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

Management of Well Differentiated Thyroid Cancer

November 18th, 2017
Family Practice Oncology CME Day

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Disclosure(s)

Genzyme/Sanofi – Advisory Board, Research Grant

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

Introduction, Epidemiology

Diagnosis, Surgical Management

Staging and Risk Assessment

Radioiodine Remnant Ablation and Therapy

Thyrotropin Suppression Therapy

Surveillance

Future Directions, Clinical Trials

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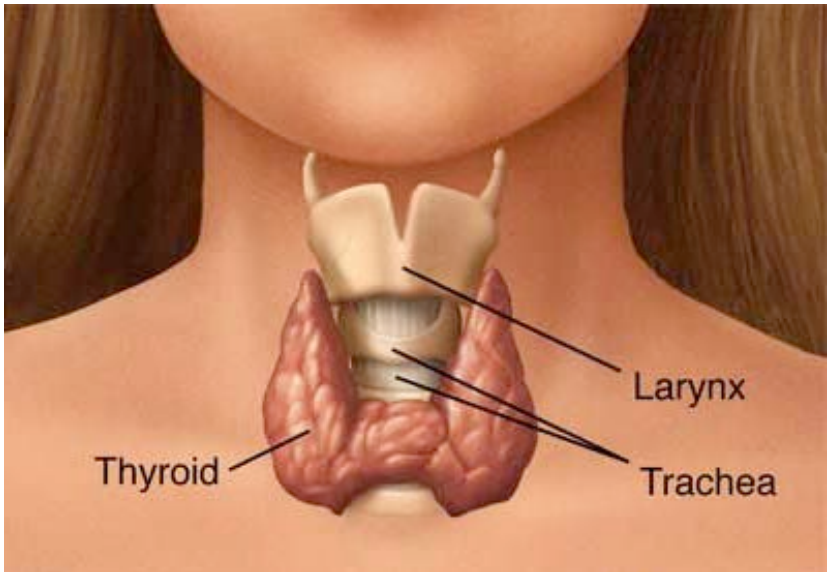
Scope of the Problem

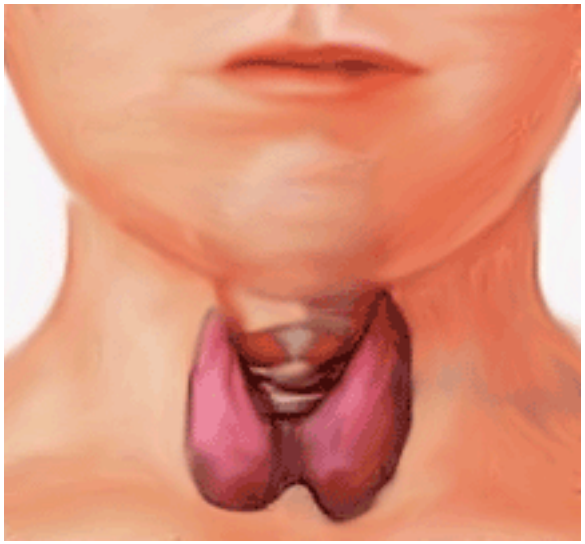
- Relatively uncommon (1%)
  - 50,000 cases in US
  - 230,000 breast
  - 230,000 lung
- 75% are Females
- Incidence tripled:
  - 1975: 4.9 / 100,000
  - 2009: 14.3 / 100,000
- Increasing 10% per year
- More “micro-carcinomas” (< 1.0 cm)
  - 1988: 25%
  - 2008: 39%



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.

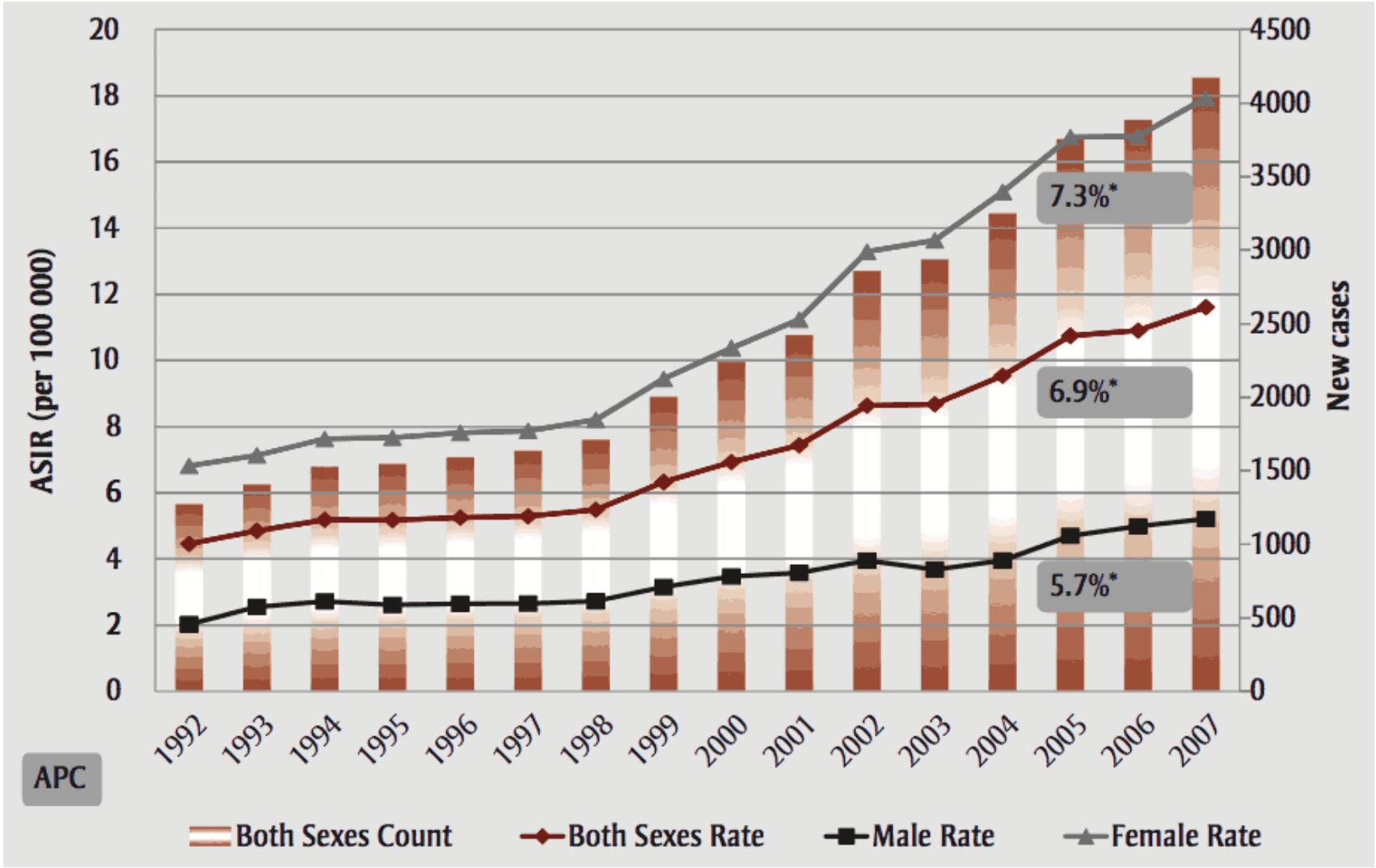
Scope of the Problem

- **Canada:**
  - **Incidence: Approximately 6,300 in 2015**
  - **Deaths: 185 deaths in 2010**



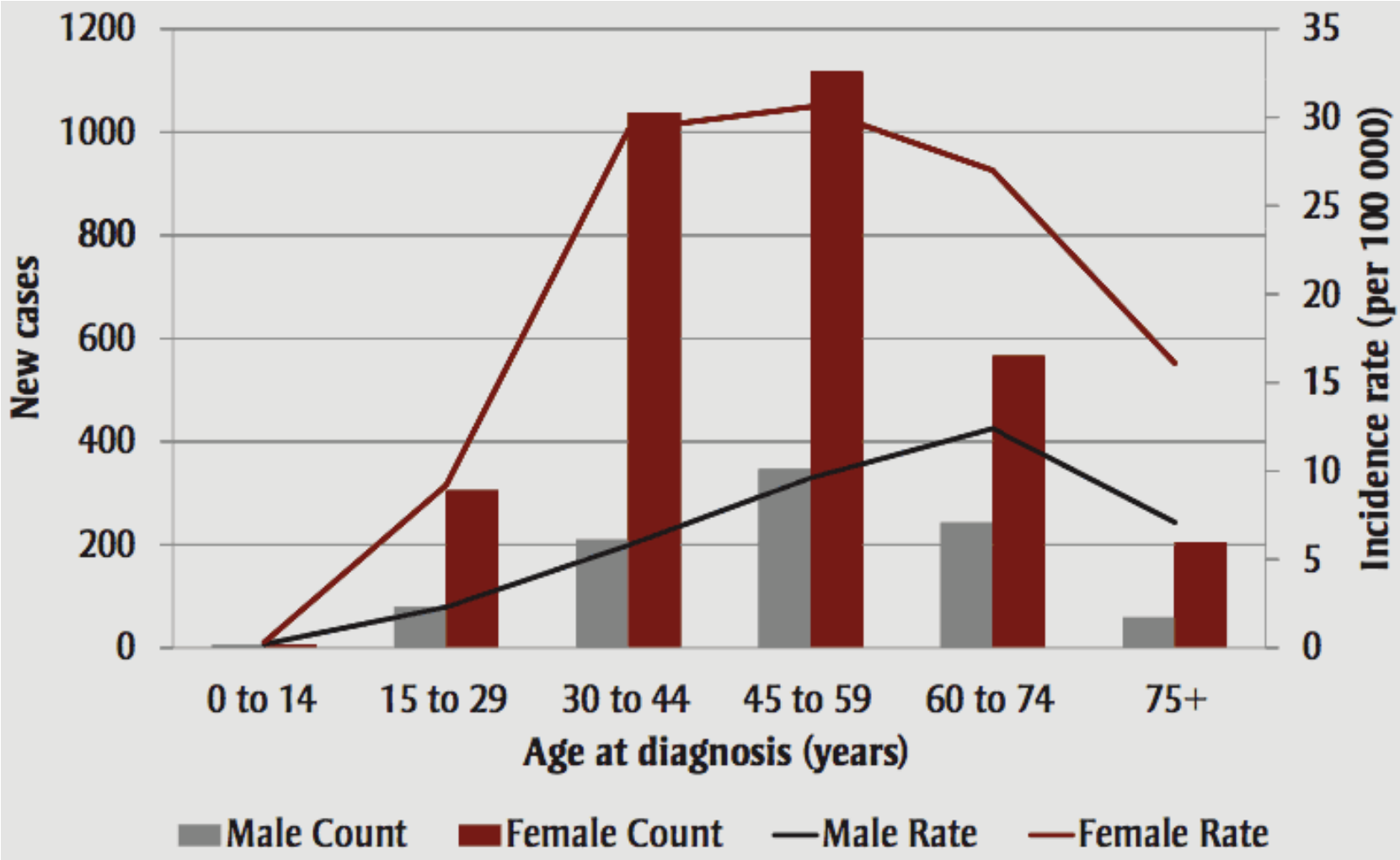
- **BC (2007):**
  - **New cases: 68 men, 211 women**
  - **Deaths: 5 men and 9 women**
  - **Most deaths in patients over 60 yrs**

Scope of the Problem



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].

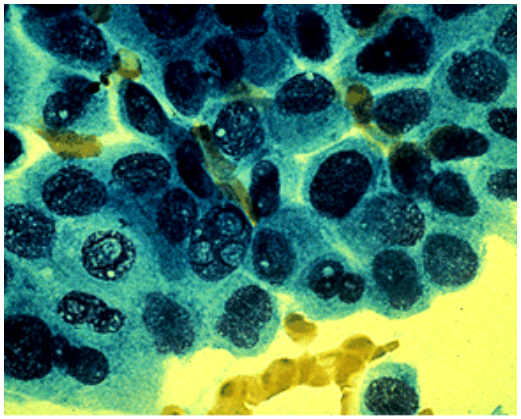
Scope of the Problem

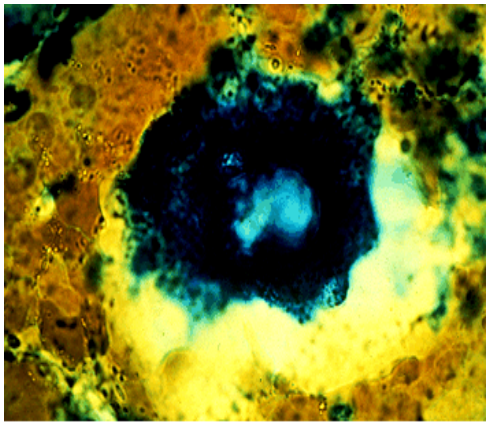


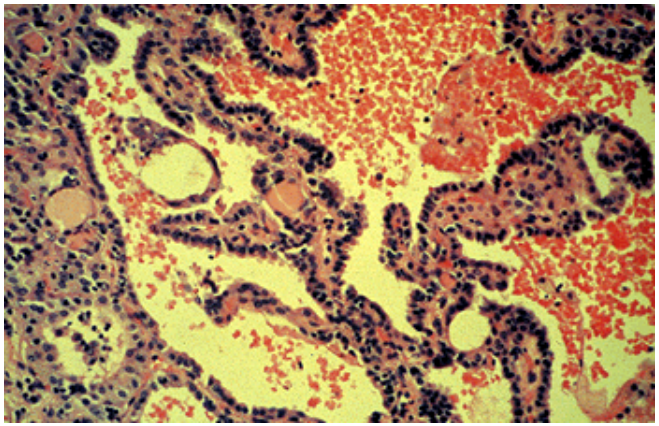
Statistics Canada. Cancer incidence in Canada, 2007 and 2008 [Internet]. Ottawa (ON): Minister of Industry; 2010 [cited 2013 May 21]. [Statistics Canada, Catalogue no.: 82- 231-X].

Thyroid Cancer: Types

- **90% Well differentiated tumours**
  - **arising from follicular epithelial cells**
  - **80% papillary +/- follicular elements**
  - **10% pure follicular (incl Hurthle cell)**
- **4% Medullary**
- **5% Anaplastic**





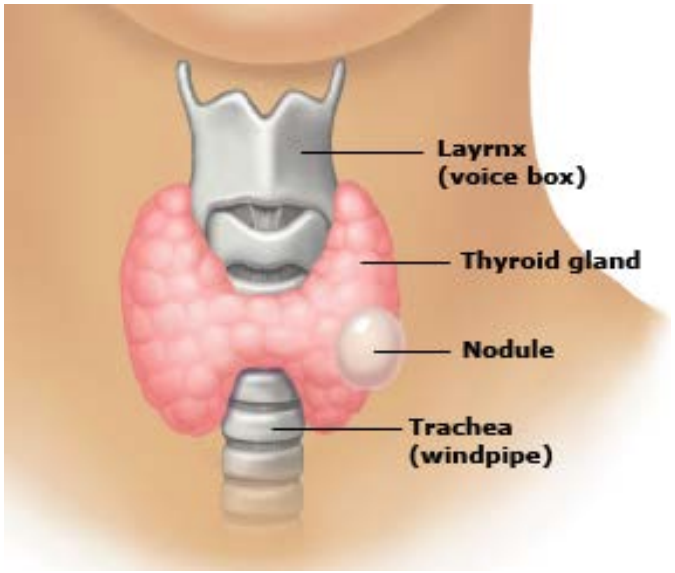


Thyroid Cancer: Survival

5 Year Survival:

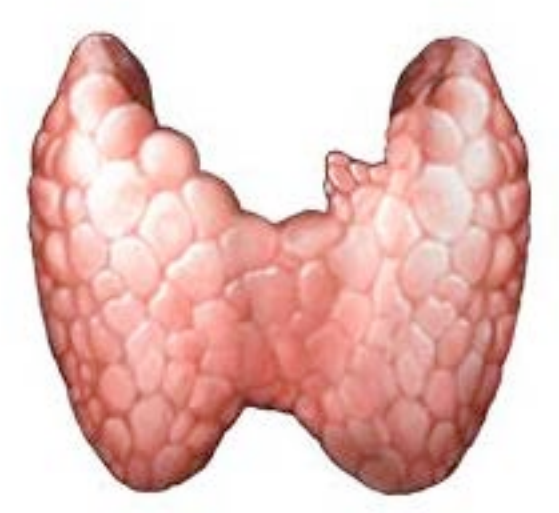
Papillary ca	98%
Follicular ca	94%
Medullary ca	80%
Anaplastic ca	< 5%

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.

Risk Factors



- Majority are sporadic
- Iodine deficiency
- Radiation exposure
- Family history
- Rare familial disorders:
  Gardner's syndrome, Cowden's disease, familial polyposis, MEN2, Werner Syndrome

Long-term risks for thyroid cancer and other neoplasms after exposure to radiation.
Schneider AB, Sarne DH
Nat Clin Pract Endocrinol Metab. 2005;1(2):82.

Increased risk for nonmedullary thyroid cancer in the first degree relatives of prevalent cases of nonmedullary thyroid cancer: a hospital-based study.
Pal T, Vogl FD, Chappuis PO, Tsang R, Brierley J, Renard H, Sanders K, Kantemiroff T, Bagha S, Goldgar DE, Narod SA, Foulkes WD
J Clin Endocrinol Metab. 2001;86(11):5307.

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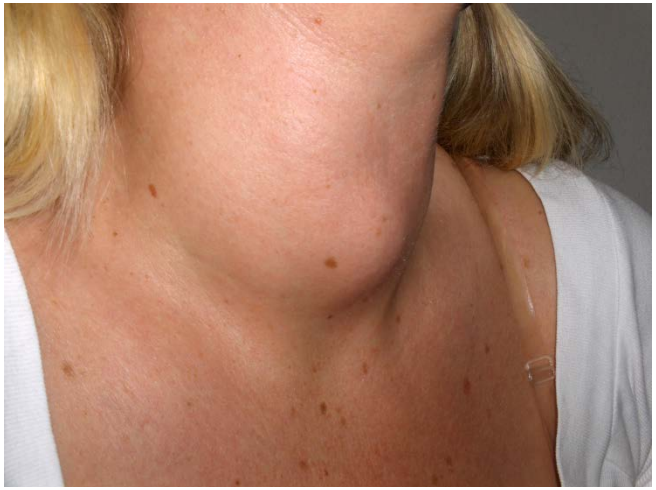
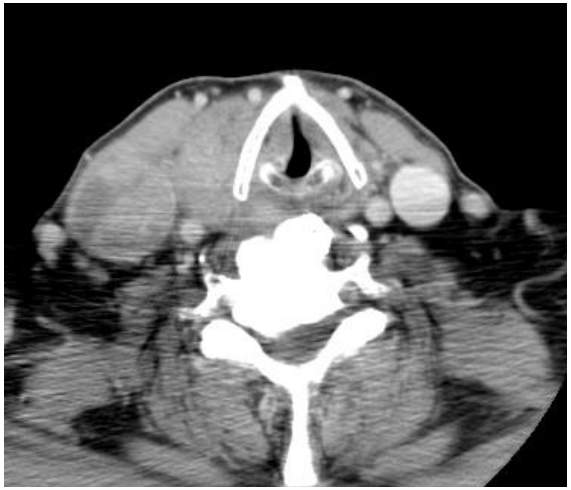
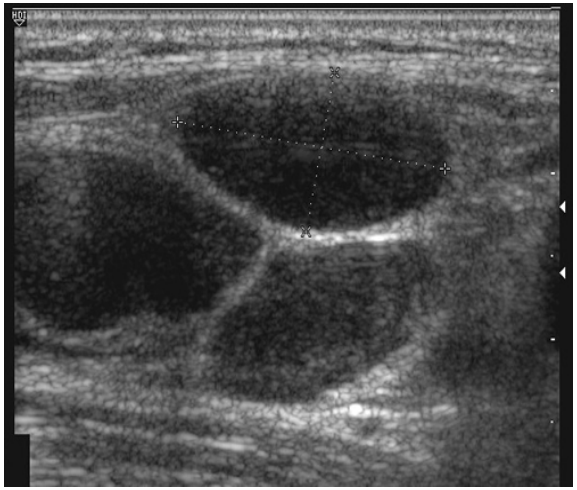
Clinical Presentation

- Palpable thyroid mass
- Palpable cervical lymphadenopathy
- Incidental finding on cross sectional imaging or ultrasound



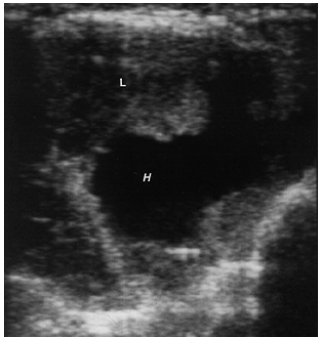


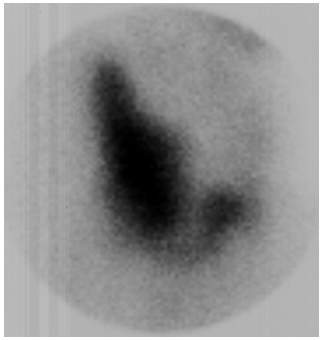


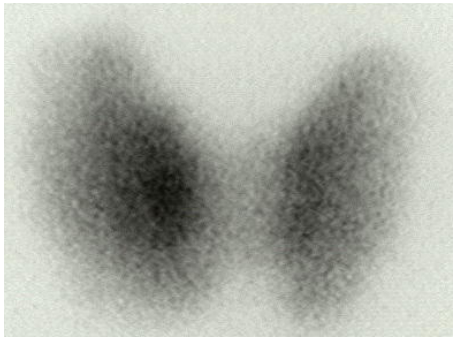
Thyroid Nodule

** Ultrasound + Fine Needle Aspiration (FNA) **

- Iodine Scan: only if thyrotoxic
- 15% inadequate – repeat
- Adequate specimen false +ve & -ve rates of 5%
- Ultrasound more sensitive than CT – but operator dependent
- Incidental nodules (<1cm) found > 50% of individuals
- These are rarely malignant







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RECOMMENDATION 6
Thyroid sonography with survey of the cervical lymph nodes should be performed in all patients with known or suspected thyroid nodules.
(Strong recommendation, High-quality evidence)

RECOMMENDATION 7
FNA is the procedure of choice in the evaluation of thyroid nodules, when clinically indicated.
(Strong recommendation, High-quality evidence)

RECOMMENDATION 9
Thyroid nodule FNA cytology should be reported using diagnostic groups outlined in the Bethesda System for Reporting Thyroid Cytopathology.
(Strong recommendation, Moderate-quality evidence)

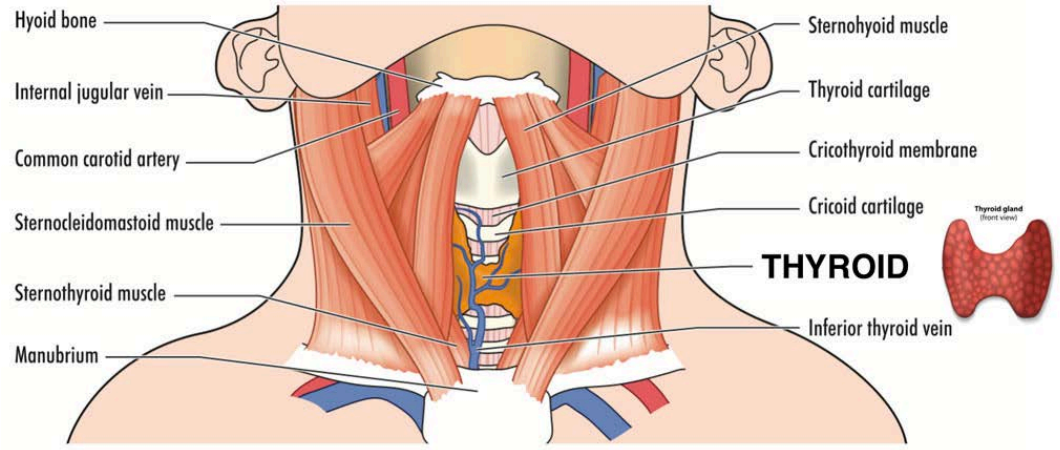
Management

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.

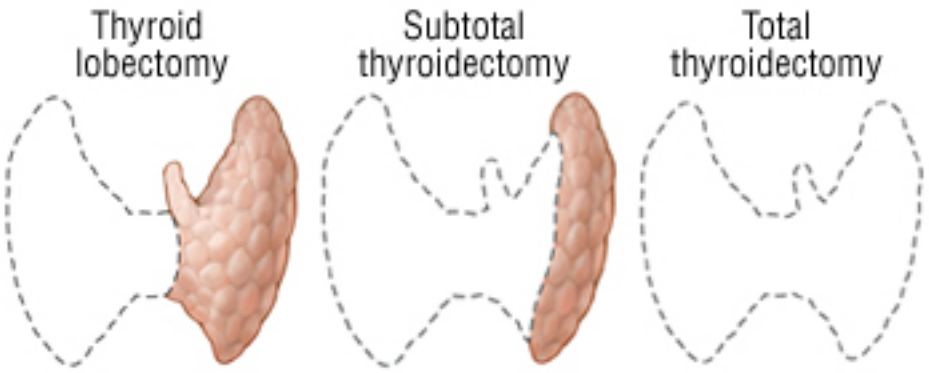
(Strong recommendation, Moderate-quality evidence)

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

Surgical Management

Primary therapy for thyroid cancer

1. (near) Total thyroidectomy +/- Central Neck Dissection
2. Lobectomy + isthmusectomy
3. And/Or Neck dissection



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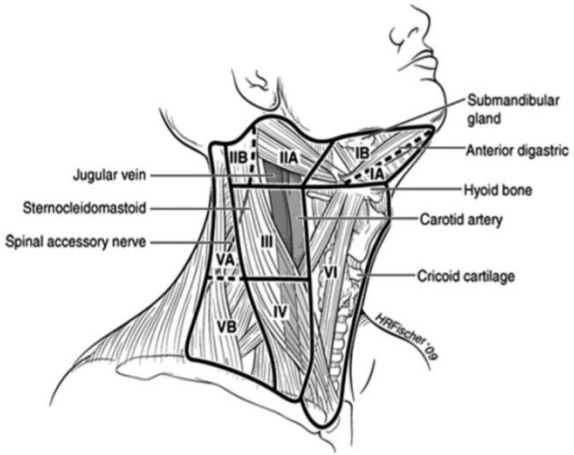
Surgical Management

Neck Dissection – Central Compartment vs Lateral

- Might improve local control
- 35% gross involvement, 80% microscopic
- +LN increases risk of recurrence
- +LN doesn't reduce survival rates



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 (ipsilateral or bilateral) should be considered in patients with papillary thyroid carcinoma with clinically uninvolved central neck lymph nodes (cN0) who have advanced primary tumors (T3 or T4) or clinically involved lateral neck nodes (cN1b), or if the information will be used to plan further steps in therapy.

(Weak recommendation, Low-quality evidence)

(C) Thyroidectomy without prophylactic central neck dissection is appropriate for small (T1 or T2), noninvasive, clinically node-negative PTC (cN0) and for most follicular cancers.

(Strong recommendation, Moderate-quality evidence)

RECOMMENDATION 37

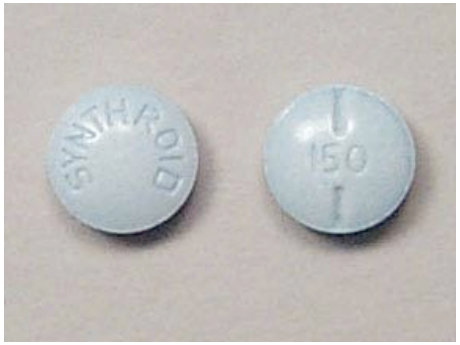
Therapeutic lateral neck compartmental lymph node dissection should be performed for patients with biopsy-proven metastatic lateral cervical lymphadenopathy.

(Strong recommendation, Moderate-quality evidence)

Post Operatively

EVERYONE needs Thyroxine

- T4 (levothyroxine)
  - Begin with 50-75 mcg
  - Average therapeutic dose is **125-200 mcg**
  - 4-6 weeks to reach steady state



Replacement vs Suppressive Therapy

(more later)

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Staging, Risk Assessment

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

Staging, Risk Assessment

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]

Staging, Risk Assessment

Risk of Recurrence – ATA Risk Stratification

TABLE 12. AMERICAN THYROID ASSOCIATION RISK STRATIFICATION SYSTEM: CLINICAL OUTCOMES FOLLOWING TOTAL THYROIDECTOMY AND RADIOIODINE REMNANT ABLATION OR ADJUVANT THERAPY

ATA risk	*Study*	*N[illegible],*	*Biochemical incomplete, %*[b]	*Structural incomplete, %*[c]
Low	Tuttle *et al.* (538)	86	11	3
	Castagna *et al.* (542)	91	ND[a]	ND[a]
	Vaisman *et al.* (539)	88	10	2
	Pitoia *et al.* (543)	78	15	7
Intermediate[a]	Tuttle *et al.* (538)	57	22	21
	Vaisman *et al.* (539)	63	16	21
	Pitoia *et al.* (543)	52	14	34
High	Tuttle *et al.* (538)	14	14	72
	Vaisman *et al.* (539)	16	12	72
	Pitoia *et al.* (543)	31	13	56

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Recurrence

Vs

Survival?

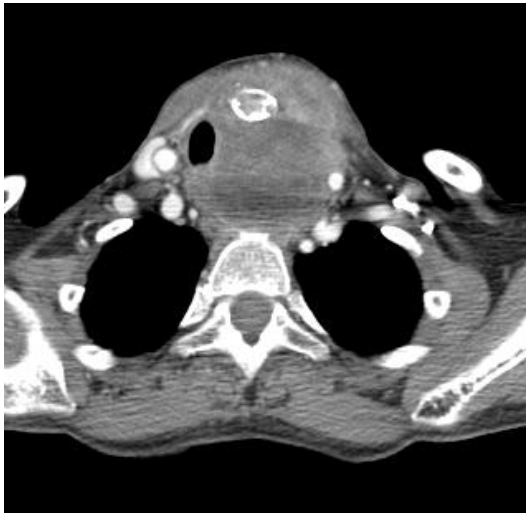
Staging, Risk Assessment

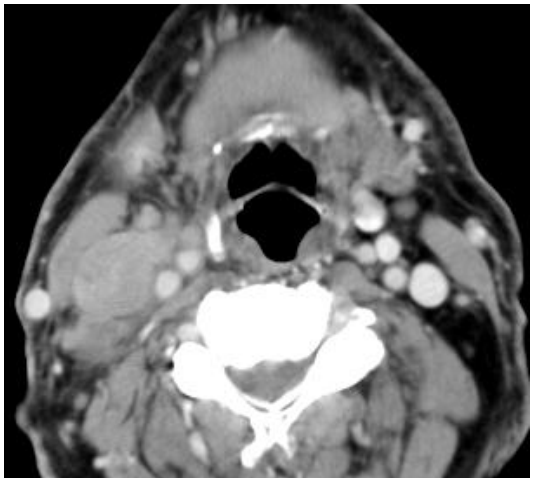
TABLE 10. AJCC 7TH EDITION/TNM CLASSIFICATION SYSTEM FOR DIFFERENTIATED THYROID CARCINOMA

	Definition
T0	No evidence of primary tumor
T1a	Tumor ≤1 cm, without extrathyroidal extension
T1b	Tumor >1 cm but ≤2 cm in greatest dimension, without extrathyroidal extension
T2	Tumor >2 cm but ≤4 cm in greatest dimension, without extrathyroidal extension.
T3	Tumor >4 cm in greatest dimension limited to the thyroid ***or*** Any size tumor with minimal extrathyroidal extension (e.g., extension into sternothyroid muscle or perithyroidal soft tissues).
T4a	Tumor of any size extending beyond the thyroid capsule to invade subcutaneous soft tissues, larynx, trachea, esophagus, or recurrent laryngeal nerve.
T4b	Tumor of any size invading prevertebral fascia or encasing carotid artery or mediastinal vessels
N0	No metastatic nodes
N1a	Metastases to level VI (pretracheal, paratracheal, and prelaryngeal/Delphian lymph nodes).
N1b	Metastases to unilateral, bilateral, or contralateral cervical (levels I, II III, IV, or V) or retropharyngeal or superior mediastinal lymph nodes (level VII)
M0	No distant metastases
M1	Distant metastases

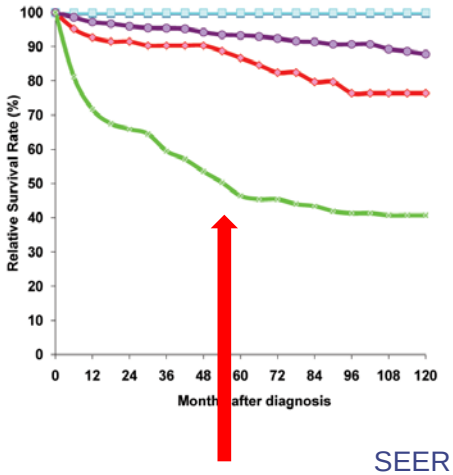
	Patient age <45 years old at diagnosis		
I	Any T	Any N	M0
II	Any T	Any N	M1
	Patient age ≥45 years old at diagnosis		
I	T1a	N0	M0
	T1b	N0	M0
II	T2	N0	M0
III	T1a	N1a	M0
	T1b	N1a	M0
	T2	N1a	M0
	T3	N0	M0
	T3	N1a	M0
IVa	T1a	N1b	M0
	T1b	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N0	M0
	T4a	N1a	M0
	T4a	N1b	M0
IVb	T4b	Any N	M0
IVc	Any T	Any N	M1

AJCC/TNM

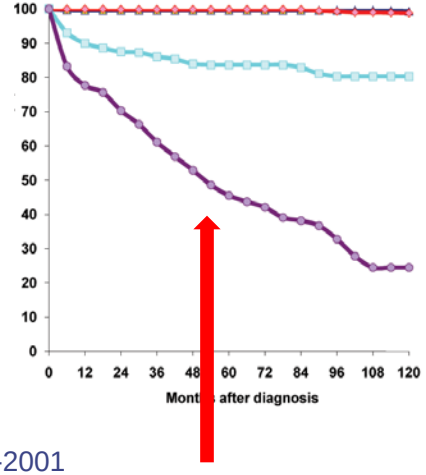




Papillary carcinoma



Follicular carcinoma



SEER 1988-2001

Staging, Risk Assessment

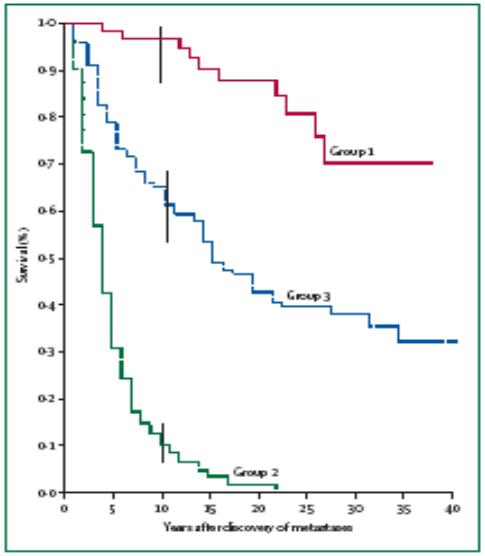
AGES

- Age: >45 years of age
- Grade: problematic
- Extrathyroidal (soft tissue) extension
- Size: 2cm (6%) vs 7cm (50%) mortality

AMES

- Age
- Metastasis
- Extrathyroidal extension
- Size

Hay et al, Surgery 1987 Dec;102(6):1088-95.



< 40 yrs
Metastases <1cm

< 40 yrs
Metastases >1cm
> 40 yrs
Metastases <1cm

> 40 yrs
Metastases >1cm

Baudin and Schlumberger, Lancet Oncology, 2007

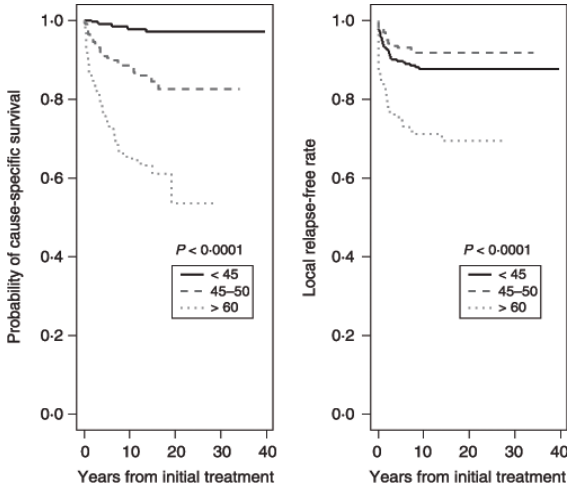


Fig. 2 Cumulative incidence of cause-specific survival and local–regional relapse-free rate by age.

Brierley et al Clin Endocrinology 2005

Staging, Risk Assessment

What we use at BCCA:

- MACIS
  - 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 !

- 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.

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Adjuvant Therapy

- Radioiodine (131-I) → **microscopic disease**
  - Ablation: help with FU, 30 mCi
  - Therapy: microscopic disease, 60-200 mCi
- External beam RT → **macroscopic disease**
- Thyroxine

Adjuvant Therapy

Radioiodine (131-I) – who should be treated?

- No randomized trials
- 131-I reduces risk of recurrence (large retrospective series)
- Evidence of survival benefit? – controversial (large retrospective series)

- **Two schools of thought**
  - Treat more! (Mazzaferri et al)
  - Treat less! (Hay et al)
- **BCCA – Weekly Provincial Thyroid Conference**
  - MACIS score > 6.0 = Treat
  - MACIS score 5.0 to 6.0 = Review at Provincial Thyroid Conference
  - Treating fewer patients
  - Using lower doses for Ablation: 30 mCi vs 60 or 100 mCi
  - More outpatient therapy

Mallick U, Harmer C, Yap B, Wadsley J, Clarke S, Moss L, Nicol A, Clark PM, Farnell K, McCready R, Smellie J, Franklyn JA, John R, Nutting CM, Newbold K, Lemon C, Gerrard G, Abdel-Hamid A, Hardman J, Macias E, Roques T, Whitaker S, Vijayan R, Alvarez P, Beare S, Forsyth S, Kadalayil L, Hackshaw A 2012 Ablation with low-dose radioiodine and thyrotropin alfa in thyroid cancer. N Engl J Med **366:**1674–1685.

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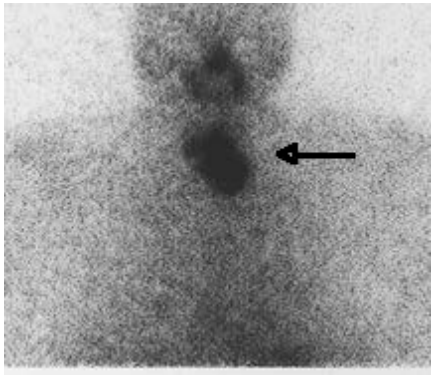
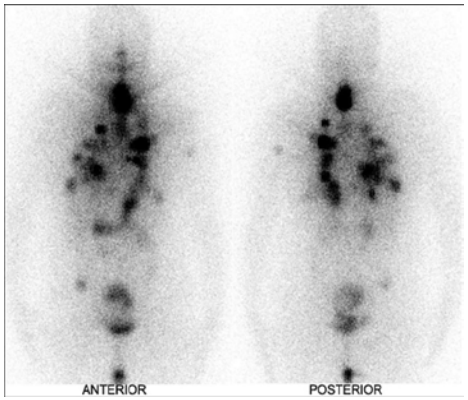
Maenpaa HO, Heikkonen J, Vaalavirta L, Tenhunen M, Joensuu H 2008 Low vs. high radioiodine activity to ablate the thyroid after thyroidectomy for cancer: a randomized study. PLoS One **3:**e1885.

Adjuvant Therapy

Radioiodine (131-I) Side Effects

- Fatigue
- Xerostomia
- Dysgeusia
- Sialodenitis
- Transient hypogonadism (spermatopenia)
- Myelosuppression (transient versus permanent)
- Hypothetical risk of aplastic anaemia and leukaemia
  - Doses >1000mCi (usual dose 80-150mCi)





RECOMMENDATION 58
A posttherapy WBS (with or without SPECT/CT) is recommended after RAI remnant ablation or treatment, to inform disease staging and document the RAI avidity of any structural disease.

(Strong recommendation, Low-quality evidence)

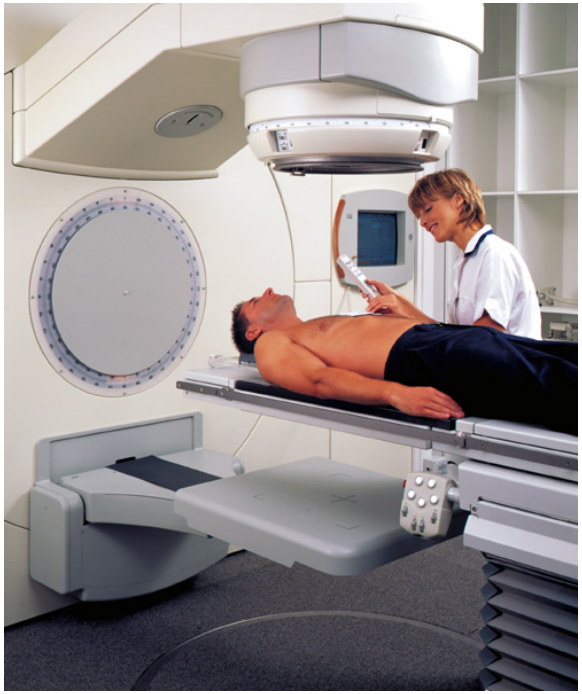
Adjuvant Therapy

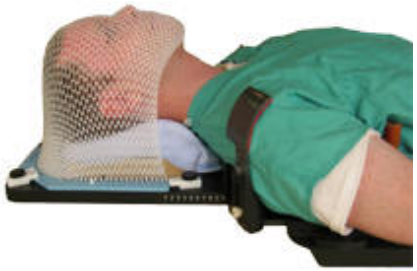
- Radioiodine (131-I) → **microscopic disease**
  - Ablation of remnant
  - Therapy of disease
- **External beam RT → macroscopic disease**
- Thyroxine
- Chemotherapy, targeted agents

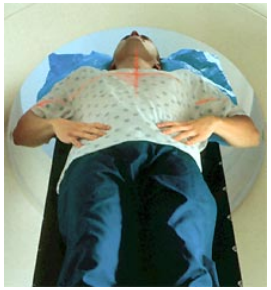
Adjuvant Therapy

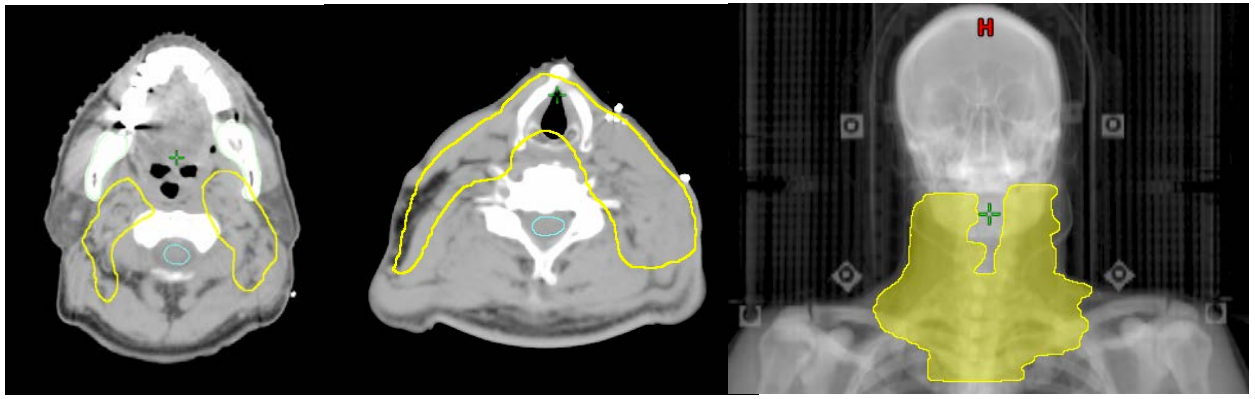
External Beam Radiotherapy

- Gross (macroscopic) disease
- Unresectable gross disease
- Gross disease not responding to 131-I
- 5 to 7 weeks, daily treatment









Sequelae:

- Xerostomia, altered taste, esophagitis, pharyngitis, laryngitis, fatigue, dry/moist desquamation

RECOMMENDATION 60
There is no role for routine adjuvant EBRT to the neck in patients with DTC after initial complete surgical removal of the tumor.

(Strong recommendation, Low-quality evidence)

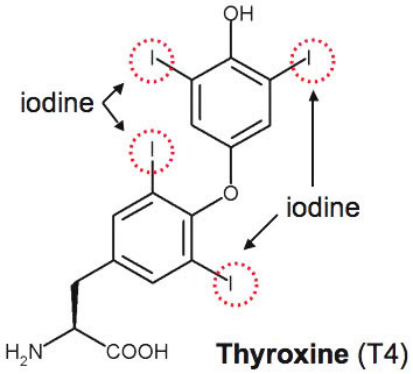
Adjuvant Therapy

- Radioiodine (131-I) → **microscopic disease**
  - Ablation of remnant
  - Therapy of disease
- External beam RT → **macroscopic disease**
- **Thyroxine**

Adjuvant Therapy

Thyroxine - Rationale:

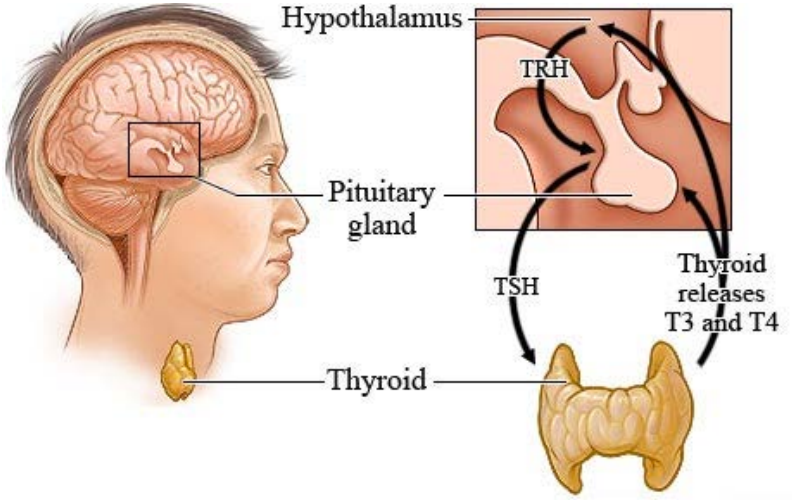
1. Replacement Therapy → FT4
2. Suppressive Therapy → TSH



Other Notes:

- 4 - 6 weeks to equilibrate
- Measure FT4 and TSH
  - FT4: Upper limits of normal
  - TSH: <0.1 to 2.0 mU/L

- TSH Suppression: How low do you go?



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

Adjuvant Therapy

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

- BCCA: Generally < 1.0 mU/L, depending on risk category
  - 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

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.

Outline

Introduction, Epidemiology

Diagnosis, Surgical Management

Staging and Risk Assessment

Radioiodine Remnant Ablation and Therapy

Thyrotropin Suppression Therapy

Surveillance

Future Directions, Clinical Trials

Surveillance

- Clinical exam: q6-12 months
- Blood tests: q3-12 months - I do all FOUR:
    1. FT4
    2. TSH
    3. **Tg (> 98% sensitivity)**
    4. Anti-Tg-Ab
- Imaging
    - **US Neck**: Yes or No? How frequent?
    - ***5 mCi 131-I Scan → Not Anymore***
    - Others: CXR, CT Neck, TSH stimulated PET/CT

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 ***** NOT a 5 mCi SCAN *****
- 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.

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Introduction, Epidemiology

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Surveillance

Future Directions, Clinical Trials

Future Directions

Clinical Trials

- Tyrosine Kinase Inhibitors: OS, QOL

Molecular Markers

- Diagnosis, prognosis, therapeutic targets

Improved Risk Stratification

- Who truly needs 131-I? US?
- Which LNs to biopsy?
- Minimally invasive follicular variant of papillary carcinoma in the absence of angio-invasion

Improve Surveillance Regimens

- Tg in the face of Anti-Tg-Antibodies

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: generally < 1.0
    3. Tg: excellent tumour marker
    4. Anti-Tg-antibodies: surrogate marker, interferes with Tg