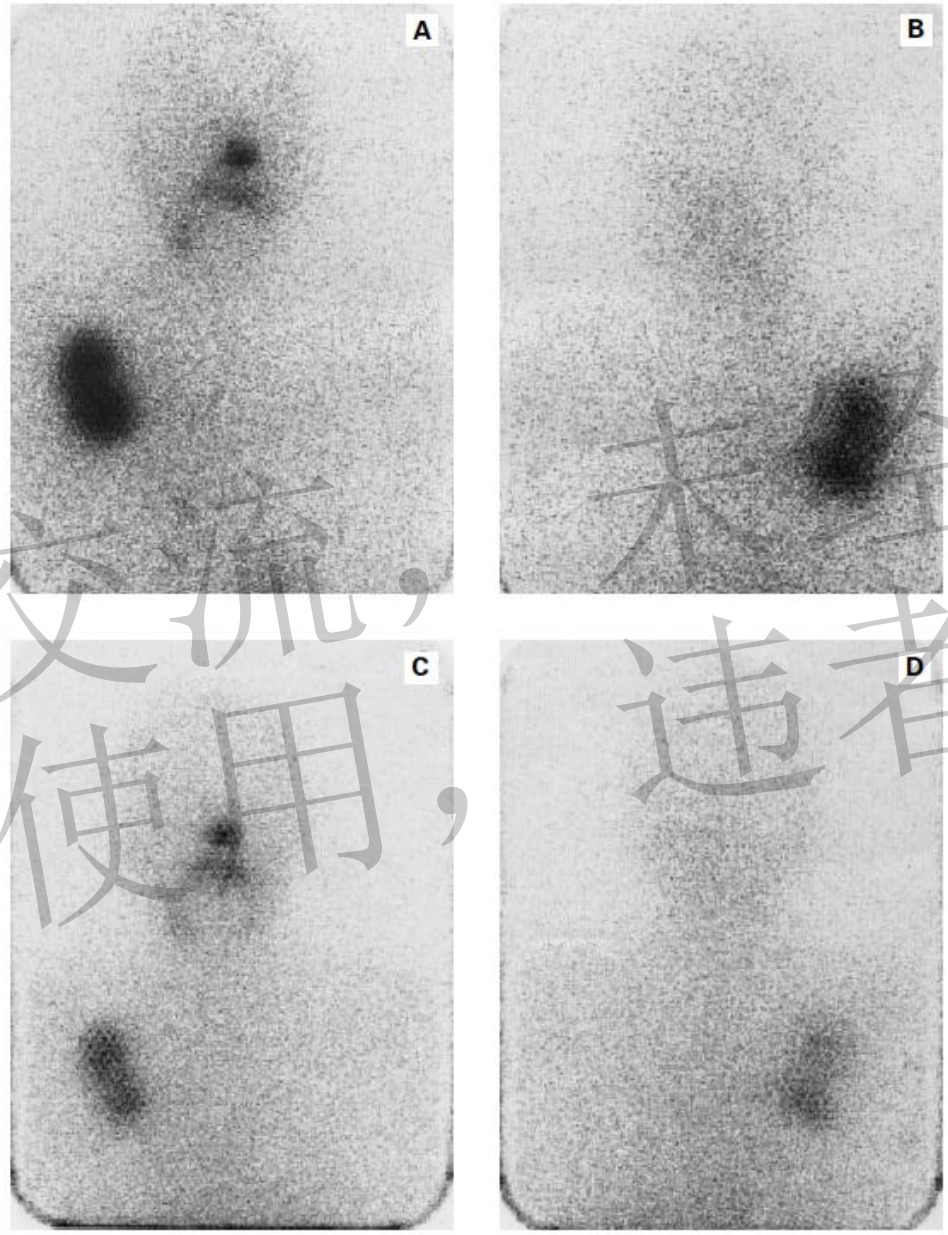
Stunning versus Iodine turnover

TABLE 2. CORRELATION OF POSITIVE AND NEGATIVE RADIOIODINE SCAN FINDINGS AFTER ADMINISTRATION OF THYROTROPIN AND AFTER WITHDRAWAL OF THYROID HORMONE IN 127 PATIENTS WITH THYROID CARCINOMA.*

POST-THYROTROPIN SCAN	POST-WITHDRAWAL SCAN	
	POSITIVE	NEGATIVE
Positive	41	3
Negative	18	65

*$P=0.001$ for the comparison of scanned findings with the two techniques.

Withdrawal scan was somewhat more sensitive but probably due to variability among centers



rhTSH

Withdrawal

Anterior

Posterior

Summary

1. Management of patients with differentiated thyroid cancer remains complicated by the lack of any large randomized trials showing real treatment benefits. This is even more of a problem in the pediatric population

2. Retrospective studies by Mazzeferri et al. (USAF and Ohio State) define treatment paradigms currently accepted by most clinicians.

3. Retrospective studies by Hay et al. (Mayo Clinic) define papillary microcarcinoma as a diagnosis that should probably receive less intensive management, although most patients receive total thyroidectomies at Mayo Clinic.

1. The ATA has developed guidelines for thyroid cancer based on best practice and heavily relying on US findings from pooled data. Not very helpful in areas that remain controversial: what to do with low and intermediate risk patients?

2. Recombinant hTSH has a role in remnant ablation and perhaps treating cervical nodes. Whether it is equivalent to thyroid hormone withdrawal needs further study.

3. Adequate surveillance is not possible in limited operations. So a limited operation mean limited surveillance.