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Adjuvant therapy for thyroid cancer

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Carcinoma of the thyroid

1% of all new malignancies
- 0.5% in men
- 1.5% in women

94% differentiated tumours arising from follicular epithelial cells
- Papillary – with or without follicular elements
- Follicular

5% Medullary

4% Anaplastic

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Carcinoma of the thyroid

Overall survival rates in US

Papillary ca	98%
Follicular ca	92%
Medullary ca	80%
Anaplastic ca	13%

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Carcinoma of the thyroid

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

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Carcinoma of the thyroid in BC in 2004

New cases: 49 men, 183 women

Incidence rates similar from age 20-80

Deaths: 10 men and 13 women

All but 2 deaths in patients over 60yrs

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Carcinoma of the thyroid

Poor prognostic features for all types

Age at diagnosis

Widespread metastatic disease

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Differentiated thyroid carcinoma

Adjuvant treatment after adequate surgery

- Thyroxine
- Radioactive iodine ablation of remnant
- Radioactive iodine therapy of disease
- External beam radiotherapy
- Chemotherapy rarely useful

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Differentiated thyroid carcinoma

Thyroxine

- Replace missing endogenous hormone
- Suppressing TSH reduces risk of recurrence
- Risks of hyperthyroidism
  - atrial fibrillation
  - cardiac hypertrophy and dysfunction
  - accelerated osteoporosis
- Balance degree of suppression with risk of recurrence and pre-existing comorbidities

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Differentiated thyroid carcinoma

TSH suppression

- Adjust TSH level to degree of risk
  - Metastatic disease - complete suppression
  - High risk disease – moderate suppression
  - Low risk disease – low end of normal range

Biondi B et al 2005

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Differentiated thyroid carcinoma

TSH suppression

- Must measure free T4 and TSH

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Differentiated thyroid carcinoma

Radioactive iodine – ^{123}Iodine and ^{131}Iodine

- Iodine is taken up by thyroid follicular cells and most malignant cells of follicular origin
- ^{123}Iodine used for scanning neck (γ)
- ^{131}Iodine used for treatment (β) and scanning body (γ)
  - Oral administration.
  - Physical half life 8 days
- Normal thyroid tissue takes up iodine better than even the most iodine avid tumours

Differentiated thyroid carcinoma

Radioactive iodine therapy - rationale

- Destroy residual malignant cells
  - Adjuvant treatment of “high risk” patients
  - Treatment of established metastases

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Differentiated thyroid carcinoma

Radioactive iodine therapy - rationale

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- Destroy residual thyroid tissue

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Differentiated thyroid carcinoma

Radioactive iodine therapy - rationale

- Destroy residual malignant cells
  - Adjuvant treatment of “high risk” patients
  - Treatment of established metastases
- Destroy residual thyroid tissue
  - Improve specificity of follow up Iodine scans

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Differentiated thyroid carcinoma

Radioactive iodine therapy - rationale

- Destroy residual malignant cells
  - Adjuvant treatment of “high risk” patients
  - Treatment of established metastases
- Destroy residual thyroid tissue
  - Improve specificity of follow up Iodine scans
  - Improve value of serum thyroglobulin as a tumour marker

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Differentiated thyroid carcinoma

- How do we assess risk?
  - Risk of death
  - Risk of recurrence

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Differentiated thyroid carcinoma

Risk factors

- Age
- Tumour size
- Certain histological subtypes
- (Multifocality)
- Extrathyroidal extension
- Incomplete excision
- (Nodal metastases)
- Distant metastases

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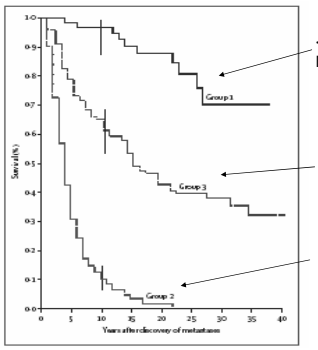
Differentiated thyroid carcinoma



< 40 yrs
Metastases <1cm

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

> 40 yrs
Metastases >1cm

Baudin and Schlumberger Lancet Oncology 2007

Differentiated thyroid carcinoma

Risk factors

- Age
- Tumour size
- Certain histological subtypes
- (Multifocality)
- Extrathyroidal extension
- Incomplete excision
- (Nodal metastases)
- Distant metastases

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Differentiated thyroid carcinoma

MACIS score

Add each of the following scores

Age $\leq$ 39 = 3.1 or if $\geq$ 40, age x 0.08

Tumour size in cm x 0.3

If extrathyroidal invasion add 1

If incompletely resected add 1

If distant metastases present add 3

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Hay et al Surgery 1993;114:1050-8.

Differentiated thyroid carcinoma

20 year cancer specific survival according to MACIS score

Score	Survival
<6.0	99%
6.0-6.99	89%
7-7.99	56%
8+	24%

Hay et al Surgery 1993;114:1050-8.

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Differentiated thyroid carcinoma

MACIS score – *assesses survival, have to add nodal and multifocal disease to include risk of recurrence*

Add each of the following scores

Age ≤ 39 = 3.1 or if ≥ 40, age x 0.08

Tumour size in cm x 0.3

If extrathyroidal invasion add 1

If incompletely resected add 1

If distant metastases present add 3

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Differentiated thyroid carcinoma

^{131}Iodine therapy

- Very localised high radiation dose (β particles)
- Potential risk of transient recurrent laryngeal nerve damage if large thyroid remnant
- Theoretical risk of pulmonary fibrosis if diffuse pulmonary metastases
- Bystander effect on
  - salivary tissue
  - germinal epithelium
  - bone marrow

Differentiated thyroid carcinoma

Radioactive iodine – side effects

- Discomfort in neck and salivary glands
- Transient hoarseness
- Xerostomia – usually short term
- Transient effect on testicular germinal epithelium
  - No risk to subsequent pregnancies if delayed 6 months
  - No risk to ovaries
  - Significant risk to fetus
- Risk of aplastic anaemia and second malignancy with higher doses (>500mCi, usual dose 80-150mCi)

Differentiated thyroid carcinoma

Radioactive iodine

- Maximum uptake when TSH elevated
  - Endogenous
  - Recombinant TSH (Thyrogen)

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Recombinant TSH -Thyrotropin alpha (Thyrogen®)

- In randomised trials has been shown to be as effective as thyroxine withdrawal for both scanning and therapy
- May reduce toxicity of ^{131}Iodine by maintaining metabolic rate
- Now fully funded in BC

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Differentiated thyroid carcinoma

Radioactive iodine

- Maximum uptake when TSH elevated
  - Endogenous
  - Recombinant TSH (Thyrogen)
- Uptake reduced by high iodine intake
  - Diet
  - CT contrast

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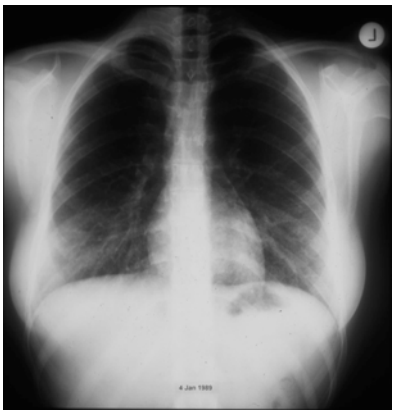
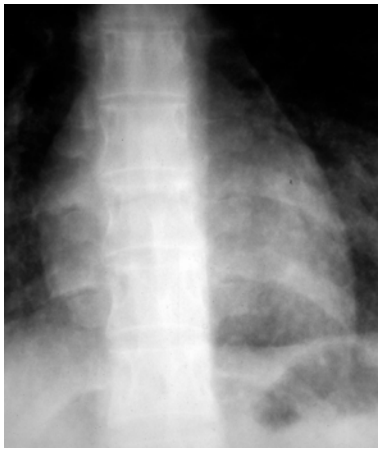
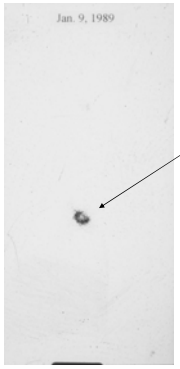
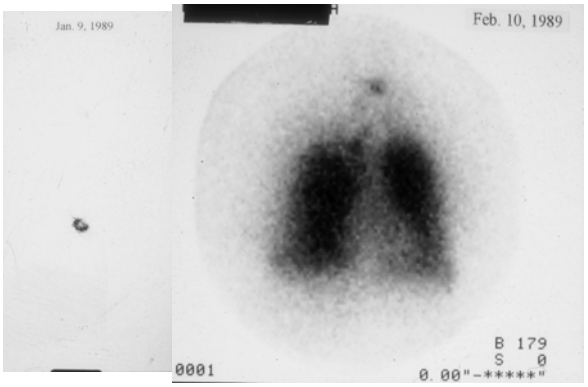






Whole body iodine scan

Only uptake is in the thyroid remnant



Differentiated thyroid carcinoma

Radioactive iodine therapy - Duration

- Continue treatment until
  - All uptake is ablated
  - Thyroglobulin is undetectable
  - Threshold for leukemia is approached

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Differentiated thyroid carcinoma

Serum thyroglobulin

- Produced by thyroid follicular cells and their tumours – sensitivity > 98%
- Most sensitive when TSH elevated
- Anti thyroglobulin antibodies make Tg assay unreliable
- Tumours that take up iodine have elevated thyroglobulin, but not all tumours with elevated thyroglobulin take up iodine

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Differentiated thyroid carcinoma

Radioactive iodine therapy - Duration

- Continue treatment until
  - All uptake is ablated
  - Thyroglobulin is undetectable
  - Threshold for leukemia is approached
- If no iodine uptake but thyroglobulin still elevated
  PET-CT with rTSH is often helpful

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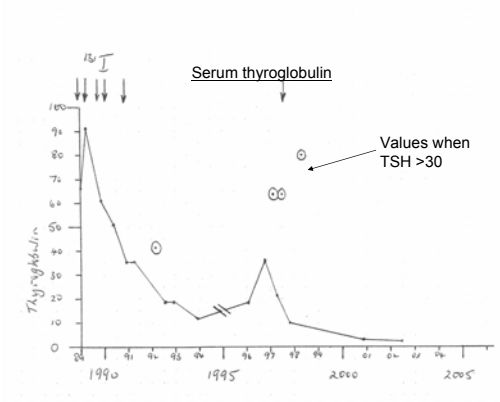

Differentiated thyroid carcinoma

External beam radiotherapy - indications

- Localised unresectable macroscopic residual disease
- Microscopic residual disease that doesn't concentrate iodine
- Palliative treatment of metastatic disease
  - bone metastases
  - brain metastases
  - bleeding or obstructing lung metastases

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Differentiated thyroid carcinoma

External beam radiotherapy – side effects

- Depend on treatment volume
- Short term
  - Acute inflammation – mucositis, dermatitis
- Long term
  - Dysphagia due to reduced lubrication of irradiated pharynx and esophagus
  - Xerostomia if volume extends above hyoid

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Differentiated thyroid carcinoma

Follow up

- Clinical examination of neck, free T4, TSH, thyroglobulin
- If given ^{131}I, repeat scan and thyroglobulin at 6-12 months unless pretreatment thyroglobulin was very low and post treatment scan was negative
- If post treatment scan is positive, repeat iodine treatment until no uptake or cumulative iodine dose is high
- If thyroglobulin is elevated and iodine scan is negative do PET scan with TSH pretreatment.
- Ultrasound of neck

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Medullary thyroid carcinoma

- Thyroxine replacement not suppression
- Doesn't concentrate iodine
- Wide field postop radiotherapy to neck and upper mediastinum unless calcitonin very low

Anaplastic thyroid carcinoma

- Thyroxine suppression if able to tolerate hyperthyroidism
- Doesn't concentrate iodine
- Wide field postop radiotherapy to neck and upper mediastinum even if apparent complete resection. Chemotherapy may be useful.