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

Adjuvant Therapy of Thyroid Cancer:

rhTSH, RAI, EBRT and Targeted Therapeutics

October 13, 2018
BC Cancer Surgeon Network Fall Update

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Disclosure(s)

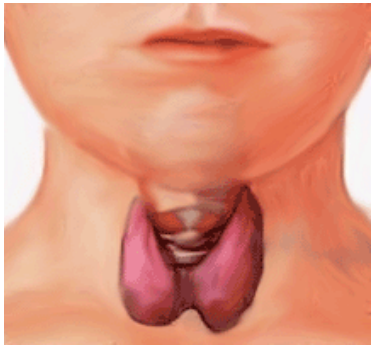
- Varian Medical Systems – Research Grants, Consultant
- Genzyme/Sanofi – Advisory Board, Research Grant
- Astra Zeneca – Advisory Board

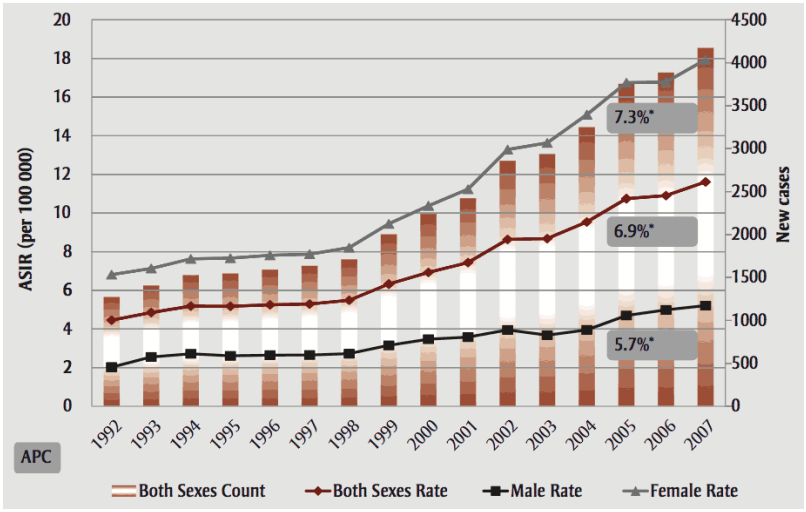
Outline

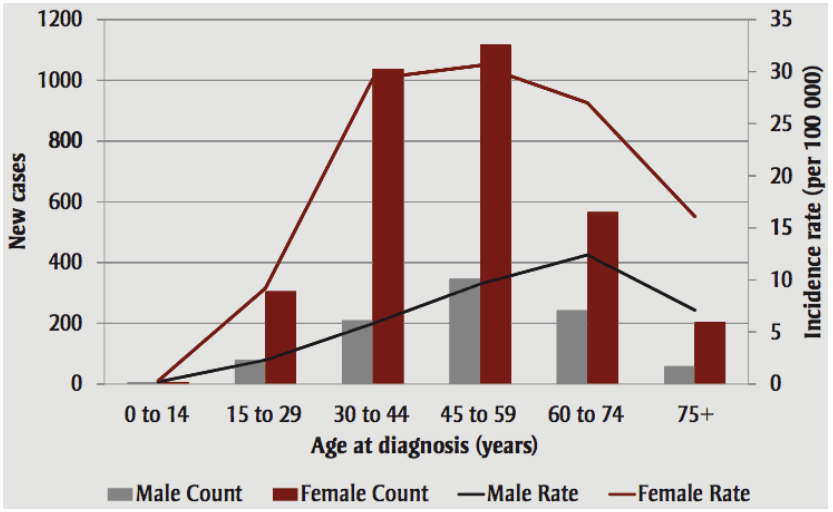
- Scope of the Problem
- Staging and Risk Assessment
- Radioiodine Remnant Ablation and Therapy
- External Beam Radiotherapy
- Targeted Therapies

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].

Scope of the Problem

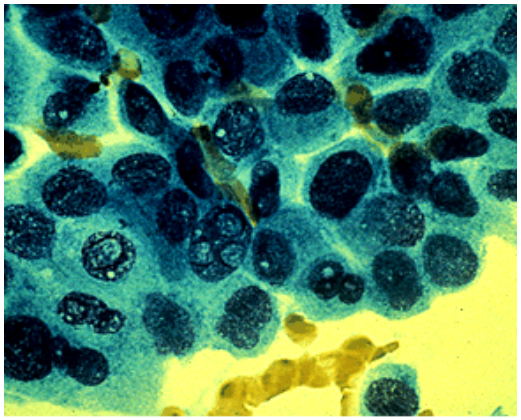
90% Well differentiated tumours

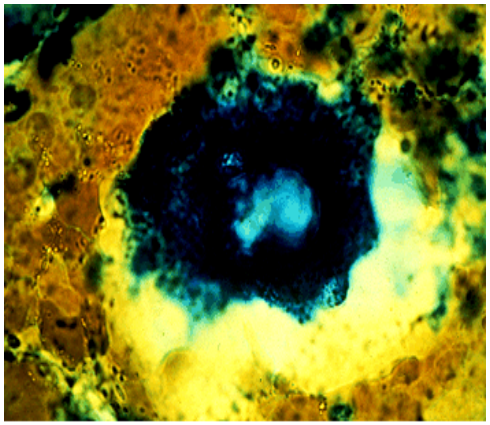
4% Medullary

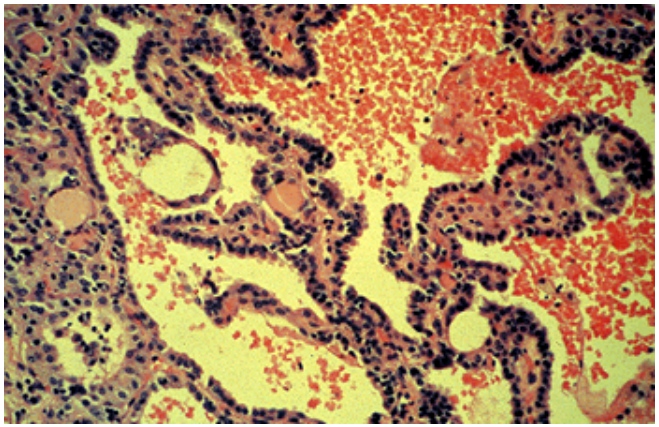
5% Anaplastic

5 Year Survival:

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







Management

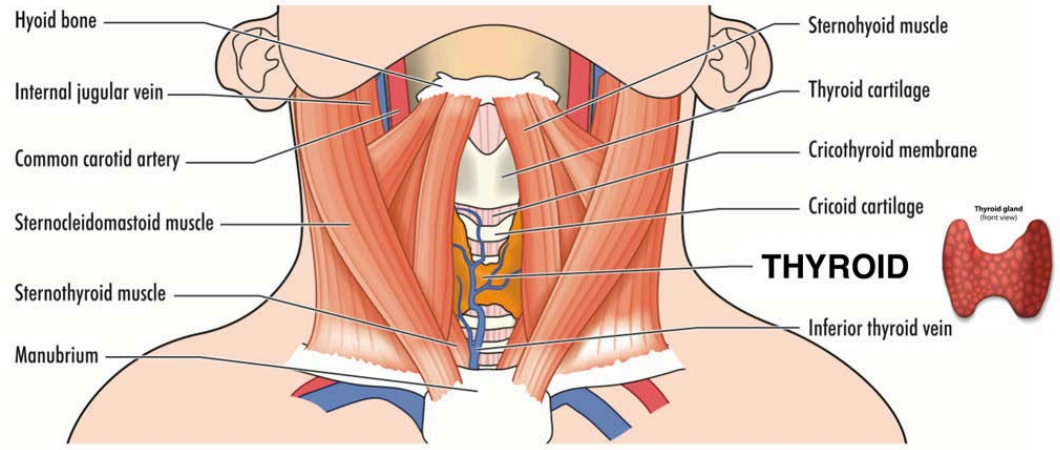
Surgery – Primary Treatment

Adjuvant Radiation

- Radioiodine (131-Iodine)
- External Beam Radiation

Thyroxine

Systemic Therapy



***** 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.

Adjuvant Therapy (How)

- Radioiodine (131-I) → **microscopic disease**
  - Therapy: 150-200 mCi
  - Remnant Ablation: 30 mCi
- External beam RT → **macroscopic disease**
- Thyroxine

Who should we treat?

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

Risk of Recurrence - ATA

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]

Risk of Recurrence - ATA

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

ATA risk	*Study*	*NED, %*	*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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2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer

Bryan R. Haugen,[1,*] Erik K. Alexander,[2] Keith C. Bible,[3] Gerard M. Doherty,[4] Susan J. Mandel,[5] Yuri E. Nikiforov,[6] Furio Pacini,[7] Gregory W. Randolph,[8] Anna M. Sawka,[9] Martin Schlumberger,[10] Kathryn G. Schuff,[11] Steven I. Sherman,[12] Julie Ann Sosa,[13] David L. Steward,[14] R. Michael Tuttle,[15] and Leonard Wartofsky[16]

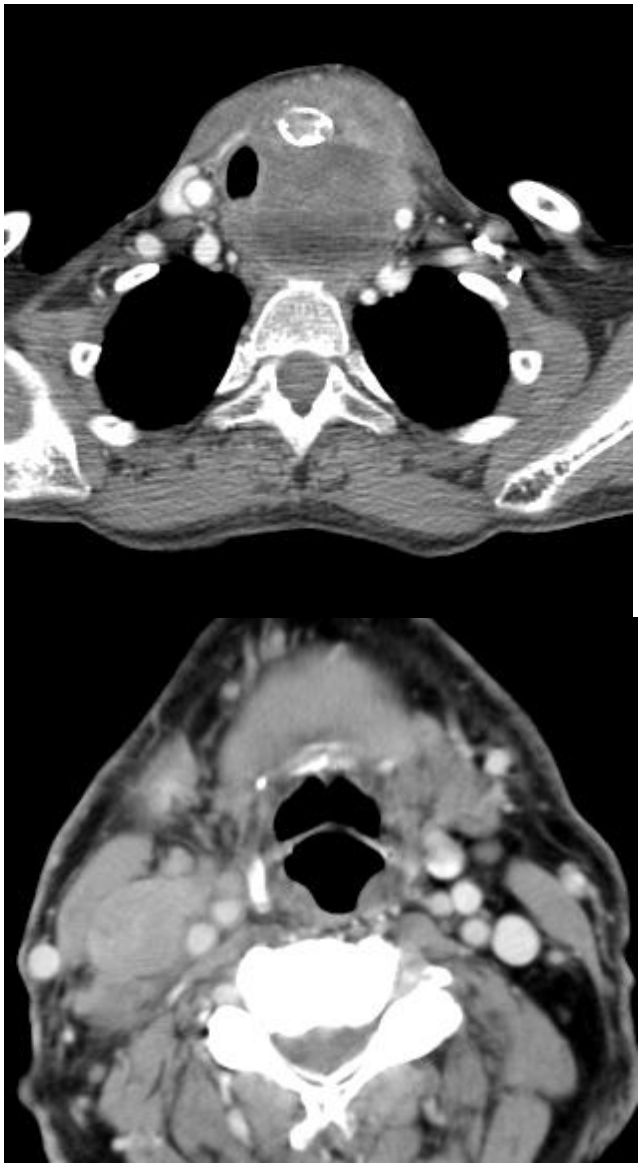
THYROID Volume 26, Number 1, 2016

Risk of Death – AJCC/TNM

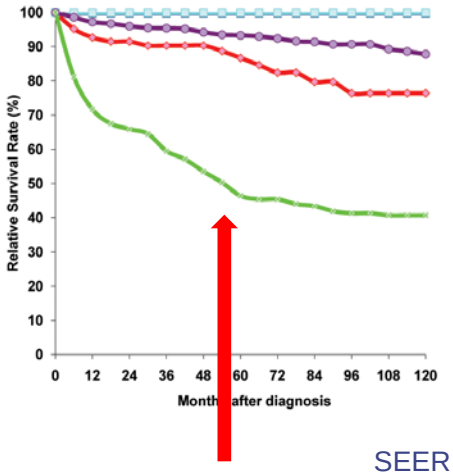
TABLE 10. AJCC 7TH EDITION/TNM CLASSIFICATION SYSTEM FOR DIFFERENTIATED THYROID CARCINOMA

	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

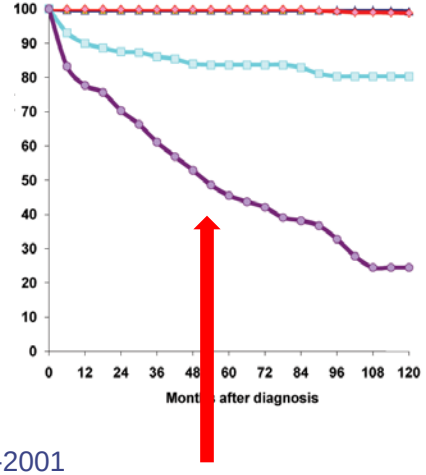
	Patient age <45 years old at diagnosis		
I	Any T	Any N	M0
II	Any T	Any N	M1
	Patient age ≥45 years old at diagnosis		
I	T1a	N0	M0
	T1b	N0	M0
II	T2	N0	M0
III	T1a	N1a	M0
	T1b	N1a	M0
	T2	N1a	M0
	T3	N0	M0
	T3	N1a	M0
IVa	T1a	N1b	M0
	T1b	N1b	M0
	T2	N1b	M0
	T3	N1b	M0
	T4a	N0	M0
	T4a	N1a	M0
	T4a	N1b	M0
IVb	T4b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



Papillary carcinoma



Follicular carcinoma



SEER 1988-2001

Risk of Death – AGES, AMES

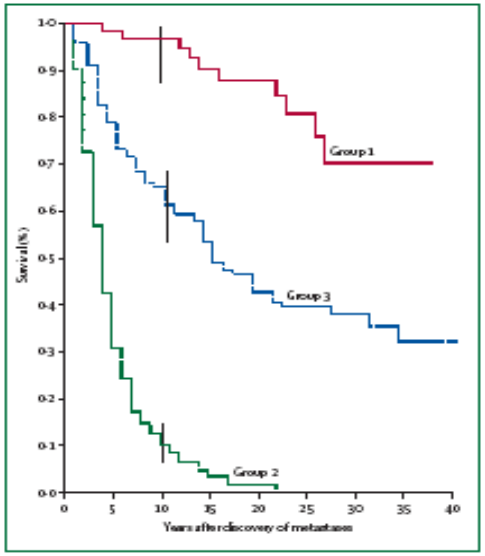
AGES

- 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

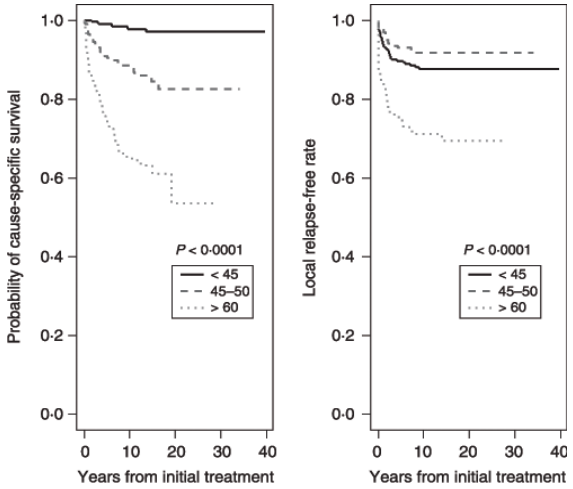


Fig. 2 Cumulative incidence of cause-specific survival and local–regional relapse-free rate by age.

Brierley et al Clin Endocrinology 2005

Risk of Death - MACIS

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.

Radioiodine 131-I – Who should we treat?

- No randomized trials
- Does RAI 131-I reduce risk of recurrence? **Maybe**
- Evidence of survival benefit? **Maybe**

- **Two schools of thought**
  - Treat more! (Mazzaferri et al)
  - Treat less! (Hay et al)

- **BCCA – Weekly Provincial Thyroid Conference**
  - MACIS score > 6.0 or ATA high risk = treatment dose
  - MACIS score 5.0 to 6.0 or ATA intermediate = Provincial Thyroid Conference
  - Treating fewer patients (therapeutic dose)
  - Lower doses for Ablation: 30 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.

Schlumberger M, Catargi B, Borget I, Deandreis D, Zerdoud S, Bridji B, Bardet S, Leenhardt L, Bastie D, Schvartz C, Vera P, Morel O, Benisvy D, Bournaud C, Bonichon F, Dejax C, Toubert ME, Leboulleux S, Ricard M, Benhamou E 2012 Strategies of radioiodine ablation in patients with low-risk thyroid cancer. N Engl J Med **366:**1663–1673.

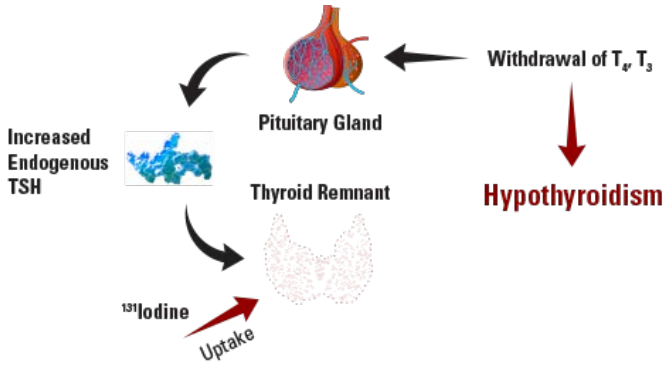
Kukulska A, Krajewska J, Gawkowska-Suwinska M, Puch Z, Paliczka-Cieslik E, Roskosz J, Handkiewicz-Junak D, Jarzab M, Gubala E, Jarzab B 2010 Radioiodine thyroid remnant ablation in patients with differentiated thyroid carcinoma (DTC): prospective comparison of long-term outcomes of treatment with 30, 60 and 100 mCi. Thyroid Res **3:**9.

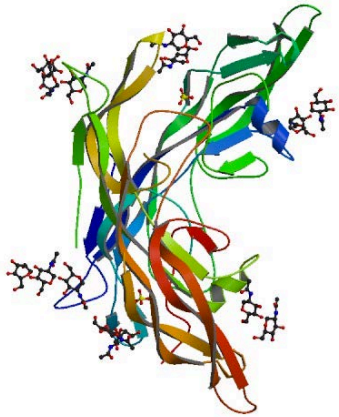
Maenpaa HO, Heikkonen J, Vaalavirta L, Tenhunen M, Joensuu H 2008 Low vs. high radioiodine activity to ablate the thyroid after thyroidectomy for cancer: a randomized study. PLoS One **3:**e1885.

Adjuvant Therapy

Radioiodine (131-I) – how do we do it?

- TSH stimulation (> 30)
- Two methods:
  - Endogenous TSH ie. Thyroxine withdrawal
  - Exogenous TSH ie. Thyrotropin alpha (rhTSH)
- rhTSH (thyrotropin alpha)
  - Two retrospective studies: rhTSH = withdrawal
  - Improved quality of life
  - Expensive
  - Side effects
    - Common: Nausea 10%, Headache: 7%
    - Rare (<3%): fatigue, insomnia, vomiting, diarrhea, weakness
- Low Iodine Diet





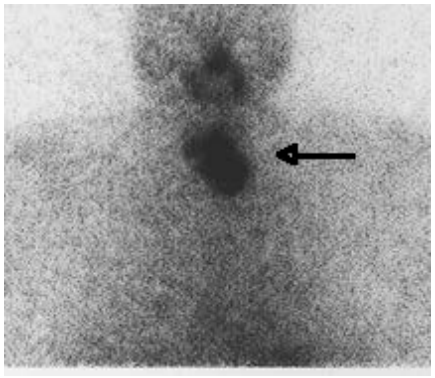
RECOMMENDATION 57
A low iodine diet (LID) for approximately 1–2 weeks should be considered for patients undergoing RAI remnant ablation or treatment.

(Weak recommendation, Low-quality evidence)

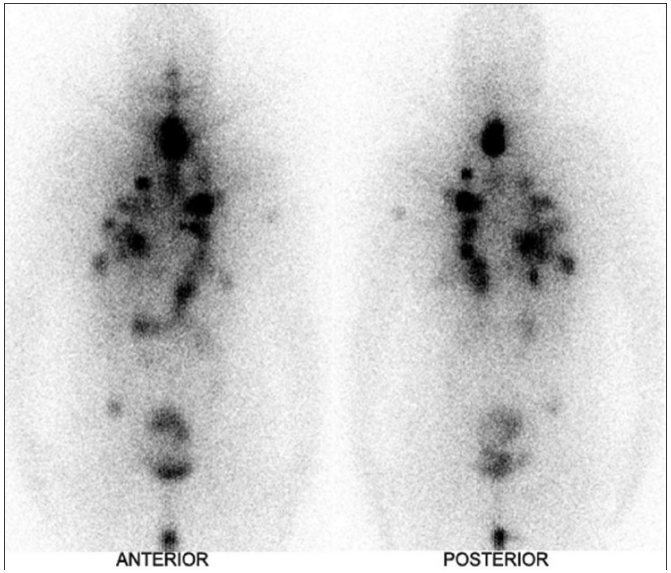
Luster, Eur J Nucl Med Mol Imaging 2003 Oct;30(10):1371-7. Epub 2003 Jul 15
Barbaro, J Clin Endocrinol Metab 2003 Sep;88(9):4110-5
Robbins, J Nucl Med 2002 Nov;43(11):1482-8
Schroeder, J Clin Endocrinol Metab. 2006 Mar;91(3):878-84. Epub 2006 Jan 4

Adjuvant Therapy

Radioiodine (131-I) Protocol



- Protocol
  - Monday: 0.9mg IM (thyrotropin alpha)
  - Tuesday: 0.9mg IM (thyrotropin alpha)
  - Wednesday: 123-I scan + 131-I therapy
    - "radioactive" Wednesday, Thursday, Friday
    - Inpatient versus Outpatient
  - Monday:
    - Whole body scan
    - Blood tests: TSH, Tg
- RAI is Diagnostic and Therapeutic



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)

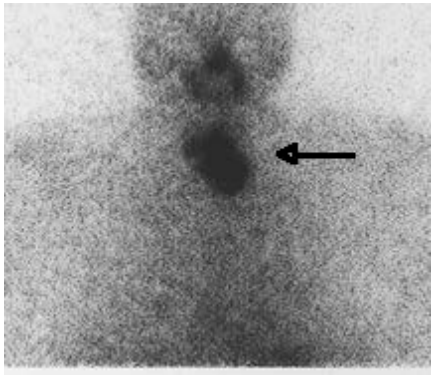
Hi-Lo Trials

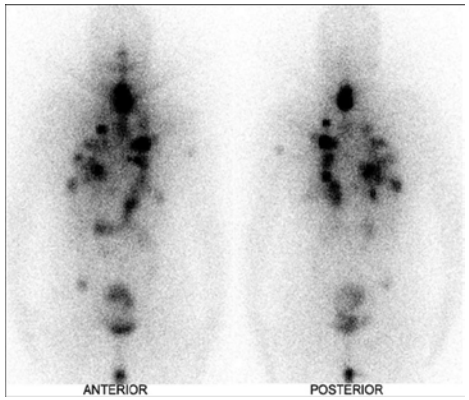
- Increasing incidence of low risk disease
- Conflicting data for RAI and low risk disease
  - ATA: no clear recommendations
  - European Thyroid Cancer Task Force: mildly yes
- **Remnant Ablation – not therapy**
- 2 trials (Mallick, Schlumberger):
  - 2 x 2
  - 30 vs 100 mCi
  - rhTSH vs withdrawal
- Results:
  - 30 mCi and rhTSH
  - No long term FU for recurrences
  - Do they even need treatment?

Adjuvant Therapy

Radioiodine (131-I) Side Effects

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





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(Strong recommendation, Low-quality evidence)

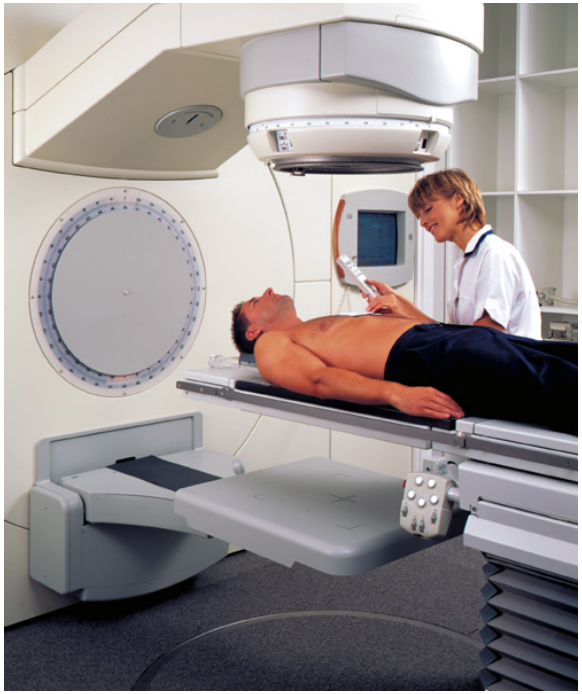
Adjuvant Therapy

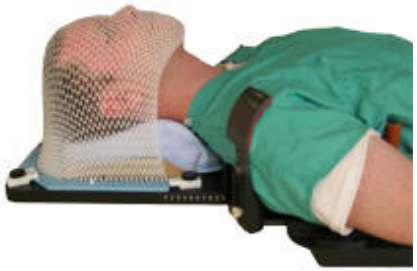
- Radioiodine (131-I) → **microscopic disease**
  - Ablation of remnant
  - Therapy of disease
- **External beam RT → macroscopic disease**
- Thyroxine
- Chemotherapy, targeted agents

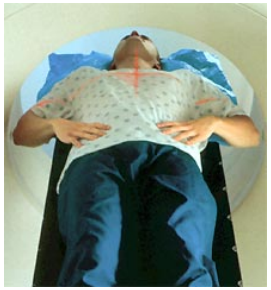
Adjuvant Therapy

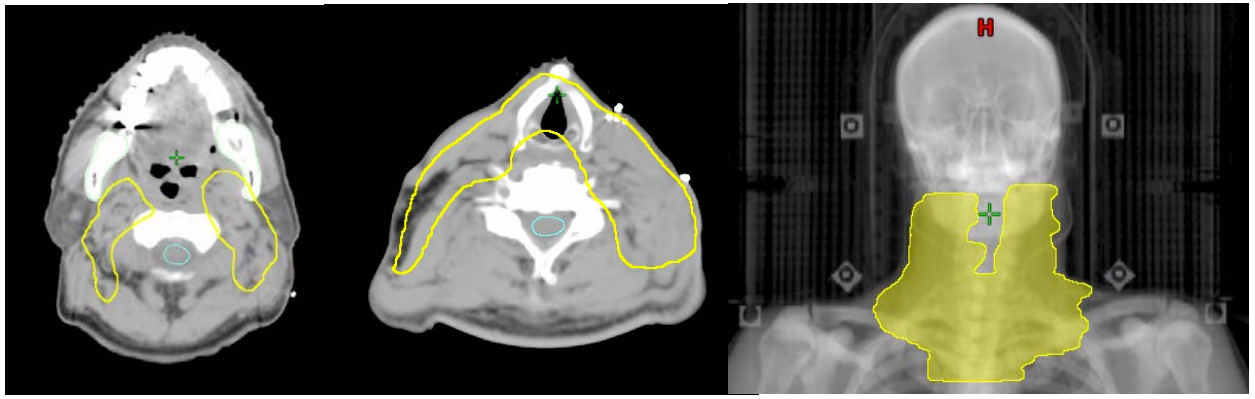
External Beam Radiotherapy

- 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

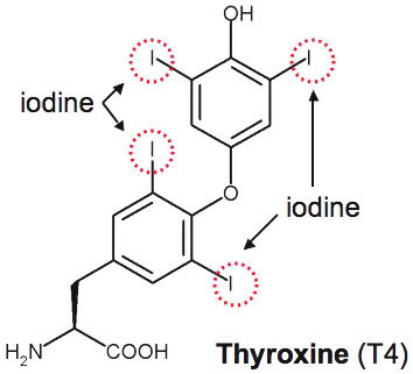
RECOMMENDATION 60
There is no role for routine adjuvant EBRT to the neck in patients with DTC after initial complete surgical removal of the tumor.

(Strong recommendation, Low-quality evidence)

Adjuvant Therapy

Thyroxine - Rationale:

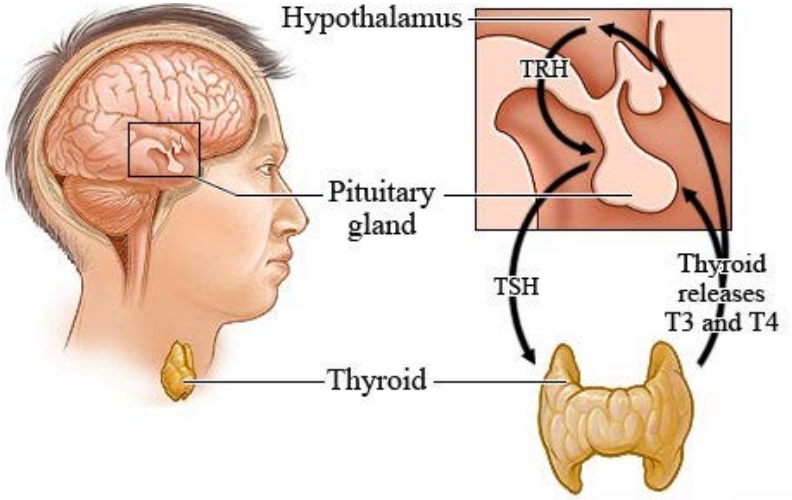
1. Replacement Therapy → FT4
2. Suppressive Therapy → TSH



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

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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

RAI resistant disease:

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

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Summary

Risk Stratification: Recurrence vs Survival

Does Adjuvant Therapy Change Outcomes?

Microscopic Disease: RAI, 150-200 mCi

- Remnant Ablation: 30 mCi, rhTSH

Macroscopic Disease: EBRT

Recurrent Disease: Surgery, RAI, EBRT

RAI-Resistant Disease: Tyrosine-Kinase Inhibitors