BC Cancer Agency
CARE + RESEARCH
An agency of the Provincial Health Services Authority

Tinkering with TSH – Thyroid Cancer Follow-up for the Primary Care Physician

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Family Practice Oncology CME Day

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Genzyme/Sanofi – Unrestricted Research Grant

Eisai – Advisory Board (lenvatinib), Unrestricted Research Grant

Research Grant:

Population based outcomes analyses

Provincial thyroid cancer database

Objectives

By the end of this session, participants will be able to describe, for well differentiated thyroid carcinomas:

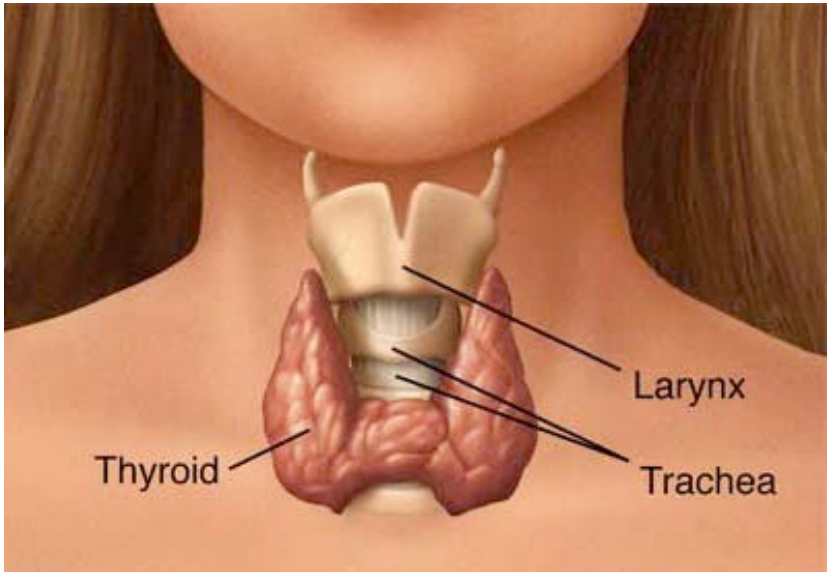
1. **the excellent prognosis for most patients;**
2. **the general management of thyroid cancers; and**
3. **management of thyroxine for thyroid cancer patients.**

Outline

- Scope of the Problem
- Management
- Risk Assessment
- Thyroxine and TSH
- Surveillance

Scope of the Problem

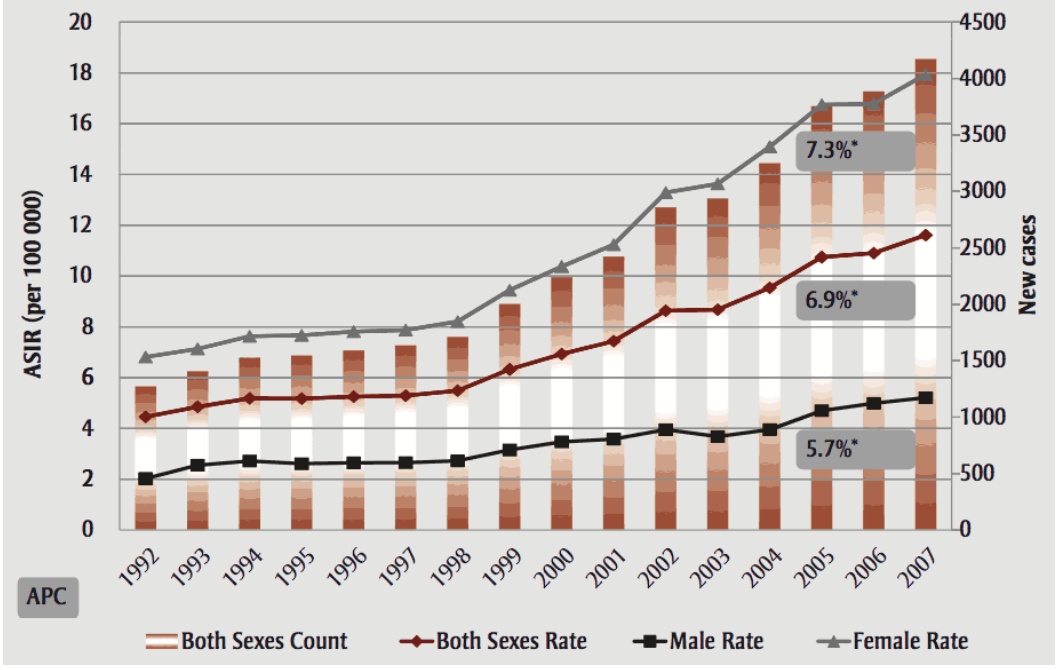
- Relatively uncommon (1%)
  - 50,000 cases in US
  - 230,000 breast
  - 230,000 lung
- 75% are Females
- Incidence tripled:
  - 1975: 4.9 / 100,000
  - 2009: 14.3 / 100,000
- Increasing 10% per year
- More “micro-carcinomas” (< 1.0 cm)
  - 1988: 25%
  - 2008: 39%

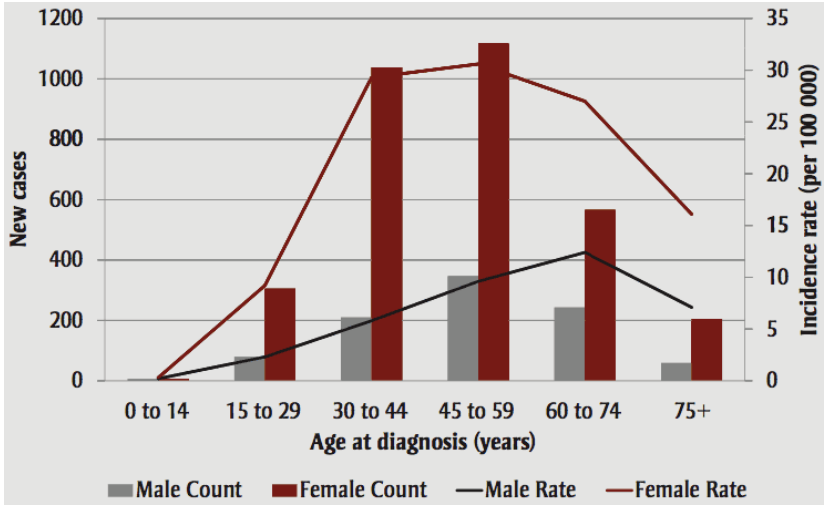


Siegel R, Ma J, Zou Z, Jemal A 2014 Cancer statistics, 2014. CA Cancer J Clin **64:**9–29.
Davies L, Welch HG 2014 Current thyroid cancer trends in the United States. JAMA Otolaryngol Head Neck Surg **140:**317–322.

Scope of the Problem

- **Canada:**
  - **Incidence: Approximately 6,300 in 2015**
  - **Deaths: 185 deaths in 2010**
- **BC (2007):**
  - **New cases: 68 men, 211 women**
  - **Deaths: 5 men and 9 women**
  - **Most deaths in patients over 60 yrs**

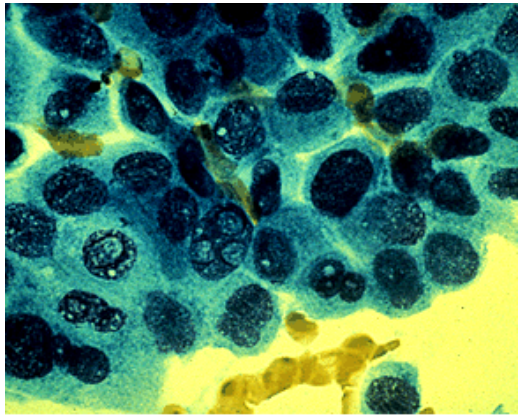


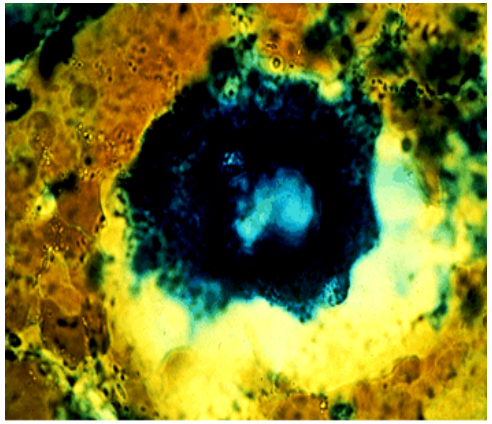


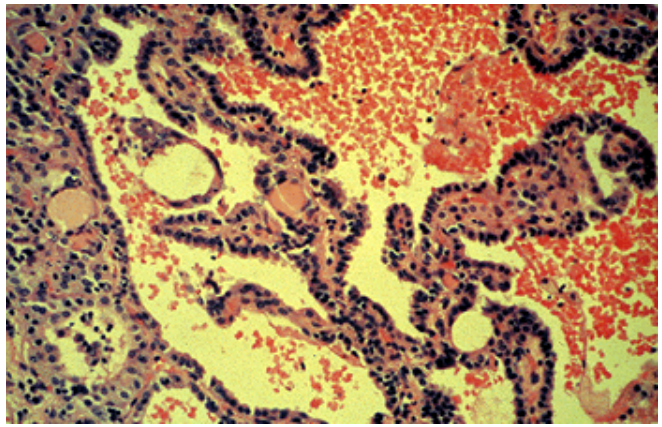
Statistics Canada. Cancer incidence in Canada, 2007 and 2008 [Internet]. Ottawa (ON): Minister of Industry; 2010 [cited 2013 May 21]. [Statistics Canada, Catalogue no.: 82- 231-X].

Thyroid Cancer: Types

- **> 90% Well differentiated tumours**
  - **arising from follicular epithelial cells**
  - **80% papillary +/- follicular elements**
  - **10% pure follicular (incl Hurthle cell)**
- **~5% Medullary**
- **< 3% Anaplastic**





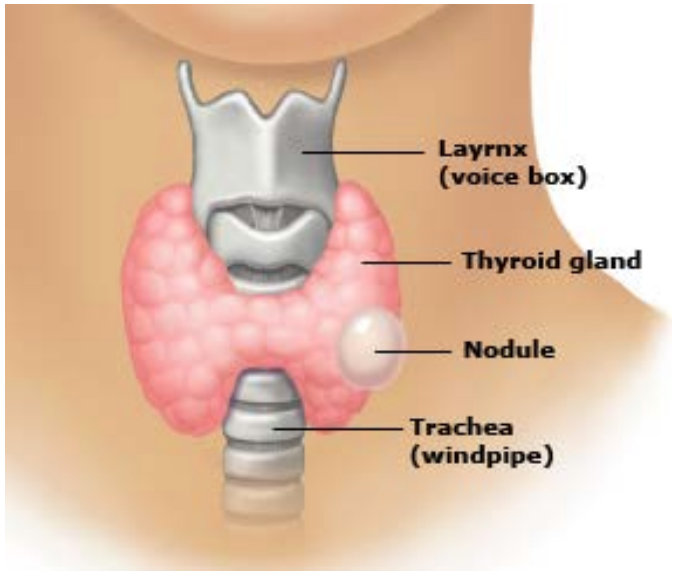


Thyroid Cancer: Survival

5 Year Survival:

Papillary ca	98%
Follicular ca	94%
Medullary ca	80%
Anaplastic ca	< 5%

Relative rarity and high survival mean that there are very few prospective randomised trials so most management is based on retrospective data



Sherman SI 2003 Thyroid carcinoma. Lancet **361**:501–511.

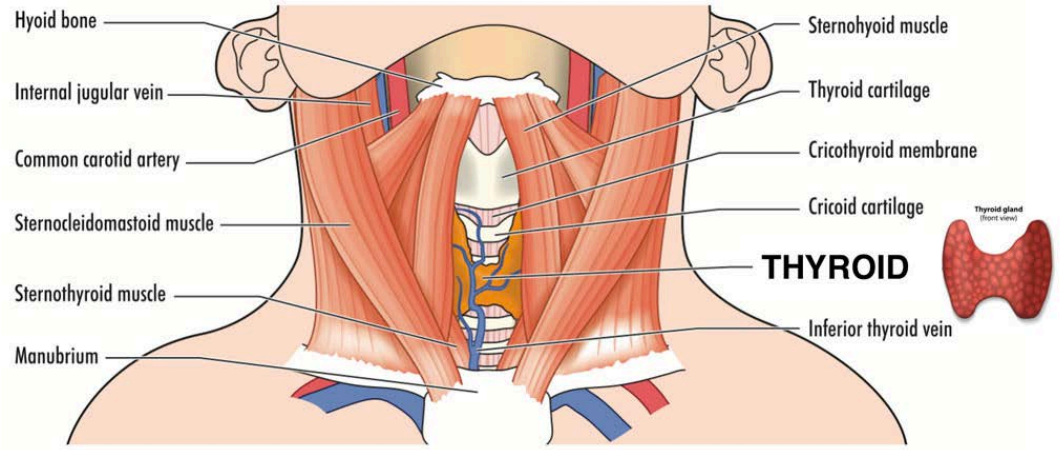
Management

Surgery – Primary Treatment

Adjuvant Radiation

- Radioiodine (131-Iodine)
- External Beam Radiation

Thyroxine



**** *No Prospective Randomized Trials* ****

RECOMMENDATION 12
If a cytology result is diagnostic for primary thyroid malignancy, surgery is generally recommended.
(Strong recommendation, Moderate-quality evidence)

Cooper et al, Thyroid. 2006 Feb;16(2):109-42.

Risk Assessment

- Risk of Recurrence
  - ATA Risk Stratification
- Risk of Death
  - TNM, AJCC
  - AMES, AGES
  - MACIS

Risk of Recurrence

ATA Risk Stratification

TABLE 11. ATA 2009 RISK STRATIFICATION SYSTEM WITH PROPOSED MODIFICATIONS

ATA low risk	Papillary thyroid cancer (with all of the following): • No local or distant metastases; • All macroscopic tumor has been resected • No tumor invasion of loco-regional tissues or structures • The tumor does not have aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) • If ^{131}I is given, there are no RAI-avid metastatic foci outside the thyroid bed on the first posttreatment whole-body RAI scan • No vascular invasion • Clinical N0 or ≤5 pathologic N1 micrometastases (<0.2 cm in largest dimension)[a] Intrathyroidal, encapsulated follicular variant of papillary thyroid cancer[a] Intrathyroidal, well differentiated follicular thyroid cancer with capsular invasion and no or minimal (<4 foci) vascular invasion[a] Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including *BRAF*^{V600E} mutated (if known)[a]
ATA intermediate risk	Microscopic invasion of tumor into the perithyroidal soft tissues RAI-avid metastatic foci in the neck on the first posttreatment whole-body RAI scan Aggressive histology (e.g., tall cell, hobnail variant, columnar cell carcinoma) Papillary thyroid cancer with vascular invasion Clinical N1 or >5 pathologic N1 with all involved lymph nodes <3 cm in largest dimension[a] Multifocal papillary microcarcinoma with ETE and *BRAF*^{V600E} mutated (if known)[a]
ATA high risk	Macroscopic invasion of tumor into the perithyroidal soft tissues (gross ETE) Incomplete tumor resection Distant metastases Postoperative serum thyroglobulin suggestive of distant metastases Pathologic N1 with any metastatic lymph node ≥3 cm in largest dimension[a] Follicular thyroid cancer with extensive vascular invasion (> 4 foci of vascular invasion)[a]

Thyroid. 2016 Jan;26(1):1-133. doi: 10.1089/thy.2015.0020.

Risk of Death

What we use at BCCA:

- MACIS Score:

  3.1 (<40yo) or 0.08 x age (if 40 or more years old)

  0.3 x tumor size (in cm)

  +1 if incompletely resected

  +1 if locally invasive

  +3 if distant metastases

No Lymph Nodes !

Multi-focal ?

- MACIS – 20yr Disease Specific Mortality

  <6.0 = 1%

  6.0 – 6.99 = 11%

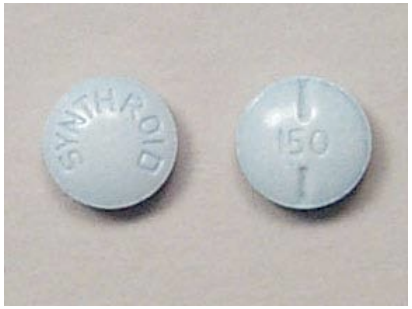
  7.0 – 7.99 = 44%

  >8 = 76%

Hay et al, Surgery 1993 Dec;114(6):1050-7; discussion 1057-8.

Thyroxine and TSH

(almost) EVERYONE needs Thyroxine
After Thyroid Surgery



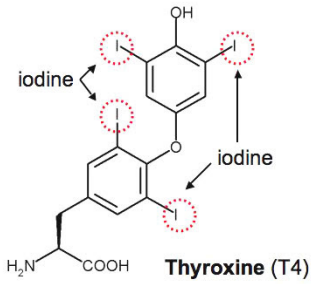
Replacement vs Suppressive Therapy

1. Replacement Therapy
2. Suppressive Therapy

Thyroxine and TSH

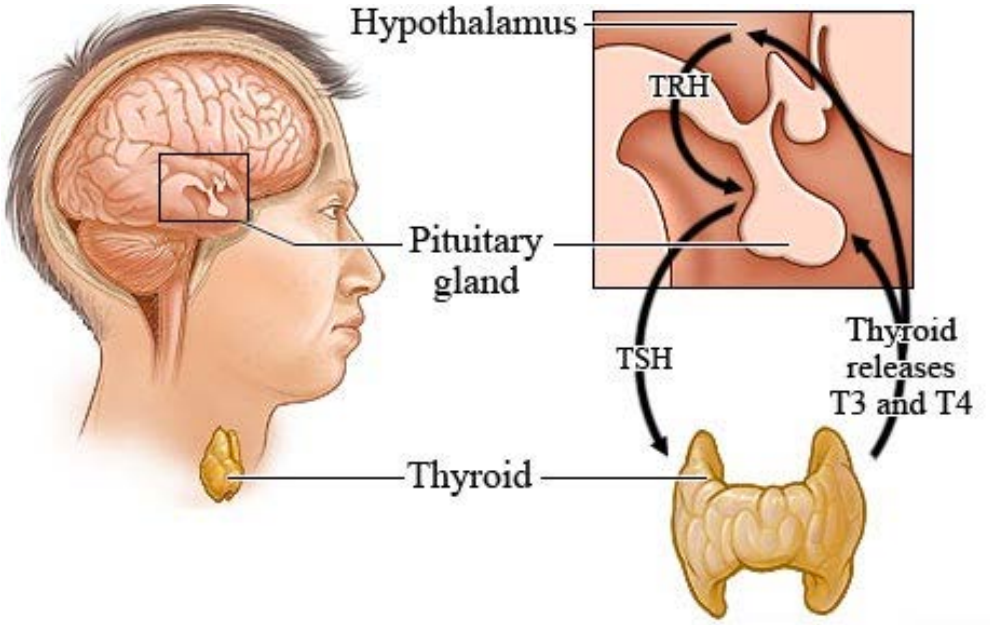
Replacement vs Suppression

1. Replacement Therapy → **Normal** TSH
2. Suppressive Therapy → **Low** TSH



How:

- Replacement: 50-125 mcg
- Suppressive: 125-250 mcg
- 4 - 6 weeks to equilibrate
- Measure FT4 ***and*** TSH
  - FT4: Upper limits of normal
  - TSH: <0.1 to 2.0 mU/L



Brabant G 2008 Thyrotropin suppressive therapy in thyroid carcinoma: what are the targets? J Clin Endocrinol Metab **93:**1167–1169.

Thyroxine and TSH

TSH Suppression: How low do you go?

- Low Risk: 0.5 to 2.0 mU/L
- Intermediate Risk: 0.1 to 0.5 mU/L
- High Risk: < 0.1 mU/L
- Evidence strongest for High Risk

Why not < 0.1 mU/L for everyone?

- Low TSH = High FT4
- Prolonged hyperthyroidism
  - atrial fibrillation
  - cardiac hypertrophy and dysfunction
  - accelerated osteoporosis
- Balance risk of recurrence vs hyperthyroidism
- No randomized trials

Pujol P, Daures JP, Nsakala N, Baldet L, Bringer J, Jaffiol C 1996 Degree of thyrotropin suppression as a prognostic determinant in differentiated thyroid cancer. J Clin Endocrinol Metab **81:**4318–4323.

Cooper DS, Specker B, Ho M, Sperling M, Ladenson PW, Ross DS, Ain KB, Bigos ST, Brierley JD, Haugen BR, Klein I, Robbins J, Sherman SI, Taylor T, Maxon HR III 1998 Thyrotropin suppression and disease progression in patients with differentiated thyroid cancer: results from the National Thyroid Cancer Treatment Cooperative Registry. Thyroid **8:**737–744.

Thyroxine and Cancer Patients

- Therapeutic dose: 125 – 250 mcg
- Free T4: Upper limits of normal (~20)
- TSH: ***VERY LOW*** ie. < 1.0 or undetectable
- Must do FT4 ***AND*** TSH
- 4-6 weeks to steady state
- Other Directions:

Everyday, same time, before breakfast
Empty stomach, only water
No food, drinks, or dairy for 60 minutes

Surveillance

- Clinical exam: q6-12 months
- Blood tests: q3-12 months
  1. Free T4
  2. TSH
  3. Thyroglobulin (Tg)
  4. Anti-Tg-Antibody
- Imaging
  - **US Neck**: Yes or No? How frequent?
  - Others: CXR, CT Neck, TSH stimulated PET/CT
- BCCA: 5-10 years… Then… (ie. low risk)

RECOMMENDATION 65

(A) Following surgery, cervical US to evaluate the thyroid bed and central and lateral cervical nodal compartments should be performed at 6–12 months and then periodically, depending on the patient's risk for recurrent disease and Tg status.

(D) Low-risk patients who have had remnant ablation, negative cervical US, and a low serum Tg on thyroid hormone therapy in a sensitive assay (<0.2 ng/mL) or after TSH stimulation (Tg <1 ng/mL) can be followed primarily with clinical examination and Tg measurements on thyroid hormone replacement.

(Weak recommendation, Low-quality evidence)

RECOMMENDATION 66

After the first posttreatment WBS performed following RAI remnant ablation or adjuvant therapy, low-risk and intermediate-risk patients (lower risk features) with an undetectable Tg on thyroid hormone with negative anti-Tg antibodies and a negative US (excellent response to therapy) do not require routine diagnostic WBS during follow-up.

(Strong recommendation, Moderate-quality evidence)

RECOMMENDATION 67

(A) Diagnostic WBS, either following thyroid hormone withdrawal or rhTSH, 6–12 months after adjuvant RAI therapy can be useful in the follow-up of patients with high or intermediate risk (higher risk features) of persistent disease (see risk stratification system, section [B19]) and should be done with ^{123}I or low activity ^{131}I.

(Strong recommendation, Low-quality evidence)

Recurrence

Gross disease:

- If resectable: Surgery
- Not resectable: 131-I +/- EBRT
- If non-iodine-avid: EBRT

Rising Tg – No gross disease?

- Empiric dose (100-200 mCi) 131-I
- TSH-stimulated PET scan

I-131-resistant disease:

- Chemotherapy: doxorubicin
- Tyrosine Kinase Inhibitors: vandetanib, sorafenib, lenvatinib
  - Sequelae: diarrhea, fatigue, HPT, hepatotoxicity, skin changes, nausea, dysgeusia, anorexia, thrombosis, heart failure,

Brose MS, Nutting CM, Jarzab B, Elisei R, Siena S, Bastholt L, de la Fouchardiere C, Pacini F, Paschke R, Shong YK, Sherman SI, Smit JW, Chung J, Kappeler C, Pena C, Molnar I, Schlumberger MJ 2014 Sorafenib in radioactive iodine-refractory, locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 3 trial. Lancet **384:**319–328.

Schlumberger M, Tahara M, Wirth LJ, Robinson B, Brose MS, Elisei R, Habra MA, Newbold K, Shah MH, Hoff AO, Gianoukakis AG, Kiyota N, Taylor MH, Kim SB, Krzyzanowska MK, Dutcus CE, de las Heras B, Zhu J, Sherman SI 2015 Lenvatinib versus placebo in radioiodine-refractory thyroid cancer. N Engl J Med **372:**621–630.

Leboulleux S, Bastholt L, Krause T, de la Fouchardiere C, Tennvall J, Awada A, Gomez JM, Bonichon F, Leenhardt L, Soufflet C, Licour M, Schlumberger MJ 2012 Vandetanib in locally advanced or metastatic differentiated thyroid cancer: a randomised, double-blind, phase 2 trial. Lancet Oncol **13:**897–905.

Summary
Well Differentiated Thyroid Cancer

- Relatively uncommon cancer
- Excellent prognosis
- Treatment: Surgery +/- Radioactive Iodine
- Life Long Thyroxine ** TSH Suppression **
- Blood Tests:
  1. FreeT4: upper limits of normal
  2. TSH: depends on risk, generally < 1.0
  3. Tg: excellent tumour marker
  4. Anti-Tg-antibodies: surrogate marker, interferes with Tg