

**Strategies for Detecting and Managing
Residual/Recurrent Thyroid Cancer**

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STRATEGIES FOR DETECTING AND MANAGING RESIDUAL/RECURRENT PAPILLARY-FOLLICULAR THYROID CARCINOMA

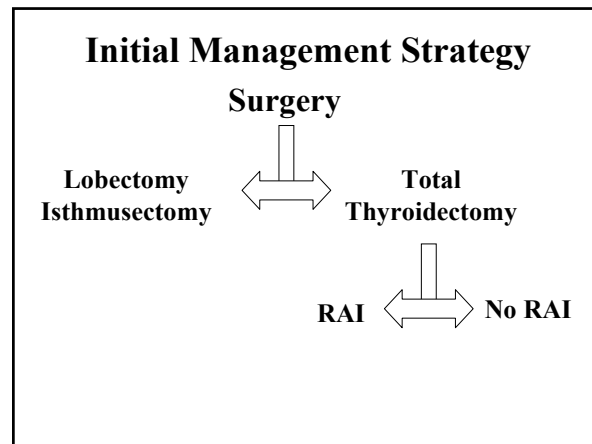
Meet the Professor with:

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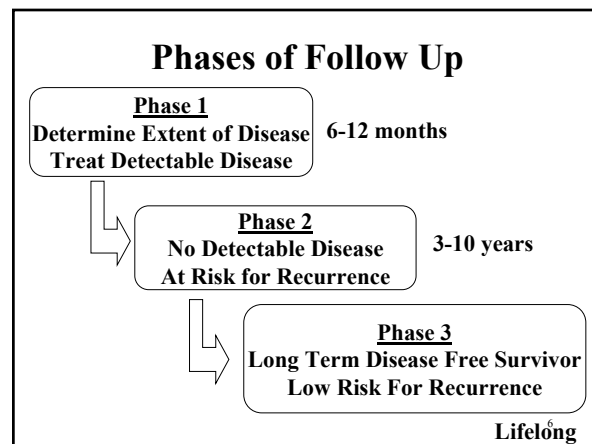
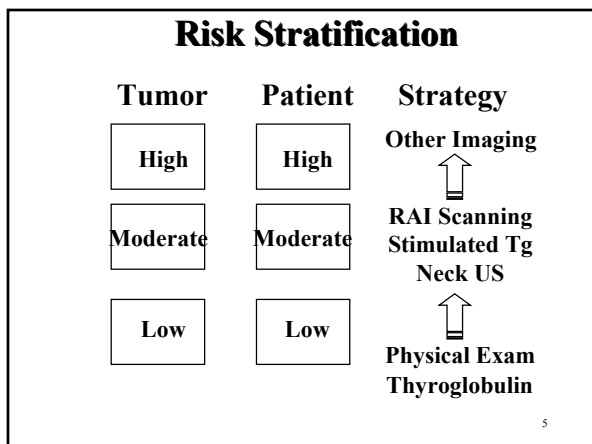
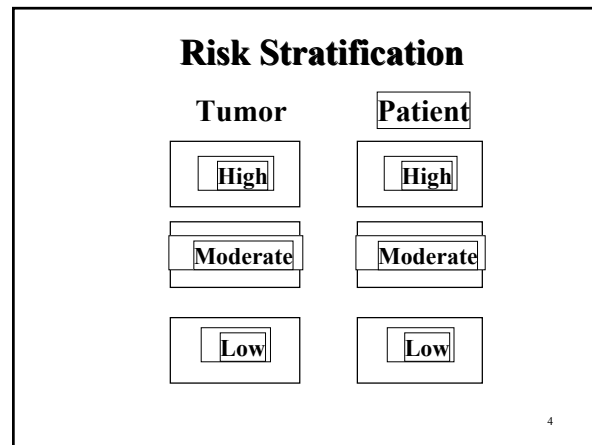
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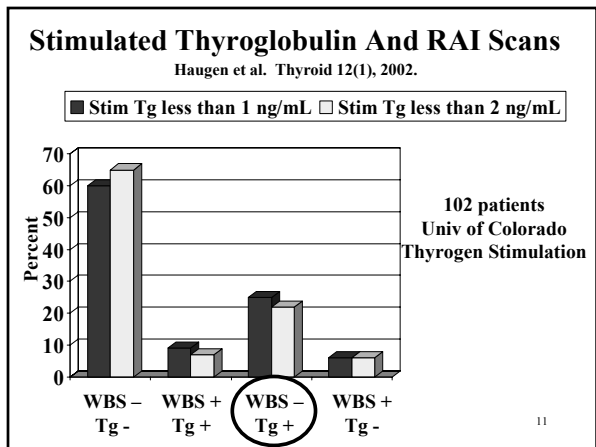
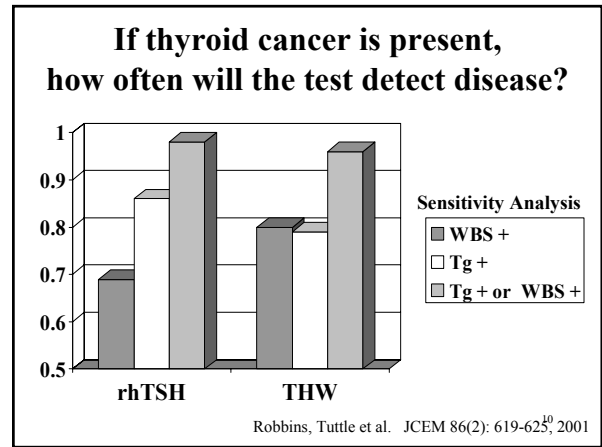
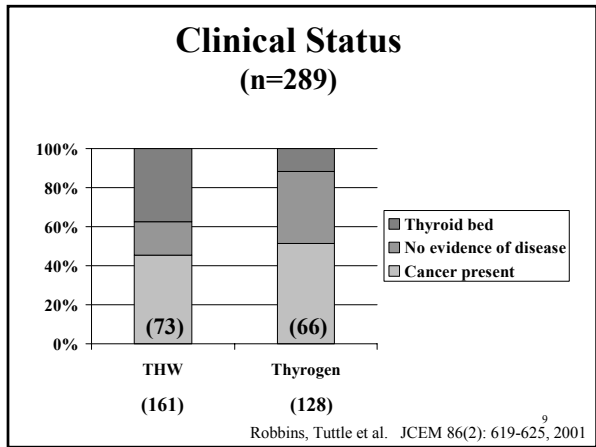
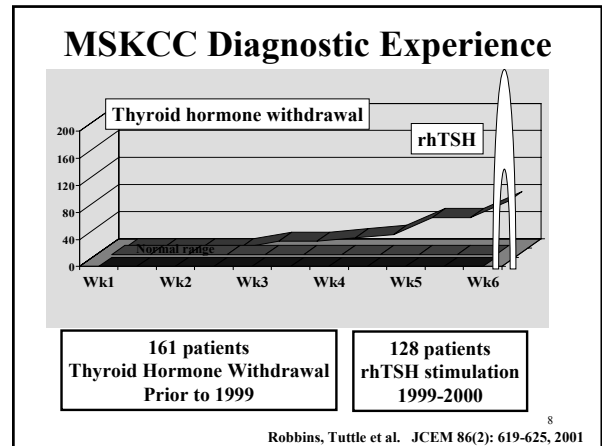
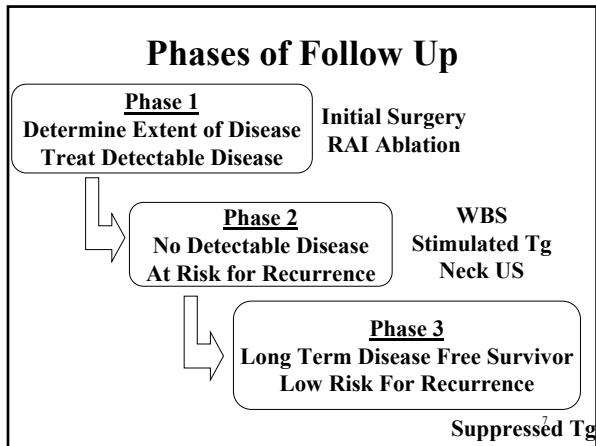


Detection of Metastatic Disease *Papillary Thyroid Cancer*

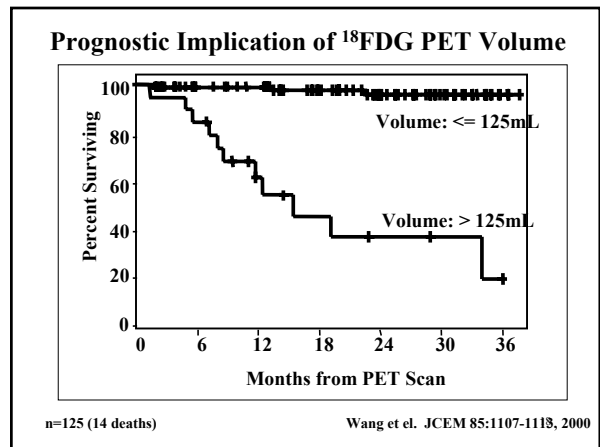
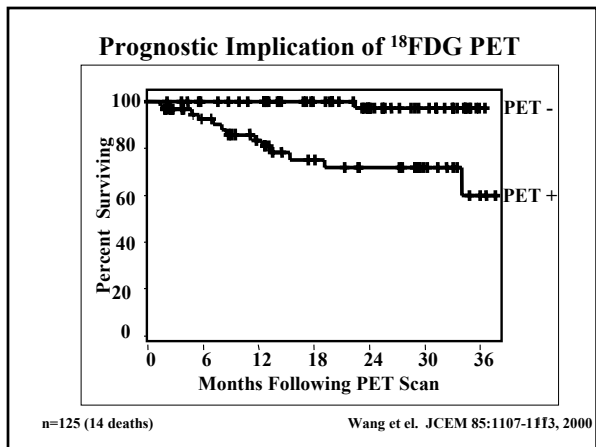
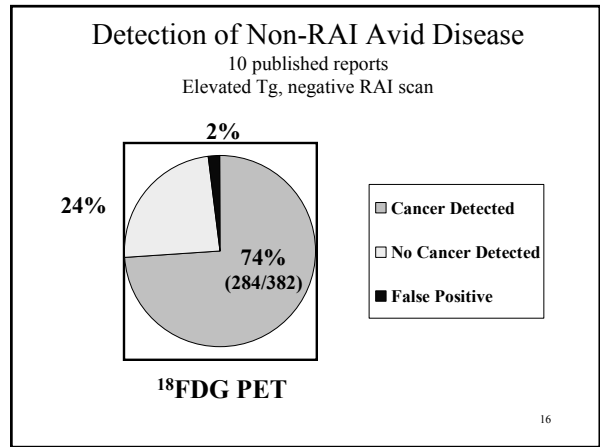
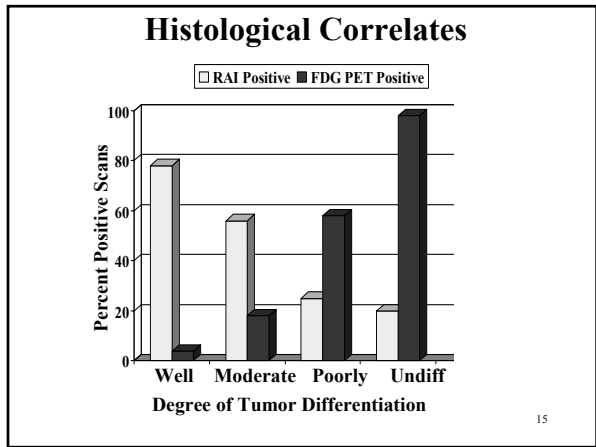
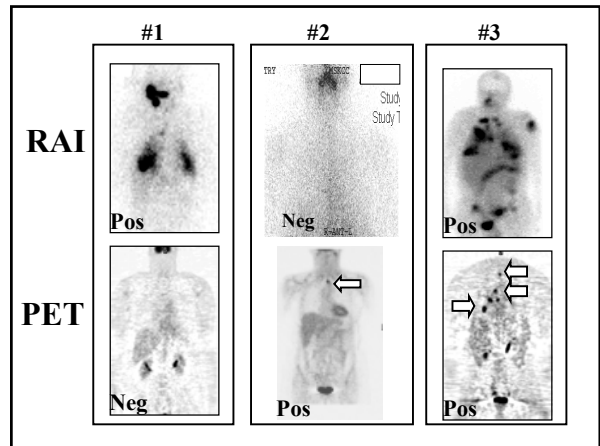
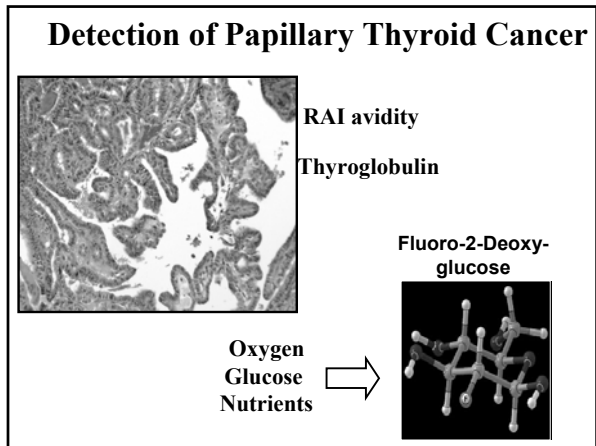
- RAI avid
- Thyroglobulin
 - Suppressed
 - TSH stimulated
 - Glucose utilization

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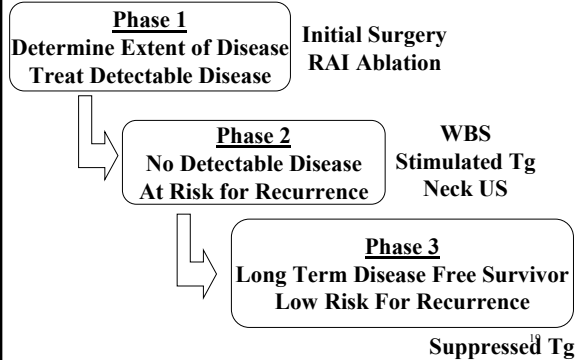




- ### Detection of Recurrent Disease
- High Risk patients*
- Structural Imaging
 - Neck US
 - MRI/CT
 - Chest CT
 - Functional Imaging
 - Other nuclear medicine studies
 - FDG PET
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Detection of Recurrent Disease



Goals of Phase III:

Long Term Follow-Up to Detect and Treat Recurrent/Residual Thyroid Carcinoma

An estimated 10-20% of patients have residual/recurrent disease on F/U over 10-20 years, with the highest risk of recurrence in the first 10 years

- 1) How do you screen patients after previous standard Phase I and II treatment?
- 2) What are the best strategies for detecting and managing residual/recurrent follicular/papillary thyroid carcinoma?

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Phase III: Common Methods for Long Term Monitoring of Thyroid Cancer

Whole Body Scan (WBS)
AND/OR
Serum Thyroglobulin (Tg)

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Accuracy of Whole Body Scanning (WBS)

- False negative findings for WBS 31.8%
(Girelli, et al, 1986)
- 69% sensitivity WBS vs 86% sensitivity Tg
(Robbins, et al, 2001)
- Only 65% of scans received a concordant diagnosis of disease.
(Haugen, et al, 2000)

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Factors Limiting Routine Application of Diagnostic WBS Monitoring

Environmental:

- Iodine contamination by diet, drugs or contrast media

Sensitivity:

- ✦ Inadequate TSH elevation
- ✦ Metastases too small to be seen
- ✦ Loss of iodine uptake by thyroid cancer cells

Logistics:

- ∞ Cost
- ∞ Return visits
- ∞ Dosimetry (1, 2, 5, 10 mCi)

Tumor Stunning:

(> 2 mCi)

Morbidity

- Loss of employment time

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Monitoring Using Serum Thyroglobulin

- Glycoprotein, produced only by normal and neoplastic thyroid cells, MW 660 kd, $t_{1/2} = 29.6 \pm 2.8$ hrs, shorter post-TT. (secretion rate - 100 mg/60 kg/day)
- First reported by Van Herle in 1973.
- Serum Tg an excellent prognostic indicator *after completion/near-total thyroidectomy, nodal clearance and effective RAI ablation therapy.*

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Monitoring Using Serum Thyroglobulin (con't)

Relation of TSH to Tg

- An increase in TSH causes a concomitant increase in serum Tg
- TSH stimulation of Tg depends on quantity and quality of the tumor and the metabolic clearance of serum Tg (i.e. hypothyroidism)
- Levels of TSH and Tg can be obscured by remnants of functioning tissue

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Serum Tg Measurement on THST vs Withdrawal

- Decreased sensitivity on T4 therapy
 - 20% lymph node mets missed
 - 5% distant mets have an undetectable Tg (Schlumberger, 1998)
 - There is an increasing recognition that measuring serum Tg after T4 withdrawal is more sensitive.
 - (Fatourech, et al, 2000, Ladenson, 2000, Girelli, et al, 1986, Pacini, et al, 1985)
 - Limitation: - Tg antibody interference
 - Tumor dedifferentiation
- 99% of patients with undetectable Tg levels after withdrawal remain disease free after 20 years.
- (Pineda, et al, 1995; supported by Schlumberger, 1999, and Callieux, et al, 2000)⁶

Phase III: Serum Tg vs. WBS

Superiority of stimulated serum Tg over WBS has very recently become widely accepted*:

Fatourech, et al, 2000
Haugen, et al, 2002 & 1999
Mazzaferri, 1995, 2002
Ozata, et al, 1994
Pacini, et al, 2001, 2002
Pineda, et al, 1995
Spencer, et al, 1998
Wartofsky, 2002

* Provided there is no TgAb interference which gives a false high or low serum Tg value *

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Platinum Standard: Serum Tg

Provided that:

- no Tg antibody interference and sensitive Tg/TgAb assay
- previous total or near-total thyroidectomy with at least one dose of radioactive iodine ablation Rx

Detectable Tg on THST
⇒ **High Risk**

→ Imaging to localize residual/recurrent disease

Undetectable Tg on THST
⇒ **Low Risk**

→ Exclude residual/recurrent disease by stimulation of Tg without Dx WBS

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Phase III:

5 Common Methods for TSH Stimulation

Option 1: T4 is stopped abruptly for 6 weeks

- **Severe hypothyroid symptoms**
- **TSH increase is highest**
- **same as used for Dx WBS and Rx RAI**
- **easiest method for practitioners to prescribe**

Option 2: T4 Δ T3 for 4 weeks and then stopped for 2 weeks

- **hypothyroid state induced by 2 wks off of T3 is comparable to 4-6 wks off T4, because of the shorter half-life of T3 in the body**
- **used in many centers**

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Phase III:

5 Common Methods for TSH Stimulation

Option 3: T4 is ↓ by 50% for 2 weeks and then stopped completely for 4 weeks
(Guimaraes & DeGroot, 1996)

- **essentially a 4 wk withdrawal after nearly euthyroid levels for 2 wks**
- **not commonly done**

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Option 4: Recombinant Human TSH (rhTSH) for WBS and Tg Monitoring

- + High TSH levels: 116 ± 38 mIU/L
- + No hypothyroid symptoms

Not FDA approved for Rx

- Logistics & Time commitment
(5 day protocol = Day 1, 2: injection of rhTSH & blood test as needed, Day 3: Tracer for scan & blood test at peak, Day 5: Scan and blood test)
- High cost: \$1118 USD (Genzyme®, Thyrogen™)
- Tg levels on Thyrogen are generally lower than Tg levels on withdrawal (Genzyme, 2001)
- Debatable efficacy due to continued hyperthyroid metabolism may cause a continued rapid Tg clearance

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Option 4: Recombinant Human TSH (rhTSH) for WBS and Tg Monitoring

“... conventional thyroid hormone withdrawal is still preferable for detection of residual tissue and cancer in most patients”

(Haugen, et al, 1999)

Protocol for rhTSH Administration:

With Dx WBS:

- Day 1: blood test and first injection
- Day 2: second injection
- Day 3: tracer dose for WBS and blood test (peak TSH)
- Day 5: blood test and WBS

Without Dx WBS:

- Day 1: blood test and first injection
- Day 2: second injection
- Day 3: blood test (peak TSH)
- Day 5: blood test (compare to Day 3)

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Option 5: 3 Week Withdrawal from T4 for TSH Stimulation

NEW!

Inclusion Criteria:

- Tg Undetectable on THST
- Negative Tg Antibody Interference

Advantages:

- Fewer hypothyroid symptoms and less prolonged duration of hypothyroid state
- More financially accessible to many patients
- Simpler administration than rhTSH--involves only 2 visits over a 3-week period for blood work and tapering dose reinstatement

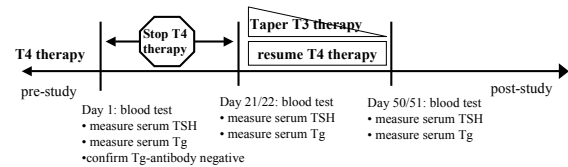
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Golger A, Fridman TR, Eski SJ, et al. J Endocrin Invest 2003, In Press

Phase III: Methods for TSH Stimulation Option 5: 3 Week Withdrawal from T4 for TSH Stimulation

NEW!

Protocol:



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Phase III: 3 Week T4 Withdrawal TSH Stimulation

Possible Serum Tg/TSH Outcomes to 3 Week T4 Withdrawal:

1. TSH ≥ 20 , Tg undetectable → considered disease free, resume THST **75%** of patients
2. Tg detectable (≥ 2 ug/L) → select for further investigation and treatment as per algorithm **10%** of patients
3. TSH < 20 , Tg undetectable → consider for rhTSH stimulation to exclude residual/recurrent disease **15%** of patients

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Golger A, Fridman TR, Eski SJ, et al. J Endocrin Invest 2003, In Press

Results for Patients with POSITIVE (10%) 3 Week Withdrawal from T4 for TSH Stimulation

Tg +, TSH < 20 mIU/L Case Presented

Pt #	Sex	Age	Class	Pathology	TSH after	TG after	CONFIRMED BY
Tg = 2, Positive Detectable Tg							
1	F	38	2	Papillary	42	2	Positive CT Chest
2	F	55	3	Papillary	61	16	Positive Neck US
3	F	33	2	Mixed	12	21	Not Available
4	F	39	1	Mixed	24	10	Positive WBS
5	F	60	1	Papillary	43	3	Positive CT Chest
6	F	16	4	Papillary	47	4	Positive WBS
7	F	55	3	Papillary	56	35	Positive Histology
8	F	29	1	Papillary	54	2	Positive Neck US
9	F	24	2	Papillary	44	2	Not Available
10	F	56	2	Papillary	48	2	Not Available
11	M	51	2	Papillary	25	26	Positive Histology
12	M	34	2	Papillary	28	2	Positive Histology
13	F	43	2	Papillary	3	3	Positive Histology
14	F	25	2	Papillary	58	3	Positive Neck US
15	F	25	2	Papillary	110	18	Positive CT Neck

Golger A, Fridman TR, Eski SJ, et al. J Endocrin Invest 2003, In Press

3 Week Withdrawal from T4 for TSH Stimulation

Conclusions:
 86% (12/14) of TSH-stimulated, Tg-positive patients had residual/recurrent disease confirmed.

Of the patients with inadequate (<25 mIU/L) TSH stimulation, 21% (4/19) still had positive Tg
 → suggesting that a TSH 15-20 mIU/L may be adequate to stimulate residual disease in low-risk cases.
 → most studies use an arbitrary 25-30 mIU/L for pre-WBS stimulation of TSH

Compared to highest Tg stimulated with rhTSH at 17.9 ug/L, our range of Tg + was 3-35 ug/L. (Mazzaferri, 2002)
 Golger A, Fridman TR, Eski SJ, et al. J Endocrin Invest 2003, In Press

Risk of Positive Tg Stimulation versus Stage at Presentation:

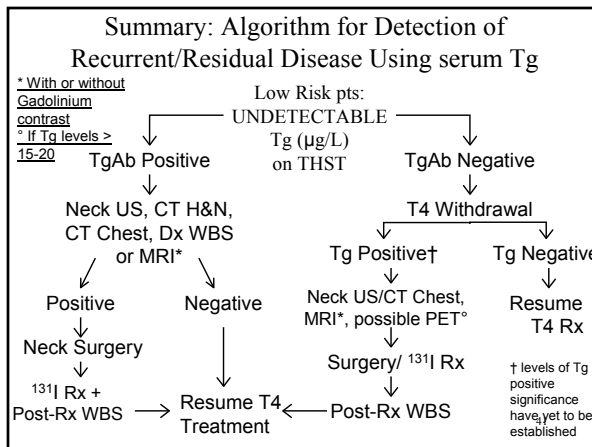
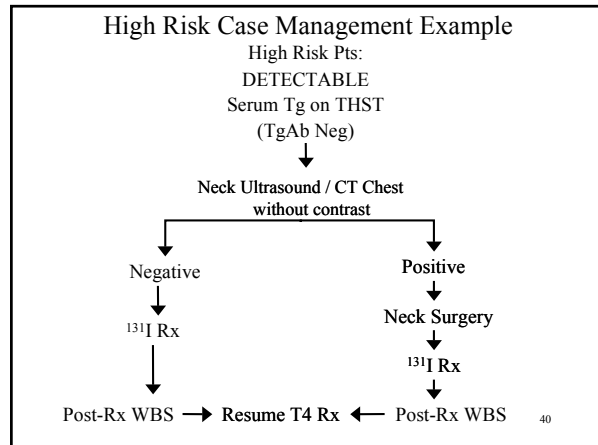
3% of Stage I patients tested positive for residual/recurrent disease
 19% of Stage II-IV patients tested positive for residual/recurrent disease

E.g. the risk of Stage II-IV patients having positive stimulated Tg is 6x the risk of Stage I patients

To date, no false negatives or false positives have been found using the standard long term follow-up methods
 Golger A, Fridman TR, Eski SJ, et al. J Endocrin Invest 2003, In Press

Phase III, Long Term F/U:
6-12 Month Standard of Management
 Follow-Up on T4 Treatment
 (Thyroid Hormone Suppression Therapy-THST)

Clinical: Neck Palpation
Blood Tests: TSH, FT4, Tg, TgAb
Imaging (Non-Isotopic): Neck Ultrasound, CT Chest/Neck without contrast (when indicated)
Dx WBS (Isotopic): Some centers do WBS with THST withdrawal at varying intervals



Management of TgAb Positive Patients:

Blood Work Follow-up:

- Follow levels of TgAb following treatment (↑ TgAb indicates possible increase in tissue volume and possible residual/recurrent disease)
- Possible RT-PCR methods yet to be determined

Imaging for TgAb Positive patients:

- US with Bx of nodes
- CT head & neck and chest
- Dx WBS
- MRI with Gd (?)
- PET Scan if suspect disease (?)

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Suggested Relevant References/Reading List

(† R. M. Tuttle, ‡ R. M. Tuttle and P. G. Walfish)

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