

## Thyroid cancer: a review of treatment and follow-up

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The importance of thyroid cancers far exceeds their frequency, since they are uncommon tumours accounting for only 1% of all malignancies and for even smaller proportion of cancer deaths (0.2%). A variety of distinct tumour types arise in the thyroid gland, with variable natural histories resulting from different rates of growth and biological aggressiveness. The long natural history of the majority of thyroid neoplasms imposes a commitment for long-term follow-up and stresses the importance of planning treatment so as to avoid delayed complications that impair the quality of life of patients.

The management of thyroid cancer is multidisciplinary, requiring consultation and active intervention by surgeons, endocrinologists and radiotherapists. Surgery is of paramount importance in the successful eradication of the tumours while radioiodine offers a unique therapeutic approach. Treatment must be strongly influenced by consideration of prognostic variables.

**Key words:** thyroid, cancer, therapy, <sup>131</sup>I

### EPIDEMIOLOGY AND AETIOLOGY

THYROID CANCER is a rare malignancy, accounting for only 1% of all cancers. The incidence is higher in Iceland, Hawaii and Malta, while in UK approximately 800 cases are registered every year.<sup>1</sup> Occult carcinoma is found at autopsy in 5-28% of the thyroid glands, indicating that many of these cancers never become clinically detectable.<sup>2</sup> It has been reported that a substantial proportion of occult primary tumours are associated with micrometastases in cervical lymph nodes. Women are affected more frequently than men and the female to male ratio varies from 1.4 : 1 to 4 : 1. Only a very small percentage of thyroid cancers occur in the young and they usually are papillary adenocarcinomas.<sup>3</sup> However, thyroid nodularity is associated with a much higher overall incidence of malignancy than in adults and in some series as many as 50% of pediatric nodules are malignant.<sup>4</sup>

The relationship between radiation and thyroid cancer is well established, with 90% of these tumours being papillary. The risk of developing thyroid cancer increases with the dose of radiation, is greater in females than in

males and is greater the younger the patient is at the time of irradiation.<sup>5</sup> The latent period may range from 5 to 35 years and there is no evidence that radiation-induced thyroid cancer exhibit unusual biological behaviour. A slightly increased incidence has been seen among survivors of the atomic bombing in Hiroshima and Nagasaki while a more dramatic increase has been recently reported in children from Belarus and Ukraine, who were contaminated by radioactive iodine after the Chernobyl accident.<sup>6</sup> So far surveys have not found any evidence of subsequent increase of thyroid tumours following the use of radioactive iodine in adults for diagnostic or therapeutic purposes.<sup>7</sup>

Papillary tumours occur more frequently in iodine-rich areas while the follicular ones appear to be more common in low iodine endemic goitre areas.<sup>8</sup> Although both chemical and dietary goitrogens produce cancer experimentally, it is difficult to assess their possible role in the aetiology of human thyroid cancer. In all these cases there is prolonged stimulation by thyroid-stimulating hormone (TSH) leading to irreversible adenomatous hyperplasia.

Familial occurrence of differentiated thyroid cancer has been reported (only in 2.5% of the families) while an elevated incidence is observed in patients with Gardner's syndrome (polyposis coli, osteomas and sebaceous cysts) and Cowden's disease (multiple hamartomas).<sup>9</sup>

Genes of the *ras* family are frequently activated by a point mutation in both papillary and follicular tumours

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**Table 1** WHO histological classification of thyroid tumours

Epithelial tumours
Benign
—follicular adenoma
Malignant
—papillary carcinoma
—follicular carcinoma
—medullary carcinoma
—undifferentiated (anaplastic) carcinoma
Non-epithelial tumours
Malignant lymphomas
Secondary tumours
Unclassified tumours
Tumour-like lesions

and point mutations inactivating the p53 gene were observed with high frequency in poorly-differentiated and anaplastic cancers.<sup>10</sup>

Approximately 25% of cases with medullary carcinoma are familial and occur as part of the syndrome multiple endocrine neoplasia (MEN 2A and 2B).<sup>11</sup> This shows an autosomal dominant pattern of inheritance and the predisposing gene has been mapped by genetic linkage on chromosome 10.<sup>12</sup>

Hashimoto's thyroiditis has been associated with the development of thyroid lymphomas<sup>13</sup> and anaplastic carcinomas have been reported in association with long standing goitre as well as anaplastic transformation of pre-existing differentiated tumours.<sup>14</sup>

## **PATHOLOGY AND NATURAL HISTORY**

The WHO classification for thyroid tumours is given in Table 1.<sup>15</sup>

**Papillary** carcinomas account for approximately 60% of all thyroid neoplasms. They are epithelial tumours showing evidence of follicular differentiation and characterised by complex branching papillae arranged on a fibrovascular stalk.<sup>16</sup> They grow very slowly and are typically well differentiated. 'Ground-glass' appearance of the nuclear chromatin is common, mitoses are rare and psammoma bodies are present in 40% of tumours. Immunohistochemical staining for calcitonin is used to confirm the diagnosis. Multicentricity is said to occur in 20–80% while mixed tumours exhibit the biological behaviour of papillary cancer and should be included in the papillary group. They have a marked propensity for lymphatic spread which is seen in about 50% of cases at presentation, while 90% of patients under 15 years of age showed cervical metastases at some time during the course of their disease.<sup>17</sup> Overall, distant metastases mainly in lungs and bones are found in less than 5% of adults, however, 20% of children present with pulmonary metastases which seem to have little impact on survival.

**Follicular** cancers represent 15–20% of thyroid

tumours. They are malignant tumours of follicular cell origin lacking the diagnostic features of papillary carcinomas. When well differentiated they look very similar to follicular adenomas and the diagnosis can be extremely difficult. Invasion of the capsule or blood vessels are often the only features to denote malignancy. Lymph node metastases are less frequent than in papillary carcinoma but haemato-genous spread mainly to bones and lungs is seen in about 15% at presentation.<sup>18</sup> The histology of metastases often differs from that of the primary tumour which is usually less well differentiated. Hurthle cell carcinoma is considered as a variant of follicular cancer but thought to behave more aggressively.<sup>19</sup>

The majority, however, of these well differentiated tumours show a mixture of papillary and follicular areas. In addition it seems that there is a continuous spectrum blurring these two distinct entities. An apparently pure follicular primary tumour may be associated with papillary lymph node metastases.

**Anaplastic** carcinomas also arise from follicular cells and make up 10% of all thyroid malignancies. They occur predominantly in the elderly and have been associated with long-standing goitre while there is some disagreement as to whether anaplastic transformation from differentiated carcinoma is involved in the pathogenesis.<sup>20</sup> Small cell, giant and spindle cell variants have been recognised and it is frequently difficult to differentiate from lymphomas. They are characterised by rapid and massive locoregional spread while over half patients have metastases outside the neck.<sup>21</sup>

**Medullary** carcinomas arise from the parafollicular 'C' cells which belong to the APUD system and they are therefore neuroendocrine tumours. They constitute 8% to 12% of thyroid cancers (the incidence may be increasing due to screening) and 25% prove to be familial. They are composed of small round cells within amyloid stroma and stain strongly with calcitonin. They are frequently multicentric or bilateral with extrathyroid invasion in 40%, involvement of cervical or mediastinal lymph nodes in 40–50% and distant metastases at diagnosis seen in 12% of patients.<sup>22</sup> Medullary cancer secretes calcitonin, which can be measured by a radioimmunoassay, as well as CEA, histaminase, serotonin, ACTH, VIP, prostaglandins and other peptides that can serve as tumour markers.<sup>23</sup>

**Lymphomas** of the thyroid are very rare representing only 2% of all extranodal lymphomas. Chronic autoimmune stimulation, as in Hashimoto's thyroiditis, was supposed to be a predisposing factor. They affect the elderly, who present with painless enlargement and grow quite quickly. The majority are of intermediate to high grade, B cell in origin (the most common type being diffuse histiocytic) and localised disease is found in 75% at presentation. Relapse following treatment not uncommonly involves the gastrointestinal tract and MALT (mucosa associated lymphoid tissue) lymphomas have better prognosis.<sup>24</sup>

**Table 2** TNM clinical classification for thyroid carcinoma

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T—Primary Tumour
T1 Tumour 1 cm or less in greatest dimension
T2 Tumour more than 1 but less than 4 cm in greatest dimension
T3 Tumour more than 4 cm in greatest dimension
T4 Tumour of any size extending beyond the thyroid capsule
All categories may be subdivided: (a) solitary tumour, (b) multifocal
N—Regional Lymph Nodes
N0 No regional nodal metastasis
N1 Regional lymph node metastasis
N1a in ipsilateral cervical lymph node(s)
N1b in bilateral, midline or contralateral cervical or mediastinal lymph node(s)
M Distant Metastasis
pTNM Pathological Classification
The pT, pN and pM categories correspond to T, N and M categories

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## DIAGNOSIS

Palpable thyroid nodules are present in 4–7% of adults and in most series a cancer incidence of 5–15% is reported. Features that may give rise to clinical suspicion of malignancy include nodules at the extremes of age, male sex, hard consistency, fixation, size greater than 4 cm, rapid growth and a nodule which is solitary. Any patient who was exposed to low dose radiation in childhood is at substantially higher risk. The most consistent sign of malignancy in a thyroid mass is probably the presence of cervical adenopathy while characteristics such as hardness or fixation must be viewed with suspicion.<sup>25</sup>

Ultrasonography will distinguish a solid from a cystic lesion and although the risk of malignancy in a cyst is small (less than 4%) aspiration should follow to confirm the diagnosis.<sup>26</sup> A thyroid scan with <sup>99m</sup>Tc or <sup>123</sup>I is suggestive of malignancy where there is a cold nodule.<sup>27</sup> However, only 10 to 20% of cold nodules are malignant and therefore needle aspiration is required. FNA cytology is a useful diagnostic tool and when done by experienced personnel the false-negative rate is probably less than 2% with a degree of reliability in excess of 95%.<sup>28</sup>

## STAGING

The clinical and pathological staging for thyroid cancer is based on the TNM staging system (Table 2). Unfortunately, this does not seem to be very satisfactory because the size of the primary tumour and the degree of lymph node involvement are much less important prognostic factors than others, which are not included in the TNM system, such as age at diagnosis, sex, degree of tumour differentiation and completeness of surgical excision. In addition to recording tumour size, grade, multicentricity, lymph node involvement and extrathyroid extension the pathologist should also comment on the margins of excision while the surgeon must indicate whether or not all visible tumour was excised.

## MANAGEMENT

### Well differentiated papillary and follicular carcinomas

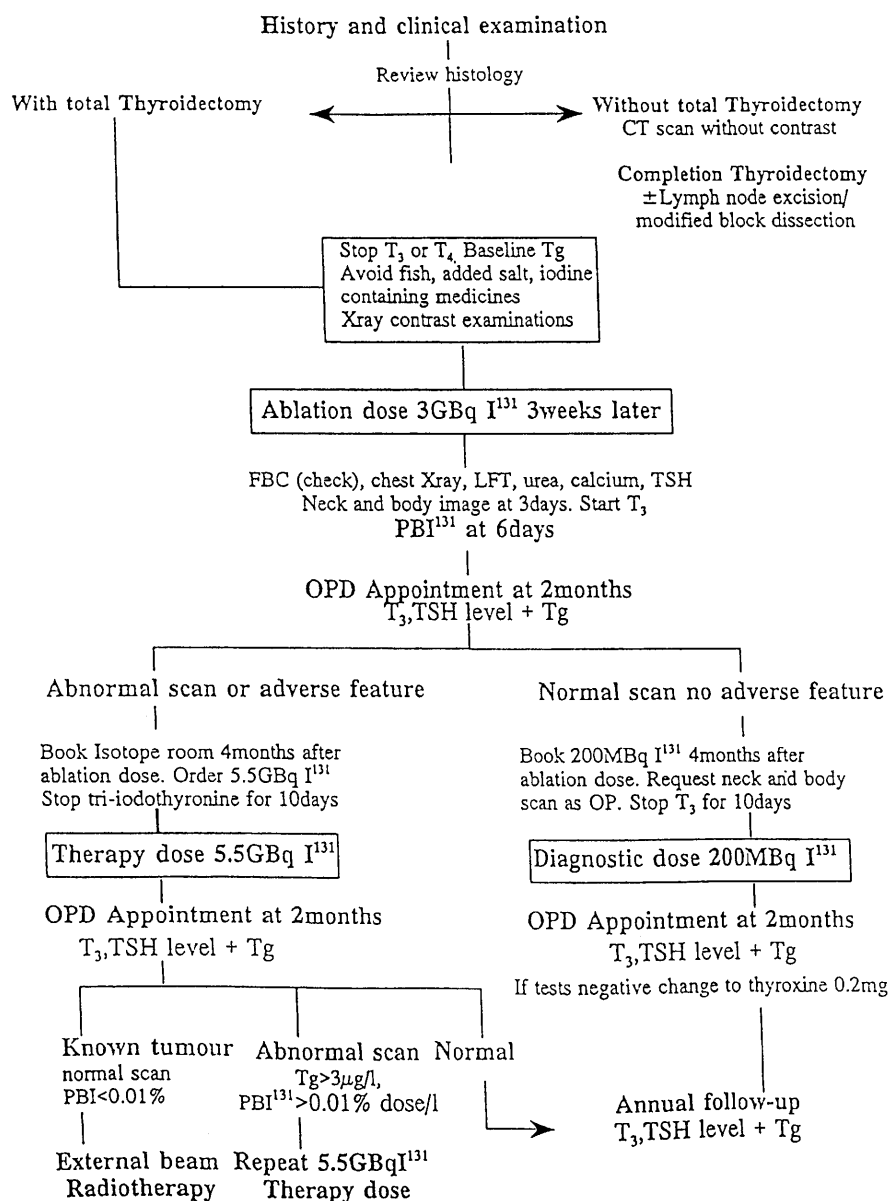
Surgery is the definite and potentially curative treatment for differentiated thyroid cancer. The extent of the operative procedure remains controversial but the minimum requirement is a near total thyroidectomy with excision of all macroscopic disease including resection of adjacent muscle should this be involved.<sup>29</sup> Routine resection of uninvolved lymph nodes is not necessary but all involved nodes should be removed and if extensively invaded a modified neck dissection will be required.<sup>30</sup>

The arguments in favour of near total thyroidectomy are as follows. There is a greater chance of removing microscopic tumour foci which are found in the contralateral lobe in 38 to 87% of patients. Some of those may be anaplastic and therefore their removal will avoid progression to anaplastic carcinoma.<sup>31</sup> Following unilateral lobectomy the 20 year locoregional recurrence was 25% as compared to 6% after total thyroidectomy, while there is some evidence that 15 year survival in patients with papillary cancer increased from 78% to 92%.<sup>32</sup> In addition surgical ablation of normal residual thyroid tissue is quicker than repeated administrations of radioiodine and avoid unnecessary whole body irradiation. Finally, iodine scanning to detect metastases and thyroglobulin monitoring for follow-up are more reliable after all normal thyroid tissue has been removed.

Knowledge of prognostic factors may dictate the extent of surgery. In fact, survival of patients with favourable prognostic indicators is similar following lobectomy or bilateral resection. Conversely, survival is improved after bilateral resection in patients with unfavourable prognostic indicators.<sup>33</sup>

The most common complications following total thyroidectomy are hypoparathyroidism requiring life-long calcium or vitamin D, which develops in 11% of patients and vocal cord paralysis due to recurrent laryngeal nerve damage.<sup>34</sup>

**Table 3** New patient referred with differentiated thyroid carcinoma



**Radioactive Iodine: ablation and treatment**

Normal thyroid tissue almost always takes up iodine more avidly than the tumour and therefore it is necessary to ablate the normal thyroid, surgically or by radioiodine, before the tumour can be effectively treated.<sup>35</sup> Post-operative <sup>131</sup>I therapy has two main advantages. First, it allows the subsequent search by a whole-body scan of residual neoplastic tissue and increases the sensitivity of Tg measurement and of whole-body <sup>131</sup>I scan for follow-up.<sup>36</sup> Second, relapse rates are lower in patients systematically treated post-operatively with <sup>131</sup>I in some series.<sup>37</sup> In some subsets of patients the prognosis is so favourable after surgery alone that little further improvement is obtained.<sup>38</sup> In addition the reasons usually given for not using <sup>131</sup>I are not convincing. After a single dose of iodine the theoretical risk of leukaemia is very small and that of genetic

defect or infertility remains unproven.<sup>39</sup>

So far a fixed activity of radioiodine is usually prescribed based on clinical experience and likely side effects. It is our practice to give all patients 3 GBq <sup>131</sup>I orally preferably 3 weeks after the operation and obtain whole body and neck scans at 3 days and also measure the protein bound <sup>131</sup>I at 6 days. In patients with residual or metastatic tumour therapeutic doses of 5.5 GBq <sup>131</sup>I are required every 6 months until all tumour has been eradicated. The patient is kept on triiodothyronine until the treatment is completed when it is replaced by thyroxine at an average daily dose of 0.2 mg (Table 3).

Following near total thyroidectomy the administration of 3 GBq <sup>131</sup>I was found to ablate 67% of patients when a mean dose of 349 Gy was delivered. Large remnants demanded a higher absorbed dose and therefore higher

**Table 4** Prognostic factors for differentiated thyroid carcinoma

Variable		Hazard ratio	p-Value
Age	< 30	1.00	p < 0.001
	30–39	4.50	
	40–49	14.9	
	50–59	25.9	
	> 60	34.1	
Grade	I, II	1.00	p < 0.01
	III	2.81	
Stage	T1, T2	1.00	p < 0.001
	T3	1.78	
	T4	3.13	
Metastases	None	1.00	p < 0.001
	Lung only	3.41	
	Other	10.1	

Derived by multivariate analysis using Cox's Regression model for 649 patients treated at the Royal Marsden Hospital between 1949–1991.

administered activity is recommended.<sup>40</sup>

Early morbidity from <sup>131</sup>I therapy is minimal including radiation thyroiditis, sialadenitis, cystitis and xerostomia while late effects are mainly related to the total dose received. Pulmonary fibrosis has been reported in patients with diffuse lung metastases receiving as little as 3.7 GBq and aplastic anaemia is more common in those with extensive bony disease. No decreased fertility or abnormal birth was seen in a 25-year follow-up study of 40 children with thyroid cancer treated with a mean activity of 7.4 GBq and a total dose of 26 GBq.<sup>41</sup> In the past an excess of acute leukaemia and solid tumours such as bladder, kidney, breast, has been reported.<sup>42</sup> Therefore, treatment with high activity <sup>131</sup>I should always be at the lowest level for effective local control.

#### *External radiotherapy—chemotherapy*

External radiotherapy is reserved for patients whose initial, recurrent or metastatic disease is unresectable and does not take up iodine.<sup>43</sup> The target volume includes the thyroid bed and the neck nodes extending occasionally to the superior mediastinum. A dose of 50 Gy is given followed by a 10 Gy boost to areas of macroscopic disease. After incomplete surgery the actuarial probability of local recurrence at 5 years was 11% following radiotherapy as compared to 23% to surgery alone.<sup>44</sup> Occasionally an inoperable tumour may become resectable after radiotherapy. Metastatic disease in bone, lungs, mediastinum, brain, frequently requires palliation but in general higher doses than usually employed are necessary.

Chemotherapy is reserved for those 20% of patients with symptomatic progression who fail to concentrate iodine. Adriamycin is the most commonly used drug with responses in 20 to 30% of cases but of very short duration.<sup>45</sup>

#### *Prognostic factors*

In the literature there is a difference in opinion over the relative importance of prognostic factors. In most univariate studies age has been identified as the single most important risk factor, while sex, histology and grade were less significant. Multivariate studies agree on the importance of tumour extension on prognosis while the impact of lymph node involvement on survival is controversial. The EORTC analysis, supported by the long-term Mayo clinic survival data, suggests that minimal treatment is required for the good prognosis group (age under 35 years, well differentiated histology, T<sub>1</sub>–T<sub>2</sub> primary tumour, no lymph node or distant metastases).<sup>46</sup> The results of multivariate analysis using Cox's Regression Model for 649 patients with differentiated thyroid cancer treated at the Royal Marsden Hospital, London, between 1949–1991 are shown on Table 4.<sup>47</sup>

#### *Follow-up*

For patients with well-differentiated thyroid cancer annual follow-up is adequate and should be lifelong since relapses can occur as long as 40 years from presentation.<sup>48</sup> It should be based on thyroglobulin (Tg) measurement which is a very reliable tumour marker. A progressively rising level demands further investigation and a whole body scan following 200 MBq <sup>131</sup>I is very likely to reveal the site of relapse.<sup>49</sup>

The majority of relapses are local with metastases outside the neck found in 10–15% of patients. Surgery should be considered first with a curative intent but if not possible radioiodine should be employed.<sup>50</sup> However, only two thirds of patients take up iodine in their metastases and although <sup>131</sup>I can eradicate small foci, for larger deposits the addition of surgery and external radiotherapy may be warranted. Overall survival from the time of detection of metastases were 54%, 37% and 29% at 5, 10 and 15 years respectively.<sup>51</sup> Histology, age at the time of discovery, <sup>131</sup>I uptake and volume have been found to be of prognostic significance on multivariate analysis. Site of disease seems to play a role with bone metastases having the worst prognosis.<sup>52</sup> In conclusion, disseminated thyroid cancer can be cured in a significant proportion of patients while durable palliation with good quality of life and prolonged survival can be achieved in others.

#### **Anaplastic carcinomas**

These are amongst the most aggressive human cancers and the patients usually present with rapidly enlarging thyroid masses causing stridor. Prognosis is dismal as these tumours are highly malignant, invade locally and extensively and metastasize rapidly mainly to the lungs. They are inoperable, they do not take up iodine and TSH suppression has little impact. Survival is not affected by treatment, however external radiotherapy can be used to relieve symptoms of tracheal compression. Combined radiotherapy and chemotherapy has been also reported as

effective in small series.<sup>53</sup> Unfortunately median survival is only 6 months and all attempts should be purely palliative.

### Medullary carcinomas

Surgery is the only potentially curative treatment and should include total thyroidectomy and central compartment lymph node dissection.<sup>54</sup> A modified lymphadenectomy is indicated if involved cervical nodes are found. The patient should have a complete family history taken while the family should be offered screening in order to exclude familial disease.<sup>55</sup> Pheochromocytoma must be excluded or managed and calcitonin levels checked post-operatively. If the levels remained elevated the patient should be investigated to try and detect residual or metastatic disease. Further surgery should always be contemplated. It can offer prolonged palliation<sup>56</sup> but if the site of disease cannot be determined then a diagnostic mIBG scan is indicated. This is occasionally positive (in 10–30%) in which cases therapeutic doses of <sup>131</sup>I labelled mIBG might be tried.

External radiotherapy to the neck and upper mediastinum has been shown to improve local control in cases with adverse features such as a difficult or incomplete operation or persistently elevated calcitonin without any demonstrable disease. However, routine use is not generally recommended. Metastatic medullary thyroid cancer is often asymptomatic and may remain indolent for years. Chemotherapy should be initiated only when metastatic disease is unresectable, progressive and symptomatic.<sup>57</sup> Drugs such as doxorubicin, etoposide and platinum have been used with responses in 30 to 50% of cases. Routine follow-up is based on clinical evaluation and serial monitoring of calcitonin and CEA.

### Lymphomas

The majority of patients present with stage I and II disease for which moderate dose radiotherapy should be given. A dose of 40 Gy to the neck and upper mediastinum usually achieves local control, however median survival is only 15 months and the majority of deaths are due to widespread disease. In some centres initial chemotherapy is preferred with irradiation to areas of bulky disease being given later.<sup>58</sup> Identification of MALT features may be the way to select patients for locoregional treatment alone since it seems that MALT positive lymphomas are associated with less aggressive nature. Patients with stage III or IV disease should be treated with chemotherapy and irradiation reserved for persistent bulky primary tumour. Most recent experience suggests an actuarial 5-year survival of approximately 65%.

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