Adjuvant therapy for thyroid cancer

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Carcinoma of the thyroid

Overall survival rates in US

<table>
<thead>
<tr>
<th>Type</th>
<th>Survival Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papillary ca</td>
<td>98%</td>
</tr>
<tr>
<td>Follicular ca</td>
<td>92%</td>
</tr>
<tr>
<td>Medullary ca</td>
<td>80%</td>
</tr>
<tr>
<td>Anaplastic ca</td>
<td>13%</td>
</tr>
</tbody>
</table>

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

Carcinoma of the thyroid

Poor prognostic features for all types

Age at diagnosis
Widespread metastatic disease

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

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
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

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 ($\gamma$)
- $^{131}$Iodine used for treatment ($\beta$) and scanning body ($\gamma$)
  - 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
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

• How do we assess risk?
  ➢ Risk of death
  ➢ Risk of recurrence
Differentiated thyroid carcinoma

Risk factors

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

MACIS score

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

### Differentiated thyroid carcinoma

#### 20 year cancer specific survival according to MACIS score

<table>
<thead>
<tr>
<th>Score</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;6.0</td>
<td>99%</td>
</tr>
<tr>
<td>6.0-6.99</td>
<td>89%</td>
</tr>
<tr>
<td>7-7.99</td>
<td>56%</td>
</tr>
<tr>
<td>8+</td>
<td>24%</td>
</tr>
</tbody>
</table>


### 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

### Differentiated thyroid carcinoma

#### ¹³¹Iodine 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

#### 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)

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

- Uptake reduced by high iodine intake
  - Diet
  - CT contrast
Only uptake is in the thyroid remnant

Whole body iodine scan

Differentiated thyroid carcinoma
Radioactive iodine therapy - Duration

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

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

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
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

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

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.