MANAGEMENT OF WELL DIFFERENTIATED THYROID CARCINOMA

These guidelines are intended to optimize the day-to-day care of patients with well-differentiated thyroid cancer of follicular origin. They are not a prescription for every patient nor is it intended that they should be followed slavishly. Management of each individual with thyroid cancer should be discussed thoroughly by all concerned and a decision should be made about the appropriateness of the guidelines for that individual. Our audit suggests that a team approach to the management of thyroid cancer patients is desirable.

Diagnosis

Palpable thyroid lumps are present in 4-7% of the population. Few are malignant. Features of the history and examination which help to distinguish benign from malignant lumps are outlined below:

History

In a series of 700 papillary thyroid cancers\(^1\), 50% were first noticed by a clinician; 72% presented with a neck mass, 7% with rapid enlargement, 3% with dysphagia, 3% with thyrotoxicosis, 2% with neck pain, < 1% with hoarseness, and < 1% with hypothyroidism. In 24% presenting symptoms were uncertain. Seventy-five percent of patients had 1 major symptom, 12% had 2, 9% were pregnant, and 6% had a second cancer. Symptom onset to treatment was 10 months.

Previous radiation increases the likelihood of thyroid cancer\(^2\) and Hashimoto's disease makes thyroid lymphoma more likely\(^3\). Age and male sex are associated with a worse prognosis\(^4\) and Graves' disease with more aggressive tumours\(^5\). MEN2, Gardner's syndrome\(^6\) and Cowden's disease\(^7\) are associated with thyroid cancer.

The following help distinguish benign from malignant thyroid nodules:
<table>
<thead>
<tr>
<th>Benign</th>
<th>Malignant</th>
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<tbody>
<tr>
<td>FH of benign goitre</td>
<td>Solitary nodule</td>
</tr>
<tr>
<td>Diffuse/multinodular goitre</td>
<td>Hard, fixed</td>
</tr>
<tr>
<td>Constant size</td>
<td>Rapid enlargement</td>
</tr>
<tr>
<td>Age &lt; 14 or &gt; 65yr</td>
<td>Hoarseness</td>
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<tr>
<td>Benign FNA</td>
<td>Suspicious FNA</td>
</tr>
<tr>
<td>Simple cyst on US</td>
<td>Cyst &gt; 4cm</td>
</tr>
<tr>
<td>Hot on scintigraphy</td>
<td>Complex cyst</td>
</tr>
<tr>
<td>Shrinkage with T4</td>
<td>Cold on scintigraphy</td>
</tr>
<tr>
<td></td>
<td>Radiation history</td>
</tr>
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<td></td>
<td>Ipsilateral adenopathy</td>
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</tbody>
</table>

**Examination**

Tumour size, and local and distant spread should be assessed and recorded.

All patients with solitary nodules should have FNA and thyroid scintigraphy. Patients with cysts and those with benign FNA under follow-up should have high resolution ultrasound scanning.

**FNA**

FNA should be performed on solitary nodules (and any doubtful lesions) in the euthyroid patient. If there is a strong clinical suspicion of malignancy consider immediate surgical excision. Specimens should be read by a single histopathologist and reported in standardized manner, which should include a bottom line such as:

Thyroid aspirate: benign
Thyroid aspirate: malignant
Thyroid aspirate: suspicious
Thyroid aspirate: inadequate specimen

According to Hamburger et al.\(^8\), false negative reports may be virtually eliminated by requiring at least 6 clusters of benign cells in at least 2 of at least 6 smears before reporting an FNA as benign.
Patients with benign FNA should be followed-up initially with repeat FNA at 6 months, and high resolution ultrasound measurement of the lump. If repeat FNA is benign and the lump does not change, the patient may be discharged after 1-2 yr. If the nodule is cold, suspicious histology or two inadequate specimens necessitates excision biopsy.

Treatment

Surgery

Patients with proven thyroid cancer should be referred for total thyroidectomy.

Mazzaferri’s data suggest that tumours of < 1.5 cm may be treated by conservative surgery but small numbers of patients have died despite tumours of < 1 cm, and total thyroidectomy is associated with lower recurrence rates and facilitates the use of scans and thyroglobulin (Tg) measurement in subsequent assessment. Lymphedema is associated with unacceptable recurrence rates and shortened survival, and even if lobectomy is performed, 30-82% of patients will have microscopic foci in the opposite lobe, with clinical recurrence occurring in 5-24% (mean 7%), half of whom will die of their disease.

Tumour size, grade and invasiveness should be reported in the operative pathology report as this may help in estimating prognosis.

Radioiodine

After thyroidectomy, patients should receive ablative I-131, which is associated with less recurrence and improves sensitivity and specificity of follow-up Tg estimation and I-131 imaging. In the absence of techniques to quantitate tumour dosimetry, an arbitrary dose of 3000 MBq is recommended for ablation and 8000 MBq for subsequent treatment doses.

Thyrotropin suppression

Tumours express active TSH receptors and respond to TSH, and most studies suggest TSH suppression favourably affects tumour recurrence, tumour progression and
mortality. All patients should therefore receive T4 to suppress TSH (usually, 200-300 mg daily).

Other Treatment Modalities
External beam radiotherapy and chemotherapy may have a place in limited numbers of patients with well-differentiated tumours for focal disease which does not take up 1-131, in bony metastases, or as a palliative measure.

Follow-up
Following their initial definitive treatment, all patients should have long-term follow-up.

Follow-up with Tg versus I-131 scans
In one study in patients treated by surgery and ablative 1-131, Tg estimation during follow-up was 50% sensitive for metastases in patients receiving suppressive T4 and 83% sensitive under TSH stimulation. Specificity was 95% with TSH stimulation and 99% on T4 treatment. Thus, detectable Tg during T4 treatment is due to metastases, but an undetectable level does not exclude metastases. 1-131 scans alone, or in addition to Tg estimation, improve detection of recurrence. For review of the relative sensitivity and specificity of 1-131 scans and Tg on and off T4 see Mazzaferri.

The disadvantage of repeat scans is that they are costly, time-consuming, and cause patients considerable discomfort during T4 withdrawal. There is also a theoretical risk of tumour growth under TSH stimulation. Patients should receive a (low-dose) 1-131 scan 6 months after surgery/ablation and if this is clear, Tg estimation on T4 thereafter. If Tg is < 2 ng ml$^{-1}$ on T4 or < 3 ng ml$^{-1}$ off T4, recurrent cancer is very unlikely. Repeat scans should be performed if Tg becomes detectable, if there is clinical evidence of recurrence, or in high risk patients, for example, those with previously treated distant metastases, or those with adverse prognostic features (to be discussed for each patient).
**I-131 Whole Body Scans**

1-131 uptake is optimized by a TSH level $> 30 \text{ mU/l}$, the minimum TSH at which scans should be performed. To achieve this, T3 should be substituted for T4 for at least 4 weeks and then the T3 should be stopped for at least 2 weeks before a scan. TSH should always be checked before the scan. Lactulose 20 ml tds and senna 2 tabs nocte should be prescribed from the day before the scan for 1 wk.

Whole body scans performed after 'treatment' doses of 1-131 are at least 400% more sensitive than 'low-dose' scans$^{21,32}$, but the discordance is only clinically significant in 10% of patients who are likely to be aged $< 45$ yr and to have received previous 1-131 (odds ratio 3.8)$^{33}$. The need for a post-treatment scan should be discussed on an individual basis.

**Tg Measurements**

Should be performed at each visit. According to Birmingham (where the assay is performed), interpretation of results is:

- **Normal range:** $< 1$ to 35 ng/ml.

<table>
<thead>
<tr>
<th>Tg</th>
<th>Off T4 (T3)</th>
<th>OnT4 (T3)</th>
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</thead>
<tbody>
<tr>
<td>$&lt;5$</td>
<td>absent</td>
<td>absent</td>
</tr>
<tr>
<td>5-35</td>
<td>ambiguous</td>
<td>present (or non-compliance)</td>
</tr>
<tr>
<td>35-50</td>
<td>? present</td>
<td>present</td>
</tr>
<tr>
<td>50-100</td>
<td>present (?mets)</td>
<td>present</td>
</tr>
<tr>
<td>$&gt;100$</td>
<td>present, mets (prob lung or bone)</td>
<td></td>
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</tbody>
</table>

However, the recent paper by Ozata et al.$^{30}$ suggests that 45% of patients with recurrence may have Tg $<5$ ng/ml on T4 and that to be confident about lack of recurrence Tg should be $<2$ ng/ml on T4 or $<3$ ng/ml off T4.

Protocol prepared by Kevin Hardy, 1994
References


18. Mazzaferri EL. Controversies in the management of differentiated thyroid carcinoma. Endocrine Societ' 42nd Annual Postgraduate Endocrine Assembly Syllabus 199();167.


